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Sleep Impairment and Prognosis of Acute Myocardial Infarction: A Prospective Cohort Study

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Study Objectives: Impaired sleep is an established risk factor for the development of cardiovascular disease, whereas less is known about how impaired sleep affects cardiovascular prognosis. The aim of this study is to determine how different aspects of impaired sleep affect the risk of case fatality and subsequent cardiovascular events following first-time acute myocardial infarction (AMI).

Design: Prospective cohort study.

Setting: The Stockholm Heart Epidemiology Program, Sweden.

Participants: There were 2,246 first-time AMI cases.

Measurements and Results: Sleep impairment was assessed by the Karolina Sleep Questionnaire, which covers various indices of impaired sleep: disturbed sleep, impaired awakening, daytime sleepiness, and nightmares. Case fatality, defined as death within 28 days of initial AMI, and new cardiovascular events within up to 10 y of follow-up were identified through national registries. In women, disturbed sleep showed a consistently higher risk of long-term cardiovascular events: AMI (hazard ratio [HR] = 1.69; 95% confidence interval [CI] 0.95–3.00), stroke (HR = 2.61; 95% CI: 1.19–5.76), and heart failure (HR = 2.43; 95% CI: 1.18–4.97), whereas no clear effect of impaired sleep on case fatality was found in women. In men, a strong effect on case fatality (odds ratio = 3.27; 95% CI: 1.76–6.06) was observed in regard to impaired awakening; however, no consistent effect of impaired sleep was seen on long-term cardiovascular prognosis.

Conclusion: Results suggest sex-specific effects of impaired sleep that differ by short- and long-term prognosis. Sleep complaints are frequent, easily recognizable, and potentially manageable. Evaluation of sleep complaints may, even if they represent prognostic markers rather than risk factors, provide additional information in clinical risk assessment that could benefit secondary cardiovascular prevention.

Keywords: cardiovascular disease, cohort study, myocardial ischemia, prognosis, recurrence, sleep impairment

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INTRODUCTION

Sleep loss, chronic sleep deprivation, and alterations in sleep quality are increasing problems in modern society.[1,2] Although previous epidemiologic studies have focused primarily on the cardiac effects of sleep duration and clinical sleep disorders, the potential effect of more common aspects of sleep quality on cardiovascular morbidity and mortality has gained momentum within recent years.[3–6] In addition to being a risk factor for development of primary disease, studies suggest that impaired sleep might also adversely affect the prognosis following cardiovascular disease even after thorough adjustment for coronary risk factors.[7–9] However, previous research on impaired sleep have mostly been concerned with indicators of clinical sleep disorders such as sleep disordered breathing and/or heavy snoring, whereas evaluation of more common sleep complaints and daytime sleepiness are less well understood. The few previous studies investigating the effect of sleep quality on prognosis following cardiovascular disease have provided inconclusive results and have mainly comprised smaller samples.[7,9–11] Despite growing evidence of sex differences in the cardiovascular effects associated with poor sleep,[12] potential sex differences in prognosis associated with sleep have not been addressed directly.

Sleep represents a daily process of physiological restitution and recovery, and lack of or impaired sleep may have far-reaching effects on endocrinology, immunology, metabolism, and eventually disease risk.[13] The body does most of its nightly restitution in the deeper slow wave stages of non-rapid eye movement (REM) sleep and regularly impaired sleep is likely to interfere with the natural rhythm of sleep stages.[14] We hypothesize that impaired sleep could hamper restitution following an acute myocardial infarction (AMI) by suppressing slow wave sleep with adverse effects on various body systems including cardiovascular processes involved in recovery.

The aim of the current study is to determine how disturbed sleep, impaired awakening, daytime sleepiness, and frequent nightmares affect the prognosis of AMI in terms of case fatality, and subsequent AMI, stroke, and heart failure among women and men with a first-time AMI.

MATERIALS AND METHODS

Study Population

The Stockholm Heart Epidemiology Program (SHEEP) is a population-based case-referent study of all Swedish citizens

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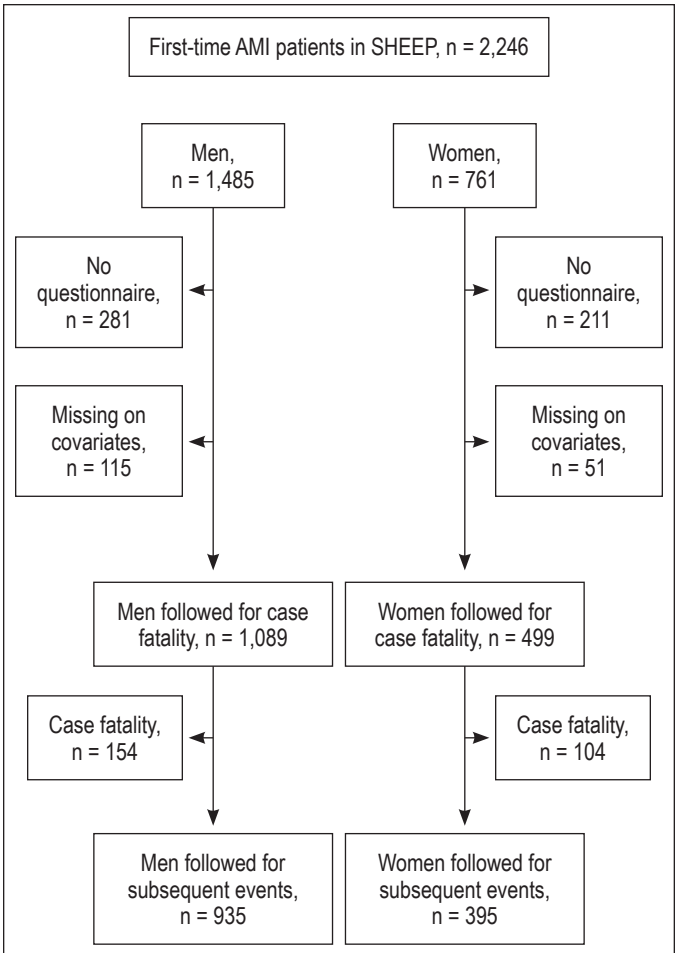

Figure 1—Flowchart illustrating the SHEEP study population.

(age 45–70 y) residing in Stockholm who developed a first-time primary AMI in the period January 13, 1992 to January 12, 1994 for men and until December 31, 1994 for women, and a similar number of age-, sex-, and hospital catchment area-matched referents. The SHEEP has been described in detail elsewhere.[15] We aimed to study prognosis, and therefore the study population for the current study comprised only the 2,246 first-time AMI patients identified in the SHEEP. Cases were identified through contacts made with the 10 emergency hospitals in the region of Stockholm. In accordance with 1991 guidelines for cardiac intensive care, criteria for AMI included (1) certain symptoms according to case history information, (2) specified changes in blood levels of the enzymes creatine kinase and lactate dehydrogenase, (3) specified electrocardiogram (ECG) changes, and (4) autopsy findings.[16] Later comparison with a population-based incidence register indicated close to complete ascertainment of all AMIs.[17] A detailed questionnaire was administered 1 w after hospital discharge (to the participant or close relatives if the participant was too ill or had died) and a health assessment was performed on surviving cases approximately 3 mo after initial AMI. The questionnaire and health assessment provided information on demographic details and important prognostic factors, e.g., blood pressure, hypertension, and diabetes, as well as various known and suspected risk factors for heart disease. Participants who did not fill in the baseline questionnaire (n = 492) or who had missing information on any of the covariates (n = 166) were excluded, leaving 499 women and 1,089 men eligible for the analyses of case fatality. Within 28 days of initial AMI, 258 participants died, leaving 395 women and 935 men for the analyses of subsequent AMI, stroke, and heart failure. Figure 1 illustrates selection of the study population, and the distribution of missing questionnaire and covariate data among the study cohort is illustrated in Table S1 (supplemental material).

Sleep Impairment

Sleep impairment in the year prior to initial AMI was assessed by the Karolinska Sleep Questionnaire (KSQ), which covers various aspects of impaired sleep: disturbed sleep (including general sleep quality, difficulty falling asleep, repeated awakenings, disturbed/uneasy sleep, and premature awakenings), impaired awakening (including difficulty rising and not feeling well rested after sleep), daytime sleepiness (including feeling sleepy during work and leisure time, tired eyes, involuntary naps at work or at home), and frequency of nightmares.[18] There were five response alternatives ranging from (1) "never/very good" to (5) "almost every day/very bad". In the current study we assessed the effect of the three indices of impaired sleep: disturbed sleep, impaired awakenings, and daytime sleepiness, as an average score of the included items corresponding to an average frequency of sleep symptoms of "at least some times a week" to reflect a clinically significant level of impaired sleep.[19;20] The same cutpoint was applied to assess the effect of frequent nightmares.

Covariates

Other covariates included age at baseline (continuous), perceived stress (continuous),[21] smoking status (smoker, ex-smoker at least 1 y before baseline, never-smoker), alcohol consumption (< 1, 1-7, 8-14, 15-21, ≥ 22 drinks/w), coffee consumption (average cups per w, continuous), average physical activity in the decade prior to initial AMI (sedentary/very light activity, few walks and/or bike trips, occasional physical activity, regular physical activity at least once a w), body mass index (BMI) (continuous), diabetes (no/yes), hypertension (no/yes), highest achieved level of education (primary school, shorter practical education/technical school, secondary school, university or higher), cohabitation (no/yes), shift work (no/yes/not working), and hereditary heart problems (heart problems in mother and/or father before age 65, no/yes).

Follow-up

All included cases have been followed in the nationwide Swedish Myocardial Infarction Register, the Swedish Hospital Discharge Register, and the National Cause of Death Register in order to obtain information on subsequent cardiovascular events and mortality. The prognostic outcomes of interest include: case fatality (death within 28 days of initial AMI), incidence of or death from AMI (International Classification of Disease [ICD]9: 410; ICD10: I21-I22), stroke (ICD9: 430-438; ICD10: I60-I69, G45), and heart failure (ICD9: 428; ICD10: I50). In the analyses of each individual outcome, participants were censored on the first occasion of that particular event, death, or end of follow-up on December 31, 2001, i.e., in analysis of stroke censoring took place upon occurrence of stroke and not AMI or heart failure had these occurred prior to stroke.

Table 1—Baseline characteristics of the 1,588 women and men participating in SHEEP by disturbed sleep

	Total population	Women Disturbed sleep [c]		Men Disturbed sleep [c]	
	n = 1,588	No (n = 418)	Yes (n = 78)	No (n = 1,008)	Yes (n = 77)
Mean age (SD)	60 (7)	62 (7)	61 (7)	59 (7)	59 (7)
Diabetics, n (%)	238 (15)	75 (18)	16 (21)	131 (13)	15 (19)
Hypertension, n (%)	627(39)	178 (43)	32 (41)	386 (38)	30 (39)
Mean BMI (SD)	27 (4)	27 (5)	26 (6)	27 (4)	28 (4)
Killip classification ≥ 3, n (%)	70 (6)	24 (8)	5 (10)	38 (5)	3 (6)
Parental history of CVD, n (%)	499 (32)	137 (33)	24 (31)	315 (31)	21 (27)
Physically inactive, n (%)	279 (18)	76 (18)	27 (35)	154 (15)	18 (23)
Smokers, n (%)	809 (51)	202 (48)	57 (73)	505 (50)	40 (52)
Alcohol above sensible drinking limits, n (%) [a]	221 (14)	20 (5)	9 (12)	169 (17)	21 (27)
Mean weekly coffee consumption (SD)	29 (19)	24 (16)	27 (19)	31 (19)	31 (21)
Mean PSS score (SD)	5 (3)	6 (3)	8 (4)	5 (2)	7 (3)
Low education, n (%) [b]	742 (47)	250 (60)	43 (55)	412 (41)	34 (44)
Living alone, n (%)	429 (27)	150 (36)	36 (46)	212 (21)	26 (34)
Shift work, n (%)	209 (13)	50 (12)	10 (13)	129 (13)	20 (26)
Postmenopausal women, n (%)	310 (90)	268 (90)	42 (95)		

[a] > 14 drinks/w for women and > 21 drinks/w for men. [b] Primary school. [c] Defined as an average index score ≥ 4. BMI, body mass index; CVD, cardiovascular disease; n, number; PSS, perceived stress score; SD, standard deviation.

Statistical Methods

Multiple logistic regression models were used to determine the association between the measures of sleep impairment and case fatality, and Cox proportional hazard models were used to determine the association with subsequent occurrence of AMI, stroke, and heart failure. Days from initial AMI was used as the underlying timescale in the Cox models. The analyses were performed separately for women and men because of the sex-difference in cardiovascular morbidity and mortality and the differential self-reporting of sleep habits between women and men supported in previous studies.[22] First, age-adjusted odds ratios (OR), hazard ratios (HR), and 95% confidence intervals (CI) were estimated in separate models to assess the effect of each index of sleep impairment on the different adverse outcomes. Second, multivariate models were fitted to adjust for potential confounding from baseline demographic and behavioral covariates. Third, cardiovascular biomarkers were added to the models. We used prior knowledge and the methods of Directed Acyclic Graphs[23] to identify potential confounders, which included age, educational attainment, cohabitation, shift work, stress, smoking status, alcohol consumption, coffee consumption, physical activity, BMI, diabetes, and hypertension.

In sensitivity analyses, the separate effect of each sleep complaint included in the indices was assessed to explore whether potential associations were caused by specific sleep complaints. Analyses of normal-weight participants were carried out to investigate potential confounding from obstructive sleep apneas syndrome (OSAS), as the prevalence of OSAS is more frequent among overweight than normal-weight individuals.[24] In addition, analyses with further adjustment for snoring, a common complaint in OSAS patients, were performed. Because menopause is an important potential effect-modifier in analyses of endogenous exposures, we performed additional analyses restricted to postmenopausal women. We performed further subanalyses to assess the robustness of the estimates: analyses restricted to participants who themselves had filled in the questionnaire; and analyses with further adjustment for degree of heart failure in initial AMI (Killip classification). To minimize potential bias from the complete case analyses, multivariate multiple imputation (syntax "mvn mi" in Stata version 12 [Stata Corp, College Station, Texas]) was performed for the 166 participants missing information on one or more covariates. Furthermore, because studies have suggested a change in sleep architecture in older ages,[25] we performed separate subanalyses of individuals older and younger than 60 y. Finally, we hypothesized that impaired sleep might better predict prognosis within a shorter timeframe than the full follow-up. Thus we conducted additional analyses restricted to the first 2 and 5 y of follow-up.

RESULTS

The mean age at baseline was 60 y (range: 45–70 y). More than 20% of men and almost one third of women experienced disturbed sleep. In general, a higher proportion of those with disturbed sleep reported a more adverse cardiac risk profile including diabetes, physical inactivity, smoking, drinking above sensible limits, not cohabiting, and shift work. For the full list of baseline characteristics see Table 1.

Impaired Sleep and Case Fatality

Within the first 28 days of AMI, 256 participants died. Daytime sleepiness was associated with a higher risk of case fatality in an age-adjusted analysis among women (OR = 2.31; 95% CI: 1.12–4.78), an association that disappeared after adjustment for potential confounders (Table 2). Daytime sleepiness was not associated with the risk of case fatality in men. However, looking at the individual items included in the

Table 2—Risk of case fatality in 1,588 women and men suffering a first-time acute myocardial infarction in association with aspects of impaired sleep

	Disturbed sleep [d]		Impaired awakening [d]		Daytime sleepiness [d]		Nightmares [e]	
	No	Yes	No	Yes	No	Yes	No	Yes
Women, Risk of case fatality								
No. of cases[a] /n	80/418	21/78	83/431	14/59	88/460	13/36	74/427	14/56
Age-adjusted OR (95% CI)	1 (ref.)	1.62 (0.92-2.84)	1 (ref.)	1.49 (0.77-2.88)	1 (ref.)	2.31 (1.12-4.78)	1 (ref.)	1.67 (0.86-3.24)
Multiple adjusted [b] OR (95% CI)	1 (ref.)	0.92 (0.46-1.84)	1 (ref.)	1.28 (0.60-2.74)	1 (ref.)	1.44 (0.59-3.54)	1 (ref.)	1.00 (0.45-2.26)
+ Biomarker adjusted [c] OR (95% CI)	1 (ref.)	0.82 (0.40-1.68)	1 (ref.)	1.18 (0.54-2.59)	1 (ref.)	1.05 (0.40-2.72)	1 (ref.)	1.19 (0.51-2.75)
Men, Risk of case fatality								
No. of cases[a] /n	135/1008	16/77	122/1004	21/71	139/1026	13/60	125/1006	8/57
Age-adjusted OR (95% CI)	1 (ref.)	1.73 (0.96-3.11)	1 (ref.)	3.62 (2.07-6.34)	1 (ref.)	1.68 (0.88-3.21)	1 (ref.)	1.05 (0.48-2.29)
Multiple adjusted [b] OR (95% CI)	1 (ref.)	1.24 (0.65-2.38)	1 (ref.)	3.16 (1.71-5.83)	1 (ref.)	1.25 (0.61-2.56)	1 (ref.)	0.66 (0.28-1.56)
+ Biomarker adjusted [c] OR (95% CI)	1 (ref.)	1.26 (0.65-2.43)	1 (ref.)	3.27 (1.76-6.06)	1 (ref.)	1.24 (0.60-2.56)	1 (ref.)	0.66 (0.27-1.58)

[a] Because of missing values, the number of cases does not add up to the total number of case fatalities. [b] Adjusted for age, educational attainment, cohabitation, shift work, physical activity, smoking, alcohol consumption, coffee consumption, and stress. [c] + Adjusted for diabetes, hypertension, and body mass index. [d] Defined as an average index score ≥ 4. [e] Defined as at least some times a week. CI, confidence interval; n, number; OR, odds ratio.

sleepiness index, "feeling sleepy during work or leisure time" (OR = 2.07; 95% CI: 1.40–3.05) and "experiencing involuntary sleep episodes during leisure time" (OR = 2.08; 95% CI: 1.40–3.14) were both associated with a higher risk of case fatality in men (data not shown). A more than three times higher risk of case fatality was also observed among men who frequently experienced impaired awakening (OR = 3.27; 95% CI: 1.76–6.06). We found no difference in the distribution of Killip classification, a strong prognostic factor, in men with and without impaired awakening, and the association did not differ substantially between normal-weight and overweight participants, with adjustment for frequent snoring, or between younger and older males. Impaired awakening was not associated with case fatality in women. Neither frequent nightmares nor the index of disturbed sleep were associated with case fatality in women or men. However, men experiencing "uneasy sleep" (OR = 2.08; 95% CI: 1.35–3.20) or "poor sleep quality" at least weekly (OR = 1.55; 95% CI: 0.98–2.47) had a higher risk of case fatality (data not shown).

Impaired Sleep and Subsequent AMI, Stroke, and Heart Failure

The participants were followed in disease registers for up to 10 y, during which 40% of those who survived the initial 28 days suffered one or more cardiovascular events.

Long-term cardiovascular prognosis was independent of disturbed sleep in men, whereas women with disturbed sleep had a higher risk of all cardiovascular events (Table 3). The higher risk of subsequent AMI seen among women in the age-adjusted analysis (HR = 1.73; 95% CI: 1.03–2.91) was minimally attenuated upon further adjustment (HR = 1.69; 95% CI: 0.95–3.00). More than twice the risk of stroke (HR = 2.61; 95% CI: 1.19-5.76) and heart failure (HR = 2.43; 95% CI: 1.18–4.97) was seen in women with disturbed sleep. In women who experienced disturbed sleep, adjustment for Killip classification, frequent snoring, or restriction to normal-weight participants, or postmenopausal status did not explain the consistently higher risk of subsequent cardiovascular events. However, the effect of disturbed sleep was mainly confined to women younger than 60 y at baseline (data not shown).

Although impaired awakening was not associated with long-term prognosis in women or men, a 50% higher risk of heart failure was suggested in men with impaired awakening (HR = 1.53; 95% CI: 0.73–3.23). Furthermore, although the combined index of daytime sleepiness was not associated with long-term prognosis in either women or men, women with frequently "irritated/tired eyes" had twice the risk of stroke relative to women without this complaint (HR = 2.11; 95% CI: 1.06–4.18). Nightmare frequency was unrelated to cardiovascular prognosis in both men and women.

The estimates from the imputation model proved very similar to the main analyses (data not shown), and the associations did not materially differ in the 2-y, 5-y, and full follow-up analyses.

DISCUSSION

In this large-scale prospective study we found sex-specific effects of some aspects of impaired sleep that differed by short- and long-term prognosis; meanwhile, other aspects of impaired sleep showed no effect on AMI prognosis. In women, disturbed sleep showed consistent effects on long-term cardiovascular events, with a higher risk of subsequent AMI, stroke, and heart failure, whereas no clear effects were found for case fatality. In men, a strong effect on case fatality was observed in regard to impaired awakening. Meanwhile, only small effects, if any, were indicated between impaired sleep and long-term cardiovascular prognosis in men. However, some of the analyses lacked sufficient statistical power to yield definitive results.

In previous studies, impaired sleep, daytime sleepiness, and symptoms of insomnia (which resemble items in the disturbed sleep index) have been shown to adversely affect the incidence of cardiovascular disease.[4-6,26,27] However, the prognostic effect of such measures in patient samples has gained little attention. One of the few studies on the matter is a previous study based on the SHEEP sample, which showed a higher risk of case fatality, but not long-term prognosis in frequent heavy snorers

Table 3—Risk of cardiovascular events in 1,330 women and men surviving at least 28 days after a first-time acute myocardial infarction in association with aspects of impaired sleep

	Disturbed sleep [d]		Impaired awakening [d]		Daytime sleepiness [d]		Nightmares [e]	
	No	Yes	No	Yes	No	Yes	No	Yes
Women								
Risk of new AMI								
No. of cases [a]	69	18	75	12	80	7	73	14
IR/1000 y	30	51	32	38	32	51	31	51
Age-adjusted HR (95% CI)	1 (ref.)	1.73 (1.03-2.91)	1 (ref.)	1.33 (0.72-2.47)	1 (ref.)	1.58 (0.73-3.44)	1 (ref.)	1.71 (0.96-3.03)
Multiple adjusted [b] HR (95% CI)	1 (ref.)	1.67 (0.94-2.96)	1 (ref.)	1.39 (0.73-2.65)	1 (ref.)	1.43 (0.63-3.23)	1 (ref.)	1.60 (0.84-3.05)
+ Biomarker adjusted [c] HR (95% CI)	1 (ref.)	1.69 (0.95-3.00)	1 (ref.)	1.18 (0.61-2.27)	1 (ref.)	1.02 (0.43-2.39)	1 (ref.)	1.46 (0.76-2.81)
Risk of stroke								
No. of cases [a]	32	10	37	5	40	2	38	4
IR/1000 y	13	26	15	15	15	13	15	13
Age-adjusted HR (95% CI)	1 (ref.)	2.06 (1.01-4.21)	1 (ref.)	1.12 (0.44-2.88)	1 (ref.)	0.89 (0.21-3.69)	1 (ref.)	0.89 (0.32-2.48)
Multiple adjusted [b] HR (95% CI)	1 (ref.)	2.46 (1.13-5.37)	1 (ref.)	1.21 (0.45-3.24)	1 (ref.)	1.04 (0.24-4.51)	1 (ref.)	0.72 (0.23-2.24)
+ Biomarker adjusted [c] HR (95% CI)	1 (ref.)	2.61 (1.19-5.76)	1 (ref.)	1.18 (0.43-3.25)	1 (ref.)	1.10 (0.25-4.89)	1 (ref.)	0.68 (0.22-2.12)
Risk of Heart failure								
No. of cases [a]	45	12	52	5	54	3	52	5
IR/1000 y	20	32	22	15	21	19	22	17
Age-adjusted HR (95% CI)	1 (ref.)	1.73 (0.92-3.28)	1 (ref.)	0.81 (0.32-2.03)	1 (ref.)	0.85 (0.26-2.72)	1 (ref.)	0.85 (0.34-2.14)
Multiple adjusted [b] HR (95% CI)	1 (ref.)	2.04 (1.01-4.15)	1 (ref.)	0.83 (0.32-2.15)	1 (ref.)	0.97 (0.28-3.31)	1 (ref.)	0.68 (0.25-1.80)
+ Biomarker adjusted [c] HR (95% CI)	1 (ref.)	2.43 (1.18-4.97)	1 (ref.)	0.75 (0.28-1.98)	1 (ref.)	0.72 (0.20-2.58)	1 (ref.)	0.72 (0.27-1.91)
Men								
Risk of new AMI								
No. of cases [a]	224	15	225	13	228	11	229	9
IR/1000 y	36	34	36	37	36	34	37	25
Age-adjusted HR (95% CI)	1 (ref.)	0.97 (0.57-1.63)	1 (ref.)	1.04 (0.59-1.81)	1 (ref.)	0.91 (0.50-1.67)	1 (ref.)	0.68 (0.35-1.33)
Multiple adjusted [b] HR (95% CI)	1 (ref.)	0.87 (0.50-1.50)	1 (ref.)	0.94 (0.53-1.68)	1 (ref.)	0.85 (0.45-1.59)	1 (ref.)	0.64 (0.32-1.27)
+ Biomarker adjusted [c] HR (95% CI)	1 (ref.)	0.86 (0.50-1.49)	1 (ref.)	0.94 (0.53-1.68)	1 (ref.)	0.85 (0.45-1.58)	1 (ref.)	0.64 (0.32-1.27)
Risk of stroke								
No. of cases [a]	113	9	114	8	118	4	112	9
IR/1000 y	17	20	17	22	18	11	17	25
Age-adjusted HR (95% CI)	1 (ref.)	1.26 (0.64-2.48)	1 (ref.)	1.48 (0.72-3.06)	1 (ref.)	0.62 (0.23-1.69)	1 (ref.)	1.42 (0.72-2.81)
Multiple adjusted [b] HR (95% CI)	1 (ref.)	1.10 (0.53-2.28)	1 (ref.)	1.24 (0.59-2.59)	1 (ref.)	0.56 (0.20-1.56)	1 (ref.)	1.26 (0.62-2.57)
+ Biomarker adjusted [c] HR (95% CI)	1 (ref.)	1.08 (0.52-2.23)	1 (ref.)	1.24 (0.59-2.61)	1 (ref.)	0.56 (0.20-1.56)	1 (ref.)	1.32 (0.64-2.69)
Risk of Heart failure								
No. of cases [a]	115	9	116	8	115	9	114	9
IR/1000 y	18	20	18	22	17	26	17	26
Age-adjusted HR (95% CI)	1 (ref.)	1.23 (0.62-2.42)	1 (ref.)	1.54 (0.75-3.17)	1 (ref.)	1.37 (0.70-2.71)	1 (ref.)	1.35 (0.68-2.66)
Multiple adjusted [b] HR (95% CI)	1 (ref.)	0.85 (0.41-1.77)	1 (ref.)	1.40 (0.67-2.96)	1 (ref.)	1.13 (1.56-2.31)	1 (ref.)	1.07 (0.52-2.19)
+ Biomarker adjusted [c] HR (95% CI)	1 (ref.)	0.91 (0.44-1.87)	1 (ref.)	1.53 (0.73-3.23)	1 (ref.)	1.21 (0.60-2.45)	1 (ref.)	1.17 (0.58-2.39)

[a] Because of missing values, the number of cases does not add up to the total number of AMI, stroke, and heart failure cases. [b] Adjusted for age, educational attainment, cohabitation, shift work, physical activity, smoking, alcohol consumption, coffee consumption, and stress. [c] + Adjusted for diabetes, hypertension, and BMI. [d] Defined as an average index score ≥ 4. [e] Defined as at least some times a week. AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; IR, incidence rate; n, number; y, years.

following AMI.[8] The current study supplements these results by establishing the effect of other qualitative measures of impaired sleep and addressing sex differences in AMI prognosis. The effect of impaired sleep on prognosis following cardiac disease has also been assessed in a small cohort of approximately 300 women younger than 65 y who had suffered an AMI or unstable angina pectoris.[7] The women were followed 5 y for recurrent AMI and revascularization procedures. In accordance with the findings of our study, more than twice the risk of recurrence was found in women with poor sleep quality. Within the same cohort a faster progression of atherosclerosis was seen in snoring than nonsnoring female cardiac patients, adding to potential mechanisms for the effects on prognosis.[9] Furthermore, studies of OSAS, a potential cause of impaired sleep, have generally been found to predict poorer prognosis in cardiac patients.[28–30] Few studies have addressed the possible sex-specific associations

between sleep complaints and AMI prognosis, despite differential self-reporting of sleep habits in women and men,[22] and the well-known sex differences in cardiovascular morbidity and mortality.[15,31,32] Unlike the current study, most previous research has been restricted to either men or women, or sex-specific analyses has not been performed. Studies on sleep and biomarkers of cardiovascular health have displayed a difference of effects in men and women, with a higher risk of hypertension associated with short sleep and sleep complaints in women than men, and higher levels of fasting insulin, fibrinogen, and inflammatory biomarkers in women but not men with poor sleep quality.[25,33–36] Thus, impaired sleep may be associated differently with mechanisms implicated in onset as well as progression of cardiovascular disease between women and men. Moreover, sex differences have been seen in stress and stress reactions, and the underlying mechanisms may be similar.[37]

Why men may be more susceptible to the consequences of impaired awakening in the unstable phase directly following an AMI, whereas women seem more susceptible to the consequences of disturbed sleep in the longer time frame, is not clear. These discrepancies are puzzling and deserve further examination in future studies, especially in light of the previously discussed sex differences in the association between sleep and cardiovascular risk factors. Similar to earlier findings, the relative effects of impaired sleep appeared stronger in younger than older individuals with AMI. Although this finding may reflect differences in the baseline hazard, it could also indicate that although poor sleep is more frequent in older age, it is more likely to imply worse cardiac health in younger patients with AMI.

Strengths and Limitations

Our study is the first to comprehensively address how common aspects of impaired sleep affect short- and long-term cardiovascular prognosis following AMI. We included detailed information on various aspects of impaired sleep combined with comprehensive information on potential confounders and established cardiovascular biomarkers. Linkage to nationwide population-based registers enabled identification of first-time AMIs, as well as subsequent AMI, stroke, and heart failure and allowed for complete long-term follow-up. The Swedish registers have previously been found to be highly comprehensive in this regard.[17]

In the current study we assessed aspects of impaired sleep by self-report at a single point in time to reflect a general level of sleep complaints within the year prior to initial AMI. This may have resulted in some level of misclassification. Although measures such as polysomnography (PSG), which more accurately reflect objectively measurable sleep patterns, would have been preferable, such measures are not feasible in large population settings. In addition, the proper application of PSG on critical patients may be questioned. However, some studies of the KSQ have indicated close correspondence of the frequency of sleep disturbances with an electroencephalographically validated sleep diary.[38]

Sleep complaints 1 y prior to first AMI were retrospectively assessed at baseline and they may not fully capture change in impaired sleep over time. Sleep may, however, be heavily affected by suffering from a major acute disorder such as AMI, and we therefore found that the measure of sleep complaints prior to diagnosis provided the best measure of how sleep affects case-fatality and prognosis in patients with AMI. Moreover, the fact that recall of sleeping patterns prior to the initial AMI event might have been affected by the severity of the event is cause for concern. The degree of heart failure assessed by the Killip classification at baseline did not, however, prove to be associated with the reporting of sleep complaints in the current study. If participants died before filling in the questionnaire or they were too ill to do so themselves, relatives were asked to complete the questionnaire. To minimize this potential source of bias, additional analyses of long-term prognosis restricted to participants who themselves had filled in the questionnaire were performed. These results proved very similar to the main analyses.

An important limitation of this study is that approximately one fifth of the participants failed to provide any questionnaire answers. Subsequent assessment showed that nonresponders did not differ in the age distribution or hospital catchment area in comparison with responders. They did, however, have a generally worse prognosis. This is not surprising because completion of the questionnaire is less likely in patients with severe AMI. If, in addition, patients with impaired sleep were more likely to be nonresponders, this could have led to an underestimation of the observed associations.

Poor sleep is closely related to psychological stress and depression,[39] both of which have been found to predict cardiovascular disease. Although we adjusted the analyses for the potential effect of perceived stress, we were unable to directly account for the potential effect of depression. Stress did not prove to be a strong confounder in the current data material, and we find it unlikely that the omission of depression (which is closely linked to mental stress) could fully explain the observed associations between impaired sleep and AMI prognosis in the current study. Further, impaired sleep was associated with baseline diabetes and more adverse health-related behavior, and although we adjusted our analyses for these factors, we cannot fully rule out that measures of impaired sleep may be risk markers for other underlying disorders that can affect prognosis in patients with AMI.

One might also be concerned whether the applied measures of impaired sleep reflect underlying clinical sleep disorders such as OSAS, which is common among cardiac patients in the current age group and is a well-established risk factor for cardiovascular disease as well as a potential trigger of cardiac events.[40,41] The results of subanalyses restricted to normal-weight participants and of analyses including frequent snoring proved very similar to the main analyses. Moreover, BMI was included in the fully adjusted regression model, which would, at least in part, have corrected for this. However, these analyses represent a very crude attempt to account for potential confounding by sleep disorders, e.g. OSAS, and although overrepresented among the overweight and obese, sleep apnea still occurs among normal-weight individuals. Therefore, we cannot exclude that the reported sleep disturbances is merely an indicator of underlying sleep disorders.

Because of the number of analyses, there is concern that the associations found in our study are merely chance findings. Formal methods for accounting for multiple testing, e.g., Bonferonni, do, however, come at a price in terms of accuracy when assessing the individual associations[42]; e.g., between distinct aspects of impaired sleep and short- and long-term prognosis. In this study, more than 11% of the conducted

analyses were significant, making it improbable that our results are artifacts created by chance findings.

Finally, the study population consisted of older Swedish adults (mostly male) and generalizability to other populations with a different composition of ethnicity, age, and risk factor structure may be limited.

CONCLUSION

Poor sleep affects not only our daily functioning and quality of life, but also disease risk and possibly prognosis following cardiovascular events such as AMI. Our study suggests that disturbed sleep in women and impaired awakening in men might be related to a moderately higher risk of a poor cardiac prognosis in patients following a first-time AMI. These associations were not explained by demographic, behavioral, or cardiac risk factors affecting prognosis. Although the observed risks were moderate, sleep complaints are frequent, easily recognizable, and potentially manageable for most patients. Consequently, evaluation of sleep complaints, even if they represent prognostic risk markers rather than risk factors, may provide additional information in clinical risk assessment. Longitudinal studies are needed to ascertain whether addressing sleep may be useful in secondary cardiovascular prevention.

ABBREVIATIONS

SHEEP, the Stockholm Heart Epidemiology Program
AMI, acute myocardial infarction
KSQ, the Karolinska Sleep Questionnaire
OSA, obstructive sleep apnea syndrome
n, number
SD, standard deviation
OR, odds ratio
HR, hazard ratio
CI, confidence interval
ICD, International Classification of Diseases
IR, incidence rate
BMI, body mass index

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SUPPLEMENTAL MATERIAL

Table S1—Distribution of missing data among 2,246 men and women suffering a first-time acute myocardial infarction

	Total	Men	Women
All SHEEP participants	2,246	1,485 (66)	761(34)
Missing questionnaire, n (%)	492 (22)	281 (19)	211 (28)
Participants with questionnaire	1,754	1,204 (69)	550 (31)
Missing on impaired sleep	100 (6)	67 (6)	33 (6)
Disturbed sleep	68 (4)	49 (4)	19 (3)
Impaired awakening	92 (5)	60 (5)	32 (6)
Daytime sleepiness	57 (3)	37 (3)	20 (4)
Nightmares	126 (7)	86 (7)	40 (7)
Missing on covariates	166 (9)	115 (10)	51 (9)
Education, n (%)	11 (1)	9 (1)	2 (< 1)
Cohabitation, n (%)	3 (< 1)	2 (< 1)	1 (< 1)
Shift work, n (%)	9 (1)	6 (1)	3 (1)
Physical activity, n (%)	18 (1)	12 (1)	6 (1)
Smoking, n (%)	2 (< 1)	2 (< 1)	0 (0)
Alcohol consumption, n (%)	56 (3)	37 (3)	19 (3)
Coffee consumption, n (%)	35 (2)	24 (2)	11 (2)
Stress, n (%)	66 (4)	50 (4)	16 (3)
Diabetes, n (%)	6 (< 1)	5 (< 1)	1 (< 1)
Hypertension, n (%)	51 (3)	37 (3)	14 (3)
BMI, n (%)	54 (3)	33 (3)	21(4)

BMI, body mass index; n, number; SHEEP, Stockholm Heart Epidemiology Program.