Sleep Medicine 50 (2018) 48–54

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

The association of sleep duration and quality with all-cause and cause-specific mortality in the Women's Health Initiative

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ARTICLE INFO

Article history:
Received 6 February 2018
Received in revised form
30 March 2018
Accepted 22 May 2018
Available online 2 June 2018

Keywords:
Sleep
characteristics
Duration
Insomnia rating scale
Total mortality
Cardiovascular mortality
Time-dependent analysis

ABSTRACT

Background/Objective: Many studies have shown a U-shaped association of sleep duration with mortality; however, this association is difficult to interpret owing to possible reverse causation, residual confounding, and measurement issues. We used data from the Women's Health Initiative to examine the associations of sleep duration, insomnia, and use of sleep aids with death from cardiovascular disease (CVD), cancer, "other" causes, and all causes combined.

Methods: Cox proportional hazards models were used in the analysis of baseline data and in time-dependent analyses of repeated measures to estimate associations of sleep-related factors with mortality. Among 158,203 women with information regarding sleep, 30,400 total deaths, 8857 CVD deaths, 9284 cancer deaths, and 11,928 other deaths were ascertained over a median of 17.8 years.

Results: In both baseline and time-dependent analyses, both short (≤5 h) and long sleep (≥9 h) durations were associated with increased risk of total, CVD, and "other" deaths, but not with cancer deaths. Insomnia showed no association with mortality, whereas use of sleep medications was associated with an increased mortality risk.

Conclusions: While our findings showed a small but robust association of sleep duration with mortality in postmenopausal women, studies including objective measurements of sleep quality and efficiency are needed to clarify these associations.

1. Introduction

Modern society has had a profound influence on our sleep habits. Since the 1960s, the average reported nightly sleep duration in the U.S. has decreased from more than 8 h–6.5 h per night, with 20–30% of middle-aged Americans reporting an average nightly sleep duration of less than 6 h [1]. Poor sleep quality and quantity have been associated with a range of adverse health outcomes, including diabetes, cardiovascular disease, and cancer as well as elevated total and cause-specific mortality [1–15].

Over the past 40 years, numerous prospective studies have shown a U-shaped association between sleep duration and mortality, with an increased risk of all-cause and cause-specific mortality among both short and long sleepers, compared with those sleeping 7–8 h per night [2–15]. However, the association is

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https://doi.org/10.1016/j.sleep.2018.05.015
1389-9457/

difficult to interpret owing to limitations of these studies, including: variation in categories of sleep duration by study; inconsistencies in the findings by sex and age; the availability of only a single assessment of sleep duration (at baseline) in all but a few studies [6,7]; the failure of some studies to take potential confounders or effect modifiers (eg, poor pre-existing health) into account; and the failure of most studies to examine sleep quality [6,12,15].

Therefore, we used data from the Women's Health Initiative(WHI) cohort to examine sleep duration, insomnia, and use of sleep medications in relation to total and cause-specific mortality. The availability of measurements of sleep-related factors at multiple time points as well as information on medical history at enrollment and on conditions reported during follow-up enabled analysis of the independent and joint effects sleep duration and sleep quality on mortality.

2. Methods

2.1. Dataset

The Women's Health Initiative is a large, multicenter study designed to improve our understanding of the determinants of major chronic diseases in postmenopausal women. It was originally composed of a clinical trial component (CT, n = 68,132) and an observational study component (OS, n = 93,676) [16]. The CT component included four randomized controlled intervention studies: hormone therapy (two trials), low-fat dietary modification, and calcium + vitamin D supplementation. Women between the ages of 50 and 79 and representing the major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998. Details of the study design and reliability of the baseline measures have been published [16,17]. Written informed consent was obtained from participants at all WHI centers in accordance with recognized ethical guidelines, and the study was approved by the institutional review board of each center, as well as by that of the Coordinating Center at the Fred Hutchinson Cancer Research Center.

2.2. Exposure information

At study entry, self-administered questionnaires were used to collect information on demographics, medical history and lifestyle factors. All participants had weight, height, and blood pressure measured by trained staff at baseline. Women were also asked about their history of chronic diseases; including diabetes, cardiovascular disease (CVD), pulmonary disease, connective tissue disorders, hematological cancer, solid tumors, or other conditions. We employed a modified version of the Charlson comorbidity index, adapted for use in the WHI, to summarize the presence of comorbidity at enrollment [18]. Depression was measured using the Center for Epidemiological Studies of Depression (CES-D) scale. A score of ≥5 on the short form of the CES-D scale was used to identify women with depressive symptoms [19].

Sleep duration was recorded as number of hours per night (≤5, 6, 7, 8, 9, ≥10) in response to the question, "About how many hours of sleep did you get on a typical night during the past four weeks?" Sleep quality was assessed using the WHI Insomnia Rating Score (IRS), which has been validated in WHI [20,21]. The IRS consists of five items pertaining to quality of sleep assessed during the previous four weeks: trouble falling asleep, waking up several times during the night, waking up earlier than planned, trouble getting back to sleep, and overall rating of how restful sleep was during this period [20,21]. Each item was measured on a scale of 0–4, with higher scores representing more frequent or severe symptoms. A final score, ranging from 0 to 20, was calculated by summing the scores of the five items. IRS measures were obtained at baseline for all WHI participants and at subsequent clinic visits, principally in year one for CT participants, and in year three in the OS cohort. Insomnia was defined as a score of ≥9 [20,21]. This threshold has been widely used in previous studies investigating insomnia and health-related outcomes in WHI [21–23]. In addition, participants were asked about the frequency of use of "any kind of medication or alcohol at bedtime to help you sleep" (response categories: "No, not in past four weeks," "Yes, <1x/wk"; "Yes, 1–2 x/wk"; "Yes, 3–4 x/wk"; "Yes, ≥5 x/wk.") (henceforth referred to as "use of sleep aids"). We excluded participants who were missing information on sleep hours at baseline or for whom the insomnia rating index could not be computed (n = 3605), leaving a study cohort of n = 158,203.

Deaths were ascertained by reviewing death certificates, medical records, autopsy reports, and by linkage to the National Death Index [24]. Death certificates and hospital records were adjudicated without knowledge of study component or randomization assignment. Initially, all deaths in WHI were centrally adjudicated [24]. Records from the most relevant hospitalization preceding death and from the time of death, autopsy records, and death certificates were used by adjudicators in determining the cause of death. For many deaths occurring out of hospital, documentation was limited to the death certificate and records of the most recent hospitalization before death. In these instances, the immediate and underlying cause of death were abstracted from the death certificate [24]. Based on review of medical records and the death certificate, CHD death was defined as death consistent with CHD as the underlying cause, and included "in-hospital fatal MI" or death due to atherosclerotic cardiac disease or suspected CHD [24]. Cancer deaths were determined from the same sources, and the anatomic site was determined based on ICD-9 codes recorded on the death certificate. Ascertainment of outcomes was complete through September 30, 2016.

Among 158,203 women with baseline information on sleep, 30,400 total deaths, including 8857 CVD deaths, 9284 cancer deaths, and 11,928 other deaths were ascertained over a median of 17.8 years.

2.3. Statistical analysis

In descriptive analyses, we examined factors associated with hours of sleep per night and insomnia as reported at baseline. Associations of sleep duration, insomnia, and use of sleep aids reported at baseline with total and cause-specific mortality were assessed using Cox proportional hazards regression models with time to death as the time-scale. For the analysis of CVD, cancer, and non-CVD/non-cancer mortality, deaths due to causes other than the event of interest were considered competing risks, and cause-specific hazards were modeled by fitting the Cox model to the event of interest and censoring competing events at the time they occurred. Follow-up time was calculated as days from either enrollment to death, end of follow-up (September 30, 2016), or loss to follow-up, whichever occurred first. Selection of covariates for inclusion in the models was based on earlier analyses of this cohort [25], including: baseline age, smoking status, pack-years of smoking, alcohol intake, hormone therapy, body mass index (kg/m^2), red meat intake, physical activity (MET-hrs/wk), history of diabetes, CVD, cancer, systolic blood pressure, health status, history of depression, use of sleep aids, marital status, educational level, ethnicity, and study participation. Alternative models included the modified Charlson comorbidity index instead of history of diabetes, CVD, or cancer and self-reported health status. Other covariates that were considered included coffee/tea intake and white blood cell count (as a measure of inflammation [25]), but these did not