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Original Contribution

Sleep Disturbances and Cause-Specific Mortality: Results From the GAZEL Cohort Study

Naja Hulvej Rod*, Jussi Vahtera, Hugo Westerlund, Mika Kivimaki, Marie Zins, Marcel Goldberg, and Theis Lange

* Correspondence to Naja Hulvej Rod, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, Postbox 2099, 1014 Copenhagen K, Denmark (e-mail: nahuro@sund.ku.dk).

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Poor sleep is an increasing problem in modern society, but most previous studies on the association between sleep and mortality rates have addressed only duration, not quality, of sleep. The authors prospectively examined the effects of sleep disturbances on mortality rates and on important risk factors for mortality, such as body mass index, hypertension, and diabetes. A total of 16,989 participants in the GAZEL cohort study were asked validated questions on sleep disturbances in 1990 and were followed up until 2009, with <1% loss to follow-up. Body mass index, hypertension, and diabetes were measured annually through self-reporting. During follow-up, a total of 1,045 men and women died. Sleep disturbances were associated with a higher overall mortality risk in men ($P = 0.005$) but not in women ($P = 0.33$). This effect was most pronounced for men <45 years of age (≥3 symptoms vs. none: hazard ratio = 2.03, 95% confidence interval: 1.24, 3.33). There were no clear associations between sleep disturbances and cardiovascular mortality rates, although men and women with sleep disturbances were more likely to develop hypertension and diabetes ($P < 0.001$). Compared with people with no sleep disturbances, men who reported ≥3 types of sleep disturbance had an almost 5 times' higher risk of committing suicide (hazard ratio = 4.99, 95% confidence interval: 1.59, 15.7). Future strategies to prevent premature deaths may benefit from assessment of sleep disturbances, especially in younger individuals.

body mass index; cause of death; diabetes mellitus; hypertension; longitudinal studies; mortality; sleep disorders

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; ICD, *International Classification of Diseases*; NHP, Nottingham Health Profile.

Sleep loss, long-term sleep deprivation, and alterations in sleep quality are substantial problems in modern society (1, 2). Sleep represents a daily process of physiologic restitution and recovery, and lack of sleep may have far-reaching effects on endocrinology, immunology, metabolism, and eventually disease risk (3). Although researchers in most previous studies have focused on sleep duration (4–12), sleep quality may also play a role in disease etiology. Human sleep is composed of rapid eye movement sleep and stages 1–4 of non-rapid eye movement sleep. The deeper stages of non-rapid eye movement sleep, that is, stages 3 and 4, are collectively called slow-wave sleep, and these sleep stages are particularly important for glucose homeostasis and general biologic restoration (13). Impaired sleep quality is likely to suppress slow-wave sleep, and results of a recent experimental study showed that reduced sleep quality without changes in sleep duration was associated with decreased insulin sensitivity and glucose tolerance (13). Only a few population studies have addressed the association between sleep disturbances and mortality rates, and there have been some inconsistencies in the results (6, 12, 14, 15).

Evidence of mechanisms that link sleep disturbances to disease risk is important in making causal inferences, but these mechanisms are far from elucidated. Experimental studies have found that relatively brief periods of severe sleep deprivation increase low-level systemic inflammation and insulin resistance (3, 13, 16), and results from several observational studies supported the status of sleep

disturbances as a risk factor for diabetes (17, 18), obesity (19, 20), and hypertension (21) in population samples. These conditions, which are known to contribute to cardiovascular disease (CVD) mortality, may partly mediate the relation between sleep and mortality. In the present study, we therefore hypothesized that sleep disturbances would be associated with higher rates of all-cause and cause-specific mortality (especially deaths due to CVD and external causes), as well as with important risk factors for mortality, that is, body mass index (BMI; weight (kg)/height $(m)^2$), hypertension, and diabetes. We tested this hypothesis in almost 17,000 men and women from the French GAZEL Cohort Study who were followed for 19 years with validated measures of sleep disturbances.

MATERIALS AND METHODS

The GAZEL cohort study

The GAZEL cohort study was initiated in 1989 and was at baseline composed of a sample of 20,625 employees, aged 35–50 years, of the French national gas and electricity company, Electricité de France–Gaz de France (22). A questionnaire was sent to the participants every year to obtain data on health status, lifestyle, social, and occupational factors. Electricité de France–Gaz de France employees hold a civil servant-like status that guarantees job stability, and typically employees are hired when they are in their 20s and stay with the company until they retire. About 75% of the questionnaires have been returned annually, and <1% of the participants have been lost to follow-up over 20 years. The vast majority of the participants were white Europeans, and all gave informed consent. The 1990 study questionnaire included questions about sleep disturbances, and this wave was used as the baseline for the present study. The 17,970 participants who responded in 1990 constituted a response rate of 87%. Participants with missing information on any of the covariates ($n = 981$) were excluded, leaving 4,465 women and 12,524 men for the analyses.

Sleep disturbances

Sleep disturbances were assessed by using the 5-item sleep dimension from part 1 of the Nottingham Health Profile (NHP), a validated and widely used method of assessing quality of life (23). We used the French version of the NHP, which included item weights adjusted for a French population (24). The 5 sleep items of the NHP are: "I take tablets to help me sleep" (French weight = 26.33); "I lie awake most of the night" (French weight = 22.86); "I sleep badly at night" (French weight = 20.36); "It takes me a long time to fall asleep" (French weight = 16.50); and "I wake up in the early hours of the morning" (French weight = 13.94). The respondents were asked if they were currently experiencing each of the abovementioned problems. We analyzed each sleep item separately and the weighted NHP sleep score, which ranged from 0 to 100 points according to the French weights. As there have been discussions on the validity of the weighted score (24), we additionally modeled sleep disturbances simply as the number of affirmative responses to the 5 sleep items.

Covariates

Covariates were measured at baseline in 1990 and included age, marital status (married/cohabiting, single, divorced/separated, or widowed), night work (never, occasionally, or regularly), current smoking (yes or no), alcohol intake (occasional, low (1–2 glasses of wine or beer per day), medium (3–4 glasses of wine or beer per day), or high (>4 glasses of wine or beer per day or daily intake of spirits)), BMI (<25, 25–29, or ≥30), and baseline morbidity (reporting 1 of the following chronic diseases within the last 12 months: hypertension, diabetes, angina pectoris, myocardial infarction, asthma, and chronic bronchitis). Socioeconomic status was determined on the basis of employment grade derived from Electricité de France–Gaz de France records and was classified into 3 groups based on categorizations from the French National Statistics Institute: high grade (managers), intermediate grade (technical staff, line managers, and administrative associated professionals), and lower grade (clerical and manual workers).

Follow-up

The participants were followed from the date of the 1990 examination until the date of death ($n = 1,045$) or the end of follow-up on September 25, 2009. Data on total number and causes of death were obtained from the French National Death Index. Cause-specific mortality was coded using the *International Classification of Diseases*, Ninth Revision (ICD-9), until 1998, and the Tenth Revision (ICD-10) thereafter. We distinguished between deaths due to cancers (ICD-9 codes: 140–208; ICD-10 codes: C00–C97), CVD (ICD-9 codes: 390–459; ICD-10 codes: I00–I99), external causes (ICD-9 codes E800–E999; ICD-10 codes: V01–X84), and suicide (a subcategory of external causes with ICD-9 codes: E950–E959; ICD-10 codes: X60–X84). BMI trajectories, as well as incidence of diabetes and hypertension, were determined on the basis of annually updated self-reported information on these conditions. Incident cases were defined as first-time reporting of hypertension or diabetes.

Statistical analyses

Data were analyzed with Cox proportional hazards models with age as the time variable. All variables met the assumption of proportional hazards. Initially, we estimated hazard ratios and 95% confidence intervals for all-cause mortality according to each of the individual sleep items, as well as according to the NHP sleep score. A multivariate model was fitted to adjust for confounding from baseline covariates. Potential confounders were identified according to the methods of directed acyclic graphs (25) and included age, socioeconomic status, marital status, smoking status, alcohol consumption, BMI, night work, and baseline morbidity. Because controlling for depression could constitute overadjustment (i.e., accounting for a variable on the causal pathway), models were created both with and without this variable. In sensitivity analyses, we excluded the first 2 years of follow-up to prevent reverse causation. We then assessed

Table 1. Baseline Characteristics of 16,989 Participants in the 1990 Wave of the GAZEL Cohort Study, 1990–2009

	Total Population (n = 16,989)			Nottingham Health Profile Sleep Score (No. of Affirmative Responses)											
				0 (n = 9,316)			1 (n = 4,633)			2 (n = 1,642)			≥3 (n = 612)		
	Mean	No.	%	Mean	No.	%	Mean	No.	%	Mean	No.	%	Mean	No.	%
Death[a]		1,045	6		516	6		293	6		116	7		52	8
Baseline age, years	45			45			45			45			45		
Female sex			26			23			25			35			48
Low socioeconomic grade			14			13			14			17			26
Married			89			92			89			84			73
Current smoker			26			25			26			25			31
High alcohol intake			9			9			10			10			10
Obese			5			5			5			5			7
Regular night work			4			4			3			3			2
Cardiovascular morbidity (hypertension, diabetes, angina, or myocardial infarction)			10			9			12			13			14
Respiratory morbidity (asthma or chronic bronchitis)			5			4			5			7			9
Taking sleeping tablets			12			0			12			57			78
Lying awake most of the night			9			0			11			29			72
Sleeping badly at night			4			0			2			10			52
Taking a long time to fall asleep			6			0			9			22			39
Waking in the early hours of the morning			31			0			67			81			86

[a] The total number of deaths was 1,045, but because of missing values on some of the items in the Nottingham Health Profile sleep score, the numbers of deaths according to the Nottingham Health Profile sleep score do not add up to 1,045.

the relation between sleep disturbances and cause-specific mortality. Because there were very few cases in each cause-specific mortality category for women, the cause-specific analysis was performed only for men. Finally, we assessed the effect of sleep quality on BMI, hypertension, and diabetes to address potential mediation by these factors. Because BMI was measured repeatedly throughout follow-up, we chose to model the whole trajectory of BMI. To accommodate the dependence induced by measuring the same person several times, we included random intercept and age effects for each person in a linear model (26). Thus, the effects reported for sleep disturbances were average up-and-down movements of the whole BMI trajectory controlled for potential confounders and random individual effects. We performed the analyses with the lmer procedure from the lme4 package (linear mixed-effects models using S4 classes, version 0.999375-28; by Douglas Bates, Department of Statistics, University of Wisconsin-Madison) in R, version 2.8.1. The associations between sleep disturbances and incidence of hypertension and diabetes were modeled using a Cox model. Individuals were excluded if they had reported hypertension or diabetes in 1990. All analyses were conducted separately for men and women.

RESULTS

Baseline characteristics

The mean age at baseline was 45 years, ranging from 36 years to 52 years. Fourteen percent of the population reported ≥2 sleep disturbances, and 58% of the population reported no sleep disturbances. Baseline characteristics of the population are shown in Table 1.

Sleep disturbances and all-cause mortality

During 19 years of follow-up, 1,045 deaths occurred (160 deaths among the 4,465 eligible women and 885 deaths among the 12,524 eligible men). The mean age at time of death was 56 years for women and 58 years for men. Neither the individual sleep items nor the NHP sleep score was associated with all-cause mortality in women (Table 2). In

Table 2. All-Cause Mortality Risk Associated With Sleep Disturbances Among 4,465 Women and 12,524 Men Who Participated in the GAZEL Cohort Study, 1990–2009

	Women					Men				
	No. of Deaths[a]	Age-Adjusted HR	95% CI	Multiply Adjusted[b] HR	95% CI	No. of Deaths[a]	Age-Adjusted HR	95% CI	Multiply Adjusted[b] HR	95% CI
I take tablets to help me sleep.										
No	115	1	Reference	1	Reference	727	1	Reference	1	Reference
Yes	35	1.16	0.75, 1.61	1.07	0.72, 1.57	126	1.56	1.29, 1.89	1.30	1.07, 1.57
I lie awake most of the night.										
No	126	1	Reference	1	Reference	754	1	Reference	1	Reference
Yes	24	1.05	0.68, 1.62	0.93	0.59, 1.44	94	1.72	1.39, 2.14	1.36	1.09, 1.70
I sleep badly at night.										
No	132	1	Reference	1	Reference	796	1	Reference	1	Reference
Yes	17	1.55	0.94, 2.57	1.07	0.62, 1.84	45	2.26	1.67, 3.05	1.69	1.25, 2.31
It takes me a long time to fall asleep.										
No	132	1	Reference	1	Reference	775	1	Reference	1	Reference
Yes	17	1.41	0.85, 2.33	1.28	0.76, 2.16	71	1.42	1.11, 1.81	1.16	0.91, 1.49
I am waking up in the early hours of the morning.										
No	109	1	Reference	1	Reference	559	1	Reference	1	Reference
Yes	40	0.77	0.54, 1.11	0.77	0.53, 1.11	293	1.12	0.97, 1.28	1.10	0.95, 1.27
Nottingham Health Profile sleep score (no. of items)										
0	80	1	Reference	1	Reference	436	1	Reference	1	Reference
1	32	0.70	0.47, 1.06	0.61	0.40, 0.93	261	1.21	1.04, 1.41	1.17	1.01, 1.37
2	20	0.86	0.53, 1.40	0.74	0.45, 1.23	96	1.44	1.16, 1.80	1.26	1.01, 1.58
≥3	14	1.17	0.67, 2.07	0.96	0.54, 1.72	38	1.96	1.41, 2.73	1.38	0.98, 1.94
P for trend		0.85		0.33			<0.001		0.005	
Nottingham Health Profile sleep score (weighted sum score)										
10-point increase	146	1.01	0.94, 1.10	0.98	0.90, 1.06	831	1.12	1.08, 1.16	1.07	1.02, 1.11

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The total number of deaths was 160 in women and 852 in men, but because of missing values, the numbers for some of the variables do not add up to the overall total.

[b] Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, baseline body mass index, night work, and baseline morbidity (hypertension, diabetes, angina pectoris, myocardial infarction, asthma, or chronic bronchitis).

contrast, men who reported taking sleeping pills (hazard ratio (HR) = 1.30, 95% confidence interval (CI): 1.07, 1.57), lying awake most of the night (HR = 1.36, 95% CI: 1.09, 1.70), or sleeping badly at night (HR = 1.69, 95% CI: 1.25, 2.31) were at a higher risk of premature death than were men who did not report these problems. Also, the number of affirmative answers to the NHP sleep score was associated with higher mortality in a dose–response manner ($P_{\text{trend}} = 0.005$), and a 10-point increase on the weighted NHP sleep score (maximum score: 100 points) was associated with a hazard ratio of 1.07 (95% CI: 1.02, 1.11) in men.

Of the 885 deaths that occurred in men during follow-up, 360 occurred in men who were ≤45 years of age at baseline, whereas the remaining 525 occurred in men who were >45 years of age at baseline. In age-stratified analyses, the excess risk associated with sleep disturbances was mainly confined to younger men (Table 3). Each individual sleep item, except for the use of sleep medication, was associated with a higher mortality risk in men ≤45 years of age. In men >45 years of age, only those who reported sleeping badly at night were at a higher risk of premature death. Also, a higher number of affirmative answers to the NHP sleep questions

Table 3. All-Cause Mortality Risk Associated With Impaired Sleep Quality Among the 12,524 Men Who Participated in the GAZEL Cohort Study, Stratified by Age at Baseline, 1990–2009

	Baseline Age ≤45 years			Baseline Age >45 years		
	No. of Deaths[a]	Multiply Adjusted[b] HR	95% CI	No. of Deaths[a]	Multiply Adjusted[b] HR	95% CI
I take tablets to help me sleep.						
No	304	1	Reference	423	1	Reference
Yes	46	1.28	0.93, 1.76	80	1.31	1.03, 1.67
I lie awake most of the night.						
No	304	1	Reference	450	1	Reference
Yes	43	1.46	1.04, 2.05	51	1.29	0.96, 1.75
I sleep badly at night.						
No	326	1	Reference	470	1	Reference
Yes	20	1.78	1.11, 2.86	25	1.70	1.13, 2.56
It takes me a long time to fall asleep.						
No	316	1	Reference	459	1	Reference
Yes	32	1.78	1.23, 2.57	39	0.89	0.64, 1.24
I am waking up in the early hours of the morning.						
No	220	1	Reference	339	1	Reference
Yes	129	1.44	1.15, 1.79	164	0.92	0.76, 1.11
Nottingham Health Profile sleep score (no. of items)						
0	174	1	Reference	262	1	Reference
1	112	1.47	1.16, 1.87	149	1.00	0.82, 1.23
2	39	1.53	1.07, 2.19	57	1.10	0.82, 1.48
≥3	19	2.03	1.24, 3.33	19	1.07	0.66, 1.72
P for trend		<0.001			0.59	
Nottingham Health Profile sleep score (weighted sum score)						
10-point increase	344	1.12	1.06, 1.19	487	1.03	0.98, 1.09

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The total number of deaths was 360 in men ≤45 years of age and 525 in men >45 years of age, but because of missing values, the numbers for some of the variables do not add up to the overall total.

[b] Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, baseline body mass index, night work, and baseline morbidity (hypertension, diabetes, angina pectoris, myocardial infarction, asthma, and chronic bronchitis).

was associated with mortality risk only in younger men ($P_{trend} < 0.001$), with those reporting ≥3 sleep disturbances experiencing about twice the risk of all-cause mortality (HR = 2.03, 95% CI: 1.24, 3.33). Excluding the first 2 years of follow-up to prevent reverse causation had only a negligible effect on the risk estimates. Adjustment for depressive symptoms at baseline attenuated the risk estimates, but several of the indicators of sleep disturbances remained associated with a higher mortality risk (data not shown). For example, younger men who reported ≥3 sleep disturbances still had a higher risk of all-cause mortality after adjustment for baseline depression (HR = 2.05, 95% CI: 1.22, 3.47).

Sleep disturbances and cause-specific mortality

Of the 885 deaths that occurred in men, 161 were due to CVD, 417 were due to cancer, and 81 were due to external causes. Apart from taking sleep medication (HR = 1.56, 95% CI: 1.03, 2.36) and sleeping badly at night (HR = 1.91, 95% CI: 0.99, 3.66), neither the individual sleep items

Table 4. Cause-Specific Disease Mortality Risk Associated With Impaired Sleep Quality Among 12,524 Men Who Participated in the GAZEL Cohort Study, 1990–2009

	Cardiovascular Disease Mortality			Cancer Mortality			Death Due to External Causes		
	No. of Deaths[a]	Multiply Adjusted[b] HR	95% CI	No. of Deaths[a]	Multiply Adjusted[b] HR	95% CI	No. of Deaths[a]	Multiply Adjusted[b] HR	95% CI
I take tablets to help me sleep.									
No	127	1	Reference	355	1	Reference	67	1	Reference
Yes	28	1.56	1.03, 2.36	51	1.08	0.80, 1.46	15	1.85	1.05, 3.27
I lie awake most of the night.									
No	139	1	Reference	362	1	Reference	68	1	Reference
Yes	16	1.21	0.71, 2.08	43	1.39	1.00, 1.93	13	2.07	1.11, 3.86
I sleep badly at night.									
No	146	1	Reference	381	1	Reference	75	1	Reference
Yes	10	1.91	0.99, 3.66	19	1.56	0.96, 2.51	6	2.54	1.09, 5.96
It takes me a long time to fall asleep.									
No	141	1	Reference	367	1	Reference	72	1	Reference
Yes	14	1.18	0.67, 2.06	35	1.22	0.86, 1.74	8	1.76	0.84, 3.69
I am waking up in the early hours of the morning.									
No	107	1	Reference	273	1	Reference	49	1	Reference
Yes	50	0.97	0.69, 1.36	130	1.00	0.81, 1.24	33	1.46	0.93, 2.29
Nottingham Health Profile sleep score (no. of items)									
0	81	1	Reference	214	1	Reference	35	1	Reference
1	47	1.09	0.76, 1.57	124	1.16	0.93, 1.45	25	1.46	0.86, 2.47
2	17	1.18	0.69, 2.00	43	1.17	0.83, 1.63	15	2.78	1.51, 5.12
≥3	8	1.42	0.68, 3.00	15	1.14	0.66, 1.97	4	2.07	0.72, 5.96
P for trend		0.30			0.22			0.002	
Nottingham Health Profile sleep score (weighted sum score)									
10-point increase	153	1.06	0.97, 1.16	396	1.05	0.99, 1.11	79	1.19	1.06, 1.33

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The total number of deaths due to cardiovascular disease, cancer, and external causes, respectively, were 161, 417, and 81 in men, but because of missing values, the numbers for some of the variables do not add up to the overall totals.

[b] Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, baseline body mass index, night work, and baseline morbidity (hypertension, diabetes, angina pectoris, myocardial infarction, asthma, and chronic bronchitis).

nor the NHP sleep score was associated with CVD mortality risk in men (Table 4).

Men who reported lying awake most of the night (HR = 1.39, 95% CI: 1.00, 1.93) or sleeping badly at night (HR = 1.56, 95% CI: 0.96, 2.51) were at a higher risk of dying of cancer than were men with no such problems, but apart from this, there were no associations between sleep disturbances and cancer deaths in men. Conversely, both the individual sleep items and the NHP sleep score were associated with higher risks of deaths due to external causes. For example, men who reported sleeping badly at night had more than twice the risk of deaths due to external causes (HR = 2.54, 95% CI: 1.09, 5.96). Suicide accounted for 44 of these deaths in men, and having ≥3 sleep disturbances was associated with a 5 times' higher risk of death due to suicide (HR = 4.99, 95% CI: 1.59, 15.7), an association that was attenuated but remained noteworthy even after further adjustment for depressive symptoms (HR = 3.84, 95% CI: 1.07, 13.8).

Sleep disturbances and risk factors for death: BMI, hypertension, and diabetes

Overall, there were no associations between sleep disturbances and BMI trajectories (Table 5). The only exception

Table 5. Differences in Body Mass Index and Risks of Hypertension and Diabetes Associated With Sleep Disturbances Among the 4,465 Women and 12,524 Men Who Participated in the GAZEL Cohort Study, 1990–2009

	Body Mass Index				Hypertension				Diabetes			
	Multiply Adjusted[a] Difference in BMI (95 % CI)				Multiply Adjusted[b] HR (95 % CI)				Multiply Adjusted[b] HR (95 % CI)			
	Women		Men		Women		Men		Women		Men	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
I take tablets to help me sleep.												
No	0	Reference	0	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Yes	0.02	−0.23, 0.28	−0.21	−0.38, −0.04	1.24	1.07, 1.44	1.27	1.14, 1.42	1.53	1.14, 2.06	1.37	1.14, 1.65
I lie awake most of the night.												
No	0	Reference	0	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Yes	0.16	−0.13, 0.44	0.06	−0.14, 0.27	1.21	1.02, 1.43	1.02	0.89, 1.18	1.54	1.11, 2.13	1.16	0.91, 1.46
I sleep badly at night.												
No	0	Reference	0	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Yes	−0.03	−0.43, 0.36	0.01	−0.32, 0.33	1.32	1.06, 1.64	1.06	0.85, 1.33	1.86	1.25, 2.76	1.49	1.07, 2.07
It takes me a long time to fall asleep.												
No	0	Reference	0	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Yes	0.95	0.58, 1.33	0.28	0.06, 0.49	1.15	0.93, 1.43	1	0.87, 1.16	1.92	1.31, 2.83	1.04	0.81, 1.33
I am waking up in the early hours of the morning.												
No	0	Reference	0	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Yes	−0.02	−0.24, 0.20	0.07	−0.04, 0.18	1.12	0.99, 1.28	1.15	1.07, 1.23	1.28	0.97; 1.69	1.1	0.96; 1.25
Nottingham Health Profile sleep score (no. of items)												
0	0	Reference	0	Reference	1	Reference	1	Reference	1	Reference	1	Reference
1	−0.08	0.16, 0.32	0.05	−0.07, 0.16	1.11	0.96, 1.29	1.14	1.05, 1.23	1.53	1.08, 2.15	1.05	0.91; 1.21
2	−0.04	0.28, 0.35	0.05	−0.13, 0.23	1.19	0.99, 1.43	1.23	1.09, 1.38	2.10	1.44, 3.07	1.28	1.04; 1.58
≥3	0.48	0.06, 0.89	0.09	−0.23, 0.41	1.56	1.24, 1.96	1.15	0.92, 1.43	2.18	1.37, 3.45	1.59	1.15; 2.20
P for trend	0.08		0.34		<0.001		<0.001		0.001		<0.001	
Nottingham Health Profile sleep score (weighted sum score)												
10-point increase	0.04	−0.02, 0.09	0.01	−0.03, 0.04	1.06	1.03, 1.09	1.05	1.02, 1.07	1.13	1.07, 1.20	1.07	1.03; 1.11

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, night work, and baseline morbidity (angina pectoris, myocardial infarction, asthma, and chronic bronchitis) in a mixed model with a random slope age effect and intercept.

[b] Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, night work, and baseline morbidity (angina pectoris, myocardial infarction, asthma, and chronic bronchitis) in a Cox regression model.

was that men who took sleep medication weighed less than men who did not (mean BMI difference between groups = −0.21 units; 95% CI: −0.38, −0.04), and both men and women who reported problems falling asleep weighed slightly more during follow-up.

Twenty-three percent ($n = 1{,}047$) of the women and 27% ($n = 3{,}409$) of the men developed hypertension during follow-up. Compared with subjects who did not use sleep medication, both women (HR = 1.24, 95% CI: 1.07, 1.44) and men (HR = 1.27, 95% CI: 1.14, 1.42) who took sleep medication were at a higher risk of developing hypertension (Table 5). Apart from this, the associations between sleep disturbances and hypertension were most pronounced for women, and women with ≥3 sleep disturbances had a more than 50% higher risk of developing hypertension (HR = 1.56, 95% CI: 1.24, 1.96) than did women without sleep disturbances.

Five percent ($n = 224$) of the women and 8% ($n = 1{,}053$) of the men developed diabetes during follow-up. Taking sleep medication and sleeping badly at night were associated with a higher risk of diabetes in both men and women (Table 5). Women who reported lying awake most of the

night (HR = 1.54, 95% CI: 1.11, 2.13) or having a hard time falling asleep (HR = 1.92, 95% CI: 1.31, 2.83) also had a higher risk of diabetes. The NHP sleep score was associated with a higher risk of diabetes in a linear dose-response manner for both women ($P_{trend} < 0.001$) and men ($P_{trend} = 0.001$).

DISCUSSION

In this large prospective study with validated measures of sleep disturbances and register-based information on mortality rates, we found sleep disturbances to be associated with higher rates of all-cause mortality in men. This association was most pronounced for younger men and for deaths due to external causes. Men who reported a high degree of sleep disturbances were found to be at an almost 5 times' higher risk of committing suicide than men with no such problems. For women, we found no relation between sleep disturbances and all-cause mortality. We initially expected some of the effect of sleep disturbances on CVD mortality to be mediated by BMI, hypertension, and diabetes. However, as we were not able to establish a main effect of sleep disturbances on CVD mortality, formal mediation analyses were not conducted. Nonetheless, both men and women with sleep disturbances were at a higher risk of developing hypertension and diabetes, which is expected to eventually lead to a higher CVD mortality risk.

Our results on sleep disturbances and all-cause mortality are largely consistent with the results of previous studies. In a large study that included more than 1.1 million American men and women, Kripke et al. (6) found that intake of sleeping pills but not sleep disturbances as assessed by a single question on frequency of insomnia were associated with a higher risk of death. Obviously, sleep disturbances were not well-defined in that study, and in agreement with the present study, the authors found some (e.g., taking sleeping pills) but not all indicators of sleep disturbances to be associated with higher all-cause mortality rates. More recently, frequent insomnia was found to be associated with higher all-cause mortality rates in a large Chinese cohort, but in contrast to our findings, results of that study showed no sex differences in the association (14). The sex differences observed in the present study are puzzling and need further examination, especially because of the recently observed sex differences in the associations between sleep and vascular risk factors and inflammatory markers (27, 28).

The present study was differentiated from previous studies on sleep and mortality because it included a relatively young cohort of women and men (36–52 years of age at baseline). In a previous study based on data from the First National Health and Nutrition Examination study, age was found to modify the relation between sleep duration and mortality risk (29), and the authors concluded that the relation was highly influenced by deaths in elderly subjects and by the measurement of sleep durations closely before death. In the present study, we accommodated this concern by primarily addressing premature deaths (mean age at death of 56 years for women and 58 years for men). Even in this relatively young cohort, we found the higher incidences of mortality to be most pronounced among younger men who reported sleep disturbances. This indicated that sleep architecture may change over time, making sleep disturbances at younger ages more deleterious to health than those at older ages.

Few studies have addressed the associations between sleep and cause-specific mortality rates (12). The distribution of causes of deaths in the present cohort differed from those of older cohorts, especially with regard to the lower proportion of deaths due to CVD and the relatively high proportion of deaths due to external causes. We found strong associations between sleep disturbances and death due to external causes, especially suicide, in men. This could partly be explained by the high correlation between sleep disturbances, depression, and suicidal ideation observed in previous studies (30–32). Contrary to these results, the risk of death due to external causes (suicide and homicide) was not consistently higher among those with short or long sleep duration or insomnia in the study by Kripke et al. (6).

We initially hypothesized that some of the association between sleep disturbances and mortality would be mediated by obesity, hypertension, and diabetes. In accordance, we found that those who reported sleep disturbances were more likely to develop hypertension and diabetes during follow-up. This was in agreement with the results of a recent meta-analysis in which sleep quantity and quality were found to consistently predict the risk of diabetes (33). Also, a clear dose-response relation has previously been reported between sleep-disordered breathing, which is one of the main causes of reduced sleep quality, and blood pressure (34). However, contrary to our expectations, we found no effect of sleep disturbances on all-cause mortality in women and no robust effects on CVD mortality in men. This might be explained by the fact that the development of hypertension and diabetes could contribute to deaths later in life. In support of this argument, only very few cases of death in the present study were due to CVD. Therefore, even though mediation through hypertension and diabetes might not explain a relation to death at younger ages, the observed associations with these potent risk factors should be taken seriously to prevent later deaths.

Strengths and limitations

The large sample size and the prospective design combined with validated measures of sleep disturbances allowed us to comprehensively address the relation between sleep disturbances and mortality. In addition, the annual collection of information on weight, hypertension, and diabetes provided a unique opportunity to assess the effect of sleep disturbances on these potent risk factors for death in a prospective design. Furthermore, the study included information on a number of important socioeconomic, demographic, and lifestyle factors, as well as detailed information on baseline morbidity, which allowed for thorough adjustment for confounding. Linkage to a nationwide death registry enabled identification of virtually all deaths and allowed for nearly complete long-term follow-up.

One could be concerned that the observed associations were merely the result of sleep being a surrogate marker of other underlying conditions. Although we could not rule out this explanation, we tried to address such concerns by adjusting for baseline morbidity, as well as by excluding the

first 2 years of follow-up from the statistical analyses, neither of which had a major impact on the risk estimates. Furthermore, we found the most pronounced associations between sleep disturbances and death by external causes, which was probably not highly dependent on underlying clinical conditions apart from depression. Unfortunately, we were not able to adjust for the obstructive sleep apnea syndrome, which could be one of the main causes of reduced sleep quality and a risk factor for premature death and CVD (15, 35).

The NHP questionnaires were administered every 5 years starting in 1990, but unfortunately, insufficient statistical power prevented a distinction between transient and chronic sleep disturbances, even after 19 years of follow-up. However, the rate of sleep disturbances seemed to be relatively stable over time in the present study, with $>70\%$ of subjects reporting ≥ 1 sleep disturbances both at baseline and 5 years later. It should also be noted that although the 5 sleep questions overlapped with one another, they varied in their ability to predict early death, and thus the combined NHP sleep score is not necessarily as good an indicator of mortality risk as are 1 or 2 of the questions alone.

Sleep disturbances and depression are most likely highly intertwined, and the relation may even be bidirectional, making it hard to separate cause from effect. We chose not to adjust for depressive symptoms in our main models to prevent unjustified adjustment for a potentially important mediator on the pathway from sleep to premature death. However, adjustment for depressive symptoms in a sensitivity analysis resulted in an attenuation of several, although not all, of the risk estimates. There may be several explanations for this finding; depressive moods could cause both sleep disturbances and higher mortality rates; sleep disturbances could affect mortality risk partly through depression; or sleep disturbances and depression could be markers of other factors affecting the risk of death. We could not exclude any of these explanations, and even if sleep disturbances are merely an indicator of underlying depression, monitoring sleep disturbances might aid in identifying the early phases of depression.

In conclusion, we found sleep disturbances to be associated with higher all-cause mortality rates in men, most pronouncedly for younger men and those whose deaths were due to external causes, including suicide. Women who reported sleep disturbances were not at a higher risk of premature death, but they were at higher risk of developing hypertension and diabetes, which may eventually contribute to higher mortality risks. Poor sleep is an important public health issue, and future preventive strategies may benefit from assessment of sleep disturbances, especially in younger individuals, accompanied by treatment of the underlying problems or disorders, to prevent premature deaths.

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Author affiliations: Department of Public Health, University of Copenhagen, Copenhagen, Denmark (Naja Hulvej Rod, Theis Lange); Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland (Jussi Vahtera); Stress Research Institute, University of Stockholm, Stockholm, Sweden (Hugo Westerlund); Department of Epidemiology and Public Health, University College London, London, United Kingdom (Hugo Westerlund, Mika Kivimaki); INSERM U1018, Epidemiology of occupational and social determinants of health—Centre for Research in Epidemiology and Population Health, Villejuif, France (Marie Zins, Marcel Goldberg); and Versailles-Saint Quentin University, Versailles, France (Marie Zins, Marcel Goldberg).

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