Insomnia and the Risk of Acute Myocardial Infarction
A Population Study

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Background—Few prospective studies have investigated insomnia in relation to risk for coronary heart disease. We assessed insomnia symptoms and risk of acute myocardial infarction (AMI) in a large, population-based study.

Methods and Results—A total of 52 610 men and women were followed up for a first AMI, and 2368 incident AMIs occurred during 11.4 years of follow-up, either identified at hospitals or by the National Cause of Death Registry. In our analyses, we adjusted for age, sex, marital status, education, shift work, blood pressure, lipids, diabetes mellitus, body mass index, physical activity, smoking, and alcohol consumption. Difficulties initiating and maintaining sleep and having a feeling of nonrestorative sleep were associated with a moderate increase in AMI risk. The multiadjusted hazard ratios for AMI were 1.45 (95% confidence interval 1.18–1.80) for people with difficulties initiating sleep almost every night, 1.30 (1.01–1.68) for those with difficulties maintaining sleep almost every night, and 1.27 (1.03–1.57) for those with a feeling of nonrestorative sleep more than once a week compared with people who never experienced these sleep difficulties. When we combined the symptoms, a dose-dependent association was seen between the number of insomnia symptoms and AMI risk (*P* for trend 0.003). Alternative multivariable models and different sensitivity analyses suggest that the results were robust, especially concerning difficulties initiating sleep.

Conclusions—Insomnia is associated with a moderately increased risk for AMI. **(*Circulation*. 2011;124:2073-2081.)**

Key Words: insomnia ■ epidemiology ■ acute myocardial infarction ■ prospective studies ■ risk factors

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Insomnia, a subjective feeling of having difficulty initiating or maintaining sleep or having a feeling of nonrestorative sleep, is a highly prevalent condition in the industrialized world. It has been estimated that the prevalence of at least 1 insomnia symptom could be as high as 33% in the general population.[1] Only a few prospective studies have investigated insomnia in relation to risk for coronary heart disease (CHD), and the results have been inconsistent.[2–14] Most previous studies were small and assessed only a few aspects of insomnia, and in many studies, outcomes were poorly defined and often based on self-report.

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There is a considerable overlap between insomnia and psychological distress, especially depressive symptoms, and insomnia is very common in several chronic somatic disorders.[15] However, only a few prospective studies of insomnia and CHD included measures of depression and anxiety or evaluated the possible role of chronic somatic disorders. Therefore, we prospectively investigated the association of insomnia symptoms with the risk of acute myocardial infarction (AMI) in a large population-based study, taking into account the effects of established cardiovascular risk factors, psychological distress, and chronic somatic disorders.

Methods

Study Population

The adult population of Nord Trøndelag County in Norway was invited to participate in a health survey (the HUNT Study) from August 1995 to June 1997. In total, 94 187 individuals were invited, and 65 215 (69%) participated in the study, filled out a questionnaire, and attended a clinical examination at baseline. Details about the study have been published elsewhere.[16] The study was approved by the regional committee for ethics in medical research, by the National Directorate of Health, and by the Norwegian Data Inspectorate.

Insomnia

Insomnia is a subjective feeling of having difficulty in initiating or maintaining sleep or having a feeling of nonrestorative sleep.[17] The HUNT questionnaire included 3 items related to insomnia. One question was related to difficulty in initiating sleep ("Have you had difficulties falling asleep in the last month?" with the following response options: never/occasionally/often/almost every night). The second question was related to difficulty in maintaining sleep ("During the last month, have you woken up too early and not been able to get back to sleep?" with the

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following response options: never/occasionally/often/almost every night). The third question was related to having a feeling of nonrestorative sleep ("How often do you suffer from poor sleep?" with the following response options: never or a few times a year/1–2 times per month/about once a week/more than once a week). The last question was restricted to individuals 20 to 69 years of age.

We assessed the influence of each insomnia symptom using the original 4 response categories. Insomnia symptoms were also dichotomized, and the highest categories, ie, difficulty initiating sleep almost every night, difficulty maintaining sleep almost every night, and nonrestorative sleep more than once a week, were compared with the rest of the categories. Those in the highest categories were assumed to have the respective insomnia symptom in the analysis of the association between the number of insomnia symptoms and AMI risk.

Apart from insomnia symptoms, participants 20 to 69 years of age were also asked whether symptoms related to sleep influenced their work situation ("During the last year, have you been troubled by insomnia to such a degree that it influenced your work performance?" with the response options "yes " or "no").

In total, 54 403 participants (83.4%) answered 1 or more of the insomnia questions. The separate response rates for the insomnia-related questions were 82.5%, 82.7%, 82.3%, and 81.3%, respectively. These response rates largely reflect the overall response rate of the questionnaire that included insomnia items (84.9%).

Outcome Ascertainment

After participating at the baseline examination, the participants were followed up for a first AMI, either identified at hospitals or by the National Cause of Death Registry. A total of 1780 participants reported a history of myocardial infarction at baseline and were therefore excluded from follow-up. An additional 13 participants were excluded because their medical records indicated a previous myocardial infarction. Therefore, 52 610 people were included in the analyses of the present study.

Hospitalizations for AMI were identified through linkage with medical records from the 2 hospitals of Nord-Trøndelag County from the baseline examination until December 31, 2008. AMI was defined and diagnosed according to the European Society of Cardiology/American College of Cardiology consensus guideline.[18] Criteria for AMI included (1) certain symptoms according to case history information, (2) specified changes in blood levels of cardiac enzymes, and (3) specified ECG changes. Case subjects with AMI who never reached the hospital were identified by the National Cause of Death Registry (International Classification of Diseases, 9th Revision, code 410; 10th Revision codes I21 and I22).

During the follow-up period of 11.4 years, 200 participants who left the county and 7226 participants who died of other causes than AMI were censored at the time of the event (emigration or death) in the statistical analysis.

Clinical Information

The clinical examination was conducted by trained nurses and included standardized assessment of blood pressure, weight, height, and waist and hip circumference. Systolic and diastolic blood pressures were measured with a Dinamap 845XT (Critikon/GE Healthcare) sphygmomanometer based on oscillometry, and the average of the second and third measurements was used in the analysis. Height and weight were recorded with participants wearing light clothes without shoes; height was measured to the nearest 1 cm and weight to the nearest 0.5 kg. Waist circumference was measured to the nearest centimeter at the level of the umbilicus. Body mass index (BMI) was computed as weight (in kilograms) divided by the squared value of height (in meters).

Information on health, lifestyle factors, and medication use was collected by means of a self-administered questionnaire. Participants extensively assessed and reported their medical history regarding common chronic somatic disorders.

The participants were asked about their usual intake of wine, beer, and spirits, indicated by their usual number of drinks over a 2-week period. We categorized participants according to their alcohol consumption as abstainers, light drinkers (0–1 drinks per day), moderate drinkers (>1 but ≤2 drinks per day), or heavy drinkers (>2 drinks per day).

The participants were also asked about their level of physical activity. Light physical activity was defined as activity that does not involve sweating or a feeling of breathlessness. The participants were classified as (1) inactive if they reported less than 1 hour of hard and less than 3 hours of light physical activity per week, (2) moderately active if they reported 1 to 3 hours of hard or >3 hours of light activity per week, and (3) physically active if they reported >3 hours of hard physical activity per week.

Responses to questions related to smoking were categorized as current, previous, or never smoking. Education was categorized as low (≤9 years), medium (between 10 and 12 years), or high (>12 years). Marital status was dichotomized as living alone or not.

Participants were asked about their use of sleep medication/sedatives ("How often have you taken tranquilizers/sedatives or sleep medication in the last month?" with the following response options: daily/every week but not every day/less than once a week/never). Type of medication was not available, but based on regional prescription statistics, benzodiazepines were the dominant type.

Depression and Anxiety

The Hospital Anxiety and Depression Scale was used to assess symptoms of anxiety and depression. The questionnaire consisted of 14 four-point Likert-scaled items, 7 for anxiety and 7 for depression. Scores on both the anxiety and depression subscales ranged from 0 to 21, and increasing score indicated increased symptom load. No somatic items or items regarding sleeping difficulties were included. The Hospital Anxiety and Depression Scale has been found to have good testing properties in the assessment of symptom severity of anxiety and depression both in primary health care and in hospital settings.[19] The psychometric properties of the scale have been validated previously in HUNT-2.[20]

Laboratory Measurements

A nonfasting serum sample was drawn from each participant and analyzed at the Central Laboratory, Levanger Hospital, with a Hitachi 911 autoanalyzer. Serum was separated from the blood by centrifugation within 2 hours at the screening site and placed in a refrigerator (4°C). Time between the last meal and the venipuncture was recorded, and the samples were sent to the laboratory on the same day (some samples drawn on a Friday were sent the following Monday).

Serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were analyzed by applying reagents from Boehringer Mannheim. The day-to-day coefficients of variation were 1.3% to 1.9%, 2.4%, and 0.7% to 1.3%, respectively. Total and high-density lipoprotein cholesterol were measured by an enzymatic colorimetric cholesterol esterase method. Measurement of high-density lipoprotein cholesterol was performed after precipitation with phosphotungsten and magnesium ions. Triglycerides were measured with an enzymatic colorimetric method.

Statistical Analysis

Comparisons of continuous variables among different groups were made by 1-way ANOVA, and χ^2 test was used to compare categorical data. We used Cox proportional hazard models to examine the association of insomnia symptoms with subsequent risk of AMI. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs). Each category of reported insomnia symptoms was compared with reporting no insomnia complaints. For tests of trend, we assigned a numeric value of 0 to 3 to the insomnia categories, with 0 having no insomnia complaints, treating the categories as a continuous variable.

In a separate analysis, we calculated the risk associated with the increasing number of dichotomized insomnia symptoms when those without any symptoms constituted the reference group. Participants having missing data on any of the insomnia symptoms were excluded from this analysis. In addition, the assessment of having a feeling of nonrestorative sleep was restricted to participants 20 to 69 years of age, and the analysis on cumulative number of insomnia symptoms was therefore also restricted to this age group.

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We used age at risk as the time dimension, which allows a very precise adjustment for age,[21] and we included sex, education, shift work, and marital status as potentially confounding factors in our models. Established cardiovascular risk factors such as high blood pressure, low physical activity, high BMI, smoking, abstinence from alcohol and heavy drinking, dyslipidemia, and diabetes mellitus may act as both confounding and mediating factors for the association of sleep disorders with AMI risk. We therefore analyzed the data both with and without the factors included in the analysis. As shown in the online-only Data Supplement, the pairwise correlations between some of the established cardiovascular risk factors were relatively strong. Therefore, we examined several alternative models, and because the estimates were robust, we chose to use a parsimonious model as a base that included BMI, smoking, systolic blood pressure, total cholesterol, physical activity, and diabetes mellitus.

It is not clear whether psychological distress is a cause or a consequence of sleep disorders. Thus, in separate analyses, we additionally adjusted for depression and anxiety.

We conducted several stratified analyses to assess whether the association of insomnia symptoms and AMI could be modified by other factors. We investigated the potential effect modification by sex, age (dichotomized at age 50 and at age 65 years), BMI (dichotomized at 35 kg/m^2), cholesterol (dichotomized at 6.5 mmol/L), education (dichotomized at 12 years), shift work, blood pressure (high blood pressure was defined as having systolic blood pressure >140 mm Hg and/or having diastolic blood pressure >90 mm Hg), smoking status (current versus no current smoking), and an aggregate risk factor variable. For the latter analysis, people who reported current smoking, with BMI ≥35 kg/m^2 and serum cholesterol ≥6.5 mmol/L, were labeled high-risk participants and analyzed separately from the rest of the study population. We also formally tested the homogeneity of stratum-specific relative risks. For these tests of interaction, we used the insomnia trend variables as defined above.

Because Nord Trøndelag County is close to the Arctic Circle, the seasonal variation in the amount of daylight is considerable, which in turn can affect sleep.[22] To address the possibility that the association of insomnia with AMI risk could be modified by the season of report, we separately examined those who reported insomnia symptoms in months with daylight predominance (April, May, June, July, and August) and in predominantly dark months (October, November, December, January, and February).

We performed several sensitivity analyses to assess the robustness of our findings. To address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 5 years of follow-up and repeated the analyses. We also restricted the analyses to AMI cases that were confirmed at the hospital; thus, we excluded cases whose diagnosis was based on death certificates alone. In another sensitivity analysis, we excluded participants with known chronic disorders, such as stroke, asthma, angina pectoris, diabetes mellitus, goiter, hypothyroidism, hyperthyroidism, fibromyalgia, arthritis, rheumatism, ankylosing spondylitis, cancer, epilepsy, diabetes mellitus, or osteoporosis. In other sensitivity analyses, we excluded participants who reported using sleep medications/sedatives on a daily basis, and we restricted the analyses to those who never used sleep medications/sedatives. Because blood sampling was nonfasting, blood lipid values, especially for triglycerides, could be influenced by time since last meal. In a sensitivity analysis, we therefore adjusted for time between the last meal and the venipuncture. In another set of separate analyses, we adjusted for intake of wine instead of overall intake of alcohol.

We tested the proportionality of hazards using log-log curves and formal tests of interaction with time or log-time. There was no evidence against the proportionality assumption (all $P>0.10$).

Statistical analyses were conducted with Stata 10.1 for windows (Stata Corp).

Results

Table 1 displays characteristics of the study population according to difficulties initiating sleep. The other 2 insomnia symptoms, difficulty maintaining sleep and that of nonrestorative sleep, showed largely similar associations to these characteristics (data not shown). Prevalence of having difficulties initiating sleep almost every night was 3.3%. The corresponding prevalences for having difficulties maintaining sleep almost every night and having nonrestorative sleep more than once a week were 2.5% and 8.0%, respectively. High frequency of insomnia symptoms was most prevalent among older participants and was more frequent in women than men. In general, insomnia symptoms were associated with cardiovascular risk factors in a dose-dependent manner. There was also a strong association between insomnia symptoms and depression, anxiety, and the use of sleep medication/sedatives.

Among 52 610 participants, a total of 2368 had a first AMI during follow-up. A total of 1813 were diagnosed at hospital admission, and 555 cases were identified based on information from the National Cause of Death Register alone.

We found that established risk factors were all associated with AMI risk in the expected direction and with the expected effect size (data not shown).

Table 2 presents the age- and sex-adjusted and several multivariable adjusted HRs for AMI in relation to insomnia symptoms. Having difficulty initiating sleep almost every night, difficulty maintaining sleep almost every night, and having the feeling of nonrestorative sleep more than once a week were associated with increased risk of AMI compared with those who reported never or almost never having these symptoms. After adjustment for established cardiovascular risk factors, the effect sizes of the associations were attenuated slightly; however, the estimates of effect were not further attenuated after adjustment for depression or anxiety.

The HRs for AMI when insomnia with influence on work was compared with insomnia that did not have such an influence were 1.25 (95% CI 1.04–1.50) and 1.22 (95% CI 0.99–1.49) in models 1 and 3, respectively, and were not substantially different in other models. The number of insomnia symptoms was associated with increased risk of AMI in a dose-dependent manner in all models (Table 3).

As shown in Table 4, compared with men, women appeared to have somewhat higher relative risks of AMI associated with difficulties initiating sleep almost every night and for the cumulative symptoms of insomnia. We found no statistical evidence for any effect modification by other stratifying factors, ie, age (Table 5), BMI, cholesterol, education, shift work, blood pressure, smoking status, or the aggregated risk variable, and the association of insomnia symptoms with AMI risk was largely consistent in these subgroup analyses.

We found some evidence that difficulty initiating sleep reported during the dark period of the year was more strongly associated with AMI risk than difficulty initiating sleep reported during months with daylight predominance. For the dark period, in model 3, the HR for the highest category was 1.63 (95% CI 1.19–2.23). For the light period, the corresponding HR was 1.08 (95% CI 0.66–1.76), and the probability value for interaction was 0.034. There was no evidence for such an interaction with regard to the other 2 insomnia symptoms.

Sensitivity Analyses

The estimates remained essentially unchanged or became slightly stronger after exclusion of the first 5 years of

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Table 1. Baseline Characteristics of Participants According to Difficulties Initiating Sleep

Variable	No. of Subjects	Difficulties Initiating Sleep				P
		Never	Sometimes	Often	Almost Every Night	
Total, % (n)	51 982	55.1 (28 630)	36.2 (18 818)	5.5 (2846)	3.3 (1691)	
Variables, % (n)						
Male sex	23 226	48.3 (14 008)	41.2 (7754)	33.0 (939)	31.0 (525)	<0.0001
Diabetes mellitus	1411	2.4 (690)	2.8 (522)	3.4 (95)	6.2 (104)	<0.0001
Smoking						
Never	24 141	49.2 (14 017)	44.7 (8369)	37.5 (1063)	41.1 (692)	
Former	12 990	25.8 (7342)	24.8 (4637)	22.6 (639)	22.1 (373)	
Current	14 611	25.1 (7145)	30.5 (5718)	39.9 (1130)	36.7 (618)	<0.0001
Alcohol						
Abstainer	19 709	38.8 (10 520)	40.1 (7083)	44.3 (1174)	59.6 (932)	
Light drinker	22 826	48.4 (13 132)	45.9 (8102)	41.9 (1110)	30.8 (482)	
Moderate drinker	5035	10.1 (2742)	10.8 (1914)	10.5 (277)	6.5 (102)	
Heavy drinker	1417	2.6 (717)	3.2 (566)	3.3 (87)	3.0 (47)	<0.0001
Physical activity						
Inactive	18 109	36.0 (9439)	36.0 (6738)	46.4 (1167)	55.8 (765)	
Moderately active	24 465	53.5 (14 033)	51.5 (8772)	45.5 (1143)	37.7 (517)	
Physically active	4564	10.5 (2760)	8.9 (1510)	8.2 (205)	6.5 (89)	<0.0001
Shift work*	7673	21.2 (4249)	23.8 (2847)	25.5 (433)	22.4 (144)	<0.0001
Living alone	20 154	37.8 (10 806)	39.6 (7421)	40.9 (1162)	45.3 (765)	<0.0001
Education						
≤9 y	17 546	31.6 (8707)	37.5 (6740)	44.7 (1205)	58.5 (894)	
10–12 y	21 763	45.5 (12 514)	42.7 (7684)	40.1 (1081)	31.7 (484)	
>12 y	10 429	22.9 (6309)	19.8 (3558)	15.2 (411)	9.9 (151)	<0.0001
Use of sleep medicine/sedatives daily	2021	1.4 (348)	4.2 (711)	11.5 (299)	42.9 (663)	<0.0001
High risk†	26 784	47.2 (13 435)	55.5 (10 370)	65.1 (1838)	68.5 (1141)	<0.0001
Variables, mean (SD)						
Age, y	51 982	47.7 (16.6)	50.8 (16.8)	52.1 (16.4)	59.4 (18.1)	<0.0001
BMI, kg/m^2	51 682	26.3 (4.0)	26.4 (4.1)	26.5 (4.4)	26.6 (4.3)	0.0003
Systolic BP, mm Hg	51 822	136.8 (21.2)	138.1 (21.9)	138.0 (22.1)	142.6 (24.6)	<0.0001
Diastolic BP, mm Hg	51 822	79.9 (12.0)	80.5 (12.2)	80.8 (12.0)	81.5 (12.7)	<0.0001
Total cholesterol, mmol/L	51 884	5.8 (1.2)	6.0 (1.3)	6.1 (1.3)	6.3 (1.3)	<0.0001
HDL cholesterol, mmol/L	51 871	1.38 (0.38)	1.40 (0.39)	1.41 (0.40)	1.40 (0.42)	<0.0001
Triglycerides, mmol/L	51 884	1.7 (1.1)	1.8 (1.1)	1.8 (1.2)	2.0 (1.2)	<0.0001
Depression score	50 554	2.8 (2.7)	3.9 (3.1)	5.3 (3.7)	6.0 (4.0)	<0.0001
Anxiety score	49 827	3.4 (2.8)	4.9 (3.3)	6.9 (4.1)	7.3 (4.5)	<0.0001

BMI indicates body mass index; BP, blood pressure; and HDL, high-density lipoprotein.

*Those who answered yes to the question, "Do you have shift work, night work, or standing by duties?"

†Individuals who were current smokers or who had a BMI ≥35 kg/m^2 or a cholesterol value ≥6.5 mmol/l were labeled as high-risk participants; all other participants were classified as not at high risk (ie, reference).

follow-up. There were 1416 AMI cases after the fifth year of follow-up. We obtained essentially similar results when we restricted follow-up to AMI cases that were confirmed at the hospital (data not shown).

There were 1024 AMI cases among 32 793 individuals free of all chronic disorders at baseline. The association of insomnia with AMI risk among these participants was similar to that observed in the entire cohort. For example, in model 3, compared with the reference category, the HRs for the highest category were 1.69 (95% CI 1.15–2.50), 1.30 (95% CI 0.82–2.08), and 1.21 (95% CI 0.86–1.68) for difficulties initiating and maintaining sleep and for nonrestorative sleep, respectively. Insomnia with influence on work performance was not associated with AMI risk (HR 0.98, 95% CI 0.71–1.36, model 3) in these sensitivity analyses. The point estimate for the association of the cumulative number of insomnia symptoms was similar to the association observed in the study population as a whole, although the precision of the estimate was lower. In model 3, the HR for 3 insomnia symptoms was 1.89 (95% CI 0.61–5.89).

After the exclusion of 2085 individuals who were daily users of sleep medications/sedatives or restriction of the analyses to never-users of sleep medication (thus excluding 11 915 individuals), the association of AMI risk with difficulty initiating sleep was somewhat strengthened. There were 1858 and 1562 AMI cases in these subcohorts, respectively. In model 3, the HRs for

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Table 2. HRs (95% CIs) for AMI According to Insomnia Symptoms

Variable	Events/Person-Time	Model 1	Model 2	Model 3	Model 4	Model 5
Difficulty initiating sleep						
Never	1166/324 352	Reference	Reference	Reference	Reference	Reference
Occasionally	840/210 079	1.01 (0.92–1.10)	1.04 (0.94–1.14)	1.02 (0.91–1.13)	1.02 (0.92–1.14)	1.04 (0.93–1.16)
Often	140/31 300	1.19 (1.00–1.42)	1.18 (0.97–1.43)	0.98 (0.78–1.22)	0.98 (0.78–1.24)	1.06 (0.84–1.34)
Almost every night	162/17 059	1.58 (1.34–1.87)	1.53 (1.27–1.84)	1.45 (1.18–1.80)	1.48 (1.18–1.84)	1.53 (1.21–1.92)
P for trend		<0.0001	<0.0001	0.019	0.018	0.005
Difficulty maintaining sleep						
Never	718/283 601	Reference	Reference	Reference	Reference	Reference
Occasionally	1265/247 383	1.06 (0.96–1.16)	1.02 (0.92–1.13)	1.06 (0.95–1.18)	1.06 (0.95–1.19)	1.10 (0.98–1.23)
Often	228/39 960	1.11 (0.96–1.30)	1.08 (0.92–1.26)	1.10 (0.91–1.32)	1.15 (0.95–1.39)	1.22 (1.01–1.48)
Almost every night	116/13 110	1.39 (1.14–1.70)	1.33 (1.07–1.65)	1.30 (1.01–1.68)	1.32 (1.01–1.72)	1.46 (1.11–1.90)
P for trend		0.003	0.033	0.049	0.025	0.002
Feeling of nonrestorative sleep						
Never, few times a year	742/350 581	Reference	Reference	Reference	Reference	Reference
1–2 Times per month	177/83 777	0.94 (0.80–1.10)	0.92 (0.77–1.09)	0.91 (0.76–1.09)	0.91 (0.76–1.09)	0.95 (0.79–1.15)
Once a week	97/35 435	1.18 (0.96–1.45)	1.18 (0.95–1.46)	1.04 (0.82–1.33)	1.05 (0.82–1.34)	1.15 (0.90–1.47)
More than once a week	133/39 801	1.30 (1.08–1.57)	1.32 (1.09–1.60)	1.27 (1.03–1.57)	1.25 (1.00–1.55)	1.41 (1.13–1.76)
P for trend		0.007	0.006	0.074	0.115	0.006

HR indicates hazard ratio; CI, confidence interval; and AMI, acute myocardial infarction.

Model 1 adjusted for age and sex; model 2, model 1 plus marital status, education, and shift work; model 3, model 2 plus systolic blood pressure, total cholesterol, diabetes mellitus, body mass index, physical activity, and smoking; model 4, model 3 plus depression; and model 5, model 3 plus anxiety.

having difficulties initiating sleep almost every night were 1.51 (95% CI 1.14–1.99) and 1.64 (95% CI 1.08–2.50). The association of the remaining insomnia complaints remained essentially unchanged (data not shown).

Adjustment for time between last meal and the venipuncture had virtually no effect on the present results. Only the inclusion of wine in the present multivariable models yielded results that were essentially the same as adjusting for total alcohol intake.

Discussion

In this large population-based study, we found that having difficulty initiating sleep almost every night, difficulty maintaining sleep almost every night, and a feeling of nonrestorative sleep more than once a week were each associated with a moderately increased risk for AMI compared with those who reported never or almost never having these insomnia symptoms. Cumulative insomnia symptoms were associated with AMI in a dose-dependent manner, and the results were fairly robust in different multivariable models. We conducted various sensitivity analyses, and the results did not materially change by excluding the first 5 years of follow-up, restricting outcomes to hospital-verified AMI, excluding participants with chronic somatic disorders, or excluding users of sleep medication/sedatives. Among the insomnia symptoms, difficulties initiating sleep appeared to have the strongest and most robust association with AMI. It is intriguing that in our sensitivity analyses, with the exclusion of users of sleep medication/sedatives, the observed association between difficulties initiating sleep and AMI risk was strengthened. Possibly, this could indicate that sleep medication may reduce AMI risk by reducing difficulties initiating sleep; however, this important question cannot be investigated properly in the present study.

Although the observed relative risks were moderate, insomnia is a frequent, easily recognizable, and potentially manageable condition for most patients.[1] Treatment options include adherence to simple recommendations concerning sleeping habits, often referred to as sleep hygiene, and several nonpharmacological and pharmacological therapies with the potential to produce reliable and durable changes among persons who suffer from chronic insomnia.[23–25]

Table 3. HRs (95% CIs) for AMI According to Number of Insomnia Symptoms

	Events/Person-Time	Model 1	Model 2	Model 3	Model 4	Model 5
No. of symptoms						
0	997/463131	Reference	Reference	Reference	Reference	Reference
1	212/37710	1.24 (1.00–1.54)	1.28 (1.03–1.59)	1.19 (0.94–1.50)	1.19 (0.94–1.51)	1.30 (1.02–1.65)
2	81/12727	1.47 (1.07–2.02)	1.44 (1.04–2.00)	1.39 (0.98–1.97)	1.34 (0.94–1.93)	1.47 (1.02–2.13)
3	13/2417	1.92 (1.11–3.33)	1.73 (0.98–3.06)	1.89 (1.04–3.44)	1.73 (0.92–3.25)	2.12 (1.13–4.00)
HR for each symptom increase		1.24 (1.11–1.38)	1.22 (1.10–1.37)	1.20 (1.06–1.35)	1.18 (1.04–1.34)	1.25 (1.08–1.45)
P for trend		<0.0001	<0.001	0.003	0.011	0.001

HR indicates hazard ratio; CI, confidence interval; and AMI, acute myocardial infarction.

For explanation of models, see Table 2.

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Table 4. HRs (95% CIs)* for AMI According to Insomnia Symptoms When Stratifying by Sex

Variable	Women	Men	*P* for Homogeneity of HR
Difficulty initiating sleep			
Never	Reference	Reference	
Occasionally	1.01 (0.84–1.22)	1.05 (0.92–1.19)	
Often	1.20 (0.89–1.63)	0.92 (0.65–1.28)	
Almost every night	1.70 (1.29–2.23)	1.27 (0.91–1.78)	0.009
Difficulty maintaining sleep			
Never	Reference	Reference	
Occasionally	1.19 (0.97–1.47)	1.01 (0.89–1.15)	
Often	1.29 (0.90–1.62)	1.04 (0.81–1.32)	
Almost every night	1.46 (1.00–2.14)	1.16 (0.81–1.67)	0.087
Feeling of nonrestorative sleep			
Never, few times a year	Reference	Reference	
1–2 Times per month	0.87 (0.61–1.24)	0.94 (0.76–1.16)	
Once a week	1.13 (0.77–1.67)	0.97 (0.71–1.33)	
More than once a week	1.44 (1.05–1.97)	1.12 (0.84–1.50)	0.090
Cumulative insomnia symptoms			
0	Reference	Reference	
1	1.14 (0.79–1.66)	1.24 (0.92–1.67)	
2	1.99 (1.27–3.12)	0.83 (0.46–1.51)	
3	2.65 (1.30–5.40)	1.02 (0.33–3.17)	0.015

HR indicates hazard ratio; CI, confidence interval; and AMI, acute myocardial infarction.
*Adjustments were performed as in model 3, Table 2.

Comparison With Previous Studies

The largest prospective cohort study on insomnia so far included >1.1 million individuals from the general population, with 6 years of mortality follow-up.[6] Insomnia was assessed by a single question related to how many nights per month the person usually experienced insomnia. The investigators found a slight reduction in all-cause mortality associated with insomnia problems but did not specifically study the association with heart disease.

Other relevant studies were considerably smaller than the present study, with numbers ranging from 416 to 10 308 participants.[2–5,7–14] Only 1 of those studies investigated the 3 aspects of insomnia simultaneously.[5] Most studies concentrated on difficulty in initiating and/or maintaining sleep and generally found a moderately increased risk for CHD associated with these symptoms.

Only Meisinger et al,[3] Siegriest et al,[11] and Chandola et al[12] included AMIs that were verified by modern standards, including diagnostic information based on ECG and cardiac enzymes. The authors combined verified AMI with other less well-defined cardiovascular outcomes, and no separate estimates for the verified AMIs were reported. In other studies, outcomes were cardiovascular death and/or self-reported cardiovascular disease.[5,7,8,10]

There is a considerable overlap between insomnia and psychological distress, especially depressive symptoms.[26] There is some evidence that depression and anxiety are associated with increased risk for AMI.[27] However, in studies of insomnia and AMI, only a few have evaluated and adjusted for depressive symptoms in the analyses.[2,3,5] Similar to the present findings, adjustment for depression did not substantially change the estimated associations in most of those studies. Inclusion of anxiety in our models somewhat strengthened the association of insomnia complaints with AMI risk. This was an unexpected and unexplained result. To the best of our knowledge, no previous study included adjustment for anxiety, and future studies are warranted to confirm or refute our finding.

Although we could examine the role of depression and anxiety, we had no data on vital exhaustion. Vital exhaustion, a construct closely related to depression, has been associated with both insomnia and the risk of AMI.[28]

Many common chronic somatic disorders cause sleep problems and are also related to AMI risk. Only the study by Mallon et al[2] attempted to address the possibility that chronic disorders could explain the insomnia-AMI association. In line with the present findings, there was no evidence that chronic disorders could explain the observed association between insomnia complaints and risk for AMI.

Several studies have suggested that women are more prone to insomnia than men,[1] and there is a well-known sex difference related to cardiovascular risk and mortality. Therefore, a sex difference in the association of insomnia with AMI also appears to be plausible. In the MONICA study (Monitoring of Trends and Determinants in Cardiovascular Disease),[3] the association between insomnia and CHD was stronger in women, whereas the opposite was found by Mallon et al.[2] Many studies were restricted either to men[7,8,10,11] or to women.[9] The present study was relatively well powered to detect differences by sex or other subgroup differences. We found no compelling evidence for a sex difference. Women had slightly higher relative risks of AMI for difficulties initiating sleep and for cumulative insomnia symptoms. However, caution is needed when interpreting this

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Table 5. HRs (95% CIs)* for AMI According to Insomnia Symptoms When Stratifying by Age at 65 Years

Variable	Age <65 y	Age ≥65 y	*P* for Homogeneity of HR
Difficulty initiating sleep			
Never	Reference	Reference	
Occasionally	0.97 (0.84–1.16)	1.01 (0.88–1.16)	
Often	1.07 (0.77–1.47)	0.89 (0.65–1.21)	
Almost every night	1.35 (0.88–2.07)	1.43 (1.12–1.83)	0.376
Difficulty maintaining sleep			
Never	Reference	Reference	
Occasionally	0.94 (0.80–1.10)	1.15 (0.98–1.35)	
Often	1.11 (0.83–1.48)	1.04 (0.81–1.34)	
Almost every night	1.18 (0.74–1.88)	1.31 (0.95–1.81)	0.138
Feeling of nonrestorative sleep			
Never, few times a year	Reference	Reference	
1–2 Times per month	0.98 (0.80–1.21)	0.75 (0.51–1.10)	
Once a week	1.16 (0.88–1.54)	0.74 (0.46–1.20)	
More than once a week	1.30 (1.01–1.66)	1.18 (0.80–1.73)	0.527
Cumulative insomnia symptoms			
0	Reference	Reference	
1	1.21 (0.92–1.60)	1.14 (0.74–1.76)	
2	1.30 (0.85–2.00)	1.46 (0.79–2.70)	
3	1.55 (0.69–3.48)	2.39 (0.97–5.87)	0.153

HR indicates hazard ratio; CI, confidence interval; and AMI, acute myocardial infarction.
*Adjustments were performed as in model 3, Table 2.

finding. It does not necessarily suggest that insomnia is more dangerous for women. Instead, the sex difference in relative risks might be explained by the lower baseline AMI risk among women.

To the best of our knowledge, no previous studies have examined the possible seasonal influence on the association of insomnia with AMI risk. We found some evidence that difficulty initiating sleep reported during the dark period of the year had a stronger association with AMI risk than difficulty initiating sleep reported during months with daylight predominance. This finding needs to be confirmed in future studies, but might indicate that difficulty initiating sleep caused by too much light during the night may be less dangerous than a more genuine form of initiating sleep difficulties that may develop even in the absence of the disturbing effect of light during the night.

Potential Mechanisms for the Observed Association

Although there are several potential mechanisms, the nature of the association between insomnia and AMI remains unclear. Insomnia may share some common risk factors with CHD or may increase the risk of AMI via metabolic or endocrine changes[29] via increased sympathetic activation and high blood pressure[30] or via elevated levels of proinflammatory cytokines.[31] In the present study, we adjusted for a large set of covariates, and the association of insomnia symptoms and AMI, especially difficulty in initiating sleep, was largely independent of the potentially confounding factors that were included in our models.

Study Limitations

Apart from its clear strengths, the present work has some important limitations. Similar to other relevant prospective studies, we did not assess sleep objectively, for example, by performing a polysomnography. However, polysomnography is not routinely used for evaluation of insomnia,[32] because difficulty initiating or maintaining sleep, or nonrestorative sleep, cannot necessarily be measured objectively. In fact, insomnia may be present even in the absence of any sign of an objective sleep disturbance from a polysomnographic evaluation.[32]

Because there was no objective measurement, we also had no information on the prevalence of sleep apnea syndrome. Sleep apnea syndrome is a well-established risk factor for cardiovascular disorders.[33] Although daytime sleepiness is the most characteristic symptom for sleep apnea syndrome, apnea patients often complain about difficulty in initiating or maintaining sleep, and they often suffer from early awakenings.[34] However, according to a large polysomnographic study, only 6% of those with insomnia symptoms had sleep apnea syndrome. Nonetheless, the authors did not evaluate nonrestorative sleep, and only initiating and maintaining sleep were used in the definition of insomnia.[35] The strength of the association between sleep apnea and insomnia is not clear, and it has been suggested that the association could be explained, at least in part, by confounding by age or depression.[34,36] In the analyses, we adjusted for age and depression as well as for blood pressure and BMI, ie, 2 very strong correlates of sleep apnea syndrome and AMI. Although we acknowledge the possibility that confounding by sleep apnea could possibly be of importance, it appears unlikely that sleep apnea alone could explain the higher risk for AMI among people with insomnia symptoms.

Length of sleep was not evaluated in the present work. Both short and long duration of sleep have been associated with increased risk of CHD.[12] However, insomnia is not

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synonymous with short sleep, and people with an average or long duration of sleep may also have insomnia symptoms.[6] Similarly, many individuals with short sleep duration do not have insomnia,[6] probably because there is a large interindividual variation in the length of sleep that is required for physiological and psychological restoration.[37] It is also important to recognize that insomnia also covers the quality of sleep, and not only its duration. Chandola et al[12] reported that the effect of short sleep on CHD risk was only present among those who reported sleep disturbances. Among participants who did not report any sleep disturbance, there was little evidence that short sleep increases CHD risk.[12] Therefore, information on sleep duration may not be as important as the individual's judgment, which also includes aspects of quality.

Observational studies inherently limit causal inference. Although we adjusted for several potential confounders in our multivariable analyses, we cannot exclude the possibility of uncontrolled confounding behind the observed associations. However, any remaining confounder potentially able to influence our results considerably would need to be strongly associated with both insomnia and risk of AMI and generally unrelated to the factors included in our models.

We performed several statistical tests in the present study. With increasing number of tests, the chance of false-positive findings increases, which means that caution is needed in the interpretation of results. Our main analyses were clearly hypothesis driven, and when we examined different insomnia symptoms or the joint effect of these symptoms, the tests we performed were closely related. Thus, formal adjustment for the number of tests, such as the Bonferroni method, would be too conservative.[38] Nevertheless, even with this correction, we would observe an association between insomnia and AMI risk. In contrast, our analysis of effect modifications had an explorative nature, and we performed a large number of tests without prespecified hypotheses. Therefore, the observed sex differences should not be interpreted as clear evidence for effect modification by sex.

Our findings from Norway cannot readily and directly be generalized to countries at different latitudes, with different underlying AMI risk, or with different sleeping/circadian habits. Moreover, the question related to nonrestorative sleep was restricted to people younger than 70 years of age, and therefore, our results concerning this particular variable, and the cumulative number of insomnia symptoms, cannot readily be generalized to elderly populations. Furthermore, these analyses also had less statistical power than the analyses on difficulties initiating and maintaining sleep.

We did not rely on a formal diagnosis of insomnia, and in the analyses, we assessed the severity of symptoms separately and in combination in relation to AMI. However, our evaluation of insomnia symptoms largely reflected the current diagnostic criteria used in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[17]

Finally, insomnia was only evaluated once at the beginning of the follow up; thus, we could not examine the possible effects of time-dependent changes in severity of insomnia.

Conclusions

In summary, we found that insomnia symptoms are associated with a moderately increased risk for AMI. Nevertheless, insomnia is a frequent, easily recognizable, and potentially manageable condition. Therefore, evaluation of insomnia might provide additional information in clinical risk assessment that could be useful in cardiovascular prevention. However, further research is needed to better establish the risk associated with insomnia and to reveal the possible pathophysiological mechanisms.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Insomnia, a subjective feeling of having difficulties initiating or maintaining sleep, or having a feeling of nonrestorative sleep, is a highly prevalent condition in the industrialized world. Only a few prospective studies have investigated insomnia in relation to risk for coronary heart disease, and these prior studies have been subjected to several potential methodological limitations. We assessed insomnia symptoms and risk of acute myocardial infarction in a large population-based study, taking into account the established cardiovascular risk factors, psychological distress, and chronic somatic disorders. In our study, insomnia symptoms were associated with a moderate increase in risk for acute myocardial infarction. The results were fairly robust in different multivariable models and sensitivity analyses. Nevertheless, insomnia is a frequent, easily recognizable, and potentially manageable condition. Treatment options include adherence to simple recommendations concerning sleeping habits, often referred to as sleep hygiene, and several nonpharmacological and pharmacological therapies, with the potential to produce reliable and durable changes among persons who have chronic insomnia. Therefore, evaluation of insomnia might provide additional information in clinical risk assessment that could be useful in cardiovascular prevention. However, further research is needed to better establish the risk associated with insomnia and to reveal the possible pathophysiological mechanisms.

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Insomnia and the Risk of Acute Myocardial Infarction: A Population Study

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SUPPLEMENTAL MATERIAL

Pair-wise Pearson correlation coefficients between potential confounding factors

	Sex	Marital status	Education	Shift work	Alcohol	BMI	Smoking	HDL	Triglycerides	DBP	SBP	Cholesterol	Physical Activity	Diabetes	Depression	Anxiety
Sex	1.0000															
Marital status	-0.0285	1.0000														
Education	0.0583	0.0258	1.0000													
Shift work	-0.0240	0.0114	0.0999	1.0000												
Alcohol	0.2634	0.0490	0.2285	0.0762	1.0000											
BMI	0.0212	-0.0581	-0.1529	-0.0433	-0.0929	1.0000										
Smoking	0.0651	-0.0230	-0.1174	0.0612	0.1579	-0.0710	1.0000									
HDL	-0.3308	-0.0152	0.0083	-0.0025	0.0281	-0.2434	-0.0624	1.0000								
Triglycerides	0.1769	-0.0390	-0.1332	-0.0442	-0.0334	0.3302	0.0462	-0.4288	1.0000							
DBP	0.1388	-0.1210	-0.2044	-0.0922	-0.0603	0.2661	-0.0002	-0.0625	0.2271	1.0000						
SBP	0.1042	-0.0413	-0.3056	-0.1519	-0.1514	0.2700	-0.0853	-0.0454	0.2278	0.7323	1.0000					
Cholesterol	-0.0539	-0.1290	-0.2728	-0.0958	-0.1557	0.2213	0.0332	0.0905	0.3632	0.3051	0.3334	1.0000				
Physical activity	0.1423	0.0596	0.1996	0.0316	0.1510	-0.1176	-0.0794	0.0234	-0.0904	-0.1020	-0.0981	-0.1407	1.0000			
Diabetes mellitus	0.0050	0.0070	-0.0791	-0.0470	-0.0798	0.1116	-0.0301	-0.0531	0.0968	0.0671	0.1358	0.0378	-0.0380	1.0000		
Depression	-0.1007	0.0247	-0.0497	0.0047	0.0050	-0.0201	0.0814	0.0250	-0.0086	-0.0486	-0.0731	-0.0069	-0.0292	-0.0047	1.0000	
Anxiety	0.0374	-0.0477	-0.1734	-0.0606	-0.0808	0.0877	0.0713	-0.0345	0.0836	0.0894	0.0943	0.1173	-0.1369	0.0504	0.5559	1.0000

BMI= body mass index, DBP= diastolic blood pressure, SBP= systolic blood pressure

Hazard ratios and 95% CI intervals for AMI according to insomnia symptoms in different models including established cardiovascular risk factors

Variable	Full model*	Full model without alcohol	Full model without HDL	Full model without triglycerides	Full model without diastolic BP	Full model without systolic BP	Full model without cholesterol
Difficulty initiating sleep							
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Occasionally	1.04 (0.93-1.16)	1.01 (0.91-1.13)	1.04 (0.94-1.16)	1.04 (0.93-1.16)	1.04 (0.93-1.16)	1.03 (0.93-1.16)	1.04 (0.93-1.16)
Often	0.98 (0.78-1.24)	0.98 (0.78-1.23)	0.98 (0.78-1.24)	0.98 (0.79-1.24)	0.98 (0.78-1.24)	0.97 (0.77-1.23)	0.98 (0.78-1.24)
Almost every night	1.45 (1.16-1.81)	1.45 (1.17-1.79)	1.43 (1.15-1.78)	1.44 (1.16-1.80)	1.45 (1.16-1.80)	1.42 (1.14-1.77)	1.45 (1.16-1.81)
P for trend	0.02	0.02	0.02	0.02	0.02	0.03	0.03
Difficulty maintaining sleep							
Never	Ref.	Ref.	Ref.	Ref.	Ref	Ref	Ref
Occasionally	1.07 (0.96-1.20)	1.07 (0.96-1.19)	1.07 (0.95-1.19)	1.07 (0.96-1.20)	1.07 (0.96-1.20)	1.07 (0.96-1.20)	1.07 (0.96-1.20)
Often	1.09 (0.90-1.32)	1.12 (0.93-1.35)	1.07 (0.89-1.30)	1.09 (0.90-1.32)	1.09 (0.90-1.32)	1.08 (0.89-1.31)	1.09 (0.90-1.32)
Almost every night	1.27 (0.97-1.66)	1.31 (1.01-1.69)	1.27 (0.97-1.66)	1.27 (0.97-1.66)	1.27 (0.97-1.66)	1.24 (0.95-1.63)	1.27 (0.97-1.32)
P for trend	0.07	0.03	0.09	0.07	0.07	0.09	0.14
Feeling of non-restorative sleep							
Never, few times a year	Ref.	Ref.	Ref	Ref	Ref	Ref	Ref
1-2 times per month	0.97 (0.80-1.16)	0.92 (0.77-1.10)	0.97 (0.80-1.16)	0.97 (0.80-1.16)	0.97 (0.80-1.16)	0.96 (0.80-1.16)	0.97 (0.80-1.16)
Once a week	1.07 (0.83-1.38)	1.04 (0.82-1.32)	1.08 (0.84-1.39)	1.07 (0.83-1.38)	1.07 (0.83-1.38)	1.06 (0.83-1.36)	1.07 (0.83-1.38)
More than once a week	1.30 (1.05-1.62)	1.29 (1.04-1.59)	1.29 (1.04-1.60)	1.30 (1.05-1.62)	1.30 (1.05-1.62)	1.29 (1.04-1.60)	1.30 (1.05-1.62)
P for trend	0.04	0.06	0.04	0.04	0.04	0.05	0.04

*Full model includes all established cardiovascular risk factors (systolic and diastolic blood pressure, triglycerides, HDL and total cholesterol, diabetes mellitus, BMI, physical activity, smoking and alcohol intake) and sex, age, marital status, education, and shift-work

Hazard ratios and 95% CI intervals for AMI according to the number of insomnia symptoms in different models including established cardiovascular risk factors

Number of symptoms	Full model*	Full model without alcohol	Full model without HDL	Full model without triglycerides	Full model without diastolic BP	Full model without systolic BP	Full model without cholesterol
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	1.20 (0.95-1.52)	1.20 (0.95-1.52)	1.20 (0.94-1.53)	1.21 (0.94-1.54)	1.20 (0.94-1.53)	1.20 (0.94-1.53)	1.21 (0.94-1.54)
2	1.39 (0.98-1.97)	1.39 (0.98-1.97)	1.37 (0.95-1.97)	1.38 (0.96-1.98)	1.35 (0.94-1.94)	1.35 (0.94-1.94)	1.38 (0.96-1.98)
3	1.85 (1.02-3.37)	1.85 (1.02-3.37)	1.69 (0.87-3.26)	1.66 (0.86-3.21)	1.62 (0.84-3.13)	1.62 (0.84-3.13)	1.66 (0.86-3.21)
HR for each symptom increase	1.20 (1.06-1.35)	1.20 (1.06-1.35)	1.18 (1.04-1.34)	1.18 (1.04-1.34)	1.19 (1.04-1.35)	1.17 (1.03-1.33)	1.18 (1.04-1.34)
P for trend	0.003	0.003	0.001	0.009	0.009	0.010	0.010

*Full model includes all established cardiovascular risk factors (systolic and diastolic blood pressure, triglycerides, HDL and total cholesterol, diabetes mellitus, BMI, physical activity, smoking and alcohol intake) and sex, age, marital status, education, and shift-work