Objectively measured sedentary time and diabetes mellitus in a general Japanese population: The Hisayama Study

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ABSTRACT

Aims/Introduction: The present study aimed to examine cross-sectional associations between objectively measured sedentary time and the prevalence of diabetes mellitus in a general Japanese population, and to elucidate possible mediating roles of diet, obesity and insulin resistance in this relationship.

Materials and Methods: A total of 1,758 community-dwelling individuals aged 40–79 years wore an accelerometer for ≥7 days and underwent a comprehensive health examination in 2012. Diabetes mellitus was diagnosed by a 75-g oral glucose tolerance test. The associations of sedentary time with the presence of diabetes mellitus and the levels of the homeostasis model assessment of insulin resistance were estimated by logistic and linear regression models.

Results: After adjustment for demographic and lifestyle factors including moderate-to-vigorous physical activity, participants who spent ≥10 h in sedentary time had a significantly higher odds ratio of the presence of diabetes than those who spent <6 h in sedentary time (odds ratio 1.84, 95% confidence interval 1.02–3.31). This significant association remained after adjusting for overall and central obesity (as measured by body mass index and waist circumference), but weakened after adjusting for dietary energy intake or homeostasis model assessment of insulin resistance. Sedentary time was positively associated with homeostasis model assessment of insulin resistance levels among non-diabetic participants after adjusted for obesity or energy intake (*P* for trend <0.01).

Conclusions: Longer sedentary time was associated with a higher prevalence of diabetes mellitus in a general Japanese population. Insulin resistance appeared to be mainly involved in this association. These results highlight the importance of public health strategies targeting reductions in sedentary time for the primary prevention of diabetes mellitus.

INTRODUCTION

There is an increasing need to explore modifiable risk factors for type 2 diabetes mellitus in order to establish public health strategies for the prevention of this disease. A large body of epidemiological literature shows that a lack of physical activity is a driving factor for the global epidemic of non-communicable diseases[1]. Alongside physical inactivity, sedentary behavior, defined as a prolonged period of behavior involving sitting or reclining, has been shown to confer a high risk of adverse metabolic and vascular health outcomes[2,3]. In addition, prolonged sedentary time might also contribute to the epidemic of diabetes mellitus. A meta-analytic review of longitudinal studies reported that longer television viewing time was associated with increased risk of diabetes mellitus[4]. However, the existing evidence investigating the link between sedentary time and diabetes mellitus is mostly based on self-reported measurement of sedentary time[5–8], which is known to have the potential for measurement error and consequently can result in incorrect inferences.

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Accelerometers are increasingly seeing regular use in epidemiological studies to assess sedentary behavior, because objective measurement devices reduce measurement error and thereby allow more accurate assessment than self-reported measures. However, there are few studies examining the relationships between objectively measured sedentary time and diabetes mellitus, especially in Asian populations. Given the ethnic differences in the pathogeneses of β-cell dysfunction and diabetes mellitus[9], additional investigations of the association between objectively measured sedentary time and diabetes mellitus are required in Asian populations. In addition, several studies have suggested that prolonged sedentary time could cause weight gain and insulin resistance[10–12]; however, it remains unknown whether diet, obesity and insulin resistance could mediate the association between sedentary time and diabetes mellitus. Although adiposity and insulin resistance are thought to be underlying culprits and important precursors of diabetes mellitus, the influence of these metabolic variables has often been neglected in the previous studies, which could account for the inconsistency in the existing evidence on the associations between total sedentary time and diabetes mellitus[13,14].

In the present study, we addressed these issues by examining the associations of objectively measured sedentary time with diabetes mellitus in a Japanese community-dwelling population. Herein, we tested whether longer sedentary time was associated with a higher prevalence of diabetes mellitus, and whether obesity and insulin resistance were involved in these associations.

METHODS
Study population
The Hisayama Study is a prospective population-based cohort study of cardiovascular diseases established in 1961 in Hisayama, a town of approximately 8,400 people located in a suburb of the Fukuoka metropolitan area on the Kyushu Island of Japan. In 2012, a screening examination for the present study was carried out in the town. A detailed description of that study was published previously[15,16]. In brief, 2,900 residents aged between 40 and 79 years (71.6% of the total population of this age range) agreed to participate in the health examination. Of these, 2,142 individuals completed physical activity assessment with an accelerometer. After excluding 358 individuals without valid accelerometer data, 22 for whom fasting blood samples were lacking and four for whom data on total energy intake were unavailable[17], the remaining 1,758 participants were included in the analyses.

The present study was carried out with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from the participants.

Definitions of Sedentary Time
Sedentary time was assessed using a tri-axial accelerometer device (Active style Pro HJA 350-IT; Omron Healthcare Co., Ltd., Kyoto, Japan). Participants were asked to wear the accelerometer device during waking hours for seven consecutive days, except while bathing or sleeping. Data were recorded in 60-s epochs. The intensity of minute-by-minute activities was estimated using a previously validated algorithm[18,19]. Non-wear time was defined as a time period of at least 60 consecutive minutes of no activity (i.e., estimated activity intensity <1.0 metabolic equivalents [METs]), with allowance for up to two consecutive minutes of activities with intensity equal to 1.0 METs. We adapted the SAS macro program for the ActiGraph monitor provided by the National Cancer Institute to compute daily non-wear time[20]. Days with at least 600 min of wear time were considered valid[21]. Participants with at least four valid days were included in the analysis.

In the present study, sedentary time was defined as time spent in activities with an accelerometer-estimated intensity ≤1.5 METs, and was considered a continuous variable (h/day) and categorized as <6, 6–<8, 8–<10 or ≥10 h/day. Moderate-to-vigorous physical activity (MVPA) was defined as activity of ≥3.0 METs. A bout of MVPA lasting for at least 10 min, with allowance for up to 2 min of non-MVPA activity, was considered an MVPA period, which is consistent with the consensus recommendation that physical activity accumulated in periods lasing for ≥10 min benefits health[22]. Individuals who carried out at least 150 min/week of MVPA were considered to be physically active[22].

Outcomes
The outcome of the present study was the presence of diabetes mellitus. Blood samples were collected after an overnight fast. All participants aged 40–79 years except for the participants with severe diabetes or insulin treatment were encouraged to undergo a 75-g oral glucose tolerance test. Among the 1,762 eligible participants, 1,671 (94.8%) underwent the 75-g oral glucose tolerance test, and the remaining participants had a single measurement of fasting plasma glucose concentration. Plasma glucose levels were determined by the hexokinase method. Diabetes was defined as a fasting plasma glucose concentration of ≥7.0 mmol/L or 2-h postload glucose ≥11.1 mmol/L or both, or the use of antidiabetic medications (oral hypoglycemic agents, injectable glucagon-like peptide analogs or insulin).

Potential Mediators
The height and weight were measured with the participant in light clothes without shoes, and body mass index (kg/m^2) was calculated. Overall obesity was defined as a body mass index ≥25.0 kg/m^2. Waist circumference was measured at the umbilical level with the participant standing by a trained staff member, and central obesity was defined as a waist circumference ≥90 cm in men and ≥80 cm in women. Daily total energy intake was estimated by using a semiquantitative food frequency questionnaire[23]. Serum insulin values were measured by a chemiluminescent enzyme immunoassay. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated

with the following formula: fasting plasma glucose (mmol/L) × fasting serum insulin (μU/mL) / 22.5[24].

Measurements of Other Factors

Each participant completed a self-administered questionnaire covering information on medical history, antidiabetic and antihypertensive medication, alcohol intake, and smoking habits. Diabetes in first- or second-degree relatives was taken to indicate a family history of diabetes. Alcohol intake and smoking habits were classified as either current use or not. Current smoking was defined as when the individuals smoked at least one cigarette per day. Current drinking was defined as when the participants consumed at least one alcoholic beverage per month.

Blood pressure was measured three times using an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare Co., Ltd.) with the participant in a seated position after rest for at least 5 min, and the average of the three measurements was used in the analyses. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the current use of antihypertensives. Serum total and high-density lipoprotein cholesterols, and triglycerides were determined enzymatically.

Statistical Analysis

The sex- and age-adjusted mean (standard error) for continuous variables and frequency for categorical variables were estimated by using analysis of covariance and a logistic regression model, respectively. Triglycerides and HOMA-IR values were shown by geometric means and 95% confidence intervals (CI) due to skewed distribution. The trends in mean values or frequencies of each variable across the categories of sedentary time were tested by linear or logistic regression analyses, respectively.

Logistic regression models were used to examine the associations between sedentary time and the presence of diabetes mellitus. The models were adjusted for age, sex, accelerometer wear time, current smoking, drinking habits, family history of diabetes, MVPA, hypertension, total cholesterol, HDL cholesterol and triglycerides. The heterogeneity in the association between subgroups by sex, age (<65/≥65 years) and physical activity (physically active/inactive) was tested by adding multiplicative interaction terms. To test the influence of overall obesity, central obesity and HOMA-IR on the association between sedentary time and diabetes, these variables were included in the multivariable-adjusted model, separately and in combination. We further examined the association of sedentary time with HOMA-IR levels in non-diabetic participants ($n = 1,483$) using an analysis of covariance with Dunnett and Hsu's multiple comparison. All statistical analyses were carried out with SAS 9.3 (SAS Institute, Cary, NC, USA). Two-sided values of $P < 0.05$ were considered statistically significant.

Table 1 | Age- and sex-adjusted characteristics of study participants according to sedentary time

Variables	Sedentary time (h/day)				P for trend
	<6 (n = 470)	6–<8 (n = 668)	8–<10 (n = 453)	≥10 (n = 167)	
Age (years)	61.0 (0.5)	61.0 (0.4)	59.7 (0.5)	63.6 (0.8)	0.42
Men (%)	36 (2.2)	34 (1.8)	48 (2.4)	62 (3.8)	<0.001
Family history of diabetes (%)	22 (1.9)	23 (1.6)	24 (2.0)	23 (3.4)	0.56
Systolic blood pressure (mmHg)	128 (0.8)	128 (0.7)	129 (0.8)	127 (1.3)	0.91
Diastolic blood pressure (mmHg)	77 (0.5)	77 (0.4)	77 (0.5)	75 (0.8)	0.58
Use of antihypertensive agents (%)	24 (2.1)	29 (1.9)	28 (2.3)	35 (4.0)	0.02
Hypertension (%)	44 (2.5)	47 (2.1)	45 (2.6)	50 (4.3)	0.30
BMI (kg/m^2)	22.8 (0.2)	23.2 (0.1)	23.4 (0.2)	23.7 (0.3)	0.002
Overall obesity (%)	22 (1.9)	28 (1.8)	28 (2.1)	33 (3.7)	0.004
Waist circumference (cm)	82.3 (0.4)	83.5 (0.4)	83.8 (0.4)	85.0 (0.7)	<0.001
Central obesity (%)	40 (2.4)	45 (2.0)	44 (2.5)	51 (4.1)	0.03
HOMA-IR	1.21 (1.15, 1.29)	1.41 (1.34, 1.48)	1.40 (1.32, 1.48)	1.49 (1.35, 1.64)	<0.001
Total cholesterol (mmol/L)	5.31 (0.04)	5.29 (0.04)	5.28 (0.04)	5.11 (0.07)	0.048
HDL cholesterol (mmol/L)	1.76 (0.02)	1.66 (0.02)	1.64 (0.02)	1.65 (0.03)	<0.001
Triglycerides[†] (mmol/L)	1.09 (1.04, 1.14)	1.19 (1.15, 1.24)	1.22 (1.16, 1.27)	1.10 (1.02, 1.19)	0.08
Current smoking (%)	12 (1.5)	11 (1.3)	11 (1.5)	10 (2.1)	0.66
Current drinking (%)	53 (2.5)	57 (2.1)	51 (2.6)	45 (4.3)	0.10
Sufficiently physically active (%)	51 (2.3)	31 (1.8)	22 (1.9)	22 (3.1)	<0.001
Dietary energy intake (kcal/day)	1,592 (14.7)	1,570 (12.4)	1,506 (15.0)	1,455 (24.9)	<0.001
Device wear time (h/day)	13.6 (0.1)	14.1 (0.1)	14.8 (0.1)	16.5 (0.1)	<0.001

Data are represented as the least squared means or percentages with standard errors except where noted. [†]Data were log-transformed before analysis due to skewed distribution, and then back-transformed for presentation. Values are represented as geometric means (95% confidence intervals). BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

RESULTS

Of the 1,758 participants, 1,036 (59%) were women and the mean age was 61 years (standard deviation 10 years). The average device wear time was 14.4 h (standard deviation 1.7 h) per day. Table 1 summarizes the characteristics of study participants according to the sedentary time. Participants with greater sedentary time were more likely to be men and physically inactive. Body mass index, waist circumference, HOMA-IR and the device wear time levels increased according to sedentary time. Sedentary time was also associated with lower total and high-density lipoprotein cholesterol levels, and lower dietary energy intake.

Of the study participants, 279 (15.9%) had diabetes mellitus. Table 2 summarizes the prevalence and the odds ratios (ORs) for diabetes according to the categories of sedentary time. The age- and sex-adjusted prevalence of diabetes mellitus was significantly higher in those who spent ≥10 h in sedentary time (18.8%) compared with the group with the least amount of sedentary time (12.5%). After adjusting for age, sex and accelerometer wear time, participants who spent ≥ 10 h in sedentary time had twofold higher odds of having diabetes compared with those who spent <6 h in sedentary time (model 1 OR 2.02, 95% CI 1.18–3.43; *P*-value = 0.01). In the multivariable model adjusted for risk factors including physical activity, these associations remained significant (model 2 OR

1.84, 95% CI 1.02–3.31; *P*-value = 0.04). There was no heterogeneity between men and women in the association between sedentary time and diabetes (*P* for interaction = 0.69). In addition, there was no evidence of any heterogeneity by age groups (*P* for interaction = 0.29) or by physical activity levels (*P* for interaction = 0.51).

Table 3 summarizes the ORs for the presence of diabetes per 2-h increment in sedentary time. In model 2, longer sedentary time was significantly associated with a higher prevalence of diabetes (OR 1.21, 95% CI 1.02–1.42). After adjusting for overall obesity, the association was attenuated, but remained significant, with an 8.4% reduction in log OR. Similarly, the association diminished slightly when central obesity was added to model 2 (% reduction in log OR, 9.3%). Sedentary time was marginally associated with the presence of diabetes after adjusting for daily energy intake, with a 17% reduction in log OR. In contrast, after additionally including HOMA-IR in the multivariable model, the associations were attenuated to the null (OR 1.15, 95% CI 0.97–1.37; % reduction in log OR, 26.3%). When energy intake and HOMA-IR were added to the model together, the log OR was reduced to a greater extent than when the model was adjusted for either variable alone (% reduction in log OR, 46.8%).

The characteristics of non-diabetic participants (*n* = 1,479) according to sedentary time are shown in Table S1. Figure 1

Table 2 | Odds ratios (95% confidence intervals) for the presence of diabetes according to levels of sedentary time

Sedentary time (h/day)	Age- and sex-adjusted prevalence, %	No. events/at risk	Model 1		Model 2	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
<6	12.5	64/470	1.00 (Ref)		1.00 (Ref)	
6–<8	13.7	101/668	1.15 (0.81–1.63)	0.43	1.08 (0.73–1.58)	0.71
8–<10	14.3	72/453	1.29 (0.87–1.91)	0.21	1.28 (0.83–1.97)	0.27
≥10	18.8	42/167	2.02 (1.18–3.43)	0.01	1.84 (1.02–3.31)	0.04
P for trend				0.02		0.05

Model 1 was adjusted for age, sex and accelerometer wear time. Model 2 was adjusted for age, sex, accelerometer wear time, family history of diabetes, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking habits, alcohol intake and moderate-to-vigorous physical activity. 95% CI, 95% confidence interval; OR, odds ratio.

Table 3 | Odds ratios (95% confidence intervals) for the presence of diabetes according to each 2-h increment in sedentary time

Model	OR (95% CI)[†]	*P* value	Log OR	%Reduction in log OR
Model 2	1.21 (1.02–1.42)	0.03	0.187	(Reference)
Model 2 + overall obesity	1.19 (1.004–1.40)	0.045	0.171	8.4
Model 2 + central obesity	1.18 (1.002–1.40)	0.047	0.169	9.3
Model 2 + dietary energy intake	1.17 (0.99–1.38)	0.07	0.155	17.2
Model 2 + HOMA-IR	1.15 (0.97–1.37)	0.12	0.138	26.3
Model 2 + dietary energy intake and HOMA-IR	1.10 (0.93–1.32)	0.27	0.099	46.8

The multivariable model (model 2) was adjusted for age, sex, wear time, family history of diabetes, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking habits, alcohol intake and moderate-to-vigorous physical activity. [†]Values represent odds ratios for each 2-h increment in sedentary time. 95% CI, 95% confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio.
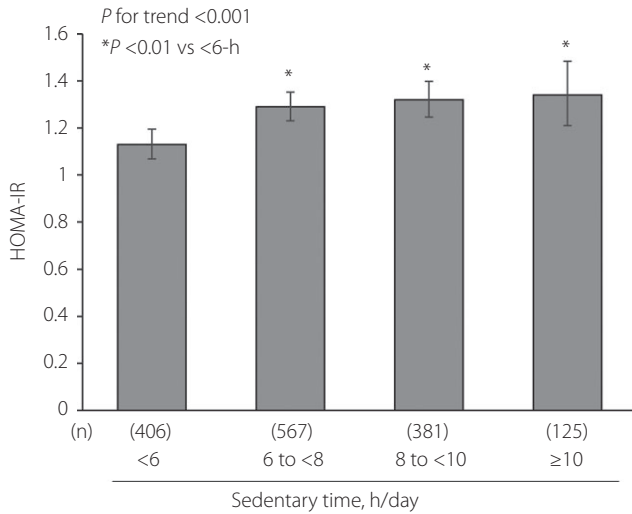
Figure 1 | Geometric means and 95% confidence intervals of the homeostasis model assessment of insulin resistance (HOMA-IR) levels according to sedentary time among non-diabetic individuals. *$P < 0.05$ versus the <6 h group. Values are presented as the geometric means adjusted for age and sex.

shows the age-and sex-adjusted mean values of HOMA-IR levels across sedentary time among non-diabetic participants. Compared with individuals who spent <6 h per day in sedentary time, those who had greater amounts of sedentary time had increased levels of HOMA-IR (all $P < 0.01$). As shown in Table 4, longer sedentary time was significantly positively associated with HOMA-IR levels after multivariable adjustment. In addition, only minor changes in the association were observed even after adjusting for overall or central obesity, or dietary energy intake (% reduction in beta coefficients ranged between −3.2 and 7.6%).

DISCUSSION

The present study clearly shows a positive association between objectively measured sedentary time and diabetes independent of demographic and lifestyle factors, including moderate-to-vigorous physical activity. In addition, the present findings suggested that the insulin resistance mainly contributed to this association. We also showed that sedentary time was positively associated with higher levels of markers of insulin resistance, even in non-diabetic individuals. To our knowledge, this is the first study examining objectively measured sedentary time and diabetes in a community-dwelling population in Asia. Our findings underscore the need for public health messages and policies to reduce sedentary time for the prevention of diabetes.

The current study found that objectively measured sedentary time was associated with diabetes independent of physical activity, which is in accordance with previous findings of accelerometer studies from the USA and the Netherlands population-based studies[25,26]. Our findings have extended these

Table 4 | Geometric means of homeostasis model assessment of insulin resistance level according to sedentary time among non-diabetic participants

	Sedentary time, h/day				P for trend	Beta coefficients (95% CI)†	P for continuous	%Reduction in beta coefficients
	<6 (n = 406)	6–<8 (n = 567)	8–<10 (n = 381)	≥10 (n = 125)				
Model 2	1.19 (1.13–1.26)	1.26 (1.21–1.31)	1.29 (1.22–1.35)	1.36 (1.24–1.50)	0.01	0.053 (0.022–0.084)	<0.001	(reference)
Model 2 + overall obesity	1.19 (1.13–1.26)	1.26 (1.21–1.31)	1.29 (1.23–1.36)	1.37 (1.24–1.50)	0.01	0.051 (0.021–0.080)	<0.001	4.2
Model 2 + central obesity	1.19 (1.13–1.26)	1.26 (1.21–1.32)	1.29 (1.23–1.36)	1.35 (1.23–1.49)	0.02	0.052 (0.022–0.082)	0.001	7.6
Model 2 + dietary energy intake	1.19 (1.12–1.25)	1.26 (1.21–1.32)	1.28 (1.22–1.35)	1.39 (1.26–1.54)	0.01	0.0546 (0.023–0.086)	<0.001	−3.2

The multivariable model (model 2) was adjusted for age, sex, wear time, family history of diabetes, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking habits, alcohol intake and moderate-to-vigorous physical activity. †Beta coefficients represent changes in the natural log of homeostasis model assessment of insulin resistance by each 2-h increment in sedentary time. 95% CI, 95% confidence interval.

works by showing the associations in an Asian population. In addition, several studies have shown an association between self-reported sitting time and the presence of diabetes mellitus[8,14,27,28]. The present findings support the notion that prolonged sedentary time increases the risk of having diabetes independent of physical activity levels.

In the current analysis, the association between sedentary time and diabetes mellitus remained significant after adjusting for overall and central obesity. Our findings suggested that adiposity had only minor effects on the association between sedentary time and diabetes mellitus. In contrast, the association was partly mediated by diet, which might have been a result of overconsumption or snacking during seated behaviors, such as television viewing[29]. In contrast, HOMA-IR attenuated the association between sedentary time and diabetes mellitus, suggesting that the association might be largely attributable to insulin resistance. In support of this idea, we observed that sedentary time was positively associated with HOMA-IR levels in non-diabetic participants in a dose–response manner. There has been some epidemiological evidence that prolonged sedentary time was unfavorably associated with markers of insulin resistance[30–32]. Two previous cross-sectional and prospective studies reported observing no evidence of significant associations, but these studies were somewhat limited by their relatively small sample sizes[33,34]. Furthermore, the present study showed that the observed association remained significant, even after adjustment for obesity and dietary energy intake, suggesting that the link between sedentary time and insulin resistance might not be explained by nutritional status. These results are suggestive of a physiological pathway in which prolonged sedentary time first induces insulin resistance, irrespective of obesity or dietary energy intake, and thereby raises the risk of having diabetes.

The mechanisms underlying the link between sedentary behavior and insulin resistance remain to be fully elucidated. One possible explanation is that prolonged muscle disuse leads to muscle atrophy and a shift in muscle fiber type, which in turn contributes to muscle insulin resistance. As shown in an experimental study, 5 days of bed rest, an extreme form of physical inactivity, can induce various metabolic risks, including insulin resistance[35]. Evidence from another study using an animal model suggested that short periods of inactivity could increase phosphorylation of some mitogen-activated protein kinases, such as p38 and c-Jun NH2-terminal kinase[36]. Excessive activation of these kinases might interact with the region upstream of the insulin-signaling cascade, and particularly with insulin receptor substrate 1, leading to the insulin resistance in skeletal muscle[37].

The strength of the present study was that sedentary time was estimated objectively by means of an accelerometer device, which has a validated low-intensity-specific algorithm for the estimation of activity intensity. In addition, diabetes mellitus was determined precisely using a 75-g oral glucose tolerance test. However, several limitations should also be noted. First, the cross-sectional nature of this study precludes conclusions regarding causality. Given the difficulty in separating direct and indirect effects in the approach for introducing intermediate terms into the regression model[38], further intervention and longitudinal studies focusing specifically on the potential mediating role of insulin resistance and other metabolic variables are required to confirm the present results. Second, the accelerometer we used is unable to differentiate standing and sitting, which might cause posture misclassification during the activities; this could lead to an underestimation of associations between accelerometer-derived sedentary time and diabetes. Finally, although the current analyses were adjusted for known demographic and lifestyle factors, the potential for unmeasured or residual confounders, such as educational level, still exists.

In conclusion, the findings of the present study suggest that time spent in sedentary behavior is associated with a greater likelihood of having diabetes mellitus, independent of physical activity, in the general Japanese population. In addition, insulin resistance seems to be involved in this association. These results highlight the importance of public health strategies targeting reductions in sedentary time for the prevention of diabetes.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Lee IM, Shiroma EJ, Lobelo F, *et al.* Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012; 380: 219–229.
2. Owen N, Healy GN, Matthews CE, *et al.* Too much sitting: the population-health science of sedentary behavior. *Exerc Sport Sci Rev* 2010; 38: 105–113.

3. Biswas A, Oh PI, Gaulkner GE, *et al*. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med* 2015; 162: 123–132.

4. Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA* 2011; 305: 2448–2455.

5. Hu FB, Leitzmann MF, Stampfer MJ, *et al*. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* 2001; 161: 1542–1548.

6. Hu FB, Li TY, Colditz GA, *et al*. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 2003; 289: 1785–1791.

7. Ford ES, Schulze MB, Kröger J, *et al*. Television watching and incident diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. *J Diabetes* 2010; 2: 23–27.

8. Hsueh MC, Liao Y, Chang SH. Associations of total and domain-specific sedentary time with type 2 diabetes in Taiwanese older adults. *J Epidemiol* 2016; 26: 1–7.

9. Chan JC, Malik V, Jia W, *et al*. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.

10. Ekelund U, Brage S, Besson H, *et al*. Time spent being sedentary and weight gain in healthy adults: reverse or bidirectional causality? *Am J Clin Nutr* 2008; 88: 612–617.

11. Helmerhorst HJF, Wijndaele K, Brage S, *et al*. Objectively measured sedentary time may predict insulin resistance independent of moderate- and vigorous-intensity physical activity. *Diabetes* 2009; 58: 1776–1779.

12. Ford ES, Li C, Zhao G, *et al*. Sedentary behavior, physical activity, and concentrations of insulin among US adults. *Metab, Clin Exp* 2010; 59: 1268–1275.

13. Smith L, Hamer M. Television viewing time and risk of incident diabetes mellitus: the English Longitudinal Study of Ageing. *Diabet Med* 2014; 31: 1572–1576.

14. Petersen CB, Bauman A, Tolstrup JS. Total sitting time and the risk of incident diabetes in Danish adults (the DANHES cohort) over 5 years: a prospective study. *Br J Sport Med* 2016; 50: 1382–1387.

15. Mukai N, Doi Y, Ninomiya T *et al*. Trends in the prevalence of type 2 diabetes and prediabetes in community-dwelling Japanese subjects: the Hisayama Study. *J Diabets Investig* 2014;5:162–169.

16. Hata J, Ninomiya T, Hirakawa Y, *et al*. Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961-2009). *Circulation* 2013; 128: 1198–1205.

17. Hata A, Doi Y, Ninomiya T *et al*. Magnesium intake decreases type 2 diabetes risk through the improvement of insulin resistance and inflammation: the Hisayama Study. *Diabet Med* 2013;30:1487–1494.

18. Oshima Y, Kawaguchi K, Tanaka S, *et al*. Classifying household and locomotive activities using a triaxial accelerometer. *Gait Posture* 2010; 31: 370–374.

19. Ohkawara K, Oshima Y, Hikihara Y, *et al*. Real-time estimation of daily physical activity intensity by a triaxial accelerometer and a gravity-removal classification algorithm. *Br J Nutr* 2011; 105: 1681–1691.

20. National Institute of Cancer: SAS Programs for Analyzing NHANES 2003-2004 Accelerometer Data. Available from https://epi.grants.cancer.gov/nhanes_pam/ Accessed November 30, 2017.

21. Matthews CE, Chen KY, Freedson PS, *et al*. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am J Epidemiol* 2008; 167: 875–881.

22. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva: Global Recommendations on Physical Activity for Health, 2010.

23. Shirota T, Yoshizumi E. A study on convenient dietary assessment [Japanese]. *Jpn J Public Health* 1990; 37: 100–108. (Japanese)

24. Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.

25. Gibbs BB, Gabriel KP, Reis JP, *et al*. Cross-sectional and longitudinal associations between objectively measured sedentary time and metabolic disease: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetes Care* 2015; 38: 1835–1843.

26. van der Berg JD, Stehouwer CD, Bosma H, *et al*. Associations of total amount and patterns of sedentary behaviour with type 2 diabetes and the metabolic syndrome: the Maastricht Study. *Diabetologia* 2016; 59: 709–718.

27. Larsen BA, Martin L, Strong DR. Sedentary behavior and prevalent diabetes in Non-Latino Whites, Non-Latino Blacks and Latinos: findings from the National Health Interview Survey. *J Pub Health* 2015; 37: 634–640.

28. Åsvold BO, Midthjell K, Krokstad S *et al*. Prolonged sitting may increase diabetes risk in physically inactive individuals: an 11 year follow-up of the HUNT Study, Norway. 2017. *Diabetologia* 2017;60:830–835.

29. Gore SA, Foster JA, DiLillo VG, *et al*. Television viewing and snacking. *Eat Behav* 2003; 4: 399–405.

30. Brocklebank LA, Falconer CL, Page AS, *et al*. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. *Prev Med* 2015; 76: 92–102.

31. Qi Q, Strizich G, Merchant G, *et al*. Objectively measured sedentary time and cardiometabolic biomarkers in US Hispanic/Latino adults: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Circulation* 2015; 132: 1560–1569.

32. Healy GN, Matthews CE, Dunstan DW, *et al.* Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *Eur Heart J* 2011; 32: 590–597.

33. Ekelund U, Brage S, Griffin SJ *et al.* Objectively measured moderate- and vigorous-intensity physical activity but not sedentary time predicts insulin resistance in high-risk individuals. *Diabetes Care* 2009;32:1081–1086.

34. McGuire KA, Ross R. Sedentary behavior is not associated with cardiometabolic risk in adults with abdominal obesity. *PLoS ONE* 2011; 6: e20503.

35. Hamburg NM, McMackin CJ, Huang AL, *et al.* Physical inactivity rapidly induces insulin resistance and

36. microvascular dysfunction in healthy volunteers. *ATVB* 2007; 27: 2650–2656.

36. Bergouignan A, Rudwill F, Simon C, *et al.* Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. *J Appl Physiol* 2011; 111: 1201–1210.

37. Kawamoto E, Koshinaka K, Yoshimura T, *et al.* Immobilization rapidly induces muscle insulin resistance together with the activation of MAPKs (JNK and p38) and impairment of AS160 phosphorylation. *Physiol Rep* 2016; 4: 1–13.

38. Cole SR, Hernán MA. Fallibility in estimating direct effects. *Int J Epidemiol* 2002; 31: 163–165.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Age- and sex-adjusted characteristics of non-diabetic participants according to sedentary time.