Sleep Duration and Sleep Complaints and Risk of Myocardial Infarction in Middle-aged Men and Women from the General Population: The MONICA/KORA Augsburg Cohort Study

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Study Objectives: To examine gender-specific associations between sleep duration and sleep complaints and incident myocardial infarction (MI).

Design: Cohort study.

Setting: A representative population sample of middle-aged subjects in Germany.

Participants: The study was based on 3508 men and 3388 women (aged 45 to 74 years) who participated in one of the 3 MONICA (Monitoring trends and determinants on cardiovascular diseases) Augsburg surveys between 1984 and 1995, who were free of MI and angina pectoris at baseline and were followed up until 2002.

Interventions: N/A

Measurements and Results: A total of 295 cases of incident MI among men and 85 among women occurred during a mean follow-up period of 10.1 years. Compared with women sleeping 8 hours, the multivariable adjusted hazard ratio (HR) of MI among women sleeping ≤5 hours was 2.98 (95% CI, 1.48-6.03), and among women sleeping ≥9 hours 1.40 (95% CI, 0.74-2.64); the corresponding HRs among men were 1.13 (95% CI, 0.66-1.92) and 1.07 (95% CI, 0.75-1.53). In multivariable analysis the relative risk of an incident MI for men and women with difficulties maintaining sleep was 1.12 (95% CI, 0.84-1.48) and 1.53 (95% CI, 0.99-2.37), respectively, and for men and women with difficulties initiating sleep the relative risk was 1.16 (95% CI, 0.82-1.63) and 1.30 (95% CI, 0.81-2.06), respectively.

Conclusions: Modest associations between short sleep duration and difficulties maintaining sleep and incident MI were seen in middle-aged women but not men from the general population.

Keywords: sleep, risk, myocardial infarction, gender, cohort study, population

Citation: Meisinger C; Heier M; Löwel H et al. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the monica/kora augsburg cohort study. *SLEEP* 2007;30(9):1121-1127.

INTRODUCTION

SLEEP DISORDERS ARE VERY PREVALENT IN THE GENERAL POPULATION, PARTICULARLY IN OLDER ADULTS AND WOMEN, AND AFFECT MILLIONS OF PEOPLE.[1] Sleep is an important modulator of cardiovascular function associated with a period of decreased physiologic workload for the cardiovascular system.[2] Relatively recently it was recognized that sleep plays an important role in the pathogenesis and progression of cardiac and vascular disease,[3] but epidemiologic data on that issue are sparse. In the few prospective studies performed to investigate the association between sleep complaints and mortality as well as cardiovascular morbidity, the findings are less consistent. While some studies found a positive relationship between sleep complaints and mortality,[4,5] in other studies insomnia was not associated with increased mortality.[6-8] The NHANES I substudy on sleep patterns and cardiovascular disease conducted in 1982 (n= 4,996 women, 2,848 men, aged 32-71 years) had observed the greatest risk for coronary heart disease and stroke during the 10-year follow-up for persons reporting both >8 hours of sleep and daytime somnolence.[9] More recently, it has been reported that persons sleeping for short durations are also at increased risk of mortality[10] and myocardial infarction.[4,11] Analyses from the Nurses Health Study showed that short and long self-reported sleep durations in women aged 45-65 years are independently associated with a modestly increased risk of coronary events.[11] So far, data from the general population, including both men and women in a similar study design and a similar medical, cultural, and ethnic environment on this issue are scarce.[9] In the present study, we investigated the association between sleep complaints and sleep duration and incident myocardial infarction (MI) in persons aged 45 to 74 years from the general population. To answer the question of whether there are gender-specific particularities, all analyses were performed separately for men and women.

METHODS

The presented data were derived from the population based MONICA (monitoring trends and determinants in cardiovascular diseases) Augsburg (Southern Germany) studies conducted between 1984 and 1995. The MONICA Augsburg project was part of the multinational WHO MONICA project and the design of the project has been described in detail elsewhere.[12,13] Three independent cross-sectional surveys were carried out in the city of Augsburg and the counties Augsburg and Aichach-Friedberg in 1984/85 (S1), 1989/90 (S2), and 1994/95 (S3) to estimate the prevalence and distribution of cardiovascular risk factors among men and women. Altogether 13,427 persons (6725 men, 6702 women, response 76.4%) aged 25 to 74 years participated in at least one of the 3 cross-sectional studies. All persons who took

Disclosure Statement

This was not an industry supported study. Drs. Meisinger, Heier, Löwel, Döring, and Ms. Schneider have indicated no financial conflicts of interest.

Submitted for publication November, 2006

Accepted for publication April, 2007

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part in more than one survey were included once only, with data collected at the first visit. All subjects were prospectively followed within the framework of the Cooperative Health Research in the Region of Augsburg (KORA). The present study was restricted to 45- to 74-year-old study participants (n = 7823; 3993 men, 3830 women), since the incidence of MI is very low in younger persons, particularly in younger women. By December 31, 2002, 943 men and 483 women in this age range had died. None of the study participants were excluded from analysis due to insufficient follow-up.

For the analyses, we excluded 599 persons with angina pectoris or prevalent myocardial infarction at baseline and 328 study participants with incomplete data on any of the included variables. Thus, the present study comprised 3508 men and 3388 women aged 45 to 74 years at baseline.

Written informed consent was obtained from each study participant, and the study was approved by the local ethics committee.

Data Collection

Baseline information on sociodemographic variables, smoking habits, physical activity level, medication use, and alcohol consumption were gathered by trained medical staff during a standardized interview. In addition all participants underwent an extensive standardized medical examination including the collection of a blood sample. All measurement procedures have been described elsewhere in detail.[12] Study participants provided information about whether they had ever smoked cigarettes regularly (never, past only, occasional, or regular). During the interview participants were also asked whether they suffer from diabetes, and if the diagnosis was made by a physician. Anthropometric measurements were taken after participants had removed shoes, heavy clothing, and belts. Body weight was measured in light clothing to the nearest 0.1 kg and height to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Actual hypertension was defined as blood pressure values ≥ 140/90 mm Hg and/or use of antihypertensive medication. Dyslipidemia was defined as the ratio of total cholesterol to HDL cholesterol ≥5.0. Each participant was questioned regarding his or her leisure time physical activity during the winter and summer. The questionnaire consisted of a 4-level graded scale for leisure time physical activity during summer and winter time (0, <1, 1 to 2, and >2 hours/week). The winter and summer responses were combined to create one variable of leisure time physical activity level. Participants were classified as active during leisure time if they regularly participated in sports in summer and winter and if they were active for at least 1 hour per week in either season. Depressive symptomatology was assessed using a subscale from the Zerssen affective symptom checklist. The DEpression and EXhaustion subscale (DEEX scale) combines 8 items (fatiguability, tiredness, irritability, loss of energy, difficulty in concentrating, inner tension, nervousness, anxiety) ranging from 0 to 3, leading to a Likert-like scoring range of 0-24. Subjects in the top third of the depressive symptom distribution were considered as subjects with a depressed mood. Sex specific cutoff points were applied.[14]

Clinical Chemical Measurements

A non-fasting venous blood sample was obtained from all study participants while sitting. Total serum cholesterol analyses were carried out using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Germany). HDL cholesterol was also measured enzymatically after precipitation of the apoprotein B-containing lipoproteins with phosphotungstate/Mg2+ (Boehringer Mannheim, Germany).

Assessment of Sleep Complaints and Sleep Duration

Two separate 3-category interview questions were asked concerning the difficulty initiating sleep ("Did you have trouble falling asleep?") and the difficulty maintaining sleep ("Did you wake up during the night?"). The subjects were classified into one of two categories: infrequent for those who indicated "sometimes" and "almost never" and frequent for those who indicated "often" in response to the questions. Furthermore, a variable "insomnia" was created by combining the variables difficulty maintaining sleep and difficulty initiating sleep. Insomnia was defined as an "often" response to any of these 2 questions.

Sleep duration was assessed by asking the study participants to give the habitual night sleep time: How many hours do you sleep usually each night? Response: hours |__|__|

Outcomes

The endpoint used in this study was incidence of nonfatal or fatal MI including sudden cardiac death. A MI was considered as incident if it was the first during follow-up in a person without a history of MI or angina pectoris in the baseline survey. Mortality was ascertained by regularly checking the vital status of all sampled persons of the MONICA surveys through the population registries inside and outside the study area; this procedure guaranteed that the vital status of cohort members who had moved out of the study area could also be assessed. Death certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person using the ninth revision of the International Classification of Diseases (ICD-9). MIs were identified through the population-based MONICA/KORA Augsburg coronary event registry which monitors the occurrence of all in- and out-of-hospital fatal and nonfatal MIs among the 25 to 74-year-old inhabitants of the study region.[15] Until December 31, 2000, the diagnosis of a major nonfatal MI was based on the MONICA algorithm taking into account symptoms, cardiac enzymes, and ECG changes.[15] Since 1 January 2001, all patients with MI diagnosed according to ESC and ACC criteria were included.[16,17] Coronary deaths were validated by death certificates, autopsy report, chart review, and information from the coroner or the last treating physician.

Statistical Analyses

For analyses, event times were computed as the time from baseline examination to the occurrence of the first event. Subjects without events were censored at death, at the date of the move outside the study area, or when they reached the age of 75 years, after which the register-based monitoring of coronary events ceases. All others were censored at December 31, 2002. To be comparable with previous studies, the study population was stratified into 5 categories of sleep duration: ≤5, 6, 7, 8, ≥9 hours per night. The reference category of 8 hours per night was chosen because this sleep duration is conventionally considered

Table 1—Means (± SD) and Prevalence of Baseline Variables According to Sleep Duration, Men Aged 45 To 74 Years at Baseline

	Sleep duration h/day					
Men (n=3508)	**≤5 (n=184)**	**6 (n=466)**	**7 (n=1181)**	**8 (n=1199)**	**≥9 (n=478)**	
Age (years)	57.4 (7.6)	56.5 (7.8)	55.5 (7.6)	58.2 (7.9)	62.0 (7.8)	<0.0001
BMI (kg/m²)	28.9 (3.9)	28.1 (3.5)	27.6 (3.4)	27.7 (3.4)	27.9 (3.9)	<0.0001
Difficulties initiating sleep (%)	38.0	15.2	9.0	5.9	7.3	<0.0001
Difficulties maintaining sleep (%)	54.9	28.1	17.3	15.4	16.7	<0.0001
Depressed mood (%)[a]	56.3	43.9	37.8	35.1	39.8	<0.0001
Diabetes (%)	6.5	7.9	5.9	6.9	9.8	0.0741
Hypertension (%)	53.8	52.4	53.3	54.2	61.9	0.0155
Dyslipidemia (%)	46.7	48.7	46.6	49.0	47.7	0.7925
Regular smoking (%)	23.9	22.8	23.4	22.8	28.5	0.1461
Alcohol intake 0 g/d (%)	24.5	15.9	14.6	16.6	18.0	0.0726
0.1- 39.9 g/d (%)	46.2	48.9	51.1	50.0	46.4	
≥ 40.0 g/d (%)	29.4	35.2	34.4	33.4	35.6	
Physically active (%)	32.1	37.6	41.0	38.8	27.8	<0.0001
Parental history of MI (yes, %)	15.2	17.6	18.1	15.3	15.5	0.3372
Education (< 12 years) %	77.7	66.5	63.3	72.8	81.0	<0.0001

[a]variable was available for 3101 men only

to be the appropriate duration of sleep. Means or proportions for baseline demographic and clinical characteristics were computed for categories of sleep duration. The χ^2-test was used to test the differences in prevalences. The general linear model was used to compare means (*F*-test). Different Cox proportional hazards models were computed to estimate the effect of sleep duration as well as sleep disturbance on the risk of an incident MI. The first model included sleep duration, age (continuous), and survey. The second model included all previous factors plus dyslipidemia (yes, no), education (</≥ 12 years), regular smoking (yes, no), alcohol intake (men: 0, >0 and < 40 g/d, or ≥40 g/d; women: 0, >0 and <20, or ≥20g/d), BMI (continuous), parental history of MI (yes/no and unknown), and physical activity (active/inactive). The third model included in addition to model 2, actual hypertension (yes, no), history of diabetes (yes, no), and menopause status (only women). The same procedure was executed to examine the association between difficulties initiating sleep as well as difficulties maintaining sleep and incident MI. To assess the contribution of depressed mood to the observed effects, secondary analyses adjusting for depressed mood were also performed (n=3101 men and n=2840 women with complete data). Furthermore, in stratified analyses it was assessed whether sleep duration would increase the risk of an incident MI in individuals with and without a complaint of insomnia.

Interactions between categories of sleep duration (coded as dummy variables) and sex were examined using likelihood ratio tests which compared the –2 log(likelihood) between the model which contained only the main effects and the model which contained both the main effects and interaction terms. The assumption of proportionality of hazards was assessed by fitting models stratified by risk factor categories, then plotting the log (-log(survival)) curves to check parallelism. No severe deviations from parallelism were evident. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Significance tests were two-tailed and P-values less than 0.05 are stated as statistically significant. All analyses were performed using the Statistical Analysis System (Version 8.2, SAS Institute Inc, Cary, NC).

RESULTS

At baseline examination significantly more women than men reported difficulties in initiating sleep (men 10.1%, women 22.2%) and in maintaining sleep (men 20.0%, women 29.4%), whereas no gender differences for the pattern of sleep duration were observed.

In total, 295 (158 fatal, 137 nonfatal) incident cases of MI among men and 85 (48 fatal, 37 nonfatal) among women were registered in the 45- to 74-year-old study population between 1984 and 2002. The mean follow-up period was 10.1 years.

Table 1 describes the baseline characteristics by sleep duration categories for men. Compared with men sleeping 7 or 8 hours per day, men with increased or decreased sleep duration were less physically active and less educated. Men who slept less tended to have a higher BMI and to report difficulties initiating sleep as well as difficulties maintaining sleep, whereas men who slept ≥9 hours were older and were more likely to have hypertension. The baseline characteristics of women in the various sleep duration categories are shown in Table 2. Women sleeping ≤5 hours reported more frequently difficulties initiating sleep, difficulties maintaining sleep, and less alcohol consumed. On the other hand, women sleeping ≥9 hours were older, had a higher BMI, and more frequently dyslipidemia. Increased and decreased sleep duration in women were associated with an increased prevalence of hypertension, diabetes mellitus, menopause status, and physical inactivity.

Women but not men who reported a high frequency of difficulty maintaining sleep had a significantly higher risk for incident MI compared with those who experienced a low frequency of difficulty maintaining sleep in age- and survey-adjusted analysis (women: HR 1.63; 95% CI, 1.06-2.53; men: HR 1.13; 95% CI, 0.85-1.49; Table 3). The P value for the interaction between difficulties maintaining sleep and sex in this model was 0.1601. After adjustment for further covariates (model 2 and model 3) the association became borderline significant in women (HR 1.53; 95% CI, 0.99-2.37) and remained nonsignificant in men (HR

Table 2—Means (± SD) and Prevalence of Baseline Variables According to Sleep Duration, Women Aged 45 To 74 Years at Baseline

Women (n=3388)	Sleep duration h/day ≤5 (n=193)	6 (n=451)	7 (n=978)	8 (n=1283)	≥9 (n=483)	
Age (years)	59.5 (8.2)	58.6 (8.2)	55.9 (7.6)	56.9 (7.9)	60.3 (8.3)	<0.0001
BMI (kg/m²)	27.2 (4.8)	27.8 (4.8)	27.2 (4.5)	27.6 (4.7)	28.5 (4.9)	<0.0001
Difficulties initiating sleep (%)	61.1	35.0	20.9	14.0	16.6	<0.0001
Difficulties maintaining sleep (%)	78.8	46.6	27.7	19.1	22.4	<0.0001
Depressed mood (%)[a]	56.2	47.0	38.7	36.2	35.3	<0.0001
Diabetes (%)	6.7	6.4	4.0	4.9	9.7	0.0002
Hypertension (%)	51.3	50.1	43.3	47.0	55.1	0.0005
Dyslipidemia (%)	25.9	24.6	22.9	23.6	36.0	<0.0001
Regular smoking (%)	13.5	14.4	13.8	10.7	10.8	0.0791
Alcohol intake 0 g/d (%)	58.0	48.1	46.5	45.7	53.4	0.0018
0.1- 19.9 g/d (%)	31.1	32.2	36.3	38.1	30.2	
≥20.0 g/d (%)	10.9	19.7	17.2	16.2	16.4	
Physically active (%)	24.4	29.5	34.7	32.7	25.1	0.0005
Parental history of MI (yes, %)	22.8	16.6	23.5	20.0	19.1	0.0260
Education (<12 years) %	88.6	87.6	86.3	88.8	91.3	0.0750
Menopause status (yes, %)	87.6	82.9	75.8	77.7	86.1	<0.0001

[a]variable was available for 2840 women only

1.12; 95% CI, 0.84-1.48). Difficulties initiating sleep were not significantly associated with incident MI in both sexes (Table 3).

Sleep duration was also associated with a modestly increased risk of incident MI in women (Table 4). For women sleeping ≤5 hours per night the HR was 3.43 (95% CI, 1.71-6.88), and for women sleeping ≥9 hours per night the HR was 1.83 (95% CI, 0.98-3.41) after age- and survey adjustment; the corresponding HRs for men were 1.13 (95% CI, 0.67-1.92) and 1.25 (95% CI, 0.88-1.78). The P value for the interaction between categories of sleep duration and sex in this model was 0.1477. After adjusting for BMI, education, dyslipidemia, alcohol intake, parental history of MI, physical activity, regular smoking, hypertension, history of diabetes, and menopause status (women only), the association between short sleep duration and incident MI was somewhat attenuated in both sexes (women: HR 2.98; 95% CI, 1.48-6.03; men: HR 1.13; 95% CI, 0.66-1.92); the P value for the sex interaction was 0.2546 in this model. In women, additional adjustment for hormone replacement therapy had virtually no impact on the observed HRs (data not shown).

Further stratification by insomnia, although limited by small numbers, revealed generally similar point estimates as the unstratified analyses (data not shown).

Inclusion of depressed mood in the models in addition to other risk factors had only a slight impact on the observed HRs. For women reporting ≤5 hours and 6 and 7 hours of sleep compared with women reporting 8 hours of sleep, the HRs were 3.27 (95% CI, 1.43-7.46), 1.05 (95% CI, 0.41-2.68), and 1.55 (95% CI, 0.81-2.98), respectively; the corresponding HRs for men were 0.73 (95% CI, 0.36-1.46), 1.09 (95% CI, 0.72-1.64), and 1.19 (95% CI, 0.88-1.61), respectively. The HRs for women and men who slept ≥9 hours daily were 1.65 (95% CI, 0.81-3.39) and 1.06 (95% CI, 0.72-1.57), respectively. In multivariable analysis after additional adjustment for depressed mood the HR was 1.10 (95% CI, 0.80-1.51) in men and 1.49 (95% CI, 0.89-2.49) in women with difficulties maintaining sleep (data not shown).

To get around the issue of reverse causation, we repeated the analyses after exclusion of all subjects with ≤2 years of follow-up (men: n=234, 52 events, women: n=150, 11 events). Multivariable adjusted HRs estimated from these models were almost the same as the HRs estimated in the whole study sample. For women sleeping ≤5 hours per night, the HR was 3.43 (95% CI, 1.61-7.29) and for women sleeping ≥9 hours the HR was 1.49 (95% CI, 0.75-2.98) after multivariable adjustment. The corresponding HRs for men were 1.10 (95% CI, 0.61-1.98) and 1.08 (95% CI, 0.72-1.62). In multivariable analysis difficulties maintaining sleep were not significantly associated with incident MI in women (HR 1.50; 95% CI, 0.94-2.40) and in men (HR 1.10; 95% CI, 0.81-1.50). In these analyses, difficulties initiating sleep were also not significantly associated with incident MI in both sexes (data not shown).

Table 3—Gender Specific Hazard Ratios (HR) and 95% CI for Developing an Acute Coronary Event According to Self-reported Sleep Disturbance at Baseline

	Men HR (95% CI)	Women HR (95% CI)
Difficulty initiating sleep	(n=353)	(n=740)
Number of incident cases	40	27
Model 1	1.34 (0.96 – 1.88)	1.50 (0.94 – 2.37)
Model 2	1.20 (0.86 – 1.69)	1.43 (0.90 – 2.27)
Model 3	1.16 (0.82 – 1.63)	1.30 (0.81 – 2.06)
Difficulty maintaining sleep	(n=701)	(n=986)
Number of incident cases	64	35
Model 1	1.13 (0.85 – 1.49)	1.63 (1.06 – 2.53)
Model 2	1.14 (0.87 – 1.51)	1.62 (1.05 – 2.50)
Model 3	1.12 (0.84 – 1.48)	1.53 (0.99 – 2.37)

Model 1: adjusted for age and survey
Model 2: adjusted for age, survey, BMI, education, dyslipidemia, alcohol intake, parental history of MI, physical activity, regular smoking
Model 3: adjusted for the same variables as in Model 2 plus adjusted for hypertension, diabetes, and menopause status (only women)

Table 4—Relative Risks of Acute Coronary Event According to Sleep Duration Among Men and Women

	Sleep duration h/day				
	≤5	6	7	8	≥9
Men (n=3508)	**(n=184)**	**(n=466)**	**(n=1181)**	**(n=1199)**	**(n=478)**
No. of incident cases	16	35	102	96	46
Person-years (PY)	1,787	4,706	12,471	11,743	3,779
Crude rate per 10,000 PY	89.5	74.4	81.8	81.8	121.7
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	1.13 (0.67-1.92)	1.00 (0.68-1.48)	1.16 (0.88-1.54)	1.0	1.25 (0.88-1.78)
Model 2	1.07 (0.63-1.83)	1.04 (0.71-1.54)	1.22 (0.92-1.61)	1.0	1.11 (0.78-1.58)
Model 3	1.13 (0.66-1.92)	1.05 (0.71-1.55)	1.22 (0.92-1.61)	1.0	1.07 (0.75-1.53)
Women (n=3388)	(n=193)	(n=451)	(n=978)	(n=1283)	(n=483)
No. of incident cases	12	9	23	24	17
Person-years (PY)	1,766	4,445	10,425	13,626	4,496
Crude rate per 10,000 PY	68.0	20.2	22.1	17.6	37.8
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	3.43 (1.71-6.88)	1.07 (0.50-2.30)	1.34 (0.76-2.37)	1.0	1.83 (0.98-3.41)
Model 2	2.93 (1.46-5.90)	1.00 (0.46-2.16)	1.29 (0.73-2.31)	1.0	1.41 (0.75-2.66)
Model 3	2.98 (1.48-6.03)	1.05 (0.49-2.27)	1.34 (0.75-2.40)	1.0	1.40 (0.74-2.64)

Model 1: adjusted for age and survey
Model 2: adjusted for age, survey, BMI, education, dyslipidemia, alcohol intake, parental history of MI, physical activity, regular smoking
Model 3: adjusted for the same variables as in Model 2 plus adjusted for hypertension, diabetes, and menopause status (only women)

DISCUSSION

In this large cohort of men and women drawn randomly from the general population, a modestly positive association between short sleep duration as well as difficulty maintaining sleep and incident MI in women but not men was observed. The association was independent of known cardiovascular risk factors including depressed mood. However, no dose-response relationship between sleep duration and incident MI was observed. Trouble falling asleep was not associated with a significantly increased risk of MI in either sex in the present study.

The Augsburg cohort did not confirm recently reported gender differences in sleep disorders,[18] with better sleep quality as well as longer sleep times in women compared to men, but the present results were in agreement with the Coronary Artery Risk Developments in Young Adults (CARDIA) cohort[19] which did not find significant gender differences with regard to sleep duration.

Several previous prospective studies have related sleep duration[4,10] or sleep complaints[20,21] to mortality. However, prospective studies on the association between sleep duration,[11] insomnia[22-25] or the combination of both[9] and incident fatal and nonfatal MI are scarce. Data of the Cancer Prevention Study II of the American Cancer Society showed that the best survival was found among men and women who slept 7 hours per night. Study participants who slept ≥8 hours experienced significantly increased mortality hazard, as did those who slept ≤6 hours. The increased risk exceeded 15% for those reporting more than 8.5 hours sleep or less than 3.5 or 4.5 hours. Conversely, men and women reporting insomnia had no increased risk of mortality.[4] Wingard and Berkman[10] found that men sleeping 6 hours or less or 9 hours or more had 1.7 times the total death rate of men sleeping 7 or 8 hours per night in age-adjusted analysis. The comparable relative risk for women was 1.6. Recently, Ayas et al reported that in the Nurses' Health Study, including 71,617 US female health professionals aged 45-65 years, short and long sleep durations were independently associated with an increased risk of coronary events.[11] In multivariable analyses, the relative risk of coronary heart disease for women reporting ≤5 and 6 and 7 hours of sleep were 1.45 (95% CI 1.10-1.92), 1.18 (95% CI, 0.98-1.42), and 1.09 (95% CI, 0.91-1.30), respectively. The relative risk for individuals who slept 9 or more hours daily was 1.38 (95% CI, 1.03-1.86). Thus, the present study confirms these results. Interestingly, in women the point estimate for the sleep duration of ≥9 hours daily in comparison to 8 hours daily was 1.40 in the present study, which is almost the same as in the study by Ayas et al.[11] However, although the point estimate was clearly elevated in the present study the association was not significant, which could be due to the relatively low power of the study.

In the Piedmont Study[24] incidence density ratios of 1.58 and 1.68, respectively, for restless sleep and trouble falling asleep with incident MI in older adults (≥ 65 years old) were observed after adjustment for classic coronary risk factors. However, the association lost significance after controlling for education, number of prescription medicines, self-rated health, and depression. Unfortunately, in that study no gender-specific analyses were done. In the Framingham Study,[23] 749 women aged 45-64 years, free of CHD at baseline were followed for 20 years. Contrary to the present study, in that study women reporting trouble falling asleep had a 3.9 time increased risk of a nonfatal MI or CHD death after multivariable adjustment. Appels et al examined whether sleep complaints increased the risk for nonfatal MI or CHD death in a 4-year longitudinal study of 3877 men, aged 39 to 65 years. After adjusting for age, cholesterol, systolic and diastolic blood pressure, and smoking the HR was 1.62 for trouble falling asleep and 1.52 for trouble staying asleep.[22] In the Caerphilly cohort compared with men who reported no such symptoms, the adjusted relative odds of ischemic heart disease was 1.47 (95% CI, 0.98-2.21) in men with any sleep disturbance.[25]

The exact pathophysiological mechanisms underlying the association between sleep complaints as well as short sleep duration and CHD have not been defined so far. However, several potential

explanations are possible. There is evidence that sleep may exert effects on the autonomic nervous system, systemic hemodynamics, cardiac function, endothelial function, and coagulation.[3] Sleep disorders are associated with an increase in sympathetic activity,[26,27] increases in blood pressure, or a decrease in glucose tolerance.[28] Furthermore, recent research has demonstrated that sleep loss is accompanied by an elevation of inflammatory markers which could enhance the development of atherosclerosis.[29,30]

The findings in the present population cohort including both middle-aged men and women extend the literature showing that sleep disturbances and sleep duration are associated with an increased risk of MI. While we found a modest association in women, we observed no relationship between sleep duration and sleep disturbances, respectively, and risk of acute coronary events in men, but a formal test for interaction did not reach significance. However, the results of the presents study were based on small numbers of incident cases, particularly in the subgroup with sleep duration of 5 hours or less. Thus, the confidence intervals surrounding the point estimates for the found associations were wide. Further studies including a greater number of subjects and incident cases would help determine the magnitude of the associations with greater precision.

Nevertheless, gender specific particularities in consequences of sleeping difficulties cannot be excluded. There are biological differences including genetics and sexual hormones that affect sleep. In addition, there are sex differences in stress and reaction to stress.[31] Further research is necessary to determine, whether there are gender-specific mechanisms underlying the association between insomnia and CHD risk.

The MONICA/KORA Augsburg Study has several limitations that need to be considered. One potential weakness of the study was that the information about insomnia and sleep duration was self-reported and that the questions were not related to a defined time frame. However, as investigated by other studies, self-reported sleep duration seems to be valid in comparison to quantitative sleep assessments with actigraphy.[32] Because habitual snoring and sleep apnea were not measured in the baseline examination, it was not possible to distinguish whether the observed associations in the present study could be due to habitual snoring, sleep debt, or both, respectively. Moreover, because the present study was observational in design, it cannot be concluded, that sleep disturbance or short sleep duration causes incident MI. Although we adjusted for a variety of confounders, residual confounding cannot be excluded. Furthermore, sleep problems reported on only one occasion were used in the prediction of MI incidence. However, all of the subjects who participated in the first survey were invited to participate in a follow-up examination in 1987/88. At follow-up, all of the subjects were again asked concerning sleep duration and sleep complaints. Sleep duration as well as reports regarding difficulties maintaining sleep and difficulties initiating sleep did not significantly differ between the two examinations in either sex. About 80% of the persons (both sexes) had a variation of sleep duration of one hour or less. Finally, further limitations are the low power of the present study to detect a modest effect and the small number of events, particularly in the group of sleeping ≤5 hours. The strengths of the MONICA/KORA Augsburg Cohort Study are primarily its prospective design, the population-representativeness of the cohort, and the availability of data on life style and a number of cardiovascular risk factors.

In conclusion, the present study suggested that short sleep duration and sleep complaints are modestly related to incident MI in middle-aged women but not men from the general population. The finding concerns a great portion of the German population and is therefore of important public health relevance. Further studies are needed to investigate the biological mechanisms underlying these associations. In particular, it remains to be investigated whether there are gender specific particularities with regard to this issue.

ACKNOWLEDGEMENTS

The KORA research platform and the MONICA Augsburg studies were initiated and financed by the GSF - National Research Center for Environment and Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Morbidity and Mortality follow-ups were in addition supported by grants from the Federal Ministry of Education, Science, Research and Technology (01 ER 9701/4) and the German Research Foundation (DFG) (TH 784/2-1). We thank all members of the GSF Institute of Epidemiology and the field staff in Augsburg who were involved in the conduct of the studies.

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