Sleep duration is associated with an increased risk for the prevalence of type 2 diabetes in middle-aged women – The FIN-D2D survey

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Abstract

Objective: To examine the association between sleep duration with type 2 diabetes and abnormal glucose tolerance among middle-aged men and women in Finland.

Methods: The FIN-D2D survey is a population-based cross-sectional multicentre study in Finland, with 1336 men and 1434 women aged 45–74 participating in the survey during 2004 and 2005. A health examination including an oral glucose tolerance test and sleep questionnaire was performed for all participants.

Results: There was an independent association between abnormal sleeping times and type 2 diabetes in middle-aged women. Even after adjustments for age, body mass index, sleep apnea probability, smoking, physical activity, and central nervous system-affecting medication, sleep duration of 6 h or less or 8 h or longer was independently associated with type 2 diabetes. There was no increase in the prevalence of diabetes in middle-aged men with abnormal sleeping times.

Conclusion: Short (≤6 h) or long (≥8 h) sleep duration is related to an increased risk of type 2 diabetes in middle-aged women but not in men.

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Keywords: Sleep; Time; Association; Type 2 diabetes; Sexes

1. Introduction

Sleep disturbances have become increasingly prevalent in the modern society, affecting millions of people. The median sleep time has decreased to 7 h per night,
and more than one out of three adults sleep even less [1,2]. Abnormal sleeping patterns have been found to have harmful effects on metabolic and endocrine function, causing a negative impact on public health in that they increase both mortality and morbidity [1,3–6]. Women are known to suffer a high prevalence of sleep disturbances [7], though most studies on sleep disturbances have been conducted in men [8]. Since the incidence of type 2 diabetes is also increasing, there is a definite need to study the association between sleep disturbances and diabetes in both sexes [9]. The objective of the present study was to examine the association between sleep duration with type 2 diabetes as well as with abnormal glucose tolerance in middle-aged men and women in a large population-based survey.

2. Patients and methods

The Finnish type 2 diabetes (FIN-D2D) survey is a population-based cross-sectional survey carried out in three hospital districts of South Ostrobothnia, Central Finland and Pirkkala during October 2004 and January 2005 to evaluate the FIN-D2D Project, a community-based type 2 diabetes prevention program [10]. A random sample of 4500 subjects aged 45–74 years, stratified according to sex, 10-year age groups (45–54, 55–64, and 65–74 years) and three geographical areas, was selected from the National Population Register in September 2004. The study protocol was approved by the research ethics committee of the Hospital District of Helsinki and Uusimaa. All of the participants provided their written informed consent prior to participation in the study.

Subjects were invited by mail to a clinical examination. Together with the invitation, they also received a self-administered questionnaire on socioeconomic background, medical history, and health behavior. The questionnaire included details about sleep habits and other important covariate data related to sleep disturbances and diabetes, including age, gender, smoking, and use of central nervous system (CNS)-affecting medications, such as sedative and antidepressant drugs. Subjects were asked to complete the questionnaire at home, and bring it with them to the health examination, which was carried out according to the multinational monitoring of trends and determinants in cardiovascular disease (MONICA) protocol [11]. At the study site, trained nurses measured height, weight and waist circumference.

The health examination included an oral glucose tolerance test (OGTT), which was carried out according to the World Health Organization (WHO) recommendations [12]. The 300 ml test solution contained 75 g anhydrous glucose and 1.6 g citric acid. The test started after a 12-h fast, and a 2-h blood sample was obtained 120 min after the ingestion of the solution. Fasting and 2-h samples for the plasma glucose determination were drawn into fluoridated tubes and centrifuged within 30 min. Plasma glucose was determined with the hexokinase method (Thermo Electron Corporation, Vantaa, Finland). All assays were performed in the Laboratory of Analytical Biochemistry of the National Public Health Institute, Helsinki.

3. Definitions

The glucose tolerance status was classified according to the WHO 1999 criteria [12]. Individuals who already had diagnosed diabetes were not included in the OGTT and were classified as known diabetics (T2D). Individuals who had not been diagnosed as diabetics, but who had a fasting plasma glucose level $\geq 7.0$ mmol/l or 2 h plasma glucose $\geq 11.1$ were classified as having screen-detected type 2 diabetes (ST2D). The known diabetics and the screen-detected diabetics were combined to create a group defined as total type 2 diabetes (TT2D). Those with 2 h plasma glucose $\geq 7.8$ and $<11.1$, and fasting plasma glucose $<7.0$ were classified as having impaired glucose tolerance (IGT). Subjects with T2D, ST2D, IGT or impaired fasting glucose (IFG, those with fasting plasma glucose $\geq 6.1$ and $<7.0$, and 2 h plasma glucose $<7.8$) were classified as having abnormal glucose tolerance (AGT).

Body mass index (BMI) was calculated as weight (kg) divided by height$^2$ (m$^2$), and overweight and obesity were defined as BMI 25–29 kg/m$^2$ and 30 kg/m$^2$ or above, respectively. Central obesity was defined according to the WHO criteria [13]: waist circumference $\geq 102$ cm in men, and $\geq 88$ cm in women.

Physical activity was assessed by self-administered questionnaire. Individuals who reported leisure-time physical activity (e.g., walking, bicycling) of more than 4 h during a week were classified as physically active.

The overall participation rates are given in Table 1.

In addition to non-participants, subjects who were non-fasting at the time of blood sample ($N = 12$), subjects for whom the time of OGTT deviated by more than 15 min from the 2-h limit ($N = 15$), and subjects who vomited during OGTT ($N = 3$) or had other technical problems with OGTT ($N = 41$) were excluded from the

| Table 1 Demographics of the study participants in the FIN-D2D survey |
|---------------------|-----|-----|
|                      | Men | Women |
| Study sample, N      | 2250 | 2250 |
| Survey respondents, N| 1336 (59.5%) | 1434 (63.7%) |
| Mean age in years (SD)| 60.3 (8.3) | 59.8 (8.5) |
| Mean weight in kg (SD) | 85.4 (14.5) | 72.9 (14.0) |
| Mean BMI in kg/m$^2$ | 27.7 (5.2) | 27.7 (5.2) |
| Mean waist circumference in cm (SD) | 99.3 (11.8) | 89.8 (13.4) |

N, number of cases.
OGTT, oral glucose tolerance test.
BMI, body mass index.
SD, standard deviation.
analyses. In all, a total of 1336 men and 1434 women were included in these analyses.

4. Sleep questionnaire

The sleep questionnaire consisted of questions concerning details about the sleep habits of the study patients. Individuals were asked about the average length of their sleep in whole hours at night. Sleep duration was categorized in three groups: 6 h or less, 7, and 8 h or more. The other four questions used were recorded using a five-point scale (0 = “never”, 1 = “sometimes”, 2 = “often”, 3 = “very often”): (a) “How often do you wake up during the night?”; (b) “Do you feel excessively sleepy during the daytime?”, (c) “Do you snore loudly?”, and (d) “Do you fall asleep involuntarily during the daytime?” Based on our earlier studies with similar questions, the sum of these four questions was calculated to form a sleep apnea probability (0–5 points was classified as “unlikely to suffer sleep apnea”, 6–7 points was classified as “low probability for sleep apnea”, 8–9 points was classified as “moderate probability for sleep apnea”, and 10–16 points as “high probability for sleep apnea”) [14]. Sleep apnea probability was used as an adjustment covariate in the present study.

5. Statistical methods

The association between disturbances in glucose metabolism and sleep habits was tested with the likelihood-ratio test using logistic regression models. Analyses were done separately for both sexes, and adjusted for age of the participants. In addition, adjustments for possible confounding variables were performed by including BMI, use of sedative or antidepressant medication, high sleep apnea probability, smoking and physical activity in the logistic regression models. Analyses were performed using the statistics package Stata (StataCorp. 2005. Stata Statistical Software: Release 9.0. College Station, TX: StataCorp LP).

6. Results

The mean self-reported sleeping time was 7.3 h (standard deviation (SD) 1.1) in both men and women. In women, a significant U-shaped association was observed between sleep duration and the prevalence of diabetes. Compared to those women who slept for 7 h, subjects with both shorter (<6 h), and longer duration of sleep (>8 h) exhibited an increased prevalence of diabetes. To determine whether abnormal sleeping times were independently associated with diabetes and glucose intolerance, we used multivariable adjustments, including adjustments for age, BMI, smoking, sleep apnea probability score, CNS-affecting medication and leisure-time physical activity. Even after these adjustments, the prevalence of total diabetes was still significantly increased in women with either short or prolonged sleep duration. The prevalence of previously known diabetes was borderline significant. In the adjustment, both BMI and waist circumference were tested as covariates, but the results from analyses with these two confounders did not differ significantly from that obtained with BMI alone. (Table 2).

The proportion of men with high probability for sleep apnea was 15% and 7% in sleep duration categories <6 h and >8 h, respectively (p = 0.003 for Fisher’s exact test). Similarly, 15% of women who reported sleep duration <6 h had high probability for sleep apnea, as compared to 6% in women with sleep duration ≥8 h (p < 0.001).

Table 2
Prevalences of type 2 diabetes and glucose intolerance according to sleep duration in men and women. FIN-D2D survey

<table>
<thead>
<tr>
<th>Sleep duration, hours</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>281</td>
<td>487</td>
</tr>
<tr>
<td>T2D, %</td>
<td>11.4</td>
<td>6.2</td>
</tr>
<tr>
<td>TT2D, %</td>
<td>21.4</td>
<td>13.6</td>
</tr>
<tr>
<td>IGT, %</td>
<td>16.4</td>
<td>15.2</td>
</tr>
<tr>
<td>AGT, %</td>
<td>45.6</td>
<td>38.4</td>
</tr>
</tbody>
</table>

T2D, previously known type 2 diabetes, TT2D, total type 2 diabetes, IGT, impaired glucose tolerance, AGT, abnormal glucose tolerance (AGT=TT2D, IGT or impaired fasting glucose, IFG).

Comparison between groups, adjusted for age, BMI, medication for sleep/antidepressants, smoking, sleep apnea probability, and physical activity, using the sleep duration “7 h” as reference category.

<sup>a</sup> Likelihood-ratio test of equality, adjusted for age.

<sup>b</sup> Adjusted for age, BMI, medication for sleep/antidepressants, smoking, sleep apnea probability, and physical activity.

(*) 0.05 < p < 0.10.
The multivariable adjusted odds ratios (OR) for T2D were 2.55 (95% confidence interval (CI), 1.21–5.35) for those with reduced (≤6 h) and 1.76 (95% CI, 1.12–2.61) for those with longer (≥8 h) sleeping times compared to women sleeping for 7 h. For TT2D, the adjusted ORs were 1.56 (95% CI, 0.95–2.58) for those sleeping 6 h or less, and 1.71 (95% CI, 1.13–2.61) for women sleeping 8 h or more compared to those individuals with a sleep duration of 7 h. For abnormal glucose tolerance, the multivariable adjusted OR for ≤6 h of sleep was 1.23 (95% CI, 0.87–1.75), and for ≥8 h of sleep was 1.24 (95% CI, 0.93–1.63) compared to a sleep duration of 7 h.

In men, there was a clear tendency towards a U-shaped association between abnormal sleeping times and diabetes, but after inclusion of the multivariable adjustments the association was no longer statistically significant.

To ensure that the above results on sleep duration were not secondary to obesity we assessed the prevalence of obesity in the study participants. The overall prevalence of men and women with at least a slight degree of being overweight (BMI > 25) was 74% and 66%, respectively, and the prevalence of obesity (BMI > 30) was 24% in men and 29% in women. The corresponding prevalence of central obesity according to the criteria of WHO was 37% in men and 52% in women. In men there was a strong association between obesity, central obesity and sleep duration but this was not the case in women. In men, both the prevalence of obesity and central obesity increased significantly with either a short (≤6 h) or a prolonged (≥8 h) sleeping time (Table 3).

7. Discussion

The present study detected an independent association between sleep duration and type 2 diabetes in middle-aged women, while the tendency seen in men was not statistically significant. Most of the studies examining the relationship between sleep disturbances and diabetes have thus far been conducted only in men. The Nurses Health Study demonstrated an association between the amount of sleep and developing symptomatic diabetes in women [15], but rarely have both genders been simultaneously examined in the same study. In contrast to our findings, in one study an independent relationship between sleep duration and diabetes was reported in both men and women [4]. A recent study demonstrated a relationship between short (<6 h) and long (>8 h) sleep duration and the development of diabetes in middle-aged and elderly men; however, neither sleep-disordered breathing nor sleep apnea were corrected for in the adjustments [16]. At first the failure to detect any association between sleep duration and diabetes in men in the present study was thought due to the fact that men are known to have higher overall incidence for sleep-disordered breathing with obstructive sleep apnea than women, and this may be one major reason for their disturbed sleep patterns [17]. Therefore, we decided to include sleep apnea probability as an adjustment covariate in these analyses. In the present study, sleep apnea was more prevalent in patients reporting short sleep duration; however, this finding was found identical in both men and women.

The average sleeping time has shortened over the years, with the mean sleep duration now being 7 h [1,4,18,19]. In the present study, mean sleep time was also found to be approximately 7 h. The prevalence of both previously known and total type 2 diabetes in women was significantly increased, with either a sleeping time of 6 h or less or 8 h or more compared with the median sleep of 7 h. These results in women are supported by the Nurses Health Study, which also showed that either a short sleep time (<6 h) or a prolonged sleep time (>9 h) were both associated with an increased risk of diabetes. The adjusted ORs of the incidence of diabetes

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Prevalences of overweight, obesity and central obesity and their association with sleep duration in men and women. FIN-D2D survey</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Sleep duration, hours</td>
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<tr>
<td></td>
<td>≤6</td>
</tr>
<tr>
<td>N</td>
<td>281</td>
</tr>
<tr>
<td>BMI 25–30</td>
<td>49.8</td>
</tr>
<tr>
<td>BMI&gt;30</td>
<td>28.1**</td>
</tr>
<tr>
<td>Central obesity</td>
<td>43.1**</td>
</tr>
</tbody>
</table>

BMI, Body mass index (kg/m²); overweight 25–30 kg/m² and obesity >30 kg/m².
Central obesity, WHO criteria, in men ≥102 cm and in women ≥88 cm.
Comparison between groups, adjusted for age, using sleep duration “7 h” as reference category.

* Likelihood-ratio test of equality, adjusted for age.
** 0.01 < p < 0.05.
*** p < 0.01.
factor-kines, such as interleukin-6 (IL-6) and tumor necrosis by elevating the levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [25]. There is growing evidence that both sleep disturbances and diabetes are strongly influenced by lifestyle factors such as obesity [5,26]. Short sleep duration is associated with decreased leptin levels, increased ghrelin levels, and, therefore, with an increase of hunger and appetite [27], which might explain the association found between short sleep and obesity. Furthermore, it has been suggested that hormones produced by adipose tissue, such as adiponectin and leptin, may affect insulin resistance in patients suffering from sleep-disordered breathing [1,28]. In the present study, neither BMI nor increased waist circumference could account for the association found between sleep curtailment and diabetes in women. In men, a significant relationship was seen between obesity and central obesity and sleep duration, but in contrast to women, no relationship between sleep curtailment and diabetes was found in men even after adjustment of age alone. Thus, sleep deprivation can exert a variety of adverse effects in the regulation of biological mechanisms.

The mechanisms explaining the association between prolonged sleeping time and the risk of diabetes and glucose abnormalities are far more speculative. In a recent study, long sleep duration was found to be associated with depression and low socio-economic conditions [29]. An association between sleep disturbances and depression was noted also in another study, which found that an elevation of one sleep apnea category was associated with a 1.8-fold increase in the risk of developing depression [30]. In the present study, depression itself was not assessed, but we did include the use of antidepressant medication as a covariate in our adjustments. The use of antidepressants had no effect on the relationship between short or long sleep duration and diabetes. The effects of prolonged sleep on biological mechanisms will presumably be topics of ongoing and future study.

Short sleep and diabetes both are recognized risk factors for cardiovascular disease. It has been shown that a decrease in subjective sleep predicts poorer glucose control in patients with type 2 diabetes. Therefore, sleep duration and quality should be recorded among all the diabetic patients, particularly in patients experiencing problems with glycemic control [31].

There are several limitations inherent in the present study. Although the study was a population-based survey covering three geographical areas and the study sample was large, we were not able to recruit all the subjects in the study sample (overall, 62% participated). The largest single group of lost patients in recruitment was men aged 45–54 years (56% participation rate). It may also be presumed that the health behavior of the people participating in clinical studies is better than those who refuse to take part. Due to the cross-sectional design of the present study, the direction of the causality cannot be inferred from our analyses. Diabetes itself may impair the quantity and quality of sleep. Only a single measurement of glucose was made, and in clinical use this would be suboptimal for an appropriate classifica-
tion of glucose metabolism. It has been indicated that menopause is a significant risk for sleep-disordered breathing in women and that hormone replacement therapy appears to be associated with reduced risk [32]. In the present study neither the onset of menopause nor the use of hormone replacement was assessed in women. Additionally, the assessment of sleep duration as well as obstructive sleep apnea in our study was based on a self-reported questionnaire and not confirmed by objective measurement (e.g., polysomnography). Nevertheless, questionnaires have been found to be useful in detecting and screening for sleep disturbances and sleep apnea in earlier studies [33,34]. The lack of studies including both sexes limits our knowledge of the possible gender-based differences in the effects of sleep disturbances. Therefore, we believe that the present study, despite some of its weaknesses, provides new and important information about a link between two common problems—sleep disturbances and type 2 diabetes—and that either short (≤6 h) or long (≥8 h) sleep is associated with an increased risk of diabetes in middle-aged women, but not in men.

Acknowledgements

The FIN-D2D survey was funded by the hospital districts of Pirkanmaa, Central Finland, and South Ostrobothnia, and the Finnish National Public Health Institute. HT has received grants for research work from Kuopio University Hospital, Juho Vainio Foundation, Yrjö Jahnsson Foundation, and Finnish Anti-Tuberculosis Foundation.

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