

# Association Between Insomnia And Mortality Is Only Evident Among Long Sleepers

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**Background:** Previous studies investigating the relationship between insomnia and mortality have been inconsistent.

**Purpose:** We aimed to assess whether nocturnal insomnia symptoms and non-restorative sleep are associated with all-cause mortality and whether they modify the associations between short and long sleep duration and all-cause mortality.

**Patients and methods:** The present report is based on a prospective cohort study of 39,139 participants with a mean follow-up time of 19.6 years. Cox proportional hazard models with attained age as timescale were used to estimate overall mortality hazard ratios (HRs) with 95% confidence intervals (CI) for different categories of sleep duration and insomnia symptoms.

**Results:** Both difficulty initiating sleep and daytime sleepiness were independently associated with increased mortality among those with sleep duration of 9 hrs or more (HR 1.51, 95% CI 1.11–2.07 and HR 1.37, 95% CI 1.03–1.82). Mortality increased with increasing severity of difficulties initiating sleep (p for trend 0.04) and daytime sleepiness (p for trend 0.01) among the long sleepers. None of the insomnia symptoms were associated with mortality among those who reported sleep duration of 8 hrs or less.

**Conclusion:** Long sleep in combination with difficulties initiating sleep and daytime sleepiness, possibly due to psychiatric or physical disorders, was thus associated with increased mortality, whereas long sleep without difficulties falling asleep or daytime sleepiness was not associated with mortality. Our study emphasizes the need to take nocturnal insomnia symptoms and daytime sleepiness into consideration when assessing the influence of sleep duration on mortality. Additional research is needed to elucidate the relationship between long sleep, insomnia and related psychiatric and physical disorders.

**Keywords:** prospective cohort study, sleep quality, sleep duration

## Introduction

A large number of studies on sleep duration and mortality have reported a significant increase in overall mortality for individuals with habitual short and long sleep duration.<sup>1–4</sup> Possible mechanisms linking sleep duration to increased mortality risk include endocrine and metabolic abnormalities, systemic inflammation, underlying disease processes and psychiatric conditions.<sup>1</sup>

Insomnia, the most common sleep disorder, is characterized by difficulty initiating sleep, difficulty maintaining sleep, early-morning awakenings, or by non-restorative sleep.<sup>5</sup> Insomnia often precedes the development of psychiatric disorders such as depression and anxiety, and the co-morbidity of these disorders has been proposed to increase the risk of mortality in those with insomnia.<sup>6</sup> Evidence also

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suggests that insomnia is associated with inflammatory processes<sup>7</sup> and cardio-metabolic outcomes such as hypertension and diabetes.<sup>8,9</sup> However, studies investigating the relationship between insomnia and mortality have been inconsistent. In several studies, difficulty initiating sleep, but not difficulty maintaining sleep or early-morning awakenings, has been associated with increased mortality,<sup>10,11</sup> and it has been suggested that delayed sleep could lead to alterations in circadian rhythms which are important for CVD pathogenesis. A pooled analysis of 10 studies that evaluated the association between insomnia and total mortality found that individuals who reported difficulty initiating sleep or non-restorative sleep had an increased and dose-dependent risk of all-cause mortality compared to individuals without these symptoms,<sup>12</sup> whereas a recent meta-analysis of 17 studies investigating the relationship between insomnia and mortality found no association.<sup>13</sup> Lovato and Lack conclude from their meta-analysis that there is a need for studies which combine sleep duration and insomnia symptoms.<sup>14</sup> They also point out the need for longer follow-up times (than the mean follow-up duration of 11.6 years in their meta-analysis), and for consideration of daytime symptoms combined with sleep symptoms. Using a large Swedish cohort with a mean follow-up time of 19.6 years, we aimed to assess whether nocturnal insomnia symptoms and non-restorative sleep are associated with all-cause mortality and whether they modify the associations between short and long sleep duration and all-cause mortality.

## Methods

The Swedish National March Cohort (SNMC) is a prospective cohort study designed to investigate associations between lifestyle factors and chronic diseases. The study was established in September 1997 during a 4-day national fundraising event for the Swedish Cancer Society. All participants were invited to fill out a questionnaire regarding demographic, lifestyle and medical information. They also provided their national registration number, a unique identifier assigned to all Swedish residents, which enables us to follow the cohort by linkage to multiple nation-wide, continuously updated and essentially complete databases.

Given the fundraising nature and nearly 3,600 Swedish cities and villages participating in the event, the number of individuals offered a questionnaire could not be assessed. In total, 43,865 subjects completed the questionnaire. After applying the following criteria for exclusions; 1) incorrect national registration number (n=11); emigration

or death before the start of follow-up (n=55); 3) age lower than 18 years (n=1,732); 4) missing values on habitual sleep duration (n=2465) or sleep quality (n=461), the final number went down to 39,139 subjects. The cohort was followed prospectively for all-cause mortality until the end of April 2018. The study was approved by the Regional Ethical Review Board of Karolinska Institutet and all subjects provided informed consent.

## Exposure Assessment

The Karolinska Sleep Questionnaire<sup>15</sup> was used to assess sleep duration and insomnia symptoms. Habitual sleep duration was assessed by asking “How many hours, approximately, do you usually sleep during a weekday night?” The response alternatives were: <5, 5, 6, 7, 8 or >8 hrs. Seven hours was set as the reference category since that is the most commonly used reference<sup>16</sup> and the one used in the largest study on sleep duration and mortality.<sup>17</sup>

Insomnia symptoms were assessed at baseline by asking participants to estimate how often they experienced difficulties initiating sleep, difficulties maintaining sleep, early-morning awakenings, not rested at awakening and daytime sleepiness. The response alternatives were never, seldom, sometimes, mostly or always. Each variable was dichotomized into yes (sometimes, mostly, or always experiencing symptoms) versus no (never or seldom experiencing symptoms). We also constructed a variable for insomnia defined as mostly or always experiencing any of the nocturnal insomnia symptoms (difficulties initiating sleep, difficulties maintaining sleep, early-morning awakenings) as well as mostly or always experiencing symptoms of non-restorative sleep (not rested at awakening, daytime sleepiness).

In order to elucidate the relationship between sleep duration, sleep quality and all-cause mortality, the participants were further categorized based on both sleep duration and insomnia symptoms.

## Follow-Up And Outcome

The cohort was followed from October 1, 1997. Follow-up ended at the time of death, emigration or April 30, 2018, whichever occurred first. Using the Swedish national registration numbers, all-cause mortality data were obtained by linkage to the Swedish Cause of Death Register held by the National Board for Health and Welfare. A total of 7655 deaths occurred during the follow-up period. The main causes of deaths were

cardiovascular diseases (ICD-10 codes I00-I99,  $n=2254$ ) and cancer (ICD-10 codes C00-C97,  $n=2654$ ).

## Statistical Analysis

Baseline characteristics of the study cohort were described in total and by categories of sleep duration. Characteristics were also described for those with and without insomnia symptoms. Differences in baseline variables across categories of sleep duration were assessed using either one-way analysis of variance (ANOVA) for continuous variables or the Kruskal–Wallis test for categorical variables. Cox proportional hazard models with attained age as time-scale were fitted to estimate overall mortality hazard ratios (HRs) with 95% confidence intervals (CI) for different categories of sleep duration and insomnia symptoms. Residual analyses were conducted to study the proportionality hazard assumption, based on the Schoenfeld residual plots and statistical tests.

We first calculated HRs of death for different categories of sleep duration, using seven hours/night as the reference group. Since the key insomnia symptoms have been differently associated with mortality in previous studies, all nocturnal symptoms as well as symptoms of non-restorative sleep were analyzed separately, overall and by sleep duration categories. We further analyzed the influence of insomnia defined as mostly or always experiencing either of the nocturnal insomnia symptoms in combination with mostly or always experiencing non-restorative sleep, overall and by sleep duration categories.

Furthermore, we calculated the HRs of death associated with sleep duration, stratified by the following categories (1) no difficulties initiating sleep, no daytime sleepiness, (2) difficulties initiating sleep, no daytime sleepiness, (3) no difficulties initiating sleep, daytime sleepiness, (4) difficulties initiating sleep, daytime sleepiness.

The full model was adjusted for potential confounding variables including sex, educational level, body mass index, smoking, alcohol consumption, physical activity, working hours, coffee consumption, cardiovascular disease and cancer. Educational level was dichotomized into those who had a university degree and those who had not. BMI was calculated by dividing weight in kilograms by height in meters squared and categorized into underweight ( $<18.5 \text{ kg/m}^2$ ), normal weight ( $18.5\text{--}24.99 \text{ kg/m}^2$ ), overweight ( $25\text{--}30 \text{ kg/m}^2$ ) or obese ( $>30 \text{ kg/m}^2$ ). Smoking was categorized into never, past or current smokers. Alcohol consumption was categorized into drinkers, non-drinkers or unknown. Physical activity was based on reported

responses on weekly exercise levels ranging from none or easy physical activity to hard physical activity and dichotomized into those active or inactive. Working hours were categorized into daytime work, shift work, no work hours, or other. Coffee consumption was categorized into 0, 1–4, 5–7 or  $>7$  cups of coffee per day. Information regarding diagnoses of cardiovascular disease and cancer at baseline was obtained from the Swedish Patient Register and the Cancer Register and the variables were dichotomized into those who had a diagnosis and those who had not.

In a sensitivity analysis, we further adjusted for alcohol as a continuous variable (total grams per months), BMI as a continuous variable ( $\text{kg/m}^2$ ), depressive symptoms, anxiety symptoms, use of sleeping pills and taking naps. Depressive symptoms were assessed by asking the participants to estimate how often they felt sad, low-spirited or depressed. Depressive symptoms were dichotomized into yes (sometimes, often or always depressive symptoms) or no (never or seldom depressive symptoms). Anxiety symptoms were assessed by asking the participants to estimate how often they felt worried, tensed or anxious. Anxiety symptoms were dichotomized into yes (sometimes, often or always anxiety symptoms) or no (never or seldom anxiety symptoms). Taking naps was dichotomized into never or seldom taking naps versus sometimes, mostly or always taking naps. The use of sleeping pills was dichotomized into never or seldom using sleeping pills versus sometimes, mostly or always using sleeping pills.

In another sensitivity analysis, we excluded the first 2 years of follow-up to prevent reverse causation. Sensitivity analyses were also conducted restricted to those without a diagnosis of cancer or cardiovascular disease before the follow-up start.

The proportion of missing data regarding confounding variables was 7.6% for smoking habits, 4.0% for BMI, 1.6% for coffee consumption, 1.1% for working hours and less than 1% for educational level, physical activity, alcohol consumption, daytime napping and use of sleeping pills. We, therefore, conducted supplementary analyses after imputing missing data using the multiple imputation chained equation procedure. All analyses were performed using Statistical Analysis System 9.4.

## Results

Characteristics of participants at baseline, overall and by category of sleep duration are presented in Table 1. Generally, women slept longer than men. Compared to

**Table 1** Baseline Characteristics, Overall And Stratified By Sleep Duration

Variable	Sleep Duration (Hours/Night)							P value
	Total	<5	5	6	7	8	≥9	
N	39,139	1,238	1,980	9,181	16,879	8,980	881	
Mean age (SD)	50.5 (15.7)	57.6 (17.1)	53.2 (15.8)	50.4 (15.1)	49.6 (14.9)	50.6 (16.8)	51.3 (18.8)	<0.0001
Women, n (%)	25,157 (64)	741 (60)	1244 (63)	5601 (61)	10,896 (65)	6068 (68)	607 (69)	<0.0001
University degree, n (%)	11,405 (29)	164 (13)	436 (22)	2681 (29)	5492 (33)	2428 (27)	204 (23)	<0.0001
Daytime work, n (%)	24,267 (62)	471 (38)	1028 (52)	5881 (64)	11,479 (68)	5056 (56)	352 (40)	<0.0001
Shift work, n (%)	2310 (5.9)	100 (8.1)	202 (10)	729 (7.9)	853 (5.1)	384 (4.3)	42 (4.8)	<0.0001
Other work hours, n (%)	802 (2.1)	31 (2.5)	58 (2.9)	212 (2.3)	314 (1.9)	178 (2.0)	9 (1.0)	0.002
No work, n (%)	9210 (24)	490 (40)	527 (27)	1824 (20)	3319 (20)	2664 (30)	386 (44)	<0.0001
Current smokers, n (%)	2890 (7.4)	113 (9.1)	180 (9.1)	821 (8.9)	1160 (6.9)	560 (6.2)	56 (6.4)	<0.0001
Past smokers, n (%)	10,241 (26)	271 (22)	518 (26)	2506 (27)	4487 (27)	2229 (25)	230 (26)	<0.0001
BMI, kg/m <sup>2</sup> (SD)	24.6 (3.5)	25.1 (3.7)	25.1 (3.9)	24.7 (3.6)	24.5 (3.4)	24.5 (3.5)	24.9 (3.9)	<0.0001
Low physical activity, n (%)	6207 (16)	217 (18)	371 (19)	1499 (16)	2623 (16)	1331 (15)	154 (17)	<0.0001
Coffee consumption, number of cups daily (SD)	2.9 (1.8)	3.0 (1.8)	3.1 (1.9)	3.1 (1.8)	2.9 (1.8)	2.7 (1.7)	2.5 (1.9)	<0.0001
Alcohol drinkers, n (%)	34,665 (89)	1049 (85)	1746 (88)	8255 (90)	15,047 (89)	7819 (87)	749 (85)	<0.0001
Standard glasses of alcohol per week (SD)	6.4 (4.3)	5.8 (4.5)	6.3 (4.4)	6.6 (4.3)	6.5 (4.3)	6.0 (4.3)	5.6 (4.5)	<0.0001
Difficulty falling asleep, n (%)	15,950 (41)	762 (62)	1259 (64)	4352 (47)	6255 (37)	3013 (34)	309 (35)	<0.0001
Difficulty maintaining sleep, n (%)	18,476 (47)	864 (70)	1424 (72)	4878 (53)	7291 (43)	3662 (41)	357 (41)	<0.0001
Early-morning awakening, n (%)	20,905 (53)	879 (71)	1469 (74)	5529 (60)	8504 (50)	4145 (46)	379 (43)	<0.0001
Unrested at awakening, n (%)	23,837 (61)	804 (65)	1564 (79)	6519 (71)	10,196 (60)	4314 (48)	440 (50)	<0.0001
Daytime sleepiness, n (%)	24,935 (64)	905 (73)	1464 (74)	6301 (69)	10,400 (62)	5256 (59)	609 (69)	<0.0001
Taking daytime naps, n (%)	16,187 (41)	668 (54)	760 (38)	3473 (38)	6530 (39)	4200 (47)	556 (63)	<0.0001
Sleeping pills, n (%)	2181 (5.6)	251 (20)	307 (16)	633 (6.9)	638 (3.8)	295 (3.3)	57 (6.5)	<0.0001
Depression, n (%)	9700 (25)	436 (35)	710 (36)	2569 (28)	3802 (23)	1915 (21)	268 (30)	<0.0001
Cancer diagnosis, n (%)	2397 (6.1)	122 (9.9)	145 (7.3)	517 (5.6)	938 (5.6)	590 (6.6)	85 (9.7)	<0.0001
Cardiovascular disease, n (%)	4024 (10)	234 (19)	229 (12)	963 (10)	1534 (9.1)	937 (10)	127 (14)	<0.0001

subjects with sleep duration of 7 hrs/night, short and long sleepers were older, less educated, reported less physical activity, had a higher BMI and consumed less alcohol. Current smoking and working shifts were more common among the short sleepers. Nocturnal insomnia symptoms were more common among short sleepers than among those who slept 7 hrs/night, whereas these symptoms were less frequent among long sleepers. Short and long sleepers more often experienced daytime sleepiness and they more often reported taking naps during the daytime and using sleeping pills. They had also to a higher degree been diagnosed with cardiovascular disease and cancer.

Table 2 presents the characteristics of participants with and without insomnia symptoms. Overall, those with insomnia symptoms had a shorter sleep duration and more often used sleep medication, compared to those without insomnia symptoms. A higher proportion of those with insomnia symptoms reported depression. Participants who reported nocturnal insomnia symptoms were older and

more often had a diagnosis of cancer or cardiovascular disease, compared to those who did not have nocturnal insomnia symptoms.

During a mean follow-up time of 19.6 years (SD 4.0), 7655 subjects died, with an estimated crude rate of 9.5 deaths per year per 1,000 people. A U-shaped association between sleep duration and both all-cause and cause-specific mortality was observed (Table 3, Supplementary Table 1). In the gender-adjusted model, the HR of death was 1.36 (95% CI 1.24–1.50) among short sleepers and 1.35 (95% CI 1.19–1.54) among long sleepers, compared to the reference group of 7 hrs/night (Table 3). The corresponding HRs were 1.24 (95% CI 1.13–1.37) and 1.27 (95% CI 1.12–1.44) in the fully adjusted model.

Overall, insomnia symptoms were not associated with mortality. When we investigated the influence of each insomnia symptom on mortality risk, stratified by sleep duration, both difficulty initiating sleep (HR 1.51, 95% CI

**Table 2** Baseline Characteristics, By Presence Or Absence Of Insomnia Symptoms

Variable	Difficulty Initiating Sleep		Difficulty Maintaining Sleep		Early-Morning Awakening		Not Rested At Awakening		Daytime Sleepiness	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	15,950	23,189	18,476	12,269	20,905	18,234	123,837	15,302	24,935	14,204
Mean age (SD)	51.9 (16.0)	49.5 (15.4)	54.8 (14.2)	46.7 (16.0)	51.9 (15.5)	48.9 (15.8)	47.6 (15.6)	55.0 (14.8)	48.6 (16.2)	53.9 (14.1)
Women, n (%)	11,305 (71)	13,852 (60)	12,888 (70)	12,269 (59)	13,445 (64)	11,712 (64)	16,124 (68)	9033 (59)	16,371 (66)	8786 (62)
University degree, n (%)	3821 (24)	7584 (33)	4673 (12)	6732 (33)	5586 (27)	5819 (32)	7442 (31)	3963 (26)	7216 (29)	4189 (29)
Daytime work, n (%)	8841 (55)	15,426 (67)	10,299 (56)	13,968 (68)	12,609 (60)	11,658 (64)	15,799 (66)	8468 (55)	15,490 (62)	8777 (62)
Shift work, n (%)	1038 (6.5)	1272 (5.5)	969 (5.2)	1341 (6.5)	1202 (5.8)	1108 (6.1)	1642 (6.9)	668 (4.4)	1664 (6.7)	646 (4.6)
Other work hours, n (%)	327 (2.1)	475 (2.1)	289 (1.6)	513 (2.5)	403 (1.9)	399 (2.2)	559 (2.4)	243 (1.6)	595 (2.4)	207 (1.5)
No work, n (%)	4496 (28)	4714 (20)	5406 (29)	3804 (18)	5281 (25)	3929 (22)	4581 (19)	4629 (30)	5718 (23)	3492 (25)
Current smokers, n (%)	1433 (9.0)	1457 (6.3)	1214 (6.6)	1676 (8.1)	1419 (6.8)	1471 (8.1)	1996 (8.4)	894 (5.8)	1977 (7.9)	913 (6.4)
Past smokers, n(%)	3980 (25)	6261 (27)	5019 (27)	5222 (25)	5557 (27)	4684 (26)	6089 (26)	4152 (27)	6431 (26)	3810 (27)
BMI, kg/m <sup>2</sup> (SD)	24.7 (3.6)	24.5 (3.4)	24.8 (3.5)	24.4 (3.5)	24.7 (3.6)	24.5 (3.5)	24.5 (3.6)	24.7 (3.4)	24.6 (3.6)	24.6 (3.4)
Low physical activity, n (%)	2542 (16)	3665 (16)	2758 (15)	3449 (17)	3230 (15)	2977 (16)	4103 (17)	2104 (14)	4238 (17)	1969 (14)
Coffee consumption, number of cups daily (SD)	2.9 (1.8)	2.8 (1.8)	2.9 (1.7)	2.8 (1.9)	2.9 (1.8)	2.9 (1.8)	2.8 (1.9)	2.9 (1.7)	2.8 (1.8)	3.0 (1.7)
Alcohol drinkers, n (%)	14,041 (88)	20,624 (89)	16,181 (88)	18,484 (89)	18,479 (88)	16,186 (89)	21,319 (89)	13,346 (87)	22,139 (89)	12,526 (88)
Standard glasses of alcohol per week (SD)	6.2 (4.3)	6.5 (4.3)	6.4 (4.4)	6.4 (4.2)	6.4 (4.4)	6.3 (4.3)	6.4 (4.2)	6.3 (4.4)	6.3 (4.3)	6.5 (4.4)
Taking daytime naps, n (%)	6774 (42)	9413 (41)	8316 (45)	7871 (38)	9101 (44)	7086 (28)	9745 (41)	6442 (42)	11,864 (48)	4323 (30)
Sleeping pills, n (%)	1868 (12)	313 (1.4)	1925 (10)	256 (1.2)	1716 (8.2)	465 (2.6)	1727 (7.3)	454 (3.0)	1637 (6.6)	544 (3.8)
Mean sleep duration (SD)	6.7 (1.1)	7.0 (0.9)	6.7 (1.1)	7.0 (0.9)	6.7 (1.1)	7.0 (0.9)	6.7 (1.0)	7.0 (1.0)	6.8 (1.0)	7.0 (0.9)
Depression, n (%)	4674 (29)	3954 (17)	5024 (27)	3604 (17)	5213 (25)	3415 (19)	6675 (28)	1953 (13)	6818 (27)	1810 (13)
Cancer diagnosis, n (%)	1213 (7.6)	1184 (5.1)	1485 (8.0)	912 (4.4)	1432 (6.9)	965 (5.3)	1358 (5.7)	1039 (6.8)	1479 (5.9)	918 (6.5)
Cardiovascular disease, n (%)	1856 (12)	2168 (9.4)	2321 (13)	1703 (8.2)	2310 (11)	1714 (9.4)	2172 (9.1)	1852 (12)	2501 (10)	1523 (10)



**Table 3** HR With 95% CI For All-Cause Mortality By Sleep Duration (Hours/night)

Sleep Duration (Hours/ Night)	N	Person-Years (SD)	Deaths (%)	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>c</sup>
<5	1238	21,467	505 (41)	<b>1.36 (1.24–1.50)</b>	<b>1.30 (1.18–1.43)</b>	<b>1.27 (1.15–1.41)</b>
5	1980	37,179	477 (24)	<b>1.10 (1.00–1.21)</b>	1.07 (0.97–1.18)	1.05 (0.95–1.17)
6	9181	176,873	1678 (18)	1.03 (0.97–1.10)	1.02 (0.96–1.08)	1.02 (0.96–1.09)
7	16,879	327,177	2816 (17)	1.0 (reference)	1.0 (reference)	1.0 (reference)
8	8980	170,088	1919 (21)	1.04 (0.98–1.10)	1.03 (0.97–1.09)	1.03 (0.97–1.09)
≥9	881	16,110	260 (30)	<b>1.35 (1.19–1.54)</b>	<b>1.29 (1.14–1.47)</b>	<b>1.26 (1.10–1.43)</b>

**Notes:** <sup>a</sup>Adjusted for gender; <sup>b</sup>adjusted for gender, educational level, working hours, smoking, alcohol consumption, body mass index, physical activity and coffee consumption; <sup>c</sup>adjusted for gender, educational level, working hours, smoking, alcohol consumption, body mass index, physical activity, coffee consumption, cardiovascular disease and cancer. Significant HRs are shown in bold.

1.11–2.07) and daytime sleepiness (HR 1.37, 95% CI 1.03–1.82) were associated with increased mortality only among those who reported a sleep duration of 9 hrs or more. Mortality risk increased with increasing severity of difficulties initiating sleep (p for trend 0.04) and daytime sleepiness (p for trend 0.01) among the long sleepers. Daytime sleepiness was associated with increased mortality among the long sleepers regardless of the presence or absence of nocturnal insomnia symptoms. When difficulties initiating sleep were combined with daytime sleepiness and long sleep (9 hrs) the HR rose to 2.16 (CI=1.41; 3.31). We also observed an inverse relationship between difficulties maintaining sleep and mortality among the long sleepers (HR 0.67, 95% CI 0.49–0.91). None of the insomnia symptoms were associated with mortality among

those who reported a sleep duration of 8 hrs or less (Table 4).

We then considered the influence of insomnia, defined as mostly or always experiencing either of the nocturnal insomnia symptoms in combination with mostly or always experiencing symptoms of non-restorative sleep. Among the long sleepers, insomnia was associated with increased mortality (HR 2.98, 95% CI 1.58–2.61) whereas no association between insomnia and mortality was observed among those who slept 8 hrs/night or less.

There was a weak correlation between difficulties initiating sleep and daytime sleepiness (r=0.13, p<0.01). When subjects were categorized based on difficulties initiating sleep and daytime sleepiness, both insomnia symptoms were independently associated with mortality among long

**Table 4** HR With 95% CI For All-Cause Mortality For Subjects With Different Insomnia Symptoms, By Sleep Duration (Hours/night)

Insomnia Symptom		Sleep Duration (Hours/Night)						
		Total	<5	5	6	7	8	≥9
		HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>a</sup>
Difficulty initiating sleep	No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Yes	1.00 (0.95–1.05)	1.04 (0.83–1.30)	0.89 (0.71–1.12)	1.00 (0.89–1.11)	1.01 (0.92–1.10)	0.96 (0.86–1.06)	<b>1.51 (1.11–2.07)</b>
Difficulty maintaining sleep	No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Yes	1.03 (0.98–1.09)	0.97 (0.75–1.25)	0.96 (0.71–1.31)	0.99 (0.88–1.13)	1.09 (0.99–1.18)	1.00 (0.91–1.12)	<b>0.67 (0.49–0.91)</b>
Early-morning awakening	No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Yes	1.04 (0.99–1.09)	1.07 (0.85–1.34)	1.00 (0.78–1.29)	1.00 (0.89–1.12)	1.04 (0.96–1.13)	1.08 (0.98–1.14)	0.94 (0.70–1.25)
Not rested at awakening	No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Yes	1.01 (0.96–1.07)	1.05 (0.85–1.29)	1.21 (0.95–1.53)	1.10 (0.98–1.23)	0.93 (0.86–1.01)	1.03 (0.93–1.12)	1.16 (0.88–1.53)
Daytime sleepiness	No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Yes	1.02 (0.97–1.07)	0.83 (0.68–1.02)	1.06 (0.86–1.31)	1.00 (0.90–1.12)	1.00 (0.92–1.08)	1.02 (0.93–1.10)	<b>1.37 (1.03–1.82)</b>
Insomnia <sup>b</sup>	No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Yes	1.01 (0.94–1.09)	0.94 (0.76–1.15)	0.91 (0.75–1.10)	0.93 (0.81–1.06)	1.03 (0.88–1.19)	1.15 (0.90–1.46)	<b>2.98 (1.58–2.61)</b>

**Notes:** <sup>a</sup>Adjusted for gender, educational level, working hours, smoking, alcohol consumption, body mass index, physical activity, coffee consumption, cardiovascular disease, cancer and when appropriate difficulty initiating sleep, difficulty maintaining sleep, early-morning awakenings, fatigue at awakening and daytime sleepiness; <sup>b</sup>at least one nocturnal insomnia symptom (mostly or always) in combination with at least one symptom of non-restorative sleep (mostly or always). Significant HRs are shown in bold.

**Table 5** HR With 95% CI For All-Cause Mortality By Sleep Duration (Hours/night), Stratified By Difficulty Initiating Sleep And Daytime Sleepiness

Sleep Duration (Hours/Night)	Total		No Difficulties Initiating Sleep, No Daytime Sleepiness N=9,661	Difficulties Initiating Sleep, No Daytime Sleepiness N=13,528	No Difficulties Initiating Sleep, Daytime Sleepiness N=4,543	Difficulties Initiating Sleep, Daytime Sleepiness N=1,407
	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>c</sup>	HR (95% CI) <sup>c</sup>	HR (95% CI) <sup>c</sup>	HR (95% CI) <sup>c</sup>
<5	<b>1.27 (1.15–1.41)</b>	<b>1.26 (1.14–1.40)</b>	<b>1.29 (1.03–1.63)</b>	<b>1.44 (1.14–1.83)</b>	1.20 (0.97–1.48)	<b>1.29 (1.11–1.50)</b>
5	1.05 (0.95–1.17)	1.04 (0.94–1.15)	1.01 (0.76–1.33)	0.96 (0.77–1.21)	1.10 (0.90–1.34)	1.05 (0.90–1.21)
6	1.02 (0.96–1.09)	1.02 (0.95–1.08)	1.02 (0.89–1.16)	1.00 (0.87–1.17)	1.04 (0.93–1.17)	1.04 (0.93–1.15)
7	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
8	1.03 (0.97–1.09)	1.03 (0.97–1.10)	1.00 (0.90–1.11)	0.99 (0.85–1.16)	1.09 (0.98–1.21)	1.04 (0.92–1.17)
≥9	<b>1.26 (1.10–1.43)</b>	<b>1.26 (1.11–1.44)</b>	0.94 (0.72–1.23)	<b>1.38 (0.93–2.05)</b>	<b>1.36 (1.10–1.67)</b>	<b>1.52 (1.19–1.94)</b>

**Notes:** <sup>a</sup>Adjusted for gender, educational level, working hours, smoking, alcohol consumption, body mass index, physical activity, coffee consumption, cardiovascular disease and cancer; <sup>b</sup>adjusted for gender, educational level, working hours, smoking, alcohol consumption, body mass index, physical activity, coffee consumption, cardiovascular disease, cancer, difficulty initiating sleep and daytime sleepiness; <sup>c</sup>adjusted for gender, educational level, working hours, smoking, alcohol consumption, body mass index, physical activity, coffee consumption, cardiovascular disease, cancer and when appropriate for difficulties initiating sleep and daytime sleepiness. Significant HRs are shown in bold.

sleepers. There was no significant association between long sleep duration and mortality among those without insomnia symptoms (Table 5).

Our findings remained almost identical when we excluded cases occurring during the first 2 years of follow-up and when the analyses were restricted to those without a diagnosis of cancer or cardiovascular disease before the follow-up start. When the analyses were further adjusted for alcohol and BMI as continuous variables, depressive symptoms, anxiety symptoms, taking naps and use of sleeping pills, the results also remained virtually unchanged. To account for depression in a clearer way than through adjustment, we also stratified for depression. This yielded an HR of mortality of 1.40 (95% CI 1.16–1.70) for long sleepers with depression and an HR of 1.20 (95% CI 1.06–1.35) for long sleepers without depression. Furthermore, our results remained stable after carrying out the analysis on the multiple imputed data (data not shown).

## Discussion

Our prospective cohort study on the association between sleep duration, insomnia symptoms and mortality included 39,139 participants with a mean follow-up time of 19.6 years. A U-shape association between sleep duration and all-cause mortality was observed that persisted in the fully adjusted model. Overall, there was no association between insomnia symptoms and mortality. However, when the analysis was stratified by sleep duration, both difficulties initiating sleep and daytime sleepiness were significantly and independently

associated with mortality among those with sleep duration of 9 hrs or longer.

Previous studies exploring the association between insomnia and mortality have been inconsistent. Some studies have found associations between and insomnia and mortality, and particularly difficulties initiating sleep have been suggested to increase the risk of mortality.<sup>10–12</sup> Other studies have found no association.<sup>17,18</sup> A recent meta-analysis of 17 studies, including a total of 36,938,981 subjects followed up for a mean of 11.6 years, showed no relationship between insomnia and mortality when those with symptoms of insomnia were compared to those without symptoms.<sup>14</sup> This is in accordance with our study as we did not observe any influence of insomnia on mortality risk when sleep duration was not taken into consideration. Apparently, it seems that it is not possible to determine whether sleep complaints or insomnia are associated with increased mortality without considering sleep duration.

However, our findings are also in line with previous studies investigating the combined effect of extreme sleep duration and insomnia on mortality risk.<sup>11,19</sup> In a prospective community-based cohort of Chinese adults, a joint analysis of insomnia and sleep duration indicated an increased risk of all-cause mortality among those with frequent insomnia and long sleep duration, compared to those sleeping 7–8 hrs.<sup>11</sup> In the Women's Health Initiative Observational Study, including 86,329 postmenopausal

women followed for 10.3 years, insomnia was associated with increased risk of coronary heart disease and cardiovascular disease only among those who reported long sleep duration.<sup>19</sup>

Long sleep duration has been associated with adverse health outcomes such as depression, cardiovascular disease, coronary heart disease, stroke and obesity,<sup>20,21</sup> and a meta-analysis of 72 cohort studies indicated that habitual long sleep was associated with systemic inflammation.<sup>7</sup> Our finding of an association between insomnia symptoms and mortality, restricted to subjects who reported long sleep duration, may indicate that underlying illness affects sleep and that this underlying illness contributes to the relationship between insomnia and mortality in long sleepers. Similarly, daytime sleepiness combined with long sleep may be a nonspecific sign of underlying illness. A significant association between daytime sleepiness and mortality has been reported,<sup>22,23</sup> but this association did not persist when depression and comorbid diseases were taken into consideration.<sup>23</sup>

The finding that difficulties maintaining sleep were associated with reduced mortality among long sleepers was unexpected – overall sleep symptoms are highly intercorrelated.<sup>15</sup> It is difficult to understand the reason for this; however, if long sleep is not only related to an underlying disease, but also to poor sleep, one could speculate that those with the latter problem are able to compensate and thus avoid the risk of earlier death. Long sleepers with a latent disease may instead suffer a higher risk because of that disease. This seems an important topic for further research.

Shared genetic factors behind sleep duration, insomnia and both psychiatric and physical disorders may also contribute to the association between insomnia and increased mortality among those with long sleep duration. Genome-wide association studies (GWAS), conducted to elucidate the genetic architecture of sleep duration and insomnia have confirmed a significant heritability.<sup>24,25</sup> A substantial genetic overlap has been identified between sleep characteristics and psychopathology, including a genetic correlation between long sleep duration and schizophrenia<sup>26,27</sup> and between insomnia and major depression.<sup>28,29</sup> Furthermore, a genetic correlation has also been observed between long sleep duration and type 2 diabetes,<sup>26</sup> as well as between insomnia and type 2 diabetes.<sup>28</sup> Shared genetic factors may thus contribute to explain our findings of increased mortality among long sleepers with insomnia symptoms.

The strengths of this prospective cohort study are the large sample size, the long follow-up duration and the almost complete follow-up ascertained by linking baseline information with nationwide, continuously updated registers. Weaknesses are that all exposure information was self-reported and only measured at baseline. Only the frequency, but not the duration of insomnia symptoms, were assessed. Potential changes in sleep duration or lifestyle habits such as smoking or physical activity during the follow-up period would go undetected. Some lifestyle habits such as physical activity are likely to have changed during follow-up.<sup>30,31</sup> Since subjects were recruited during a fund-raising event in order to support cancer research, the cohort may be prone to a potential healthy volunteer bias. However, while poor response rates and incomplete follow-up is a problem in many population-based studies, the shortcomings of a non-representative sample must be weighed against the fact that choosing a restricted sample can increase the feasibility of the study, the prevalence of the exposure and completeness of the follow-up. These factors all increase the validity and precision of the study.<sup>32</sup> For example, the level of missing data was remarkably low in our study.

Major disease is regarded as a crucial variable to adjust for in studies of sleep duration and mortality. All analyses were adjusted for cardiovascular disease and cancer at baseline and in a sensitivity analysis, we also excluded those with a diagnosis at baseline, with virtually unchanged results. It has been suggested that yet undetected diseases could affect the results when studying sleep duration and mortality,<sup>33</sup> and in order to minimize the risk of reverse causation, we excluded cases occurring during the first 2 years of follow-up, but the results remained almost identical.

In conclusion, difficulties initiating sleep and daytime sleepiness were associated with increased mortality among those who reported a sleep duration of 9 hrs or longer and may contribute to the observed association between long sleep duration and all-cause mortality. Our study emphasizes the need to take nocturnal insomnia symptoms and symptoms of non-restorative sleep into consideration when assessing the influence of sleep duration on mortality. Additional work is needed to elucidate the relationship between long sleep, insomnia and related psychiatric and physical disorders.



## Author Contributions

All authors contributed to study concept and design. AKH performed the statistical analyses and drafted the manuscript. All authors interpreted the data and critically revised the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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