**Sleep duration and cardiometabolic risk factors among individuals with type 2 diabetes**

Andrew JM Cooper [1]

Kate Westgate [1]

Soren Brage[1]

A. Toby Prevost [2]

Simon J Griffin [1, 3]

Rebecca K Simmons [1]


[1] MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Box 285, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, United Kingdom.

[2] Department of Primary Care and Public Health Science, King's College London, London, SE1 3QD, United Kingdom.

[3] The Primary Care Unit, Institute of Public Health, University of Cambridge, Cambridge, United Kingdom.


**Corresponding author:** Dr Andrew Cooper. Email: andrew.cooper@mrc-epid.cam.ac.uk;
Telephone: +44 (0)1223-330315; Fax: +44 (0)1223-330316

**Word count – main text (including Figure legends):** 3,647

**References:** 49

**Word count – abstract:** 200

**Number of Tables:** 2

**Abstract**

**Objective:** To examine the association between sleep duration and cardiometabolic risk factors among individuals with recently diagnosed type 2 diabetes (n=391).

**Methods:** Sleep duration was derived using a combination of questionnaire and objective heart rate and movement sensing in the UK *ADDITION-Plus* study (2002-2007). Adjusted means were estimated for individual cardiometabolic risk factors and clustered cardiometabolic risk (CCMR) by five categories of sleep duration.

**Results:** We observed a J-shaped association between sleep duration and CCMR – individuals sleeping 7-<8 hours had a significantly better CCMR profile than those sleeping ≥9 hours. Independent of physical activity and sedentary time, individuals sleeping 7-<8 hours had lower triacylglycerol (0.62 mmol/l [0.29, 1.06]) and higher HDL-cholesterol levels (0.23 mmol/l [0.16, 0.30]) compared with those sleeping ≥9 hours, and a lower waist circumference (7.87 cm [6.06, 9.68]) and BMI (3.47 kg/m$^2$ [2.69, 4.25]) than those sleeping <6 hours. Although sleeping 7-<8 hours was associated with lower levels of systolic- and diastolic- blood pressure, HbA$_{1c}$, total cholesterol and LDL-cholesterol, these associations were not statistically significant.

**Conclusions:** Sleep duration has a J-shaped association with CCMR in individuals with diabetes, independent of potential confounding. Health promotion interventions might highlight the importance of adequate sleep in this high risk population.

**Keywords:** sleep duration, type 2 diabetes, cardiovascular risk, waist circumference, lipids, BMI

## 1. Introduction

It is currently recommended that adults should aim to get 7 to 9 hours of sleep each day [1]. However, a large majority of adults report sleeping less than this, a trend which has become increasingly prevalent in modern society. Recent data from 'The Great British Bedtime Report' revealed that in 2013 70% of the adult population slept for ≤7 hours, and 33% slept for <6 hours per night compared to 27% in 2010 [2]. Sleep duration in adult Americans follows a similar declining trend [3]. In the last decade, an increasing number of laboratory and epidemiological studies have linked short sleep duration with increases in hunger and appetite [4], decreased glucose tolerance [5] and an increased risk of weight gain [6, 7], obesity [6, 7], hypertension [8, 9], type 2 diabetes [10] and cardiovascular outcomes [11].

While laboratory studies provide important insights into the potential pathways linking acute short sleep duration with cardiovascular health, major limitations are that they are conducted in artificial settings and usually have small sample sizes [12]. Whether prolonged short sleep duration is associated with factors predisposing to cardiovascular disease in free-living populations remains unclear. Although a number of epidemiological studies have examined associations between habitual sleep duration and cardiovascular health outcomes, they have traditionally used self-report measures of sleep duration [13] which are prone to error and bias and which have only moderate agreement with objectively assessed sleep duration [14]. Furthermore, though physical activity and sedentary time may confound the association between sleep duration and cardiovascular health [15, 16], only a small number of studies have adjusted for self-reported physical activity [17, 18]; to our knowledge no studies have adjusted for objective measures of physical activity and sedentary time. These important limitations preclude a clear understanding of the potential role that sleep duration may have in cardiovascular health. Finally, few studies have examined the role of sleep duration among individuals with type 2 diabetes, who are, as a consequence, at higher risk of developing cardiovascular risk [17-21]. Improved understanding of this relationship will inform future intervention programmes aimed at identifying and managing high-risk individuals.

The objective of the current study was to quantify the association between sleep duration derived using a combination of self-report questionnaire and objectively measured free-living data and established cardiometabolic risk factors, independent of potential confounding by physical activity and sedentary time, among a population at high risk of developing cardiovascular disease.

## 2. Methods

The design and rationale for the *ADDITION-Plus* study has been reported previously (2002-2007) [22]. In brief, *ADDITION-Plus* is a randomised controlled trial nested within the intensive treatment arm of the *ADDITION-Cambridge* study, which evaluated the efficacy of a facilitator-led, theory-based behaviour change intervention for recently diagnosed type 2 diabetes patients. 34 general practices in

East Anglia participated. Eligible individuals were those aged 40-69 years diagnosed with diabetes following screening in the *ADDITION* study or clinically diagnosed during the three previous years in participating GP surgeries. Exclusion criteria included women who were pregnant or lactating or anybody with a psychotic illness or an illness with a likely prognosis of less than one year. 478 out of 1,109 eligible individuals agreed to participate in *ADDITION-Plus* and were individually randomised to receive either intensive treatment alone (n=239), or intensive treatment plus a facilitator-led individual behaviour change intervention (n=239). All participants gave written informed consent, and the study was approved by the Eastern Multi-Centre Research Ethics Committee (reference number: 02/5/54). The trial is registered as ISRCTN 99175498.

### 2.1. Assessment of physical activity and sleep duration

Participants activity intensity was assessed using a combined heart-rate and movement sensor (Actiheart, CamNtech, Cambridge, UK) worn continuously for four days at 30-second resolution, as described in detail elsewhere [23]. A graded treadmill walk test was used to individually calibrate heart-rate, as described elsewhere [15, 24]. For participants who did not complete an individual calibration test, all valid calibration tests in the rest of the sample were used to derive an age, sex, beta-blocker, and sleeping heart-rate adjusted group calibration equation for the translation of heart-rate to activity intensity. Heart-rate data collected during the free-living period were processed using noise classification followed by Gaussian robust regression [25] and average activity intensity (J min$^{-1}$ kg$^{-1}$) was estimated using a branched equation framework [26]. Resulting time-series data were summarised into physical activity energy expenditure (PAEE; kJ kg$^{-1}$ day$^{-1}$) and sedentary time whilst minimising diurnal information bias caused by non-wear periods (segments of non-physiological data). Sedentary time was defined as a MET value (metabolic equivalent of task) of <1.5 in accordance with current convention [27] using the Oxford estimate of resting metabolic rate (RMR) to define 1 MET [28]. To derive sleep duration, time-series data from the combined heart-rate and movement sensor were summarised after constraining assessment to within each participant's mean self-reported getting up and going to bed times (self-reported using open-ended questions asking "at what time do you normally get up?" and "at what time do you normally go to bed?" on weekdays and on weekend days [29]) in combination with the requirement that intensity was ≤1.04 METs. This intensity threshold was applied according to recent research demonstrating that values below this MET cut-point are symptomatic of being in a reclined posture (indicative of sleep) as opposed to a seated posture [30]. The appropriateness of this method was verified by visual inspection by overlaying self-reported getting up and going to bed times on the objective time-series data.

### 2.2. Outcome measurements

Body weight and height were measured in light clothing and without shoes using a scale (SECA, UK) and a fixed rigid stadiometer, respectively. BMI was calculated as weight in kilograms divided by height in metres squared (kg/m$^2$). Waist circumference was calculated as the average of two

measurements taken halfway between the lowest point of the rib cage and the anterior superior iliac crests while standing. Blood pressure was calculated as the mean of three measurements performed after 10 minutes of rest and with participants seated with a cuff placed on the predominant arm at the level of the heart, using an automatic sphygmomanometer (Omron M4, UK). $HbA_{1c}$ was measured in venous samples using an ion-exchange high-performance liquid chromatography method (Tosoh Bioscience, Redditch, UK). Serum triacylglycerol, total cholesterol, HDL- and LDL-cholesterol were measured using enzymatic techniques (Dade Behring Dimension analyser, Newark, USA). All measures were carried out by trained staff following standard operating procedures and who were unaware of participants' sleep patterns.

A summary clustered cardiometabolic risk score (CCMR-score) was created, incorporating measures of central obesity (waist circumference), dyslipidaemia (fasting triacylglycerol and HDL-cholesterol), hypertension (systolic blood pressure) and hyperglycaemia ($HbA_{1c}$). Individual measures were standardised (i.e. z-scores were computed: z = [value – mean]/SD) after log-transformation (ln) of triacylglycerol due to a non-normal distribution. Next, individual z-scores were summed after inverting HDL-cholesterol values. CCMR was also calculated without the inclusion of BMI ($CCMR_{no\ BMI}$), thereby allowing examination of the association of sleep duration on CCMR independent of BMI.

### 2.3. Covariates

PAEE and sedentary time were assessed using combined heart-rate and movement sensing (see: *Assessment of physical activity and sleep duration*). Standardised self-report questionnaires were used to collect information on socio-demographic characteristics, smoking status and prescribed medication. Total energy and alcohol intake were assessed using a validated food frequency questionnaire [31]. As psychological disorders can contribute to chronic sleep deprivation, and are positively associated with weight gain [32], we adjusted for the mental components of health status using the short-form-36 (SF-36) health survey questionnaire [33].

Complete data on objectively measured sleep duration, PAEE, time spent sedentary, metabolic risk factors and potential confounding variables were available on 391 participants.

### 2.4. Statistical analysis

The data for this analysis were treated as a cohort and not analysed by trial arm because the intervention used in *ADDITION-Plus* was not designed to influence sleep duration and no evidence of interaction by trial arm was found in the proceeding multivariate analyses (all p-interaction ≥0.09). Descriptive characteristics of the participants were summarised by categories of sleep duration (<6 hours, 6 to <7 hours, 7 to <8 hours, 8 to <9 hours and ≥9 hours) using means with SDs, medians with interquartile ranges or frequencies. *P* for trend, Kruskal-Wallis and $chi^2$ tests were used to examine differences in participant characteristics across categories of sleep duration.

We examined associations between sleep duration categories (<6 hours, 6 to <7 hours, 7 to <8 hours, 8 to <9 hours and ≥9 hours) and CCMR, CCMR $_{no\ BMI}$, waist circumference, BMI, systolic- and diastolic- blood pressure, HbA$_{1c}$, triacylglycerol, total cholesterol, and HDL- and LDL-cholesterol using multivariate linear regression analyses. Triacylglycerol values were log-transformed (ln) for statistical analysis due to a non-normal distribution. We estimated the adjusted means and 95% CIs of CCMR, CCMR $_{no\ BMI}$, waist circumference, BMI, systolic- and diastolic- blood pressure, HbA$_{1c}$, triacylglycerol (ln), total cholesterol, and HDL- and LDL-cholesterol for each sleep category and tested for linear and nonlinear trends across categories using the post-estimation polynomial 'contrast' command in Stata. We included potential confounders in the models based on previously published associations, biological reasoning and statistical associations between exposure and outcomes in the current dataset. All regression models are presented adjusted for age, sex and trial arm (age- sex adjusted) and adjusted for age, sex, trial arm, occupational socio-economic class, PAEE, time spent sedentary, smoking status, alcohol intake, day-time tiredness, mental health score and sleep affecting medication e.g. beta-blockers, sleeping tablets and minor tranquilisers [34] (multivariate adjusted). Triacylglycerol values were back-transformed and reported as adjusted geometric means and their 95% CIs. When the outcome of interest was either blood pressure, HbA$_{1c}$, triacylglycerol or HDL- and LDL-cholesterol, we additionally adjusted for use of anti-hypertensive, glucose lowering, or lipid-lowering medication, respectively. For CCMR we adjusted for use of anti-hypertensive, glucose lowering and lipid-lowering medications and additionally for BMI when examining CCMR $_{no\ BMI}$. The variance inflation factor did not exceed 4 in any of the models, indicating absence of multicollinearity. To investigate differences between sleep duration categories we used Dunnett's significant difference post hoc test to compare each category of sleep duration with those sleeping 7 to <8 hours/night (comparison category). 7 to <8 hours/night of sleep was chosen as the comparison category a posteriori based on this category having the lowest CCMR risk profile. We formally examined whether associations between sleep duration categories and CVD risk factors were modified by sex by entering cross-product terms in the multivariate models.

In sensitivity analyses we assessed whether our findings were sensitive to: 1) the inclusion of energy intake in all multivariate models, 2) inclusion of waist circumference as opposed to BMI in all multivariate models adjusted for BMI, and 3) using a cut-point of ≤1.04 METs for the definition of sleep as opposed to a cut-point of ≤1.00 MET. All statistical analyses were performed using Stata/SE 13.1 (Stata-Corp, College Station, TX).

## 3. Results

The mean (SD) age of study participants was 60.3 (7.4) years. 97.7% of participants were of white European decent. 41.9% of participants reported having a managerial job. More men than women (n=248 vs. 143, respectively) met the inclusion criteria for the study and agreed to participate. Mean

duration of diabetes did not differ across categories of sleep duration ($P$ =0.43). The percentage of study participants who slept <6 hours and >9 hours per night was 11.3% and 5.9%, respectively. **Table 1** shows the characteristics of the study population by categories of sleep duration. Compared with participants with short sleep durations, participants with longer sleep durations were older, were more likely to be female and were less likely to be employed in a managerial position. When expressed in absolute terms, both PAEE and sedentary time decreased across increasing sleep categories. In contrast, when expressed relative to hours awake, participants sleeping 7 to <8 hours/day had the highest PAEE level and spent the lowest proportion of the day sedentary. Sleep duration was weakly inversely correlated with sedentary time ($r$ = -0.22; $p$ <0.001) and PAEE ($r$ = -0.26; $p$ <0.001). Sedentary time was strongly inversely correlated with PAEE ($r$ = -0.73; $p$ <0.001). The mean duration of valid combined heart rate and movement sensing data was 4.02 (SD: 0.40) days.

As shown in **Table 2**, after adjustment for age, sex and trial arm, participants sleeping 7 to <8 hours/night had a lower CCMR and CCMR $_{no\ BMI}$ than all other sleep categories, which was significantly lower when compared with those sleeping ≥9 hours/night (p<0.05). The J-shaped associations between sleep duration and CCMR and CCMR $_{no\ BMI}$ remained after additional adjustment for other potential confounding factors including objectively assessed physical activity, sedentary time, feelings of daytime tiredness, sleep affecting medication ($P$-quadratic-trend: 0.004) and BMI in the CCMR $_{no\ BMI}$ model ($P$-quadratic-trend: 0.025). After multivariate adjustment, sleep duration was inversely associated with waist circumference and BMI ($P$-linear-trend both <0.001), such that participants sleeping 7 to <8 hours/night had a 7.9 cm lower waist circumference and 3.5 kg/m$^2$ lower BMI than those sleeping <6 hours/night (p<0.05). In adjusted analyses, triacylglycerol levels were lowest among participants sleeping 7 to <8 hours/night, and were significantly lower when compared with those sleeping ≥9 hours/night (p<0.05). HDL-cholesterol levels did not differ across sleep categories except for individuals sleeping ≥9 hours/night, among whom levels were significantly lower than those sleeping 7 to <8 hours/night (mean 0.98 mmol/l [95% CI: 0.86, 1.11] vs. 1.21 mmol/l [95% CI: 1.16, 1.25], respectively). We found no consistent associations between sleep duration and systolic- or diastolic blood pressure, HbA$_{1c}$, total cholesterol or LDL-cholesterol, although the lowest levels tended to be observed among those sleeping 7 to <8 hours/night.

We found no evidence of interaction by sex (all p-values:≥0.08) except for the association with diastolic blood pressure (p-for-interaction: 0.03). When stratified by sex, men sleeping 6 to <7 hours/night had a diastolic blood pressure 9.53 mmHg (95% CI: 5.29, 13.77) higher than women sleeping 6 to <7 hours/night; no other differences between men and women across sleep categories were found. Additional adjustment for total energy intake in the multivariate models did not materially change our findings (data not shown). Using a cut-point of ≤1.00 MET to define sleep, as opposed to a cut-point of ≤1.04 METs, did not materially change our findings (data not shown).

## 4. Discussion

This study demonstrates that patients with type 2 diabetes who sleep 7 to <8 hours per night have a better cardiometabolic risk profile, including measures of waist circumference, BMI, triacylglycerol and HDL-cholesterol than those who sleep fewer than 6 hours or more than 9 hours per night. To the best of our knowledge, this is the first epidemiological study to investigate the association between objectively measured sleep duration and a wide range of cardiovascular risk factors independent of potential confounding by objectively measured physical activity and sedentary time. Our findings support the hypothesis that sleep duration is a potentially important and modifiable behaviour related to cardiometabolic risk in individuals with type 2 diabetes who are at high risk of cardiovascular disease.

An inverse association between sleep duration and anthropometric measures is consistent with previous literature. In a meta-analysis of 18 cross-sectional studies, which included a total of more than 604,000 adults [35], each additional hour of sleep was found to be associated with a pooled $\beta$-coefficient for BMI of -0.35 kg/m$^2$ (95% CI: -0.57, -0.12). Several [6, 7], but not all [36], prospective studies have also reported inverse associations between sleep duration and weight gain. For example, in the Quebec Family Study cohort, individuals sleeping 5-6 hours/day gained 1.98 (95% CI: 1.16, 2.82) kg more than those sleeping an average of 7-8 hours/day, over a period of 6-years [6]. Additionally, the risk for developing obesity was shown to be 27% higher among short duration sleepers compared with those sleeping 7-8 hours/day after 6-years of follow-up. Several studies have indicated that a J-shaped association may exist between sleep duration and weight in healthy adults, such that sleeping more than 8 hours/day is similarly related to excess weight as sleeping too few hours [37]. However, we did not find strong evidence indicative of deviation from linearity, which is consistent with a recent study in individuals with type 2 diabetes [18]. Previous studies have found that sleep restriction can adversely affect glucose metabolism in response to a glucose challenge, but not fasting glucose or insulin levels [5, 38]. A recent cross-sectional study also reported no association between sleep duration and fasting glucose, insulin or the homeostatic model assessment (HOMA) index in individuals with or without type 2 diabetes [20], which is consistent with our finding of no clear association between sleep duration and HbA$_{1c}$.

Previous studies examining the association between sleep duration and lipid levels have yielded mixed results [17, 39, 40]. Consistent with our findings, it has previously been shown that longer sleep durations are associated with relatively higher triacylglycerol levels and lower HDL-cholesterol levels [40]. In a cross-sectional study comprised mostly of participants free from diabetes, it was also observed that individuals sleeping >8 hours per night had a borderline significantly lower HDL-cholesterol level relative to individuals sleeping 7-8 hours per night [39]. However, in a similar study to ours, but which included only women with diabetes, Williams et al [17] found no association

between sleep duration and lipid levels, although HDL-cholesterol levels did appear to increase with increasing sleep duration, but only among normotensive individuals.

In the NHANES study, sleeping ≤5 hours compared with sleeping 7-8 hours per night was associated with a 60% higher risk of hypertension in healthy adults aged 32-59 years, but not among individuals aged over 60 years [8]. In a prospective analysis of sleep duration and hypertension in the Whitehall-II study [41], a non-significant inverse association between sleep duration and hypertension was found among women, but not men, sleeping ≤5 hours per night. In our study, we observed no clear associations between sleep duration and blood pressure across sleep duration categories. Explanations for differences between study findings, other than diabetes status, might be the method used for sleep assessment, differences in the age of the participants and differences in covariate selection and adjustment.

The biological mechanisms underlying the relationship between short sleep duration and cardiometabolic risk factors remain to be fully elucidated, but several plausible mechanisms have been suggested in relation to the risk of overweight and obesity [12]. One plausible mechanism to explain our finding is provided by Spiegel et al [4]. In a randomised cross-over trial which involved two days of sleep restriction preceded/followed by two days of sleep extension, Spiegel et al showed that the appetite-stimulating hormone, ghrelin, increased by 28% whereas the appetite suppressing hormone, leptin, decreased by 18% following the two days of sleep restriction. Resultantly, appetite increased by 23%, especially for calorie-dense, high carbohydrate foods. To examine whether the association between sleep duration and anthropometric measures was mediated by energy intake in our analyses we additionally adjusted for total energy intake, but this did not materially change our findings, suggesting that our findings are unlikely explained by self-reported increased food intake. As short sleep duration can also increase feelings of fatigue [42], which may lead to relative reductions in physical activity [43] and resting metabolic rate [44], this may also partly explain the associations we observed. Indeed, we did find that participants sleeping 7 to <8 hours per night tended to be more physically active and less sedentary than those sleeping fewer than 7 hours per night (when expressed relative to time awake).

The current study has a number of strengths. First, to derive sleep duration we used a combination of self-report questionnaire and objectively measured free-living data from a combined heart rate and movement sensor worn continually for four days, unlike previous studies which have tended to use self-report data only [13]. While this method has not been used previously, our MET definition of sleep has been shown to be consistent with a posture indicative of sleep as opposed to a seated posture [30]. MET thresholds are commonly used in the scientific literature to define both low energy expenditure activities such as reading and watching television as well as vigorous intensity activities such as running [45]. In addition, combining self-report and objective data for the assessment of sleep

duration has been recommended in order to overcome the limitations of subjective and objective data when used in isolation [46]. Unlike previous studies, a major strength of our study was that we accounted for objectively measured physical activity and sedentary time in our models, both of which differ by sleep duration. Our study also has a number of limitations. The cross-sectional analysis of our study precludes inference of the direction or causal nature of the observed associations. As such, it is equally plausible that obesity may have influenced sleep duration. However, our results are consistent with the epidemiological evidence indicating that short sleep duration is adversely associated with cardiovascular risk factors [6-9, 13, 33, 47]. We were unable to account for potential confounding by sleep apnoea, the prevalence of which may be as high as 83% in patients with type 2 diabetes [48]. Nevertheless, we have adjusted our analyses for several factors known to be associated with sleep apnoea, and which are currently used for the screening of sleep apnoea (i.e. Berlin Questionnaire [49]), including age, sex, feelings of daytime tiredness and BMI. Finally, although we included many potential confounding variables we cannot exclude the possibility of residual confounding, for example by variation in day-time napping. To address the limitations of the current study future well designed prospective studies are needed which have measures of sleep duration, physical activity, sedentary time and which also account for potential confounding by sleep apnoea and sleep quality.

In summary, our results provide further evidence of the potentially important role of sleep on cardiometabolic risk in people with type 2 diabetes. Examining the prospective association between sleep duration and a wide range of cardiometabolic risk factors, and the likely multiple determinants of sleep duration, will be important for improving the future design of lifestyle interventions aimed at reducing cardiovascular morbidity in this high risk population.

## Acknowledgements

Author contributions

AJMC had full access to all the data in the study and takes responsibility for the accuracy of the data analysis. SJG is a principal investigator for the ADDITION-Plus trial. AJMC, SJG and RKS are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SJG acquired the data. AJMC, SJG and RKS conceived and designed the study. AJMC and KW analysed the data and AJMC, KW, SB, ATP, SJG and RKS interpreted the data. AJMC drafted the manuscript, and all authors critically revised the manuscript for important intellectual content and have approved the final version.

Conflicts of interest

The authors declare that they have no competing interests.

**References**

[1] National Sleep Foundation. How Much Sleep Do We Really Need? . Available from http://www.sleepfoundation.org/article/how-sleep-works/how-much-sleep-do-we-really-need, accessed 20/02 2013

[2] The Sleep Council. (2013) The Great British Bedtime Report. Available from http://www.sleepcouncil.org.uk/wp-content/uploads/2013/02/The-Great-British-Bedtime-Report.pdf, accessed 6th March 2013

[3] The National Sleep Foundation. (2013) National Sleep Foundation 2013 Poll. Available from http://www.sleepfoundation.org/sites/default/files/RPT336%20Summary%20of%20Findings%2002%2020%202013.pdf, accessed 6th March 2013

[4] Spiegel K, Tasali E, Penev P, Van Cauter E (2004) Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Annals of internal medicine 141: 846-850

[5] Spiegel K, Leproult R, Van Cauter E (1999) Impact of sleep debt on metabolic and endocrine function. Lancet 354: 1435-1439

[6] Chaput JP, Despres JP, Bouchard C, Tremblay A (2008) The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. Sleep 31: 517-523

[7] Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB (2006) Association between reduced sleep and weight gain in women. American journal of epidemiology 164: 947-954

[8] Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. (2006) Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension 47: 833-839

[9] Knutson KL, Van Cauter E, Rathouz PJ, et al. (2009) Association between sleep and blood pressure in midlife: the CARDIA sleep study. Archives of internal medicine 169: 1055-1061

[10] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA (2010) Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes care 33: 414-420

[11] Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA (2011) Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. European heart journal 32: 1484-1492

[12] Killick R, Banks S, Liu PY (2012) Implications of sleep restriction and recovery on metabolic outcomes. J Clin Endocrinol Metab 97: 3876-3890. doi: 3810.1210/jc.2012-1845.

[13] Knutson KL (2010) Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. Best practice & research Clinical endocrinology & metabolism 24: 731-743

[14] Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ (2008) Self-reported and measured sleep duration: how similar are they? Epidemiology 19: 838-845. doi: 810.1097/EDE.1090b1013e318187a318187b318180.

[15] Cooper AJ, Brage S, Ekelund U, Wareham NJ, Griffin SJ, Simmons RK (2014) Association between objectively assessed sedentary time and physical activity with metabolic risk factors among people with recently diagnosed type 2 diabetes. Diabetologia 57: 73-82. doi: 10.1007/s00125-00013-03069-00128. Epub 02013 Oct 00123.

[16] Booth JN, Bromley LE, Darukhanavala AP, Whitmore HR, Imperial JG, Penev PD (2012) Reduced physical activity in adults at risk for type 2 diabetes who curtail their sleep. Obesity (Silver Spring) 20: 278-284. doi: 210.1038/oby.2011.1306.

[17] Williams CJ, Hu FB, Patel SR, Mantzoros CS (2007) Sleep duration and snoring in relation to biomarkers of cardiovascular disease risk among women with type 2 diabetes. Diabetes care 30: 1233-1240

[18] Ohkuma T, Fujii H, Iwase M, et al. (2012) Impact of Sleep Duration on Obesity and the Glycemic Level in Patients With Type 2 Diabetes Mellitus: The Fukuoka Diabetes Registry. Diabetes care

[19] Knutson KL, Ryden AM, Mander BA, Van Cauter E (2006) Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. Archives of internal medicine 166: 1768-1774

[20] Knutson KL, Van Cauter E, Zee P, Liu K, Lauderdale DS (2011) Cross-sectional associations between measures of sleep and markers of glucose metabolism among subjects with and without diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study. Diabetes care 34: 1171-1176

[21] Trento M, Broglio F, Riganti F, et al. (2008) Sleep abnormalities in type 2 diabetes may be associated with glycemic control. Acta diabetologica 45: 225-229

[22] Griffin SJ, Simmons RK, Williams KM, et al. (2011) Protocol for the ADDITION-Plus study: a randomised controlled trial of an individually-tailored behaviour change intervention among people with recently diagnosed type 2 diabetes under intensive UK general practice care. BMC public health 11: 211

[23] Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ (2005) Reliability and validity of the combined heart rate and movement sensor Actiheart. European journal of clinical nutrition 59: 561-570

[24] Brage S, Ekelund U, Brage N, et al. (2007) Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity. J Appl Physiol 103: 682-692.

[25] Stegle O, Fallert SV, MacKay DJ, Brage S (2008) Gaussian process robust regression for noisy heart rate data. IEEE transactions on bio-medical engineering 55: 2143-2151

[26] Brage S, Brage N, Franks PW, et al. (2004) Branched equation modeling of simultaneous accelerometry and heart rate monitoring improves estimate of directly measured physical activity energy expenditure. J Appl Physiol 96: 343-351. Epub 2003 Sep 2012.

[27] Sedentary Behaviour Research Network (2012) Letter to the Editor: Standardized use of the terms "sedentary" and "sedentary behaviours". Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 37: 540-542

[28] Henry CJ (2005) Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr 8: 1133-1152.

[29] Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE (2002) Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. International journal of epidemiology 31: 168-174

[30] Newton RL, Jr., Han H, Zderic T, Hamilton MT (2013) The energy expenditure of sedentary behavior: a whole room calorimeter study. PLoS One 8: e63171.

[31] Bingham SA, Gill C, Welch A, et al. (1997) Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. Int J Epidemiol 26: S137-151.

[32] Magee CA, Iverson DC, Huang XF, Caputi P (2008) A link between chronic sleep restriction and obesity: methodological considerations. Public health 122: 1373-1381

[33] Ware JE SC, Davies AR, Stewart AL. In: The MOS Short-Form General Health Survey: Development and Test in a General Population. Publication No. P-7444, Santa Monica, CA: Rand Corp; 1988

[34] Harvard Medical School (2013) Medications that can affect sleep. Available from http://www.health.harvard.edu/newsletters/Harvard_Womens_Health_Watch/2010/July/medications-that-can-affect-sleep, accessed 18/04 2013

[35] Cappuccio FP, Taggart FM, Kandala NB, et al. (2008) Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31: 619-626

[36] Lauderdale DS, Knutson KL, Rathouz PJ, Yan LL, Hulley SB, Liu K (2009) Cross-sectional and longitudinal associations between objectively measured sleep duration and body mass index: the CARDIA Sleep Study. American journal of epidemiology 170: 805-813

[37] Taheri S, Lin L, Austin D, Young T, Mignot E (2004) Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS medicine 1: e62

[38] Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK (2010) Sleep restriction for 1 week reduces insulin sensitivity in healthy men. Diabetes 59: 2126-2133

[39] Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB (2008) Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep 31: 635-643.

[40] Kaneita Y, Uchiyama M, Yoshiike N, Ohida T (2008) Associations of usual sleep duration with serum lipid and lipoprotein levels. Sleep 31: 645-652.

[41] Cappuccio FP, Stranges S, Kandala NB, et al. (2007) Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. Hypertension 50: 693-700

[42] Goel N, Rao H, Durmer JS, Dinges DF (2009) Neurocognitive consequences of sleep deprivation. Seminars in neurology 29: 320-339

[43]    Schmid SM, Hallschmid M, Jauch-Chara K, et al. (2009) Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. The American journal of clinical nutrition 90: 1476-1482

[44]    Tremblay A, Fontaine E, Poehlman ET, Mitchell D, Perron L, Bouchard C (1986) The effect of exercise-training on resting metabolic rate in lean and moderately obese individuals. International journal of obesity 10: 511-517

[45]    Ainsworth BE, Haskell WL, Whitt MC, et al. (2000) Compendium of physical activities: an update of activity codes and MET intensities. Medicine and science in sports and exercise 32: S498-504

[46]    Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC (2001) Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep medicine 2: 389-396

[47]    Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB (2005) Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 28: 1289-1296

[48]    Pamidi S, Tasali E (2012) Obstructive sleep apnea and type 2 diabetes: is there a link? Front Neurol 3: 126. eCollection 2012.

[49]    Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP (1999) Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of internal medicine 131: 485-491

Table 1. Characteristics of the UK *ADDITION-Plus* study (2002-2007) participants according to sleep duration

| | Sleep duration (hours/day) | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | **<6** | **6 to <7** | **7 to <8** | **8 to <9** | **≥9** | **P value** |
| *N* | 44 | 102 | 138 | 84 | 23 | |
| Sleep duration (hours/day) | 5.2 (0.7) | 6.6 (0.3) | 7.4 (0.3) | 8.4 (0.3) | 9.5 (0.7) | |
| Age (years) | 58.6 (6.5) | 58.5 (7.4) | 60.3 (7.2) | 61.9 (7.5) | 65.9 (5.4) | <0.001 |
| Male (%) | 77 | 75 | 66 | 48 | 26 | <0.001 |
| Duration of diabetes (years) | 2.1 (2.3) | 2.2 (1.7) | 2.0 (1.8) | 2.4 (2.1) | 2.4 (2.2) | 0.43 |
| Sex-adjusted energy intake (kcal/ day$^{-1}$) | 1762 (492) | 1834 (494) | 1735 (490) | 1651 (499) | 1662 (499) | 0.15 |
| Total PAEE (kJ kg$^{-1}$ day$^{-1}$) | 40.7 (17.7) | 36.2 (17.4) | 36.7 (16.2) | 29.7 (16.0) | 22.6 (8.2) | <0.001 |
| PAEE/hour (kJ kg$^{-1}$ woken hour$^{-1}$) | 2.17 (0.95) | 2.07 (0.99) | 2.22 (0.97) | 1.91 (1.02) | 1.55 (0.55) | 0.005 |
| Total sedentary time (hours/day) | 11.1 (2.8) | 10.9 (2.6) | 9.4 (2.5) | 9.8 (2.0) | 9.6 (1.8) | <0.001 |
| Percentage woken hour$^{-1}$ sedentary (%) | 0.59 (0.15) | 0.62 (0.15) | 0.57 (0.15) | 0.63 (0.13) | 0.66 (0.12) | 0.008 |
| Managerial socio-economic class (%) | 41 | 51 | 44 | 32 | 26 | 0.02 |
| Current smoker (%) | 20 | 19 | 10 | 10 | 17 | 0.15 |
| Sex-adjusted alcohol intake (g/d) | 11.2 (1.6) | 6.5 (1.0) | 6.6 (0.9) | 9.6 (1.1) | 7.8 (2.2) | 0.03 |
| Tiredness during the day (%) | 34 | 32 | 23 | 27 | 17 | 0.33 |
| Mental health score | 73 (22) | 78 (16) | 79 (18) | 75 (18) | 80 (14) | 0.27 |
| Sleep medication user (%) | 14 | 14 | 12 | 21 | 9 | 0.29 |
| Use anti-hypertensive drugs (%) | 70 | 76 | 67 | 73 | 87 | 0.28 |
| Use hypoglycaemic drugs (%) | 50 | 56 | 50 | 49 | 52 | 0.88 |
| Use lipid-lowering drugs (%) | 73 | 76 | 78 | 74 | 74 | 0.95 |

Values are expressed as means (SD) unless stated otherwise. *P*-values are from *P*-trend, Kruskal-Wallis and chi$^2$ tests, as appropriate.

IQR = interquartile range. PAEE = physical activity energy expenditure.

Table 2. Adjusted means (95% CIs) for cardiovascular risk factors according to sleep duration categories for UK *ADDITION-Plus* study (2002-2007) participants

| | Sleep duration (hours/day) | | | | | P for linear trend | P for quadratic trend |
|---|---|---|---|---|---|---|---|
| | **<6** | **6 to <7** | **7 to <8** | **8 to <9** | **≥9** | | |
| *N* | 44 | 102 | 138 | 84 | 23 | | |
| **CCMR-score** | | | | | | | |
| Age- and sex adjusted | 0.17 (-0.58, 0.92) | 0.08 (-0.42, 0.58) | -0.44 (-0.86, -0.02) | -0.20 (-0.74, 0.35) | 1.33 (0.27, 2.39)* | 0.154 | **0.005** |
| Multivariate adjusted | 0.53 (-0.26, 1.32) | 0.10 (-0.41, 0.61) | -0.39 (-0.81, 0.02) | -0.37 (-0.93, 0.18) | 0.92 (-0.16, 2.00) | 0.839 | **0.004** |
| **CCMR $_{no\,BMI}$** | | | | | | | |
| Age- and sex adjusted | -0.09 (-0.73, 0.55) | 0.07 (-0.35, 0.49) | -0.34 (-0.69, 0.02) | -0.09 (-0.55, 0.37) | 1.29 (0.39, 2.19)* | **0.032** | **0.011** |
| Multivariate adjusted | -0.05 (-0.74, 0.64) | -0.02 (-0.46, 0.43) | -0.29 (-0.65, 0.07) | -0.07 (-0.55, 0.42) | 1.22 (0.28, 2.17)* | 0.075 | **0.013** |
| Multivariate + BMI | -0.24 (-0.94, 0.46) | -0.06 (-0.50, 0.38) | -0.27 (-0.63, 0.09) | 0.02 (-0.46, 0.51) | 1.31 (0.37, 2.25)* | **0.024** | **0.025** |
| **Waist (cm)** | | | | | | | |
| Age- and sex adjusted | 112.92 (109.11, 116.72) | 109.95 (107.42, 112.48) | 108.03 (105.90, 110.16) | 107.41 (104.62, 110.19) | 108.50 (103.08, 113.92) | 0.118 | 0.193 |
| Multivariate adjusted | 116.18 (112.38, 119.98)* | 111.08 (108.64, 113.53) | 108.31 (106.32, 110.30) | 104.98 (102.28, 107.67) | 104.42 (99.19, 109.64) | **<0.001** | 0.201 |
| **BMI (kg/m$^2$)** | | | | | | | |
| Age- and sex adjusted | 33.60 (31.97, 35.23) | 32.42 (31.34, 33.51) | 31.74 (30.82, 32.65) | 31.57 (30.38, 32.77) | 32.35 (30.03, 34.68) | 0.285 | 0.153 |
| Multivariate adjusted | 35.23 (33.59, 36.88)* | 33.00 (31.94, 34.06) | 31.76 (30.90, 32.63) | 30.46 (29.29, 31.62) | 30.57 (28.30, 32.83) | **<0.001** | 0.110 |
| **Systolic BP (mmHg)** | | | | | | | |
| Age- and sex adjusted | 130.40 (125.43, 135.38) | 129.44 (126.11, 132.76) | 129.93 (127.13, 132.73) | 130.11 (126.47, 133.75) | 131.12 (124.03, 138.21) | 0.825 | 0.701 |
| Multivariate adjusted | 132.45 (127.03, 137.87) | 130.28 (126.77, 133.78) | 129.60 (126.74, 132.46) | 129.02 (125.17, 132.86) | 129.48 (122.04, 136.92) | 0.513 | 0.572 |
| Multivariate + BMI | 132.48 (126.94, 138.02) | 130.29 (126.76, 133.81) | 129.60 (126.73, 132.46) | 129.00 (125.12, 132.89) | 129.47 (121.99, 136.94) | 0.515 | 0.571 |
| **Diastolic BP (mmHg)** | | | | | | | |
| Age- and sex adjusted | 77.82 (75.15, 80.49) | 74.75 (72.97, 76.53) | 76.54 (75.04, 78.04) | 76.20 (74.25, 78.15) | 76.69 (72.89, 80.50) | 0.875 | 0.325 |
| Multivariate adjusted | 78.78 (75.87, 81.70) | 75.28 (73.39, 77.17) | 76.18 (74.64, 77.72) | 75.79 (73.72, 77.85) | 76.18 (72.17, 80.18) | 0.427 | 0.205 |
| Multivariate + BMI | 78.44 (75.47, 81.41) | 75.20 (73.31, 77.09) | 76.22 (74.68, 77.76) | 75.96 (73.87, 78.04) | 76.34 (72.32, 80.35) | 0.567 | 0.245 |
| **HbA$_{1c}$ (%)** | | | | | | | |
| Age- and sex adjusted | 6.63 (6.36, 6.90) | 6.80 (6.62, 6.97) | 6.53 (6.38, 6.68) | 6.63 (6.44, 6.83) | 6.79 (6.41, 7.17) | 0.750 | 0.484 |
| Multivariate adjusted | 6.63 (6.36, 6.90) | 6.74 (6.57, 6.92) | 6.56 (6.42, 6.71) | 6.64 (6.44, 6.83) | 6.79 (6.42, 7.17) | 0.688 | 0.482 |
| Multivariate + BMI | 6.60 (6.32, 6.88) | 6.74 (6.56, 6.91) | 6.57 (6.43, 6.71) | 6.65 (6.46, 6.85) | 6.81 (6.43, 7.18) | 0.551 | 0.546 |
| **Triacylglycerol (mmol/l) [1]** | | | | | | | |
| Age- and sex adjusted | 1.75 (1.49, 2.05) | 1.63 (1.46, 1.80) | 1.55 (1.42, 1.70) | 1.67 (1.48, 1.86) | 2.12 (1.70, 2.66)* | 0.175 | **0.014** |
| Multivariate adjusted | 1.66 (1.40, 1.97) | 1.58 (1.41, 1.76) | 1.58 (1.45, 1.73) | 1.73 (1.53, 1.95) | 2.16 (1.71, 2.75)* | 0.075 | **0.035** |
| Multivariate + BMI | 1.59 (1.33, 1.89) | 1.56 (1.40, 1.74) | 1.59 (1.46, 1.74) | 1.76 (1.56, 1.99) | 2.21 (1.75, 2.80)* | **0.026** | 0.059 |
| **Total cholesterol (mmol/l)** | | | | | | | |
| Age- and sex adjusted | 4.40 (4.14, 4.66) | 4.22 (4.05, 4.39) | 4.25 (4.11, 4.40) | 4.39 (4.20, 4.57) | 4.34 (3.97, 4.71) | 0.919 | 0.440 |
| Multivariate adjusted | 4.30 (4.04, 4.56) | 4.21 (4.04, 4.38) | 4.29 (4.15, 4.42) | 4.41 (4.22, 4.59) | 4.30 (3.95, 4.66) | 0.696 | 0.958 |
| Multivariate + BMI | 4.29 (4.03, 4.56) | 4.21 (4.04, 4.37) | 4.29 (4.15, 4.42) | 4.41 (4.22, 4.60) | 4.31 (3.95, 4.67) | 0.664 | 0.977 |
| **HDL-cholesterol (mmol/l)** | | | | | | | |
| Age- and sex adjusted | 1.23 (1.15, 1.32) | 1.18 (1.12, 1.23) | 1.21 (1.16, 1.25) | 1.21 (1.15, 1.27) | 0.99 (0.87, 1.10)* | **0.004** | **0.023** |
| Multivariate adjusted | 1.23 (1.14, 1.32) | 1.19 (1.13, 1.25) | 1.21 (1.16, 1.25) | 1.20 (1.13, 1.26) | 0.98 (0.86, 1.11)* | **0.009** | **0.018** |
| Multivariate + BMI | 1.25 (1.16, 1.34) | 1.20 (1.14, 1.26) | 1.20 (1.15, 1.25) | 1.18 (1.12, 1.25) | 0.97 (0.85, 1.09)* | **0.002** | **0.031** |
| **LDL-cholesterol (mmol/l)** | | | | | | | |
| Age- and sex adjusted | 2.26 (2.02, 2.49) | 2.28 (2.12, 2.43) | 2.28 (2.15, 2.41) | 2.38 (2.22, 2.55) | 2.38 (2.05, 2.70) | 0.424 | 0.902 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multivariate adjusted | 2.20 (1.97, 2.42) | 2.27 (2.13, 2.42) | 2.31 (2.20, 2.43) | 2.37 (2.22, 2.53) | 2.33 (2.03, 2.63) | 0.415 | 0.580 |
| Multivariate + BMI | 2.21 (1.98, 2.43) | 2.28 (2.13, 2.42) | 2.31 (2.19, 2.43) | 2.37 (2.21, 2.53) | 2.33 (2.03, 2.63) | 0.463 | 0.604 |

Numbers in parentheses represent the 95% Confidence Intervals.

Age- and sex adjusted models also included adjustment for trial arm. Multivariate adjusted models included age, sex, trial arm, occupational socio-economic class, PAEE, sedentary time, smoking status, alcohol consumption, self-reported feelings of tiredness, mental health score and sleep affecting medication.

Systolic- and diastolic blood pressure were additionally adjusted for prescription of anti-hypertensive drugs; $HbA_{1c}$ was additionally adjusted for prescription of glucose lowering drugs; triacylglycerol, total cholesterol, HDL- and LDL-cholesterol were additionally adjusted for prescription of lipid-lowering drugs.

[1] Data are geometric means (95% CIs)

* Denotes significant difference from those sleeping 7 to <8 hours/night at p<0.05 using Dunnett's significant difference comparison.