



# Sleep duration, insomnia, and markers of systemic inflammation: Results from the Netherlands Study of Depression and Anxiety (NESDA)



Aric A. Prather<sup>a,\*</sup>, Nicole Vogelzangs<sup>b</sup>, Brenda W.J.H. Penninx<sup>b</sup>

<sup>a</sup> Department of Psychiatry, University of California, San Francisco, United States

<sup>b</sup> Department of Psychiatry, EMGO Institute for Health and Care Research, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

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## ABSTRACT

Systemic inflammation has emerged as a potential pathway linking depressive and anxiety disorders with disease risk. Short and long sleep duration, as well as insomnia, are common among psychiatric populations and have previously been related to increased inflammation. The aim of the present study was to investigate associations between sleep duration and insomnia with biomarkers of inflammation and to explore whether these associations varied by psychiatric diagnostic status. To this end, self-reported measures of sleep duration, insomnia symptoms, and markers of inflammation, including C-reactive protein (CRP), interleukin-(IL)-6, and tumor necrosis factor (TNF)- $\alpha$ , were obtained in 2553 adults (aged 18–65 years) diagnosed with current/recent or remitted depressive and/or anxiety disorders and healthy controls enrolled in the Netherlands Study of Depression and Anxiety (NESDA). Regression analyses revealed associations between sleep duration and levels of CRP and IL-6 with higher levels observed in long sleepers. These associations remained statistically significant after controlling for age, gender, education, body mass index, smoking, alcohol consumption, medical comorbidities, medication use, psychotropic medication use, and psychiatric diagnostic status. There were no clear associations between insomnia symptoms and levels of inflammation. Relationships between sleep duration and inflammation did not vary as a function of psychiatric diagnostic status. These findings suggest that elevated levels of systemic inflammation may represent a mechanism linking long sleep duration and disease risk among those with and without depressive and anxiety disorders.

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## 1. Introduction

Depression and anxiety disorders are highly prevalent and comorbid psychiatric disorders with substantial consequences for physical health, including increased incidence and progression of a number of age-related diseases such as cardiovascular disease, diabetes, and the metabolic syndrome (Eaton et al., 1996; Lett et al., 2004; Raikonen et al., 2007; Suls and Bunde, 2005). The biological mechanisms linking these psychiatric conditions to physical health remain unclear; however, low-grade chronic inflammation has emerged as a key biological pathway.

Several meta-analytic reviews support elevations in inflammatory markers, such as pro-inflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , and acute phase proteins, such as C-reactive protein (CRP), in depressed compared to non-depressed patients (Dowlati et al., 2010; Howren et al., 2009; Zorrilla et al., 2001). Elevations are also observed in those with clinical anxiety (O'Donovan et al., 2010; Vogelzangs et al., 2013); however, this link is less well characterized (O'Donovan et al., 2013). Not all studies have been consistent, however, which may reflect the heterogeneity that exists within the diagnostic categories of Depressive and Anxiety Disorders (Goldberg, 2011; Insel and Wang, 2010). Accordingly, researchers have begun to focus attention on symptoms relevant across psychiatric conditions (i.e., transdiagnostic processes); sleep disturbance has emerged as one such symptom (Harvey et al., 2011).

Growing evidence suggests that disturbed sleep is associated with elevations in systemic levels of inflammation. For instance, in

\* Corresponding author. Department of Psychiatry, University of California, San Francisco, 3333 California St., Suite 465, San Francisco, CA 94118, United States. Tel.: +1 415 476 7758.

E-mail address: [aric.prather@ucsf.edu](mailto:aric.prather@ucsf.edu) (A.A. Prather).

several though not all laboratory studies (reviewed in Solarz et al. (2012)) healthy sleepers subjected to total and partial sleep restriction show significant elevations in inflammatory activity compared to an undisturbed sleep condition (Irwin et al., 2006; Shearer et al., 2001; Vgontzas et al., 1999, 2004). Further, compared to nondepressed controls, depressed patients displayed higher nocturnal levels of IL-6, a difference that is partially accounted for by a longer time to sleep onset in the depressed patients (Motivala et al., 2005). Whether these associations extend beyond the laboratory setting remains unclear. In this regard, greater inflammation has been documented in patients with insomnia compared to non-disturbed sleepers (Burgos et al., 2006). Further, short (e.g., sleeping less than 5 or 6 h per night) and/or long sleep duration (e.g., sleeping more than 9 or 10 h per night) have been associated with higher levels of inflammation compared to those reporting typical sleep duration (i.e., 7–8 h per night) in several large epidemiologic investigations (Dowd et al., 2011; Miller et al., 2009). While curvilinear associations are not supported in all studies, these findings map onto prevalence rates of several chronic diseases and early mortality observed at higher frequency among short and long sleepers (Ayas et al., 2003a, 2003b; Cappuccio et al., 2010a, 2010b; Hall et al., 2008; Heslop et al., 2002). For instance, Hall et al. found that compared to normal sleepers (7–8 h) both short (<6 h per night) and long (>8 h) showed significantly increased odds of meeting diagnostic criteria for the metabolic syndrome, independent of other sociodemographic characteristics and health behaviors (Hall et al., 2008).

Despite converging evidence for a link between psychopathology, namely depression and to some extent anxiety, sleep, and markers of inflammation, no study has sought to systematically examine their inter-relationships in a large sample. The goals of the present study are to 1) estimate the associations between poor sleep, as characterized by short and/or long sleep duration and insomnia symptoms, with markers of systemic levels of inflammation (CRP, IL-6, and TNF- $\alpha$ ) in a large sample of patients with current and past psychopathology (depressive and/or anxiety disorder) and never diagnosed controls and 2) determine whether psychopathology status moderates the sleep-inflammation link. The proposed study utilizes data from the Netherlands Study of Depression and Anxiety (NESDA) which have previously demonstrated differential elevations in markers of inflammation in patients with psychopathology compared to healthy controls (Vogelzangs et al., 2013; Vogelzangs et al., 2012). Given that sleep is a modifiable health behavior, understanding the extent to which sleep drives inflammatory activity in the context of psychopathology may have important implications for treatment.

## 2. Methods

### 2.1. Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders. Participants were adults aged 18–65 recruited from community (19%), general practice (54%), and secondary mental health (27%) facilities. A total of 2981 participants, including persons with current/recent or past depressive and/or anxiety disorders and healthy controls, were assessed at baseline between 2004 and 2007. Exclusion criteria for the NESDA study were not speaking the Dutch language and a known clinical diagnosis of bipolar disorder, obsessive–compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder.

A detailed description of the NESDA study design can be found elsewhere (Penninx et al., 2008). Briefly, the baseline assessment

was comprised of a face-to-face interview, including a standardized diagnostic psychiatric interview, a medical assessment, computer tasks, written questionnaires, and biological measurement (among which was a blood draw in a fasting state). The research protocol was approved by the Ethical Committee of participating universities and after complete description of the study all respondents provided written informed consent.

Of the final 2981 participants included in the baseline assessment of NESDA, 428 had missing data concerning sleep duration ( $n = 358$ ) or inflammation ( $n = 70$ ) and were excluded from the current study, resulting in a sample size of 2553 participants. An additional 4 participants were missing data on the Insomnia Rating Scale (IRS) yielding 2549 participants in analyses that include IRS data.

Compared to those included in the present analysis, excluded participants were significantly younger ( $t(2979) = -6.08$ ,  $p < 0.001$ ), more likely to be male ( $X^2(1) = 5.99$ ,  $p = 0.01$ ), less educated ( $t(2979) = -6.57$ ,  $p < 0.001$ ), more likely to be a current smoker ( $X^2(2) = 55.23$ ,  $p < 0.001$ ), to use benzodiazepines ( $X^2(1) = 6.46$ ,  $p = 0.01$ ), less likely to be on anti-inflammatory medication ( $X^2(1) = 4.91$ ,  $p = 0.03$ ), less likely to be free from antidepressant medication ( $X^2(3) = 12.59$ ,  $p < 0.001$ ) and more likely to be diagnosed with comorbid current/recent depressive and anxiety disorders ( $X^2(4) = 46.07$ ,  $p < 0.001$ ).

### 2.2. Measures

#### 2.2.1. Sleep duration and insomnia

Measures of sleep duration and insomnia were obtained as part of a questionnaire that participants completed after the interview or at home. Sleep duration was obtained by asking participants' "How many hours per night did you sleep on average during the last 4 weeks?" Answer options were: "10 or more hours", "9 h", "8 h", "7 h", "6 h", "5 or less h." In descriptive analyses, sleep duration scores were used to categorize participants as short sleepers ( $\leq 6$  h per night), normal sleepers (7–9 h per night), and long sleepers ( $\geq 10$  h per night); however, in the primary regression analyses, sleep duration was treated as a continuous variable.

Insomnia was assessed using the Women's Health Initiative Insomnia Rating Scale (IRS) (Levine et al., 2003a). This scale consists of five questions that address trouble falling asleep, waking up during the night, early morning awakenings, trouble getting back to sleep after waking up, and sleep quality in the past month. The total score for this scale ranges from 0 (no insomnia) to 20 (severe insomnia). The IRS has good test-retest reliability and is strongly associated with other actigraphy-related sleep measures (Levine et al., 2003b). The IRS showed good internal validity in this sample (Cronbach  $\alpha = 0.83$ ). Scores on the IRS were dichotomized at the cut-off point of 9 for descriptive analyses. This cut point has shown to indicate clinically significant insomnia (Levine et al., 2003a); however, in primary regression analyses, scores on the IRS were treated as a continuous variable.

#### 2.2.2. Psychopathology

The presence of psychiatric disorders was determined by using the Composite International Diagnostic Interview (CIDI, versions 2.1). The CIDI is a standardized psychiatric diagnostic interview that follows the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria to establish diagnoses. The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders (Wittchen, 1994) and was administered by specially trained research staff. Depressive disorder (major depressive disorder, dysthymia) status was categorized as follows: current/recent diagnosis (i.e., past 6 months), remitted (i.e., lifetime diagnosis but not in the past 6 months), controls (no lifetime

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