JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
SHORT REPORT

Characteristics of sleep–wake cycle and sleep duration in Japanese type 2 diabetes patients with visceral fat accumulation

Shiro Fukuda[1], Ayumu Hirata[1†], Hitoshi Nishizawa[1]*, Hirofumi Nagao[1], Takekazu Kimura[1], Yuya Fujishima[1], Masaya Yamaoka[1], Junji Kozawa[1], Akihisa Imagawa[1], Tohru Funahashi[2‡], Norikazu Maeda[2], Iichiro Shimomura[1]

Departments of [1]Metabolic Medicine, and [2]Metabolism and Atherosclerosis, Graduate School of Medicine, Osaka University, Osaka, Japan

Keywords
Sleep, Type 2 diabetes mellitus, Visceral fat

***Correspondence**
Hitoshi Nishizawa
Tel.: +81-6-6879-3737
Fax: +81-6-6879-3739
E-mail address: hitoshin1127@endmet.med.osaka-u.ac.jp

J Diabetes Investig 2018; 9: 63–68

doi: 10.1111/jdi.12643

ABSTRACT

Sleep pattern has been shown to be associated with type 2 diabetes mellitus. Here, we investigated the difference in bedtime, waking time and estimated sleep duration in type 2 diabetes mellitus patients with or without visceral fat accumulation, using a questionnaire on sleep patterns. The study participants were 59 Japanese type 2 diabetes mellitus patients (men/women 34/25, age 64.5 ± 12.1 years). Visceral fat accumulation was defined as estimated visceral fat area ≥100 cm^2. The patients with visceral fat accumulation (n = 40) showed significantly later bedtime (23.51 ± 01.27 h in the [+] group vs 22.49 ± 01.23 h in the [–] group) and shorter estimated sleep duration (6.6 ± 1.4 h in the [+] group vs 7.9 ± 1.0 h in the [–] group) on weekdays, compared with those without (n = 19). Later bedtime and shorter estimated sleep duration existed in the type 2 diabetes mellitus patients with visceral fat accumulation, compared with those without.

INTRODUCTION

The prevalence of obesity-related type 2 diabetes mellitus has been increasing worldwide, especially in Asia[1–3]. It is known that Asian diabetes patients have lower body mass indexes (BMI) compared with those of Caucasians[3,4]. Irrespective of BMI (< or ≥25 kg/m^2), visceral fat accumulation leads to dysregulation of adipocytokines, such as hypoadiponectinemia, and results in type 2 diabetes mellitus and metabolic syndrome[5–9]. Recently, we reported that Japanese type 2 diabetes mellitus patients with visceral fat accumulation showed a higher prevalence of dyslipidemia and hypertension, lower plasma adiponectin, and more advanced systemic arteriosclerosis than those without[6,10].

Sleep duration has decreased in the modern lifestyle[11]. Several researchers showed that shorter or longer sleep durations were associated with type 2 diabetes mellitus and metabolic syndrome[12–14]. Recently, we reported that sleep–wake cycle irregularities (later bedtime and later waking time) existed in type 2 diabetes mellitus patients compared with non- type 2 diabetes mellitus patients, although sleep duration was not different[15]. However, there is no report to compare sleep duration or sleep–wake cycle irregularities between type 2 diabetes mellitus patients with visceral fat accumulation and those without.

Here, we show the difference in bedtime, waking time and estimated sleep duration in type 2 diabetes mellitus patients with or without visceral fat accumulation, using a questionnaire on sleep patterns.

METHODS

Participants

The present study was a subanalysis of our previous report[6]. The study participants with type 2 diabetes were enrolled from April 2012 to December 2012 among the patients hospitalized for the control of diabetes at the Division of Endocrinology and Metabolism of Osaka University Hospital, Osaka, Japan, and the patients who visited the 'Diabetes & Metabolic Station' outpatient clinic of Osaka University Hospital. Patients excluded were those whose questionnaires on sleep habits were not completed. All participants were Japanese, and there were no shift-workers in this study. Written consent was obtained. This study complied with the Guidelines of the Ethnical Committees of Osaka University.

Present addresses: †Department of Endocrinology and Metabolism, Ikeda Municipal Hospital, Ikeda, Osaka, Japan.
‡Osaka Health Support Center, Sumitomo Mitsui Banking Corporation, Osaka, Japan.
Received 10 November 2016; revised 25 January 2017; accepted 5 February 2017

Clinical examinations and laboratory tests

Duration of diabetes, weekly alcohol consumption and medications were retrieved through medical interview. The bioelectrical impedance analysis method[16] was used to measure estimated visceral fat area (eVFA). Serum levels of total adiponectin were measured by enzyme-linked immunosorbent assay (human adiponectin ELISA kit; Otsuka Pharmaceutical Co. Tokushima, Japan)[17]. The systemic arteriosclerosis was assessed with vascular ultrasonography, described previously[6,18,19]. The score, '≥2 points,' means that the participants had arteriosclerotic lesions in two or more arteries, which significantly predicts the existence of coronary artery disease[18]. The definitions of visceral fat accumulation (eVFA ≥100 cm^2), diabetic retinopathy, diabetic nephropathy, hypertension, dyslipidemia and metabolic syndrome were the same as previously reported[6].

Questionnaire on sleep patterns

Using the questionnaire as shown in Figure 1, usual bedtime and waking time (at 1-h intervals) were retrieved. Estimated sleep duration (hours) was calculated as waking time − bedtime, as described previously[15].

Statistical analysis

The differences between the two groups were compared by Welch's *t*-test (for continuous variables with normal distribution), Mann–Whitney's *U*-test (for continuous variables with skewed distribution or non-continuous variables) or Fisher's exact test (for frequencies). *P*-values of <0.05 were considered statistically significant. All analyses were carried out with the JMP Pro 11.2.0 (64 bit) for Windows (SAS Institute, Cary, North Carolina, USA).

RESULTS

Participant characteristics

Of the 75 Japanese type 2 diabetes mellitus patients (58 inpatients and 17 outpatients; all patients had eVFA data) enrolled in our previous study[6], we excluded 16 patients (9 inpatients and 7 outpatients) who did not answer the questionnaire on sleep patterns, and finally enrolled 59 patients (49 inpatients and 10 outpatients) in the present study (Table 1). The participants were divided into two groups based on eVFA. We defined 40 participants with an eVFA ≥100 cm^2 as the visceral fat accumulation (+) group, and the 19 remaining participants as the visceral fat accumulation (−) group.

Compared with the visceral fat accumulation (−) group, the (+) group had a significantly higher prevalence of dyslipidemia, higher serum C-peptide and triglyceride, and lower high-density lipoprotein cholesterol. Furthermore, the (+) group showed lower serum adiponectin levels and a higher percentage of participants with systemic vascular score ≥2 points than those of the (−) group, as seen in our previous reports[6,10], whereas there were no significant differences in sex and age.

Assessment of sleep pattern: bedtime, waking time and estimated sleep duration

Figure 2 shows the distribution of bedtime, waking time, and estimated sleep duration on weekdays and holidays in each group. On weekdays, the bedtime was significantly later in the visceral fat accumulation (+) group, compared with the (−) group (23.51 ± 01.27 h in the [+] group vs 22.49 ± 01.23 h in the [−] group; Figure 2a). There was no significant difference in the waking time between the two groups. The estimated sleep duration was significantly shorter in the (+) group than in the (−) group (6.6 ± 1.4 h in the [+] group vs 7.9 ± 1.0 h in the [−] group). Similar results were obtained in the sleep pattern on holidays (Figure 2b). Age in the visceral fat accumulation (−) group tended to be slightly higher than that of the visceral fat accumulation (+) group, although not statistically significant (Table 1). Then, we carried out multivariate analysis, and confirmed a significant correlation between eVFA and estimated sleep duration after adjustment of age (data not shown).

DISCUSSION

In the present study, we showed that type 2 diabetes mellitus patients with visceral fat accumulation had significantly later bedtime and shorter estimated sleep duration compared with those without. Various studies have shown that short sleep duration is an independent risk factor for weight gain[20,21]. It

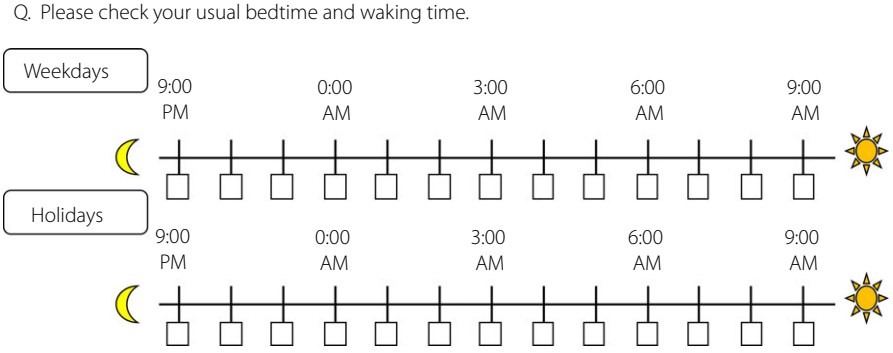

Figure 1 | The questionnaire on sleep patterns used in the present study. The usual 'bedtime' and 'waking time' were retrieved, and the estimated sleep duration was calculated as the difference between 'bedtime' and 'waking time.'

Table 1 | Baseline characteristics of participants

	All	Visceral fat accumulation		*P*-value
		(+) Group	(–) Group	
Total *n* (men/women)	59 (34/25)	40 (25/15)	19 (9/10)	NS[†¶]
Age (years)	64.5 ± 12.1	62.4 ± 13.6	69.1 ± 6.5	NS[‡]
Body mass index (kg/m^2)	26.0 ± 6.2	28.5 ± 6.0	20.8 ± 2.1	<0.001[‡]
Waist circumferences (cm)	93.2 ± 13.8	99.3 ± 11.9	80.3 ± 6.6	<0.001[‡]
eVFA (cm^2)	133.8 ± 70.2	165.4 ± 62.8	67.4 ± 21.2	<0.001[‡]
Duration of diabetes (years)	15.1 ± 10.7	13.2 ± 8.8	19.1 ± 13.2	NS[‡]
Diabetic retinopathy	17 (29%)	9 (23%)	8 (42%)	NS[§]
Diabetic nephropathy	16 (27%)	12 (30%)	4 (21%)	NS[§]
Hypertension	41 (69%)	27 (68%)	14 (74%)	NS[§]
Dyslipidemia	43 (73%)	33 (83%)	10 (53%)	<0.05[§]
Alcohol consumption (g/week)	46.0 ± 103.2	54.8 ± 118.7	23.3 ± 38.9	NS[‡]
Systolic BP (mmHg)	126 ± 16	127 ± 17	124 ± 15	NS[¶]
Diastolic BP (mmHg)	73 ± 13	75 ± 13	70 ± 12	NS[¶]
Glucose (mg/dL)	150 ± 44	153 ± 46	142 ± 40	NS[‡]
HbA1c, NGSP (%)	8.8 ± 1.6	9.0 ± 1.5	8.4 ± 1.9	NS[‡]
Serum C-peptide (ng/mL)	2.2 ± 1.8	2.5 ± 2.0	1.4 ± 0.8	<0.05[‡]
TG (mg/dL)	163 ± 249	192 ± 299	104 ± 42	<0.01[‡]
LDL-C (mg/dL)	104 ± 30	107 ± 32	100 ± 26	NS[¶]
HDL-C (mg/dL)	50 ± 16	45 ± 13	60 ± 17	<0.01[¶]
UA (mg/dL)	5.4 ± 1.5	5.6 ± 1.6	5.0 ± 1.2	NS[¶]
eGFR (mL/min/1.73 m^2)	72.5 ± 20.7	73.8 ± 23.1	70.0 ± 14.5	NS[‡]
uACR (mg/gCr)	72.1 ± 160.9	79.7 ± 184.5	54.6 ± 86.8	NS[‡]
CCA max IMT (mm)	1.76 ± 0.78	1.74 ± 0.82	1.79 ± 0.71	NS[‡]
CCA mean IMT (mm)	0.96 ± 0.26	0.95 ± 0.26	0.98 ± 0.26	NS[‡]
Serum adiponectin (μg/mL)	7.0 ± 5.4 (*N* = 47)	5.4 ± 3.6 (*N* = 32)	10.3 ± 7.0 (*N* = 15)	<0.01[‡]
Systemic vascular score ≥2 points[††]	33 (61%) (*N* = 54)	25 (71%) (*N* = 35)	8 (42%) (*N* = 19)	<0.05[§]
Medications				
For diabetes				
Sulfonylureas	28 (47%)	19 (48%)	9 (47%)	NS[§]
Glinides	5 (8%)	3 (8%)	2 (11%)	NS[§]
Biguanides	18 (31%)	14 (35%)	4 (21%)	NS[§]
Alpha-GIs	13 (22%)	7 (18%)	6 (32%)	NS[§]
Thiazolidinediones	5 (8%)	3 (8%)	2 (11%)	NS[§]
DPP-4 inhibitors	20 (34%)	16 (40%)	4 (21%)	NS[§]
Insulin	12 (20%)	8 (20%)	4 (21%)	NS[§]
GLP-1 analogs	5 (8%)	4 (10%)	1 (5%)	NS[§]
For hypertension				
ACEI/ARBs	24 (41%)	16 (40%)	8 (42%)	NS[§]
For dyslipidemia				
Statins	26 (44%)	18 (45%)	8 (42%)	NS[§]
Sleeping pills	13 (22%)	6 (15%)	7 (37%)	NS[§]

Data are represented as mean ± standard deviation, or number of participants (frequency [%]). [†]Fisher's exact test (men vs women). [‡]Mann–Whitney *U*-test ([+] group vs [–] group). [§]Fisher's exact test ([+] group vs [–] group). [¶]Welch's *t*-test ([+] group vs [–] group). [††]'Systemic vascular score ≥2 points' means the participant had multiple arteriosclerotic lesions. For more information, see the 'Methods' section. ACEI, angiotensin-converting enzyme inhibitor; Alpha-GI, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCA, common carotid artery; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; eVFA, estimated visceral fat area; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; TG, triglyceride; UA, uric acid; uACR, urine albumin-to-creatinine ratio.

was also reported that late bedtime or short sleep duration was associated with eating habits in primary school children[22] and in daytime workers[23]. However, little has been known on the difference in sleep–wake cycle and sleep duration between type 2 diabetes mellitus with visceral fat accumulation and those without. We have shown that type 2 diabetes mellitus patients

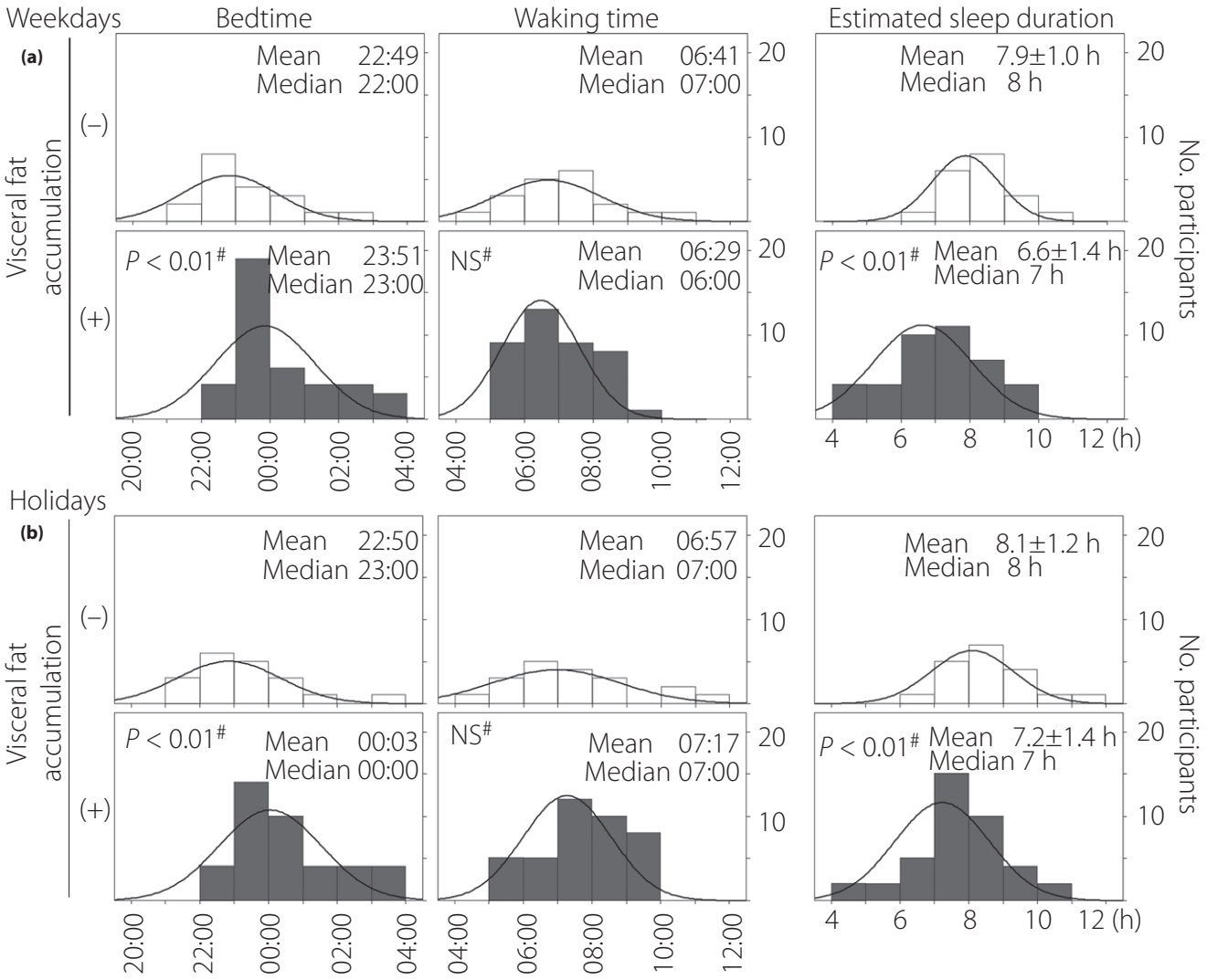

Figure 2 | Histograms of the numbers of type 2 diabetes mellitus participants with visceral fat accumulation (gray) and without (white) for each bedtime, waking time and estimated sleep duration. (a) On weekdays. (b) On holidays. #Mann–Whitney *U*-test (visceral fat accumulation [+] group vs [–] group). NS, not significant.

with visceral fat accumulation showed different eating behavior from those without[6]. A series of recent studies showed that sleep loss resulted in metabolic and endocrine alterations, including reduction of leptin, elevation of ghrelin, dysregulation of cortisol and growth hormone, and impaired glucose tolerance[24–27]. Thus, it is possible that sleep duration, sleep–wake cycle and eating behavior might be reciprocally associated with visceral fat accumulation in type 2 diabetes mellitus patients. In contrast, the present study also showed that visceral fat accumulation was associated with hypoadiponectinemia and elevated systemic vascular score (Table 1). As estimated sleep duration was significantly associated with serum adiponectin level (Figure S1), but not with systemic vascular score in the present study (data not shown), larger studies are required to elucidate the direct association between sleep duration, adiponectin and arteriosclerosis in type 2 diabetes mellitus patients. Taken together, to combat against visceral fat accumulation and arteriosclerosis, it might be helpful for physicians to inquire about the bedtime, waking time and sleep duration of type 2 diabetes mellitus patients, and to support them for modification of their sleep habits.

There were several limitations to the present. First, bedtime, waking time and sleep duration were estimated from the questionnaire. Second, sleep quality (such as sleep apnea syndrome) could not be considered. Third, the influence of factors such as sex and ethnicities cannot be excluded.

In conclusion, type 2 diabetes mellitus patients with visceral fat accumulation showed significantly later bedtime and shorter estimated sleep duration compared with those without visceral fat accumulation.

ACKNOWLEDGMENTS

We thank all members of the Adiposcience Laboratory at Department of Metabolic Medicine, Osaka University for helpful discussions and suggestions. This work was supported in part by Grants-in-Aid for Scientific Research (C) no. 24591351 (HN) and no. 16K09782 (MY), Scientific Research on Innovative Areas no. 22126008 (TF), and Pfizer Health Research Foundation (HN).

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. World Health Organization. Obesity and overweight; WHO Fact Sheet No311; 2013. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html Accessed March 13, 2017.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87: 4–14.
3. Yoon KH, Lee JH, Kim JW, *et al*. Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; 368: 1681–1688.
4. Chan JC, Malik V, Jia W, *et al*. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
5. Okauchi Y, Nishizawa H, Funahashi T, *et al*. Reduction of visceral fat is associated with decrease in the number of metabolic risk factors in Japanese men. *Diabetes Care* 2007; 30: 2392–2394.
6. Fukuda S, Hirata A, Nishizawa H, *et al*. Systemic arteriosclerosis and eating behavior in Japanese type 2 diabetic patients with visceral fat accumulation. *Cardiovasc Diabetol* 2015; 14: 8.
7. Pischon T, Girman CJ, Hotamisligil GS, *et al*. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; 291: 1730–1737.
8. Weyer C, Funahashi T, Tanaka S, *et al*. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001; 86: 1930–1935.
9. Hotta K, Funahashi T, Arita Y, *et al*. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; 20: 1595–1599.
10. Nagao H, Kashine S, Nishizawa H, *et al*. Vascular complications and changes in body mass index in Japanese type 2 diabetic patients with abdominal obesity. *Cardiovasc Diabetol* 2013; 12: 88.
11. Kronholm E, Partonen T, Laatikainen T, *et al*. Trends in self-reported sleep duration and insomnia-related symptoms in Finland from 1972 to 2005: a comparative review and re-analysis of Finnish population samples. *J Sleep Res* 2008; 17: 54–62.
12. Kim J, Kim HM, Kim KM, *et al*. The association of sleep duration and type 2 diabetes in Korean male adults with abdominal obesity: the Korean National Health and Nutrition Examination Survey 2005. *Diabetes Res Clin Pract* 2009; 86: e34–e36.
13. Ju SY, Choi WS. Sleep duration and metabolic syndrome in adult populations: a meta-analysis of observational studies. *Nutr Diabetes* 2013; 3: e65.
14. Ohkuma T, Fujii H, Iwase M, *et al*. U-shaped association of sleep duration with metabolic syndrome and insulin resistance in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *Metabolism* 2014; 63: 484–491.
15. Nakanishi-Minami T, Kishida K, Funahashi T, *et al*. Sleep-wake cycle irregularities in type 2 diabetics. *Diabetol Metab Syndr* 2012; 4: 18.
16. Ryo M, Maeda K, Onda T, *et al*. A new simple method for the measurement of visceral fat accumulation by bioelectrical impedance. *Diabetes Care* 2005; 28: 451–453.
17. Arita Y, Kihara S, Ouchi N, *et al*. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; 257: 79–83.
18. Hirata A, Kishida K, Hiuge-Shimizu A, *et al*. Qualitative score of systemic arteriosclerosis by vascular ultrasonography as a predictor of coronary artery disease in type 2 diabetes. *Atherosclerosis* 2011; 219: 623–629.
19. Hirata A, Kishida K, Nakatsuji H, *et al*. Metabolic syndrome correlates with polyvascular lesions detected by systemic vascular ultrasonography in Japanese people with type 2 diabetes. *Diabetes Res Clin Pract* 2012; 96: e26–e29.
20. Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 731–743.
21. Morselli LL, Guyon A, Spiegel K. Sleep and metabolic function. *Pflugers Arch* 2012; 463: 139–160.
22. Thivel D, Isacco L, Aucouturier J, *et al*. Bedtime and sleep timing but not sleep duration are associated with eating habits in primary school children. *J Dev Behav Pediatr* 2015; 36: 158–165.
23. Nishitani N, Sakakibara H, Akiyama I. Characteristics of short sleeping time and eating behaviors related to obesity. *Obes Res Clin Pract* 2012; 6: e91–e174.
24. Ohkuma T, Fujii H, Iwase M, *et al*. Impact of sleep duration on obesity and the glycemic level in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *Diabetes Care* 2013; 36: 611–617.
25. Taheri S, Lin L, Austin D, *et al*. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004; 1: e62.
26. Kumari M, Badrick E, Ferrie J, *et al*. Self-reported sleep duration and sleep disturbance are independently associated with cortisol secretion in the Whitehall II study. *J Clin Endocrinol Metab* 2009; 94: 4801–4809.

27. Spiegel K, Leproult R, L'hermite-Balériaux M, *et al.* Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab* 2004; 89: 5762–5771.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1| Correlation plot between estimated sleep duration on weekdays and adiponectin. Pearson's correlation coefficient (*r*), its probability value (*P*) and 95% confidence ellipse were overlaid.