Incidence of Diabetes in Middle-Aged Men Is Related to Sleep Disturbances

PETER M. NILSSON, MD, PHD[1]
MATTIAS RÖÖST, MD[1]
GUNNAR ENGSTRÖM, MD, PHD[2]

BO HEDBLAD, MD, PHD[2]
GÖRAN BERGLUND, MD, PHD[1]

OBJECTIVE — Sleep deprivation in healthy men has been experimentally found to result in disturbances in glucose metabolism and in sympathovagal imbalance. The aim of the present study was to investigate whether sleep disturbances and elevated resting heart rate are associated with increased risk of developing diabetes.

RESEARCH DESIGN AND METHODS — A group of 6,599 initially healthy, nondiabetic men aged 44.5 ± 4.0 years took part in a prospective, population-based study in Malmö, Sweden. The incidence of diabetes during a mean follow-up of 14.8 ± 2.4 years was examined in relation to self-reported difficulties in falling asleep and resting heart rate at baseline. Diabetes was assessed at follow-up in all subjects by questionnaire and in a subgroup of 1,551 men by blood glucose measurement.

RESULTS — A total of 615 (9.3%) subjects reported either difficulties in falling asleep or regular use of hypnotics (seen as markers of sleep disturbances), and 158 (2.4%) subjects reported both of these. Altogether, 281 (4.3%) of the men developed diabetes during the follow-up period. Logistic regression models showed difficulties in falling asleep or regular use of hypnotics (odds ratio [OR] 1.52 [95% CI 1.05–2.20]) and resting heart rate (OR per 10 bpm 1.13 [0.99–1.30]) to be associated with development of diabetes when full adjustments were made for baseline age, biological risk factors, lifestyle, family history of diabetes, and social class.

CONCLUSIONS — The results suggest that sleep disturbances and, possibly, elevated resting heart rate, in middle-aged men, are associated with an increased risk of diabetes.

Diabetes Care **27:2464–2469, 2004**

S leep problems are common in the adult population according to several epidemiological studies (1), as the amounts of hypnotics prescribed reflect as well (2). Although long-term sleep loss is often secondary to somatic or psychiatric illness (3), it appears that insomnia may also play a more central role in the pathogenesis of somatic illness and metabolic dysregulation (4).

Divergent sleep duration, either excessively long or excessively short, has been shown (5), together with self-reported poor sleep quality (6), to be a predictor of overall mortality. Sleep disturbances are associated with increased levels of cardiovascular risk factors and coronary artery disease mortality (7,8). The sleep cycle is closely related to endocrine and metabolic functioning and to sympathovagal balance, with sleep deprivation having negative consequences for these systems. Sleep disturbances are associated with an increased concentration of cortisol and such indicators of increased sympathetic activity as elevations in pulse rate, body temperature, and epinephrine secretion (9,10). Experimentally, sleep deprivation has been shown to negatively affect glucose metabolism and to enhance variables associated with type 2 diabetes (11). An elevated heart rate is a risk marker for cardiovascular disease and may, like sleep problems, reflect increased psychosocial stress.

A clinical study has shown sleep disorders to be much more common in patients with diabetes than in control subjects (12). Studies of the obstructive sleep apnea (OSA) syndrome have indicated it to be associated with both insulin resistance and type 2 diabetes, with the causality being unclear, but it has been proposed that they are independently associated with it (13,14).

The aim of the present study was to investigate, in a large sample of middle-aged urban men taken from a prospective population-based study, to what extent sleep disturbances and increased resting heart rate, both of which are established cardiovascular risk markers, are also independently associated with the risk of diabetes.

RESEARCH DESIGN AND
METHODS — All subjects had participated originally in the Malmö Preventive Project (MPP) (15,16), which was carried out at the Department of Medicine of Malmö University Hospital. A total of 22,444 men born between 1921 and 1949 and recruited from 1974 to 1984 (age range when first tested 35–51 years), constituting 70–75% of the total male population in these birth cohorts within the city of Malmö (85% born in Sweden, 99% Caucasian), were included in that project. A follow-up of a subgroup of these men was conducted in 1994–1996 in another screening investigation called the Malmö Diet and Cancer (MDC) study (17). The mean time between initial testing and this follow-up was 15 years (range 7–22). The primary aim of the original project, the methodology and general results of which have been described earlier (15,16), had been to find high-risk individuals for preventive interventions directed at cardiovascular disease, diabetes,

and overconsumption of alcohol. The MDC project thereafter, encompassing 6,851 subjects from the MPP project, all with fasting glucose measurements, involved an individual health examination, use of a questionnaire, and screening for cardiovascular risk factors (17).

The present study concerned all of those in this latter group, except for 252 men who were excluded either because of having had diabetes at baseline, which was defined as blood glucose ≥6.1 mmol/l, or on the basis of their questionnaire results at follow-up (n = 44). The 6,599 men who remained and constituted the present study group had a mean age at baseline of 44.5 ± 4.0 years and were followed up after an average period of 14.8 ± 2.4 years (median 14.7 years).

Physical examination at baseline screening

During the baseline screening period for the MPP study of 1974–1984, participants were given a physical examination by a trained nurse, and their weight in light indoor clothing and height were measured, which allowed their BMI to be calculated. Blood pressure and heart rate were measured twice in the supine position after 10 min of rest, using a sphygmomanometer of modifiable cuff width and a chronometer, and the mean of the two measurements were recorded (7). At follow-up, BMI was determined again, and changes from baseline were described in terms of $\Delta -$ BMI.

Laboratory investigations at baseline screening

Blood was sampled at screening after an overnight fast; fasting blood glucose and plasma insulin were analyzed by the methods routinely used at the Department of Clinical Chemistry at Malmö University Hospital. Diabetes was diagnosed at baseline if there was a positive medical history of it and/or there was a single fasting whole-blood glucose value ≥6.1 mmol/l, which was in line with the 1998 World Health Organization definition (18). A 2-h oral glucose tolerance test (OGTT) (glucose load 30 g/m^2 body surface area) was performed on a random sample of 4,453 of the original subjects; the 224 men who later developed diabetes were among these. Information on OGTT and insulin levels at baseline was available for 2,096 of the men at screening; 101 of whom later developed diabe-

tes. The overall prevalence of diabetes in Sweden is 2–5% in the adult population, varying in different regions of the country.

Questionnaire results at baseline and at follow-up

A self-administered structured questionnaire was used at follow-up to assess smoking habits, physical activity, history of hypertension, sleeping problems, and use (yes/no) of medications (7,15).

Smoking was defined as self-reported daily smoking. Only 4.2% of the men reported regular use of smokeless tobacco.

A questionnaire used at baseline considered two categories of physical activity (sedentary or not). At follow-up, a questionnaire adapted from the Minnesota Leisure Physical Activity Questionnaire and used in Malmö previously (19) was used. It contained questions concerning 18 different physical activities that differed for the four seasons of the year. The overall leisure time physical activity score obtained was used as a continuous variable (19).

Social class was retrieved by data linkage with the Swedish Population Censuses conducted in 1980 and 1985. Manual and low-level nonmanual workers as well as early retirees were categorized as "low social class." Medium- and high-level nonmanual workers, self-employed individuals, and farmers (n = 19) were categorized as "high social class" (20).

Alcohol consumption was assessed at follow-up. A menu book was used to prospectively record the intake of alcoholic beverages during 7 consecutive days (21). Alcohol consumption (grams/week) was log transformed due to its skewed distribution.

Sleep disturbances were coded for answers to two questions concerning separate aspects of insomnia. The results were coded as either, both, or neither for *1*) "Do you have difficulties in falling asleep (yes/no)" and *2*) "Do you generally use sleeping pills more than three times a week (yes/no)."

Follow-up of diabetes prevalence at rescreening

At follow-up, diabetes was assessed in all subjects by questionnaire and in a subgroup of 1,551 subjects (22) by fasting blood glucose measurement. Diabetes was identified on the basis of whole blood

glucose ≥6.1 mmol/l, use of antidiabetes drugs, or self-report of diabetes provided in the follow-up questionnaire.

Statistical analysis

Statistical analysis made use of SPSS (version 8.0, 1997). ANOVA (with age-adjusted *P* values) was used for group comparisons involving numerical data, and Pearson's χ^2 was used for testing proportions. Logistic regression was used to estimate odds ratios (ORs, 95% CI) for sleep disturbances and risk of future diabetes. Adjustments in the statistical analyses were made for age (with use of logistic regression analysis), BMI at screening, change (Δ) in BMI until follow-up, fasting blood glucose at baseline, length of the period to the follow-up, physical activity at screening and at follow-up, smoking, alcohol habits, family history of diabetes, and social class at baseline. Prediction of diabetes involved use of sleep variables for 6,549 subjects and heart rate for 6,510 subjects in a multivariate analysis. *P* < 0.05 was considered significant. Data analyses based on register linkages between the MPP and MDC studies were approved by the Ethical Committee of the Medical Faculty of the University of Lund.

RESULTS

Baseline findings

At baseline, 615 (9.3%) subjects declared either having problems falling asleep or using hypnotics regularly, and 158 (2.4%) subjects reported both types of sleep disturbances. There were no statistically significant age-adjusted, between-group differences in mean BMI, fasting blood glucose, or resting heart rate, but significant differences in lifestyle variables (smoking, physical inactivity) and social class were obtained (Table 1).

Prevalence of diabetes at follow-up

At follow-up, 281 (4.3%) subjects had developed diabetes, 166 (2.5%) of these subjects provided self-reports of diabetes or use of antidiabetes medication. There was an overrepresentation of patients who had developed diabetes among those patients who had reported difficulties in falling asleep or regular use of hypnotics (15.3%) as compared with those to whom this did not apply (9.1%, P < 0.005) and also among those reporting both types of sleep-related problems (4.6%) as com-

Table 1—*Baseline and 15-year follow-up data on clinical characteristics of initially nondiabetic men and incidence of diabetes in relation to self-report of difficulty in falling asleep and regular use of hypnotics*

	Neither type of sleep disturbance	Difficulty falling asleep or regular use of hypnotics	Both types of sleep disturbance	Whole study sample
n	5,826	615	158	6,599
At baseline				
Age (years)	44.3 ± 4.1	46.2 ± 2.7§	46.3 ± 2.5§	44.5 ± 4.0
Systolic blood pressure (mmHg)	125.7 ± 13.7	126.6 ± 15.5	126.4 ± 14.4	125.8 ± 13.9
Diastolic blood pressure (mmHg)	85.0 ± 9.2	86.1 ± 10.0	86.4 ± 10.0	85.1 ± 9.3
Use of antihypertensive medication (%)	2.8	5.7‖	5.7	3.2
Heart rate (bpm)	69.3 ± 10.4	69.7 ± 10.5	69.5 ± 10.8	69.4 ± 10.4
Fasting whole blood glucose (mmol/l)	4.8 ± 0.5	4.7 ± 0.5	4.7 ± 0.5	4.8 ± 0.5
BMI (kg/m^2)	24.5 ± 3.0	24.6 ± 3.1	24.2 ± 3.1	24.5 ± 3.0
Current smoker (%)	40.5	53.2§	57.6§	42.1
Use of smokeless tobacco (%)*	2.5	3.4	5.1‖	2.7
Low physical activity (%)	48.2	61.5§	57.6¶	49.7
Social class				
Nonmanual worker (%)	44.1	36.9§	32.9‖	43.1
Manual worker (%)	52.4	56.4	53.2	52.8
Other classifications (%)	3.5	6.7§	13.9§	4.1
Diabetes heredity (%)†	11.9	12.7	14.6	12.0
Follow-up				
Follow-up time (years)	14.7 ± 2.4	15.2 ± 2.5	15.1 ± 2.5	14.8 ± 2.4
Change in BMI from baseline (kg/m^2)	1.78 ± 1.88	1.90 ± 2.14¶	2.01 ± 2.20¶	1.80 ± 1.91
Low physical activity (%)	25.0	25.4	25.9	25.1
Diabetes at follow-up (%)	3.9	7.0†	8.2¶	4.3
HbA$_{1c}$ (%)‡	4.87 ± 0.71	5.11 ± 0.93§	4.89 ± 0.44	4.89 ± 0.73

Data are means ± SD or proportions. *Based on 4,229 men; †a positive family history of diabetes in first-degree relatives; ‡based on 1,549 men, e.g., 1,362, 148, and 39 men in respective category; §*P* < 0.001; ‖*P* < 0.01; ¶*P* < 0.05; *P* values indicate significant age-adjusted (except for age) differences from the reference group, e.g., with neither type of sleep disturbance.

pared with those reporting neither type (2.3%, *P* < 0.034) (Table 2). Thus, sleep disturbances at baseline were associated with a higher prevalence of diabetes at follow-up.

There was an age-adjusted, statistically significant difference in resting heart rate at baseline between the men who later developed diabetes (heart rate 72.1 ± 11.4 bpm) and those who did not (heart rate 69.2 ± 10.3 bpm) (*P* < 0.001). Other variables showing a significant difference between groups with and without having developed diabetes were age, BMI at screening, BMI increase during follow-up time, fasting glucose, blood pressure, use of antihypertensive medication, family history of diabetes (heredity), current smoking, and social class (Table 2).

Independent predictors of diabetes at follow-up
A multivariate analysis of sleep disturbances and diabetes, involving full adjust-ments for age, BMI at screening, changes in BMI until follow-up, blood glucose at baseline, follow-up time, physical activity at both screening and follow-up, family history of diabetes, smoking, social class, and alcohol intake, likewise revealed a significant relationship between indica-tors of sleep disturbance and appearance of diabetes at follow-up. Difficulties in falling asleep or regular use of hypnotics showed an OR for future diabetes of 1.52 (95% CI 1.05–2.20), and the presence of both sleep disturbances showed an OR of 1.78 (0.96–3.32). Resting heart rate, ad-justed for confounding factors, provided a less-than-significant (*P* = 0.068) pre-diction of risk of future diabetes, with an OR of 1.13 (0.99–1.30) (Table 2).

Subgroup-analysis 1: group with fasting blood glucose at follow-up
In the 1,551-subject group for which blood glucose measurements were made, the differences between those with fasting blood glucose at follow-up and those without were small with respect to age (44.9 vs. 44.4 years), BMI (26.2 vs. 26.3 kg/m^2), and fasting blood glucose at base-line (4.8 vs. 4.8 mmol/l). The two groups were also similar in the proportions with and without self-reported diabetes at fol-low-up. In addition, the associations be-tween sleep disturbances and diabetes as revealed by blood glucose level were vir-tually the same in this group as in the larger group.

Difficulties in falling asleep showed an OR for developing diabetes of 1.67 (95% CI 1.001–2.79) (*P* < 0.05), and regular use of hypnotics showed an OR of 2.01 (1.01–3.99). The multivariate-adjusted relationships were largely the same for self-reported diabetes as for that shown by use of antidiabetes drugs, re-gardless of the blood glucose level (diffi-culties in falling asleep having an OR of 1.7 [1.1–2.6] and regular use of sleeping pills an OR of 1.7 [0.91–3.2]).

Table 2—*Baseline characteristics and predictors (OR with 95% CI) of the incidence of diabetes during a 15-year follow-up period*

Characteristic	Incident diabetes		Univariate age-adjusted P value	Multivariate logistic regression	
	No	Yes		OR (95% CI)	P
n	6,318	281	—	—	—
Sleep disturbances					
None (%)	88.7	80.1	<0.001	Reference	—
Difficulty falling asleep or regular use of hypnotics (%)	9.1	15.3	0.005	1.52 (1.05–2.20)	0.025
Both types of sleep disturbance (%)	2.3	4.6	0.034	1.78 (0.96–3.32)*	0.070
Age (years)	44.5 ± 4.1	45.9 ± 3.3	<0.001	1.11 (1.07–1.17)	<0.001
Systolic blood pressure (mmHg)	125.5 ± 13.7	131.8 ± 16.7	<0.001	1.06 (0.94–1.20)†	0.317
Diastolic blood pressure (mmHg)	84.9 ± 9.2	89.6 ± 10.8	<0.001	—	—
Use of antihypertensive medication (%)	2.9	8.2	<0.001	1.58 (0.95–2.61)	0.077
Fasting whole blood glucose (mmol/l)	4.8 ± 0.5	5.1 ± 0.5	<0.001	1.72 (1.49–1.99)†	<0.001
Heart rate (bpm)	69.2 ± 10.3	72.1 ± 11.4	<0.001	1.13 (0.99–1.30)‡	0.068
BMI (kg/m^2)	24.4 ± 3.0	26.9 ± 3.5	<0.001	1.21 (1.17–1.26)	<0.001
Change in BMI from baseline (kg/m^2)	1.82 ± 1.88	1.48 ± 2.60	0.015	0.99 (0.93–1.05)	0.986
Follow-up time (years)	15.2 ± 2.4	14.8 ± 2.4	0.561	1.03 (0.96–1.09)	0.433
Diabetes heredity (%)	11.5	23.5	<0.001	2.05 (1.50–2.80)	<0.001
Current smoker (%)	41.0	52.0	<0.001	1.87 (1.44–2.42)	<0.001
Use smokeless tobacco (%)	2.7	2.8	0.266	—	—
Low physical activity (%)	49.4	55.5	0.126	0.97 (0.75–1.25)	0.801
Social class					
Nonmanual worker (%)	43.6	32.7	<0.001	Reference	—
Manual worker (%)	52.6	58.4	0.054	1.37 (1.04–1.80)	0.025
Other classifications (%)	3.8	8.9	<0.001	2.63 (1.58–4.37)	<0.001

Data are means ± SD or proportions unless otherwise indicated. Results are from univariate and multivariate logistic regression analysis of predictors. Fasting blood glucose was log transformed in the multivariate analysis due to its skewed distribution. ORs are given for increase per unit. Diastolic blood pressure and use of smokeless tobacco were not included in the multivariate model. *P for trend 0.007; †OR for systolic blood pressure and log fasting blood glucose are given per SD increase, e.g., 13.7 mmHg and 0.107 mmol/l, respectively; ‡OR for heart rate is given per increase of 10 beats/min.

Subgroup-analysis 2: after exclusion of OGTT-defined diabetes at baseline

To exclude the possibility of a confounding effect based on preexisting glucose intolerance at baseline not being revealed by fasting blood glucose alone, a further subgroup analysis was made in which all subjects with a baseline 2-h blood glucose (post-OGTT) level ≥10 mmol/l were excluded. A total of 4,453 subjects were analyzed, including 224 with future diabetes. Both sleep variables provided significant predictions of diabetes when adjusted for potential confounders. Difficulties in falling asleep showed an OR of 1.62 (95% CI 1.11–2.38) and regular use of hypnotics an OR of 1.94 (1.18–3.19). Heart rate also provided significant predictions, showing an OR of 1.22 (1.06–1.41). To exclude the possibility that use of hypnotic drugs alone could explain the results, a subgroup analysis was made in which subjects (n = 158) with both difficulties in falling asleep and regular use of hypnotics were excluded. Here too, diffi-

culties in falling asleep could significantly predict the incidence of type 2 diabetes, showing an OR of 1.61 (1.07–2.42).

Subgroup-analysis 3: adjustment for baseline fasting insulin

A final analysis involved adjustment for the baseline fasting insulin level in the group with 2-h OGTT glucose value <10 mmol/l. The associations were statistically significant for both the sleep variables but not for heart rate. The men with difficulties in falling asleep showed an OR of 1.77 (1.00–3.12), those with regular use of hypnotics an OR of 2.37 (1.13–4.94), and those with an elevated heart rate OR of 1.17 (0.94–1.47).

CONCLUSIONS — This long-term study supports the hypothesis, based on earlier experimental research, that sleep problems are associated with alterations in metabolic variables, with glucose intolerance, and with type 2 diabetes (11,12,23). At the same time, our study expands the earlier findings by showing

that sleep disturbances are able to predict future diabetes in middle-aged men. Difficulties in falling asleep, regular use of hypnotics, and elevated resting heart rate at baseline were each found to be associated with future risk of diabetes. Because these variables remained statistically significant when adjusted for potential confounders (Table 2), with heart rate of borderline significance, they may represent separate pathways for neuroendocrine activation, as previously discussed in connection with the MPP project (7).

There are obvious limitations to our study. Our conclusions regarding sleep problems are based on self-reports for which we have no objective validation, such as by sleep laboratory recordings. Although diabetes was assessed at baseline on the basis not only of self-reports but also of fasting blood glucose levels and in most cases of OGTT as well, it was usually assessed at follow-up on the basis of self-reports. Nevertheless, the results at follow-up for the subgroup of 1,551 men for whom objective information on the

fasting blood glucose levels was available were similar. It could be asked whether reverse causation could explain the results through impaired glucose metabolism at baseline causing difficulties in falling asleep. However, because in the group with normal OGTT levels the results were similar after adjustments for insulin level had been made, reverse causation appears an unlikely explanation. Also, because at baseline we did not have OGTT results for all of the subjects, we may well have underestimated the true number of patients with diabetes on the basis of the 2-h glucose level criterion.

Although previous studies have shown there to be an association between OSA and changes in metabolism, such as insulin resistance and concomitant glucose intolerance (24,25), and we were unable to identify individuals with OSA, the possibility of such an association influencing the results cannot be excluded. However, it appears unlikely that individuals with OSA would report difficulties in falling asleep because, instead, their problem is that of disturbed sleep patterns.

Our study, like a similar but smaller study in Japan (26), concerns middle-aged men. Although the results obviously cannot be generalized to women, it was recently shown in a study of 70,026 female nurses, in which the methodology for classifying diabetes outcome was similar to ours, that both short and long sleep duration were able to predict diabetes (27). A sex-comparative study would be of considerable interest because it has been shown that a high percentage of women report sleep disturbances (28).

Because it is known that depression, both diagnosed and subclinical, is associated both with insomnia (29) and with the risk of diabetes (30), there may be certain difficulties in separating the effects of insomnia per se from those of mild undiagnosed depression.

An elevated heart rate is known to be a marker of sympathetic nervous activation (SNA) (31), which in turn has been shown to influence insulin resistance and, thus, abnormalities in metabolism (32). Insomnia has also been found to be associated with a decrease in heart rate variability, which is one aspect of sympathovagal imbalance (10), and, in addition, to be a marker of the normal aging process (33). Thus, the findings of an elevated heart rate at baseline in diabetes-prone subjects could be a marker for the dys-

regulation of SNA, which can contribute to the development of insulin resistance—a risk factor for diabetes.

Sleep deprivation has been found to be associated with an increased cortisol concentration (11) and to have a stimulatory effect on the hypothalamopituitary adrenal (HPA), axis (9). A hypothesis of the neuroendocrine mediation of stress in somatic disease through HPA stimulation, and SNA has been proposed to explain the morbidity associated with stress and depression (34). Sleep disturbances may not only be a marker of psychosocial stress but also represent a primary stressor. Sleep disturbances could influence these systems by hypothalamic activation, e.g., through HPA and SNA, possibly causing insulin resistance and increasing the risk of type 2 diabetes (7). Chronic low-grade inflammation, known to be associated with insomnia (35–37), risk of future diabetes (38–40), and cardiovascular morbidity (40,41), is another possible mediating mechanism. Inflammation has a clear role in the development of diabetes and cardiovascular disease (40), although its relation to insomnia has yet to be investigated.

Not everyone with sleep problems reports insomnia or seeks medical help (42). The increasing social and occupational pressures of modern society have resulted in a decrease in average sleeping time. In western cultures, it has come to be accepted that a large proportion of the population is sleep deprived (43). This can have detrimental effects on overall health (4) as well as on specific morbidity.

In summary, sleep disturbances and elevated resting heart rate in self-reported healthy middle-aged men were found to be predictive of diabetes at a 15-year follow-up. It appears that impaired sleep physiology can have serious long-term health effects and increase the risk of diabetes.

References
1. Janson C, Gislason T, De Backer W, Plaschke P, Bjornsson E, Hetta J, Kristbjarnason H, Vermeire P, Boman G: Prevalence of sleep disturbances among young adults in three European countries. *Sleep* 18:589–597, 1995
2. Silva JAC, Chase M, Sartorius N, Roth T: Special report from the symposium held by the World Health Organization and the World Federation on Sleep Research Societies: an overview of insomnia and related disorders—recognition, epidemiology and rational management. *Sleep* 19:412–416, 1996
3. Gislason T, Almqvist M: Somatic diseases and sleep complaints: an epidemiological study of 3,201 Swedish men. *Acta Med Scand* 221:475–481, 1987
4. Åkerstedt T, Nilsson PM: Sleep as restitution: an introduction. *J Intern Med* 254:6–12, 2003
5. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR: Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 59:131–136, 2002
6. Kojima M, Wakai K, Kawamura T, Tamakoshi A, Aoki R, Lin Y, Nakayama T, Horibe H, Aoki N, Ohno Y: Sleep patterns and total mortality: a 12-year follow-up study in Japan. *J Epidemiol* 10:87–93, 2000
7. Nilsson PM, Nilsson JA, Hedblad B, Berglund G: Sleep disturbance is associated with elevated pulse rate for prediction of mortality: consequences of mental strain? *J Intern Med* 250:521–529, 2001
8. Mallon L, Broman J-E, Hetta J: Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. *J Intern Med* 251:207–216, 2002
9. Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP: Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. *Clin Endocrinol* 51:205–215, 1999
10. Bonnet MH, Arand DL: Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med* 60:610–615, 1998
11. Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. *Lancet* 354:1435–1439, 1999
12. Stridhar GR, Madhu K: Prevalence of sleep disturbances in diabetes mellitus. *Diabetes Res Clin Pract* 23:183–186, 1994
13. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 85:1151–1158, 2000
14. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G: 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, 2000

15. Nilsson P, Berglund G: Prevention of cardiovascular disease and diabetes: lessons from the Malmö Preventive Project. *J Intern Med* 248:455–462, 2000

16. Berglund G, Nilsson P, Eriksson KF, Nilsson JA, Hedblad B, Kristenson H, Lindgarde F: Long-term outcome of the Malmö preventive project: mortality and cardiovascular morbidity. *J Intern Med* 247:19–29, 2000

17. Berglund G, Elmståhl S, Janzon L, Larsson SA: The Malmö Diet and Cancer study: design and feasibility. *J Intern Med* 233:45–51, 1993

18. Alberti KGMM, Zimmet P for the WHO Consultation Group: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. Diagnosis and classification of diabetes mellitus. *Diabet Med* 15:539–553, 1998

19. Mattisson I, Wirfält E, Gullberg B, Berglund G: Fat intake is more strongly associated with lifestyle factors than with socio-economic characteristics, regardless of energy adjustment approach. *Eur J Clin Nutr* 55:452–461, 2001

20. Hedblad B, Jonsson S, Nilsson P, Engström G, Berglund G, Janzon L: Obesity and myocardial infarction-vulnerability related to occupational level and marital status: a 23-year follow-up of an urban male Swedish population. *J Intern Med* 252:542–550, 2002

21. Wallström P, Wirfält E, Janzon L, Mattisson I, Elmståhl S, Johansson U, Berglund G: Fruit and vegetable consumption in relation to risk factors for cancer: a report from the Malmö Diet and Cancer Study. *Public Health Nutr* 3:263–271, 2000

22. Hedblad B, Nilsson P, Engström G, Janzon L, Berglund G: Insulin resistance and cardiovascular disease in the Malmö Diet and Cardiovascular Disease Study. *Diabet Med* 19:470–475, 2002

23. Scheen AJ, Byrne MM, Plat L, Leproult R, Van Cauter E: Relationships between sleep quality and glucose regulation in normal humans. *Am J Physiol* 271:261–270, 1996

24. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL: Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 165:677–682, 2002

25. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS: Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 165:670–676, 2002

26. Kawakami N, Takatsuka N, Shimizu H: Sleep disturbance and onset of type 2 diabetes (Letter). *Diabetes Care* 27:282–283, 2004

27. Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, Speizer FE, Patel S, Hu FB: A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 26:380–384, 2003

28. Owens JF, Matthews KA: Sleep disturbance in healthy middle-aged women. *Maturitas* 30:41–50, 1998

29. Ohayon MM, Caulet M, Lemoine P: Comorbidity of mental and insomnia disorders in the general population. *Compr Psychiatry* 39:185–197, 1998

30. Golden SH, Williams JE, Ford DE, Yeh HC, Paton Sanford C, Nieto FJ, Brancati FL: Depressive symptoms and the risk of type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 27:429–435, 2004

31. Grassi G, Vailati S, Bertinieri G, Seravalle G, Stella ML, Dell'Oro R, Mancia G: Heart rate as a marker of sympathetic activity. *J Hypertens* 16:1635–1639, 1998

32. Palatini P, Casiglia E, Pauletto P, Staessen J, Kaciroti N, Julius S: Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. *Hypertension* 30:1267–1273, 1997

33. May O, Arildsen H, Moller M: Parasympathetic function during deep breathing in the general population: relation to coronary risk factors and normal range. *J Intern Med* 245:287–294, 1999

34. Björntorp P, Holm G, Rosmond R: Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. *Diabet Med 1999*

16:373–383, 1999

35. Vgontzas AN, Zoumakis M, Papanicolaou DA, Bixler EO, Prolo P, Lin HM, Vela-Bueno A, Kales A, Chrousos GP: Chronic insomnia is associated with a shift in interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism* 51:887–892, 2002

36. Mullington JM, Hinze-Selch D, Pollmacher T: Mediators of inflammation and their interaction with sleep: relevance for chronic fatigue syndrome and related conditions. *Ann N Y Acad Sci* 933:201–210, 2001

37. Vgontzas AN, Chrousos GP: Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinol Metab Clin North Am* 31:15–36, 2002

38. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM: Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes* 51:1131–1137, 2002

39. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001

40. Engström G, Stavenow L, Hedblad B, Lind P, Eriksson K-F, Janzon L, Lindgarde F: Inflammation-sensitive plasma proteins, diabetes and mortality and incidence of myocardial infarction and stroke: a population-based study. *Diabetes* 52:442–447, 2003

41. Zebrack JS, Anderson JL: The role of inflammation and infection in the pathogenesis and evolution of coronary artery disease. *Curr Cardiol Rep* 4:278–288, 2002

42. Rosekind MR: The epidemiology and occurrence of insomnia. *J Clin Psychiatry* 53 (Suppl.):4–6, 1992

43. Bonnet MH, Arand DL: We are chronically sleep deprived. *Sleep* 18:908–911, 1995