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Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation

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ABSTRACT

BACKGROUND: Sleep disturbance is associated with inflammatory disease risk and all-cause mortality. Here, we assess global evidence linking sleep disturbance, sleep duration, and inflammation in adult humans.

METHODS: A systematic search of English language publications was performed, with inclusion of primary research articles that characterized sleep disturbance and/or sleep duration or performed experimental sleep deprivation and assessed inflammation by levels of circulating markers. Effect sizes (ES) and 95% confidence intervals (CI) were extracted and pooled using a random effect model.

RESULTS: A total of 72 studies ($n > 50{,}000$) were analyzed with assessment of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor α (TNFα). Sleep disturbance was associated with higher levels of CRP (ES .12; 95% CI = .05–.19) and IL-6 (ES .20; 95% CI = .08–.31). Shorter sleep duration, but not the extreme of short sleep, was associated with higher levels of CRP (ES .09; 95% CI = .01–.17) but not IL-6 (ES .03; 95% CI: −.09 to .14). The extreme of long sleep duration was associated with higher levels of CRP (ES .17; 95% CI = .01–.34) and IL-6 (ES .11; 95% CI = .02–20). Neither sleep disturbances nor sleep duration was associated with TNFα. Neither experimental sleep deprivation nor sleep restriction was associated with CRP, IL-6, or TNFα. Some heterogeneity among studies was found, but there was no evidence of publication bias.

CONCLUSIONS: Sleep disturbance and long sleep duration, but not short sleep duration, are associated with increases in markers of systemic inflammation.

Keywords: Inflammation, Insomnia, Interleukin-6, Meta-analysis, Sleep deprivation, Sleep disturbance, Sleep duration

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Over the past decade, compelling evidence has demonstrated that disturbances of sleep such as insomnia complaints and extremes of sleep duration adversely influence risk of inflammatory disease and contribute to all-cause mortality (1–4). Because about 25% of the population of the United States report insomnia complaints (5) and nearly 10% fulfill diagnostic criteria for chronic insomnia (6,7), which is persistent for as long as 3 years in nearly 50% (6), the burden of insomnia has substantial public health implications. Indeed, the Centers for Disease Control and Prevention has identified insufficient sleep as a public health epidemic (www.cdc.gov/features/dssleep/). Increasingly, research on sleep health (8) has focused on the biological mechanisms underlying these effects, with substantial interest in the role of sleep disturbance on measures of innate immunity (9).

Inflammatory mechanisms contribute to the risk of a wide spectrum of medical conditions. Increases in circulating markers of inflammation, such as high sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6), predict cardiovascular events (10,11), hypertension (12), weight gain in older adults (13), and type 2 diabetes (14,15). However, it is difficult to draw robust conclusions about the effects of sleep on inflammation, given the variety of studies with differences in the characterization of sleep disturbance, varying assessment methods used to evaluate sleep disturbance (i.e., sleep quality, sleep complaints) and sleep duration, and various markers of inflammation (9). Systematic evaluation of the associations between sleep disturbance and sleep duration, as well as experimental sleep deprivation on inflammatory outcomes, and related effect sizes (ES) has not been previously undertaken. Moreover, understanding the magnitude and specificity of different aspects of sleep (i.e., sleep disturbance, sleep duration) on inflammation has further health implications, because inflammation appears to be amenable to modification by way of treatments that target insomnia complaints (16–18).

The aims of this study were to 1) systematically review published studies evaluating sleep and inflammatory outcomes and 2) carry out a meta-analysis to assess the global evidence that links sleep disturbance, sleep duration, or experimental sleep loss with circulating markers of

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inflammation in adult humans. This meta-analysis focuses on CRP and IL-6, because the vast majority of research on sleep and inflammation has predominantly measured these markers of systemic inflammation and because these markers have been consistently found to have health relevance (9–13,15). Effects on tumor necrosis factor α (TNFα) are also explored. This meta-analysis considers the combination of results across different studies, increasing the overall statistical power as well as precision of estimates with evaluation of bias and random error.

METHODS AND MATERIALS

Study Selection

A search strategy was developed to identify studies that examined the relationship between sleep disturbance and/or sleep duration, including experimental sleep deprivation and inflammation. The following databases were searched for primary studies through September 2013: MEDLINE, PsycINFO, EMBASE, PsycArticles, and Scopus. The MEDLINE search strategy used PubMed medical subject heading terms and the text words of key articles that we identified a priori, with a similar strategy for other electronic sources. The following search terms were used: Sleep or insomnia or sleep initiation and maintenance disorders or sleep deprivation, and inflammation or inflammatory or proinflammatory or C-reactive protein or CRP or C-Reactive Protein or interferon or Interferons or interleukin-6 or Interleukin-6 or tumor necrosis factor or tumor necrosis factor-α or interleukin-8 or Interleukin-8. In addition, reference lists of included articles, relevant review articles, and related systematic reviews were used to identify articles that might have been missed in the database searches. Limits were imposed based on English language but not on date of publication, although all identified articles were found since 1989. Studies that evaluated the effects of sleep apnea and/or restless legs syndrome on inflammation were excluded, as these associations have been previously reported (19).

Inclusion Criteria and Screening Review

Three trained investigators independently reviewed titles and abstracts; studies were excluded as not being relevant in a consensus meeting (M.R.I., J.E.C., R.O.). Criteria for inclusion were: 1) indication of number of subjects studied and sample characteristics; 2) sleep disturbance (i.e., poor sleep quality, insomnia complaints) was characterized by either survey items, questionnaire, interview, and/or standard diagnostic criteria using ICD-10, DSM-III, DSM-IIIR, or DSM-IV; 3) sleep duration was characterized by survey items, questionnaire, interview, and/or objective measures including actigraphy or polysomnography; 4) sleep deprivation was performed by an experimental manipulation of sleep duration over one or several nights; 5) assessment of inflammation as an outcome by levels of circulating markers of inflammation; and 6) primary research articles (i.e., review articles or abstracts were not included). If multiple published reports from the same study were available, we included only the one with the most detailed information for both sleep and inflammation.

Data Extraction

Three investigators (M.R.I., R.O., J.E.C.) independently extracted data; discussion and additional consensus meetings resolved differences. Relevant data included the first author's surname, title of article, year of publication, number of participants, participants age and gender, study design (i.e., epidemiologic, naturalistic, prospective, case-control, and experimental), number of participants, methods used to evaluate sleep disturbance (i.e., single survey item, multiple symptoms reporting, validated questionnaire, or diagnosis), methods used to evaluate sleep duration (i.e., single survey item, validated questionnaire, sleep diary, actigraphy, or polysomnography), methods used to manipulate experimentally sleep duration (i.e., partial night sleep deprivation over one night, sleep restriction over several nights, total sleep deprivation over one or more nights, but not sleep fragmentation); and circulating inflammatory markers (i.e., CRP, IL-6, TNFα, or other).

Definition of Sleep Disturbance and Sleep Duration Categories

Studies evaluating sleep disturbance data were categorized into three groups as determined by the assessment method: symptom reporting (single or multiple items) (20–32), questionnaire (33–57), or diagnosis (34,58–60). Studies evaluating sleep duration were grouped into those that treated sleep duration as a continuous measure subjectively (24,31,38,45,54,61–66) or objectively (21,22,25,34,39,54,65,67–70) versus those that categorized sleep duration as short or long sleep (27,38,62,71–75). Consistent with prior meta-analyses (76,77), the reference category for sleep duration was 7 to 8 hours per night in the majority of studies. Hence, short sleep was defined as < 7 hours per night, and long sleep was defined as > 8 hours per night. Additionally, for sleep duration, the assessment method was considered, i.e., self-report or objective. Finally, we evaluated studies that experimentally manipulated sleep duration over one night (78–88) or multiple nights (89–94), analyzing the sample obtained first in the morning.

Statistical Analyses

The quality of the studies included in the meta-analysis was evaluated by the Downs and Black Quality Index score system (95), a validated checklist for assessing the quality of both randomized and nonrandomized studies (cohort and case-control studies), which consists of five subscales (i.e., reporting, external validity, bias, confounding, and power) with a maximum score of 14 for nonrandomized, nonprospective studies. Included studies scored between 12 and 14.

For all sources that met inclusion criteria, methods provided by Wilson and Lipsey (96) were utilized to calculate effect sizes in the Cohen's *d* metric and associated standard errors. For sources in which the study's methods section indicated that the relationship between selected sleep and immune measures were tested but either were not reported or reported as nonsignificant without sufficient information to calculate effect size, the effect size was assumed to be zero with appropriate standard errors for the sample. If multiple estimates of effect