Diabetologia (2005) 48: 235–241
DOI 10.1007/s00125-004-1634-x

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Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population

Received: 19 April 2004 / Accepted: 11 September 2004 / Published online: 11 January 2005

Abstract *Aims/hypothesis:* To examine gender specific associations between sleep disturbance and incident type 2 diabetes mellitus in a representative population sample in Germany. *Methods:* The study was based on 4,140 men and 4,129 women (aged 25–74 years) who participated in one of the three MONICA Augsburg surveys between 1984 and 1995, and who were free of diabetes at baseline. Incident cases of type 2 diabetes were assessed using a follow-up questionnaire in 1998. Gender specific hazard ratios were estimated from Cox proportional hazard models. *Results:* A total of 119 cases of incident type 2 diabetes among men and 69 among women were registered during the mean follow-up period of 7.5 years. In both sexes, difficulty maintaining sleep was associated with a higher risk of type 2 diabetes. After adjustment for age, survey, hypertension, dyslipidemia, parental history of diabetes, history of angina pectoris, regular smoking, physical activity, alcohol intake, body mass index and education, the hazard ratio in men was 1.60 (95% CI: 1.05–2.45) and the hazard ratio in women was 1.98 (95% CI: 1.20–3.29). In contrast, difficulty initiating sleep was not associated with a significantly increased risk of developing type 2 diabetes mellitus after multivariable adjustment in both sexes in the present study. *Conclusions/interpretation:* Difficulty maintaining sleep was associated with an increased risk of type 2 diabetes in men and women from the general population. Although, the causal pathway is not entirely clear, it seems that both insulin resistance and chronic low-grade systemic inflammation may be involved.

Keywords Cohort study · Diabetes · Gender · Predictor · Sleep disturbance

Abbreviations HR: Hazard ratio

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Introduction

Sleep quantity and quality are associated with mortality, but also with an increased risk of cardiovascular morbidity [1, 2]. A new and interesting aspect of sleep disturbance is its impact on glucose metabolism and diabetes. Findings from the Sleep Heart Health Study have shown that subjects with type 2 diabetes report more sleep problems than non-diabetic subjects; however, it was not clear whether central sleep disturbances may be caused by diabetes or whether they may specifically relate to effects of diabetic complications [3]. Other cross-sectional studies indicated that habitual snoring and sleep apnoea, symptoms of a group of disorders known as sleep-disordered breathing are associated with abnormal fasting glucose and insulin values independent of age and BMI [4, 5]. Also, prospective data from the Nurses Health Study [6] and a population-based Swedish study [7] showed that habitual snoring is associated with more than a twofold risk of developing type 2 diabetes mellitus over a 10-year period, independent of BMI and other confounding variables. Recently, in the Nurses Health Study it was shown that sleeping less than 6 h was associated with a greater risk of incident type 2 diabetes mellitus in women [8]. Since sleep disorders are becoming increasingly common and are affecting millions of people [9], an association between sleep disorders and incident type 2 diabetes may have great public health implications. In the present study, we examined sleep disturbance in relation to risk for type 2 diabetes prospectively in a large cohort of men and women from the general population.

Materials and methods

The presented data were derived from the population-based MONICA (Monitoring trends and determinants on cardiovascular diseases) Augsburg (southern Germany) studies conducted between 1984 and 1995. The MONICA Augsburg project was part of the multinational WHO MONICA project and the design of both projects has been described in detail elsewhere [10, 11]. Three independent cross-sectional surveys were carried out in the city of Augsburg and the counties Augsburg and Aichach-Friedberg in 1984/1985, 1989/1990, and 1994/1995 to estimate the prevalence and distribution of cardiovascular risk factors among men and women. Altogether 13,428 persons (6,725 men, 6,703 women, response 77%) aged 25 to 74 years participated in at least one of the three cross-sectional studies.

In 1998, vital status was assessed for all sampled persons of the three MONICA surveys through the population registries. In the meantime, 772 participants (531 men, 241 women) had died. Vital status could not be assessed for 56 persons (31 men, 25 women) who had moved to a foreign country or to an unknown location. A questionnaire assessing the health status was mailed to the remaining 12,600 living persons (6,163 men, 6,437 women) with a known address in 1998. A total of 8,548 subjects (4,210 men, 4,338 women) returned the questionnaire (total response rate 67.8%; response rate for men 68.3%, for women 67.4%). All subjects who had died between baseline and follow-up were also included in the analyses because their medical records were searched for or their last treating physician was asked for a diagnosis of type 2 diabetes mellitus (see the section "Ascertainment of diabetes").

Because sleep disturbance may be an early symptom of diabetes, possibly predating its official diagnosis, for the present analysis we excluded persons with a follow-up time less than 2 years (n=242). Further, we excluded persons with prevalent diabetes (n=405), subjects from whom no information about diabetes status or no calendar year of diagnosis of diabetes at follow-up was available (n=96), and subjects with other types of diabetes than type 2 diabetes (n=5). Furthermore, we excluded all subjects with incomplete data on all required factors (n=303). Finally, the prospective analyses comprised 8,269 non-diabetic MONICA participants (4,140 men and 4,129 women) aged 25–74 years.

All participants gave their informed consent and the study was approved by the ethics committee of the Bavarian Medical Association.

Data collection Baseline information on sociodemographic variables, smoking habits, physical activity level, medication use, parental history of disease, and alcohol consumption were gathered by trained medical staff during a standardised interview. In addition, all participants underwent an extensive standardised medical examination, including the collection of a non-fasting blood sample. All measurement procedures have been described elsewhere in detail [10, 12]. Hypertension was defined as blood pressure values ≥160/95 mmHg and/or use of antihypertensive medication, given that the subjects were aware of being hypertensive. Dyslipidaemia was defined as total cholesterol to high density cholesterol ratio ≥5.0. Participants were classified as active during leisure time if they regularly participated in sports in summer and winter and if they were active for at least 1 h/week in either season. Two separate three-category interview questions were asked concerning the difficulty initiating sleep ("Did you have trouble falling asleep?") and the difficulty maintaining sleep ("Did you wake up during the night?"). The subjects were classified into one of two categories: low for those who indicated "sometimes" and "almost never" and high for those who indicated "often" in response to the questions.

Ascertainment of diabetes In the 1998 follow-up questionnaire, we inquired about a diagnosis of diabetes. Self-reported incident cases of diabetes mellitus and the date of diagnosis were validated by hospital records or by contacting the proband's treating physician. Furthermore, the hospital records of those deceased during the follow-up period without a diagnosis of type 2 diabetes mellitus at baseline were also examined and/or their last treating physicians were contacted. The records were searched for or the doctors were asked for a history concerning diabetes and if a person had suffered from diabetes, the type of diabetes and the date of diagnosis were ascertained. If a participant was not found in any of the medical records and if no information from the last treating physician could be obtained, the participant was excluded from analysis.

Statistical analyses The duration of the follow-up was calculated as the interval between the baseline-examination and the diagnosis of type 2 diabetes mellitus, death, or the date, when the 1998 questionnaire was completed. All analyses were performed separately for male and female subjects. Mean values or percentages of variables considered to be related to sleep disturbance or development of diabetes were displayed by difficulty initiating sleep and difficulty maintaining sleep. Statistical associations between continuous variables were assessed by t-test. The chi square test was used to examine associations between categorical variables. To examine how the association of sleep disturbance with incident type 2 diabetes mellitus was affected by other factors, we computed different Cox proportional hazards models. The first model included sleep disturbance as the sole explanatory variable. The second model included in addition age (continuous) and survey. The third model included all previous factors plus education (</≥12 years), and parental history of diabetes (yes/no/unknown). In addition, the fourth model included hypertension (yes/no), history of angina pectoris (yes/no), dyslipidaemia (yes/no), physical activity (active/inactive), smoking status (regular smoking, that is a subject who smoked at least one cigarette per day at baseline, yes/no), alcohol intake (non-drinkers (0 g/day), intake of 0.1–19.9 and ≥20 g/day for women and 0.1–39.9 and ≥40 g/day for men, respectively). The fifth model included, in addition to all previous factors, BMI (continuous). We controlled

Table 1 Means and prevalences (%) of baseline characteristics in 4,140 men and 4,129 women with and without difficulty initiating sleep

	Men			Women		
	Difficulty initiating sleep (*n*=301)	No difficulty initiating sleep (*n*=3,839)	*p*	Difficulty initiating sleep (*n*=565)	No difficulty initiating sleep (*n*=3,564)	*p*
Age (years)	51.5	47.2	<0.0001	54.0	45.4	<0.0001
Obesity (BMI≥30 kg/m^2) (%)	20.9	16.1	0.0304	19.5	15.9	0.0353
Hypertension (%)	25.6	22.0	0.1485	23.5	15.2	<0.0001
History of angina pectoris (%)	8.3	3.0	<0.0001	6.4	2.9	<0.0001
Alcohol intake (%)						
0 g/day	21.9	14.9	0.0053	41.2	39.6	0.5505
0.1–19.9 g/day (women), 0.1–39.9 g/day (men)	48.5	52.7		40.2	40.0	
≥20 g/day (women), ≥40 g/day (men)	29.6	32.4		18.6	20.5	
Regular smoking (%)	31.6	25.6	0.0234	14.0	17.0	0.0729
Dyslipidaemia (%)	47.2	44.0	0.2887	23.7	14.9	<0.0001
Active during leisure time (%)	38.5	47.8	0.0019	33.8	43.5	<0.0001
Positive parental history of diabetes (%)	16.6	18.0	0.5525	19.5	20.9	0.4343
Education<12 years (%)	75.4	60.5	<0.0001	86.7	77.2	<0.0001

Table 2 Means and prevalences (%) of baseline characteristics in 4,140 men and 4,129 women with and without difficulty maintaining sleep

	Men			Women		
	Difficulty maintaining sleep (*n*=596)	No difficulty maintaining sleep (*n*=3,544)	*p*	Difficulty maintaining sleep (*n*=786)	No difficulty maintaining sleep (*n*=3,343)	*p*
Age (years)	54.0	46.4	<0.0001	53.9	44.8	<0.0001
Obesity (BMI≥30 kg/m^2) (%)	20.1	15.9	0.0092	19.3	15.7	0.0141
Hypertension (%)	29.5	21.0	<0.0001	24.9	14.4	<0.0001
History of angina pectoris (%)	7.6	2.7	<0.0001	5.2	3.0	0.0017
Alcohol intake (%)						
0 g/day	17.8	15.0	0.2288	42.4	39.2	0.2374
0.1–19.9 g/day (women), 0.1–39.9 g/day (men)	50.8	52.7		37.8	40.5	
≥20 g/day (women), ≥40 g/day (men)	31.4	32.3		19.9	20.3	
Regular smoking (%)	20.5	27.0	0.0008	11.2	17.9	<0.0001
Dyslipidaemia (%)	47.5	43.7	0.0860	22.8	14.5	<0.0001
Active during leisure time (%)	43.5	47.8	0.0509	32.7	44.4	<0.0001
Positive parental history of diabetes (%)	16.3	18.1	0.2707	20.9	20.7	0.9033
Education<12 years (%)	70.6	60.1	<0.0001	85.5	76.8	<0.0001

Table 3 Gender-specific crude incidence rates of type 2 diabetes mellitus by difficulty initiating and maintaining sleep respectively

	Difficulty initiating sleep		Difficulty maintaining sleep	
	Yes	No	Yes	No
Men (*n*=4,140)	(*n*=301)	(*n*=3,839)	(*n*=596)	(*n*=3,544)
No. of incident cases	12	107	29	90
Person years (PY)	2,187	28,680	3,960	26,907
Crude incidence per 10,000 PY	54.9	37.3	73.2	33.4
Women (*n*=4,129)	(*n*=565)	(*n*=3,564)	(*n*=786)	(*n*=3,343)
No. of incident cases	17	52	27	42
Person years (PY)	4,207	27,359	5,450	26,116
Crude incidence per 10,000 PY	40.4	19.0	49.5	16.1

for all these factors, given that any of them can be associated with sleep disturbance and/or type 2 diabetes. Results are presented as hazard ratios (HRs) and 95% CI. Significance tests were two-tailed and *p*-values less than 0.05 are stated as statistically significant. All analyses were performed using the Statistical Analysis System (Version 8.2, SAS Institute, Cary, NC, USA).

Results

In total, 119 incident cases of type 2 diabetes among men and 69 among women were registered in the 25- to 74-year-old study population between 1984 and 1998 (mean follow-up period 7.5 years).

Tables 1 and 2 describe the baseline characteristics of this population by difficulty initiating sleep and difficulty maintaining sleep, respectively. Men and women with difficulty initiating sleep or with difficulty maintaining sleep were older, were more likely to be obese, to have a history of hypertension and angina pectoris, to be regular smokers, to have an education <12 years, and were less likely to be active during leisure time. Women with difficulty initiating sleep respectively with difficulty maintaining sleep also had a higher prevalence of dyslipidaemia.

Table 3 describes the observed crude incidence rates of type 2 diabetes mellitus by difficulty initiating and maintaining sleep, respectively. In all subgroups, the diabetes incidence was higher in men than in women. The crude incidence rate was 54.9/10,000 person years (PY) in men with difficulty initiating sleep and 73.2/10,000 PY in men with difficulty maintaining sleep; the corresponding values for women were 40.4/10,000 PY and 49.5/10,000 PY, respectively.

In Cox proportional hazards models (Table 4), the men and women who reported a high frequency of difficulty maintaining sleep had a significantly higher risk for type 2 diabetes mellitus compared with those who experienced a low frequency of difficulty maintaining sleep (men: crude HR 2.29, 95% CI=1.51–3.48; women: crude HR 3.24, 95% CI=2.00–5.25). Adjustment for age and survey considerably attenuated the HRs for men (HR 1.63, 95% CI=1.07–2.50) and women (HR 1.95, 95% CI=1.18–3.23). Further adjustment for education, parental history of diabetes, and other covariates (Model 3 and Model 4) only slightly changed the HRs. Finally, further adjustment for BMI (Model 5) did not substantially alter the associations in men (HR 1.60, 95% CI=1.05–2.45) and women (HR 1.98, 95% CI=1.20–3.29). Difficulties initiating sleep were significantly associated with incident type 2 diabetes mellitus in women (crude HR 2.15, 95% CI=1.24–3.71) but not in men (crude HR 1.50, 95% CI=0.83–2.72). However, adjustment for age and survey considerably attenuated the observed HRs, which were no longer significant in women (HR 1.30, 95% CI=0.74–2.28). After multivariable adjustment, the HR was 1.10 (95% CI=0.59–2.03) in men and 1.42 (95% CI=0.81–2.50) in women.

Because smoking may be linked to sleep-related disorders, we repeated the analyses after excluding all subjects who reported smoking regularly. After adjustment

Table 4 Gender-specific hazard ratios (HR) and 95% CI for developing diabetes according to self-reported sleep disturbance at baseline

	Men HR (95% CI)	Women HR (95% CI)
Difficulty initiating sleep	(*n*=301)	(*n*=565)
Number of incident cases	12	17
Model 1	1.50 (0.83–2.72)	2.15 (1.24–3.71)
Model 2	1.22 (0.67–2.23)	1.30 (0.74–2.28)
Model 3	1.24 (0.68–2.26)	1.28 (0.73–2.24)
Model 4	1.22 (0.66–2.23)	1.33 (0.76–2.34)
Model 5	1.10 (0.59–2.03)	1.42 (0.81–2.50)
Difficulty maintaining sleep	(*n*=596)	(*n*=786)
Number of incident cases	29	27
Model 1	2.29 (1.51–3.48)	3.24 (2.00–5.25)
Model 2	1.63 (1.07–2.50)	1.95 (1.18–3.23)
Model 3	1.62 (1.06–2.48)	1.97 (1.20–3.24)
Model 4	1.71 (1.12–2.63)	1.96 (1.19–3.23)
Model 5	1.60 (1.05–2.45)	1.98 (1.20–3.29)

Model 1: unadjusted
Model 2: adjusted for age and survey
Model 3: adjusted for age, survey, education, and parental history of diabetes
Model 4: adjusted for age, survey, education, parental history of diabetes, regular smoking, alcohol intake, hypertension, physical activity, dyslipidaemia, history of angina pectoris
Model 5: adjusted for age, survey, education, parental history of diabetes, regular smoking, alcohol intake, hypertension, physical activity, dyslipidaemia, history of angina pectoris, and body mass index

for age, survey, education, parental history of diabetes, alcohol intake, hypertension, physical activity, dyslipidemia, history of angina pectoris, and body mass index a high frequency of difficulty maintaining sleep remained independently associated with type 2 diabetes mellitus in men (HR 1.73, 95% CI=1.03–2.92) and women (HR 2.14, 95% CI=1.28–3.59). Also, the estimated HRs for the association between difficulty initiating sleep and type 2 diabetes became stronger. However, adjustment for age and survey considerably attenuated the HRs and they were no longer significant (data not shown).

Discussion

In this large cohort of men and women, drawn randomly from the general population, we observed a significantly positive association between difficulty maintaining sleep and incident type 2 mellitus diabetes in men and women. The association was independent of known risk factors for type 2 diabetes. In contrast, trouble falling asleep was not associated with a significantly increased risk of developing type 2 diabetes mellitus in the present study.

The association between sleep-related disorders and incident diabetes has been examined only in a few studies, so far. In the Nurses' Health Study including 69,852 US female nurses aged 40–65 years 1,957 women were diagnosed with type 2 diabetes during a 10-year follow-up period [6]. In multivariable analyses, snoring was associated with the risk of diabetes (for regular snoring versus non-snoring, relative risk (RR=2.03, 95% CI=1.71–2.40). Analyses stratified by BMI, smoking history, and parental history of diabetes showed a consistent association between snoring and diabetes within the categories of these variables. Furthermore, in a population-based Swedish study 2,668 men aged 30–69 years were followed up from 1984 to 1994 [7]. In that study 5.4% of the snorers developed diabetes in comparison with only 2.4% of the non-snorers. In a multiple logistic regression model, the odds ratio (OR) for development of diabetes was higher in obese snorers (OR 7.0, 95% CI=2.9–16.9) than in obese non-snorers (OR 5.1, 95% CI=2.7–9.5) after multivariable adjustment. In agreement with the present results, a study conducted in a group of Japanese male employees demonstrated a strong positive association between difficulty maintaining sleep and diabetes even after controlling for other factors relevant to type 2 diabetes. In contrast to the present analysis, those men who experienced a high frequency of difficulty initiating sleep also had a significantly higher risk of a later onset of type 2 diabetes [13]. Recent results from the Nurses Health Study showed that short sleep duration (<6 h) was also associated with an increased risk of diabetes. This association persisted even after adjustment for multiple confounders. However, after controlling for body mass index, the association was strongly attenuated and no longer significant [8].

Habitual snoring and sleep apnoea, both parts of a spectrum of sleep-related breathing disorders, are associated with abnormal fasting glucose and insulin resistance [5, 14]. However, there is an emerging body of literature showing that sleep itself, independent of snoring and sleep apnoea, is important in glucose and insulin regulation [9, 15]. Spiegel et al. [9] demonstrated that sleep restriction in healthy subjects causes higher fasting glucose levels and decreased insulin sensitivity. Until now, the mechanism behind the positive association between sleep restriction and fragmentation and type 2 diabetes is not entirely clear. There is evidence that sleep disorders are associated with an increase in sympathetic activity [16, 17]. Sympathetic hyperactivity can alter glucose homeostasis and induce insulin resistance by increasing glycogen breakdown and gluconeogenesis. Further predisposition toward the insulin-resistant state in persons with sleep disorders might occur through their effects on the adrenal axis with consequent elevations in serum cortisol [9, 18, 19]. Repetitive cycles of intermittent hypoxaemia that are followed by reoxygenation may also trigger the formation of reactive oxygen species [20] that can, in turn, elicit the release of inflammatory cytokines, such as TNFa and interleukin-6 (IL-6) [21]. Recent research has also demonstrated that sleep loss resulted in elevated high-sensitivity C-reactive protein concentrations, a stable marker of inflammation that has been shown to be associated with the syndrome of insulin resistance [22]. Thus, sleep disorders would seem to enhance inflammatory responses that could, in the long run, contribute to the development of type 2 diabetes mellitus [23].

One interpretation of the present findings is that the effects of sleep disturbance are partly explained by lifestyle factors. It is well known, that sleep apnoea and habitual snoring are closely linked to the cluster of cardiovascular risk factors known as "syndrome X" and the converse is also likely [24, 25]. Lifestyle factors like obesity, smoking, and physical inactivity are related to both cardiovascular disease risk and sleep-related disorders. Therefore, confounding by lifestyle factors was a major concern with regard to our analyses. Thus, we carried out a stepwise regression analysis for all covariates. Adjustment for a variety of confounders did not substantially change the observed significant association between difficulty maintaining sleep and type 2 diabetes mellitus. However, the associations observed in this study could be due to a confounding by unmeasured variables. Because the relationship remained significant even after adjustment for smoking, physical activity and the main confounding factor BMI, we assume that residual confounding is unlikely to explain the observed association.

The MONICA/KORA Augsburg Study has several limitations that need to be considered. One potential weakness of the study was the low number of incident cases of type 2 diabetes. Hence, stratified analyses could not be performed in the present investigation. Furthermore, it is likely that the group of non-diabetic persons may include subjects with undetected diabetes mellitus. This implies that the observed hazard ratios in the present study may underestimate the effect of sleep disturbance on total diabetes incidence. The possibility of reverse causation could not be ruled out either. Sleep disturbance may be an early symptom of diabetes, possibly predating its official diagnosis. For the present analysis we excluded persons with a follow-up time less

than 2 years to minimise such bias. A further limitation is that the questions used were not related to a defined time-frame. Because the questions about sleep were not repeated in the follow-up questionnaire, no information about the concordance with the baseline data was available. Furthermore, we did not measure habitual snoring or sleep apnoea. Therefore, we were not able to distinguish, whether the observed associations in the present study could be due to habitual snoring, sleep debt or both. Moreover, other reasons of waking up at night, for example, noisy neighborhoods, mood or social problems were not ascertained and could therefore have biased the present findings. In addition, the follow-up was not complete for all participants of the original study who were still alive in 1998, which might have introduced a selection bias. Since diabetic patients have an increased risk of dying of a cardiovascular disease [26, 27] they could also be lost by selective mortality during follow-up. Because the follow-up rate of our study was 68%, response bias cannot be excluded. The strengths of the MONICA/KORA Augsburg Cohort Study are primarily its prospective design, the representativeness of the cohort, based on a random sample of the general population and the availability of data on lifestyle and multiple cardiovascular risk factors. Furthermore, in contrast to most other prospective studies of this kind in which diagnosis of diabetes was based upon self-report, diabetes diagnosis in the present study was based on physician-validated diagnosis of type 2 diabetes.

In conclusion, the present study suggests that sleep disturbance, particularly difficulty maintaining sleep, is associated with an increased risk of type 2 diabetes in men and women from the general population. Disturbances of sleep have effects on endocrinology, immunology and metabolism, changes that may be linked to the development of type 2 diabetes. So far, the causal pathway is not entirely clear. It seems that both insulin resistance and chronic low-grade systemic inflammation may be involved. Further studies are needed to investigate the biological mechanisms underlying this association.

Acknowledgements The KORA research platform (KORA: Cooperative Research in the Region of Augsburg) and the MONICA Augsburg studies were initiated and financed by the GSF-National Research Center for Environment and Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. We thank all members of the GSF Institute of Epidemiology and the field staff in Augsburg who were involved in the planning and conduct of the study. Finally, we express our appreciation to all study participants.

References

1. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR (2002) Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 59:131–136
2. Ayas NT, White DP, Manson JE et al. (2003) A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 163:205–209
3. Resnick HE, Redline S, Shahar E et al. (2003) Diabetes and sleep disturbances. Diabetes Care 26:702–709
4. Jennum P, Schultz-Larsen K, Christensen N (1993) Snoring, sympathetic activity and cardiovascular risk factors in a 70-year-old population. Eur J Epidemiol 9:477–482
5. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J (1993) Snoring and sleep apnea in men, association with central obesity and hypertension. Int J Obes Relat Metab Disord 17:533–540
6. Al-Delaimy W, Manson JE, Willett WC, Stampfer MJ, Hu FB (2002) Snoring as a risk factor for type II diabetes mellitus: a prospective study. Am J Epidemiol 155:387–393
7. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G (2000) The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. J Intern Med 248:13–20
8. Ayas NT, White DP, Al-Delaimy WK et al. (2003) A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 26:380–384
9. Spiegel K, Leproult R, Van Cauter E (1999) Impact of sleep debt on metabolic and endocrine function. Lancet 354:1435–1439
10. Keil U, Liese AD, Hense HW, Filipiak B, Döring A, Stieber J, Löwel H (1998) Classical risk factors and their impact on incident non-fatal and fatal myocardial infarction and all-cause mortality in southern Germany. Results from the MONICA Augsburg Cohort Study 1984–1992. Eur Heart J 19:1197–1207
11. Tunstall-Pedoe H, WHO MONICA Project Principal Investigators (1988). The World Health Organization MONICA project (monitoring of trends and determinants in cardiovascular disease): a major international collaboration. J Clin Epidemiol 34:105–114
12. Meisinger C, Thorand B, Schneider A, Stieber J, Doering A, Loewel H (2002) Sex differences in risk factors for incident type 2 diabetes mellitus. The MONICA Augsburg Cohort Study. Arch Intern Med 162:82–89
13. Kawakami N, Takatsuka N, Shimizu H (2004) Sleep disturbance and onset of type 2 diabetes. Diabetes Care 27:282–283
14. Stoohs RA, Faccini F, Guilleminault C (1996) Insulin resistance and sleep disordered breathing in healthy humans. Am J Respir Crit Care Med 154:170–174
15. Punjabi NM, Sorkin JD, Katzel L, Goldberg A, Schwartz A, Smith PL (2002) Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 165:677–682
16. Akerstedt T, Nilsson PM (2003) Sleep as restitution: an introduction. J Intern Med 254:6–12
17. Fletcher EC (1997) Sympathetic activity and blood pressure in the sleep apnea syndrome. Respiration 64(1):22–28
18. Bratel T, Wennlund A, Carlstrom K (1999) Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea. Effects of continuous positive airway pressure treatment (CPAP). Respir Med 93:1–7
19. Scheen AJ, Van Cauter E (1998) The roles of time of day and sleep quality in modulating glucose regulation: clinical implications. Horm Res 49:191–201
20. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F (2000) Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. Am J Respir Crit Care Med 162:566–570
21. Vgontzas AN, Bixler EO, Chrousos GP (2003) Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. J Intern Med 254:32–44
22. Meier-Ewert HK, Ridker PM, Rifai N et al. (2004) Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol 43:678–683
23. Thorand B, Loewel H, Schneider A et al. (2003) C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men. Results from the MONICA Augsburg Cohort Study, 1984–1998. Arch Intern Med 163:93–99
24. Parish JM, Shepard JW Jr (1990) Cardiovascular effects of sleep disorders. Chest 97:1220–1226

25. Wilcox I, McNamara SG, Collins FL, Grunstein RR, Sullivan CE (1998) "Syndrome Z": the interaction of sleep apnoea, vascular risk factors and heart disease. Thorax 53[Suppl 3]: S25–S28
26. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, Nathan DM, Manson JE (2001) The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med 161:1717–1723
27. Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Eckfeldt JH (1997) A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes: the atherosclerosis risk in communities (ARIC) study. Diabetes Care 20:935–942