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Original Article

ORIGINAL ARTICLE

Insomnia in the context of short sleep increases suicide risk

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Abstract

Study Objectives: The relationship between insomnia and suicide risk is not completely understood. We aimed to investigate the influence of insomnia on suicide risk, taking both sleep duration and depression into consideration.

Methods: The present study is based on a Swedish prospective cohort study of 38,786 participants with a mean follow-up time of 19.2 years. Cox proportional hazards models with attained age as time-scale were used to estimate hazard ratios (HRs) of death by suicide with 95% confidence intervals (CI) for participants categorized by frequency of insomnia symptoms. Causal mediation analysis was performed to assess to what extent the relationship between insomnia and suicide risk is mediated by depression.

Results: Insomnia was only associated with suicide risk among short sleepers, whereas no significant association was observed among those who slept 7 h/night or more. The total effect of insomnia in the context of short sleep on suicide risk, expressed on the HR scale, was 2.85 (95% CI 1.42–5.74). The direct effect was 2.25 (95% CI 1.12–4.54) and the indirect effect, mediated by depression, was 1.27 (95% CI 1.05–1.53). Of the total effect, 32% was mediated by depression. The association between insomnia and suicide risk became more pronounced with decreasing depressive symptoms (p value for trend <0.05).

Conclusions: Insomnia in the context of short sleep increases suicide risk, both directly and indirectly by affecting the risk of depression. Abnormalities of sleep duration and insomnia symptoms should be evaluated when assessing suicide risk.

Statement of Significance

Our finding that insomnia is associated with suicide risk predominantly among persons with short sleep emphasizes the need to evaluate both insomnia symptoms and abnormalities of sleep duration when assessing suicide risk. Insomnia in the context of short sleep increases suicide risk both directly, but also indirectly by increasing the onset or reoccurrence of depression. No significant association was observed between insomnia and suicide risk among those who slept 7 h/night or more. Additional work is needed to further elucidate the relationship between insomnia, sleep duration, and depression, including investigations of shared neurobiological pathways.

Key words: insomnia; sleep duration; suicide; depression

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Introduction

Suicide is a significant public health concern and a leading cause of death worldwide. The risk of suicide is modulated by a range of factors both at the population and individual levels [1]. Increased understanding of the factors underlying suicidal behavior is crucial for improving risk assessment and intervention strategies.

Sleep disturbances have been identified as an early and important marker for suicidal behavior, both in the general population and in patients with psychiatric disorders [2, 3]. Insomnia is one of the most prevalent sleep disorders, characterized by difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings, in combination with non-restorative sleep [4]. Numerous studies have found that insomnia constitutes an independent risk factor for suicidality [5–10]. However, insomnia often co-occurs with psychiatric disorders such as depression and anxiety [11], and other studies have found that the relationship between insomnia and suicidality is mediated by psychiatric disorders [12–14].

A U-shaped association has been observed between sleep duration and suicidal behavior [15–17]. Both short and long sleep duration have been associated with depression [18, 19], and short sleep has been associated with insomnia in both the general population [20] and in those with psychiatric disorders [21]. It is thus possible that the relationship between insomnia and suicidality is affected by sleep duration. However, most studies that have investigated the influence of insomnia on suicide risk have not considered sleep duration.

Using a large Swedish cohort with a mean follow-up time of 19.2 years, we aimed to assess the influence of insomnia on suicide risk, taking depression, and sleep duration into consideration.

Methods

The Swedish National March Cohort is a prospective cohort study established in 1997 during a 4-day national fundraising event promoted by the Swedish Cancer Society in order to investigate associations between lifestyle factors and chronic diseases [22]. All those who participated in the event were invited to complete a 36-page questionnaire regarding demographic, lifestyle, and medical information together with their national registration number, a unique identifier assigned to all Swedish residents.

Nearly 3,600 Swedish cities and villages participated in the fundraising event and the number of individuals offered a questionnaire could not be assessed. In total, 43,863 subjects completed the questionnaire. Those with incorrect national registration number were excluded (n = 11) as were those who were younger than 18 years (n = 1,732), or had emigrated or died (n = 55) before the start of follow-up. We also excluded subjects with missing values on habitual sleep duration (n = 2,465), insomnia symptoms (n = 461), or depressive symptoms (n = 353). Our final study population included 38,786 subjects followed prospectively for all-cause mortality until April 30, 2018. The study was approved by the Regional Ethical Review Board of Karolinska Institutet and all subjects provided informed consent to participate. The cohort was followed from baseline on October 1, 1997. Follow-up ended at the time of death, emigration or April 30, 2018, whichever occurred first. Using the individually unique Swedish national registration numbers, all-cause mortality data was obtained by linkage to Statistic Sweden and the Swedish Cause of Death Register held by the National Board for Health and Welfare. A total of 7,512 deaths occurred during the follow-up period. Of these, 66 were suicides (ICD-10 codes X60-X84 and Y10-Y34).

Exposure assessment and definitions

The Karolinska Sleep Questionnaire [23] 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 less than 5, 5, 6, 7, 8, or 9+ h. Since several systematic reviews on sleep duration and mortality have found the optimal sleep duration to be 7 h/night [24]. Sleep duration was dichotomized into less than 7 h/night or 7+ h/night, and less than 7 h/night will be referred to as short sleep duration.

Insomnia symptoms were assessed by asking participants to estimate how often they experienced difficulties initiating sleep, difficulties maintaining sleep, early morning awakenings, tired at awakening, and daytime tiredness. The response alternatives were never, seldom, sometimes, often, or always. Each variable was categorized into never or seldom suffering from the insomnia symptom, sometimes suffering from it, or often or always suffering from it. Insomnia was defined as often or always experiencing at least one of the nocturnal insomnia symptoms (difficulties initiating sleep, difficulties maintaining sleep, early morning awakenings), in combination with sometimes, often, or always experiencing at least one of the symptoms of non-restorative sleep (tired at awakening, daytime tiredness).

Information regarding diagnoses of psychiatric disorders was obtained from the Swedish Patient Register. A diagnosis of depression was defined according to the following: ICD-8 codes 296.0–296.3, 296.8–296.9, 298.0, 300.4 or ICD-9 codes 296B-E, 298A, 300E before baseline, or ICD-10 codes F31–F33 during follow-up.

Depressive symptoms at baseline were assessed by asking the participants to estimate how often they felt sad, low-spirited, or depressed. The response alternatives were never/seldom, sometimes, often or always/almost always. Depressive symptoms was dichotomized into yes (sometimes, often or always depressive symptoms) or no (never or seldom depressive symptoms).

Statistical analysis

Baseline characteristics were described overall and by frequency of nocturnal insomnia symptoms. Differences in baseline variables by nocturnal insomnia status were assessed using one-way analysis of variance (ANOVA) for continuous variables and the Kruskal–Wallis test for categorical variables. Baseline characteristics of the study cohort were also summarized by sleep duration.

Cox proportional hazards models with attained age as timescale were used to estimate hazard ratios (HRs) of suicide with 95% confidence intervals (CI) for subjects with different frequencies of insomnia symptoms, based on the delta method. Residual analyses were conducted to study the proportionality hazard assumption, based on the Schoenfeld residual plots and statistical tests. The analysis was performed overall and stratified by sleep duration. Subjects were also categorized by insomnia and sleep

duration in order to estimate the separate effect of each factor on the risk of suicide.

Among subjects without a diagnosis of depression at baseline, we used logistic regression to assess the risk of receiving a diagnosis of depression during follow-up among those who suffered from insomnia, compared to those who did not. Causal mediation analysis was used to asses to what extent the relationship between insomnia and suicide risk is mediated by depression [25, 26]. The causal effects were estimated on the HR scale. Subjects with a diagnosis of depression at baseline were excluded in the mediation analyses.

All analyses were adjusted for potential confounding variables including sex, employment status, working hours, educational level, body mass index, smoking, physical activity, coffee consumption, cardiovascular disease, and cancer. Employment status was categorized into working, retired, student, unemployed, long-term sick-leave or other. Working hours were categorized into daytime work, shift work, no work hours, or other. 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 kg/m^2), normal weight (18.5–24.99 kg/m^2), overweight (25–30 kg/m^2), or obese (>30 kg/m^2). Smoking was categorized into never, past, or current smokers, or smokers with unknown current smoking status. 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 (180 min or more) or inactive (<180 min). Coffee consumption was categorized into 0, 1–4, 5–7, or greater than 7 cups of coffee per day. Information regarding diagnoses of cardiovascular disease (ICD-10 codes I00-I99) and cancer (ICD-10 codes C00-C97) at baseline were 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. When appropriate, analyses were also adjusted for sleep duration as a continuous variable (hours/night).

Participants with missing data on habitual sleep duration, insomnia or depressive symptoms were excluded in our study. After applying the exclusion criteria, the proportion of missing data was relatively low (3.9% for BMI, 1.6% for coffee consumption, 1.2% for smoking and less than 1% for employment status, working hours, educational level, and physical activity). For each variable, missing data was treated as a separate unknown category.

We performed several supplementary analyses: (1) We conducted the analyses restricted to participants who reported that they never used hypnotic medications. Hypnotic use at baseline was assessed by asking the participants to estimate how often they used sleeping pills. (2) In a sensitivity analysis, we further adjusted the analyses for heavily snoring among participants who had provided information on this, with the answer alternatives never, seldom, sometimes, mostly, or always. Snoring heavily was defined as mostly or always snoring heavily. (3) Some deaths might have been recorded as non-suicidal because of unclear circumstances of death. Therefore, we also calculated the HR of all-cause mortality associated with each sleep variable, stratified by sleep duration (<7 or 7+ h/night). (4) We performed supplementary analyses including all participants with incomplete data. The proportion of missing data was therefore slightly changed (5.9% for sleep duration, 4.0% for BMI, 1.6% for coffee consumption, 1.2% for ever smoking, 1.1% for insomnia, and < 1% for employment status, working hours, educational level, physical activity, and depressive symptoms). Missing data were imputed 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 insomnia status, are presented in Table 1. Insomnia was more common among women than among men. Compared to subjects without insomnia, subjects suffering from insomnia had shorter sleep duration and more depressive symptoms. They were older, less educated, had a higher BMI, reported lower physical activity and had more often been diagnosed with cancer or cardiovascular disease.

Baseline characteristics of participants are also presented by sleep duration (Table 2). Generally, women slept longer than men. Subjects who slept less than 7 h/night were older and less educated. They more often reported shift work, depressive symptoms, current smoking, and physical inactivity, compared to subjects who slept 7 h/night or more.

The relationships between insomnia, sleep duration, depression and suicide risk

During a mean follow-up time of 19.2 years (median 20.6), 66 deaths by suicide occurred. Overall, insomnia was associated with increased risk of suicide (HR 1.87, 95% 1.04–3.43). Of the separate nocturnal symptoms, difficulty initiating sleep was most strongly associated with risk of suicide (Table 3).

The association between insomnia and suicide risk became more pronounced with decreasing depressive symptoms (p value for trend <0.05).

When the analysis was stratified by self-reported sleep duration, the association between insomnia and suicide risk remained significant among those who slept 6 h/night or less (HR 2.53, 95% CI 1.13–5.66), whereas no significant association was observed among those who slept 7 h/night or more (HR 1.27, 95% CI 0.45–3.57) (Table 4).

When subjects were categorized based on insomnia status and sleep duration, the risk of suicide was only increased among those exposed to both factors, whereas neither factor increased suicide risk in the absence of the other factor (Table 5).

The influence of insomnia symptoms on the risk of depression

Among subjects without a diagnosis of depression at baseline, the odds of depression during follow-up were higher among those who suffered from insomnia than among those who did not (Table 6). There was a significant trend that showed increasing odds of receiving a diagnosis of depression during follow-up with increasing frequency of insomnia symptoms at baseline (p value for trend <0.05) *Mediation analysis* The causal mediation analysis revealed that the total effect, expressed on the HR scale, of insomnia in the context of short sleep on suicide risk was 2.85 (95% CI 1.42–5.74). The direct effect was 2.25 (95% CI 1.12–4.54) and the indirect effect, mediated by

Table 1. Baseline Characteristics, Overall and Stratified by Insomnia Status

Variable	Total	Insomnia		*p* values for difference between groups
		Yes	No	
N	38,786	5,283	33,503	
Mean age (SD)	50.4 (15.7)	52.5 (15.7)	50.1 (15.7)	<0.05
Women, *n* (%)	24,951 (64)	3,616 (68)	21,335 (64)	<0.05
University degree, *n* (%)	11,342 (29)	1,290 (24)	10,052 (30)	<0.05
Daytime work, *n* (%)	24,103 (62)	2,943 (56)	21,160 (63)	<0.05
Shift work, *n* (%)	2,299 (5.9)	312 (5.9)	1,987 (5.9)	1.00
Other work hours, *n* (%)	798 (2.1)	94 (1.8)	704 (2.1)	0.13
No work, *n* (%)	9,088 (23)	1,503 (28)	7.585 (23)	<0.05
Mean sleep duration, hours/night (SD)	6.8 (1.0)	6.1 (1.2)	7.0 (0.9)	<0.05
Sometimes depressive symptoms, *n* (%)	19,686 (51)	3166 (60)	16,520 (49)	<0.05
Often/always depressive symptoms, *n* (%)	2,450 (6.3)	910 (17)	1,541 (4.6)	<0.05
Current smokers, *n* (%)	2,869 (7.4)	478 (9.8)	2,391 (7.6)	<0.05
Past smokers, *n* (%)	10,185 (26)	1,393 (29)	8,792 (28)	0.28
BMI, kg/m^2 (SD)	24.6 (3.5)	24.8 (3.8)	24.6 (3.5)	<0.05
Low physical activity, *n* (%)	6,008 (15)	888 (17)	5,120 (15)	<0.05
Coffee, no of cups/daily (SD)	2.8 (1.8)	2.8 (1.8)	2.8 (1.8)	0.93
Alcohol drinkers, *n* (%)	34,370 (89)	4,630 (88)	29,740 (89)	0.02
Standard glasses of alcohol per week (SD)	6.4 (4.3)	6.2 (4.3)	6.4 (4.3)	0.41
Cancer, *n* (%)	2,361 (6.1)	448 (8.5)	1,913 (5.7)	<0.05
Cardiovascular disease, *n* (%)	3,969 (10)	699 (13)	8,270 (10)	<0.05

Differences in baseline variables were assessed using one-way analysis of variance (ANOVA) for continuous variables and the Kruskal–Wallis test (Mann–Whitney *U* test) for categorical variables. Insomnia was defined as often or always experiencing at least one nocturnal insomnia symptoms in combination with sometimes, often or always experiencing at least one symptom of non-restorative sleep.

Table 2. Baseline Characteristics, Overall and Stratified by Sleep Duration

Variable	Total	Sleep duration		*p* values for difference between groups
		<7 h/night	7+ h/night	
N	38,786	12,273	26,513	
Mean age (SD)	50.4 (15.7)	51.4 (15.6)	49.9 (15.7)	<0.05
Women, *n* (%)	24,951 (64)	7,511 (61)	17,440 (66)	<0.05
University degree, *n* (%)	11,342 (29)	3,262 (27)	8,080 (30)	<0.05
Daytime work, *n* (%)	24,103 (62)	7,327 (60)	16,776 (63)	<0.05
Shift work, *n* (%)	2,299 (5.9)	1,028 (8.4)	1271 (4.8)	<0.05
Other work hours, *n* (%)	798 (2.1)	300 (2.4)	498 (1.9)	<0.05
No work, *n* (%)	9,088 (23)	2,794 (23)	6,294 (24)	0.04
Sometimes depressive symptoms, *n* (%)	19,686 (51)	6,569 (54)	13,117 (49)	<0.05
Often/always depressive symptoms, *n* (%)	2,450 (6.3)	1,060 (8.6)	1,390.(5.2)	<0.05
Insomnia, *n* (%)	5,283 (14)	3,260 (27)	2,023 (7.6)	<0.05
Current smokers, *n* (%)	2,869 (7.4)	1,108 (9.0)	1,761 (6.6)	<0.05
Past smokers, *n* (%)	10,185 (26)	3,275 (27)	6,910 (26)	0.20
BMI, kg/m^2 (SD)	24.6 (3.5)	24.8 (3.6)	24.5 (3.4)	<0.05
Low physical activity, *n* (%)	6,008 (15)	2,010 (16)	3,998 (15)	<0.05
Coffee, no of cups/daily (SD)	2.8 (1.8)	3.1 (1.8)	2.8 (1.8)	<0.05
Alcohol drinkers, *n* (%)	34,370 (89)	10,942 (89)	23,428 (88)	0.02
Standard glasses of alcohol per week (SD)	6.4 (4.3)	6.5 (4.4)	6.3 (4.3)	<0.05
Cancer, *n* (%)	2,361 (6.1)	773 (6.3)	1,588 (6.0)	0.24
Cardiovascular disease, *n* (%)	3,969 (10)	1,404 (11)	2,565 (10)	<0.05

Differences in baseline variables were assessed using one-way analysis of variance (ANOVA) for continuous variables and the Kruskal–Wallis test (Mann–Whitney *U* test) for categorical variables.

depression, was 1.27 (95% CI 1.05–1.53). Of the total effect, 32% was mediated by depression. There was no significant interaction between insomnia in the context of short sleep and depression with regard to suicide risk.

Hypnotic use at baseline was highly correlated with insomnia complaints, short sleep, depression, and suicide. However, our findings remained similar when the analyses were restricted to include those who reported that they never used hypnotic medications. The HR of death by suicide was 2.57 (95% CI 1.06–6.26) among short sleepers with insomnia who never used hypnotic medications at baseline. Snoring heavily was significantly associated with both insomnia complaints, short sleep and depression. However, snoring heavily was not associated with suicide (HR 0.86, 95% CI 0.45–1.67).

Table 3. HR with 95% CI of Suicide among Subjects Suffering from Insomnia Symptoms, Compared to Subjects without Insomnia Symptoms

Insomnia symptoms		N	Person years	Deaths due to suicide (%)	HR (95% CI)*	HR (95% CI)†
Difficulty initiating sleep	Never, seldom	22,997	443,010	31 (0.13)	1.0 (reference)	1.0 (reference)
	Sometimes	13,709	260,927	27 (0.20)	**1.70 (1.01–2.87)**	**1.61 (0.95–2.72)**
	Often, always	2,080	38,906	8 (0.38)	**3.40 (1.56–7.43)**	**3.00 (1.32–6.81)**
Difficulty maintaining sleep	Never, seldom	20,517	399,523	34 (0.17)	1.0 (reference)	1.0 (reference)
	Sometimes	15,554	292,871	26 (0.17)	1.12 (0.66–1.89)	1.05 (0.62–1.78)
	Often, always	2,715	50,450	6 (0.22)	1.58 (0.65–3.83)	1.33 (0.56–3.39)
Early-morning awakening	Never, seldom	18,099	349,314	28 (0.15)	1.0 (reference)	1.0 (reference)
	Sometimes	17,333	329,947	28 (0.16)	1.04 (0.61–1.75)	1.01 (0.60–1.71)
	Often, always	3,354	63,583	10 (0.30)	1.92 (0.93–3.96)	1.76 (0.84–3.75)
Tired at awakening	Never, seldom	15,133	283,360	26 (0.17)	1.0 (reference)	1.0 (reference)
	Sometimes	17,918	346,564	29 (0.16)	1.08 (0.63–1.86)	1.10 (0.64–1.90)
	Often, always	5,735	112,919	11 (0.19)	1.34 (0.64–2.77)	1.28 (0.61–2.71)
Daytime tiredness	Never, seldom	14,061	267,031	22 (0.16)	1.0 (reference)	1.0 (reference)
	Sometimes	21,847	419,401	36 (0.16)	1.15 (0.68–1.97)	1.11 (0.65–1.89)
	Often, always	2,878	56,410	8 (0.28)	2.11 (0.91–4.85)	1.83 (0.78–4.28)
Insomnia‡	No	33,503	643,316	51 (0.15)	1.0 (reference)	1.0 (reference)
	Yes	5,283	99,527	15 (0.28)	**1.99 (1.12–3.55)**	**1.87 (1.04–3.43)**

Significant HRs are in bold.
*Adjusted for gender.
†adjusted for gender, occupational status, working hours, educational status, smoking, physical activity, coffee consumption, sleep duration, cardiovascular disease, and cancer.
‡Insomnia was defined as often or always experiencing at least one nocturnal insomnia symptoms in combination with sometimes, often or always experiencing at least one symptom of non-restorative sleep.

Table 4. HR with 95% CI of Suicide among Subjects Suffering from Insomnia Symptoms, Compared to Subjects without Insomnia Symptoms, Stratified by Sleep Duration

		Sleep duration							
		<7 h/night				7+ h/night			
Insomnia symptoms		N	Person years	Deaths due to suicide (%)	HR (95% CI)‡	N	Person years	Deaths due to suicide (%)	HR (95% CI)*
Difficulty initiating sleep	Never, seldom	5,967	114,800	6 (0.10)	1.0 (reference)	17,030	328,210	25 (0.15)	1.0 (reference)
	Sometimes	4,900	92,388	14 (0.29)	**3.25 (1.24–8.52)**	8,809	168,539	13 (0.15)	1.09 (0.52–2.15)
	Often, always	1,406	26,235	5 (0.36)	**4.12 (1.23–13.8)**	674	12,672	3 (0.45)	3.10 (0.93–10.4)
Difficulty maintaining sleep	Never, seldom	5,198	101,525	6 (0.12)	1.0 (reference)	15,319	297,998	28 (0.18)	1.0 (reference)
	Sometimes	5,149	96,265	13 (0.25)	**3.00 (1.09–8.28)**	10,405	196,606	13 (0.12)	0.65 (0.33–1.28)
	Often, always	1,926	35,634	6 (0.31)	**4.46 (1.32–15.1)**	789	14,816	0	-
Early-morning awakening	Never, seldom	4,489	86,841	6 (0.13)	1.0 (reference)	13,610	262,473	22 (0.16)	1.0 (reference)
	Sometimes	5,749	108,416	10 (0.17)	1.36 (0.50–3.78)	11,584	221,531	18 (0.16)	0.93 (0.50–1.73)
	Often, always	2,035	38,166	9 (0.44)	**3.73 (1.29–10.8)**	1,319	25,417	1 (0.08)	0.72 (0.10–3.14)
Tired at awakening	Never, seldom	3,457	63,716	8 (0.23)	1.0 (reference)	11,676	219,645	18 (0.15)	1.0 (reference)
	Sometimes	5,952	113,545	12 (0.20)	1.06 (0.43–2.65)	11,966	233,020	17 (0.14)	1.09 (0.56–2.15)
	Often, always	2,864	56,162	5 (0.17)	0.88 (0.27–2.87)	2,871	56,756	6 (0.21)	1.77 (0.68–4.57)
Daytime tiredness	Never, seldom	3,684	69,142	6 (0.16)	1.0 (reference)	10,377	197,890	16 (0.15)	1.0 (reference)
	Sometimes	7,233	137,780	15 (0.21)	1.30 (0.50–3.40)	14,614	281,622	21 (0.14)	1.03 (0.53–1.98)
	Often, always	1,356	26,501	4 (0.29)	1.64 (0.43–6.25)	1,522	29,910	4 (0.16)	2.16 (0.70–6.67)
Insomnia†	No	9,013	172,399	14 (0.16)	1.0 (reference)	24,490	470,917	37 (0.15)	1.0 (reference)
	Yes	3,260	61,024	11 (0.34)	**2.53 (1.13–5.66)**	2,023	38,503	4 (0.20)	1.27 (0.45–3.57)

Significant HRs are in bold.
*Adjusted for gender, occupational status, working hours, educational status, smoking, physical activity, coffee consumption, cardiovascular disease, and cancer.
†Insomnia was defined as often or always experiencing at least one nocturnal insomnia symptoms in combination with sometimes, often or always experiencing at least one symptom of non-restorative sleep.

Our results remained almost identical after adjustment for heavily snoring.

Neither of the sleep variables were associated with all-cause mortality among short sleepers (<7 h/night), whereas daytime tiredness was associated with increased mortality among those who slept 7 h/night or longer (HR 1.18, 95% CI 1.01–1.37).

Our results remained stable after carrying out the analyses on the multiple imputed data (data not shown).

Table 5. HR with 95% CI of Suicide among Subjects with Different Combinations of Insomnia and Short Sleep

Insomnia*	Short sleep†	N	Person years	Deaths (%)	HR (95% CI)‡	HR (95% CI)§
No	No	24,490	470,917	37 (0.15)	1.0 (reference)	1.0 (reference)
No	Yes	9,013	172,399	14 (0.16)	0.94 (0.51–1.75)	0.96 (0.52–1.78)
Yes	No	2,023	38,503	4 (0.20)	1.35 (0.48–3.77)	1.26 (0.45–3.54)
Yes	Yes	3,260	61,024	11 (0.34)	**2.36 (1.20–4.63)**	**2.26 (1.15–4.44)**

Significant HRs are in bold.
*Insomnia was defined as often or always experiencing at least one nocturnal insomnia symptoms in combination with sometimes, often or always experiencing at least one symptom of non-restorative sleep.
†Short sleep was defined as sleeping 6 h/night or less.
‡Adjusted for gender.
§Adjusted for gender, occupational status, working hours, educational status, smoking, physical activity, coffee consumption, cardiovascular disease, and cancer.

Table 6. OR with 95% CI of Receiving a Diagnosis of Depression during Follow-up among Subjects with Insomnia, Compared to Those without Insomnia

Insomnia	*N*	Incident depression, *n* (%)	OR (95% CI)*	OR (95% CI)†
No	33,137	1,079 (3.3)	1.0 (reference)	1.0 (reference)
Yes	5,145	296 (5.8)	**1.77 (1.55–2.03)**	**1.75 (1.53–2.00)**

Significant ORs are in bold.
*Adjusted for gender.
†Adjusted for gender, occupational status, educational status, smoking, alcohol consumption habits, physical activity, coffee consumption, sleep duration, cardiovascular disease, and cancer.

Discussion

In this Swedish prospective cohort study, we show that insomnia in the context of short sleep increases suicide risk. Causal mediation analysis revealed both a direct effect on suicide risk as well as an indirect effect, mediated by depression.

The association between insomnia and suicide risk was highly dependent on sleep duration. Only insomnia in the context of short sleep was associated with increased suicide risk, whereas no significant association was observed between insomnia and suicide among those who slept 7 h/night or more. Short sleep negatively affects cognitive functions and emotional regulation [27]. Impaired sleep also results in a gradual reduction of serotonergic receptor expression that may further affect cognitive functions and mood regulation, and increase the risk of depression and suicide [28–30]. Additional work is needed to further elucidate the relationship between insomnia, sleep duration, and depression, including investigations of shared neurobiological pathways.

The association between insomnia and suicide risk became more pronounced with decreasing depressive symptoms, which is in line with findings from the 2013 Canadian Forces Mental Health Survey [6]. Subjects without depressive symptoms who suffer from insomnia may be at a greater risk of developing a depressive episode [31], and consequently have a higher risk of committing suicide, compared to non-depressed subjects without insomnia. Our findings also indicate that there may be a ceiling effect of the impact of insomnia on suicide risk. When depressive symptoms are present, the influence of insomnia symptoms on suicide risk may be less pronounced due to already existing mental health problems.

Neither of the sleep variables were associated with all-cause mortality among subjects who slept less than 7 h/night, whereas daytime tiredness was associated with increased mortality among those who slept 7 h/night or longer. Daytime sleepiness combined with long sleep may be a nonspecific sign of underlying illness. It is thus possible that underlying illness contributes to the association between daytime tiredness and all-cause mortality.

Important strengths of our study are the prospective design and 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. The main limitation is that all exposure information was self-reported and only measured at baseline. Potential changes in any of the investigated parameters during the follow-up period would go undetected in our study. Information regarding medications, some of which are associated with both sleep parameters and suicide risk, was not available in our study except from self-reported use of hypnotics at baseline. Our findings remained similar when those who used hypnotic medication at baseline were excluded from the analyses. However, a substantial proportion of subjects initiates or discontinues hypnotic use in a relatively short period of time, and we could not consider the subsequent use of hypnotics after baseline. 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. For example, the level of missing data was remarkably low in our study.

Future prospective cohort studies with follow-up questions regarding sleep duration, sleep quality and depression would be valuable in order to study whether habitual sleep duration is longitudinally stable, and investigate the associations between sleep duration, depression and suicide in more detail.

In conclusion, insomnia in the context of short sleep increases suicide risk, both directly and indirectly by affecting the risk of depression. Abnormalities of sleep duration and insomnia symptoms should be evaluated when assessing suicide risk.

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