

Sleep and Mortality: A Population-Based 22-Year Follow-Up Study

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Study Objectives: Long and short sleep have been associated with increased mortality. We assessed mortality and 3 aspects of sleep behavior in a large cohort with 22-year follow-up.

Design/Setting: Prospective, population-based cohort study.

Participants: 21,268 twins aged ≥ 18 years responding to questionnaires administered to the Finnish Twin Cohort in 1975 (response rate 89%), and 1981 (84%).

Interventions: N/A

Measurements: Subjects were categorized as short (< 7 h), average, or long (> 8 h) sleepers; sleeping well, fairly well, or fairly poorly/poorly; no, infrequent, or frequent users of hypnotics and/or tranquilizers. Cox proportional hazard models were used to obtain hazard ratios (HR) for mortality during 1982–2003 by sleep variable categories and their combinations. Adjustments were done for 10 sociodemographic and lifestyle covariates known to affect risk of death.

Results: Significantly increased risk of mortality was observed both for

short sleep in men (+26%) and in women (+21%), and for long sleep (+24% and +17%), respectively, and also frequent use of hypnotics/tranquilizers (+31% in men and +39% in women). Snoring as a covariate did not change the results. The effect of sleep on mortality varied between age groups, with strongest effects in young men. Between 1975 and 1981, sleep length and sleep quality changed in one-third of subjects. In men there was a significant increase for stable short (1.34) and stable long (1.29) sleep for natural deaths, and for external causes in stable short sleepers (1.62).

Conclusions: Our results show complicated associations between sleep and mortality, with increased risk in short and long sleep.

Keywords: Follow-up study, mortality, population, sleep, hypnotics

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INTRODUCTION

ABOUT 40 YEARS AGO, THE FIRST REPORT ON THE ASSOCIATION BETWEEN SLEEP LENGTH AND SUBSEQUENT MORTALITY INDICATED A U-SHAPED CURVE, showing that those sleeping 7 hours had the lowest mortality.¹ The U-shaped association between sleep length and mortality has been found in most of the nearly 20 published epidemiologic studies.² The significance of short sleep has generally decreased or disappeared after adjustment for factors known to be associated with mortality, such as smoking, alcohol use, and physical inactivity. As for long sleep, Youngstedt and Kripke concluded that “studies with a relative large number of subjects ($> 10,000$) have without exception shown that sleep of 8 hours or longer is associated with a significant mortality risk.”² While this excess risk has been rather robust to adjustment for lifestyle and other factors, its precise nature and extent still remain obscure. Earlier studies have not investigated the effect of stability in sleep length on subsequent mortality.

Other aspects of sleep behavior (such as sleep quality) and the association to mortality have been little investigated. Increased risk of mortality associated with the use of medication for sleep

has been reported.^{3,4} However, it is not clear which medications (prescribed hypnotics or nonprescribed sleep promoting agents) might account for this.⁵ The only study with verification of the drugs being taken indicated that sedative-hypnotics are not associated with increased mortality risk.⁶

Our objective was to continue to probe the relationship between these 3 aspects of sleep behavior (self-report of sleep length, sleep quality, and use of sleep promoting medication), changes in behavior, and mortality in a large, prospective, population-based cohort of Finnish adults with 22-year mortality follow-up data and detailed information on potential confounding or effect-modifying factors.

METHODS

The Finnish Twin Cohort

The Older Finnish Twin Cohort consists of all Finnish twin pairs of the same sex born before 1958 with both co-twins alive in 1975. These twin pairs were selected from the Central Population Registry of Finland in 1974.⁷ The Cohort includes adult twins and individuals who were not twins, because twin candidates were selected by identifying pairs of persons with the same surname at birth, the same birth date, and the same community at birth. Biological twinship was confirmed from a questionnaire and local parish birth records.

The first questionnaire was mailed in autumn 1975, and the response rate was 89%. The 97-item questionnaire included questions on sociodemographics, health status, lifestyle and psychosocial factors, and sleep patterns. In autumn 1981, a second questionnaire including 100 similar items (response rate 84%) was mailed to the twins that had responded to the first questionnaire;

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non-twins were not contacted. The present analyses include those twin individuals responding to both questionnaires with information on sleep length and sleep quality, and resident in Finland in 1981 (N = 21,268; 52.3% women; mean age in 1981, 40.7 years, SD 13.5 years, range 24-101 years).

The study was approved by the ethical committee of the Department of Public Health, University of Helsinki. Informed consent was obtained from all respondents.

Questionnaire Data

Information on sleep length was obtained by asking "How many hours do you usually sleep per 24 hours?" In 1975 seven response alternatives were used (<4 hours, 5, 6, 7, 8, 9, and ≥ 10 hours), and in 1981 nine alternatives (≤ 6 hours, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, and ≥ 10 hours). Information on quality of sleep was obtained both in 1975 and 1981 by asking: "Do you usually sleep well?" The 5 response alternatives were: "well," "fairly well," "fairly poorly," "poorly," and "cannot say." Use of hypnotics and use of tranquilizers were included in both questionnaires in the question "On how many days in total during the last year have you used the following types of medications?" with alternatives "no use," "on less than 10 days," "on 10-59 days," "on 60-180 days," and "on more than 180 days." We included tranquilizers in our analyses because they are widely used interchangeably with hypnotics in clinical practice, and the majority of the compounds in both groups have similar pharmacological profile (they are benzodiazepines or benzodiazepine-like agents acting on the GABA system in the brain).

We assessed the following sociodemographic and lifestyle covariates (asked both in 1975 and 1981; selected characteristics given in Table 1): married (yes/no), social class (6 categories: upper or lower white collar, skilled or unskilled workers, farmers, others), education (9 categories by years of school, high school equals to 12 years), working status (employed yes/no), BMI

[body mass index (kg/m^2) computed from self-reported weight and height], smoking status (4 categories: never, occasional, ex-, or current cigarette smoker), binge drinking,⁸ grams of alcohol consumed daily (based on self-reported average quantities of use of beer, wine, and spirits consumed⁹), conditioning physical activity (3 categories: sedentary, intermediate, vigorous physical activity¹⁰), and life satisfaction.¹¹ Life satisfaction correlates highly ($r = -0.63$) with depression as assessed concurrently by the Beck Depression Inventory.¹² Snoring was asked in 1981 only with response alternatives "never," "occasionally," "often," "almost always," and "do not know."

Follow-up Data

Vital status (alive in Finland on December 31, 2003, date of death, or date of migration from Finland) was obtained from the Population Register Centre of Finland. The follow-up for mortality was from the exact date of response (date questionnaire returned) to December 31, 2003. The follow-up time is denoted in Tables as 1982-2003. Our analyses are based on 431,782 person-years and 3700 deaths during follow-up. Cause-of-death statistics up to the end of 2003 were obtained from Statistics Finland. Both registers cover all Finnish citizens and permanent residents. These data were linked to the Finnish Twin Cohort data using the unique personal identification numbers assigned to every permanent resident of Finland. Deaths were categorized as natural (ICD-8 and ICD-9 codes 1-799, or ICD-10 codes A-R) or due to external causes (violent deaths; ICD-8 and ICD-9 codes 800-999, or ICD-10 codes S-Y.)

Data Analysis and Statistical Methods

Cox proportional hazard models were used to obtain hazard ratios (HR) and their 95% confidence intervals (CI) for mortality by

Table 1—Selected Demographic Characteristics in 1981 of the Entire Cohort with Complete Sleep Behavior Data. Percentage of Those in the Specified Category of Potential Confounder; Number of Men/Women Given in Column Header

	Sleep Length*			Sleep Quality			Use Of Hypnotics And/or Tranquilizers**		
	Short N (m/f) = 1539 / 1500	Average N (m/f) = 7113 / 7247	Long N (m/f) = 1488 / 2381	Sleeping well N(m/f) = 4388 / 4586	Sleeping fairly well N (m/f) = 4804 / 5486	Sleeping fairly poorly/poorly N (m/f) = 948 / 1056	No N (m/f) = 8209 / 8329	Infrequent N (m/f) = 454 / 776	Frequent N (m/f) = 261 / 347
Age									
24-39 years	52.1 / 44.7	56.8 / 56.4	52.8 / 57.3	62.7 / 64.5	52.3 / 51.4	38.3 / 32.0	60.9 / 62.3	40.8 / 46.4	35.3 / 34.3
40-54 years	30.2 / 25.3	29.5 / 26.3	25.6 / 22.3	26.0 / 23.2	30.7 / 27.0	34.4 / 25.9	27.7 / 23.7	37.9 / 29.1	36.8 / 29.1
55 years or more	17.7 / 30.1	13.7 / 17.3	21.6 / 20.5	11.3 / 12.3	17.0 / 21.6	27.3 / 42.1	11.4 / 14.0	21.4 / 24.5	28.0 / 36.6
Married	70.1 / 58.4	74.7 / 68.5	68.4 / 66.8	74.4 / 66.6	72.7 / 67.7	69.0 / 62.5	73.7 / 69.1	73.6 / 63.7	58.2 / 47.0
Employed	82.5 / 76.6	87.8 / 85.1	75.0 / 76.1	89.9 / 87.0	84.5 / 81.4	65.9 / 63.7	90.0 / 86.7	76.2 / 79.6	41.0 / 51.6
Social class: skilled and unskilled workers	63.3 / 48.9	55.7 / 42.2	51.1 / 42.6	54.1 / 39.6	57.3 / 45.0	60.0 / 49.3	56.0 / 42.3	54.2 / 37.3	45.6 / 43.2
Education: high school or more	8.2 / 10.8	12.8 / 16.4	11.8 / 13.0	13.8 / 18.9	11.1 / 13.1	7.9 / 7.4	12.9 / 16.7	15.2 / 20.5	10.3 / 12.2
Current smoker	47.6 / 24.5	35.5 / 19.9	30.3 / 16.3	35.9 / 21.7	35.2 / 18.3	43.2 / 18.5	36.7 / 20.8	42.8 / 21.5	40.1 / 26.5
Binge drinker	47.0 / 10.8	41.3 / 8.8	37.1 / 8.6	37.2 / 8.4	43.8 / 9.3	50.2 / 10.6	42.1 / 9.2	48.9 / 13.1	38.1 / 12.0
BMI*** ≥ 25	42.0 / 30.9	38.1 / 24.5	41.7 / 26.5	37.5 / 21.1	40.1 / 27.4	42.8 / 37.8	37.3 / 22.3	40.7 / 26.1	52.5 / 37.9
Sedentary	15.4 / 15.8	11.8 / 11.3	14.5 / 13.2	13.3 / 11.9	11.3 / 11.7	17.6 / 16.8	12.5 / 11.8	11.7 / 13.0	15.3 / 17.6
Low life satisfaction	23.3 / 23.9	14.1 / 14.5	18.2 / 16.0	9.8 / 10.3	17.4 / 17.1	39.0 / 36.4	13.6 / 13.0	30.0 / 28.7	46.4 / 43.6
Deceased 1982-2003	27.1 / 24.7	17.2 / 12.4	25.7 / 16.9	15.0 / 10.9	21.2 / 15.5	36.8 / 30.9	15.5 / 10.8	29.3 / 16.4	42.9 / 35.2

* short = <7 hours, average = 7-8 hours, and long = >8 hours; ** infrequent use = 1-59 days/year; frequent use = 60 or more days/year; *** body mass index

sleep length, sleep quality, and the use of hypnotics and/or tranquilizers. We ascertained that the proportional-hazards assumption was not violated by using log-log plots, (i.e. $-\ln\{-\ln(\text{survival})\}$ curves versus $\ln(\text{analysis time})$) of survival curves of the 3 categories of sleep length, sleep quality, and use of hypnotics and/or tranquilizers, to check that the curves were parallel. Because the study sample included twin pairs, standard errors and CIs were adjusted for possible within-pair correlations using robust estimators of variance.¹³ All statistical analyses were performed with Stata version 9.2 (Stata Corporation, College Station, TX, USA).

Sleep length was categorized in 3 classes: short (< 7 hours), average (7-8 hours), and long (> 8 hours). Sleep quality was also dealt with in 3 categories (well, fairly well, and fairly poorly/poorly). Use of hypnotics and/or tranquilizers was similarly assessed in 3 categories (no use of either hypnotics or tranquilizers, infrequent use = 1-59 days per year of either medication, frequent use = 60 or more days per year of either medication). Because some subjects had missing data on use of both hypnotics and tranquilizers, we created a fourth category for those with missing data. This was included in the modelling in order not to lose subjects, but results for this class are not shown. Subjects in the reference group had average sleep length, slept well, and used no hypnotics and/or tranquilizers.

The association between mortality and the stability of the 3 sleep-related variables (sleep length, sleep quality, and use of hypnotics and/or tranquilizers) was assessed using combinations of categories (3 alternatives both in 1975 and 1981 giving 9 subgroups in each sleep related variable) in modeling. Age-adjusted HRs for total mortality are given, and results for men and women are presented separately because of significant gender differences.

Gender by sleep behavior interactions were tested by assessing the difference in model fit between a model with gender by sleep variable interactions (all 3 variables) compared with a model with main effects of the sleep variables and sex alone. The difference in model fit is chi-square distributed. This likelihood ratio test chi-square probability for overall presence of any sex-interactions was 0.07 in the youngest age-group; correspondingly for the age group 40-54 years 0.34 and for 55+ years 0.59, and for the total population 0.03 (Table 10).

In fully-adjusted models, adjustments were made for the sociodemographic and lifestyle covariates (measured in 1981) known to affect risk of death (see "Questionnaire data" above). Subjects with missing data on any of the covariates (N given in each Table) were excluded from the fully-adjusted models. When a sleep-related variable was not dependent, it was included as a covariate in the model. The effect of snoring (3 categories: never, occasionally, and often/almost always) was also assessed by separate models. The joint effects of sleep related variables measured in 1981 were also assessed.

RESULTS

Descriptive data of the study population is given in Table 1 by categories of the self-reported sleep length, sleep quality, and use of hypnotics and/or tranquilizers. In the last row, the percentage of deaths in each category is given; it is lowest in those with average sleep length, sleeping well, and no use of hypnotics and/or tranquilizers. Covariates have been surveyed both in 1975 and 1981 and their stability was variable: the kappa-value of, e.g., for being married was 0.56, level of education 0.89, binge drinking 0.57, ciga-

rette smoking 0.70, overweight (BMI ≥ 25) 0.67, sedentary physical activity 0.30, low life satisfaction 0.26, and being employed 0.45.

There was information on the frequency of use of hypnotics and/or tranquilizers in 1975 and 1981 in 86.4% of the study population. Of all users (N = 1881) 22.9% used only hypnotics, 48.3% only tranquilizers, and 28.8 % used both types of medication.

To assess the interrelationships between sleep length, sleep quality, and use of hypnotics and/or tranquilizers (medication) poly-choric correlation matrices of the 3-class variables measured in 1975 and 1981 were computed, and all correlations in both genders were statistically significant ($P \leq 0.02$). In men the correlation between 1975 and 1981 in sleep length was 0.49 (kappa-value 0.25), in sleep quality 0.64 (0.40), and in use of medication 0.43 (0.21); in women 0.50 (0.27), 0.63 (0.38), and 0.44 (0.22), correspondingly.

Risk of mortality by each sleep variable category is given in Table 2. In the fully-adjusted model, there was a significant increase in mortality in the 2 genders in both short and in long sleepers: 26% in men and 21% in women for short sleep, and for long sleep 24% and 17%, respectively. Sleep quality (sleeping worse than well) was significant only in men in the age-adjusted model, indicating no independent association between sleep quality and mortality. Frequent use of hypnotics and/or tranquilizers significantly increased risk of mortality by 31% in men and by 39% in women. Including snoring as a covariate or exclusion of deaths during the first 3 years of follow-up (up to the end of 1985) did not essentially change the HRs or the statistical significance.

Table 3 shows age-adjusted risk of total mortality by age groups separately for men and women in different sleep variable categories. In men, short sleep was significantly associated with increased risk in all ages, most clearly in the youngest group (+ 96%). In women there was a similar but nonsignificant trend. Sleep quality significantly affected the risk only in young men with an increase of 129% in those sleeping fairly poorly/poorly. Frequent use of hypnotics and/or tranquilizers was associated with increased risk of mortality in all age groups in both genders (even more clearly in men), but the effect attenuated with age (HRs in the youngest group in men 2.90 and in women 2.57, in the oldest group 1.38 and 1.50, respectively). In the fully-adjusted model the HRs were clearly attenuated and half of the significant hazard ratios became nonsignificant, and the pattern of decreasing HRs related to sleep abnormalities with increasing age was mainly lost. Due to smaller numbers of subjects in the age-group specific analyses, the power to detect differences was less than in the overall sample.

Table 4 shows the association between stability of sleep length and total mortality. Length category remained unchanged in 68.8% of men and in 66.2% of women from 1975 to 1981, and respectively, sleep shortened in 16.6% and 16.7% and lengthened in 14.6% and 17.1%. In both age-adjusted and fully-adjusted models in men, but not in women, stable short (HR 1.36) and stable long (1.32) sleep was associated with a significantly increased risk of mortality. A decrease of sleep length to short resulted in significantly increased mortality in women (1.24-2.17), and there was a similar trend in men. Lengthening of sleep from average to long significantly increased risk of mortality in both genders (about 1.20). Thus, in men there was a U-shaped association with significantly increased risk of mortality in short and long sleepers at the beginning of the follow-up, but in women the pattern was less clear, but with some significant associations. Including snoring as a covariate in the fully-adjusted model did not significantly change the HRs otherwise, but in men the category average to

Table 2—Sleep Length, Sleep Quality, Use of Hypnotics and/or Tranquilizers, and Risk of Total Mortality (Hazard Ratio and 95% Confidence Interval) in 1982-2003. All Three Sleep Variables Mutually Adjusted in the Same Model and Measured in 1981

	All-Cause Mortality In 1982-2003			
	Age-adjusted (men) N = 10140	Age-adjusted (women) N = 11128	Fully-adjusted model (men) N = 9529	Fully-adjusted model (women) N = 10265
Sleep Length*				
short	1.34 (1.19, 1.51)	1.12 (0.98, 1.28)	1.26 (1.11, 1.43)	1.21 (1.05, 1.40)
average	1.00	1.00	1.00	1.00
long	1.32 (1.17, 1.48)	1.20 (1.06, 1.35)	1.24 (1.09, 1.41)	1.17 (1.03, 1.34)
Sleep Quality				
sleeping well	1.00	1.00	1.00	1.00
sleeping fairly well	1.14 (1.03, 1.25)	0.95 (0.85, 1.07)	1.04 (0.93, 1.17)	0.93 (0.82, 1.05)
sleeping fairly poorly/poorly	1.31 (1.12, 1.53)	1.03 (0.88, 1.21)	1.08 (0.91, 1.29)	0.93 (0.78, 1.12)
Use Of Hypnotics And/Or Tranquilizers**				
no	1.00	1.00	1.00	1.00
infrequent	1.17 (0.95, 1.43)	0.98 (0.81, 1.19)	1.10 (0.89, 1.36)	1.01 (0.83, 1.25)
frequent	1.71 (1.36, 2.16)	1.64 (1.32, 2.03)	1.31 (1.02, 1.69)	1.39 (1.11, 1.75)

*short = < 7 □

Covariates measured in 1981 (in addition to age) in fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, and life satisfaction.

Table 3—Sleep Length, Sleep Quality, Use of Hypnotics and/or Tranquilizers, and Risk of Total Mortality (Age-Adjusted Hazard Ratio and 95% Confidence Interval) in 1982-2003 by Age Groups (Age at Entry of the Follow-Up). All 3 Variables Measured in 1981 and Mutually Adjusted in the Same Model

	24-39 Years		40-54 Years		55 Years Or More	
	Men N = 5629	Women N = 6118	Men N = 2941	Women N = 2818	Men N = 1570	Women N = 2192
Sleep Length*						
short	1.96 (1.53, 2.51)	1.52 (0.99, 2.33)	1.29 (1.03, 1.62)	1.23 (0.88, 1.74)	1.19 (1.01, 1.40)	1.07 (0.92, 1.23)
average	1.00	1.00	1.00	1.00	1.00	1.00
long	1.33 (0.98, 1.79)	1.45 (1.03, 2.04)	1.06 (0.82, 1.37)	1.31 (0.97, 1.76)	1.37 (1.18, 1.60)	1.13 (0.98, 1.30)
Sleep Quality						
sleeping well	1.00	1.00	1.00	1.00	1.00	1.00
sleeping fairly well	1.36 (1.09, 1.69)	0.98 (0.72, 1.34)	1.15 (0.96, 1.38)	1.00 (0.77, 1.30)	1.03 (0.89, 1.18)	0.91 (0.79, 1.05)
sleeping fairly poorly/poorly	2.29 (1.62, 3.24)	1.42 (0.83, 2.44)	1.26 (0.95, 1.68)	1.12 (0.73, 1.70)	1.18 (0.96, 1.45)	0.98 (0.82, 1.17)
Use Of Hypnotics And/or Tranquilizers**						
no	1.00	1.00	1.00	1.00	1.00	1.00
infrequent	1.68 (1.08, 2.61)	1.45 (0.85, 2.47)	1.50 (1.11, 2.05)	1.07 (0.70, 1.64)	0.87 (0.65, 1.16)	0.89 (0.71, 1.13)
frequent	2.90 (1.76, 4.76)	2.57 (1.27, 5.21)	2.07 (1.43, 3.01)	1.94 (1.21, 3.13)	1.38 (1.01, 1.88)	1.50 (1.18, 1.92)

* short = < 7 □

short decreased from 1.20 to 1.15 and became nonsignificant. Excluding sleep quality and use of hypnotics and/or tranquilizers as covariates did not change HRs substantially.

Table 5 gives the mortality risks (HRs) on the association between stability of sleep quality and total mortality. Sleep quality from 1975 to 1981 remained unchanged in 65.6% of men and in 64.5% of women and became worse in about 20% and better in about 15% in both genders. There was a gender difference in age-adjusted model showing significant increases in risk of mortality in men in most combinations of sleep quality (highest with fairly poor/poor quality either in 1975 or 1981, 1.72-1.98), but in the fully-

adjusted model, almost all associations lost their significance indicating that the effect of sleep quality is not an independent effect but reflects the influence of other factors affecting mortality. Snoring as a covariate made all HRs nonsignificant (fairly poorly/poorly-fairly well decreased from 1.34 to 1.19 in men). Excluding sleep length and use of hypnotics and/or tranquilizers as covariates did not change HRs substantially.

Table 6 gives the results on the association between stability of use of hypnotics and/or tranquilizers and the risk of mortality. The majority (87.6% of men and 81.8% of women) did not use these medications either in 1975 or in 1981. Use remained unchanged in

Table 4—Stability of Sleep Length Between 1975 and 1981 and Total Mortality in 1982-2003: Hazard Ratios with 95% Confidence Intervals. Percentage of Subjects in Each Sleep Length Category Combination Given for Men and Women.

Sleep length*		Percentage		All-Cause Mortality 1982-2003			
1975	1981	Men	Women	Age-adjusted (men) N = 10140	Age-adjusted (women) N = 11128	Fully-adjusted model (men) N = 9529	Fully-adjusted model (women) N = 10265
Short	Short	5.0	4.3	1.60 (1.36, 1.89)	1.07 (0.90, 1.28)	1.36 (1.13, 1.63)	1.07 (0.86, 1.32)
Average	Short	9.7	8.5	1.44 (1.25, 1.67)	1.22 (1.05, 1.42)	1.20 (1.02, 1.41)	1.24 (1.05, 1.48)
Long	Short	0.5	0.7	2.43 (1.51, 3.89)	2.08 (1.18, 3.67)	1.63 (0.89, 2.99)	2.17 (1.33, 3.53)
Short	Average	4.5	3.8	1.48 (1.20, 1.82)	1.03 (0.83, 1.29)	1.19 (0.94, 1.49)	0.94 (0.74, 1.18)
Average	Average	59.2	53.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Long	Average	6.4	7.5	0.97 (0.80, 1.18)	1.02 (0.81, 1.27)	0.90 (0.72, 1.12)	0.98 (0.77, 1.25)
Short	Long	0.4	0.5	1.47 (0.78, 2.78)	1.73 (1.04, 2.86)	1.25 (0.63, 2.47)	1.34 (0.77, 2.34)
Average	Long	9.7	12.8	1.27 (1.11, 1.47)	1.18 (1.02, 1.36)	1.20 (1.03, 1.40)	1.19 (1.02, 1.40)
Long	Long	4.6	8.1	1.49 (1.24, 1.78)	1.21 (1.00, 1.46)	1.32 (1.07, 1.62)	1.09 (0.89, 1.35)

*short = < 7 hours, average = 7-8 hours, and long = > 8 hours.

Covariates measured in 1981 (in addition to age) in fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, life satisfaction, sleep quality, and use of hypnotics and/or tranquilizers.

Table 5—Stability of Sleep Quality Between 1975 and 1981 and Total Mortality in 1982-2003: Hazard Ratios (95% Confidence Intervals) for Each Combination of Self-Reported Sleep Quality. Percentage of Subjects in Each Sleep Quality Category Combination Given for Men and Women

Sleep Quality: Sleeping		Percentage		All-Cause Mortality 1982-2003			
1975	1981	Men	Women	Age-adjusted (men) N = 10140	Age-adjusted (women) N = 11128	Fully-adjusted model (men) N = 9529	Fully-adjusted model (women) N = 10265
Well	Well	31.3	28.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fairly well	Well	11.4	11.6	1.26 (1.07, 1.48)	1.11 (0.92, 1.34)	1.15 (0.96, 1.38)	1.04 (0.85, 1.28)
Fairly poorly/ poorly	Well	0.6	0.7	1.87 (1.24, 2.82)	1.40 (0.90, 2.17)	1.08 (0.71, 1.63)	1.03 (0.62, 1.71)
Well	Fairly well	14.7	14.6	1.13 (0.97, 1.32)	0.99 (0.82, 1.19)	1.06 (0.90, 1.26)	0.96 (0.78, 1.18)
Fairly well	Fairly well	30.1	31.5	1.23 (1.09, 1.39)	0.97 (0.84, 1.12)	1.08 (0.94, 1.24)	0.92 (0.78, 1.09)
Fairly poorly/ poorly	Fairly well	2.6	3.2	1.98 (1.58, 2.49)	1.22 (0.97, 1.53)	1.34 (1.03, 1.74)	1.01 (0.78, 1.31)
Well	Fairly poorly/ poorly	1.1	0.8	1.72 (1.08, 2.73)	0.89 (0.54, 1.46)	1.12 (0.69, 1.81)	0.54 (0.30, 0.99)
Fairly well	Fairly poorly/ poorly	4.1	4.6	1.76 (1.43, 2.16)	1.24 (1.02, 1.52)	1.19 (0.93, 1.51)	0.99 (0.77, 1.26)
Fairly poorly/ poorly	Fairly poorly/ poorly	4.1	4.1	1.73 (1.43, 2.09)	1.18 (0.98, 1.42)	1.10 (0.87, 1.39)	0.99 (0.77, 1.27)

Covariates measured in 1981 (in addition to age) in fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, life satisfaction, sleep length, and use of hypnotics and/or tranquilizers.

2.7% of men and in 4.0% of women, and, respectively, increased in 4.0% and 7.2%, and decreased in 4.7% and 7.1%. In age-adjusted HRs, there was increased mortality risk in recent frequent use (in men 1.63-2.17 and in women 1.47-2.24), which in the fully-adjusted model attenuated clearly in men and somewhat in women. The increase in mortality was most consistent and significant in those who were non-users of hypnotics and/or tranquilizers in 1975 who reported frequently use in 1981. There was no change in the HRs when including snoring as a covariate. Excluding sleep length and sleep quality as covariates did not change HRs substantially.

Joint effects of sleep length and sleep quality on total mortality in 1981 are shown in Table 7. In the fully-adjusted model in

men there was a significant increase in mortality in short sleepers in all 3 quality categories (1.32-1.45), and in 2 of 3 classes of long sleepers (1.26-1.42, but not in the poorest quality class). In women the only significant HR was in short sleepers with good sleep quality. The results are parallel with those of the stability of sleep length (Table 4). Snoring as a covariate slightly lowered the HRs in men, leading to nonsignificance in the categories of short and fairly poorly/poorly (from 1.33 to 1.22), and long and fairly well (from 1.26 to 1.17).

Table 8 gives the HRs for joint effects of sleep quality and the use of hypnotics and/or tranquilizers. In the small group sleeping well and taking medication frequently, the estimates of risk of

Table 6—Stability of Hypnotic and/or Tranquilizers Use Between 1975 and 1981 and Total Mortality in 1982-2003: Hazard Ratios (95% Confidence Intervals) for Each Combination of Self-Reported Medication Use. Percentage of Subjects in Each Medication Use Category Combination Given for Men and Women

Use*		Percentage		All-Cause Mortality 1982-2003			
1975	1981	Men	Women	Age-adjusted (men) N = 8796	Age-adjusted (women) N = 9326	Fully-adjusted model (men) N = 8412	Fully-adjusted model (women) N = 8824
No	No	87.6	81.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Infrequent	No	3.7	5.4	1.13 (0.89, 1.43)	1.19 (0.94, 1.52)	1.01 (0.79, 1.30)	1.10 (0.85, 1.41)
Frequent	No	0.7	1.0	1.31 (0.82, 2.10)	1.36 (0.86, 2.15)	1.13 (0.70, 1.84)	1.35 (0.75, 2.43)
No	Infrequent	3.3	5.1	1.21 (0.94, 1.56)	0.97 (0.75, 1.25)	1.04 (0.79, 1.37)	0.97 (0.73, 1.28)
Infrequent	Infrequent	1.4	2.5	1.30 (0.92, 1.84)	0.98 (0.70, 1.37)	1.19 (0.85, 1.67)	1.06 (0.73, 1.53)
Frequent	Infrequent	0.3	0.7	2.40 (1.46, 3.94)	1.37 (0.87, 2.17)	1.36 (0.81, 2.27)	1.45 (0.90, 2.33)
No	Frequent	1.2	1.3	2.17 (1.52, 3.08)	2.24 (1.66, 3.03)	1.63 (1.14, 2.33)	1.90 (1.36, 2.65)
Infrequent	Frequent	0.5	0.8	1.63 (0.92, 2.86)	1.47 (0.96, 2.25)	1.30 (0.70, 2.40)	1.19 (0.72, 1.96)
Frequent	Frequent	1.3	1.5	2.10 (1.56, 2.83)	1.59 (1.18, 2.13)	1.28 (0.90, 1.83)	1.46 (1.05, 2.01)

*infrequent = 1-59 days per year; frequent = 60 or more days per year.

Covariates measured in 1981 (in addition to age) in fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, life satisfaction, sleep length, and sleep quality.

Table 7—Joint Effects of Sleep Length and Sleep Quality in 1981 on Total Mortality: Hazard Ratios (95% Confidence Intervals) for Mortality in 1982-2003. Hazard Ratios with 95% Confidence Intervals Given. Percentage of Subjects in Each Sleep Behavior Combination Given for Men and Women

Sleep Length*	Sleep Quality: Sleeping	Percentage		Fully-Adjusted Model Hazard Ratios Men N = 9529	Fully-Adjusted Model Hazard Ratios Women N = 10265
		Men	Women		
Short	Well	5.0	3.7	1.32 (1.03, 1.68)	1.35 (1.02, 1.78)
Short	Fairly well	6.3	5.6	1.45 (1.20, 1.76)	1.17 (0.94, 1.47)
Short	Fairly poorly/Poorly	4.0	4.1	1.33 (1.05, 1.68)	1.08 (0.85, 1.36)
Average (reference)	Well	30.8	27.1	1.00	1.00
Average	Fairly well	34.8	33.7	1.09 (0.94, 1.26)	0.93 (0.79, 1.11)
Average	Fairly poorly/Poorly	4.5	4.4	1.25 (0.99, 1.58)	0.97 (0.76, 1.25)
Long	Well	7.5	10.4	1.42 (1.17, 1.73)	1.16 (0.93, 1.44)
Long	Fairly well	6.3	10.0	1.26 (1.02, 1.56)	1.08 (0.88, 1.32)
Long	Fairly poorly/Poorly	0.9	1.0	1.18 (0.80, 1.73)	1.39 (0.92, 2.09)

* short = < 7 hours, average = 7-8 hours, and long = > 8 hours.

Covariates measured in 1981 (in addition to age) in this fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, life satisfaction, and use of hypnotics and/or tranquilizers.

mortality were increased both in men (1.56, nonsignificant) and in women (2.82, significant). Additionally, sleeping fairly well and frequent medication was associated with significantly increased HR in men (2.03). In those sleeping fairly poorly/poorly there were no significant increased in risk of mortality with any frequency of medication use. Including snoring as a covariate did not change results.

In Table 9, risk of mortality for natural and external causes of death and stability of sleep length is assessed. In men, there was a significant increase for stable short (1.34) and stable long (1.29) sleep in natural deaths, while for external causes we saw a significantly increased mortality in short sleep at the beginning of follow-up (1.62-3.16). In women the results were less consistent, but a significant increase was observed in risk of natural death in those with sleep becoming short in 1981 (1.24-2.23). Including snoring as a covariate did not change the results in women, but in men slightly attenuated the HRs in external causes of death,

making the combinations “short-short” (from 1.62 to 1.54) and “long-short” (from 3.16 to 2.90) nonsignificant. In natural deaths, there were significant association in young men with short sleep and in old men with long sleep as well as in old women with short sleep and frequent use of hypnotics and/or tranquilizers (data not shown). In deaths due to external causes, there were significant associations in young men with short sleep, decreased sleep quality, and frequent use of medication; in middle-aged men with frequent use of medication; in young women frequent use of medication; and in old women short sleep, long sleep, and frequent use of medication (data not shown).

DISCUSSION

This is the first study to assess the stability (i.e., more than one measurement done) of 3 aspects of sleep behavior in relation to long-term mortality. Over a 6-year period, sleep length and sleep

Table 8—Joint Effects of Sleep Quality and Use of Hypnotics and/or Tranquilizers in 1981 on Total Mortality: Hazard Ratios (95% Confidence Intervals) for Mortality in 1982-2003. Percentage of Subjects in Each Sleep Quality and Medication Use Category Combination Given for Men and Women

Sleep Quality: Sleeping	Use Of Hypnotics and/or Tranquilizers*	Percentage		Fully-adjusted Model Hazard Ratios Men N = 9529	Fully-adjusted Model Hazard Ratios Women N = 10265
		Men	Women		
Well	No	43.2	40.8	1.00 (reference)	1.00 (reference)
Well	Infrequent	0.8	1.8	1.13 (0.59, 2.16)	1.18 (0.76, 1.84)
Well	Frequent	0.6	0.6	1.56 (0.93, 2.62)	2.82 (1.88, 4.24)
Fairly well	No	43.4	42.5	1.08 (0.95, 1.23)	0.94 (0.80, 1.10)
Fairly well	Infrequent	2.8	4.5	1.19 (0.90, 1.56)	0.86 (0.63, 1.19)
Fairly well	Frequent	1.0	1.7	2.03 (1.46, 2.83)	1.14 (0.76, 1.70)
Fairly poorly/Poorly	No	5.4	4.8	1.18 (0.94, 1.48)	0.93 (0.71, 1.23)
Fairly poorly/Poorly	Infrequent	1.5	2.0	1.21 (0.85, 1.72)	1.00 (0.72, 1.40)
Fairly poorly/Poorly	Frequent	1.3	1.4	1.12 (0.77, 1.64)	1.16 (0.84, 1.60)

*infrequent = 1-59 days per year; frequent = 60 or more days per year.

Covariates measured in 1981 (in addition to age) in this fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, life satisfaction, and sleep length.

Table 9—Stability of Sleep Length Between 1975 and 1981 in Relation to Risk of Death From Natural and External Causes of Death in 1982-2003. Hazard Ratios with 95% Confidence Intervals Given

Sleep Length*		Risk Of Mortality 1982-2003			
1975	1981	Natural Causes Of Death Men N = 9529	Natural Causes Of Death Women N = 10265	External Causes Of Death Men N = 9529	External Causes Of Death Women N = 10265
Short	Short	1.34 (1.11, 1.63)	1.07 (0.86, 1.33)	1.62 (1.01, 2.60)	1.39 (0.55, 3.50)
Average	Short	1.10 (0.92, 1.31)	1.24 (1.03, 1.48)	1.86 (1.31, 2.65)	1.49 (0.71, 3.16)
Long	Short	1.24 (0.48, 3.21)	2.23 (1.35, 3.68)	3.16 (1.10, 9.05)	1.60 (0.20, 12.8)
Short	Average	1.24 (0.96, 1.59)	0.89 (0.69, 1.13)	1.08 (0.60, 1.93)	1.86 (0.75, 4.60)
Average	Average	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Long	Average	0.96 (0.76, 1.22)	0.98 (0.77, 1.25)	0.67 (0.35, 1.26)	1.18 (0.45, 3.07)
Short	Long	1.27 (0.63, 2.56)	1.01 (0.58, 1.78)	1.09 (0.14, 8.43)	6.30 (1.96, 20.3)
Average	Long	1.16 (0.98, 1.37)	1.20 (1.02, 1.41)	1.43 (0.95, 2.15)	1.09 (0.50, 2.35)
Long	Long	1.29 (1.03, 1.62)	1.08 (0.87, 1.34)	1.18 (0.64, 2.17)	1.55 (0.67, 3.57)

* short = < 7 hours, average = 7-8 hours, and long = > 8 hours.

Covariates measured in 1981 (in addition to age) in this fully-adjusted model: education, marital status, working status, social class, BMI, smoking status, binge drinking, grams of alcohol consumed daily, conditioning physical activity, life satisfaction, sleep quality, and use of hypnotics and/or tranquilizers.

quality changed in about one-third of the population; more than 80% did not use hypnotics and/or tranquilizers. Generally, the association with an increased risk of mortality was strongest in short sleep, long sleep, and frequent use of medication. Compared to previous reports, the present study has several strengths: the study sample is representative of the general population with very high response rates; 3 aspects of sleep behavior were assessed simultaneously; they were measured twice; the follow-up is long; and the statistics on deaths and causes of death are comprehensive and reliable.

Our results support a U-shaped association between sleep length and all-cause mortality² – risk of death being the smallest in average sleepers (7-8 hours). After adjustment for factors known to be associated with mortality, a significant increase in risk of mortality by 26% in men and by 21% in women was observed in short sleepers (<7 hours) and in long sleepers (>8 hours) by 24%

and 17%, respectively. Among men, stable short and stable long sleep was associated with a significantly increased risk of mortality, but this was not seen in women. A decrease of sleep length to short increased mortality in both genders, as did lengthening of sleep from average to long.

Sleep quality was only minimally associated with increased mortality in the fully-adjusted models, indicating that it does not independently affect the risk of mortality. We find this somewhat unexpected, as it may be speculated that in sleep, the significance of quality could equal quantity. There are problems with the accuracy of self-reports of sleep length, and such reports may represent time spent in bed rather than actual physiological sleep. It is well known in sleep medicine that subjects with insomnia underestimate their sleeping times. It is also possible that much of the extended time in bed reported by many long sleepers may

Table 10—Age and Sex Adjusted Risk of Total Mortality (Hazard Ratio and 95% Confidence Interval) in 1982-2003 by Age-Groups (Age at Entry to the Follow-Up). All Three Variables Measured in 1981 and Mutually Adjusted in the Same Model

	All N = 21268	24-39 Years N = 11747	40-54 Years N = 5759	55 Years Or More N = 3762
Sleep Length				
short	1.27 (1.16-1.39)	1.84 (1.48-2.27)	1.28 (1.07-1.55)	1.15 (1.03-1.29)
average	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
long	1.27 (1.17-1.38)	1.40 (1.12-1.76)	1.15 (0.95-1.39)	1.25 (1.12-1.39)
Sleep Quality				
sleeping well	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
sleeping fairly well	1.06 (0.98-1.14)	1.22 (1.02-1.46)	1.10 (0.95-1.28)	0.96 (0.87-1.07)
sleeping fairly poorly/poorly	1.17 (1.04-1.31)	2.00 (1.50-2.66)	1.22 (0.96-1.54)	1.05 (0.91-1.21)
Use Of Hypnotics And/Or Tranquilizers				
no	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
infrequent	1.07 (0.93-1.23)	1.58 (1.12-2.21)	1.33 (1.04-1.71)	0.88 (0.73-1.06)
frequent	1.70 (1.45-1.99)	2.72 (1.82-4.08)	2.01 (1.50-2.70)	1.49 (1.23-1.80)

* short = < 7 □

have been spent awake.^{2,14} Subjective sleep quality is strongly associated to the amount of slow wave sleep¹⁵ which is considered together with REM sleep to be most important for the function of sleep, although incompletely understood. It seems that sleep quantity and quality are so closely interrelated that controlling for sleep length when assessing quality neutralizes its significance.

In our results, the association between stability of use of hypnotics and/or tranquilizers and mortality was modest, showing significantly increased risk only when non-users became frequent users. Results in earlier studies have been contradictory, either showing increased mortality in hypnotic use⁴ or no increase.⁶ However, the increase in use of these medications may considerably attenuate the effect seen in our study: In Finland from 1975 to 2005, use of hypnotics has almost tripled (from 18.8 to 54.4 DDD/1000 persons/day), and use of tranquilizers has almost doubled (from 17.6 to 31.2; statistics of National Agency for Medicines, Finland). Since the mid 1970s practically all these medications have been benzodiazepines or benzodiazepine-like compounds.

When we examined natural and external causes of death separately, there were consistent and also statistically significant increase in men in risk of death from natural causes both in stable short and stable long sleepers, and in deaths due to external causes in short-sleeping men. There were significant differences between the age groups in associations of sleep variables with the 2 groups of death causes, and the clearest was between frequent use of hypnotics and/or tranquilizers and deaths due to external causes. Our results suggest a complex association between sleep and mortality, probably with various mechanisms in different age and cause-of-death groups.

There are some contradictions in the results and the methodological heterogeneity among the more than 20 studies on sleep length and mortality, interfering with the comparability of their conclusions.² These include differences in population characteristics (e.g., sex and age of the subjects), the size of the study population (<2,000–1.1 million), length of follow-up (3–23 years) and the number of covariates adjusted for (none to 32). Differences in the formulation of the questions assessing sleep length and other sleep related aspects may also have affected the results.¹⁶ With proper covariate control, the association for short sleep, in particular, has weakened and in many studies lost statistical signifi-

cance. It seems that much, but not all excess mortality among long and short sleepers may be attributed to differences in lifestyle and health/disease-related factors between the sleep length groups. In some occasions, the representativeness of the study population has been questioned. This is the case with the large American studies by Kripke et al,^{3,17} which have been considered to be from “a convenience population,” friends and associates of volunteers of the American Cancer Society who do not reflect the general population of the United States. That sample has a lower mortality rate and may have other unknown differences.¹⁸ It is also noteworthy that in our sample, sleep length and sleep quality changed in one-third of the subjects over a relatively short (6-year) period. It is probable that this is not unique for our population but occurs in other populations as well; this may include those from which results on the association between sleep length and mortality have been published. This may be one major reason to explain at least partly the variable results of these studies, especially regarding short sleep.² Despite the methodological differences the present study is fairly consistent with the results of the previous reports.

The reasons for the association between sleep length and mortality is not clear, and even the existence of the association has been questioned, with the conclusion that previous studies have not proven the association in the absence of other contributing factors.¹⁸ As groups, short and long sleepers are obviously heterogeneous; they include healthy subjects sleeping according to their needs (natural short sleepers or natural long sleepers) as well as subjects with health-associated factors that either shorten or lengthen their sleep. Several possible mechanisms to explain the association between sleep length and mortality have been suggested.² First, depression has been associated with mortality and changes in sleep length^{19,20} and could thus account for the relation. Our results do not support this conclusion, as adjustment for life satisfaction, which strongly correlates with depression,¹² was done. Secondly, sleep disordered breathing has been suggested as an explanation of increased mortality in long sleepers.²¹ This explanation also seems improbable because adjustment for BMI and inclusion of snoring as a covariate only slightly attenuated the hazard ratios. Thirdly, the possible effect of underlying undetected major disease affecting sleep at baseline could cause confounding, and this has been taken into ac-

count only in few previous studies.²² However this explanation does not seem plausible. In our study the possible confounding by undetected major disease affecting sleep at baseline was controlled for because subjects had to be alive at the end of the 6-year period (1975-81) between the 2 measurements of the 3 aspects of sleep behavior. Moreover, exclusion of deaths in the first 3 years of the follow-up did not change our results. Other possible explanations for the proposed association include a large number of lifestyle and health-related factors potentially associated with both sleep length and mortality, such as low socioeconomic status.²³ In the present study, the adjustment for various important covariates attenuated but did not fully explain the association between sleep behavior and mortality. Moreover, some residual confounding by measured or unmeasured factors may still have been present. Our results suggest the possibility of several mechanisms underlying the association between sleep and mortality, probably being different in e.g., short and long sleepers and in different causes of death.

In conclusion, there is an association between sleep behavior (most notably in sleep length) and mortality. The exact mechanisms remain unclear, and they should be assessed in experimental settings and other longitudinal studies. Morbidity and functional limitations as less severe outcomes should also be considered. Although the effect of sleep on mortality is fairly modest compared to e.g., smoking or components of the metabolic syndrome, it is still of considerable significance as it is associated with several common disorders such as cardiovascular diseases and diabetes. Optimizing sleep—in addition to disorder-specific treatment—could improve prognosis in these disorders. Our results add evidence to the association between sleep and health outcomes.

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