Change in Sleep Duration and Type 2 Diabetes: The Whitehall II Study

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OBJECTIVE

Evidence suggests that short and long sleep durations are associated with a higher risk of type 2 diabetes. Using successive data waves spanning >20 years, we examined whether a change in sleep duration is associated with incident diabetes.

RESEARCH DESIGN AND METHODS

Sleep duration was reported at the beginning and end of four 5-year cycles: 1985–1988 to 1991–1994 (n = 5,613), 1991–1994 to 1997–1999 (n = 4,193), 1997–1999 to 2002–2004 (n = 3,840), and 2002–2004 to 2007–2009 (n = 4,195). At each cycle, change in sleep duration was calculated for participants without diabetes. Incident diabetes at the end of the subsequent 5-year period was defined using *1*) fasting glucose, *2*) 75-g oral glucose tolerance test, and *3*) glycated hemoglobin, in conjunction with diabetes medication and self-reported doctor diagnosis.

RESULTS

Compared with the reference group of persistent 7-h sleepers, an increase of ≥2 h sleep per night was associated with a higher risk of incident diabetes (odds ratio 1.65 [95% CI 1.15, 2.37]) in analyses adjusted for age, sex, employment grade, and ethnic group. This association was partially attenuated by adjustment for BMI and change in weight (1.50 [1.04, 2.16]). An increased risk of incident diabetes was also seen in persistent short sleepers (average ≤5.5 h/night; 1.35 [1.04, 1.76]), but this evidence weakened on adjustment for BMI and change in weight (1.25 [0.96, 1.63]).

CONCLUSIONS

This study suggests that individuals whose sleep duration increases are at an increased risk of type 2 diabetes. Greater weight and weight gain in this group partly explain the association.

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Recent meta-analyses of prospective studies have provided evidence of a U-shaped association between sleep duration and a higher incidence of type 2 diabetes, with both short and long sleep duration associated with greater risk (1–3). The association between short sleep and diabetes is biologically credible (4). Laboratory studies have shown sleep restriction and poor sleep quality to be linked to glucose dysregulation, with increases in hunger and appetite via downregulation of satiety and upregulation of appetite-stimulating hormones (5), indicating pathways to diabetes via adiposity and insulin resistance (6). In contrast, the association observed between long sleep and adverse health outcomes has mostly been attributed to reverse causation from subclinical or undetected morbidity (7).

Increasing concerns about reductions in nighttime sleep duration due to the 24/7 society (1) cannot be addressed by studies based on a one-off measurement of sleep duration, a limitation that pertains to almost all observational studies to date (1,2). From such studies it is impossible to determine whether associations observed between short or long sleep and diabetes are generated by persistent exposure or whether decreases or increases from a more normal average of 7 h per night also confer risk. A decrease or increase in sleep duration from normal to short or long sleep has been associated with increased all-cause mortality (8), but we are not aware of any population-level investigations of change in sleep duration and incidence of type 2 diabetes.

In this article, we examined potential longitudinal associations between changes in sleep duration over 5-year exposure periods and incident type 2 diabetes in the subsequent 5-year period. Using a large, prospective study of middle-aged women and men, we took account of changes in adiposity, a potential confounder and mediator of these associations (7).

RESEARCH DESIGN AND METHODS

Study Population

The target population for the Whitehall II study was all London-based office staff aged 35–55 years in 20 civil service departments in 1985. Of these, 10,308 enrolled, a response proportion of 73% (9). Data collection at enrollment, 1985–1988, and in 1991–1994, 1997–1999, 2002–2004, 2007–2009, and 2012–2013 involved a clinical examination and self-administered questionnaire. Additional limited data collections via self-administered questionnaire only were conducted in 1989, 1995, 2001, and 2006. The current study takes advantage of these data to examine associations between changes in sleep duration and incident type 2 diabetes over four successive data cycles (10). One data cycle includes three phases of data: change in sleep duration over a 5-year exposure period, e.g., 1985–1988 to 1991–1994, and incident diabetes over the subsequent 5-year period, 1991–1994 to 1997–1999 (Supplementary Table 1).

Assessment of Exposure

Sleep duration was measured using the question "How many hours of sleep do you have on an average week night?"

Response categories were ≤5, 6, 7, 8, and ≥9 h. Sleep duration in 1985–1988, 1991–1994, 1997–1999, 2002–2004, and 2007–2009 was used to determine change in sleep duration over four exposure periods: 1985–1988 to 1991–1994, 1991–1994 to 1997–1999, 1997–1999 to 2002–2004, and 2002–2004 to 2007–2009. To calculate change, baseline sleep duration was subtracted from sleep duration at follow-up. As sleep duration was measured only in whole numbers of hours, durations of sleep that differed by 0 or 1 h between successive phases were considered not to be different and classified as "no change in sleep duration." For these "stable" sleepers, average sleep duration was calculated and categorized into five levels: ≤5.5, 6.0–6.5, 7.0, 7.5–8.0, and ≥8.5 h. Decreased sleep was defined as a decrease of ≥2 h and increased sleep as an increase of ≥2 h in sleep over the 5-year sleep exposure period.

Ascertainment of Incident Type 2 Diabetes

At the end of the 5-year sleep exposure period for each data cycle (which coincided with the start of the 5-year incident diabetes outcome period for that cycle), participants reporting use of diabetes medication or diabetes diagnosed by a doctor (doctor diagnosed) or identified via the Whitehall II clinical examination were classified as prevalent diabetes cases and removed from analyses of the outcome for that data cycle. The clinical examination included a 75-g oral glucose tolerance test (OGTT) with determination of fasting and 2-h postload glucose (venous blood after ≥5-h fast). Samples were drawn into fluoride monovette tubes and centrifuged on site within 1 h. Blood glucose was measured using the glucose oxidase method, as previously described (11). In addition to the fasting glucose sample, glycated hemoglobin (HbA$_{1c}$) was measured in EDTA whole blood using a calibrated high-performance liquid chromatography system with automated hemolysis before injection.

Incident type 2 diabetes over the 5-year outcome period was defined as follows: either 1) fasting glucose ≥7.0 mmol/L or participant report of doctor-diagnosed diabetes (data cycles 1–4); 2) OGTT criteria (12), fasting glucose ≥7.0 mmol/L, or 2-h postload glucose ≥11.1 mmol/L or participant

report of doctor-diagnosed diabetes (data cycles 1–3); or 3) HbA$_{1c}$ ≥6.5% (48 mmol/mol) or participant report of doctor-diagnosed diabetes (data cycles 3 and 4) (13). For three of the incident diabetes outcome periods (1991–1994 to 1997–1999, 1997–1999 to 2002–2004, and 2002–2004 to 2007–2009), questionnaire-only data were also available midway between the main data collection points, in 1995, 2001, and 2006, respectively. Participants identified as incident cases of diabetes by self-reported doctor diagnosis in these questionnaires were included among the incident cases for that 5-year outcome period. Since the definition of incident diabetes changed across the data cycles, we created an all-inclusive definition that used all glycemic data available at each data cycle. This all-inclusive definition of incident diabetes used OGTT criteria or participant report of doctor diagnosis for data cycles 1 and 2, OGTT or HbA$_{1c}$ criteria or participant report of doctor diagnosis for data cycle 3, and fasting glucose or HbA$_{1c}$ criteria or participant report of doctor diagnosis for data cycle 4.

Assessment of Covariates

At each data cycle, covariates included age and sex from the beginning of the outcome period, BMI in kg/m^2 at the beginning of each exposure and outcome period (1991–1994, 1997–1999, 2002–2004, 2007–2009, and 2012–2013), socioeconomic position measured as employment grade (low, intermediate, or high), and ethnicity (white, South Asian, or black). All measures were obtained as described previously (9).

Statistical Analysis

The data from each cycle were combined to form a single dataset of person-observations. Conditional logistic regression models, stratified by data cycle, with incident diabetes as the outcome, were fitted to estimate odds ratios (ORs) at each data cycle for 1) stable sleepers with averages of ≤5.5, 6.0–6.5, 7.5–8.0, and ≥8.5 h sleep per night and 2) those whose sleep duration decreased or increased by ≥2 h. Those who slept 7 h per night on both occasions were used as the reference group in both cases. These ORs were estimated using a single unified model. Of the 6,449 participants who contributed to these analyses, 24, 21, 11, and 44% contributed data from one, two, three, and four cycles of data,

respectively. The nonlinear effect of average sleep on incident diabetes in stable sleepers was tested by fitting linear and quadratic terms for average sleep in these participants. All models were initially adjusted for age and sex at the beginning of the outcome period. Further adjustments were made for ethnicity and employment grade. Last, the analyses were adjusted for BMI at the beginning of each exposure and outcome period using two separate terms. Missing data on covariates were present in 9% of the person-observations. These observations were excluded from all analyses so that the increasing degrees of adjustment for covariates were conducted on the same dataset. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Supplementary Table 1 presents the numbers of participants that contributed to the analyses of average sleep duration and change in sleep duration across the four data cycles. The analyses of diabetes defined using a fasting glucose of $\geq$7.0 mmol/L included 17,841 person-observations for normoglycemic participants at baseline, among whom 574 were diagnosed as incident diabetes cases during follow-up. Of these cases, 280 had a fasting glucose of $\geq$7.0 mmol/L, and the remaining 294 reported doctor-diagnosed diabetes. For type 2 diabetes based on the OGTT criteria, there were 13,435 person-observations and 587 incident diabetes cases, of whom, 133 had a fasting glucose of $\geq$7.0 mmol/L, 221 had a 2-h postload glucose $\geq$11.1 mmol/L, 60 had both measures elevated, and 173 reported doctor-diagnosed diabetes. For type 2 diabetes defined according to the level of HbA_{1c}, there were 8,181 person-observations and 401 diabetes cases, of whom, 269 had HbA_{1c} $\geq$6.5% (48 mmol/mol) and the remaining 132 reported doctor-diagnosed diabetes. The all-inclusive definition of incident diabetes using all glycemic data available at each cycle was used in the main analyses. These analyses included 17,778 person-observations and 816 diabetes cases.

Characteristics of the participants included in the incident diabetes analyses for each data cycle are presented in Table 1. An expected pattern of age-related changes was seen; sleep duration tended to decrease and BMI tended to increase over time.

Findings for the association between sleep duration and diabetes defined using all incident cases are presented in Table 2. There is evidence of a nonlinear (reverse J-shaped) association between average sleep duration and incident diabetes in participants whose sleep duration did not change over the sleep exposure period for each data cycle. The strong association observed between persistent short sleep and incident diabetes in the age- and sex-adjusted analyses (OR 1.59 [95% CI 1.22, 2.05]) was somewhat attenuated by adjustment for ethnic group and employment grade (1.35 [1.04, 1.76]). Further adjustment for BMI at the beginning and end of the exposure and outcome period partly explained this association (1.25 [0.96, 1.63]).

Compared with a constant duration of 7 h sleep at the beginning and end of the exposure period, there was strong evidence of an association between an increase in sleep duration $\geq$2 h and incident diabetes in the age- and sex-adjusted analyses (OR 1.83 [95% CI 1.28, 2.60]) (Table 3). These associations were slightly attenuated on further adjustment for ethnic group and employment grade (1.65 [1.15, 2.37]). Although further adjustment for BMI at the beginning and end of the exposure and outcome period partly explained this association (1.50 [1.04, 2.16]), an independent association between an increase in sleep duration and incident diabetes remained.

Sensitivity Analysis

The analyses presented in Tables 2 and 3 use the most inclusive definition of diabetes at each data cycle. Depending on the cycle, this includes diabetes self-reported as doctor diagnosed and/or diagnosed by fasting glucose (all four data cycles), and/or by 2-h postload glucose (first three data cycles), and/or by HbA_{1c} (last two data cycles). As these different diagnostic criteria lead slightly different groups of participants to be diagnosed with diabetes, our findings are presented separately by diagnostic criteria in Supplementary Tables 2–4. Overall, the findings from these sensitivity analyses are remarkably consistent across the definitions most commonly used for the diagnosis of diabetes. They also provide some evidence to support an association between a decrease in sleep and incident diabetes in the age- and sex-adjusted analyses, but this is attenuated on further adjustment.

Further analyses, which compare the age- and sex-adjusted ORs presented in Tables 2 and 3 and Supplementary Tables 2–4 with those obtained from including the observations with missing covariate data, showed the two sets of analyses to be close, with similar patterns observed between sleep duration and change in sleep duration and incident diabetes (Supplementary Table 5).

CONCLUSIONS

Our findings among stable sleepers suggest a nonlinear (reverse J-shaped) association between sleep duration and incident diabetes. This is reassuring as it partly replicates previous findings and provides some external validity of our data (1,2). We also found that persistent short sleep and an increase of 2 h or more in sleep duration over a 5-year exposure period, compared with a constant 7 h per night, were associated with an increased risk of developing type 2 diabetes in analyses adjusted for age, sex, ethnic group, and employment grade. A set of sensitivity analyses showed these findings to be remarkably consistent across the definitions most commonly used for the diagnosis of diabetes: fasting glucose, OGTT, and HbA_{1c}. Further adjustment for BMI and change in weight weakened the association between persistent short sleep and diabetes. Although similar adjustment explained part of the association between an increase in sleep and incident diabetes, a strong independent association remained.

It is an interesting and new observation that persistent short sleep is more deleterious than a decrease in sleep duration over a 5-year period. This may be related to the longer exposure to short sleep among persistent short sleepers, or because decreases in sleep duration are common with increasing age and may lead to age-specific "normal" values of sleep duration. There are a number of potential mechanisms through which short sleep may affect glucose metabolism (4). One is via alterations in the neurohormonal regulation of eating habits. Laboratory studies have shown sleep restriction to be associated with increased appetite, especially for

Table 1—Characteristics of participants at the end of the exposure period/beginning of outcome incidence follow-up for each data cycle used in the analyses of incident type 2 diabetes, defined using all available glycemic data and participant report of doctor-diagnosed diabetes*

Characteristics	Cycle 1[†]	Cycle 2	Cycle 3	Cycle 4
Exposure period	1985–1988 to 1991–1994	1991–1994 to 1997–1999	1997–1999 to 2002–2004	2002–2004 to 2007–2009
Outcome follow-up period	1991–1994 to 1997–1999	1997–1999 to 2002–2004	2002–2004 to 2007–2009	2007–2009 to 2012–2013
Number of participants‡	5,545	4,117	3,878	4,238
Age (years), mean (SD)	49.8 (6.0)	55.4 (5.9)	60.6 (5.9)	65.2 (5.7)
Sex (% male)	71.2	71.3	72.7	73.9
Ethnicity (% white)	92.0	93.1	94.0	94.7
Employment grade (% low grade)	15.9	13.9	12.5	11.4
BMI (kg/m^2), mean (SD)	24.4 (3.2)	25.0 (3.4)	25.9 (3.8)	26.2 (4.0)
Sleep duration at beginning of exposure period (%)				
≤5 h	4.1	3.7	7.0	7.3
6 h	27.1	20.6	33.4	32.3
7 h	52.4	47.7	43.2	43.0
8 h	15.6	25.1	15.0	15.7
≥9 h	0.8	2.8	1.5	1.6
Sleep duration at end of exposure period (%)				
≤5 h	4.0	7.3	7.7	7.3
6 h	21.0	32.9	32.3	29.2
7 h	46.8	43.3	42.6	42.3
8 h	25.4	15.0	15.8	19.4
≥9 h	2.9	1.5	1.7	1.8

*Definition of diabetes uses OGTT criteria or participant record of doctor-diagnosed diabetes for cycles 1 and 2, combined OGTT and HbA$_{1c}$ criteria or participant record of doctor diagnosis for cycle 3, and combined fasting glucose and HbA$_{1c}$ criteria or participant record of doctor diagnosis for cycle 4. †Average sleep duration and change in sleep duration over the exposure period, years 1985–1988 to 1991–1994, and incident diabetes over the outcome follow-up period, 1991–1994 to 1997–1999. ‡Number of participants in the 2-h postload glucose and HbA$_{1c}$ analyses differ slightly from those presented here.

calorie-dense foods, via downregulation of satiety and upregulation of appetite-stimulating hormones (5). Were the resulting hunger to translate into additional calorie intake, weight gain, which is associated with the development of diabetes, would be expected to occur over time. Given this potential association between sleep duration and increases in adiposity, it is unsurprising that adjustment for this important risk factor for type 2 diabetes attenuated the association observed between persistent short sleep and incident diabetes.

Activation of inflammatory pathways may also play a role in the association between persistent short sleep and diabetes, as there is a well-established association between inflammation and incident type 2 diabetes (14). Experiments suggest that prolonged sleep deprivation in rats is associated with an evolving proinflammatory state (15), and common forms of sleep loss, such as reductions of 25–50% across consecutive nights, appear to induce an increase in levels of interleukin-6 and C-reactive protein (16,17). Another potential mechanism is through melatonin, which is regulated by the circadian clock and is inhibited by light

Table 2—Association between average sleep duration and subsequent incident diabetes, defined using all available glycemic data and participant report of doctor-diagnosed diabetes, using four data cycles

Average sleep duration among those with no change in sleep duration	No. events	n*	Confounder adjustments			
			Age and sex	Age, sex, and ethnic group	Age, sex, ethnic group, and employment grade	Age, sex, ethnic group, employment grade, and BMI at the beginning and end of each exposure period
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
≤5.5 h	90	1,303	1.59 (1.22, 2.05)	1.43 (1.10, 1.85)	1.35 (1.04, 1.76)	1.25 (0.96, 1.63)
6.0–6.5 h	253	5,957	0.98 (0.81, 1.19)	0.96 (0.79, 1.16)	0.94 (0.78, 1.14)	0.88 (0.73, 1.07)
7 h	204	4,875	1.00 (reference†)	1.00 (reference†)	1.00 (reference†)	1.00 (reference†)
7.5–8.0 h	179	4,183	1.00 (0.82, 1.23)	0.98 (0.80, 1.21)	0.98 (0.80, 1.21)	0.98 (0.80, 1.21)
≥8.5 h	18	361	1.11 (0.67, 1.82)	1.00 (0.61, 1.66)	1.01 (0.61, 1.67)	0.94 (0.57, 1.56)
P value for quadratic model			0.002	0.017	0.049	0.23

*Number of person-observations. †ORs compared with those who had 7 h sleep on both occasions.

Table 3—Association between change in sleep duration and subsequent incident diabetes across four data cycles using all available glycemic data and participant report of doctor-diagnosed diabetes

			Confounder adjustments			
			Age and sex	Age, sex, and ethnic group	Age, sex, ethnic group, and employment grade	Age, sex, ethnic group, employment grade, and BMI at the beginning and end of each exposure period
Change in sleep duration	No. events	*n**	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
≥2 h decrease in sleep	32	533	1.44 (0.97, 2.12)	1.24 (0.83, 1.84)	1.22 (0.82, 1.81)	1.16 (0.78, 1.73)
No change in sleep†	204	4,875	1.00 (reference‡)	1.00 (reference‡)	1.00 (reference‡)	1.00 (reference‡)
≥2 h increase in sleep	40	566	1.83 (1.28, 2.60)	1.69 (1.18, 2.42)	1.65 (1.15, 2.37)	1.50 (1.04, 2.16)

*Number of person-observations. †Seven hours at each data cycle. ‡ORs compared with those who had 7 h sleep on both occasions.

to the retina. Melatonin and its receptors, which are widely expressed, are associated with metabolic pathways (18). Melatonin is reduced in short sleepers, and recent work has shown lower levels of melatonin secretion to be independently associated with a higher risk of developing type 2 diabetes (19).

Contrary to expectations and seemingly at odds with our findings for persistent short sleep, we did not find any consistent association between a decrease in sleep and incident diabetes in these analyses, possibly due to the relatively small number of participants and events in this category.

As the current study appears to be the first to demonstrate an association between increased sleep and incident diabetes, potential mechanisms are based on those underlying the association between long sleep duration and increased diabetes. In addition to an association with obesity, long sleep has been shown to be associated with other risk factors for diabetes, such as depression, low socioeconomic status, poor physical health, and low physical activity (20,21). Long sleep could also be a marker of associated sleep disorders. Obstructive sleep apnea, for example, is a cause of increased need for sleep, and moderate to severe apnea is also associated with an increased risk of type 2 diabetes (22). Similarly, reports of long sleep may be a proxy for time in bed to compensate for poor quality sleep, which in turn has been shown to be associated with poor glucose regulation (23,24). Long sleep can also be an epiphenomenon of comorbidity or the result of prodromal disease, including prediabetes, which may result in tiredness. Finally, both short and long sleepers may be characterized by a distinctive phenotype (20)

or even a genotype that may confound observed associations (25).

Future work in this field should address the following limitations of this study. First, our sleep measure was self-reported, with sleep duration categories that ranged only from ≤5 h per night to ≥9 h per night. In our analyses, we treated these groups as if they were 5 and 9 h exactly. At the short sleep end of the sleep duration distribution, this may have resulted in some misclassification of participants who move from 6 to ≤5 h, or vice versa. They are currently allocated to the no change, short sleep group, although some of them might have decreased or increased sleep. As our analyses show that those with decreased sleep tend to have a lower risk of diabetes than the group of stable short sleepers and those with increased sleep a higher risk, such potential misclassification would have little effect on the estimates for stable short sleepers, although it may result in slightly fewer participants in the change in sleep groups. A similar misclassification might have occurred at the long sleep end of the distribution (the stable long sleep group), with the result that this group contains some participants whose sleep duration did change and who are at higher risk of diabetes. The OR in the stable long sleep group may, therefore, be slightly overestimated. Self-reported sleep duration is strongly associated with objectively ascertained health outcomes (8,26), and assessments in the primary health care setting rely on self-reports from patients. In addition, small-scale investigations have shown moderately good correlations between subjective estimates and sleep diaries, actigraphy, or polysomnography (27). Nonetheless, large-scale studies using more objective measures of sleep

duration are needed, although they remain costly.

Second, our definition of an increase or decrease in sleep duration was conservative, resulting in few incident diabetes events in these categories. Larger studies with more finely graded data on sleep duration are required to address this limitation. Third, our study did not include measures of chronotype, sleep quality, and sleep disorders, such as sleep apnea. There is some evidence that evening chronotype is associated with risk of type 2 diabetes (28), and disturbances in sleep quality are associated with impaired glucose regulation (25). Sleep apnea is highly prevalent in people with type 2 diabetes (29). Control for BMI, as in the current study, may partially attenuate these associations, but further research should include measures of sleep quality and sleep disorders, in particular sleep apnea. Last, findings from an occupational cohort of middle-aged, white-collar civil servants may not be generalizable, so these should be confirmed in further prospective studies based on the general population. However, despite marked differences in both risk factors and disease incidence that favor the Whitehall II study, standard risk factor–cardiovascular disease associations are in close agreement with those observed in a U.K.-wide general population study (British Regional Heart Study) and the community-based Framingham Heart Study (30).

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