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PERSISTENT INSOMNIA IS ASSOCIATED WITH MORTALITY RISK

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Abstract

Background—Insomnia has been associated with mortality risk, but whether this association is different in subjects with persistent versus intermittent insomnia is unclear. Additionally, the role of systemic inflammation in such an association is unknown.

Methods—We used data from a community-based cohort to determine whether persistent or intermittent insomnia, defined based on persistence of symptoms over a six-year period, were associated with death during the following 20-years of follow-up. We also determined whether changes in serum C-reactive protein (CRP) levels measured over two decades between study

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initiation and insomnia determination were different for the persistent, intermittent, and never insomnia groups. The results were adjusted for confounders such as age, sex, body mass index, smoking, physical activity, alcohol and sedatives.

Results—Of the 1409 adult participants, 249 (18%) had intermittent and 128 (9%) had persistent insomnia. During a 20-year follow-up period, 318 participants died (118 due to cardiopulmonary disease). In adjusted Cox proportional-hazards models, participants with persistent insomnia (adjusted Hazards Ratio [HR] 1.58, 95%CI: 1.02-2.45) but not intermittent insomnia (HR 1.22, 0.86-1.74), were more likely to die than participants without insomnia. Serum CRP levels were higher and increased at a steeper rate in subjects with persistent insomnia as compared with intermittent ($p=0.04$) or never ($p=0.004$) insomnia. Although CRP levels were themselves associated with increased mortality (adjHR: 1.36, 1.01-1.82, $p=0.04$), adjustment for CRP levels did not notably change the association between persistent insomnia and mortality.

Conclusions—In a population-based cohort, persistent, and not intermittent, insomnia was associated with increased risk for all-cause and cardiopulmonary mortality and was associated with a steeper increase in inflammation.

Keywords

sleep; chronic insomnia; sleep; cardiovascular; mortality

Introduction

Insomnia is a common medical complaint that affects 20% of U.S. adults, but *persistent* (or chronic) insomnia is estimated to occur in only half (10%) of such individuals¹⁻⁵. Although insomnia has been associated with death⁶⁻¹⁷, whether this association holds true both for persistent and intermittent insomnia remains unknown. An enhanced understanding of the association between persistence of insomnia and death would inform treatment of the “at-risk” population. We hypothesized that insomnia that was *persistent* over 8 years – rather than intermittent insomnia – was associated with death independent of the effects of sedatives, opportunity for sleep (to distinguish it from sleep deprivation), and other confounding factors in a representative sample of the general adult community.

The mechanistic basis for the association between insomnia and increased risk of death is unclear. Systemic inflammation has been posited as a potential mechanism because sleep curtailment leads to, or is associated with, elevation in biomarkers of inflammation¹⁷⁻²⁰. Such systemic inflammation, measured as circulating levels of C-reactive protein (CRP), has in turn been independently associated with increased risk for cardiovascular disease and death²¹. We hypothesized that persistent insomnia is associated with elevated circulating levels of CRP.

We tested the above hypotheses by assessing the persistence of insomnia complaints in 1409 adult participants from the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD) and linking such information to the temporal trajectories of their serum CRP levels and to their mortality risk over 38 years of follow-up.

Methods

Study population

The community-based, prospective cohort study (Tucson Epidemiological Study of Airway Obstructive Disease [TESAOD]) was conducted on a multistage, stratified cluster sample of non-Hispanic white households in Tucson, Arizona. As a population-based study aimed at studying risk for obstructive airway disease, study entry did not require the presence of respiratory symptoms but was based upon door-to-door campaigning and recruitment of community-dwelling participants. The study methodology and population have been described previously²². Briefly, the study commenced in 1972 with multiple follow-up surveys up to 1996 and continuous mortality follow-up data up to 2011²². Blood was collected and serum samples cryopreserved at baseline in 1972 and subsequently at multiple time-points. At each survey, weight and height were measured by study nurses and questions regarding demographic data, medical history, medication history (consumption of hypnotics), smoking history, pulmonary symptoms, and social and environmental information were posed through questionnaires. Questions regarding sleep and related habits were inserted in the two surveys completed between 1984 and 1985 (hereafter survey 1984-85) and between 1990 and 1992 (hereafter survey 1990-92).

The present study included 1409 adult participants who completed sleep-related questions in both surveys and were 21 to 75 years old at the time of completion of the 1990-92 survey. The study received approval by the University of Arizona Institutional Review Board and written informed consent was obtained from all participants.

Insomnia definition

Insomnia definition was derived from the International Classification of Sleep Disorders criteria, specifically by the presence of any of the following symptoms – persistent symptoms of trouble falling asleep, staying asleep, or waking up too early in the morning – accompanied by at least one symptom of impaired daytime function (concern about not getting enough sleep or daytime sleepiness)²³. Adequate opportunity to sleep was gauged by at least 7 hours spent sleeping or reclining on a typical weekday and on a typical weekend day²⁴. The persistence of insomnia was assessed based upon whether insomnia was present in both the 1984-85 and 1990-92 surveys (*persistent insomnia*), in either but not both (*intermittent insomnia*), or in neither of the two surveys (*never insomnia*).

CRP measurements

CRP was measured using the enzymatic solid-phase chemiluminescent immunometric assay supported by Immulite 2000 (Siemens Diagnostics, Tarrytown, NY)²⁵ in 722 available cryopreserved serum samples that were collected either at the 1990-92 survey or at the previous survey (completed in 1988-89; median time interval between the two surveys: 1.75 years). Of these 722 subjects, 389 were already ≥ 21 years old and had available serum samples at the initial survey in 1972-73 and their enrollment samples were also assayed for CRP levels.

Outcomes, covariates, and statistical analysis

A complete review of vital status of participants as of January 1st, 2011 was completed through direct contact with the family or designated next of kin and linkage with the National Death Index (NDI) ²⁶. The main causes of death were obtained directly from death certificates for events that occurred up to 1978 and from NDI records for events that occurred after 1978. We evaluated all-cause mortality (318 events) and death due to each of the three main causes of death: heart disease (95 events), cancer (78 events), and chronic obstructive pulmonary disease (COPD, 23 events). Because the number of deaths due to COPD was relatively small, these events were combined with death due to heart disease into the category of cardiopulmonary mortality.

Cox proportional hazard models with household clustered sandwich estimators of standard errors were used to calculate the hazard ratios (HRs) for mortality with 95% confidence intervals (CIs) for persistent and intermittent insomnia as compared with never insomnia. Multivariable Cox models included important confounders such as age, sex, body mass index (BMI; categorized as underweight [BMI<18.5 Kg/m²], normal weight [18.5 BMI<25], overweight [25 BMI<30], and obese [BMI ≥ 30]), smoking status, pack-years of smoking, regular physical activity, and use of alcohol or medications to get to sleep. Additional confounders that were tested in sensitivity models were marital status, habitual snoring, diabetes mellitus, and hypertension. Results were also tested after restricting analyses to subjects with sufficient opportunity to sleep and without any report of heart disease. All confounders and stratifying factors were assessed at the 1990-92 survey, which represented the starting point of survival analyses. In Cox models, time to event was defined as the time from the date of participation in the 1990-92 survey to the date of death for deceased participants and to January 1st, 2011 for subjects who were still alive as of that date. Analyses on cause-specific mortality were completed using both 1) Cox models with death events due to causes other than the specific cause of interest treated as censored observations and 2) competing-risks survival regressions.

Results

Overall, complete information on insomnia at both surveys was available for 1409 participants. Their characteristics are shown in **Table I**. By the 1990-92 survey, the study population had a mean age of 47 years, with 55% proportion of females, and a 51% proportion of ever smokers. In each of the two surveys, 18% of participants had insomnia and about 10% were currently using alcohol or medications to get to sleep. When combining information from both surveys, 249 (18%) participants had intermittent and 128 (9%) had persistent insomnia. As compared with the 540 participants who had insomnia information from only one of the two surveys and were therefore excluded from this study, the 1409 participants included in this study were older (mean age as of January 1st 1984: 36 vs 40 years, respectively; $p < 0.001$). By the time of survey 1990-92, they were also more likely to be never smokers (42% vs 49%, $p = 0.02$). However, no significant differences were found between the two groups in terms of insomnia rates, mortality risk, sex, BMI, physical activity, hypnotics use, and hours spent sleeping or reclining.

Factors associated with the longitudinal insomnia categories are shown in **Table II**. Females were more likely to have both intermittent and persistent insomnia than males. Persistent insomnia was also associated with higher BMI and current smoking, although no significant differences in pack-years were found among smokers across the insomnia categories. As expected, both insomnia categories were associated with hypnotic use and the highest rates were recorded among subjects with persistent insomnia (**Table II**). When compared with subjects with no insomnia, those with intermittent and persistent insomnia had no significant differences in age and regular physical activity.

Of the 1409 participants, 318 (23%) died by January 1st, 2011. Heart disease was the underlying cause for 95 and COPD for 23 death events, for a total of 118 cardiopulmonary deaths. Cancer was the main cause of death for 78 participants. The Kaplan-Meier curves for all-cause mortality across the longitudinal insomnia categories are shown in **Figure 1**. After adjusting for sex and age, both intermittent and persistent insomnia were associated with all-cause mortality risk. As compared with subjects with no insomnia, those with intermittent insomnia were 54% and those with persistent insomnia 98% more likely to die during the study follow-up (Hazard Ratios, 95% CI: 1.54, 1.18-2.00, $p=0.001$; and 1.98, 1.42-2.77, $p<0.001$; respectively). These associations were confirmed after further adjustment for BMI categories, smoking status, pack-years, and regular physical activity (**Table III, Model 1**). **Table III** shows that persistent, but not intermittent, insomnia remained a significant predictor of all-cause mortality in additional multivariate Cox models that included hypnotics use among covariates (**Models 2 and 5**) and that were restricted to subjects not using hypnotics (**Models 3 and 4**) and to subjects reporting reclining at least 7 hours per day on both weekdays and week-end days (**Models 4 and 5**). Stratification by sex, exclusion of participants with heart disease at baseline, and further adjustment for marital status, habitual snoring (as a surrogate for obstructive sleep apnea), diabetes mellitus, and hypertension did not influence results tangibly (results not shown).

In secondary analyses on cause-specific mortality, we found the effects of persistent insomnia to be largely explained by heart disease and cardiopulmonary mortality (**Figures E1 and E2 of online supplement**). In Cox models, after adjusting for covariates, the HRs associated with persistent insomnia were 2.02 ($p=0.02$) for heart disease and 2.11 ($p=0.004$) for cardiopulmonary mortality. The corresponding adjusted subdistribution HRs (SHR) from competing risk regression models were 1.50 ($p=0.18$) for heart disease and 1.71 ($p=0.04$) for cardiopulmonary mortality. In contrast, no significant associations were found between either intermittent or persistent insomnia and cancer mortality (**Figure E3 of online supplement**).

In analyses pertaining to systemic inflammation, we found subjects with persistent insomnia to have higher serum CRP levels by the 1990-92 survey than did subjects with intermittent or no insomnia (geometric means: 2.86, 1.61, and 1.52 mg/L, respectively; ANOVA $p = 0.02$). When temporal trajectories of serum CRP between the initial 1972-73 survey and the 1990-92 survey were analyzed in mixed models, we found that, after adjustment for sex, age, BMI categories, smoking status, and pack-years, subjects with persistent insomnia experienced a CRP increase during that time interval that was 0.018 log[mg/L] faster than that of subjects with no insomnia ($p=0.003$) and 0.014 log[mg/L] faster than that of subjects

with intermittent insomnia ($p=0.04$). In Figure 2, CRP levels from the initial 1972-73 and the 1990-92 survey are compared across the three insomnia groups among the 389 subjects who were ≥ 21 years of age when they completed both surveys. Among the 722 subjects with available CRP data, persistent insomnia was associated with a 97% (adjHR: 1.97, 1.35-2.88, $p<0.001$) increased mortality risk after adjustment for sex, age, BMI categories, smoking status, pack-years, and regular physical activity. This association was only modestly reduced by further adjustment for CRP levels (adjHR: 1.93, 1.32-2.82, $p=0.001$), although CRP levels were themselves associated with increased mortality (adjHR: 1.36, 1.01-1.82, $p=0.04$).

Discussion

In a community-based prospective cohort, we have observed that persistent – but not intermittent – insomnia was associated with mortality risk. We found that participants with persistent insomnia were at increased risk of dying independent of the effects of hypnotics, opportunity for sleep (as distinguished from sleep deprivation), sex, age, and other known confounding factors.

Morin and colleagues found that only half of participants with insomnia manifested persistent insomnia over a 3-year period ¹, indicating the importance of analyzing temporal patterns of insomnia in mortality studies. In our study, we found a strong association between persistent, but not intermittent, insomnia and mortality risk. Most prior reports that demonstrated an association between insomnia and increased all-cause mortality did not distinguish persistent from intermittent insomnia ⁶⁻¹⁵. Use of the two determinations of insomnia spanning 6 years in our longitudinal cohort that permitted us to distinguish between persistent and intermittent insomnia served to better quantify the level (or duration) of “exposure” to the adverse biological effects of insomnia.

There are many postulated mechanisms to explain the relationship between insomnia and increased mortality. Studies have suggested associations between insomnia and known risk factors for mortality such as hypertension, carotid intima-media thickness, increased Framingham risk score, and systemic inflammation ²⁷⁻³⁰. Although systemic inflammation measured by circulating levels of CRP has been individually associated with cardiovascular death and also with insufficient sleep, to our knowledge, there have not been any longitudinal cohorts that simultaneously assessed the mortality effects of persistent insomnia and serum CRP levels ^{24,25,31}. Moreover, the associations between insomnia and inflammatory biomarkers reported in previous studies only when subgroup analyses by age-group or race were performed ^{32,33}. In our study, we simultaneously assessed CRP levels by insomnia categories and mortality risk and demonstrated a steeper rise in serum CRP levels in participants with persistent insomnia when compared to those with intermittent or no insomnia. However, such a relationship did not appear to explain the mechanistic basis for the observed insomnia-related mortality risk, because the increased mortality risk associated with insomnia persisted after adjustment for serum CRP levels. Such a finding suggests that other mechanistic pathways may be additionally contributing to the insomnia-mortality association.

The requirement of sufficient opportunity to sleep (≥ 7 hours) used in our insomnia definition is an important distinguishing feature of our study compared to prior investigations that did not entirely exclude the effects of sleep deprivation while measuring insomnia^{23,34}. The lack of such requirement would include participants who are curtailing their sleep because of work or other reasons (sleep deprivation) as opposed to those who are unable to sleep despite sufficient opportunity to sleep (insomnia)³⁵. Interestingly the relationship between persistent insomnia and the rate of increase in serum CRP levels in our study was unidirectional, as opposed to “U” shaped relationships or lack of relationship noted in other population-based studies that have studied the relationship between sleep duration and serum CRP levels^{19,36}.

In our study, in sensitivity analyses, we adjusted for hypertension and excluded participants with baseline heart disease, and were able to confirm the relationship between persistent insomnia and increased all-cause mortality. Further adjustment for marital status, habitual snoring (as a surrogate for obstructive sleep apnea), and diabetes mellitus did not influence results tangibly. Additionally, stratification by sex revealed that the association between persistent insomnia and mortality was present in both men and women.

Some investigators have noted that increased mortality risk from insomnia was attributable to the related use of hypnotic medications rather than insomnia per se^{37,38}. However, others have shown that insomnia may be associated with increased mortality after adjusting for hypnotic intake^{17,38,39}. Nevertheless, even in studies that adjusted for the consumption of hypnotics (including our study [see **model 4; table III**]), results could be affected by possible indication bias and residual confounding. Therefore, the association between insomnia and death cannot be assumed to be independent of the effect of hypnotics unless participants consuming hypnotics are excluded from analyses^{17,38-40}. In our study, the association between persistent insomnia and death remained when we excluded participants who were consuming hypnotics (**model 5; Table III**).

Interestingly, although we found a relationship between persistent insomnia and cardiopulmonary mortality, we did not find a relationship between persistent insomnia and cancer-related mortality. This finding is in line with a recent study in men¹⁷, although it is conceivable that our study may have lacked sufficient power to detect such a relationship. While a putative relationship between sleep apnea and cancer-related mortality has been demonstrated and mechanisms are being elucidated, the question of whether insomnia is related to cancer mortality needs further study⁴¹.

Our study has limitations. Although habitual snoring has been used as a surrogate for obstructive sleep apnea there is potential for misclassification. Nevertheless, we did not find a difference in prevalence of obstructive sleep apnea across the insomnia categories in a subcohort of our study that underwent sleep studies¹⁷. Our study population only included non-Hispanic white subjects and therefore results may not be generalizable to other races or ethnicities.

In conclusion, in a population-based prospective cohort we have observed that persistent insomnia over an eight-year period was associated with increased risk for all-cause and

cardiopulmonary mortality independent of the effects of hypnotics, opportunity for sleep, systemic inflammation, and other potential confounding factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Morin CM, Belanger L, LeBlanc M, et al. The natural history of insomnia: a population-based 3-year longitudinal study. *Arch Intern Med*. 2009; 169:447–53. [PubMed: 19273774]
2. Buysse DJ. Insomnia. *JAMA*. 2013; 309:706–16. [PubMed: 23423416]
3. Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. *Sleep*. 1999; 22(Suppl 2):S359–65. [PubMed: 10394608]
4. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002; 6:97–111. [PubMed: 12531146]
5. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. *Sleep*. 1999; 22(Suppl 2):S347–53. [PubMed: 10394606]
6. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep*. 1995; 18:425–32. [PubMed: 7481413]
7. Althuis MD, Fredman L, Langenberg PW, Magaziner J. The relationship between insomnia and mortality among community-dwelling older women. *J Am Geriatr Soc*. 1998; 46:1270–3. [PubMed: 9777910]
8. Newman AB, Spiekerman CF, Enright P, et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *J Am Geriatr Soc*. 2000; 48:115–23. [PubMed: 10682939]
9. Rockwood K, Davis HS, Merry HR, MacKnight C, McDowell I. Sleep disturbances and mortality: results from the Canadian Study of Health and Aging. *J Am Geriatr Soc*. 2001; 49:639–41. [PubMed: 11380758]
10. Nilsson PM, Nilsson JA, Hedblad B, Berglund G. Sleep disturbance in association with elevated pulse rate for prediction of mortality--consequences of mental strain? *Journal of internal medicine*. 2001; 250:521–9. [PubMed: 11902821]
11. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. *Journal of internal medicine*. 2002; 251:207–16. [PubMed: 11886479]
12. Suzuki E, Yorifuji T, Ueshima K, et al. Sleep duration, sleep quality and cardiovascular disease mortality among the elderly: a population-based cohort study. *Preventive medicine*. 2009; 49:135–41. [PubMed: 19573557]
13. Rod NH, Vahtera J, Westerlund H, et al. Sleep disturbances and cause-specific mortality: Results from the GAZEL cohort study. *Am J Epidemiol*. 2011; 173:300–9. [PubMed: 21193534]
14. Almeida OP, Alfonso H, Yeap BB, Hankey G, Flicker L. Complaints of difficulty to fall asleep increase the risk of depression in later life: the health in men study. *Journal of affective disorders*. 2011; 134:208–16. [PubMed: 21680026]

15. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *Am J Epidemiol.* 1992; 135:854–64. [PubMed: 1585898]
16. Vgontzas AN, Liao D, Pejovic S, et al. Insomnia with short sleep duration and mortality: the Penn State cohort. *Sleep.* 2010; 33:1159–64. [PubMed: 20857861]
17. Li Y, Zhang X, Winkelman JW, et al. The Association between Insomnia Symptoms and Mortality: A Prospective Study of US Men. *Circulation.* 2013
18. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol.* 2001; 107:165–70. [PubMed: 11150007]
19. Grandner MA, Buxton OM, Jackson N, Sands-Lincoln M, Pandey A, Jean-Louis G. Extreme sleep durations and increased C-reactive protein: effects of sex and ethnorracial group. *Sleep.* 2013; 36:769–79E. [PubMed: 23633760]
20. Zee PC, Badr MS, Kushida C, et al. Strategic opportunities in sleep and circadian research: report of the Joint Task Force of the Sleep Research Society and American Academy of Sleep Medicine. *Sleep.* 2014; 37:219–27. [PubMed: 24501434]
21. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England journal of medicine.* 2000; 342:836–43. [PubMed: 10733371]
22. Lebowitz MD, Knudson RJ, Burrows B. Tucson epidemiologic study of obstructive lung diseases. I: Methodology and prevalence of disease. *Am J Epidemiol.* 1975; 102:137–52. [PubMed: 1155443]
23. American Academy of Sleep Medicine. 2nd. American Academy of Sleep Medicine; Westchester, IL: 2005. International Classification of Sleep Disorders.
24. Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: The evidence, the possible mechanisms, and the future. *Sleep Med Rev.* 2010; 14:181–203.
25. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *The New England journal of medicine.* 2008; 358:2107–16. [PubMed: 18480203]
26. Davis KB, Fisher L, Gillespie MJ, Pettinger M. A test of the National Death Index using the Coronary Artery Surgery Study (CASS). *Control Clin Trials.* 1985; 6:179–91. [PubMed: 4042662]
27. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best practice & research Clinical endocrinology & metabolism.* 2010; 24:775–84. [PubMed: 21112025]
28. Nakazaki C, Noda A, Koike Y, Yamada S, Murohara T, Ozaki N. Association of insomnia and short sleep duration with atherosclerosis risk in the elderly. *American journal of hypertension.* 2012; 25:1149–55. [PubMed: 22854638]
29. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertension research : official journal of the Japanese Society of Hypertension.* 2013; 36:985–95. [PubMed: 24005775]
30. Okun ML, Reynolds CF, Buysse DJ, et al. Sleep variability, health-related practices, and inflammatory markers in a community dwelling sample of older adults. *Psychosom Med (3rd).* 2011; 73:142–50. [PubMed: 21097658]
31. van Leeuwen WM, Lehto M, Karisola P, et al. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PLoS One.* 2009; 4:e4589. [PubMed: 19240794]
32. Zhang J, Lamers F, Hickie IB, He JP, Feig E, Merikangas KR. Differentiating nonrestorative sleep from nocturnal insomnia symptoms: demographic, clinical, inflammatory, and functional correlates. *Sleep.* 2013; 36:671–9. [PubMed: 23633749]
33. Laugsand LE, Vatten LJ, Bjorngaard JH, Hveem K, Janszky I. Insomnia and high-sensitivity C-reactive protein: the HUNT study, Norway. *Psychosom Med.* 2012; 74:543–53. [PubMed: 22685243]
34. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2008; 4:487–504. [PubMed: 18853708]

35. Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. *Sleep Med Rev.* 2010; 14:239–47. [PubMed: 19896872]
36. Taheri S, Austin D, Lin L, Nieto FJ, Young T, Mignot E. Correlates of serum C-reactive protein (CRP) - no association with sleep duration or sleep disordered breathing. *Sleep.* 2007; 30:991–6. [PubMed: 17702268]
37. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry.* 2002; 59:131–6. [PubMed: 11825133]
38. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open.* 2012; 2:e000850.
39. Hublin C, Partinen M, Koskenvuo M, Kaprio J. Heritability and mortality risk of insomnia-related symptoms: a genetic epidemiologic study in a population-based twin cohort. *Sleep.* 2011; 34:957–64. [PubMed: 21731146]
40. Levine M. ACP Journal Club. Hypnotic drugs were associated with increased risk for mortality. *Ann Intern Med.* 2012; 156:JC6–13. [PubMed: 22711114]
41. Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *American journal of respiratory and critical care medicine.* 2013; 187:99–105. [PubMed: 23155146]

HIGHLIGHTS

- Persistent insomnia, but not intermittent insomnia, was associated with mortality.
- Systemic inflammation rose at a steeper rate in persistent insomnia than others.
- Mortality in those with persistent insomnia was cardiovascular-rather than cancer-related.

Figure 1.

Kaplan-Meier curves across the longitudinal categories of insomnia. Insomnia was defined by ICSD criteria and participants categorized into three groups: never insomnia (*green*), intermittent insomnia (*blue*), or persistent insomnia (*red*).

Figure 2.

C-reactive protein (CRP) levels across longitudinal insomnia categories (never insomnia, intermittent insomnia, and persistent insomnia) for both the baseline (1972-73, closed circles) and the 1990-92 (open circles) survey. Plotted CRP values are geometric means and standard errors.

Table I

Characteristics of the TESAOD participants included in the present study.*

	Survey 1984-85	Survey 1990-92
Sex		
Male	636 (45.1%)	636 (45.1%)
Female	773 (54.9%)	773 (54.9%)
Age in years: mean $\pm$ SD	41 $\pm$ 15	47 $\pm$ 14
BMI: mean $\pm$ SD	24.9 $\pm$ 4.6	25.9 $\pm$ 4.9
Smoking		
Current	349(24.8%)	270(19.2%)
Past	432(30.7%)	447(31.8%)
Never	625(44.5%)	688(49.0%)
Pack-years [§]: median, IQR	17.0, 6.3 – 32.7	21.5, 10.2 – 38.4
Regular physical activity		
Yes	N/A	802(57.6%)
No		590(42.4%)
Use of alcohol or medications to get to sleep		
Current	139(9.9%)	133(9.5%)
Former	118(8.4%)	160(11.4%)
Never	1146(81.7%)	1108(79.1%)
Insomnia		
Present	254(18.0%)	251(17.8%)
Absent	1155(82.0%)	1158(82.2%)
Insomnia prospective		
Never	N/A	1032(73.2%)
Intermittent		249(17.7%)
Persistent		128(9.1%)
Hours sleeping or reclining		
On weekdays: mean $\pm$ SD	N/A	7.8 $\pm$ 1.6
On weekend days: mean $\pm$ SD		8.1 $\pm$ 1.6

[§] Among smokers

Table II

Subjects characteristics across the three longitudinal insomnia categories.

	Never (N=1032)	Intermittent (N=249)	Persistent (N=128)	P value
Sex				
Male	496(78.0%)	97(15.3%)	43(6.8%)	0.001
female	536(69.3%)	152(19.7%)	85(11.0%)	
Age in years: mean $\pm$ SD	47.1 $\pm$ 14.3	46.6 $\pm$ 14.0	49.4 $\pm$ 15.6	0.18
BMI	25.6 $\pm$ 4.2	26.0 $\pm$ 5.8	27.6 $\pm$ 7.5	0.009
Smoking				
Current	174(64.4%)	63(23.3%)	33(12.2%)	0.007
Former	329(73.6%)	79(17.7%)	39(8.7%)	
Never	525(76.3%)	107(15.6%)	56(8.1%)	
Pack-years[*]: median, IQR	20.6, 9.8 – 36.8	24.1, 9.5 – 47.9	23.0, 16.5 – 37.5	0.29 ^{**}
Regular physical activity				
Yes	595(74.2%)	140(17.5%)	67(8.4%)	0.51
No	424(71.9%)	107(18.1%)	59(10.0%)	
Use of alcohol or medications to get to sleep[§]				
Current	50(4.9%)	40(16.1%)	43(33.9%)	<0.001
Past	93(9.1%)	38(15.3%)	29(22.8%)	
Never	882(86.0%)	171(68.7%)	55(43.3%)	

^{*} Among smokers (N=713)^{**} P value from non-parametric test[§] Percentages are calculated by insomnia category

Table III

Cox proportional hazard models for all-cause mortality.

	Model 1**	Model 2 Model 1 + hypnotics	Model 3 Model 1 among subjects not taking hypnotics	Model 4 Model 3 among subjects reclining 7 hrs	Model 5 Model 2 among subjects reclining 7 hrs
	N=1383	N=1375	N=1090	N=992	N=989
Insomnia	1.0	1.0	1.0	1.0	1.0
Never	1.35(1.02, 1.79)*	1.25(0.94, 1.67)	1.35(0.95, 1.92)	1.32(0.93, 1.88)	1.22(0.86, 1.74)
Intermittent	1.95(1.42, 2.69)*	1.56(1.09, 2.22)*	2.06(1.21, 3.51)*	1.92(1.27, 2.89)*	1.58(1.02, 2.45)*
Persistent					
Sex: male	1.14(0.88, 1.47)	1.18(0.91, 1.54)	1.20(0.89, 1.63)	1.13(0.83, 1.54)	1.14(0.83, 1.55)
Age	1.11(1.10, 1.13)*	1.11(1.10, 1.13)*	1.12(1.11, 1.14)*	1.11(1.09, 1.12)*	1.11(1.09, 1.12)*
BMI	1.0	1.0	1.0	1.0	1.0
Normal (ref)	1.85 (0.51, 6.71)	2.10(0.60, 7.33)	2.41(0.60, 9.73)	1.18(0.38, 3.72)	1.37(0.45, 4.18)
Underweight	0.74(0.53, 1.03)	0.76(0.55, 1.06)	0.87(0.57, 1.31)	0.67(0.46, 0.97)*	0.68(0.47, 0.99)*
Overweight	1.11(0.74, 1.64)	1.18(0.80, 1.74)	1.11(0.69, 1.79)	1.05(0.66, 1.67)	1.14(0.73, 1.80)
Obese					
Smoking	1.0	1.0	1.0	1.0	1.0
Never (ref)	1.13(0.82, 1.56)	1.13(0.82, 1.56)	1.27(0.87, 1.87)	1.17(0.79, 1.73)	1.19(0.80, 1.76)
Former	1.52(0.97, 2.39)	1.63(1.03, 2.58)*	1.78(1.05, 3.03)*	1.48(0.88, 2.47)	1.59(0.94, 2.69)
Current					
Pack-years	1.01(1.002, 1.01)*	1.01(1.001, 1.01)*	1.00(1.00, 1.01)	1.01(1.002, 1.02)*	1.01(1.001, 1.02)*
Regular physical activity	0.64(0.50, 0.82)*	0.63(0.49, 0.81)*	0.60(0.44, 0.82)*	0.66(0.49, 0.89)*	0.65(0.49, 0.87)*
Use of alcohol or medications to get to sleep		1.0			1.0
Never	-	2.08(1.48, 2.94)*	-	-	1.82(1.21, 2.75)*
In the past	-	1.51(1.09, 2.10)*	-	-	1.79(1.23, 2.61)*
Currently	-		-	-	

* P < 0.05;

** Model was adjusted for sex, age, body mass index, smoking, pack-years of smoking, and regular physical activity.