Sleep disturbances and cause-specific mortality: Results from the GAZEL Cohort Study

Naja Hulvej Rod[1], Jussi Vahtera[2], Hugo Westerlund[3], Mika Kivimaki[4], Marie Zins[5,6], Marcel Goldberg[5,6], Theis Lange[1]

[1] Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[2] Department of Public Health, University of Turku, Turku, Finland

[3] Stress Research Institute, University of Stockholm, Stockholm, Sweden

[4] Department of Epidemiology and Public Health, University College London, London, UK

[5] Inserm U1018, Epidemiology of occupational and social determinants of health - Centre for Research in Epidemiology and Population Health, Villejuif, France

[6] Versailles-Saint Quentin University, France

Correspondence to:

Naja Hulvej Rod (nahuro@sund.ku.dk)

Department of Public Health, University of Copenhagen

Øster Farimagsgade 5, Postbox 2099

1014 Copenhagen K, Denmark

Tel: (+45) 3532 6735, Fax: (+45) 3535 1181

Abstract

Poor sleep is an increasing problem in modern society, but most previous studies on sleep and mortality have addressed only duration, and not quality, of sleep. We prospectively examined the association of sleep disturbances with mortality as well as with important risk factors for mortality, i.e. body mass index, hypertension, and diabetes. In 1990, the 16,989 participants of the GAZEL cohort study, France, were asked validated questions on sleep disturbances and were followed-up until 2009; with <1 % loss to follow-up. Annually updated information allowed for prospective assessments of body mass index, hypertension and diabetes. During follow-up, 1,045 men and women died. Sleep disturbances were associated with higher mortality risk in men (*P*=0.005), but not in women (*P*=0.33). This was most pronounced for men <45 years (3+ symptoms vs. none: HR=2.03; 95 % CI: 1.24-3.33). There were no clear associations with cardiovascular mortality, although men and women with sleep disturbances were more likely to develop hypertension and diabetes (P<0.001). Compared to no sleep disturbances, men who reported 3+ sleep disturbances had almost five times higher risk of committing suicide (HR=4.99; 95 % CI: 1.59-15.7). Future strategies to prevent premature deaths may benefit from assessment of sleep disturbances, especially in younger individuals.

Key words: Body mass index; Cause of death; Diabetes Mellitus; Hypertension; Longitudinal studies; Mortality; Sleep disorders

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 physiological restitution and recovery, and lack of sleep may have far-reaching effects on endocrinology, immunology, metabolism and eventually disease risk.(3) While most previous studies have focused on sleep duration, (4-11) sleep quality may also play a role in disease etiology. Human sleep is composed of rapid eye movement (REM) sleep and stages 1 to 4 of non-REM sleep. The deeper stages of non-REM sleep, i.e. stages 3 and 4, are collectively called slow wave sleep and these sleep stages are particularly important to glucose homeostasis and general biological restoration.(12) Impaired sleep quality is likely to suppress slow wave sleep, and a recent experimental study found that reduced sleep quality without changes in sleep duration was associated with decreased insulin sensitivity and glucose tolerance.(12) Only few population studies have addressed the association between sleep disturbances and mortality, with inconsistent results.(6, 13, 14)

Evidence of mechanisms linking sleep disturbances to disease risk is important in making causal inferences, but these mechanisms are far from elucidated. Experimental studies have found relatively brief periods of severe sleep deprivation to increase low-level systemic inflammation and insulin resistance,(3, 12, 15) and sleep disturbances is becoming an established risk factor for diabetes,(16, 17) obesity,(18, 19) and hypertension(20) in population samples. These potent risk factors for CVD may partly explain a relation between sleep and mortality. We hypothesized that sleep disturbances would be associated with higher all-cause and cause-specific mortality (especially deaths due to CVD and external causes) as well as with important risk factors for mortality, i.e. body mass index (BMI), hypertension, and diabetes. We tested this hypothesis in

almost 17,000 men and women from the French GAZEL Cohort Study followed for 19 years with validated measures of sleep disturbances.

Material and methods

The GAZEL Cohort Study

The GAZEL cohort was initiated in 1989 and was at baseline composed of a sample of 20,625 employees, aged 35 to 50 years, of the French national gas and electricity company: Electricité de France - Gaz de France (EDF-GDF).(21) A questionnaire is sent to the participants every year in order to obtain data on health status, lifestyle, social, and occupational factors. EDF-GDF 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 retirement. 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 are white Europeans and all gave informed consent. The 1990 wave of the study included information on sleep disturbances and this wave is used as the baseline for the present study. The 17,970 participants in 1990 constituted a response proportion of 87 percent. 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 the 5-item sleep dimension in the Nottingham Health Profile (NHP). The NHP is a widely used and well validated method of assessing quality of life.(22) The NHP have been translated into French and item weights have been derived for a French population.(23) The five sleep items of the NHP include (French weights, w): I take tablets to help me sleep (w=26.33); I lie awake most of the night (w=22.86); I sleep badly at night (w=20.36); It

takes me a long time to fall asleep (w=16.50); I am waking up in the early hours of the morning (w=13.94). The respondents were asked if they were currently experiences each of the abovementioned problems. We will address the effect of each sleep item separately as well as based on the weighted NHP sleep score ranging from 0 to 100 points according to the French weights. However, as there have been discussions on the validity of the weighted score,(23) we will also model sleep disturbances simply as the number of affirmative responses to the five sleep items.

Covariates

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

Follow-up

The participants were followed from the date of the 1990 examination until date of death (n=1045) or end of follow-up on September 25, 2009. Information on total mortality and causes of

death was obtained from the French National Death Index (Inserm CépiDC). Cause-specific mortality was coded using the International Classification of Diseases, 9th version up to 1998 and 10th version onwards. We distinguished deaths due to: cancers (ICD9 codes: 140-208; ICD10 codes: C00-C97), cardiovascular disease (ICD9 codes: 390-459; ICD10 codes: I00-I99), external causes (ICD9 codes E800-E999; ICD10 codes: V01-X84), and suicide (a sub-category of external causes with ICD9 codes: E950-E959; ICD10 codes: X60-X84). BMI trajectories as well as incidence of diabetes and hypertension were based on 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 by means of 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 (CI) of 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(24) and included age, socioeconomic status, marital status, smoking status, alcohol consumption, BMI, night work, and baseline morbidity. Since 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 two years of follow-up in order to prevent reversed causation. Second, we assessed the relation between sleep disturbances and cause-specific mortality. Due to very few cases in each cause-specific mortality category for women, the cause-specific analysis was only performed for men. Finally, we assessed the effect of sleep quality on BMI, hypertension, and diabetes in order to address potential mediation by these factors. As 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 effect for each person in a linear model. Thus the effects reported for sleep disturbances are average up-and-down movements of the whole BMI trajectory controlled for potential confounders and random individual effects. The associations between sleep disturbances and incidence of hypertension and diabetes were modelled by a Cox model. Individuals were excluded if they had reported hypertension or diabetes, respectively, in 1990. All analyses were conducted separately for men and women.

Results

Baseline characteristics

The mean age a baseline was 45 years, ranging from 36 to 52 years. Fourteen percent of the population reported two or more sleep disturbances, and only 58 percent 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 were associated with all-cause mortality in women (Table 2). In contrast, men who reported taking sleeping pills (HR=1.30; 95 % CI: 1.07-1.57), to lie awake most of the night (1.36; 1.09-1.70) or to sleep badly at night (1.69; 1.25-2.31) were at higher risk of premature death compared to 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_{trend}=0.005) and a 10-

point increase on the weighted NHP sleep score (max 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, while the remaining 525 occurred in men who were >45 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 from sleep medication, were associated with higher mortality risk in men ≤45 years, but not in those >45 years. As an exception, those who reported sleeping badly at night were at higher risk of premature death regardless of age. Also, number of affirmative answers to the NHP sleep score was only associated with mortality risk in younger men (P_{trend}<0.001). Younger men who reported 3+ sleep disturbances experienced about twice the risk of all-cause mortality (HR=2.03; 95 % CI: 1.24-3.33). Excluding the first two years of follow-up in order to prevent reversed causation had only 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 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 due to cancer, and 81 due to external causes. Apart from sleep medication (HR=1.56; 95 % CI: 1.03-2.36) and sleeping badly at night (1.91; 0.99; 3.66), neither the individual sleep items nor the NHP sleep score were associated with CVD mortality 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 (1.56; 0.96-2.51) were at higher risk of cancer mortality compared to men with no such problems, but apart from this there were no associations between sleep disturbances and cancer mortality 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, despite of the low numbers, 3+ sleep disturbances were associated with a five times higher risk of death due to suicide (4.99; 1.59-15.7), an association which attenuated but remained noteworthy even after adjustment of depressive symptoms (3.84; 1.07-13.8).

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

Overall, there were no associations between sleep disturbances and BMI trajectories (Table 5). The only exception being that men who took sleep medication weighed less (-0.21 kg/m^2; 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 percent (n=3,409) of the men developed hypertension during follow-up. Compared to no sleep medication, both women (HR=1.24; 95 % CI: 1.07-1.44) and men (1.27; 1.14-1.42) who took sleep medication were at 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 percent higher risk of developing hypertension (HR=1.56; 95 % CI: 1.24-1.96) compared to women without sleep disturbances.

Five percent (n=224) of the women and 8 percent (n=1,053) of the men developed diabetes during follow-up. Sleep medication and sleeping badly at night were associated with higher risks 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 (1.92; 1.31-2.83) also had a higher risk of diabetes. The NHP sleep score was associated with 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, we found sleep disturbances to be associated with higher 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 almost five time 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 through BMI, hypertension and diabetes. But, as we were not able to establish a main effect of sleep disturbances on CVD mortality, formal mediation analyses were not conducted. However, both men and women with sleep disturbances were at 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 including more than 1.1 million American men and women, Kripke and colleagues found intake of sleeping pills, but not sleep disturbances as assessed by a single question on frequency of insomnia, to be associated with higher mortality risk.(6) Obviously, sleep disturbances were not well defined in this study and in agreement with the present study, they found some (e.g. sleeping pills) but not all indicators of sleep disturbances to be associated with higher all-cause mortality. More recently, frequent insomnia was found to be associated with higher all-cause mortality in a Chinese cohort study, but opposite to the present study they found no sex differences in the results. (13) The sex differences observed in the present study are puzzling, but may be a result of low statistical power to address the association in women.

The present study differentiates itself from previous studies on sleep and mortality by including a relatively young cohort of women and men (36 to 52 years at baseline). In a previous study based on data from the NHANES 1 study, age was found to modify the relation between sleep duration and mortality,(25) and the authors concluded that the relationship was highly influenced by deaths in elderly subjects and by the measurement of sleep durations closely before death. In the present study we accommodate this concern by primarily addressing quite premature deaths (mean age at deaths being 56 years for women and 58 years for men). Even in this relative young cohort we found the excess mortality to be most pronounced among younger men who reported sleep disturbances. This indicates that sleep architecture may change over time making sleep disturbances at younger ages more deleterious to health than at older ages.

Fewer studies have addressed the associations between sleep and cause-specific mortality. The distribution of causes of deaths in the present cohort is unlike that of older cohorts, especially

with a low proportion of deaths due to CVD and a relatively high proportion of deaths due to external causes. We found relatively strong associations between sleep disturbances and death due to external causes, especially suicide. This may partly be explained by the high correlation between sleep disturbances, depression and suicidal ideation observed in previous studies. (26-28) 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 previously mentioned study by Kripke and colleagues.(6)

We initially hypothesised that some of the association between sleep disturbances and mortality would be mediated through obesity, hypertension and diabetes. In accordance, we found those who reported sleep disturbances, to be more likely to develop hypertension and diabetes during follow-up. This is in agreement with the results a recent meta-analysis where sleep quantity and quality were found to consistently predict the risk of diabetes.(29) 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.(30) But contrary to expectation, we found no total effect of sleep disturbances on all-cause mortality in women and no clear effects on CVD mortality in men. This may be explained by the fact that the development of hypertension and diabetes may first 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. So, even though mediation through hypertension and diabetes may not explain a relation to death at younger ages, the observed associations with these potent risk factors should be taken seriously in order 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, annual 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. Further, the study included information on a number of important socioeconomic, demographic, and lifestyle factors as well as detailed information on baseline morbidity, allowing 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 may be concerned that the observed associations are merely the result of sleep being a surrogate marker of other underlying conditions. Although we cannot fully dismiss this explanation, we tried to address such concerns by adjusting for baseline morbidity as well as exclude the first two years of follow-up from the statistical analyses; neither of which had a major impact on the risk estimates. Also, we found the most pronounced associations between sleep disturbances and death by external causes, which is probably not highly dependent on underlying clinical conditions. Unfortunately, we were not able to adjust for the obstructive sleep apnea syndrome , which may be one of the main causes of reduced sleep quality as well as risk factor for premature death and CVD.(14, 31)

The NHP were administered every five year, 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, sleep disturbances seem to be relative stable over time in

the present study, with more than 70 percent reporting one or more sleep disturbances both at baseline and five years later. It should also be noted that the five sleep questions varied in their ability to predict mortality and the combined NHP sleep score may therefore not be as good an indicator of sleep quality as one or two of the questions alone.

Sleep disturbances and depression are most likely highly intertwined, and the relation may even be bidirectional, making it hard to tell 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 to 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 may be markers of other factors affecting the risk of death. We cannot exclude any of these explanations, and even if sleep disturbances are merely an indicator of underlying depression, monitoring sleep disturbances may aid in identifying the early phases of depression.

In conclusion, we find sleep disturbances to be associated with higher all-cause mortality in men, most pronouncedly for younger men and deaths due to external causes, including suicide. Women who reported sleep disturbances were not at 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, in order to prevent premature deaths.

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Conflicts of interests

None declared

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Table 1. Baseline characteristics of 16,989 participants in the 1990 wave of the GAZEL cohort study

	Total population	**NHP sleep score (number of affirmative responses)**			
	(n=16,989)	0 (n=9,316)	1 (n=4,633)	2 (n=1,642)	3+ (n=612)
Deaths*; n (%)	1,045 (6)	516 (6)	293 (6)	116 (7)	52 (8)
Baseline age; mean	45	45	45	45	45
Women; %	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, myocardial infarction); %	10	9	12	13	14
Respiratory morbidity (asthma, chronic bronchitis); %	5	4	5	7	9
Take sleeping tablets; %	12	0	12	57	78
Lie awake most of the night; %	9	0	11	29	72
Sleep badly at night; %	4	0	2	10	52
Long time to fall asleep; %	6	0	9	22	39
Wake up in the early hours of the morning; %	31	0	67	81	86

* The total number of deaths was 1,045, but because of missing values on some of the items in the NHP sleep score, the number of deaths according to the NHP sleep score does not add up to 1,045.

Table 2. All-cause mortality risk associated with impaired sleep quality among 4,465 women and 12,524 men who participated in the GAZEL cohort study in 1990

	Women			Men		
	No. of deaths*	Age-adjusted HR (95 % CI)	Multiple adjusted† HR (95 % CI)	No. of deaths*	Age-adjusted HR (95 % CI)	Multiple adjusted† 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)
NHP sleep score (number 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-value for trend		0.85	0.33		<0.001	0.005
NHP sleep score (weighted sum score)						
10 points 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)

* 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 these numbers.
† Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, baseline BMI, night work, and baseline morbidity (hypertension, diabetes, angina pectoris, myocardial infarction, asthma, chronic bronchitis)

Table 3. All-cause mortality risk associated with impaired sleep quality among 12,524 men who participated in the GAZEL cohort study in 1990 stratified by age at baseline

	Baseline age ≤ 45 years		**Baseline age > 45 years**	
	No. of deaths*	Multiple adjusted† HR (95 % CI)	No. of deaths*	Multiple adjusted† 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)
NHP sleep score (number 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-value for trend		<0.001		0.59
NHP sleep score (weighted sum score)				
10 points increase	344	1.12 (1.06; 1.19)	487	1.03 (0.98; 1.09)

* The total number of deaths was 360 in men ≤ 45 years and 525 in men >45 years, but because of missing values, the numbers for some of the variables do not add up.
† Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, baseline BMI, night work, and baseline morbidity (hypertension, diabetes, angina pectoris, myocardial infarction, asthma, chronic bronchitis)

Table 4. Cause-specific disease mortality risk associated with impaired sleep quality among 12,524 men who participated in the GAZEL cohort study in 1990

	Cardiovascular disease mortality		Cancer mortality		Death due to external causes	
	No. of CVD deaths*	Multiple adjusted† HR (95 % CI)	No. of cancer deaths*	Multiple adjusted† HR (95 % CI)	No. of deaths*	Multiple adjusted† 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)
NHP sleep score (number 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-value for trend		0.30		0.22		0.002
NHP sleep score (weighted sum score)						
10 points increase	153	1.06 (0.97; 1.16)	396	1.05 (0.99; 1.11)	79	1.19 (1.06; 1.33)

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

† Adjusted for age, socioeconomic status, marital status, current smoking, alcohol consumption, baseline BMI, night work, and baseline morbidity (hypertension, diabetes, angina pectoris, myocardial infarction, asthma, chronic bronchitis)

Table 5. Differences in BMI and risk of hypertension and diabetes associated with impaired sleep quality among 4,465 women and 12,524 men who participated in the GAZEL cohort study in 1990

	Body mass index		**Hypertension**		**Diabetes**	
	Multiple adjusted† difference in BMI (95 % CI)		Multiple adjusted†† HR (95 % CI)		Multiple adjusted†† HR (95 % CI)	
	Women	Men	Women	Men	Women	Men
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)
NHP sleep score (number 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)	2.1 (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; 2.2)
P-value for trend	0.08	0.34	<0.001	<0.001	0.001	<0.001
NHP sleep score (weighted sum score)						
10 points 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; 1.2)	1.07 (1.03; 1.11)

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

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