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

Michael R. Irwin, Richard Olmstead, and Judith E. Carroll

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

size were possible, based upon underlying distributional assumptions, the smallest effect size was included. For some studies, effects were reported for separate groups, most commonly by gender. Rather than create pooled effect sizes, effects were treated separately as independent groups. Some studies also provided effect size estimates in more than one category (e.g., sleep disturbance and sleep duration, CRP, and IL-6). The heterogeneity among studies was tested by Q statistics and quantified by H statistics and I^2 statistics (97). Funnel plot asymmetry was used to detect publication bias, and Egger's regression test was applied to measure funnel plot asymmetry (98).

A priori, the set of studies selected was assumed to represent a random effects model; thus, pooled effect size estimates were calculated as such. Estimates of heterogeneity supported this decision. Pooled effect size estimates were generated according to the categories noted above, as well as overall pooled estimates. Based upon the availability of information, meta-regression (96) examined the impact of mean/median age of the sample and proportion of female versus male subjects upon the effect size estimates; the experimental studies were not tested, as both the age and gender distributions were largely restricted.

RESULTS

As shown in Figure S1 in Supplement 1, a total of 1,802,699 articles were retrieved; 2206 articles were identified that included both sleep and inflammation terms. A total of 340 articles were duplicates, yielding 1866 articles for abstract review. An additional 1751 articles were excluded as not being relevant by review of title and abstract. Hence, 156 articles underwent full-text review with discussion during consensus meetings. Additional studies were excluded for the following reasons: review articles (n = 6); absence of sleep assessment (n = 13); absence of inflammation assessment (n = 3); absence of analyses evaluating the relationship between sleep and inflammation (n = 20); absence of assessment of circulating markers of inflammation (i.e., studies that included only cellular or genomic markers of inflammation were excluded) (n = 22); circadian only studies (n = 5); and sleep disturbance was the target of a treatment intervention with inflammation as a secondary outcome (n = 4). Specifically, none of the intervention studies tested the relationship between change in sleep and inflammation; only main effects of the intervention were reported.

Following careful scrutiny of each article during data extraction, 11 additional studies were excluded for the following

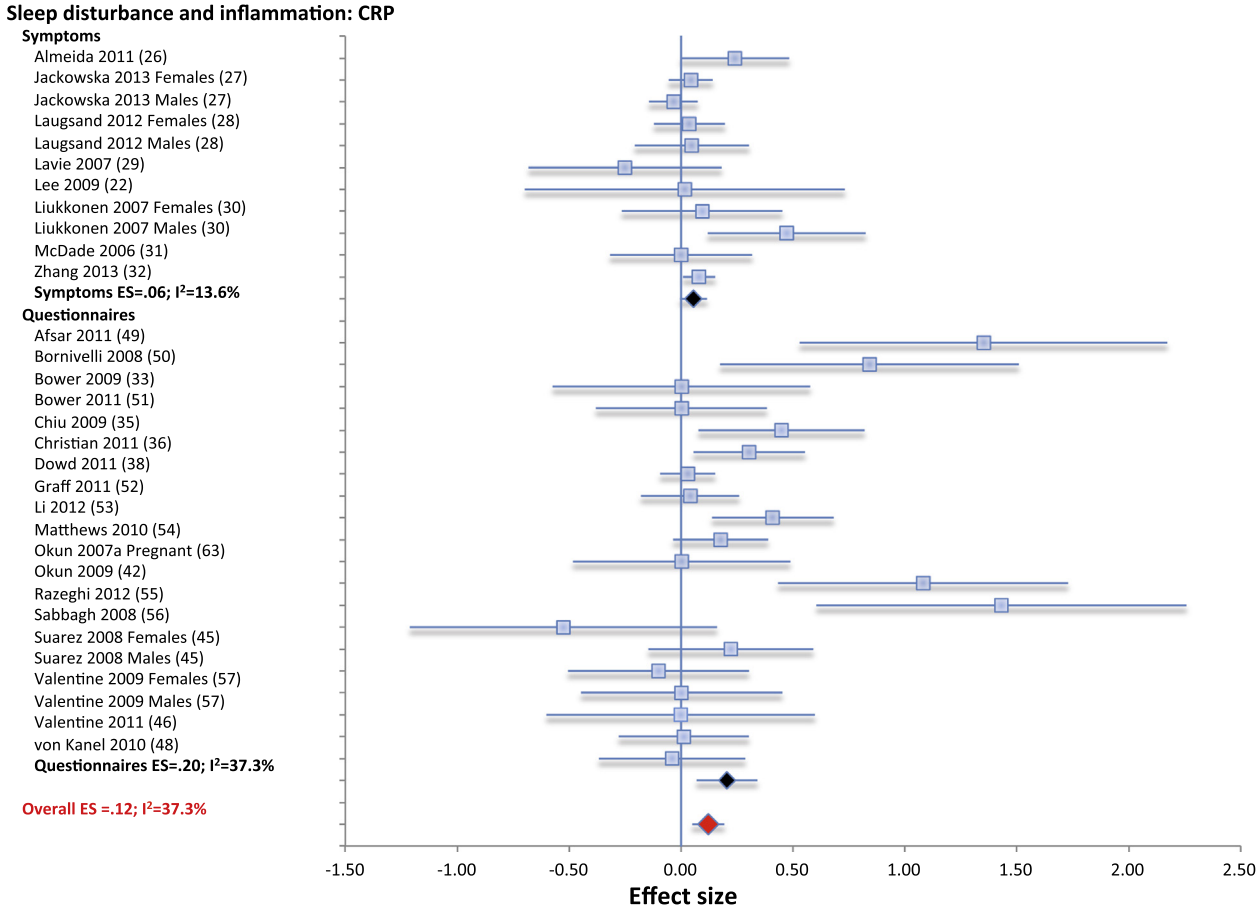

Figure 1. Forest plot of sleep disturbance associated with inflammation as indexed by C-reactive protein (CRP). Sleep disturbance is assessed by self-reported symptoms and questionnaires. Results are expressed as effect sizes (ES) and 95% confidence intervals.

reasons: 1) statistics could not be estimated for associations, which reduced the Down and Black Quality index to below the minimum threshold of 12 (n = 3) (43,99,100); 2) sleep, rather than inflammation, was the outcome (n = 5) (101–105); and 3) no assessment of at least one of the selected measures of inflammation (i.e., CRP, IL-6, TNFα) (n = 3) (106–108). In addition to CRP, IL-6, or TNFα, studies assessed other circulating markers of inflammation including interleukin-1β (n = 8); interleukin-1 receptor antagonist (n = 4); soluble IL-6 receptor (n = 3); interleukin-8 (n = 2); tumor necrosis factor receptor I (n = 5); or tumor necrosis factor receptor II (n = 2), but analyses related to these additional markers were not performed given the limited number of studies. Hence, 72 empirical studies were included, of which 28 evaluated sleep disturbance, 14 evaluated sleep duration, 13 evaluated both sleep disturbance and sleep duration, and 17 were experimental sleep deprivation or sleep restriction studies. Tables S1 through S3 in Supplement 1 summarize the characteristics of the included studies.

Sleep Disturbance and Inflammation

Three categories of assessment of sleep disturbance (i.e., symptom reporting using single or multiple items, questionnaire, diagnosis) were used to evaluate the link between sleep disturbance and CRP, IL-6, and TNFα; these varying assessment methods were analyzed separately and in combination for CRP and IL-6. For TNFα, only effects of combined assessment categories were analyzed due to the few studies. First, symptom reporting of sleep disturbance was not associated with CRP (11 samples; n = 31,569; effect size .06; 95% confidence interval [CI] −.005 to .12; Q_v = 10.9; p = .37; I^2 = 7.9) (Figure 1) but was associated with higher levels of IL-6 (6 samples; n = 380; ES .55; 95% CI .36–.74; Q_v = 4.8; p = .44; I^2 = 0) (Figure 2). Second, sleep disturbance as assessed by questionnaire was associated with higher levels of CRP (20 samples; n = 3374; ES .20; 95% CI .07–.33; Q_v = 30.3; p = .05; I^2 = 37.7) (Figure 1) and with higher levels of IL-6 (19 samples; n = 2785; ES .10; 95% CI .01–.20; Q_v = 18.4; p = .43; I^2 = 2.3) (Figure 2). Third, sleep disturbance as assessed using diagnostic criteria for insomnia disorder was not associated with IL-6 (4 samples; n = 174; ES .41; 95% CI −.22 to 1.03; Q_v = 2.8; p = .42; I^2 = .00); the association between diagnostic insomnia and CRP has not been determined. Finally, when all available methods of assessment were combined, sleep disturbance was associated with higher levels of CRP (31 samples; n = 34,943; ES .12; 95% CI .05–.19; Q_v = 47.9; p = .02; I^2 = 37.3) and with higher levels of

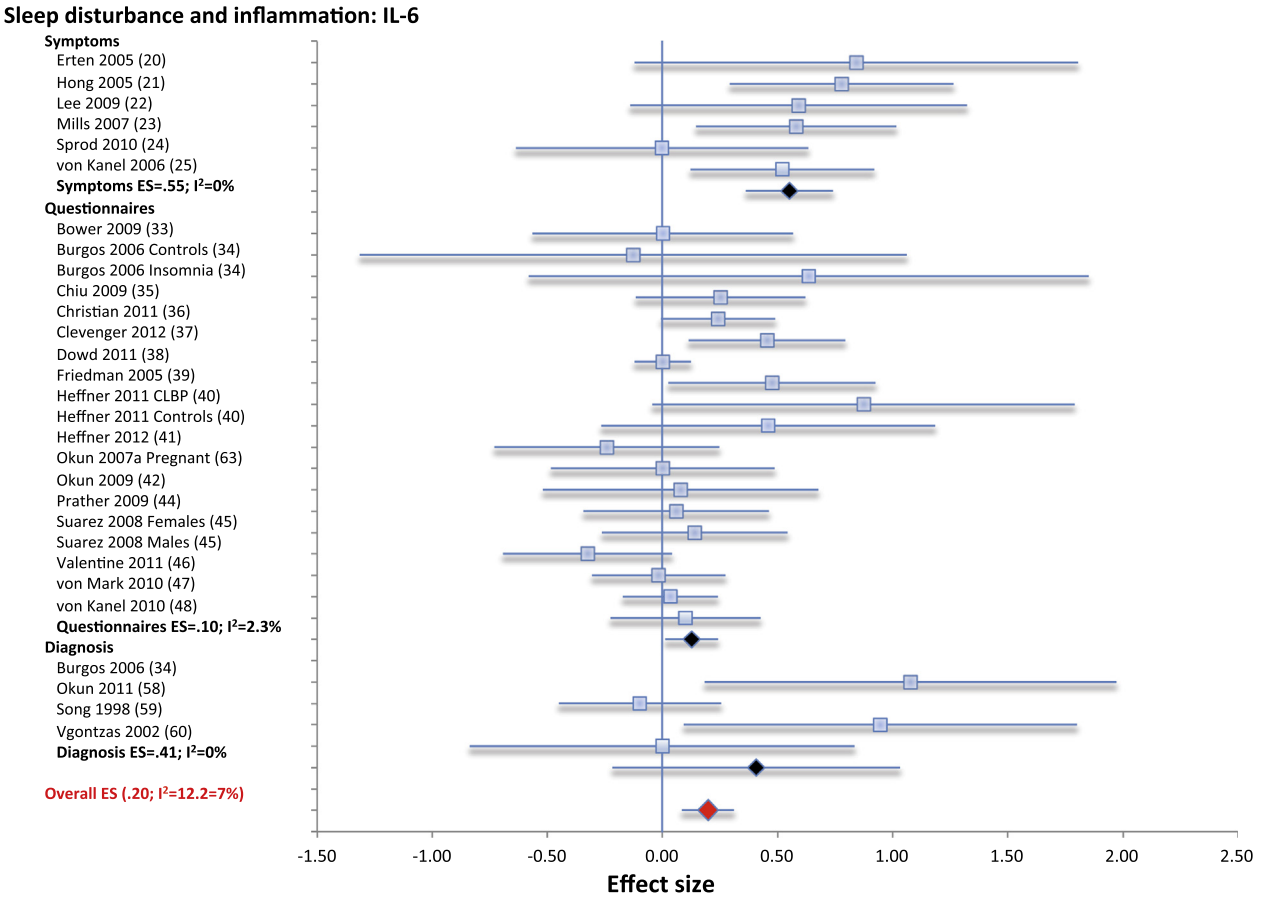

Figure 2. Forest plot of sleep disturbance associated with inflammation as indexed by circulating levels of interleukin-6 (IL-6). Sleep disturbance is assessed by self-reported symptoms and questionnaires. Results are expressed as effect sizes (ES) and 95% confidence intervals.

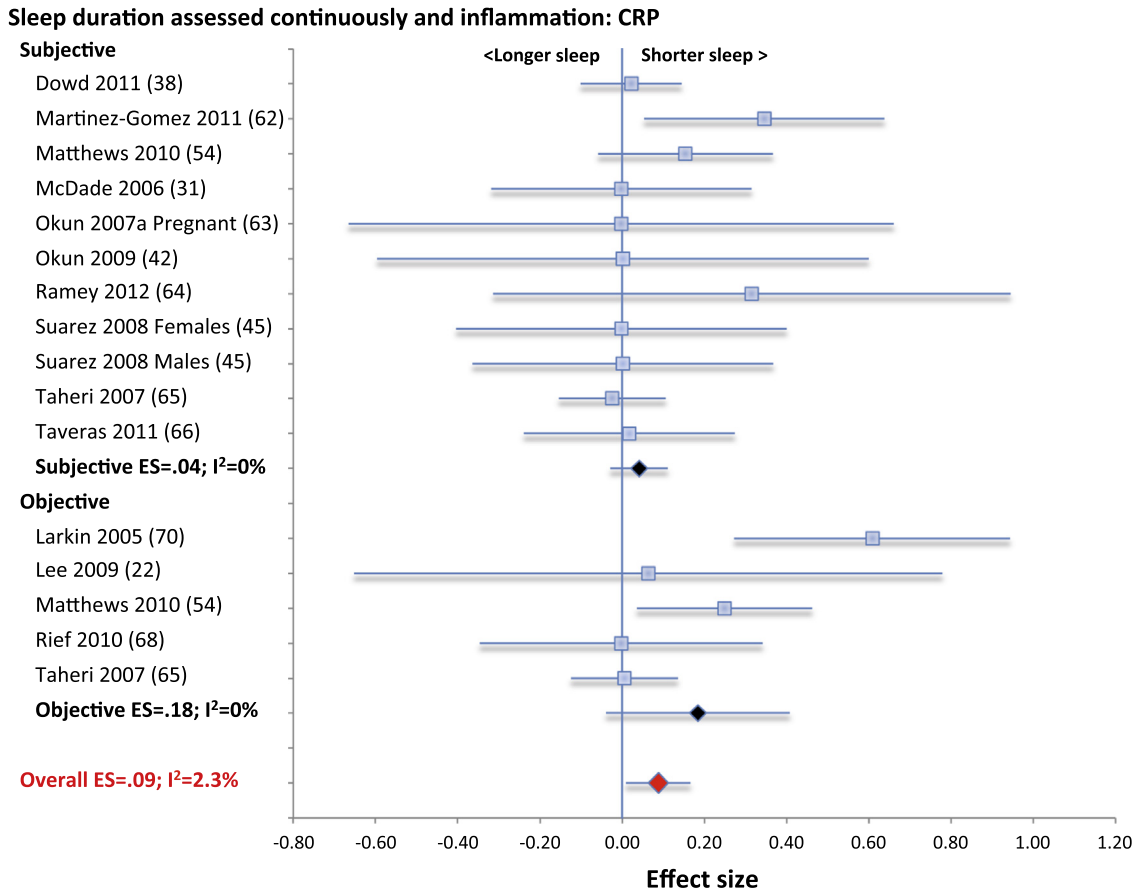

Figure 3. Forest plot of sleep duration associated with inflammation as indexed by C-reactive protein (CRP). Sleep duration is assessed continuously by subjective and objective measures. Results are expressed as effect sizes (ES) and 95% confidence intervals.

IL-6 (29 samples; $n = 3339$; ES .20; 95% CI .08–.31; $Q_v = 29.6$; $p = .29$; $I^2 = 12.2$) but not TNFα (8 samples; $n = 672$; ES .07; 95% CI −.13 to .28, $Q_v = 8.0$; $p = 34$; $I^2 = 12.1$) (Figure S2 in Supplement 1).

Sleep Duration and Inflammation

Two categories of assessment of sleep duration (i.e., sleep duration as a continuous variable using either subjective or objective measures or short and long sleep duration compared with reference normal of 7 to 8 hours) (76,77) were identified for evaluation in relation to CRP, IL-6, and TNFα. Sleep duration as a continuous variable using subjective measures was not associated with CRP (11 samples; $n = 3490$; ES .04; 95% CI −.03 to .11; $Q_v = 7.3$; $p = .70$; $I^2 = .00$) (Figure 3) or IL-6 (9 samples; $n = 2084$; ES .03; 95% CI −.09 to .14; $Q_v = 8.5$; $p = .39$; $I^2 = 6.1$) (Figure 4). When sleep duration was treated continuously using objective measures, sleep duration was also not associated with CRP (5 samples; $n = 1550$; ES .18; 95% CI −.04 to .41; $Q_v = 4.0$; $p = .41$; $I^2 = .00$) (Figure 3), although short sleep duration was associated with higher levels of IL-6 (9 samples; $n = 489$; ES .29; 95% CI .05–.52; $Q_v = 8.2$; $p = .41$; $I^2 = 3.0$) (Figure 4). In analyses that combined subjective and objective measures, short sleep duration was associated with higher levels of CRP (16 samples; $n = 5040$; ES .09; 95% CI .01–.17; $Q_v = 15.4$; $p = .43$; $I^2 = 2.3$) (Figure 3) but not with IL-6 (18 samples; $n = 2573$; ES .11; 95% CI −.01 to .23; $Q_v = 203$; $p = .26$; $I^2 = 16.1$) (Figure 4) or TNFα (4 samples; $n = 157$; ES .29; 95% CI −.27 to .84; $Q_v = 3.1$; $p = .38$; $I^2 = 3.2$) (Figure S3 in Supplement 1).

When extremes of sleep duration (i.e., short versus long sleep duration) were analyzed as compared with normal sleep reference (7 to 8 hours), short sleep duration was not associated with CRP (11 samples; $n = 19,573$; ES .08; 95% CI −.01 to .16; $Q_v = 11.5$; $p = .32$; $I^2 = 12.9$) (Figure 5), IL-6 (8 samples; $n = 12,925$; ES .08; 95% CI −.02 to .18; $Q_v = 7.8$; $p = .35$; $I^2 = 9.7$) (Figure 6), or TNFα (3 samples; $n = 1979$; ES .11; 95% CI −.01 to .22; $Q_v = .1$; $p = .97$; $I^2 = 0$) (Figure S4 in Supplement 1). However, long sleep duration was associated with higher levels of CRP (11 samples; $n = 19,573$; ES .17; 95% CI .01–.34; $Q_v = 10.6$; $p = .39$; $I^2 = 5.4$) (Figure 5) and with higher levels of IL-6 (8 samples; $n = 12,925$; ES .11; 95% CI .02–.20; $Q_v = 7.3$; $p = .39$; $I^2 = 4.6$) (Figure 6) but not TNFα (3 samples; $n = 1979$; ES .08; CI −.06 to .22; $Q_v = 2.2$; $p = .34$; $I^2 = 8.0$) (Figure S4 in Supplement 1). Subjective and objective methods for assessment of sleep duration were combined because there were too few studies that objectively evaluated sleep duration objectively.

Overall, meta-regression results suggested that larger effect sizes were associated younger age and greater

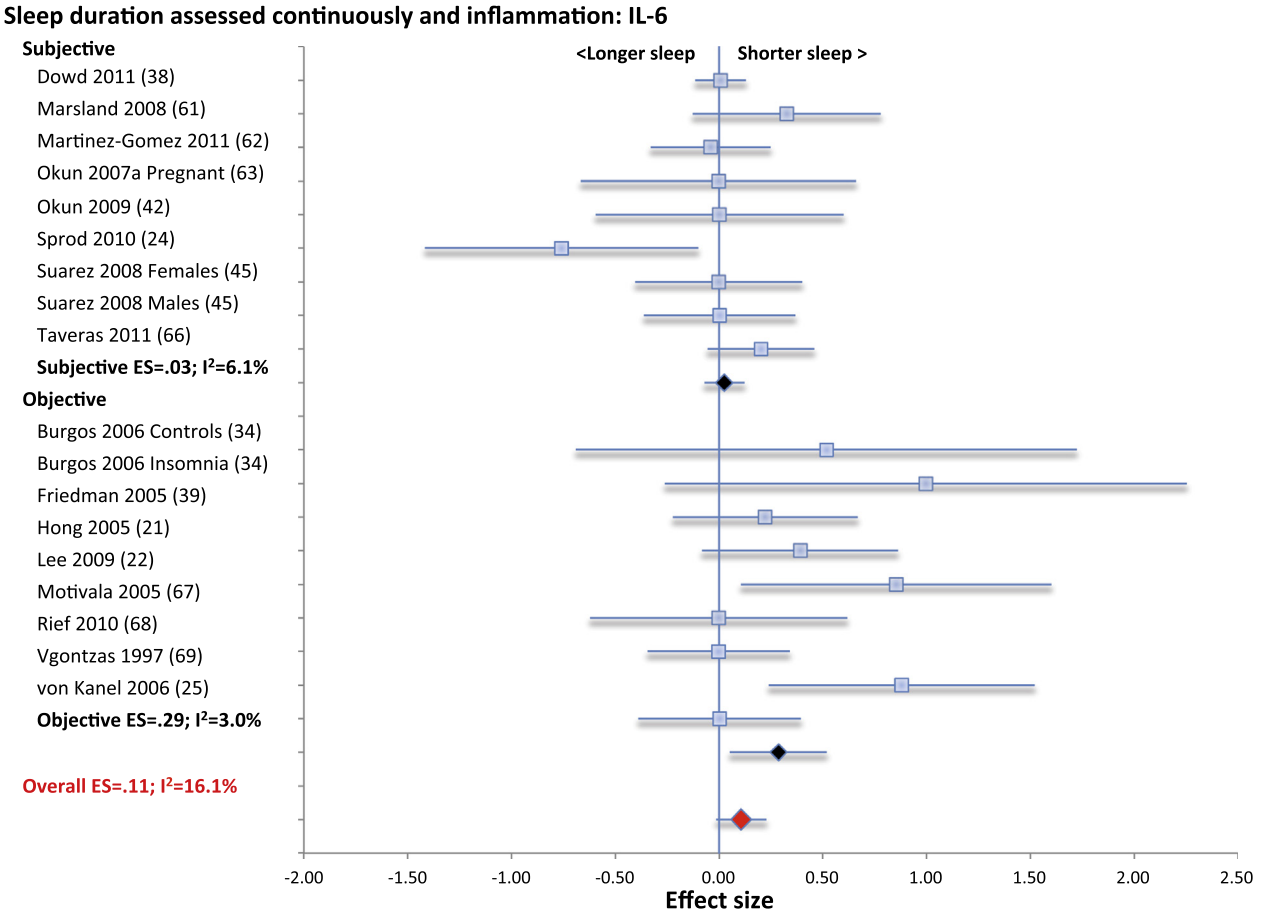

Figure 4. Forest plot of sleep duration associated with inflammation as indexed by circulating levels of interleukin-6 (IL-6). Sleep duration is assessed continuously by subjective and objective measures. Results are expressed as effect sizes (ES) and 95% confidence intervals.

proportion of female subjects within the sample; however, these findings were only statistically significant for two subsamples: sleep disturbance predicting IL-6 (female percentage of sample beta = .36, $p = .03$) and sleep duration continuously predicting CRP (age beta = −.54, $p = .02$).

Experimental Sleep Deprivation and Inflammation

Experimental sleep deprivation, either for partial or total night, was not associated with CRP (4 samples; $n = 30$; ES −.43; 95% CI −1.62 to .77; $Q_v = .1$; $p = .99$; $I^2 = 0$) (Figure 7), IL-6 (12 samples; $n = 165$; ES .16; 95% CI −.11 to .43; $Q_v = 11.4$; $p = .41$; $I^2 = 3.3$) (Figure 8), or TNFα (5 samples; $n = 61$, ES .04; 95% CI −.32 to .39; $Q_v = .4$; $p = .98$; $I^2 = 0$) (Figure S5 in Supplement 1). Likewise, sleep restriction over several days was not associated with CRP (4 samples; $n = 188$; ES .61; 95% CI −1.09 to 2.30; $Q_v = .1.$; $p = .99$; $I^2 = 0$) (Figure 7), IL-6 (5 samples; $n = 98$; ES .13; 95% CI −.21 to .47; $Q_v = 4.1$; $p = .39$; $I^2 = 2.1$) (Figure 8), or TNFα (4 samples; $n = 48$, ES .06; 95% CI −.34 to .46; $Q_v = .8$; $p = .86$; $I^2 = 0$) (Figure S5 in Supplement 1).

Publication Bias

There was some indication of publication bias, although this was evidenced only for sleep disturbance with outliers in the funnel plot. Trimming studies with effect sizes greater than 1.0 in absolute value eliminated this bias (Egger's regression test $p > .20$), and the relevant findings were largely unchanged: sleep disturbance by questionnaire remained associated with CRP (revised ES .12; 95% CI .02–.22; $Q_v = 16.5$; $p = .34$; $I^2 = 9.5$) and with IL-6 (revised ES .10; 95% CI .003–.21; $Q_v = 17.6$; $p = .41$; $I^2 = 3.6$), and sleep disturbance by diagnosis remained associated with IL-6 (revised ES .20; 95% CI −.40 to .80; $Q_v = 2.1$; $p = .35$; $I^2 = 5.3$).

Furthermore, when all methods to assess sleep disturbance were combined, sleep disturbance remained associated with CRP (ES .09; 95% CI .03–.14; $Q_v = 30.1$; $p = .26$; $I^2 = 13.7$) and with IL-6 (ES .19; 95% CI .08–.30; $Q_v = 26.7$; $p = .32$; $I^2 = 10.3$), though there was little evidence of publication bias for the TNFα findings due both to the smaller number of studies and the larger percentage of null results.

DISCUSSION

This study provides a comprehensive review and quantitative estimates of the associations between sleep disturbance, as well as extremes of sleep duration, and inflammation in population-based samples and varying clinical samples around the world. It adds to a growing body of evidence that

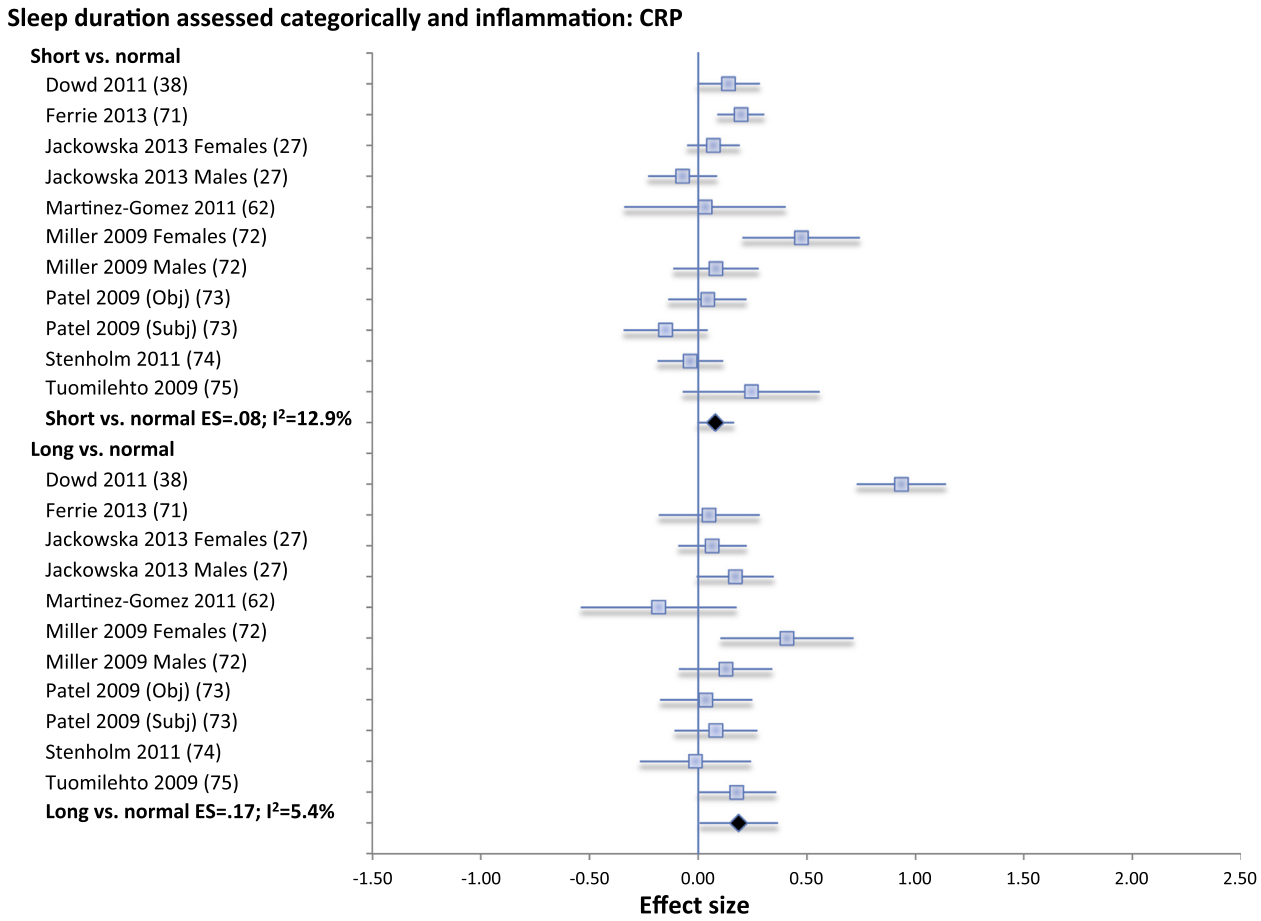

Figure 5. Forest plot of sleep duration associated with inflammation as indexed by C-reactive protein (CRP). Sleep duration is assessed categorically with normal sleep being defined by sleep duration of 7 to 8 hours per night, short sleep as < 7 hours per night, and long sleep as > 8 hours per night. Results are expressed as effect sizes (ES) and 95% confidence intervals.

sleep disturbance is associated with inflammatory disease risk and all-cause mortality, possibly by effects of sleep disturbance on inflammatory mechanisms.

These results confirm the presence of an association between sleep disturbance and two markers of systemic inflammation, CRP and IL-6, with some heterogeneity among studies, no presence of publication bias, and a high statistical power conferred by nearly 34,000 participants for CRP and over 3000 participants for IL-6. Whereas sleep disturbance was not related to TNFα, this conclusion is tempered by low statistical power with only 672 participants. The effect sizes linking sleep disturbance with IL-6 were larger than those found for CRP. Sleep disturbance is thought to have proximal effects on IL-6; in turn, IL-6 induces CRP. Hence, increases of CRP might be due to more persistent or severe sleep disturbance (109). Evidence also showed that assessment of sleep disturbance by validated questionnaires was associated with increases in CRP and in IL-6, whereas assessment by symptom reporting had mixed effects. Questionnaires provide comprehensive assessment of sleep disturbance, and symptom reporting often relies on a single question.

The effects of sleep disturbance on inflammation were not associated with age, and relationships were comparable in men and women, although individual high-quality studies showed that women, as compared with men, may be more vulnerable to the effects of sleep disturbance and show greater increases of CRP and IL-6 (45,110), greater increases in toll-like receptor 4 (TLR-4) stimulated monocyte production of inflammatory cytokines, and greater increases of nuclear factor (NF)-κB (111,112). During undisturbed sleep, women also show greater TLR-4 stimulated production of IL-6 than men, a difference that is moderated by sex differences in tonic sympathovagal activity (113). Together, these findings have implications for understanding the differential risk profile for inflammatory disorders between the sexes (114). For example, subjective symptoms of disturbed sleep are associated with a greater risk of cardiovascular disease in women than men, even after control for relevant confounders (115,116).

In contrast to the associations between sleep disturbance and inflammation, sleep duration, as measured as a continuous variable using either subjective or objective methods, showed no significant association with IL-6, although a small effect was noted for CRP. When the extremes of sleep duration were evaluated, long sleep duration, but not short sleep duration, was associated with increases in CRP and with increases in IL-6. Shortening of sleep duration by experimental

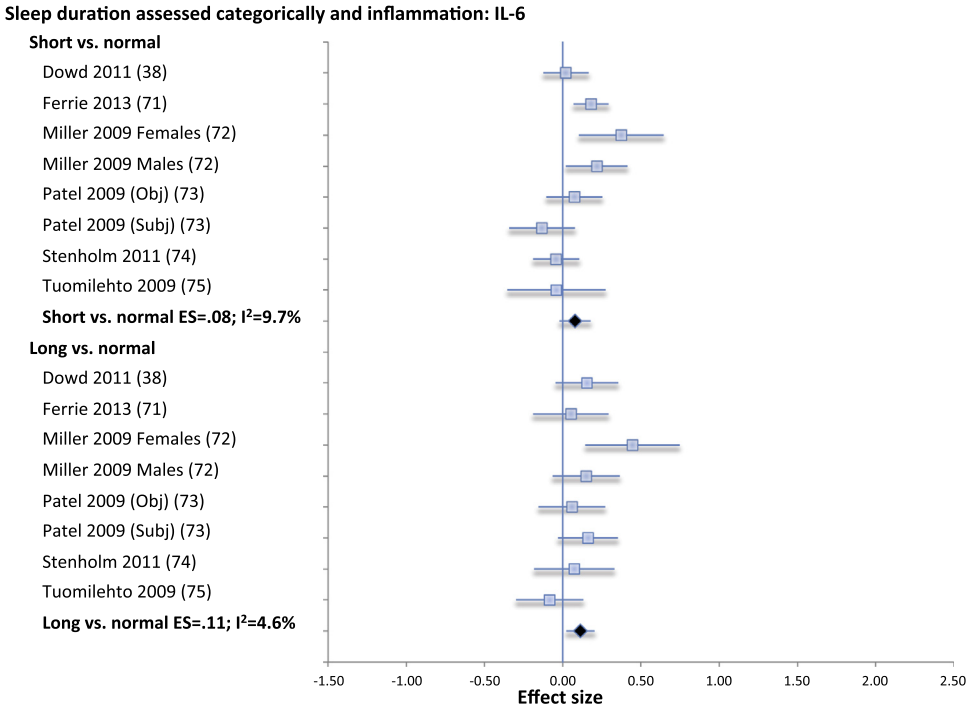

Figure 6. Forest plot of sleep duration associated with inflammation as indexed by circulating levels of interleukin-6 (IL-6). Sleep duration is assessed categorically with normal sleep being defined by sleep duration of 7 to 8 hours per night, short sleep as < 7 hours per night, and long sleep as > 8 hours per night. Results are expressed as effect sizes (ES) and 95% confidence intervals.

sleep deprivation was also not associated with CRP or IL-6, and this was the case for studies that either deprived participants of sleep for one night or for part of a single night or for several consecutive nights. Interestingly, the associations between sleep duration and inflammation parallel the findings linking sleep and mortality; prior meta-analytic findings on sleep duration and mortality have found a U-shaped association, in which long sleepers (>8 hours per night) have a 30% greater risk, whereas short sleepers (<7 hours per night) have a 12% greater risk of dying than those who sleep 7 to 8 hours per night (76).

It is not known what aspect of sleep disturbance contributes to increases in inflammation. Sleep disturbance when combined with short duration are thought to be particularly caustic for health outcomes (4,117–120), although studies of inflammation have predominantly examined sleep disturbance and sleep duration in separate models. Sleep fragmentation, as opposed to shortened sleep amounts, might also contribute to sleep disturbance, and such disruption of sleep continuity is uniquely associated with daytime dysfunction (121) and increases rates of mortality (1).

Experimental sleep loss did not alter circulating markers of inflammation, which stands in sharp contrast with findings that have evaluated upstream pathways of cellular and genomic markers of inflammation. For example, cellular production of IL-6 and TNFα is due, in part, through activation of TLR-4 activity, and partial night sleep deprivation induces an increase in TLR-4 stimulated production of inflammatory cytokines (122), as well as activation of the key transcription control pathway in the inflammatory signaling cascade, NF-κB (111), which, in turn, drives effects on transcriptome dynamics with an upregulation of a gene ensemble that includes the master circadian regulator, several immediate early genes marking cellular signal transduction, and multiple inflammatory response genes (122). More persistent disturbances of sleep may be needed to translate inflammatory signaling into increases in systemic markers of inflammation.

The mechanisms that might explain the associations between sleep disturbance and inflammation are relatively unexplored. Sleep influences two primary effector systems, the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system, which together shift the basal gene expression profile toward increased proinflammatory skewing (14,123). Activation of β-adrenergic signaling induces increases in NF-κB, inflammatory gene expression, production of proinflammatory cytokines, and markers of systemic inflammation (14). Given that normal nocturnal sleep is associated with a drop in sympathetic outflow (124), activation of the sympathetic effector pathway is one biologically plausible mechanism to explain the associations between sleep disturbance, short sleep duration, and increases in markers of inflammation. The association between long sleep and inflammation may be the result of underlying comorbidities, which were not fully controlled.

The quality of these meta-analytic data cannot go beyond the quality of the individual studies included. Although all studies fulfilled a minimum threshold of quality and the majority of studies considered confounding variables, a meta-analysis of observational data is open to residual

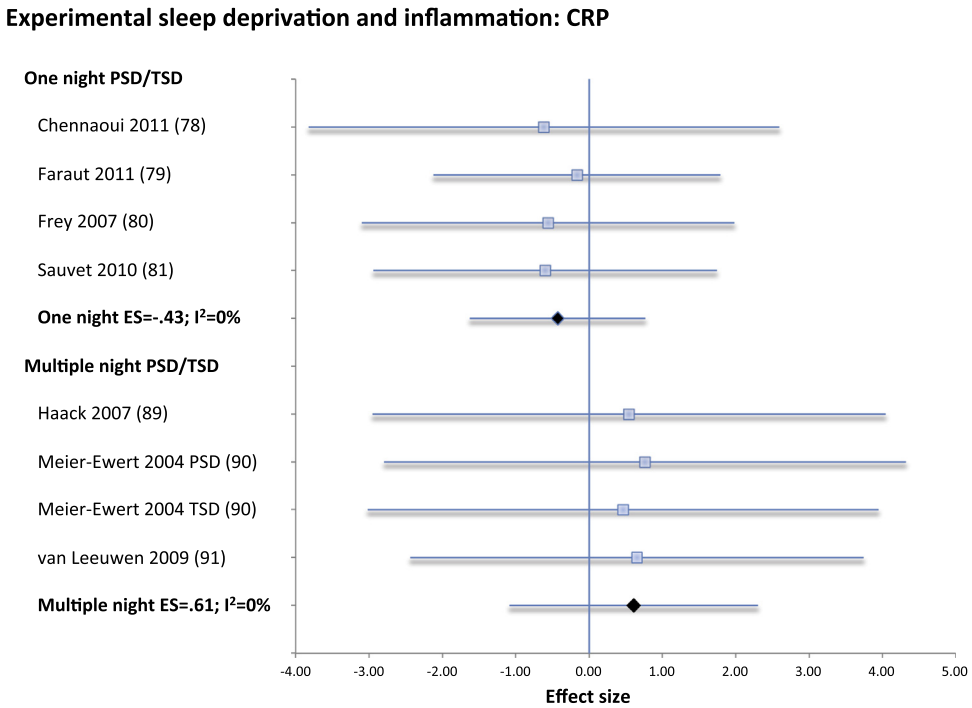

Figure 7. Forest plot of experimentally shortened sleep duration associated with inflammation as indexed by C-reactive protein (CRP). Sleep duration was shortened by either partial sleep deprivation (PSD) or total sleep deprivation (TSD) for one night or for multiple nights. Results are expressed as effect sizes (ES) and 95% confidence intervals.

confound and bias. Whereas we made an attempt to allow for multiple confounding by including adjusted estimates from multivariate models from each contributing study, many studies did not report adjusted estimates. Second, the results can only be representative of the studies that have been included, although there was no evidence of publication bias

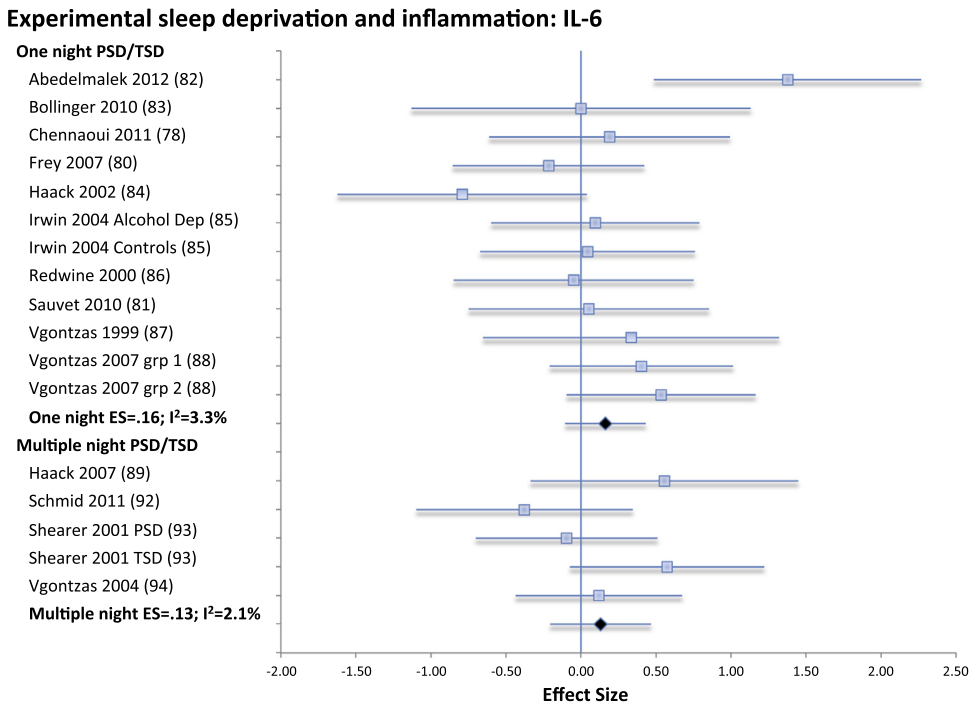

Figure 8. Forest plot of experimentally shortened sleep duration associated with inflammation as indexed by circulating levels of interleukin-6 (IL-6). Sleep duration was shortened by either partial sleep deprivation (PSD) or total sleep deprivation (TSD) for one night or for multiple nights. Results are expressed as effect sizes (ES) and 95% confidence intervals.

for the primary findings. Third, the vast majority of studies used sleep questionnaires, as opposed to diagnostic criteria or objective measures such as actigraphy or polysomnography, to assess sleep disturbance and sleep duration. Nevertheless, sleep diaries, actigraphy, and polysomnography from some large population and small-scale investigations have shown high correlations with subjective estimates of sleep duration (125,126). Fourth, sleep disturbance and/or sleep duration was assessed at one point in time in all studies, which neglects testing the possibility that persistent sleep problems may have more robust effects on inflammation. Fifth, insufficient data were available to examine systematically whether those with clinically severe insomnia (34) or extreme short sleep duration (<5 hours) (27,71,72) were more likely to evidence inflammation. Finally, none of these studies were prospective in design, which limits any conclusions about the direction of the associations, as acute elevations in markers of inflammation can also alter sleep amounts and sleep depth (9).

Whereas no study has systematically evaluated whether elevated levels of inflammation mediate the association between sleep disturbance and cardiovascular disease or other diseases that have an inflammatory component including cancer and depression, extensive data show that sleep disturbance, as well as extremes of sleep duration, are linked to multiple morbidities and mortality (9). Sleep disturbance and long sleep duration should be regarded as additional behavioral risk factors for inflammation, which are amenable to modification through treatments that target sleep behaviors. Indeed, treatment of insomnia has been found to reduce inflammation (17,18) and together with diet and physical activity represents a third component in the promotion of sleep health.

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ARTICLE INFORMATION

From the Cousins Center for Psychoneuroimmunology (MRI, RO, JEC), UCLA Semel Institute for Neuroscience; Department of Psychiatry and Biobehavioral Sciences (MRI, RO, JEC), UCLA David Geffen School of Medicine; and Department of Psychology (MRI), University of California, Los Angeles, Los Angeles, California.

Address correspondence to Michael R. Irwin, M.D., UCLA Semel Institute, Cousins Center for Psychoneuroimmunology, 300 UCLA Medical Plaza, Room 3130, Los Angeles, CA 90095-7076; E-mail: mirwin1@ucla.edu

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