

**The Association between Insomnia Symptoms and Mortality:
A Prospective Study of US Men**

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Abstract

Background—Insomnia complaints are common in older adults and may be associated with mortality risk. However, evidence regarding this association is mixed. We thus prospectively examined whether men with insomnia symptoms had an increased risk of mortality during 6 years of follow-up.

Methods and Results—A prospective cohort study of 23,447 US men participating in the Health Professionals Follow-up Study and free of cancer, reported on insomnia symptoms in 2004 were followed through 2010. Deaths were identified from state vital statistic records, the National Death Index, family reports, and the postal system. We documented 2025 deaths during 6 years of follow-up (2004-2010). The multivariable-adjusted hazard ratios (HRs) of total mortality were 1.25 (95% confidence interval (CI):1.04-1.50) for difficulty initiating sleep, 1.09 (95%CI:0.97-1.24) for difficulty maintaining sleep, 1.04 (95%CI:0.88-1.22) for early-morning awakenings, and 1.24 (95%CI:1.05-1.46) for non-restorative sleep, comparing men with those symptoms most of the time to men without those symptoms, after adjusting for age, lifestyle factors and presence of common chronic conditions. Men with difficulty initiating sleep and non-restorative sleep most of the time had a 55% (HR:1.55; 95% CI:1.19-2.04; P-trend= 0.01) and 32% (HR:1.32; 95% CI:1.02-1.72; P-trend=0.002) increased risk of CVD mortality, respectively, relative to men without those symptoms.

Conclusions—Some insomnia symptoms, especially difficulty initiating asleep and non-restorative sleep, are associated with a modestly higher risk of mortality.

Key words: sleep disorders, mortality, cardiovascular outcomes, insomnia

Insomnia, the most common sleep/wake disorder, is characterized by difficulty initiating sleep, difficulty maintaining sleep, early morning awakenings or by non-restorative sleep^{1,2}.

Inadequate or unrefreshing nighttime sleep of insomniacs is accompanied by significant distress, daytime fatigue, and the likelihood of falling asleep during the day^{1,3-8}. Insomnia affects ten percent to one third of the general population in the United States⁷ depending on its definition.

The total cost associated with insomnia is estimated at \$92.5 to \$107.5 billion annually in the US⁹.

Insomnia in older adults is of particular concern because it could increase risk of injury¹⁰, impaired quality of life⁶, cognitive impairment¹¹, depression¹² and metabolic syndrome.¹³

Insomnia is also associated with a moderately increased risk for cardiovascular diseases^{14,15}. In this context, insomnia has been thought to influence total mortality, and cardiovascular mortality specifically, but regarding results to date have been inconsistent¹⁶⁻¹⁹. We thus examined whether men with insomnia symptoms had an increased risk of all cause and cause specific mortality in the Health Professionals Follow-up Study (HPFS), taking into account the effects of a variety of lifestyle factors and prevalent medical morbidities which are known to be associated with mortality risk. To further test our research hypothesis, we also conducted a meta-analysis including the current study with another 9 previously published studies^{8,20-27} regarding the association between insomnia symptoms and mortality.

Materials and Methods

Ethics Statement

The institutional review board at Brigham and Women's Hospital and Harvard School of Public Health reviewed and approved this study, and receipt of each questionnaire implied participant's consent.

Study population

The HPFS was established in 1986, when 51,529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 years completed a mailed questionnaire about their medical history and lifestyle. Follow-up questionnaires were mailed to participants every 2 years to update information on potential risk factors and to ascertain newly diagnosed diseases.

In 2004, 34,884 men responded to the 2004 questionnaire, which included questions about insomnia. We excluded men with a cancer diagnosis (other than non-melanoma skin cancer, $n=7590$) to reduce the potential for an effect of disease on insomnia symptoms, and men with missing values for insomnia questions ($n=3847$), leaving 23,447 men for this analysis.

Assessment of insomnia symptoms

In 2004, the participants in HPFS were asked how often (rarely/never, sometimes or most of the time) they: (1) “have difficulty falling asleep” (referred to as “difficulty initiating sleep” in the manuscript), (2) “have trouble with waking up during the night” (referred to as “difficulty maintaining sleep”), (3) “are troubled by waking up too early and not being able to fall asleep again” (referred to as “early-morning awakenings”), and (4) “feel really rested when waking up in the morning” (we code non-restorative sleep frequency as the opposite of feeling rested when waking up in the morning (referred to “non-restorative sleep”). Excessive daytime sleepiness was also assessed in 2004 with a question of “get so sleepy during the day or the evening that have to take a nap”.

In addition to individual insomnia symptoms described above, we defined insomnia disorder as the combination of a nocturnal insomnia symptom and a resulting consequence, in two ways: having one or more of the three nocturnal insomnia symptoms (difficulty initiating sleep,

difficulty maintaining sleep, and early morning awakenings), accompanied by 1) non-restorative sleep (“insomnia disorder A”); and 2) excessive daytime sleepiness (“insomnia disorder B”).

Ascertainment of deaths

Deaths were identified from state vital statistics records, the National Death Index, reported by the families, and the postal system²⁸. The follow-up for death in the HPFS was at least 98% complete. Cause of death was identified from death certificates or review of medical records. In the current analysis, we evaluated all-cause mortality, and also death from cardiovascular diseases (CVD) (International Classification of Diseases, eighth revision (ICD-8) codes 390 through 458), cancer (ICD-8 codes 140 through 207), and other conditions.

Assessment of other covariates

Information on potential confounders, such as age, ethnicity, smoking status, weight, height, physical activity, marriage status, living status, medication use (e.g., aspirin, antidepressant, tranquilizers, melatonin and antihypertensive drugs), and history of major chronic conditions {e.g., elevated total cholesterol, elevated triglyceride, hypertension, diabetes, myocardial infarction, stroke, and lower urinary tract symptoms(LUTS)²⁹} was collected via biennial questionnaires. Information on sleep duration and snoring frequency was collected in the 2000 questionnaire. Information on food and alcohol consumption was collected every four years via a validated semi-quantitative food frequency questionnaire³⁰.

Body mass index (BMI) was calculated as weight (kg)/height (m)². High blood pressure was considered as either professionally diagnosed hypertension or use of antihypertensive medications. A participant was considered as having depression symptoms if he reported “sad, blue or depressed” for two weeks or longer in the past two years or regular use of antidepressant medications. The phobic anxiety status was assessed by the Crown-Crisp phobia index³¹.

Information on LUTS was collected based on the American Urological Association symptom index (AUASI) (29). Diet quality was assessed by the Alternate Healthy Eating Index (AHEI), which is associated with a lower risk of major chronic diseases and death in this cohort³².

Statistical analyses

We used Cox proportional hazard models to calculate the hazard ratios (HRs) of mortality and their 95% confidence intervals (CIs), across categories of each insomnia symptom. For tests of trend, we assigned a numeric value of 0 to 2 to the insomnia categories (0: rarely/never have insomnia complaint; 1: sometimes; 2: most of the time) and treated it as a continuous variable.

In addition to an age-adjusted model, we also ran two multivariable adjusted models. In the first model, we simultaneously adjusted for the known risk factors of mortality, except for presence of chronic conditions and sleep related variables, because they are possible biologic intermediates in the relationship between insomnia symptoms and total mortality. The adjusted covariates in the multivariable model 1 included: age, ethnicity, smoking status, alcohol drinking, BMI, physical activity, alternate healthy eating index, marriage status, and living status. The second model further included regular use of aspirin, the Crown-Crisp phobic anxiety index, LUTS, presence of chronic conditions, use of medications, sleep duration and snoring frequency. Time-varying covariates were used to reflect the most recent information, except for ethnicity, sleep duration and snoring frequency. If data were missing at a given time point, the last observation was carried forward for 1 cycle. We also did secondary analyses by using baseline covariates in the models.

We examined the joint effect on total mortality of difficulty initiating sleep with non-restorative sleep and excessive daytime sleepiness, separately. Because insomnia could result in depression symptoms¹², we also tested the joint effect between difficulty initiating sleep and

depression. We tested the interaction by comparing the -2 log likelihood of the models with and without interaction term. To minimize potential residual confounding due to co-morbidities of insomnia, we conducted sensitivity analyses excluding men with prevalent cardiovascular disease, and then further excluding frequent snoring (snoring every night or most night), diabetes and Parkinson's disease at baseline. We conducted another sensitivity analysis by excluding men who reported tranquilizer use (e.g., valium and xanax) or melatonin, two groups of commonly used hypnotic medications, through the end of follow-up, because benzodiazepines can cause several adverse effects³³ and thus bias the observed insomnia-mortality relationship.

Finally, we conducted a meta-analysis to combine our study with previously published studies on insomnia symptoms and total and CVD mortality. Relevant studies were identified through searches of PubMed using the keywords of (insomnia OR sleep complaints OR difficulty falling asleep OR difficulty initiating sleep OR waking up at night OR waking up early OR early-morning awakening OR difficulty maintaining sleep OR non-restorative sleep OR no restorative sleep) AND (dead OR death OR mortality OR survival) for all published studies in English by July 31th, 2013. In addition, the reference lists from the relevant publications were used to identify additional studies. We focused on individual insomnia symptoms in the meta-analysis because there was no universal definition of insomnia across previous studies¹⁶⁻²⁷. In this meta-analysis, we did not include the studies 1) that reported the association between insomnia and mortality but did not provide results regarding individual insomnia symptoms; 2) that reported association but did not provide relative risk value; or 3) that did not include control individuals assessed in the same study. We identified 9 studies^{8,20-27} which met our criteria for the meta-analysis (**Supplemental Table 1**). We used the Q statistic to examine heterogeneity among the studies. We used random-effects models to calculate the pooled HR because a significant

heterogeneity ($P < 0.1$) was observed. Publication bias was assessed using the Begg's test.

We used the SAS statistical package (version 9; SAS Institute, Cary, NC) for the cohort analyses, and STATA (version 9.0; College Station, TX) for the meta-analysis.

Results

Basic characteristics

In this cohort, 4.1%, 25.2%, 7.7%, 6.2% and 11.1% of men reported difficulty initiating sleep, difficulty maintaining sleep, early-morning awakenings, non-restorative sleep or excessive daytime sleepiness most of the time at baseline, respectively. The characteristics of the study population according to difficulty initiating sleep were presented in **Table 1**. The other three insomnia symptoms showed similar associations to these characteristics (data not shown). In general, insomnia symptoms were associated with lower physical activity, a higher BMI, and a higher prevalence of depression symptoms, hypertension, elevated total cholesterol, elevated triglycerides, diabetes, myocardial infarction and stroke.

Insomnia symptoms and total mortality

We documented 2025 deaths during 6 years of follow-up (127, 768 person years). Men with difficulty initiating sleep and non-restorative sleep had an increased risk of total mortality compared to men without those symptoms in a dose-dependent manner (**Table 2**), which was independent of a variety of risk factors for mortality. In the fully adjusted models, the HRs (95% CIs) of total mortality were 1.25 (95% CI: 1.04-1.50) for men with difficulty initiating sleep most of the time and 1.24 (1.05-1.46) for men with non-restorative sleep most of the time, compared to those without those symptoms (P -trend < 0.03 for both). We found no significant associations between difficulty maintaining sleep or early-morning awakenings and total mortality (**Table 2**).

Similarly, excessive daytime sleepiness was also significantly associated with total mortality; the multivariable-adjusted HR comparing the two extreme categories of this symptom was 1.24 (95% CI: 1.09-1.42; *P-trend*=0.0006). The associations between the insomnia symptoms and mortality did not materially change after further adjustment for use of tranquilizers or excessive daytime sleepiness (data not shown).

The multivariable-adjusted HR of total mortality was 1.13 (95% CI: 1.03-1.25) for the insomnia disorder A, defined as having any of the three nocturnal insomnia symptoms accompanied by non-restorative sleep, and 1.13 (1.03-1.24) for the insomnia disorder B defined as having any of the three nocturnal symptoms accompanied by excessive daytime sleepiness.

We also observed that men with both difficulty initiating sleep and non-restorative sleep (**Figure 1A**) or both difficulty initiating sleep and excessive daytime sleepiness (**Figure 1B**) had the highest risk of total mortality compared to those without these symptoms. A similar pattern was observed for the combination of difficulty initiating sleep and depression symptoms (**Figure 1C**).

Insomnia and cause-specific mortality

Men with difficulty initiating sleep and non-restorative sleep most of the time had a 55% (HR: 1.55; 95% CI: 1.19-2.04; *P-trend*= 0.01) and 32% (HR: 1.32; 95% CI: 1.02-1.72; *P-trend*=0.002) increased risk of CVD mortality, respectively, relative to men without those symptoms (**Table 3**). We did not observe significant associations between insomnia symptoms and mortality due to cancer or other causes, but these results were limited to rapidly fatal cancer, as those with prevalent cancer were excluded at baseline.

Sensitivity analyses:

After we excluded men with prevalent cardiovascular diseases at baseline, the

multivariable-adjusted HRs were 1.25 (95% CI: 0.99-1.56; P-trend=0.02) for total mortality and 1.45 (95% CI: 1.02-2.06; P-trend=0.04) for CVD mortality, comparing men with difficulty initiating sleep most of the time to those without this symptom. The multivariable-adjusted HRs among men with non-restorative sleep most of the time were 1.26 (95% CI: 1.04-1.54; P-trend=0.02) for total mortality and 1.37 (95% CI: 0.98-1.91; P-trend=0.005) for CVD mortality. The significant associations between difficulty initiating sleep, non-restorative sleep and total mortality were basically unchanged even after we further excluded participants with frequent snoring, diabetes and Parkinson's disease, or when we used covariates at baseline in the models (P trend<0.05 for both). Because a previous study¹⁹ suggested that a short sleep duration insomnia (<6 hours) was associated with increased mortality risk, we also treated the covariate of sleep duration as a binary variable (<6 versus ≥6 hours) and obtained similar results (data not shown). After we excluded participants who used tranquilizers or melatonin through the follow-up, the adjusted HRs comparing the two extreme categories were 1.34 (95% CI: 1.09-1.66; P-trend=0.02) for difficulty initiating sleep and 1.21 (95% CI: 1.01-1.45; P-trend=0.01) for non-restorative sleep.

Meta-analysis

We pooled the present study and 9 other published studies^{8,20-27} that evaluated the associations between individual insomnia symptoms and total mortality. The pooled HRs of total mortality were 1.14 (95%CI: 1.04-1.24) for difficulty initiating sleep, 1.08 (95%CI: 0.96-1.22) for difficulty maintaining sleep, 1.00 (95%CI: 0.94-1.06) for early-morning awakenings, and 1.17 (95%CI: 1.01-1.36) for non-restorative sleep, relative to individuals without those symptoms (**Figure 2**). The results did not change materially after excluding two studies^{21,23} with low quality score (**Supplemental Table 1**) based on Newcastle-Ottawa Quality Assessment Scale (**Figure 2**). We

also conducted a meta-analysis using data from present study and five published studies^{22,25-27,34} that examined the associations between insomnia symptoms and CVD mortality. The pooled HR of CVD mortality was 1.45 (95% CI: 1.09-1.93) for difficulty initiating sleep, 1.03 (95% CI: 0.89-1.17) for difficulty maintaining sleep, and 1.00 (95% CI: 0.89-1.13) for early-morning awakenings (**Figure 3**). However, the association between non-restorative sleep and CVD mortality was not examined previously. Further excluding the present prospective study from the meta-analyses did not change the pooled results between insomnia and total/CVD mortality materially (**Supplemental Figure 1** and **Supplemental Figure 2**).

Discussion

In this large prospective cohort, we observed that men with difficulty initiating sleep and those with non-restorative sleep had a modest but significantly increased and dose-dependent risk of total mortality compared to men without those symptoms. The increased risk was independent of a variety of risk factors for mortality including lifestyle factors and presence of several medical morbidities.

Normal sleep continuity is considered to be important for the maintenance of cardiovascular, metabolic and immune function, physiological homeostasis and psychological balance^{35,36}. Suboptimal sleep disturbs both circadian rhythms and other physiological systems^{35,36}. Sleep disturbance has been shown to adversely influence metabolism and endocrine function similar to the effects of premature aging³⁷, including reducing endogenous testosterone levels³⁸, altering the hypothalamic pituitary adrenal axis³⁹, and elevating markers of chronic inflammation³⁵. Insomnia has also been associated with incident depression¹², a risk factor for cardiovascular morbidity and mortality⁴⁰. Thus, insomnia may increase mortality risk through

effects on several biological pathways. This notion has been supported by a study conducted by Dew and colleagues¹⁶, who assessed sleep status of 184 healthy older adults via polysomnography. They found that insomnia symptoms, such as difficulty falling asleep and poor sleep efficiency, were associated with an almost doubled risk of all-cause mortality (n=66) during 12 years of follow-up¹⁶. The current study with a much larger sample size and the meta-analysis further confirmed that observation. In the present study, we controlled for multiple confounders using updated information on lifestyle risk factors and common chronic diseases over the course of follow-up. In addition, we conducted a sensitivity analysis by excluding the participants with CVD and depression, and found that the association between insomnia symptoms and mortality was basically unchanged. Though the possibility of residual confounding cannot be completely excluded, our study, together with the previous studies^{14,41} suggests that chronic disorders cannot totally explain the observed association between insomnia symptoms and total mortality. It is thus likely that sleep disturbances characterized by insomnia symptoms represent novel risk factors for mortality.

Several epidemiological studies have found significant associations between insomnia and CVD intermediate markers and risk factors, such as carotid intima-media thickness⁴²; cardiorespiratory fitness⁴³, and Framingham risk score⁴⁴. Difficulty initiating sleep was associated with 20-year incidence of myocardial infarction or coronary death among women in the Framingham Study³⁴. Trouble initiating sleep, but not difficulty maintaining sleep or early-morning awakenings, was reported to be associated with a higher risk of CVD mortality in a cohort of middle-aged Swedish men²², the Piedmont Health Survey^{15,45} and the Malmo Preventive study²⁵. Difficulty initiating sleep also appeared to have the strongest and the most robust association with acute myocardial infarction¹⁴. Biologically, it is plausible that prolonged sleep

latency or reduced sleep maintenance have different effects on sleep stage distribution and associated neurohormonal activities^{16,46}. Further, delayed sleep could also lead to alterations in circadian rhythms⁴⁷, which are important for cardiovascular disease pathogenesis. Most previous epidemiological studies focused on three nocturnal insomnia symptoms: difficulty initiating sleep, difficulty maintaining sleep and early-morning awakenings^{20,21,23,26,27}. Non-restorative sleep, another important component of insomnia, is included in criteria of insomnia recommended by NIH¹, DSM-IV⁴⁸ and ICSD-II⁴⁹, but few studies have addressed its potential effects on mortality^{8,24}, because there is controversy as to whether individuals with this complaint share similar pathophysiologic mechanisms with the other nocturnal symptoms. The finding of the present cohort study and meta-analysis indicates an increased higher risk of total mortality among people with non-restorative sleep. Excessive daytime sleepiness has also been increasingly recognized as a major health hazard and has been linked to an increased risk of all-cause mortality^{8,23}. In the Cardiovascular Health Study, women with excessive daytime sleepiness and frequent nighttime awakenings were more likely to develop congestive heart failure²³. In the present study, men with the combination of difficulty initiating sleep and excessive daytime sleepiness most of the time were the most prone to total mortality. As we did not find a significant interaction on risk of mortality, it was more likely that both symptoms were independently associated with mortality.

The strengths of our study include a relatively large sample size, with a sufficient number of cases to explore the CVD and cancer-specific mortality, and detailed and repeated assessments of life style risk factors and common chronic diseases over the course of follow-up. Another important strength is the high follow-up rate. In each 2- or 4-year cycle of the HPFS survey, follow-up rates have averaged 94 percent. The follow-up for death in the HPFS is at least 98%

completed.

Our study has several potential limitations. First, assessment of insomnia symptoms was based on self-report, and objective measures of sleep quality were not available in our cohort. Such perceived symptoms may reflect a negative self-view or early onset of depression, and the latter is associated with mortality⁴⁰. Though we adjusted for depressed mood and use of antidepressants in the main analyses, we still could not totally rule out the confounding effects due to depression. Likewise, we employed frequent snoring as surrogate measure of obstructive sleep apnea (OSA). Frequent snoring has been shown to correlate closely with OSA in men and has been used as a surrogate of OSA in previous epidemiological studies⁵⁰, though misclassification is inevitably introduced. To minimize the residual confounding effects due to imperfect measure of OSA, we excluded men with frequent snoring, and other common chronic disorders in the sensitivity analysis and generated similar results. Second, we did not ask a specific question in the HPFS regarding use of hypnotic drugs, except for benzodiazepine and melatonin, until 2008. Previous studies suggested that hypnotics were associated with several adverse health outcomes, including dementia and mortality³³. However, the observed association between insomnia symptoms and mortality did not materially change after excluding men using benzodiazepine or melatonin. Further excluding those who reported hypnotic drugs in 2008 also did not change our results (data not shown). It is worth noting that if the observed associations were due to hypnotic medication use, rather than insomnia per se, we would expect to observe similar associations for all individual insomnia symptoms. However, in our cohort study and the meta-analysis, the significant associations were consistently observed only in some, but not all insomnia symptoms. In this context, although we cannot rule out the possibility of residual confounding due to hypnotic drug use, the effects are likely to be modest. Another limitation was that this cohort

included mostly Caucasian men, thus these findings might not be generalizable to female or nonwhite male populations. However, in the meta-analysis including populations with diverse social and economic backgrounds, we observed similar patterns between different insomnia symptoms and mortality. It is also worth noting that only 9 published studies were included in the meta-analyses, which precludes use to conduct subgroup analysis to explore potential sources of the observed heterogeneity across studies, suggesting further works in this area should be a priority.

In conclusion, this large prospective cohort study indicates that difficulty initiating sleep and non-restorative sleep are associated with a modestly higher risk of total and CVD specific mortality and these associations persisted even after we excluded participants with cardiovascular diseases and depression. These observations were supported by our concurrent meta-analysis including results of the present study and nine previously published studies. Future research in this field is warranted, especially the long-term epidemiological studies about the association between individual insomnia symptoms and mortality, and experimental and clinical studies probing mechanisms underlying the insomnia-mortality associations. Although future studies are still needed before a firm conclusion can be reached, our study provides consistent evidence that insomnia symptoms may be an important modifiable risk factor affecting longevity.

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Table 1. Baseline characteristics of participants according to difficulty initiating sleep *

	Difficulty Initiating Sleep		
	Rarely or never	Sometimes	Most of the time
Participants (n)	16811	5666	970
Percentage, %	71.7	24.2	4.1
Age, years	68.5	68.6	68.7
Body mass index, kg/m ²	26.1	26.3	26.6
Caucasian, %	96.6	95.3	96.0
Marriage status (married), %	88.6	86.2	84.6
Living alone, %	8.3	10.5	11.7
Past smokers, %	53.3	55.1	55.0
Current smoker, %	3.3	3.9	3.9
Alcohol, g/day	13.4	12.4	11.6
Physical activity, MET-h/week	47.2	42.8	37.9
Alternate Healthy Eating Index	51.6	50.9	50.2
Use of aspirin, %	59.8	62.3	60.1
Use of Valium or other tranquilizers, %	3.6	8.3	18.0
Use of melatonin	2.8	5.1	11.0
Sleep duration (hours/day)	7.1	6.9	6.5
Frequent snoring, %	35.0	34.1	35.3
Phobic Anxiety Index	1.9	2.2	2.4
Lower Urinary Tract Symptoms Score	5.0	6.0	7.2
Depression symptoms, % [†]	7.9	16.1	30.5
Elevated cholesterol, %	58.6	63.0	70.3
Elevated triglycerides, %	41.0	47.5	56.3
High blood pressure, % [‡]	53.8	58.2	68.0
Diabetes, %	9.1	10.7	14.7
Myocardial infarction, %	8.7	10.8	12.7
Stroke, %	2.8	3.4	3.6

Abbreviation: MET, metabolic equivalents from recreational and leisure-time activities.

* Values are means or percentages and are standardized to the age distribution of the study population except age.

[†] Depression symptom was defined as use of antidepressant medications or feel blue, sad or depressed

[‡] High blood pressure was considered as either hypertension or use of antihypertensive medications.

Table 2. Hazard ratio of mortality according to insomnia symptoms

Insomnia symptoms	Death /Person years	Hazard Ratio (95% Confidence Interval)		
		Model 1*	Model 2†	Model 3‡
Difficulty initiating sleep				
Rarely or never	1285/91 993	Reference	Reference	Reference
Sometimes	594/30 661	1.11(1.00-1.22)	1.06(0.96-1.17)	1.05(0.95-1.17)
Most of the time	146/5114	1.41(1.19-1.68)	1.27(1.07-1.52)	1.25(1.04-1.50)
<i>P</i> for trend		0.0001	0.01	0.03
Yes <i>versus</i> No§		1.15(1.05-1.26)	1.09(1.00-1.20)	1.08(0.99-1.19)
Difficulty maintaining sleep				
Rarely or never	542/38 183	Reference	Reference	Reference
Sometimes	878/57 573	0.99(0.89-1.10)	1.06(0.96-1.19)	1.08(0.97-1.21)
Most of the time	605/32 012	1.02(0.91-1.14)	1.09(0.97-1.23)	1.09(0.97-1.24)
<i>P</i> for trend		0.76	0.15	0.15
Yes <i>versus</i> No§		1.00(0.91-1.11)	1.07(0.97-1.19)	1.09(0.98-1.20)
Early-morning awakenings				
Rarely or never	1006/63 318	Reference	Reference	Reference
Sometimes	840/54 747	0.92(0.83-1.00)	0.96(0.87-1.05)	0.96(0.88-1.06)
Most of the time	179/9703	1.00(0.85-1.17)	1.02(0.87-1.20)	1.04(0.88-1.22)
<i>P</i> for trend		0.30	0.73	0.87
Yes <i>versus</i> No§		0.93(0.85-1.01)	0.97(0.89-1.06)	0.97(0.89-1.07)
Non-restorative sleep				
Rarely or never	1326/90 340	Reference	Reference	Reference
Sometimes	519/29 665	1.24(1.12-1.37)	1.13(1.02-1.25)	1.09(0.98-1.21)
Most of the time	180/7763	1.54(1.32-1.80)	1.35(1.15-1.58)	1.24(1.05-1.46)
<i>P</i> for trend		<0.0001	<0.0001	0.006
Yes <i>versus</i> No§		1.31(1.19-1.43)	1.18(1.07-1.29)	1.12(1.02-1.24)

* Model 1 adjusted for age;

† Model 2: model 1 plus ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker), alcohol drinking (g/d: 0, 0.1-9.9, 10.0-19.9, 20.0-29.9, and ≥ 30), body mass index (kg/m^2 : <23, 23-24.9, 25-26.0, 27-29.9, ≥ 30), physical activity (quintiles), alternate healthy eating index (quintile), marriage status (married, divorced/separate/single, widowed); living status (alone or not);‡ Model 3: model 2 plus regular use of aspirin (yes/no), the Crown-Crisp phobic anxiety index (0-1,2,3 or >3), lower urinary tract symptoms (0-6, 7-14, ≥ 15), feel sad, blue or depressed two more weeks (yes/no), use of antidepressant drugs (yes/no), presence of elevated total cholesterol, high blood pressure, elevated triglyceride, diabetes, myocardial infarction and stroke (each yes *vs.* no), sleep duration (hours: ≤ 5 , 6, 7, 8, ≥ 9), and snoring frequency (every night, most night, few night per week, occasionally, once a week or less, missing).§ Yes *versus* No: having the insomnia symptom sometimes or most of the time versus rarely/never.

Table 3. Risk of cause-specific mortality according to insomnia symptoms*

Insomnia symptoms	CVD mortality (case #=741)	Cancer mortality (case #=493)	Others (case #=791)
Difficulty initiating sleep			
Rarely or never	Reference	Reference	Reference
Sometimes	1.06(0.89-1.25)	0.96(0.78-1.19)	1.11(0.95-1.30)
Most of the time	1.55(1.19-2.04)	1.04(0.69-1.58)	1.02(0.75-1.40)
<i>P</i> for trend	0.01	0.90	0.38
Difficulty maintaining sleep			
Rarely or never	Reference	Reference	Reference
Sometimes	1.02(0.85-1.22)	1.20(0.96-1.50)	1.05(0.88-1.25)
Most of the time	0.99(0.81-1.21)	1.12(0.87-1.44)	1.12(0.92-1.36)
<i>P</i> for trend	0.94	0.37	0.26
Early-morning awakenings			
Rarely or never	Reference	Reference	Reference
Sometimes	1.04(0.89-1.21)	0.96(0.79-1.15)	0.91(0.78-1.05)
Most of the time	1.09(0.83-1.43)	1.08(0.77-1.51)	0.97(0.74-1.27)
<i>P</i> for trend	0.49	0.99	0.39
Non-restorative sleep			
Rarely or never	Reference	Reference	Reference
Sometimes	1.32(1.12-1.57)	0.88(0.70-1.10)	1.02(0.86-1.21)
Most of the time	1.32(1.02-1.72)	1.14(0.80-1.61)	1.16(0.89-1.50)
<i>P</i> for trend	0.002	0.92	0.35

*Adjusted for age, ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker), alcohol drinking (g/d: 0, 0.1-9.9, 10.0-19.9, 20.0-29.9, and ≥ 30), body mass index (kg/m^2 : <23, 23-24.9, 25-26.0, 27-29.9, ≥ 30), physical activity (quintiles), alternate healthy eating index (quintile), marriage status (married, divorced/separate/single, widowed); living status (alone or not), regular use of aspirin (yes/no), the Crown-Crisp phobic anxiety index (0-1,2,3 or >3), lower urinary tract symptoms (0-6, 7-14, ≥ 15), feel sad, blue or depressed two more weeks (yes/no), use of antidepressant drugs (yes/no), presence of elevated total cholesterol, high blood pressure, elevated triglyceride, diabetes, myocardial infarction and stroke (each yes vs. no), sleep duration (hours: ≤ 5 , 6, 7, 8, ≥ 9), snoring frequency (every night, most night, few night per week, occasionally, once a week or less, missing).

Figure Legends:

Figure 1. Hazard ratio of total mortality according to the joint classification of difficulty initiating sleep with non-restorative sleep (A), excessive daytime sleepiness (B) and Depression symptoms (C) ^{*,†,‡,§}. *Up to six years of follow-up (2004-2010) of the Health Professionals Follow-up

Study; †Multivariable adjusted hazard ratio estimated from Cox proportional hazards models adjusted for age, ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker), alcohol drinking (g/d: 0, 0.1-9.9, 10.0-19.9, 20.0-29.9, and ≥ 30), body mass index (kg/m²: <23, 23-24.9, 25-26.0, 27-29.9, ≥ 30), physical activity (quintiles), alternate healthy eating index (quintile), marriage status (married, divorced/separate/single, widowed); living status (alone or not), regular use of aspirin (yes/no), the Crown-Crisp phobic anxiety index (0-1,2,3 or >3), lower urinary tract symptoms (0-6, 7-14, ≥ 15), presence of elevated total cholesterol, high blood pressure, elevated triglyceride, diabetes, myocardial infarction and stroke (each yes vs. no), sleep duration (hours: ≤ 5 , 6, 7, 8, ≥ 9), snoring frequency (every night, most night, few night per week, occasionally, once a week or less, missing); feel sad, blue or depressed two more weeks, use of antidepressant drugs, non-restorative sleep and excessive daytime sleepiness, except the joint variable. ‡P for interaction was 0.98 for difficulty initiating sleep and non-restorative sleep (A), 0.96 for difficulty initiating sleep and excessive daytime sleepiness (B), and 0.72 for difficulty initiating sleep and depression symptom (C), tested by comparing the -2 log likelihood of the model including interaction term with the model that contained only the main effects.

Figure 2. Meta-analysis of the association between individual insomnia symptoms and total mortality^{*,†,‡}. *Publication bias are estimated by the Begg's test, all $P > 0.4$; †The name of the study and full list of covariates each study adjusted for were listed in Supplemental Table 1; ‡Pooled, Total = pooled relative risk for all studies listed in the Figure; Pooled sensitivity = pooled relative risk for studies excluded the two studies, e.g. Althuis, 1998 (21) and Newman, 2000 (23), with the Newcastle-Ottawa Quality Score <7 (Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos

M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at:

http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed August 8, 2013.).

Figure 3. Meta-analysis of the association between individual insomnia symptoms and cardiovascular mortality (publication bias are estimated by the Begg's test, all $P > 0.4$, there is no other published data of non-restorative sleep and cardiovascular mortality).



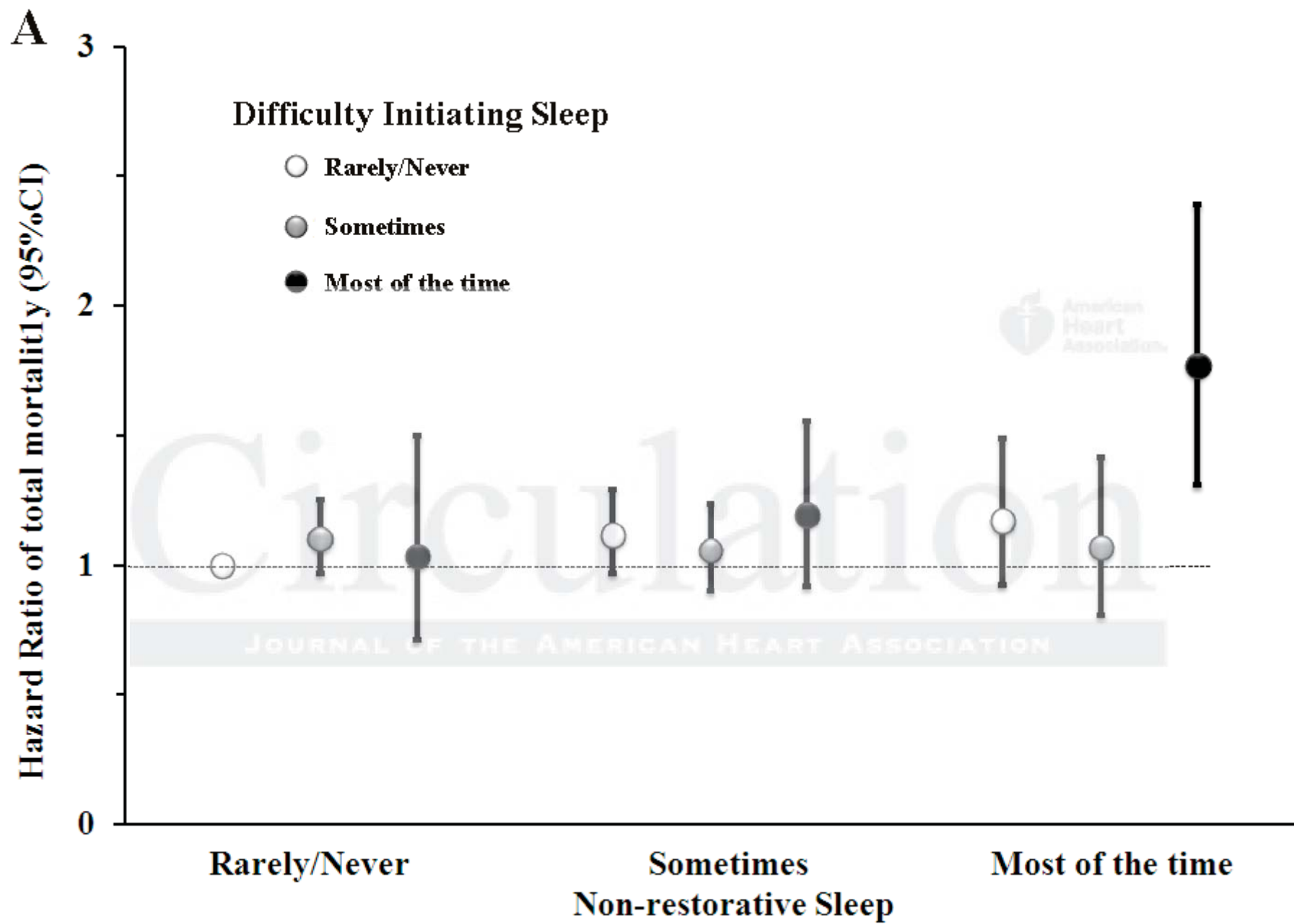


Figure 1A

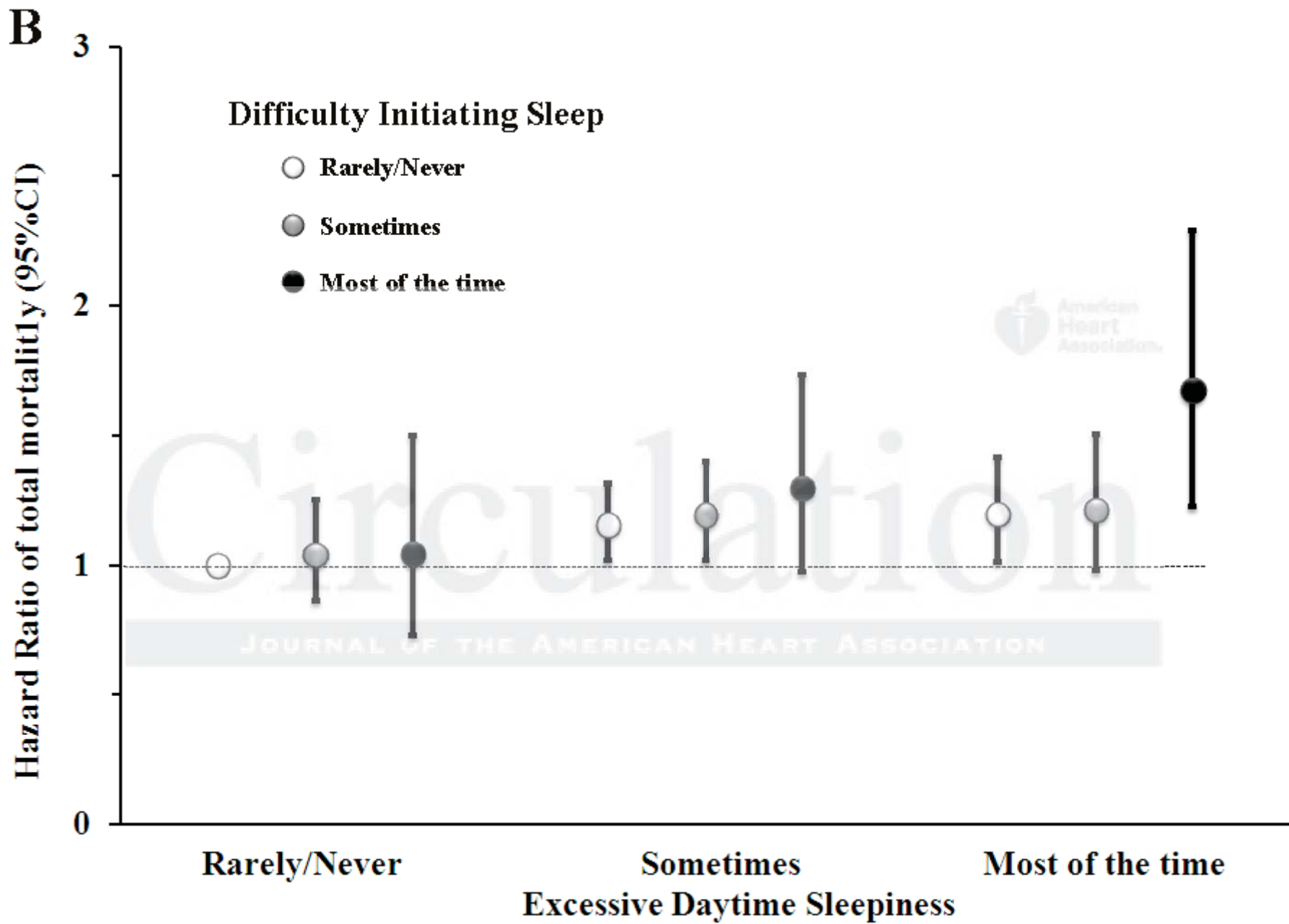


Figure 1B

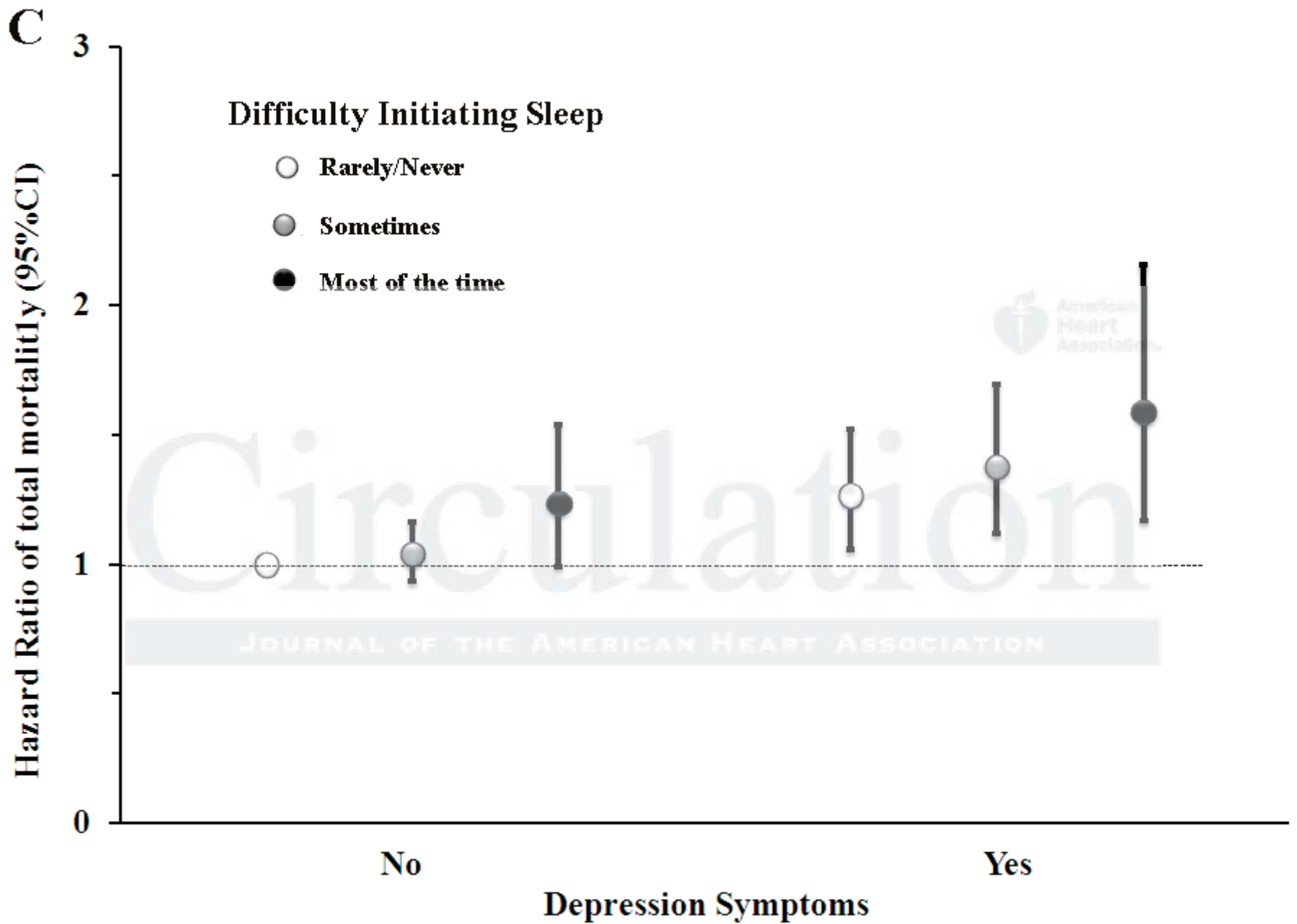


Figure 1C

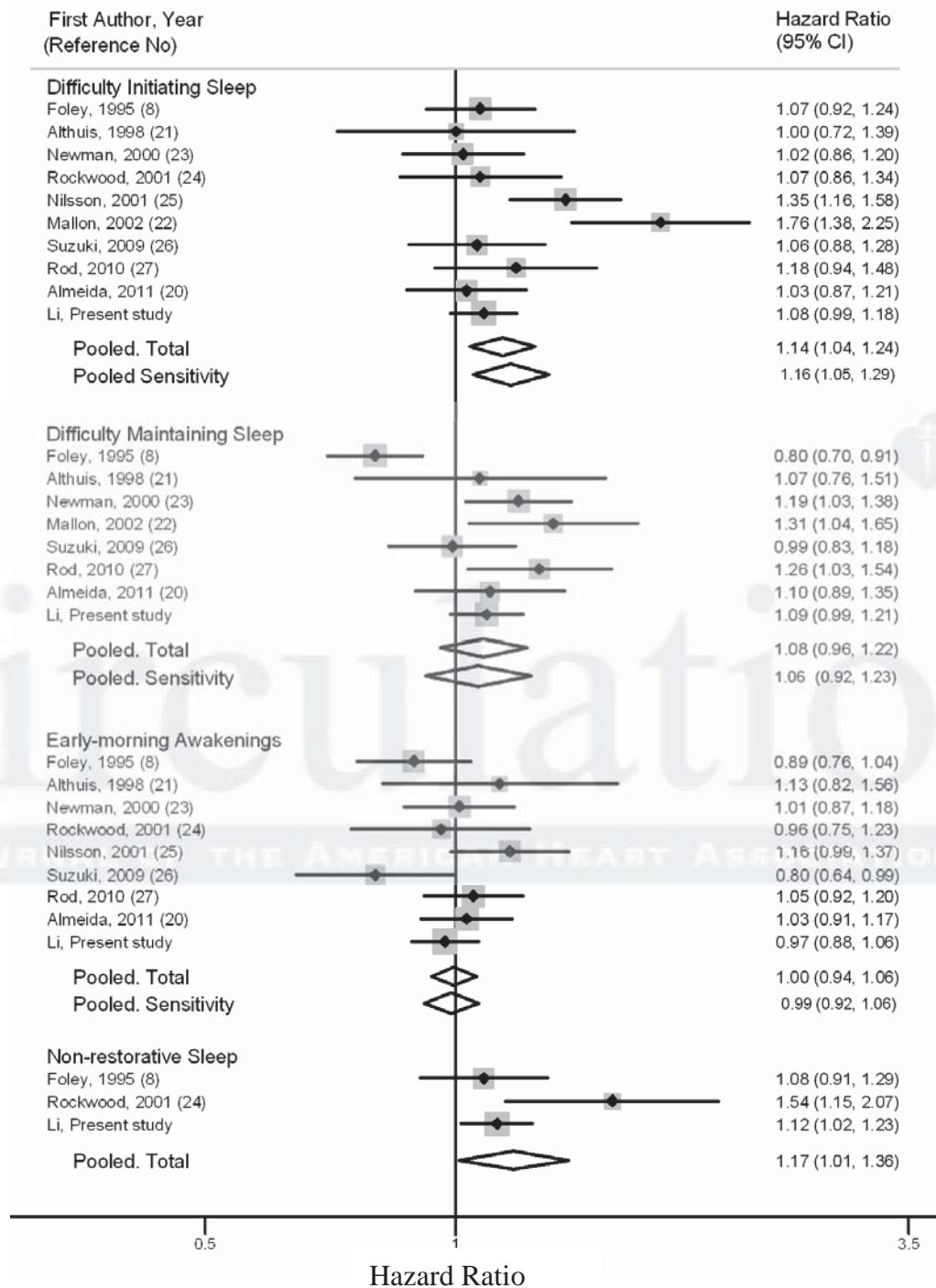


Figure 2

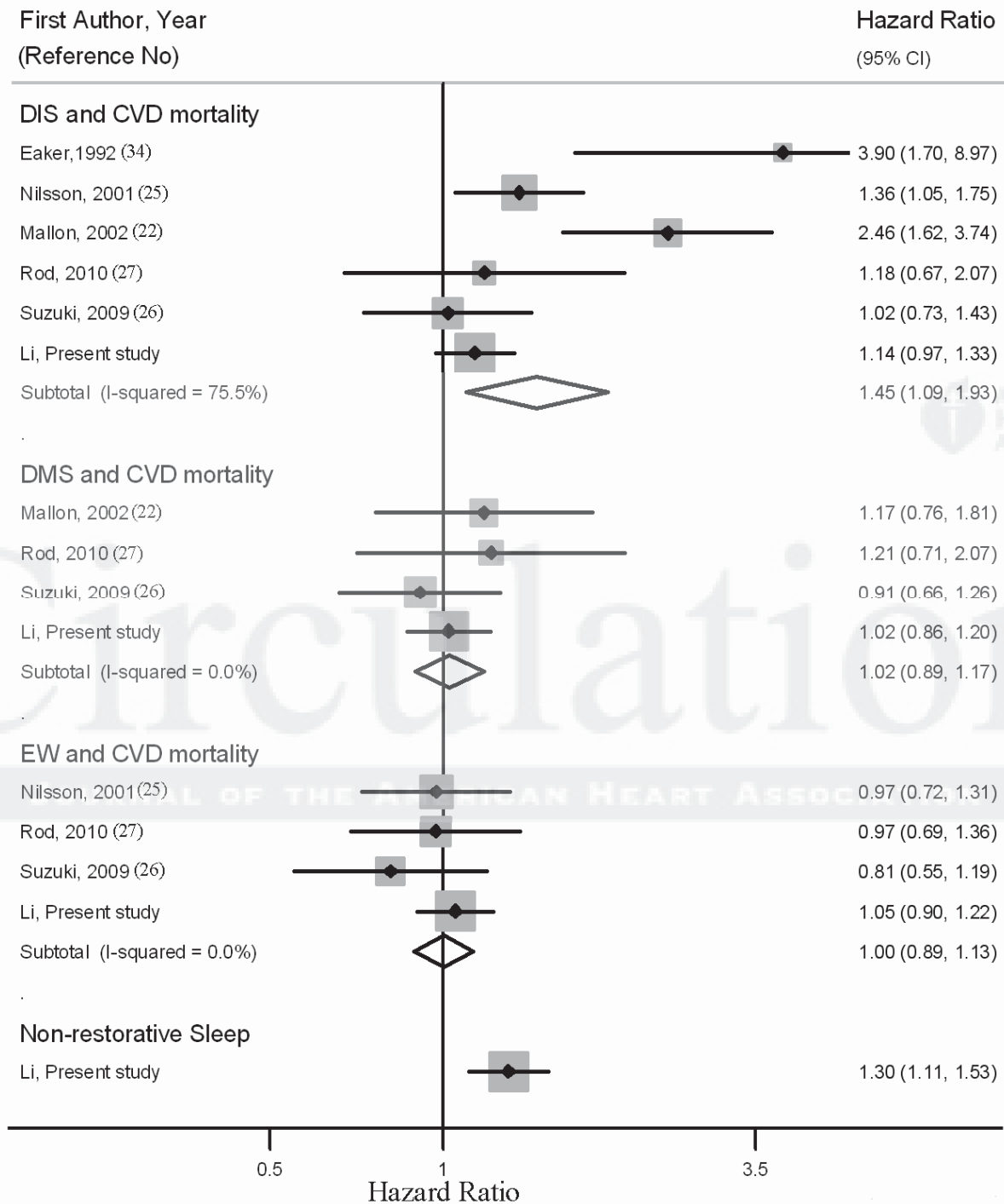


Figure 3