Published in final edited form as:
Diabetes Care. 2015 August ; 38(8): 1467–1472. doi:10.2337/dc15-0186.

Change in sleep duration and type 2 diabetes: the Whitehall II study

Jane E Ferrie, PhD[1,2,*], **Mika Kivimäki, PhD**[2], **Tasnime N Akbaraly, PhD**[2,3], **Adam Tabak, MD**[2,4], **Jessica Abell, PhD**[2], **George Davey Smith, MD**[1,5], **Marianna Virtanen, PhD**[6], **Meena Kumari, PhD**[2,7], and **Martin J Shipley, MSc**[2]

[1]School of Social and Community Medicine, University of Bristol, UK [2]University College London, Department of Epidemiology and Public Health, London, UK [3]Inserm U 1198, Montpellier F-34000, France. University Montpellier, Montpellier, F-34000, France. EPHE, Paris, France [4]1st Department of Medicine, Semmelweis University Faculty of Medicine, Budapest, Hungary [5]MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, UK [6]Finnish Institute of Occupational Health, Helsinki, Finland [7]Institute for Social and Economic Research, University of Essex, Colchester

Abstract

Objective—Evidence suggests that short and long sleep are associated with a higher risk of type 2 diabetes. Using successive data waves spanning more than 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: 1985-88 to 1991-94 (N=5613); 1991-94 to 1997-99 (N=4193); 1997-99 to 2002-04 (N=3840); 2002-04 to 2007-09 (N=4195). 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) 75g oral glucose tolerance test; and (3) glycated hemoglobin, in conjunction with diabetes medication and self-reported doctor diagnosis.

Results—Compared to the reference group of persistent 7-hour sleepers, an increase of ≥2hours sleep per night was associated with a higher risk of incident diabetes; Odds Ratios (95% Confidence Intervals) 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 body mass index and change in weight; 1.50 (1.04, 2.16). An increased risk of incident diabetes was also seen

[*]Author for correspondence Jane Ferrie, Senior Research Fellow, School of Social and Community Medicine, University of Bristol, UK, jane.ferrie@bristol.ac.uk telephone, (+44) 117 331 0052.

AUTHOR CONTRIBUTIONS

Jane Ferrie and Martin Shipley conceived and designed the original study. Jane Ferrie wrote the first draft of the paper. Martin Shipley performed the analyses with input from Adam Tabak and Mika Kivimaki. All the authors, Jane Ferrie, Mika Kivimäki, Tasnime Akbaraly, Adam Tabak, Jessica Abell, George Davey Smith, Marianna Virtanen, Meena Kumari, Martin Shipley, contributed to collecting the data, revising drafts of the manuscript and preparing the final manuscript.

Dr. Jane Ferrie is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest: None declared.

Europe PMC Funders Author Manuscripts

in persistent short sleepers (average ≤5.5 hours/night); 1.35 (1.04, 1.76), but this evidence weakened on adjustment for body mass index and change in weight; 1.25 (0.96, 1.63).

Conclusion—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.

Europe PMC Funders Author Manuscripts

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 down-regulation of satiety and up-regulation 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 night time 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-hours 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 paper, 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 in 20 civil service departments in 1985. Of these, 10 308 enrolled, a response proportion of 73% (9). Data collection at enrolment, 1985-88, and in 1991-94, 1997-99, 2002-04, 2007-09 and 2012-13 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. 1985-88 to 1991-94, and incident diabetes over the subsequent 5-year period, 1991-94 to 1997-99 – Appendix 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. Sleep duration in 1985-88, 1991-94, 1997-99, 2002-04 and 2007-09 was used to determine change in sleep duration over four exposure periods: 1985-88 to 1991-94; 1991-94 to 1997-99; 1997-99 to 2002-04; and 2002-04 to 2007-09. 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 hour 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 hours. Decreased sleep was defined as a decrease of ≥2 hours and increased sleep as an increase of ≥2 hours 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 75g oral glucose tolerance test (OGTT) with determination of fasting and 2-hour postload glucose (venous blood after ≥5-hour fast). Samples were drawn into fluoride monovette tubes and centrifuged on site within one hour. Blood glucose was measured using the glucose oxidase method, as previously described (11). In addition to the fasting glucose sample, glycated hemoglobin (HbA1c) was measured in EDTA whole blood using a calibrated high-performance liquid chromatography system with automated hemolysis before injection.

Incident type 2 diabetes at the end of each outcome period was defined as follows: either (i) fasting glucose ≥7·0 mmol/L or participant report of doctor-diagnosed diabetes (data cycles 1-4); (ii) or OGTT criteria (12), fasting glucose ≥7·0 mmol/L, or 2 hour post-load glucose ≥11·1 mmol/L or participant report of doctor-diagnosed diabetes (data cycles 1-3); or (iii) HbA1c ≥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; 1991-94 to 1997-99, 1997-99 to 2002-04, and 2002-04 to 2007-09, 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 which 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 HbA1c criteria or participant report of doctor diagnosis for data cycle 3 and fasting glucose or HbA1c 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, body mass index (BMI) in kg/m^2 at the beginning of each exposure and outcome period (1991-94, 1997-99, 2002-04, 2007-09, 2012-13), socioeconomic position measured as employment grade (low, intermediate, high) and ethnicity (white, south Asian, 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 at each data cycle: (i) for stable sleepers with averages of ≤5.5, 6.0-6.5, 7.5-8.0 and ≥8.5 hours sleep per night and (ii) those whose sleep duration decreased or increased by ≥2 hours. Those who slept 7 hours per night on both occasions were used as the reference group in both cases. These odds ratios were estimated using a single unified model. Of the 6449 participants who contributed to these analyses, 24%, 21%, 11% and 44% contributed data from 1, 2, 3 and 4 cycles of data, respectively. The non-linear 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. Lastly 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, USA).

RESULTS

Appendix 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 ≥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 ≥7.0 mmol/L, while 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 ≥7.0 mmol/L, 221 had a 2 hour post-load glucose ≥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 glycated hemoglobin, there were 8 181 person-observations and 401 diabetes cases, of whom, 269 had HbA1c ≥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 were seen; sleep duration tended to decrease and BMI 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 non-linear (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, Odds Ratio (95% Confidence Interval) 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 to a constant duration of 7 hours sleep at the beginning and end of the exposure period, there was strong evidence of an association between an increase in sleep duration ≥2 hours and incident diabetes in the age and sex adjusted analyses, 1.83 (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-hour post-load glucose (first 3 data cycles), and/or by HbA1c (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 Appendix 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 odds ratios presented in Tables 2 and 3 and Appendix 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 – Appendix Table 5.

DISCUSSION

Our findings among stable sleepers suggest a non-linear (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 two hours or more in sleep duration over a five-year

exposure period, compared to a constant 7 hours 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 HbA1c. Further adjustment for body mass index 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 calorie dense foods, via down-regulation of satiety and up-regulation 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 (15). Experiments suggest that prolonged sleep deprivation in rats is associated with an evolving pro-inflammatory state (16), 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 (17:18). Another potential mechanism is through *melatonin*, which is regulated by the circadian clock and is inhibited by light to the retina. Melatonin and its receptors, which are widely expressed, are associated with metabolic pathways (20). 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 (21).

Contrary to expectations and at seemingly 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 (22:23). 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 (24). 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 (25:26). Long sleep can also be an epiphenomenon of comorbidity or the result of prodromal disease, including pre-diabetes, which may result in tiredness. Finally, both short and long sleepers may be characterized by a distinctive phenotype (22), or even genotype that may confound observed associations (27).

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 hours per night to ≥9 hours per night. In our analyses we treated these groups as if they were 5 hours and 9 hours exactly. At the short sleep end of the sleep duration distribution this may have resulted in some misclassification of participants who move from 6 hours to ≤5 hours, 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 odds ratio in the stable long sleep group may, therefore, be slightly overestimated. Self-reported sleep duration is strongly associated with objectively ascertained health outcomes (8:28), and assessments in the primary healthcare 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 (29). 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. Thirdly 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 (30), and disturbances in sleep quality are associated with impaired glucose regulation (27). Sleep apnea is highly prevalent in people with type 2 diabetes (31). Control for body mass index, as in the present study, may partially attenuate these associations but further research should include measures of sleep quality and sleep disorders, in particular sleep apnea. Lastly, findings from an occupational cohort of middle-aged, white-collar civil servants may not be generalizable, so 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 UK-wide general population study (British Regional Heart Study) and the community-based Framingham study (32).

ACKNOWLEDGEMENTS

This work was performed at Department of Epidemiology and Public Health, University College London Medical School. The Whitehall II study has been supported by grants from the Medical Research Council; British Heart Foundation; National Heart Lung and Blood Institute (R01HL36310), US, NIH: National Institute on Aging (R01AG13196 and R01AG34454), US, NIH; Agency for Health Care Policy Research (HS06516); the Dunhill Medical Trust (R247/0512); and the BUPA Foundation, UK. MKi is supported by the Medical Research Council (K013351), Academy of Finland, an ESRC professorship and NordForsk, the Nordic Council of Ministers (grant 75021). MJS is partly supported by the British Heart Foundation. TNA was supported by the National Heart Lung and Blood Institute (R01HL36310). MKu is partly supported by the Economic and Social Research Council (RES-596-28-0001). MV is supported by Academy of Finland (258598, 265174). AT is supported by TÁMOP 4.2.4.A/1-11-1-2012-0001 National Excellence Program – research fellowship co-financed by the European Union and the European Social Fund.

Appendix

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Appendix Table 1

Study design, numbers of participants with average sleep duration and change in sleep duration information, numbers eligible and numbers of outcomes

Exposure and outcomes	Cycle 1*	Cycle 2	Cycle 3	Cycle 4	Total†
Exposure period	1985-8 to 1991-4	1991-4 to 1997-9	1997-9 to 2002-4	2002-4 to 2007-9	
All participants	8815	7870	6968	6761	30414
Average sleep duration and change in sleep duration information available	8262	6760	6151	6054	27227
As above, but excluding those with missing values in covariates	7824	5168	4719	5533	23244
Outcome follow-up period	1991-4 to 1997-9	1997-9 to 2002-4	2002-4 to 2007-9	2007-9 to 2012-13	
Diabetes outcomes					
Using fasting glucose definition:-					
Non diabetics at beginning of period	5613	4193	3840	4195	17841
Incident Type 2 diabetes during period, N (%)	137 (2.4)	149 (3.6)	163 (4.2)	125 (3.0)	574
Using OGTT definition:-					
Non diabetics at beginning of period	5545	4117	3773	-	13435
Incident Type 2 diabetes during period, N (%)	188 (3.4)	176 (4.3)	223 (5.9)		587
Using HbA1c definition:-					
Non diabetics at beginning of period	-	-	3941	4240	8181
Incident Type 2 diabetes during period, N (%)			247 (6.3)	154 (3.6)	401
Using all glycemic data‡ definition:-					
Non diabetics at beginning of period	5545	4117	3878	4238	17778
Incident Type 2 diabetes during period, N (%)	188 (3.4)	176 (4.3)	290 (7.5)	162 (3.8)	816

*Cycle 1 – average sleep duration and change in sleep duration over the exposure period, years 1985/8 to 1991/4, and incident diabetes over the outcome follow-up period, 1991/4 to 1997/9

†Total person-observations and numbers of incident cases of type 2 diabetes across all available cycles.

‡Uses OGTT criteria for cycles 1 and 2, combined OGTT and HbA1c definitions for cycle 3 and combined fasting glucose and HbA1c definitions for cycle 4

Europe PMC Funders Author Manuscripts

Appendix Table 2

Association between average sleep duration and change in sleep duration and subsequent incident diabetes, defined using fasting glucose, using four data cycles*

Sleep duration			Adjustments			
			Age, sex	Age, sex, ethnic group	Age, sex, ethnic group, employment grade	Age, sex, ethnic group, employment grade and BMI at the beginning and end of each exposure period
	No. events (n=574)	N† (N=17841)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Average sleep duration among those with no change in sleep duration						
≤ 5.5 hours	65	1299	1.82 (1.34, 2.47)	1.60 (1.17, 2.18)	1.52 (1.11, 2.07)	1.38 (1.00, 1.89)
6.0 - 6.5 hours	179	5985	1.10 (0.87, 1.38)	1.07 (0.85, 1.34)	1.05 (0.83, 1.32)	0.96 (0.76, 1.21)
7 hours	130	4893	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)
7.5 - 8.0 hours	132	4201	1.16 (0.91, 1.48)	1.13 (0.88, 1.45)	1.13 (0.88, 1.44)	1.13 (0.88, 1.45)
≥ 8.5 hours	16	362	1.58 (0.93, 2.69)	1.41 (0.83, 2.41)	1.43 (0.84, 2.44)	1.29 (0.75, 2.22)
P-value for quadratic model			0.006	0.050	0.097	0.27
Change in sleep duration						
≥2 hours decrease in sleep	26	537	1.70 (1.10, 2.64)	1.44 (0.92, 2.23)	1.42 (0.91, 2.20)	1.31 (0.83, 2.06)
≥2 hours increase in sleep	26	564	1.87 (1.21, 2.88)	1.73 (1.12, 2.67)	1.69 (1.09, 2.62)	1.51 (0.97, 2.37)

*6473 participants contributed to these analyses with 24%, 21%, 10% and 45% having 1, 2, 3 and 4 cycles of data respectively

†Number of person-observations

‡Odds ratios compared to those who had 7 hours sleep on both occasions

Europe PMC Funders Author Manuscripts

Appendix Table 3

Association between average sleep duration and change in sleep duration and subsequent incident diabetes, defined using the OGTT criteria, using three data cycles*

Sleep duration	No. events (n=587)	N† (N=13435)	Adjustments: Age, sex	Age, sex, ethnic group	Age, sex, ethnic group, 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)
Average sleep duration among those with no change in sleep duration						
≤ 5.5 hours	62	897	1.51 (1.11, 2.05)	1.35 (0.99, 1.84)	1.28 (0.94, 1.75)	1.21 (0.88, 1.65)
6.0 - 6.5 hours	166	4418	0.84 (0.67, 1.05)	0.82 (0.66, 1.03)	0.80 (0.64, 1.01)	0.75 (0.60, 0.94)
7 hours	159	3736	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)
7.5 - 8.0 hours	135	3239	0.95 (0.75, 1.20)	0.93 (0.74, 1.18)	0.93 (0.73, 1.18)	0.93 (0.73, 1.18)
≥ 8.5 hours	14	260	1.16 (0.66, 2.05)	1.08 (0.61, 1.90)	1.08 (0.61, 1.91)	0.99 (0.56, 1.76)
P-value for quadratic model			0.027	0.12	0.21	0.43
Change in sleep duration						
≥2 hours decrease in sleep	22	464	1.08 (0.68, 1.72)	0.95 (0.59, 1.51)	0.93 (0.58, 1.48)	0.86 (0.54, 1.38)
≥2 hours increase in sleep	29	421	1.68 (1.11, 2.54)	1.58 (1.04, 2.39)	1.54 (1.01, 2.34)	1.43 (0.94, 2.19)

*5996 participants contributed to these analyses with 31%, 13% and 56% having 1, 2 and 3 cycles of data respectively

†Number of person-observations

‡Odds ratios compared to those who had 7 hours sleep on both occasions

Europe PMC Funders Author Manuscripts

Appendix Table 4

Association between average sleep duration and change in sleep duration and subsequent incident diabetes, defined using $HbA1_c$, using two data cycles*

Sleep duration			Adjustments			
			Age, sex	Age, sex, ethnic group	Age, sex, ethnic group, employment grade	Age, sex, ethnic group, employment grade and BMI at the beginning and end of each exposure period
	No. events (n=401)	N† (N=8181)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Average sleep duration among those with no change in sleep duration						
≤ 5.5 hours	47	764	1.80 (1.24, 2.62)	1.58 (1.08, 2.32)	1.51 (1.03, 2.21)	1.36 (0.92, 2.00)
6.0 - 6.5 hours	150	3024	1.41 (1.07, 1.87)	1.36 (1.03, 1.81)	1.35 (1.01, 1.78)	1.28 (0.96, 1.71)
7 hours	78	2157	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)
7.5 - 8.0 hours	88	1685	1.42 (1.04, 1.95)	1.39 (1.02, 1.91)	1.40 (1.02, 1.92)	1.42 (1.03, 1.96)
≥ 8.5 hours	10	176	1.53 (0.78, 3.02)	1.38 (0.69, 2.74)	1.40 (0.71, 2.79)	1.35 (0.68, 2.70)
P-value for quadratic model			0.058	0.22	0.33	0.68
Change in sleep duration						
≥2 hours decrease in sleep	12	152	2.18 (1.16, 4.12)	1.87 (0.98, 3.56)	1.87 (0.98, 3.56)	1.81 (0.93, 3.53)
≥2 hours increase in sleep	16	223	2.24 (1.28, 3.92)	1.99 (1.13, 3.53)	1.95 (1.11, 3.46)	1.76 (0.99, 3.15)

*4923 participants contributed to these analyses with 34% and 66% having 1 and 2 cycles of data respectively

†Number of person-observations

‡Odds ratios compared to those who had 7 hours sleep on both occasions

Europe PMC Funders Author Manuscripts

Appendix Table 5

Age and sex adjusted associations between average sleep duration and change in sleep duration and subsequent incident diabetes among all participants, including those with missing data on the other covariates controlled for in the main analyses

Sleep duration	Definition of incident diabetes			
	Participant report of doctor-diagnosed diabetes or diabetes defined using all glycemic data*	Participant report of doctor-diagnosed diabetes or high fasting glucose	Participant report of doctor-diagnosed diabetes or high 2-hour postload glucose	Participant report of doctor-diagnosed diabetes or high HbA1c
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
No. incident diabetes events	921	638	676	458
Number of person-observations	19434	19513	14984	9114
Average sleep duration among those with no change in sleep duration				
≤ 5.5 hours	1.52 (1.19, 1.95)	1.80 (1.34, 2.42)	1.47 (1.10, 1.96)	1.61 (1.13, 2.29)
6.0 - 6.5 hours	0.99 (0.83, 1.19)	1.10 (0.88, 1.37)	0.87 (0.70, 1.07)	1.33 (1.03, 1.73)
7 hours	1.00 (ref†)	1.00 (ref†)	1.00 (ref†)	1.00 (ref†)
7.5 - 8.0 hours	1.01 (0.83, 1.23)	1.23 (0.97, 1.55)	0.98 (0.79, 1.23)	1.37 (1.03, 1.83)
≥ 8.5 hours	1.29 (0.83, 1.99)	1.59 (0.96, 2.64)	1.37 (0.84, 2.24)	1.48 (0.80, 2.76)
P-value for quadratic model	0.002	0.005	0.017	0.14
Change in sleep duration				
≥2 hours decrease in sleep	1.52 (1.07, 2.18)	1.73 (1.15, 2.60)	1.25 (0.83, 1.88)	1.94 (1.06, 3.56)
≥2 hours increase in sleep	1.74 (1.24, 2.45)	1.84 (1.21, 2.79)	1.47 (1.10, 1.96)	1.89 (1.11, 3.23)

*Odds ratios compared to those who had no change in sleep duration and had an average 7 hours sleep

†Uses OGTT criteria for cycles 1 and 2, combined OGTT and HbA1c definitions for cycle 3 and combined fasting glucose and HbA1c definitions for cycle 4

REFERENCES

1. Larcher S, Benhamou PY, Pépin JL, Borel AL. Sleep habits and diabetes. Diabetes Metab. Jan 23.2015 pii: S1262-3636(14)00199-2.
2. Shan Z, Ma H, Xie M, et al. Sleep Duration and Risk of Type 2 Diabetes: A Meta-analysis of Prospective Studies. Diabetes Care. 2015; 38:529–537. [PubMed: 25715415]
3. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of Type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010; 33:414–420. [PubMed: 19910503]
4. Schmid SM, Hallschmid M, Schultes B. The metabolic burden of sleep loss. Lancet Diabetes Endocrinol. 2014 Pub March 25 (http://dx.doi.org/10.1016/S2213-8587(14)70012-9).
5. Spiegel K, Tasali E, Leproult R, Van CE. Effects of poor and short sleep on glucose metabolism and obesity risk. Nat Rev Endocrinol. 2009; 5:253–261. [PubMed: 19444258]
6. Van Couter E. Sleep disturbances and insulin resistance. Diabet Med. 2011; 28:1455–62. [PubMed: 21950773]
7. Marshal, NS.; Stranges, S. Sleep duration: risk factor or risk marker for ill-health? Chap 3 Sleep Health and Society: From Aetiology to Public Health. Cappuccio, FP.; Miller, MA.; Lockley, SW., editors. Oxford University Press; Oxford: 2010.
8. Ferrie JE, Shipley MJ, Cappuccio FP, et al. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. Sleep. 2007; 30:1659–66. [PubMed: 18246975]
9. Marmot M, Brunner E. Cohort Profile: the Whitehall II study. Int J Epidemiol. 2005; 34:251–6. [PubMed: 15576467]
10. Brunner EJ, Shipley MJ, Britton AR, et al. Depressive disorder, coronary heart disease, and stroke: dose-response and reverse causation effects in the Whitehall II cohort study. Eur J Prev Cardiol. 2014; 21:340–6. [PubMed: 24491401]
11. Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of Type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009; 373:2215–21. [PubMed: 19515410]
12. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. WHO; 2006.
13. Abbreviated Report of a WHO Consultation Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. World Health Organization; 2011.
14. Barr RG, Nathan DM, Meigs JB, Singer DE. Tests of glycemia for the diagnosis of type 2 diabetes mellitus. Ann Intern Med. 2002; 137:263–72. [PubMed: 12186517]
15. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing Type 2 diabetes mellitus. JAMA. 2001; 286:327–34. [PubMed: 11466099]
16. Everson CA. Clinical assessment of blood leukocytes, serum cytokines, and serum immunoglobulins as responses to sleep deprivation in laboratory rats. Am J Physiol Regul Integr Comp Physiol. 2005; 289:R1054–63. [PubMed: 15947073]
17. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 2004; 43:678–83. [PubMed: 14975482]
18. Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab. 2004; 89:2119–26. [PubMed: 15126529]
19. Ferrie JE, Kivimäki M, Akbaraly TN, et al. Associations between change in sleep duration and inflammation: Findings on C-reactive protein and interleukin 6 in the Whitehall II study. Am J Epidemiol. 2013; 178:956–61. [PubMed: 23801012]
20. Nduhirabandi F, du Toit EF, Lochner A. Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? Acta Physiol (Oxf). 2012; 205:209–23. [PubMed: 22226301]

21. McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin secretion and the incidence of Type 2 diabetes. JAMA. 2013; 309:1388–96. [PubMed: 23549584]
22. Stranges S, Dorn JM, Shipley MJ, et al. Correlates of short and long sleep duration: a cross-cultural comparison between the United Kingdom and the United States: the Whitehall II Study and the Western New York Health Study. Am J Epidemiol. 2008; 168:1353–6449. [PubMed: 18945686]
23. Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. Sleep. 2006; 29:881–889. [PubMed: 16895254]
24. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Respirology. 2013; 18:140–146. [PubMed: 22988888]
25. Hung HC, Yang Y-C, Ou H-Y, Wu J-S, Lu F-H, Chang C-J. The relationship between impaired fasting glucose and self reported sleep quality in a Chinese population. Clin Endochrinol (Oxf). 2013; 78:518–24. [PubMed: 22548278]
26. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep Duration as a Risk Factor for Diabetes Incidence in a Large US Sample. Sleep. 2007; 30:1667–1673. [PubMed: 18246976]
27. Gottlieb DJ, Hek K, Chen TH, et al. Novel loci associated with usual sleep duration: the CHARGE Consortium Genome-Wide Association Study. Mol Psychiatry. Dec 2.2014 Epub ahead of print.
28. Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep and mortality: a population-based 22-year follow-up study. Sleep. 2007; 30:1245–53. [PubMed: 17969458]
29. Signal TL, Gale J, Gander PH. Sleep measurement in flight crew: comparing actigraphic and subjective estimates to polysomnography. Aviat Space Environ Med. 2005; 76:1058–63. [PubMed: 16313142]
30. Merikanto I, Lahti T, Puolijoki H, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiol Int. 2013; 30:470–7. [PubMed: 23281716]
31. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. Impact of untreated obstructive sleep apnea on glucose control in Type 2 diabetes. Am J Respir Crit CareMed. 2010; 181:507–513.
32. Batty GD, Shipley M, Tabák A, et al. Generalizability of occupational cohort study findings. Epidemiology. 2014; 25:932–3. [PubMed: 25265141]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

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	1985-8 to 1991-4	1991-4 to 1997-9	1997-9 to 2002-4	2002-4 to 2007-9
Outcome follow-up period	1991-4 to 1997-9	1997-9 to 2002-4	2002-4 to 2007-9	2007-9 to 2012-3
Number of participants‡	5545	4117	3878	4238
Age (y), 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 (k/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 hours	4.1	3.7	7.0	7.3
6 hours	27.1	20.6	33.4	32.3
7 hours	52.4	47.7	43.2	43.0
8 hours	15.6	25.1	15.0	15.7
≥ 9 hours	0.8	2.8	1.5	1.6
Sleep duration at end of exposure period, %				
≤ 5 hours	4.0	7.3	7.7	7.3
6 hours	21.0	32.9	32.3	29.2
7 hours	46.8	43.3	42.6	42.3
8 hours	25.4	15.0	15.8	19.4
≥ 9 hours	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 HbA1c criteria or participant record of doctor diagnosis for cycle 3 and combined fasting glucose and HbA1c criteria or participant record of doctor diagnosis for cycle 4

†Cycle 1 – average sleep duration and change in sleep duration over the exposure period, years 1985-88 to 1991-94, and incident diabetes over the outcome follow-up period, 1991-94 to 1997-99

‡Number of participants in the 2-hour postload glucose and HbA1c analyses differ slightly from those presented here

Europe PMC Funders Author Manuscripts

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, sex	Age, sex, ethnic group	Age, sex, ethnic group, 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 hours	90	1303	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 hours	253	5957	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 hours	204	4875	1.00 (ref†)	1.00 (ref†)	1.00 (ref†)	1.00 (ref†)
7.5 - 8.0 hours	179	4183	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 hours	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

†Odds ratios compared to those who had 7 hours sleep on both occasions

Europe PMC Funders Author Manuscripts

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

Change in sleep duration	No. events	N*	Confounder adjustments			
			Age, sex	Age, sex, ethnic group	Age, sex, ethnic group, 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)
≥2 hours 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	4875	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)	1.00 (ref‡)
≥2 hours 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

†7 hours at each data cycle

‡Odds ratios compared to those who had 7 hours sleep on both occasions