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Khan, H., Kella, D., Kunutsor, S., Savonnen, K., & Laukkanen, J. (2018). Sleep Duration and Risk of Fatal Coronary Heart Disease, Sudden Cardiac Death, Cancer Death, and All-Cause Mortality. *American Journal of Medicine*. https://doi.org/10.1016/j.amjmed.2018.07.010

Peer reviewed version

Link to published version (if available):
10.1016/j.amjmed.2018.07.010

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Sleep duration and risk of fatal coronary heart disease, sudden cardiac death, cancer death and all-cause mortality

Running Title: Sleep Duration and mortality

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Conflict of Interest: None.

Authorship: All authors had access to the data and a role in writing the manuscript.

Abstract words: 230.

Word count: (excluding abstract and references): 2,000

ABSTRACT

Background: Sleep duration has been shown to be associated with all-cause mortality, however its relationship with cause-specific fatal events remains uncertain. We examined the relationship between sleep duration and risk of fatal coronary heart disease (CHD), sudden cardiac death, cancer related death and all-cause mortality.

Methods Sleep duration was self-reported at baseline examinations performed between March 20, 1984 and December 5, 1989 in 2,361 men aged 42-61 years old from the Kuopio Ischemic Heart Disease study. Of these 1734 (73.4%) men were free from CHD and cancer at baseline.

Results: A total of 802 all cause deaths, 202 fatal coronary heart disease events, 141 sudden cardiac events and 229 cancer related deaths were reported during a median follow-up of 25.9 (IQR: 20.6-28.2) years. Multi-variable adjusted hazard ratios (HR) comparing the top quartile (> 10 hours) of sleep duration versus the bottom quartile (<8 hours) was 1.19 (95% CI: 1.01-1.43) for all-cause mortality, 1.27 (95% CI: 0.88-1.84) for fatal coronary heart disease, 1.20 (95% CI: 0.78-1.86) for sudden cardiac death and 1.29 (95% CI: 0.92-1.80) for cancer death. No differences in association of sleep duration with outcomes were found in clinically relevant subgroups including age, history of coronary heart disease, body mass index, physical activity, and C-reactive protein levels.

Conclusion: Longer duration of sleep was associated with significantly increased all-cause mortality. Mechanistic link between these findings remains to be explored further.

Key words: sudden cardiac death; coronary heart disease; cancer death; sleep duration.

Introduction:

Sleep duration and its impact on health outcomes has received considerable attention in recent times [1]. Several studies have demonstrated the association of sleep duration with incident diabetes mellitus, cardiovascular disease and obesity [2-4]. Similarly it has also been associated with increased all-cause mortality, as several studies have reported a non-linear yet significant relationship between sleep duration and all-cause mortality[5,6]. However, data remains inconsistent in regards to sleep duration and cause-specific mortality [2,7].

With changing sleep trends globally, due to the increased work hours, shift work and necessity of 24 hour availability across several professions, it has become increasingly important to examine the relationship between sleep and health outcomes. These relationships have potential important health implications and may guide future policies in health care sector. We report the association of self-reported sleep duration with risk of fatal coronary heart disease, sudden cardiac death, cancer related death and all-cause mortality in a large cohort of healthy middle aged men, prospectively followed for over two decades.

Methods

Study population

The study population is a representative sample of men living in the city of Kuopio and its surrounding rural communities in Eastern Finland. Subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study, a longitudinal population-based study designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes [8]. The men were 42-61 years of age during baseline examinations performed between March 20, 1984 and December 5, 1989. Of 3,235 potentially randomly selected eligible men, 2,682 (83 %) volunteered to participate in this study, 186 did not respond to the invitation, and 367 declined to give informed consent. Individuals with preexisting coronary heart disease or cancer at baseline were excluded from the analysis (N=709). This was done so as to avoid bias due to reverse causation. That is individuals who have heart disease may be prone to sleep more or less due to their disease state than vice versa. The present analysis is based on 1,734 men with no missing data on, covariates, all-cause mortality, fatal coronary events, sudden cardiac death and cancer related death. The study was approved by the Research Ethics Committee of the University of Eastern Finland, and each participant gave written informed consent.

Assessment of sleep duration and risk factors

Sleep duration was self-reported at baseline examinations. The lifelong exposure to smoking (cigarette pack-years) was estimated as the product of the number of years smoked and the number of tobacco products smoked daily. Resting blood pressure was measured between 8 and 10 AM with a random-zero sphygmomanometer. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters. Diabetes was defined as a fasting blood glucose level greater than 121 mg/dl (>6.7 mmol/L) or clinical diagnosis of diabetes with dietary, oral, or insulin treatment. The collection of blood specimens and the measurement of serum lipids, lipoproteins, creatinine, C-reactive protein and glucose have been described elsewhere[9,10]

Definition of Follow-up Events

All-cause, coronary heart disease and cancer related deaths that occurred by the end of 2014 were checked against the hospital documents, health centres and death certificates. Incident cancer cases were derived from the population-based Finnish Cancer Registry[11]. There were no losses to follow-up. A death was classified as sudden cardiac death when it occurred within 24 hours of the onset of symptoms including non-witnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death. The unwitnessed subject was to have been seen alive and symptom free within 24 hours before the event[12]. Sudden cardiac deaths that occurred in out-of-hospital conditions were also defined as places in which the events occurred had been reported accurately in hospital documents. The deaths due to aortic aneurysm rupture, cardiac rupture or tamponade and pulmonary embolism were not included as sudden cardiac death. The sources of information were interviews, hospital documents, death certificates, autopsy reports and medico-legal reports. The diagnostic classification of events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80%) and history of coronary heart disease together with the clinical and electrocardiographic findings of the paramedic staff. All the documents related to the death were cross-checked in detail by two physicians. Non- sudden cardiac deaths were also carefully documented using standardized criteria. Cardiac deaths that did not lead to death during the following 24 hours of the onset of symptoms were considered as non- sudden cardiac death. Data on incident acute coronary events were obtained by computer linkage to the national hospital registers. The independent events committee, blind to clinical data, performed the classification of deaths[13].

Statistical analyses

Values of skewed variables were log-transformed to achieve approximately symmetrical distributions. Descriptive analyses summarized baseline characteristics by participants within quartiles of sleep duration. Cross-sectional associations of sleep duration with several risk factors were assessed using linear regression models adjusted for age. The primary outcomes were all-cause mortality, fatal coronary heart disease, sudden cardiac death and cancer related death. Cumulative survival plots were constructed for cause specific fatal events across quartiles of

sleep duration and compared with the log rank test. Time-to-event analyses were conducted using Cox proportional hazards models to examine the association of sleep duration with fatal outcomes after confirming that the assumption of proportionality of hazards was met. All models were adjusted for age and subsequently adjusted for body mass index, systolic blood pressure, history of diabetes, systolic blood pressure, serum LDL-c, serum creatinine and physical activity. The shape of the association with cause specific fatal outcomes was assessed by plotting hazard ratios (HRs) calculated within quartiles of baseline sleep duration against the mean sleep duration within each quartile.[14] Furthermore, multivariate fractional polynomial models were also fitted to assess the shape of the association. Subgroup analyses were conducted using interaction tests to assess statistical evidence of any differences in HRs across levels of pre-specified individual level characteristics age at survey, prevalent CVD, body mass index, physical activity, and inflammatory markers such as C-reactive protein levels). All statistical analyses were conducted using Stata version 12 (Stata Corp, College Station, Texas)[15].

Results

Baseline characteristics

The mean age of participants at baseline was 51.7 (SD 5.6) years. The average sleep duration was 9.1 (SD 2.0) hours, (**Supplementary Figure-1)**. Baseline descriptive characteristics of the participants according to quartiles of sleep duration are shown in **Table 1.**

During a median follow-up of 25.9 (IQR: 20.6-28.2) years, there were 802 all cause deaths, 202 fatal coronary heart disease events, 141 sudden cardiac events and 229 cancer related deaths reported. At baseline, sleep duration was significantly lower in men with prevalent coronary heart disease at baseline, current smokers, subjects with prevalent diabetes, and those with a history of hypertension at baseline (**Supplementary Table 1**). Somewhat weaker but significant correlations were observed with body mass index (r=0.05), systolic blood pressure (r=0.08), total cholesterol (r=-0.06), high-density lipoprotein cholesterol (r=-0.06), LDL cholesterol (r=0.07) and serum C=reactive protein (r=0.10).

Sleep duration and cause specific mortality

Cumulative survival curves demonstrated a significant association of all cause, coronary heart disease, sudden cardiac death and cancer death in the top quartile of sleep duration compared to those in the bottom quartile (*P*-value for log rank test <0.001: **Figure-1**). Age-adjusted hazard ratio (HR) comparing the top quartile (> 10 hours) of sleep duration versus the bottom quartile (<8 hours) was 1.36 (95% CI: 1.13-1.62) for all-cause mortality, 1.56 (95% CI: 1.08-2.24) for coronary heart disease, 1.47 (95% CI: 0.96-2.26) for sudden cardiac death and 1.39 (95% CI: 1.0-1.94) for cancer death. Further adjustment for risk factors including systolic blood pressure, history of cardiovascular disease, diabetes, smoking, alcohol use, renal function and serum LDL cholesterol attenuated these associations further to 1.19 (95% CI: 1.01-1.43) for all-cause mortality, 1.27 (95% CI: 0.88-1.84) for fatal coronary heart disease, 1.20 (95% CI: 0.78-1.86) for sudden cardiac death and 1.29 (95% CI: 0.92-1.80) for cancer death . Progressive adjustments for physical activity and serum C-reactive protein did not attenuate these associations, **Table 2.** Sleep

duration was non-linearly associated with all-cause mortality, fatal coronary heart disease and cancer death, **Figure-2**. No differences in association of sleep duration with outcomes were found in clinically relevant subgroups **(Supplementary Figure-2)**. Further evaluation of cause specific cancer outcomes found significant association with gastrointestinal cancer subtype 1.71(95% 1.13-2.55) comparing top versus bottom quartile for sleep duration **(Figure-3)**.

Discussion:

In this large prospective cohort, sleep duration was significantly associated with all-cause mortality. We also report significant associations with fatal coronary heart disease and cancer events which were attenuated on further adjustment.

The association of sleep duration with all-cause mortality has been extensively documented, with both short and long sleepers noted to be at higher risk [5,6]. Sleep duration has been associated with diabetes mellitus, lower physical activity, depression, hypertension and smoking, which in turn increase the overall risk of mortality [16-18]. Moreover longer sleep duration may be a manifestation of a clinical disorder rather than a causal risk factor, such as obstructive sleep apnea. It may also reflect difficulty in falling asleep which has been associated with increased risk of coronary heart disease mortality [19]. Retrospective studies have linked sleep duration to clinical coronary heart disease [20]. However, studies examining the association between sleep duration and cardiovascular disease mortality have yielded mixed results, with most suggesting a J or U-shaped relationship and the association was attenuated to some extent after adjusting for confounders [2]. In a prospective study, sleep duration of 6-8 hours/day was found to be one of the protective lifestyle factors against cardiovascular disease related mortality [21]. There was a significant association between longer sleep duration and fatal coronary heart disease in the present study. The prospective nature of our study allowed us to control for several cardiovascular risk factors, which have not been comprehensively accounted for in many of the retrospective studies.

Our findings are also in line with a large meta-analysis of prospective studies that showed that long, not short duration of sleep was significantly associated with increased cancer related mortality [7]. We here further explored cancer specific mortality data and found that gastrointestinal cancer subtype was significantly associated with mortality. Long sleep duration has been associated with colorectal cancer, but the association was limited to overweight individuals or whom snored regularly, suggesting hypoxemia due to sleep apnea contributing to the increased risk [22]. Long sleep duration has been related to systemic inflammation, increase in cytokines and change in several metabolic pathways[23]. In the present study adjustments for CRP did not attenuate the association of sleep duration with cancer

mortality, suggesting that the relationship is independent of inflammatory response. The lack of physiological challenge due to increased sleep has also been proposed as a mechanism that may increase mortality [24]. Longer sleep duration has also been linked to depression and other psychiatric disorders, which are known to be associated with increased all-cause as well as CVD and cancer-specific mortality events [25-27]. The change in photoperiod has been shown to accelerate ageing and increase mortality in mammalian species [28]. However all these proposed mechanisms are speculative at best and require more research.

This study is best understood in the context of its limitations. The study population involved only middle-aged men from eastern Finland, thus generalizability of the results to other age groups, populations and women may not be possible. Of note, the average sleep duration in our study was 9.1 hours with the lowest quartile being 8.2 hours. This is longer compared to previously reported data from western population. Sleep duration was self-reported and did not account for quality of sleep or nocturnal vs. diurnal timing of the sleep. However, an objective measurement of sleep duration and quality, such as polysomnography is not practical in large-scale population-based cohorts. We were unable to evaluate individuals with shorter duration of sleep <5 hrs as less than 1% of the cohort slept less than 5 hours. Further prospective studies are needed to investigate the mechanistic link and to determine if duration of sleep is a modifiable risk factor or not.

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