Objectively Measured Physical Activity and Sedentary Time Are Associated With Cardiometabolic Risk Factors in Adults With Prediabetes: The PREVIEW Study

Nils Swindell,[1] Kelly Mackintosh,[1] Melitta McNarry,[1] Jeffrey W. Stephens,[1] Diewertje Sluik,[2] Mikael Fogelholm,[3] Mathijs Drummen,[4] Ian MacDonald,[5] J. Alfredo Martinez,[6] Teodora Handjieva-Darlenska,[7] Sally D. Poppitt,[8] Jennie Brand-Miller,[9] Thomas M. Larsen,[10] Anne Raben,[10] and Gareth Stratton[1]

Diabetes Care 2018;41:562–569 | https://doi.org/10.2337/dc17-1057

OBJECTIVE

The aim of the present cross-sectional study was to examine the association among physical activity (PA), sedentary time (ST), and cardiometabolic risk in adults with prediabetes.

RESEARCH DESIGN AND METHODS

Participants (*n* = 2,326; 25–70 years old, 67% female) from eight countries, with a BMI >25 kg · m^{-2} and impaired fasting glucose (5.6–6.9 mmol · L^{-1}) or impaired glucose tolerance (7.8–11.0 mmol · L^{-1} at 2 h), participated. Seven-day accelerometry objectively assessed PA levels and ST.

RESULTS

Multiple linear regression revealed that moderate-to-vigorous PA (MVPA) was negatively associated with HOMA of insulin resistance (HOMA-IR) (standardized β = −0.078 [95% CI −0.128, −0.027]), waist circumference (WC) (β = −0.177 [−0.122, −0.134]), fasting insulin (β = −0.115 [−0.158, −0.072]), 2-h glucose (β = −0.069 [−0.112, −0.025]), triglycerides (β = −0.091 [−0.138, −0.044]), and CRP (β = −0.086 [−0.127, −0.045]). ST was positively associated with HOMA-IR (β = 0.175 [0.114, 0.236]), WC (β = 0.215 [0.026, 0.131]), fasting insulin (β = 0.155 [0.092, 0.219]), triglycerides (β = 0.106 [0.052, 0.16]), CRP (β = 0.106 [0.39, 0.172]), systolic blood pressure (BP) (β = 0.078 [0.026, 0.131]), and diastolic BP (β = 0.106 [0.39, −0.172]). Associations reported between total PA (counts · min^{-1}), and all risk factors were comparable or stronger than for MVPA: HOMA-IR (β = −0.151 [−0.194, −0.107]), WC (β = −0.179 [−0.224, −0.134]), fasting insulin (β = −0.139 [−0.183, −0.096]), 2-h glucose (β = −0.088 [−0.131, −0.045]), triglycerides (β = −0.117 [−0.162, −0.071]), and CRP (β = −0.104 [−0.146, −0.062]).

CONCLUSIONS

In adults with prediabetes, objectively measured PA and ST were associated with cardiometabolic risk markers. Total PA was at least as strongly associated with cardiometabolic risk markers as MVPA, which may imply that the accumulation of total PA over the day is as important as achieving the intensity of MVPA.

[1]Swansea University, Swansea, Wales, U.K.
[2]Division of Human Nutrition, Wageningen University & Research, Wageningen, the Netherlands
[3]University of Helsinki, Helsinki, Finland
[4]Maastricht University, Maastricht, the Netherlands
[5]University of Nottingham, Nottingham, U.K.
[6]University of Navarra, Pamplona, Spain, and CIBERObn and IMDEA, Instituto de Salud Carlos III, Madrid, Spain
[7]Medical University of Sofia, Sofia, Bulgaria
[8]University of Auckland, Auckland, New Zealand
[9]University of Sydney, Sydney, Australia
[10]University of Copenhagen, Copenhagen, Denmark

Corresponding author: Nils Swindell, 835228@swansea.ac.uk.

Received 26 May 2017 and accepted 4 November 2017.

Clinical trial reg. no. NCT01777893, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1057/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

The global prevalence of diabetes among adults has almost quadrupled since 1980 to 422 million cases in 2014, and continued growth is expected (1). This dramatic rise in prevalence is largely due to the increase in type 2 diabetes, which accounts for the majority of all diagnosed cases in adults (1). Changes in lifestyle factors such as sedentary behavior, insufficient physical activity (PA), dietary choices, and excess weight are important contributors to the development of type 2 diabetes (2). PA plays an important role, independent of weight, in the prevention of type 2 diabetes through its effect on insulin resistance (3). PA leads to the translocation of GLUT4 transporters to the plasma membrane, increasing glucose uptake into skeletal muscle (4). Sedentary time (ST) has also been associated with insulin resistance and fasting triglyceride levels, independent of PA and obesity (5). ST is thought to affect carbohydrate metabolism by decreasing muscle GLUT4 concentrations while also reducing lipoprotein lipase activity and triglyceride clearance (6,7).

Light activity is also associated with cardiometabolic health and, together with ST, occupies the majority of waking hours (8). Indeed, light-intensity activity substantially contributes to overall daily energy expenditure and may also mean spending less time in sedentary behaviors.

Many studies reporting associations between PA, ST, and cardiometabolic risk factors are limited by the self-reported measures of PA and ST (9,10), which are susceptible to reporting and recall bias. In the limited number that have used objective measures of PA, investigations of international samples measured concurrently with the same protocol are lacking and little consistency exists with regard to the devices, wear-time criteria, intensity cut points, or epoch lengths used, thereby limiting the ability to make comparisons between these studies. Furthermore, despite those with prediabetes being at the highest risk of developing type 2 diabetes and representing the population for which many lifestyle interventions are targeted, few studies have described the relationship between PA and insulin resistance in this population.

Typically, epidemiological research assessing the effect of PA and ST on cardiometabolic risk factors has been conducted in the general population (8,11,12). The few studies conducted in high-risk populations have included participants based on a risk score questionnaire (5) or family history of type 2 diabetes (9,13), or participants diagnosed with diabetes and prediabetes have been combined (14). Consequently, physical characteristics and metabolic parameters of study participants varied substantially. As a result, it is unclear to what extent reported associations could be inferred to individuals with prediabetes.

Therefore, the purpose of this study was to quantify the relationship between objectively measured PA and ST with cardiometabolic health and risk of diabetes.

RESEARCH DESIGN AND METHODS

Participants and Setting

A detailed account of the PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World (PREVIEW) project has previously been published (15). Participants were recruited into PREVIEW between June 2013 and February 2015. PREVIEW is a large multinational diabetes prevention intervention being conducted at eight study sites: University of Copenhagen (Denmark), University of Helsinki (Finland), University of Maastricht (the Netherlands), University of Nottingham (U.K.), University of Navarra (Spain), Medical University of Sofia (Bulgaria), University of Sydney (Australia), and University of Auckland (New Zealand).

Participants were selected through an Internet-based prescreening tool or telephone interview using the Finnish Diabetes Risk Score (16). A total of 15,611 individuals were contacted for prescreening. Potential participants were sent a written description of the trial, were given verbal information at the study site, and signed informed consent prior to a laboratory screening. The laboratory screening was attended by 5,472 participants and included assessment of body mass, stature, and resting blood pressure (BP) and a 2-h oral glucose tolerance test (OGTT) (17). Glucose concentrations were analyzed at each study site (HemoCue, Angelholm, Sweden; Reflotron, Roche Diagnostics, Switzerland; or EML105 Radiometer, Copenhagen, Denmark) to identify people with preexisting diabetes.

At the end of this process, 2,326 participants met the following inclusion criteria and were found eligible to take part in the study: age 25–70 years, BMI >25 kg/m^2, and prediabetes confirmed at OGTT. Prediabetes was defined in line with World Health Organization/International Diabetes Federation and American Diabetes Association criteria (17) as either *1*) impaired fasting glucose, with venous plasma glucose concentration of 5.6–6.9 mmol $\cdot$ L^{-1}, or *2*) impaired glucose tolerance, with venous plasma glucose concentration of 7.8–11.0 mmol $\cdot$ L^{-1} at 2 h and fasting plasma glucose <7.0 mmol $\cdot$ L^{-1}. Participants were free of preexisting type 2 diabetes and of any illness and/or medication with a potential effect on compliance or the outcomes of the study.

Measurements and Procedures

Physical Activity

Participants wore an ActiSleep+ (ActiGraph LLC, Pensacola, FL) accelerometer attached to an elastic waist belt worn over the right midaxillary line. The ActiSleep+ was worn 24 h $\cdot$ day^{-1} for seven consecutive days, with removal only for water-based activities. The principal output from the ActiSleep+ is an activity count, which represents raw accelerations that have been rescaled and filtered. Activity counts were collected at 100 Hz and aggregated to 60-s epochs (18). Sleep time was determined using a fully automated algorithm developed for use in 24-h waist-worn accelerometer protocols. The algorithm produces estimates of a nocturnal sleep period that are compared with an expert visual inspection of accelerometer trace (19). After the removal of nocturnal sleep episodes, participants were included in the analyses if they wore the monitor for $\geq$10 h on $\geq$4 days (18) including 1 weekend day (20). Mean activity count during valid wear time (counts $\cdot$ min^{-1} [CPM]) has been shown to correlate well with total activity energy expenditure measured by the doubly labeled water technique (21) and was used as an indicator of total PA volume (18,22). Troiano cut points (18) were used to determine time (min $\cdot$ day^{-1}) spent at different intensity categories (sedentary $<$100, moderate $<$2,020, and vigorous $<$5,999 CPM). Moderate and vigorous activity were summed to obtain moderate-to-vigorous PA (MVPA).

Cardiometabolic Risk Factors

In all study centers, standardized procedures were followed and measurements were performed by trained personnel. Self-administered questionnaires, accelerometer data, and fasting blood samples were collected at baseline. Blood was

drawn from the vein in the antecubital fossa after fasting (>10 h). Blood samples were initially stored locally at −80°C and then transported and analyzed centrally at the National Institution for Health and Welfare (THL) in Helsinki, Finland, where they were analyzed for insulin, HbA_{1c}, glucose, hs-CRP, total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol concentrations. Insulin resistance was calculated using HOMA of insulin resistance (HOMA-IR) with the following equation: HOMA-IR = fasting insulin ($mU \cdot L^{-1}$) × fasting glucose ($mmol \cdot L^{-1}$)/22.5. HOMA-IR has been validated against the gold standard hyperinsulinemic-euglycemic clamp technique (23). Total adiposity was assessed by DEXA at four sites (Copenhagen, Nottingham, Sydney, and Auckland), by bioelectrical impedance at three (Helsinki, Sofia, and Navarra), and with BOD POD (Maastricht) at one. Self-administered questionnaires assessed general and socioeconomic variables, including ethnicity, educational status, and household income.

Statistical Analysis

Descriptive statistics (mean ± SD) were calculated for continuous variables and frequencies (%) for categorical variables.

Two-fifths of the participants had a missing value on at least one variable; HOMA-IR was missing in 7.8% of all cases, while 17% of values were missing for the accelerometer values (CPM, MVPA, and ST). Multiple imputation with a fully conditional specification model (Markov chain Monte Carlo) was used to impute missing values. All variables were included in the imputation, and all variables with skewed distribution were log_{10}- or square root–transformed prior to imputation (24). Ten multiple imputed data sets were generated, and pooled estimates were reported. Owing to their positively skewed distribution, HDL cholesterol, triglycerides hs-CRP, and waist circumference were logarithmically transformed (log_{10}), while HOMA-IR was square root–transformed.

Separate multiple linear regression models were performed to test the independent association of MVPA, CPM, and ST with cardiometabolic health markers (HOMA-IR, fasting insulin, fasting plasma glucose, 2-h glucose, HbA_{1c}, waist circumference, triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol) and CRP with adjustment for potential confounders.

Model 1 was adjusted for age, sex, ethnicity (Caucasian, Asian, black, Arabic, Hispanic, or other), smoking (daily, less than weekly, and no smoking), accelerometer wear time, intervention center, sleep duration, body fat%, education level (no formal education, primary/junior school, secondary school, secondary vocational education, higher vocational education, or university education), and household income (less than £9,360, £9,360–12,479.99, £12,480–15,599.99, £15,600–18,719.99, £18,720–22,879.99, £22,880–27,559.99, £27,560–32,759.99, £32,760–41,079.99, £41,080–53,559.99, and £53,560 or more per year). Model 2 was additionally adjusted for ST when MVPA was the main exposure variable or for MVPA when ST was the main exposure variable.

Sex, age (<45.9, 46–54.9, and >55 years), BMI, and intervention center differences in the associations between MVPA, ST, or CPM and each cardiometabolic risk factor were tested for by adding interaction terms to the model.

A variance inflation factor of <4 confirmed that multicollinearity was not a concern (25). Square root and log transformations were directly compared across cardiometabolic markers and results of linear regression analysis presented as standardized β-coefficients. Data were analyzed using the Statistical Package for the Social Sciences, version 22.0 (SPSS, Chicago, IL), and α was set to $P < 0.05$.

RESULTS

Table 1 displays the descriptive physical and biochemical characteristics of the 2,326 participants (32% male, age 52.2 ± 11.5 years). Waking accelerometer wear time was 928.40 ± 83.37 and 933.10 ± 83.85 min/day for men and women, respectively. Mean ST was 617.54 ± 98.06 for men and 579.46 ± 91.76 min/day for women. Mean MVPA was 31.58 ± 20.62 min/day for men and 26.18 ± 17.03 min/day for women. Only 50% of participants met the recommended guidelines of 30 min of MVPA per day (26).

Tables 2–4 show the standardized regression coefficients of CPM, MVPA, and ST with the cardiometabolic risk factors.

CPM

Table 2 shows the standardized regression coefficients of CPM with the cardiometabolic risk factors. After adjustment for age, sex, ethnicity, smoking, accelerometer wear time, intervention center, sleep duration, body fat%, education level, and household income, CPM had significant inverse associations with HOMA-IR, waist circumference, fasting insulin, 2-h glucose, triglycerides, and CRP and a positive association with HDL cholesterol.

MVPA

Table 3 shows the standardized regression coefficients for MVPA with the cardiometabolic risk factors. In model 1, adjusted for age, sex, ethnicity, smoking, accelerometer wear time, intervention center, sleep duration, body fat%, education level, and household income, MVPA was significantly and negatively associated with HOMA-IR, waist circumference, fasting insulin, 2-h glucose, triglycerides, and CRP and positively associated with HDL cholesterol.

After adjustment for ST in model 2, the association with HDL cholesterol was lost. Associations with other biochemical factors were slightly attenuated, but all remained significant.

Sedentary Time

Table 4 shows the standardized regression coefficients for ST with the cardiometabolic risk factors. In model 1, adjusted for age, sex, ethnicity, smoking, accelerometer wear time, intervention center, sleep duration, body fat%, education level, and household income, ST was positively associated with waist circumference, systolic BP, diastolic BP, mean arterial pressure, fasting insulin, 2-h glucose, HOMA-IR, triglycerides, and CRP and negatively associated with HDL. After adjustment for MVPA in model 2, associations with 2-h plasma glucose were no longer significant.

Fasting plasma glucose, total cholesterol, and LDL cholesterol were not associated with any of our exposure variables.

Two-way interactions indicate that associations between MVPA and fasting insulin were greater in the older age-group (Table 3). We did not observe any significant sex, center, or BMI interactions between measures of PA or ST and any cardiometabolic risk factors.

CONCLUSIONS

This study investigated the associations between objectively measured PA and ST and metabolic variables in a worldwide sample of overweight and obese adults

Table 1—Descriptive, metabolic, and PA characteristics of 2,326 adults with prediabetes from PREVIEW

Characteristics	Female (*n* = 1,570)	Male (*n* = 755)
Age (years)	51.6 ± 11.6	53.5 ± 11.6
Height (m)	1.64 ± 0.07	1.77 ± 0.07
Weight (kg)	95.88 ± 20.33	108.87 ± 20.98
BMI (kg · m^2)	35.70 ± 6.76	34.55 ± 6.01
Fat (%)	46.45 ± 5.85	36.67 ± 6.92
Waist (cm)	107.7 ± 14.6	116.8 ± 14.5
Systolic BP (mmHg)	126.98 ± 5.88	133.10 ± 14.8
Diastolic BP (mmHg)	77.07 ± 11.15	80.88 ± 9.96
Fasting insulin (mU · L^{-1})	12.53 ± 6.54	14.03 ± 6.68
Fasting plasma glucose (mmol · L^{-1})	6.08 ± 0.67	6.33 ± 0.66
2-h plasma glucose (mmol · L^{-1})	7.64 ± 2.21	7.73 ± 2.24
HbA_{1c} (mmol · L^{-1})	36.61 ± 4.03	36.73 ± 4.06
HbA_{1c} (%)	5.50 ± 0.37	5.51 ± 0.37
HOMA-IR	3.44 ± 1.90	4.00 ± 2.01
Triglycerides (mmol · L^{-1})	1.45 ± 0.77	1.62 ± 0.82
Total cholesterol (mmol · L^{-1})	5.25 ± 0.99	5.03 ± 0.97
HDL cholesterol (mmol · L^{-1})	1.33 ± 0.29	1.15 ± 0.23
LDL cholesterol (mmol · L^{-1})	3.28 ± 0.84	3.16 ± 0.85
CRP (mg · L^{-1})	4.81 ± 4.02	3.46 ± 3.35
Accelerometer variables		
Waking wear time (min · day^{-1})	933.10 ± 83.85	928.40 ± 83.37
Sleep (min · day^{-1})	474.69 ± 80.26	471.83 ± 85.16
ST (min · day^{-1})	579.46 ± 91.76	617.54 ± 98.06
Light activity (min · day^{-1})	320.84 ± 82.62	280.12 ± 78.20
Moderate activity (min · day^{-1})	25.30 ± 6.88	30.33 ± 20.33
MVPA (min · day^{-1})	26.18 ± 17.03	31.58 ± 20.62
CPM	294.30 ± 96.77	297.98 ± 17.28
Ethnicity (%)		
Caucasian	86.02	89.9
Asian	2.66	2.71
Black	1.82	1.2
Arabic	0.2	0.3
Hispanic	2.33	1.38
Other	6.61	4.25
Smoking (%)		
Yes (daily)	10.72	9.57
Sometimes (less than weekly)	3.3	2.93
No	85.98	87.48
Education (%)		
No formal education	0.5	—
Primary/junior school	2.1	2.8
Secondary school	15.1	14.2
Secondary vocational education	17.7	19.2
Higher vocational education	16.4	18.6
University education	40.5	35.6
Other	7.6	9.7
Household income per year (%)		
Less than £9,360	8.8	5.3
£9,360–12,479.99	5.8	2.9
£12,480–15,599.99	5.1	2.5
£15,600–18,719.99	6.5	3.5
£18,720–22,879.99	5.7	4.6
£22,880–27,559.99	8.1	5.9
£27,560–32,759.99	10.6	8.1
£32,760 –41,079.99	11.2	10.9
£41,080–53,559.99	13.4	14.2
£53,560 or more	24.9	42

Data are means ± SD unless otherwise stated.

(BMI >25 kg/m^2) with prediabetes confirmed through an OGTT (27). To our knowledge, this is the first international investigation of associations between objectively measured PA and ST with cardiometabolic risk factors in a population that exclusively meet the criteria for prediabetes (impaired fasting glucose [5.6–6.9 mmol · L^{-1}] or impaired glucose tolerance [7.8–11 mmol · L^{-1}]). Previous studies conducted in high-risk populations have included participants based on a risk score questionnaire (5) or family history of type 2 diabetes (9,13), or participants with diabetes and prediabetes have been combined (14). Consequently, physical characteristics and metabolic parameters reported in these studies varied substantially from those in the current study. In our population of participants with prediabetes, MVPA was negatively associated with HOMA-IR, waist circumference, fasting insulin, 2-h glucose, triglycerides, and CRP after accounting for potential confounders (sleep duration and ST). Our study also demonstrated that total PA volume (CPM) was at least as strongly associated with the aforementioned risk factors as was MVPA.

Before ST was controlled for in model 2, total PA volume also accounted for greater variance in cardiometabolic risk factors than did MVPA. Hence, it appears that in this population, although both are significant, the accumulation of total PA over a day is a stronger indicator of insulin resistance and some related cardiometabolic risk factors than MVPA.

Previous studies in populations with a family history of diabetes and newly diagnosed diabetes have shown that total energy expenditure spent on PA (14), CPM (13), and MVPA (9) were negatively associated with waist circumference, fasting serum triglycerides, systolic BP, fasting plasma glucose, fasting plasma insulin, HOMA-IR, and a clustered metabolic risk score. In agreement with our findings, Ekelund, Griffin, and Wareham (13) reported that total counts · day^{-1} was more strongly associated with clustered risk and individual cardiometabolic risk factors than was MVPA. In the general population, Balkau et al. (28) reported associations between MVPA and total PA with insulin resistance using the gold standard clamp technique for determining insulin sensitivity. However, after adjustment for total PA, associations with MVPA were lost (28). These findings, in

Table 2—Standardized β-coefficients for associations between total PA (CPM) and cardiometabolic risk factors

Characteristics	β	95% CI	*P*	R^2
Waist (cm)	−0.179	−0.224, −0.134	*	0.2057
Systolic BP (mmHg)	−0.033	−0.074, 0.007		0.1927
Diastolic BP (mmHg)	−0.02	−0.057, 0.017		0.3448
Fasting insulin (mU · L^{-1})	−0.139	−0.183, −0.096	*	0.1293
Fasting glucose (mmol · L^{-1})	−0.028	−0.074, 0.018		0.1647
2-h plasma glucose (mmol · L^{-1})	−0.088	−0.131, −0.045	*	0.1139
HbA_{1c} (%)	−0.049	−0.098, −0.001		0.1337
HOMA-IR	−0.151	−0.194, −0.107	*	0.1306
Triglycerides (mmol · L^{-1})	−0.117	−0.162, −0.071	*	0.0812
Total cholesterol (mmol · L^{-1})	−0.007	−0.053, 0.038		0.095
HDL (mmol · L^{-1})	0.088	0.048, 0.129	*	0.1856
LDL (mmol · L^{-1})	0.002	−0.045, 0.049		0.0566
CRP (mg · L^{-1})	−0.104	−0.146, −0.062	*	0.2657

Adjusted for age, sex, ethnicity, smoking, household income, education level, body fat%, wear time, sleep time, and intervention center. *$P < 0.001$.

keeping with the current study, would support the hypothesis that the accumulation of total PA volume accounts for greater variance in insulin resistance and some related cardiometabolic risk factors than does MVPA.

The current study also demonstrated that after confounders were controlled for, ST was positively associated with waist circumference, systolic BP, diastolic BP, fasting insulin, HOMA-IR, triglycerides, CRP, and HDL cholesterol independent of time spent in MVPA.

Table 3—Standardized β-coefficients for associations between MVPA (min · day^{-1}) and cardiometabolic risk factors

Characteristics	β	95% CI	*P*	R^2
Model 1				
Waist (cm)	−0.177	−0.122, −0.134	***	0.2046
Systolic BP (mmHg)	−0.005	−0.047, 0.083		0.1915
Diastolic BP (mmHg)	−0.007	−0.044, 0.031		0.3441
Fasting insulin (mU · L^{-1})	−0.115	−0.158, −0.072	***	0.1237
Fasting glucose (mmol · L^{-1})	−0.028	−0.072, 0.017		0.1645
2-h plasma glucose (mmol · L^{-1})	−0.069	−0.112, −0.025	**	0.1108
HbA_{1c} (%)	−0.046	−0.096, 0.004		0.1334
HOMA-IR	−0.122	−0.166, −0.078	***	0.1235
Triglycerides (mmol · L^{-1})	−0.091	−0.138, −0.044	***	0.0762
Total cholesterol (mmol · L^{-1})	−0.01	−0.056, 0.035		0.0952
HDL (mmol · L^{-1})	0.055	0.009, 0.101	*	0.1808
LDL (mmol · L^{-1})	0.002	−0.044, 0.048		0.0567
CRP (mg · L^{-1})	−0.086	−0.127, −0.045	***	0.262
Model 2				
Waist (cm)	−0.127	−0.173, −0.081	***	0.2215
Systolic BP (mmHg)	0.02	−0.026, 0.067		0.1961
Diastolic BP (mmHg)	0.011	−0.03, 0.053		0.3467
Fasting insulin (mU · L^{-1}) main effect	−0.078	−0.127, −0.03	**	0.1337
25–45.9 years (reference)	—	—	—	—
46.0–54.9 years	0.025	−0.120, 0.170		0.1313
55.0–71 years	−0.098	−0.195, −0.001	*	0.1313
Fasting glucose (mmol · L^{-1})	−0.014	−0.063, 0.035		0.1659
2-h plasma glucose (mmol · L^{-1})	−0.053	−0.1, −0.006	*	0.1129
HbA_{1c} (%)	−0.036	−0.095, 0.023		0.1345
HOMA-IR	−0.08	−0.129, −0.031	**	0.1368
Triglycerides (mmol · L^{-1})	−0.067	−0.117, −0.017	**	0.0804
Cholesterol (mmol · L^{-1})	−0.013	−0.064, 0.037		0.0953
HDL (mmol · L^{-1})	0.028	−0.081, 0.383		0.1867
LDL (mmol · L^{-1})	0	−0.053, −0.052		0.0572
CRP (mmol · L^{-1})	−0.061	−0.108, −0.015	**	0.2665

Model 1 adjusted for age, sex, ethnicity, smoking, household income, education level, body fat%, wear time, sleep time, and intervention center. Model 2 additionally adjusted for ST. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

In agreement with our findings, Henson et al. (5) reported positive associations between ST, 2-h plasma glucose, triglycerides, and HDL cholesterol, independent of total PA, in a population at risk for type 2 diabetes (5). Similarly, positive associations between ST, waist circumference, insulin, HOMA-IR, and HDL cholesterol were reported in an older group with newly diagnosed type 2 diabetes (22). There is a lack of consensus on the role of ST in pathology of cardiometabolic risk factors. Some authors have reported that once total energy expenditure is taken into account, the associations between ST and cardiometabolic health are lost. These findings suggest that ST reduces total energy expenditure by displacing other activities that are more energy costly (28,29). Other investigators have found that the mechanism linking ST to glucose metabolism and metabolic health differ from those of PA and may be related to static posture and unloading of large skeletal muscle groups when seated (7,30). ST is thought to affect glucose homeostasis and lipid metabolism by reducing muscle GLUT4 content and insulin-stimulated glucose uptake (6) while also reducing lipoprotein lipase activity, leading to impaired triglyceride and HDL cholesterol metabolism (7).

Further, light activity is associated with marked improvements in cardiometabolic health (8), while interventions have shown that replacing ST with postural changes such as standing or light ambulatory activity can improve glycemic control to a greater extent than structured exercise of the same energy cost (31). In the present analysis, ST was associated with HDL cholesterol; however, associations between MVPA and HDL cholesterol were lost after controlling for ST. Similarly, ST was positively associated with systolic and diastolic BP independent of MVPA, while no association was found between CPM or MVPA with either BP variable. Associations of PA and ST with BP variables reported by observational studies have been inconsistent (8,12,14). However, experimental studies in overweight/obese populations have suggested that a reduction of ST and the interruption of prolonged sedentary

Table 4—Standardized β-coefficients for associations between ST (min · day^{-1}) and cardiometabolic risk factors

Characteristics	β	95% CI	*P*	R^2
Model 1				
Waist (cm)	0.215	0.146, 0.267	***	0.2088
Systolic BP (mmHg)	0.078	0.026, 0.131	**	0.1957
Diastolic BP (mmHg)	0.057	0.007, 0.106	*	0.3464
Fasting insulin (mU · L^{-1})	0.155	0.092, 0.219	***	0.1291
Fasting glucose (mmol · L^{-1})	0.052	−0.004, 0.108		0.1656
2-h plasma glucose (mmol · L^{-1})	0.072	0.015, 0.129	*	0.1106
HbA_{1c} (%)	0.047	−0.022, 0.117		0.1332
HOMA-IR	0.175	0.114, 0.236	***	0.1316
Triglycerides (mmol · L^{-1})	0.106	0.052, 0.16	***	0.0766
Total cholesterol (mmol · L^{-1})	−0.006	−0.062, 0.051		0.0953
HDL (mmol · L^{-1})	−0.103	−0.165, −0.042	***	0.1859
LDL (mmol · L^{-1})	−0.007	−0.062, 0.048		0.0568
CRP (mg · L^{-1})	0.106	0.039, 0.172	**	0.2632
Model 2				
Waist (cm)	0.165	0.109, 0.221	***	0.2215
Systolic BP (mmHg)	0.086	0.028, 0.143	**	0.1961
Diastolic BP (mmHg)	0.061	0.006, 0.116	*	0.3467
Fasting insulin (mU · L^{-1})	0.126	0.055, 0.198	**	0.1337
Fasting glucose (mmol · L^{-1})	0.047	−0.014, 0.108		0.1659
2-h plasma glucose (mmol · L^{-1})	0.053	−0.009, 0.114		0.1129
HbA_{1c} (%)	0.034	−0.045, 0.113		0.1345
HOMA-IR	0.145	0.077, 0.213	***	0.1368
Triglycerides (mmol · L^{-1})	0.08	0.023, 0.138	**	0.0804
Total cholesterol (mmol · L^{-1})	−0.011	−0.074, 0.052		0.0953
HDL (mmol · L^{-1})	−0.093	−0.163, −0.022	*	0.1867
LDL (mmol · L^{-1})	−0.007	−0.069, 0.055		0.0572
CRP (mg · L^{-1})	0.083	0.01, 0.156	*	0.2665

Model 1 adjusted for age, sex, ethnicity, smoking, household income, education level, body fat%, wear time, sleep time, and intervention center. Model 2 additionally adjusted for MVPA. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

bouts with light or moderate activity are associated with improved systolic and diastolic BP (32).

While PA guidelines continue to focus on participation in MVPA (26), our data demonstrated that in a population with prediabetes, total volume of PA was as strongly associated with cardiometabolic health as was MVPA. The implications of this finding may be important considering the levels of PA in this population. Light activity may be more readily adopted by individuals with prediabetes, particularly if they are physically inactive, overweight/obese, or reluctant to engage in structured exercise (31).

The lack of associations observed for all exposure variables with fasting glucose is consistent with previous research (5,8). This finding reflects the fact that PA predominantly affects peripheral insulin sensitivity, which is responsible for lowering blood glucose levels after an OGTT, when most of the glucose is taken up by skeletal muscle. Conversely, in a fasted state, peripheral insulin sensitivity has little effect on plasma glucose (33).

The strengths of this study are the implementation of a 24-h accelerometer wear-time protocol that resulted in a greater mean waking wear time (15.5 h) than seen in many studies of a similar nature (5,18,22). Longer monitoring duration provides greater reliability of average activity estimates. This approach also allowed an objective assessment of sleep time using an algorithm to detect sleep onset and wake time from a 24-h waist-worn accelerometer trace (19). This allowed the study team to control for the confounding effects of sleep on cardiometabolic risk factors (34).

Type 2 diabetes is high on public health agendas, with attention on the prevention or delay of diabetes onset and the management of cardiometabolic risk factors (35,36). National and international guidelines focus on, first, identifying high-risk individuals and, second, controlling modifiable risk factors such as body weight, diet, ST, and PA through targeted interventions (37,38). This study provides new evidence of associations of PA and ST with cardiometabolic markers in a population to whom the results are most applicable.

While this study has numerous strengths, it is also important to acknowledge its limitations. First, the cross-sectional design does not allow insight into the direction of causality between each exposure variable and markers of cardiometabolic health, and although we controlled for many potential confounding factors, we did not account for dietary intake or alcohol consumption, which may have influenced our results. Second, although accelerometers offer more robust assessments of PA than self-report (39), they are not without limitation. Hip-worn accelerometers capture most movement during locomotion but cannot account for upper-body movement, movement that occurs during activities such as cycling or weight lifting (40), or distinguish between light-intensity activities such as sitting and standing. Furthermore, the accelerometer is removed during water-based activities and contact sports. Therefore, PA may be underestimated. Given the fixed nature of accelerometer-derived variables (sleep, light activity, ST, and MVPA) as proportions of 24 hours, time spent in behaviors within the day are inherently collinear; every increase in time spent in one behavior unavoidably causes a decrease in the time spent in one or a combination of the other behaviors. Thus, it is not possible to include all subcomponents of the day (sleep, ST, light activity, and MVPA) in a regression model without violating collinearity assumptions. Consequently, in the current study it is not possible to say with certainty that the positive associations observed between cardiometabolic risk factors and ST are truly independent and not, in fact, negative associations with light activity. Finally, participants in this study were volunteers for a lifestyle intervention from the eight study sites worldwide, approximately 50% of whom were between 55 and 70 years of age. While this may limit the applicability of the current findings to this older age range, it is this group who is at greater risk of type 2 diabetes and is perhaps more likely to participate in such interventions given their greater availability of time compared with those still employed.

In conclusion, this study provides new evidence that in a large diverse population of adults with prediabetes, objective measures of PA and ST are associated with

markers of cardiometabolic health. Furthermore, associations with total PA volume are at least as strong as with MVPA. Taken together, these findings suggest that replacing ST with light activity may provide a practical approach to improve cardiometabolic health in a population with low engagement in MVPA.

Acknowledgments. The authors acknowledge particularly the medical and scientific experts, who helped in building up the study, Arne Astrup (University of Copenhagen, Denmark), Stephen Colagiuri (University of Sydney, Australia), Peter Mansell (University of Nottingham U.K.), and the PREVIEW Scientific Advisory Board, Louise Dye (University of Leeds, U.K.), Richard L. Atkinson (Virginia Commonwealth University), Boyd Swinburn (University of Auckland, New Zealand; Deakin University, Melbourne, Australia), Lauren Lissner (University of Göteborg, Sweden), and Grethe Andersen (Danish Agriculture & Food Council, Copenhagen, Denmark). Furthermore, the authors acknowledge the great staff working on PREVIEW around the world for their phenomenal efforts in recruitment and in the running of the project. The authors are especially grateful for the participants for volunteering their time to the study.
Funding. PREVIEW received grants from the EU Seventh Framework Programme (FP7-KBBE-2012), grant no. 312057; the New Zealand Health Research Council, grant no. 14/191; and the NHMRC-EU Collaborative Grant, Australia. Dietary products were provided by Cambridge Weight Plan, Corby, U.K.
Duality of Interest. I.M. is an International Life Sciences Institute Europe member of the Dietary Carbohydrates Task Force and a member of the expert group on "Efficacy Markers of Diabetes Risk" and expert group on "Carbohydrate-Based Recommendations as a Basis for Dietary Guidelines: A Scientific Review." In all cases, travel and subsistence are paid but not attendance fees. I.M. received honorarium as part of the Nature Publishing Group (Springer Nature) and as Editor of the *International Journal of Obesity*. I.M. has had research travel and accommodation reimbursed for a Nestle Research Centre Consultancy for Nutrition in the Life Cycle (honorarium paid to the University of Nottingham). I.M. received honorarium from Mars Incorporated–Waltham Centre for Pet Nutrition for providing peer-review of pet nutrition research (amount received per annum less than £5,000). I.M. has had travel and subsistence costs reimbursed by Mars UK/Europe as a Member of Nutrition Advisory Board and Health and Wellbeing Committee (honorarium paid to the University of Nottingham). I.M. has had travel and subsistence costs reimbursed as an Ikea Member of the Science and Health Committee (honorarium paid to the University of Nottingham). S.D.P. holds the Fonterra Chair in Human Nutrition at the University of Auckland. J.B.-M. is the President of the Glycemic Index Foundation, Director of the Sydney University Glycemic Index Research Service, and the author of books about the glycemic index of foods. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. N.S. conducted analysis and wrote the manuscript. K.M. was involved in the study conception, PA analyses, and editing of the manuscript. M.M. was involved in the study conception, analyses, and editing of the manuscript. J.W.S. assisted in the preparation of the manuscript and study design. D.S. advised on analysis and preparation of the manuscript. M.F. was the principle investigator of the Helsinki site and was involved in conception of the study and editing of the manuscript. M.D. was an investigator of the Maastricht University site and participated in editing of the manuscript. I.M. was principle investigator of the Nottingham site and was involved in conception of the study and editing of the manuscript. J.A.M. was principle investigator of the Navarra site and was involved in editing of the manuscript. T.H.-D. was principle investigator of the Sofia site and was involved in the design of the study, recruitment and implementation of the trial, data interpretation, and approval of the manuscript. S.D.P. was principle investigator of the Auckland site and participated in editing of the manuscript. J.B.-M. was principal investigator of the Sydney site and was involved in editing of the manuscript. T.M.L. was principal investigator of the Copenhagen site and involved in editing of the manuscript. A.R. was the project coordinator of PREVIEW and was involved in the conception of the study and editing of the manuscript. G.S. contributed to study design and conception, supervision of PA analyses, and editing of the manuscript. N.S., K.M., M.M., and G.S. formed the writing group. G.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513–1530
2. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380:219–229
3. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. Diabetes Care 2003;26:557–562
4. Holloszy JO. Exercise-induced increase in muscle insulin sensitivity. J Appl Physiol (1985) 2005;99:338–343
5. Henson J, Yates T, Biddle SJH, et al. Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. Diabetologia 2013;56:1012–1020
6. Megeney LA, Neufer PD, Dohm GL, et al. Effects of muscle activity and fiber composition on glucose transport and GLUT-4. Am J Physiol 1993;264:E583–E593
7. Bey L, Hamilton MT. Suppression of skeletal muscle lipoprotein lipase activity during physical inactivity : a molecular reason to maintain daily low-intensity activity. J Physiol 2003;551:673–682
8. Healy GN, Wijndaele K, Dunstan DW, et al. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care 2008;31:369–371
9. Ekelund U, Brage S, Griffin SJ, Wareham NJ; ProActive UK Research Group. 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
10. Rosique-Esteban N, Díaz-López A, Martínez-González MA, et al.; PREDIMED-PLUS Investigators. Leisure-time physical activity, sedentary behaviors, sleep, and cardiometabolic risk factors at baseline in the PREDIMED-PLUS intervention trial: a cross-sectional analysis. PLoS One 2017;12:e0172253
11. Nelson RK, Horowitz JF, Holleman RG, et al. Daily physical activity predicts degree of insulin resistance: a cross-sectional observational study using the 2003-2004 National Health and Nutrition Examination Survey. Int J Behav Nutr Phys Act 2013;10:10
12. Knaeps S, Lefevre J, Wijtzes A, Charlier R, Mertens E, Bourgois JG. Independent associations between sedentary time, moderate-to-vigorous physical activity, cardiorespiratory fitness and cardio-metabolic health: a cross-sectional study. PLoS One 2016;11:e0160166
13. Ekelund U, Griffin SJ, Wareham NJ. Physical activity and metabolic risk in individuals with a family history of type 2 diabetes. Diabetes Care 2007;30:337–342
14. Hamasaki H, Noda M, Moriyama S, et al. Daily physical activity assessed by a triaxial accelerometer is beneficially associated with waist circumference, serum triglycerides, and insulin resistance in Japanese patients with prediabetes or untreated early type 2 diabetes. J Diabetes Res 2015;2015:526201
15. Raben A, Fogelholm M, Feskens E, et al.; PREVIEW Consortium. PREVIEW: PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World. Obes Facts 2013;6(Suppl. 1):194
16. Silventoinen K, Pankow J, Lindström J, Jousilahti P, Hu G, Tuomilehto J. The validity of the Finnish Diabetes Risk Score for the prediction of the incidence of coronary heart disease and stroke, and total mortality. Eur J Cardiovasc Prev Rehabil 2005;12:451–458
17. World Health Organization, International Diabetes Federation. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia : Report of a WHO/IDF Consultation*. Geneva, World Health Org., 2006
18. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–188
19. Tudor-Locke C, Barreira TV, Schuna JM Jr, Mire EF, Katzmarzyk PT. Fully automated waist-worn accelerometer algorithm for detecting children's sleep-period time separate from 24-h physical activity or sedentary behaviors. Appl Physiol Nutr Metab 2014;39:53–57
20. Aadland E, Ylvisåker E. Reliability of objectively measured sedentary time and physical activity in adults. PLoS One 2015;10:e0133296
21. Rabinovich RA, Louvaris Z, Raste Y, et al.; PROactive Consortium. Validity of physical activity

monitors during daily life in patients with COPD. Eur Respir J 2013;42:1205–1215
22. Cooper AR, Sebire S, Montgomery AA, et al. Sedentary time, breaks in sedentary time and metabolic variables in people with newly diagnosed type 2 diabetes. Diabetologia 2012;55:589–599
23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27: 1487–1495
24. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393
25. Field A. Discovering Statistics Using SPSS Statistics. Vol. 81, 3rd ed. London, Sage Publications, 2013, p. 169–170
26. World Health Organization. *Global Recommendations on Physical Activity for Health*. Geneva, World Health Org., 2010
27. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl. 1):S62–S69
28. Balkau B, Mhamdi L, Oppert JM, et al.; EGIR-RISC Study Group. Physical activity and insulin sensitivity: the RISC study. Diabetes 2008;57: 2613–2618
29. Maher C, Olds T, Mire E, Katzmarzyk PT. Reconsidering the sedentary behaviour paradigm. PLoS One 2014;9:e86403
30. Peddie MC, Bone JL, Rehrer NJ, Skeaff CM, Gray AR, Perry TL. Breaking prolonged sitting reduces postprandial glycemia in healthy, normal-weight adults: a randomized crossover trial. Am J Clin Nutr 2013;98:358–366
31. Dempsey PC, Owen N, Yates TE, Kingwell BA, Dunstan DW. Sitting less and moving more: improved glycaemic control for type 2 diabetes prevention and management. Curr Diab Rep 2016;16:114
32. Dempsey P, Sacre J, Owen N, et al. Interrupting prolonged sitting reduces resting blood pressure in adults with type 2 diabetes. Heart Lung Circ 2015;24:S127–S128
33. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? Diabetologia 2009;52:1714–1723
34. Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. Best Pract Res Clin Endocrinol Metab 2010;24:731–743
35. Richardson E, Zaletel J, Nolte E; Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). *National Diabetes Plans in Europe. What Lessons Are There for the Prevention and Control of Chronic Diseases in Europe?* Copenhagen, Denmark, World Health Organization Regional Office for Europe, 2016
36. International Diabetes Federation. Global diabetes plan 2011-2021 [Internet]. Available from https://www.idf.org/component/attachments/attachments.html?id=1307&task=download. Accessed 4 March 2017
37. Paulweber B, Valensi P, Lindström J, et al. A European evidence-based guideline for the prevention of type 2 diabetes. Horm Metab Res 2010; 42(Suppl. 1):S3–36
38. Chatterton H, Younger T, Fischer A, Khunti K. Risk identification and interventions to prevent type 2 diabetes in adults at high risk: summary of NICE guidance. BMJ 2012;345:e4624–e4624
39. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56
40. Welk G. *Physical Activity Assessments for Health-Related Research*. Vol 1. Champaign, IL, Human Kinetics, 2002, p. 269