Sleep Disturbances in Midlife Unrelated to 32-Year Diabetes Incidence

The prospective Population Study of Women in Gothenburg

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OBJECTIVE — To study the relation between diabetes incidence and sleep problems in a population-based sample of women followed for 32 years.

RESEARCH DESIGN AND METHODS — The researchers conducted a prospective population study initiated in 1968–1969, with follow-ups in 1974–1975, 1980–1981, 1992–1993, and 2000–2001 in Gothenburg, Sweden. A total of 1,462 women born in 1908, 1914, 1918, 1922, and 1930, representative of women of the same ages in the general population, initially participated (90% participation rate). Reported sleep duration, sleep problems, and use of sleeping medication were related to incident diabetes from 1968 to 2000. Associations between sleep problems and diabetes were corrected for waist-to-hip ratio (WHR), BMI, subscapular skinfold, fasting blood glucose and serum lipid concentrations, blood pressure, heart rate, smoking, physical activity, education, and socioeconomic status. Additionally, associations between BMI, WHR, and sleep problems were examined.

RESULTS — Over 32 years, 126 women (8.7%) developed diabetes. Associations between diabetes and initial sleep problems were tested in a Cox regression analysis, taking into consideration factors associated ($P < 0.1$) with diabetes. Sleep problems in 1968 did not increase risk of developing diabetes during the following 32 years. Obesity, particularly centralized, was associated with sleep problems.

CONCLUSIONS — No association between sleep problems and developing diabetes was seen in this 32-year follow-up of middle-aged women. Obesity, on the other hand, known to cause increased risk of diabetes, was associated with current sleep problems.

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Insomnia is becoming increasingly common (1). Stressful life events, mediated by personal vulnerability, have been found to be closely related to the onset of chronic insomnia (1,2). The current prevalence of insomnia varies in different population studies and depends on the definition used. When asked about insomnia problems, 26% of American older adults (1) and 38% of adults in Finland (3) reported insomnia. On the other hand, using the Diagnostic and Statistical Manual of Mental Disporders, Fourth Edition insomnia diagnosis yielded a prevalence rate of 12% in both Norway and Finland (3,4). The predisposition to insomnia increases with age (5–7) and somatic health status, although women show a more inconsistent relationship (4,6). Sleeping difficulty including insomnia is a common complaint among older women and is associated with use of sleeping medications (4,6–8).

The question of whether insomnia and other sleep problems can specifically contribute to type 2 diabetes has been much debated in recent years, as diabetes becomes an urgent worldwide public health concern. Insulin resistance may be induced via psychoneuroendocrine mechanisms and by disruption of the hypothalamic-pituitary-adrenal (HPA) axis (9). The HPA axis is a major component of the stress system, and dysfunction of the HPA axis leads to elevated levels of circulating cortisol. Further hypercortisolemia results in metabolic abnormalities, including lipid and glucose metabolism (10).

Research highlighting the relation between sleep quality and its input on the HPA axis is still very limited. Two recent studies (11,12) found that sleep deprivation and insomnia has stimulatory effects on the HPA axis. However, these findings were observed in young healthy volunteers and in sleep laboratories. In 1999, Spiegel, Leproult, and Van Cauter (13) demonstrated increased insulin resistance in sleep-deprived men. Sleeping <6 h (reported by a self-administrated questionnaire) was a significant risk factor for insulin resistance, whereas both sleeping <6 h and sleeplessness beyond midnight were significantly associated with obesity. A recent review (14) concerning sleep and the endocrine system suggests that good sleep should be an essential aim of diabetes management, based on a finding of significant relation between HbA_{1c} and poor sleep quality. In a study (15) of men and women aged 53–93 years with a high prevalence of diabetes (21%) and impaired glucose tolerance (28%), both short (<6 h per night) and long (≥9 h) sleep duration was associated with diabetes and impaired glucose tolerance. Results from the Nurses Health Study suggested that the association between a reduced self-reported sleep duration and incident diagnosis of diabetes could be due to confounding by BMI, or sleep re-

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Abbreviations: HPA, hypothalamic-pituitary-adrenal; OSA, obstructive sleep apnea; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Year of birth, age at the different examinations, and number of women who participated in the Population Study of Women in Gothenburg and participation frequency and diabetes 32-year incidence in the different age cohorts*

Year of birth	Participants (1968–1969)		Participants (1974–1975)		Participants (1980–1981)		Number of women contracting diabetes (1968–1980)	Participants (1992–1993)		Number of women contracting diabetes (1981–1992)	Participants (2000–2001)		Number of women contracting diabetes (1993–2000)	Diabetes incidence (1968–2001)
	Age	*n* (%)*	Age	*n* (%)†	Age	*n* (%)†	*n*	Age	*n* (%)†	*n*	Age	*n* (%)†	*n*	*n* (%)
1930	38	372 (90)	44	336 (90)	50	308 (83)	4	62	249 (67)	7	70	231 (73)	18	29 (7.8)
1922	46	431 (90)	52	387 (90)	58	332 (77)	10	70	270 (63)	11	78	201 (64)	25	46 (10.7)
1918	50	398 (91)	56	351 (89)	62	325 (82)	10	74	213 (54)	15	82	176 (73)	7	32 (8.2)
1914	54	180 (89)	60	163 (90)	66	140 (78)	7	78	79 (44)	4	86	45 (63)	3	14 (7.9)
1908	60	81 (84)	66	65 (82)	72	49 (61)	3	84	19 (23)	2	92	8 (50)	0	5 (6.5)
Total		1,462 (90)		1,302 (89)		1,054 (72)	34		830 (70.2)	39		661 (71)	53	126 (8.7)

*Percent of women originally sampled. †Percent of women who participated in 1968–1969 and were alive in the year of the examination.

striction could mediate its effect on diabetes through weight gain (16).

People with sleep-disordered breathing are often obese, as are those with type 2 diabetes, and it has been speculated that when sleep-disordered breathing and diabetes coexist, diabetes was caused by obesity (17,18). Impaired glucose tolerance has been reported in a number of studies in patients with obstructive sleep apnea (OSA), which affects 10% of middle-aged men and 5% of middle-aged women (19).

In 2000, Vgontzas et al. (20) investigated premenopausal women with polycystic ovarian syndrome, which is often linked to obesity and insulin resistance. It was reported that women with polycystic ovarian syndrome were 30 times more likely to experience sleep-disordered breathing than age- and weight-matched control subjects. The difference between fasting insulin levels in the OSA versus non-OSA subjects remained significant even after controlling for BMI. This supported the hypothesis that obesity was not the only culprit in the development of insulin resistance in these young women (18).

Heavy snoring is the major manifestation of OSA, is associated with sleep disturbances, and is also found to be a predictor of OSA. In a U.S. female population, occasional and regular snoring was associated with increased risk of developing diabetes, even after adjustment for BMI and waist-to-hip ratio (WHR) (21).

In Gothenburg, Sweden, a prospective population study has been going on since 1968, following women initially aged 38, 46, 50, 54, and 60 for >32 years. During this time, four follow-up examinations have been carried out, during which information on sleep problems, sleep duration, sleep medication use, and diabetes incidence have been recorded. This information together with data from medical examinations make it possible to investigate whether sleep problems increase the long-term risk of developing diabetes. The purpose of this report was to examine the relation between diabetes 32-year incidence and existence of sleep problems, sleep medication, and sleep duration recorded in this population-based sample of women, with special attention to the possible role of obesity.

RESEARCH DESIGN AND METHODS

— Gothenburg is the second largest city in Sweden, with ~430,000 inhabitants at the time of the first examination in 1968–1969. In 1968–1969, a representative sample of 1,622 women living in Gothenburg were invited to a free health examination. A total of 1,462 women (90.1%), aged 38, 46, 50, 54, and 60 years, accepted the invitation and participated in the prospective Population Study of Women in Gothenburg (22). The sample was obtained from the Revenue Office Register based on date of birth. All women born on day 6, 12, 18, 24, and 30 of each month were invited. Therefore, the participants, described in Table 1, were recruited in such a way that they constituted a representative cross-section of women in the community in the age-groups studied. Recent analysis of survival rates among participants versus nonsampled women born the same years revealed no major differences, providing additional evidence that participants were representative of the general population from which they were selected (23). The survey was performed during a 12-month period, examining those born in the beginning of the year first, thus reducing the influence of age differences within each age-group as much as possible.

All women examined in 1968–1969 were offered a second examination in 1974–1975 (24), a third in 1980–1981 (25), and a fourth in 1992–1993 (22). Of the women originally examined and who were still alive, 70.2% participated in this 24-year follow-up. Most recently in 2000–2001, all women who participated in the 1968–1969 examination and who were still alive according to the Revenue Register Office were invited to a fifth examination (26). During the examinations, it appeared that many women, especially those belonging to the oldest cohorts (92 and 86 years), did not participate due to physical impairment, although they were offered taxi transportation. An extension of the examination was then initiated, in which the nonparticipants were offered a home visit with a reduced examination protocol performed by one or two nurses. Age-specific participation in the five examinations is further described in Table 1.

Clinical examination

The following independent variables included in this analysis were measured at the baseline examination in 1968–1969.

Leisure time exercise. Women were classified as being physically active during leisure time if they reported usually spending >4 h per week gardening, running, dancing, or playing golf, tennis, or similar activities (physician interview).

Table 2—Participants who reported sleep complaints, sleep medication use, and <6 h sleep per 24 h and women included in the composite variable sleep problems as well as mean values of baseline variables in the 1968–1969 examination of the Population Study of Women in Gothenburg

	No sleep problems	Sleep complaints	Sleep medication	Sleep <6 h	Composite variable: sleep problems	All
n	1,077 (74)	289 (20)	165 (11)	99 (7)	370 (26)	1,447
Age (in 1968)	46.4 ± 6.1	47.9 ± 6.0	48.4 ± 6.0	48.0 ± 6.0	48.0 ± 6.0*	46.8 ± 6.2
BMI	24.2 ± 3.8	23.8 ± 3.8	23.5 ± 4.0	24.4 ± 4.0	23.8 ± 4.0	24.1 ± 3.8
WHR	0.74 ± 0.1	0.75 ± 0.1	0.74 ± 0.1	0.76 ± 0.1	0.75 ± 0.1†	0.75 ± 0.1
Systolic blood pressure	134 ± 21	132 ± 22	129 ± 22	130 ± 20	131 ± 22	133 ± 22
Blood glucose	4.1 ± 0.7	4.0 ± 0.6	4.0 ± 0.6	4.0 ± 0.7	4.0 ± 0.6†	4.1 ± 0.7
Serum cholesterol	6.8 ± 1.2	6.9 ± 1.2	7.1 ± 1.3	7.1 ± 1.2	7.0 ± 1.2†	6.9 ± 1.2
Serum triglycerides	1.2 ± 0.6	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.7†	1.2 ± 0.6
Smoking	47	55	53	57	55†	49
Low social group	34	40	29	43	35	34
Low physical activity	17	19	24	27	19	17

Data are means ± SD, *n* (%), or percent. *P for age trend <0.001; no sleep problems vs. sleep problems. †P for age trend <0.05; no sleep problems vs. sleep problems.

Socioeconomic group. The women reported their own occupation and, if they were married, their husbands' occupation. This information was transformed into three sociooccupational levels: large-scale employers and officials of high or intermediate rank were identified as belonging to the "high social group," small-scale employers, officials of lower rank, and foremen as belonging to the "middle social group," and skilled and unskilled workers were identified as belonging to the "low social group" (questionnaire filled out at home) (27).

Smoking habits. Smokers were identified as those women who reported currently smoking one or more cigarettes per day (physician interview).

Anthropometric measurements. Body height, body weight, and waist and hip circumferences were measured with the subjects wearing only briefs. BMI was calculated as body weight in kilograms divided by the square of the height in meters. WHR was calculated by dividing waist circumference by hip circumference. Subscapular skinfold was measured to the nearest 0.1 mm on the right side of the subject over the subscapular area.

Blood pressure. Systolic and diastolic blood pressure measurements were performed after 5 min rest in the sitting position.

Heart rate. Heart rate measurement was performed after 5 min rest in the sitting position.

Blood sampling. Blood samples were drawn in the fasting state for determination of concentrations of blood (or, in 2000–2001, plasma) glucose, serum triglycerides, and serum total cholesterol concentrations. Blood and plasma glucose values were standardized so that values were comparable over the years.

Information about sleep problems. Information about sleep and sleep problems was obtained by means of standardized interviews at all examinations. In 1968–1969, 1974–1975, and 1980–1981, "sleep complaints" were defined as having reported sleep problems (without specified time frame) and/or having consulted a doctor for sleep problems and/or hospital admission for this reason. In connection with questions concerning medication, the women were also asked if they had used sleeping pills (never, sometime[s] per month, sometime[s] per week, almost daily, or daily). Information on duration of sleep was obtained by the question, "How many hours do you sleep during one 24-h period? " This definition implicitly includes napping. A composite variable indicating sleep problems was constructed out of the three formerly mentioned variables consisting of *1*) sleep complaints according to the above definition and/or *2*) use of sleeping pills and/or *3*) sleep <6 h during 24 h. Only baseline sleep data were used in the analyses of associations between 32-year diabetes incidence and sleep.

Definition of diabetes. A subject was defined as having diabetes if the diagnosis had been made by a doctor or if the subject was on antidiabetes therapy (insulin and/or tablets) or if two fasting blood samples showed glucose concentrations according to the current World Health Organization definition of diabetes, i.e., in 2000–2001, plasma glucose concentration of ≥7.0 mmol/l or more. Further, diabetes was accepted as a diagnosis if it was written on the death certificate.

Statistical methods

The κ test was used when assessing intra-individual agreement for sleep problems in the different examinations. The Pearson correlation test was used to test correlations between sleep and other baseline variables. Cox regression analysis was used when testing univariate and multivariate associations between different sleep variables and 32-year diabetes incidence. Results from the Cox regressions are presented with hazards ratios (relative risks), *P* values, and 95% CIs. Based on the assumption of a 3-to-1 unexposed-to-exposed ratio and 9% diabetes incidence, this study had 80% power to detect a relative risk increase of 1.6 ($\alpha = 0.05$). SAS System was used in the statistical analysis. The study was approved by the ethics committee of Göteborg University.

RESULTS

Baseline sleep variables

Sleep complaints increased across the age-groups, from 16% in the 38-year-old to 30% in the 60-year-old women. Use of sleep medication also increased with age from 8% in 38-year-old to 20% in 54-year-old women and 17% in 60-year-old women. The percentages of women who slept <6 h did not vary by age. The composite variable describing any sleep problems increased from 19% in 38-year-old women to ~35% in 54- and 60-year-old women. There was a significant agreement between indications of subjective

Table 3—*Cox regression analysis of associations between incidence of diabetes during 32 years (dependent variable) and composite variable sleep problems, as well as sleep complaints, sleep medication, and hours slept per 24 h when controlling for age as well as including different variables indicating obesity in the model*

	Relative risk (95% CI)	Likelihood ratio χ^2	df
Composite variable sleep problems			
Plus age	1.22 (0.82–1.08)	7	2
Plus age and BMI	1.4 (0.95–2.1)	113	3
Plus age and WHR	1.1 (0.73–1.64)	90	3
Plus age and subscapular skinfold	1.24 (0.84–1.84)	118	3
Sleep complaints			
Plus age	1.03 (0.91–1.17)	6	2
Plus age and BMI	1.06 (0.94–1.2)	111	3
Plus age and WHR	0.99 (0.88–1.13)	90	3
Plus age and subscapular skinfold	1.04 (0.91–1.18)	118	3
Sleep medication			
Plus age	1.16 (0.89-1.53)	8	2
Plus age and BMI	1.25 (0.96–1.62)	113	3
Plus age and WHR	1.21 (0.93–1.57)	91	3
Plus age and subscapular skinfold	1.31 (0.99–1.73)	120	3
Hours slept per 24 h			
Plus age	0.95 (0.81-1.12)	6	2
Plus age and BMI	0.97 (0.83–1.14)	111	3
Plus age and WHR	1.01 (0.86–1.18)	90	3
Plus age and subscapular skinfold	0.98 (0.83–1.15)	118	3
Multivariate extended			
Composite variable sleep problems plus age plus BMI plus WHR plus triglycerides plus B-glucose plus systolic blood pressure plus education plus socioeconomic group plus subscapular skinfold plus exercise	1.35 (0.89–2.1)	160	10

The variables are presented first once at a time controlled for age then in the extended multivariate analysis with all significant variables included. df, degrees of freedom.

sleep complaints, sleep duration, and sleep medication in the 1968–1969 examination and in the following examinations (κ for sleep complaints 1968 until 2001: 0.18, sleep medication: 0.21, and sleep duration: 0.11). Intercorrelations between the three sleep variables were high (all $P < 0.001$) in both 1968–1969 and 1980–1981 examinations. Table 2 presents descriptive data for the different groups.

Prevalence and incidence of diabetes

Eleven women (0.8% of the total number studied) had manifest diabetes at the first examination in 1968–1969 and were thus excluded from the statistical analyses. Among 1,451 women initially free from diabetes, 126 (8.7%) developed diabetes during the 32-year follow-up period (Table 1). In four women, diabetes diagnoses could not be confirmed, and these women were excluded from all analyses. Of 126 incident cases, 49 (39%) were smokers in 1968–1969.

Baseline sleep variables in relation to diabetes incidence

There was no significant association between hours of sleep and 32-year incidence of diabetes in 1968–1969 when using hours slept per 24 h as a continuous variable (correlation coefficient [CC] −0.018, $P < 0.5$), when using quintiles (2–4, 4.5–6, 6.5–8, 8.5–10, or 10.5–15 h) (CC −0.02, $P < 0.54$), or when using a high versus low outpoint of hours (CC −0.02, $P < 0.48$). Furthermore, there was no significant association between other individual variables (sleep complaints, sleep medication) or the composite variable sleep problems and 32-year diabetes incidence (Table 3). In all analyses, age was taken into account.

Further multivariate analyses

Other variables showing significant or close to significant association ($P < 0.1$) with 32-year incidence of diabetes in this sample (BMI, WHR, subscapular skinfold, systolic blood pressure, blood glucose, serum triglycerides, exercise, and socioeconomic group) or in other studies shown to be associated with diabetes (serum cholesterol, heart rate, education, and smoking) were included in multivariate models (Table 3). There were no significant associations between sleep problems and 32-year incidence of diabetes when controlling for these variables one at a time or simultaneously in a fully adjusted model (Table 3).

Associations between sleep problems and obesity

Cross-sectional associations between sleep problems (sleep complaints, sleep medication, and hours slept per 24 h) on one hand and BMI and WHR on the other were tested in correlation analyses. There was a significant positive correlation between WHR and sleep problems (CC 0.08, $P = 0.002$), sleep complaints (CC 0.07, $P = 0.01$), and a significant negative correlation between BMI and WHR and hours slept per night (CC −0.06, $P = 0.03$ and CC −0.08, $P = 0.004$, respectively) (Fig. 1).

Finally, we also tested the reverse hypothesis that sleep problems may induce subsequent weight gain by comparing weight gain during the different periods (1968–1974, 1968–1980, 1968–1992, and 1968–2001) in the group of women who reported sleep problems with the group of women who did not report sleep problems in 1968–1969. There was no significant difference between weight gain during any of these periods between women with and without sleep problems (figures not shown).

CONCLUSIONS— In this population-based sample, 1,462 women aged 38–60 years in 1968–1969 were followed until 2000–2001 for 32-years; 8.7% of whom developed diabetes. Diabetes incidence was examined in relation to sleep problems defined as subjective sleep complaints reported by participant and/or sleep medication and/or <6 h sleep per 24 h. Possible confounding factors such as age, obesity, abdominal obesity, subscapular skinfold thickness, serum lipid values, blood pressure, resting heart rate, physical activity, education, and socioeconomic status were

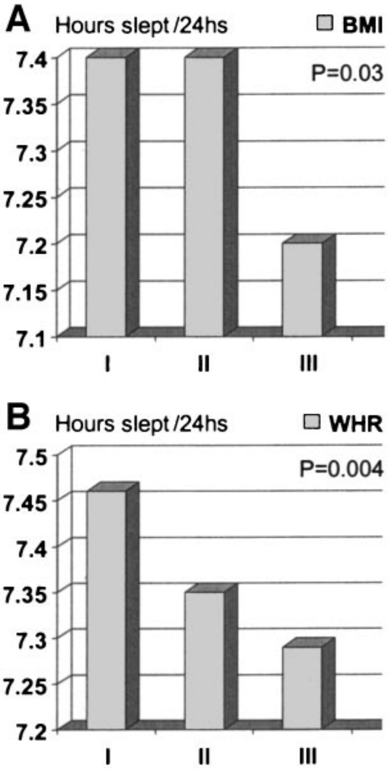

Figure 1—*Mean hours of sleep per 24 h in different (age-standardized) tertiles of BMI and WHR in the Population Study of Women in Gothenburg. I, first tertile; II, second tertile; III, third tertile.*

included when studying possible associations between sleep problems and 32-year diabetes incidence. No significant associations or trends were observed using any of the available sleep indicators.

The strength of this study is the longitudinal design, the high participation rates, the thorough investigation of diabetes end points, and standardized questions concerning sleep and sleep problems across the study period. However, a limitation of the study is the relatively low number of participants, which was compensated for by the long follow-up time of 32 years. Major sleep disturbances indicated by the composite variable sleep problems were reported by 16–30% of the study population depending on age. Sleep problems reported on only one occasion were used in the prediction of diabetes incidence, but there was a significant concordance in reporting having sleep problems between the subsequent examinations. Finally, it must be noted that diagnosis of diabetes has slightly changed during the 32 years of follow-up. It was not possible to use exactly the same criteria over time, as some of the diagnoses were made by the patients' own doctors between the examinations. However, all laboratory-based cut points have been standardized across examinations.

In many previous studies (9,13,18, 20,21) concerning diabetes incidence and sleep problems, indirect end points such as abnormal glucose and lipid metabolism (metabolic syndrome, insulin resistance, and glucose intolerance) have been used. In contrast, our study used the end point diabetes, and no association between sleep problems and subsequent development of diabetes could be shown. Given that obesity was significantly associated with both sleep problems and diabetes, obesity would have been expected to be an important confounding factor in our study for the association between sleep problems and diabetes. However, we detected no association between sleep problems and diabetes with or without adjustment for obesity-related variables. When analyzing correlations between sleep problems and BMI and WHR in our study, there was a significant association between abdominal obesity and sleep problems and subjective sleep complaints, as well as abdominal and general obesity on one hand and low number of hours slept per 24 h. But the recently reported observation (28) that short sleep duration induces weight gain and obesity, and thus could constitute a mediating factor between sleep and diabetes, could not be confirmed. No difference in weight gain could be observed between women with sleep <6 h per 24 h or sleep problems and women not reporting short sleep duration or sleep problems during any of the 6-, 12-, 24-, or 32-year observation periods.

It should be underscored that the results of our study apply to a female population aged 38–60 years and followed-up for 32 years. In a recent population-based study (29) concerning incidence of diabetes in middle-aged men, a significant association between sleep disturbances (self-reported difficulties in falling asleep and/or use of hypnotics) and development of diabetes over 15 years was demonstrated. To our knowledge there are no population-based studies in women showing such an association, which could indicate an interesting sex difference.

In this longitudinal study of middle-aged women who were followed for many years, no association between sleep problems and developing diabetes was observed. Obesity and central obesity, on the other hand, known to cause increased risk of diabetes, showed associations with sleep problems.

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