Cross-sectional and Longitudinal Associations Between Objectively Measured Sedentary Time and Metabolic Disease: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Bethany Barone Gibbs,[1] Kelley Pettee Gabriel,[2] Jared P. Reis,[3] John M. Jakicic,[1] Mercedes R. Carnethon,[4] and Barbara Sternfeld[5]

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OBJECTIVE

Prolonged sedentary time (ST) might be contributing to the diabetes epidemic, but most studies have been cross-sectional and few have objectively measured ST. The purpose of this study was to evaluate cross-sectional and 5-year longitudinal relationships between ST and metabolic parameters and outcomes.

RESEARCH DESIGN AND METHODS

This was an analysis of 2,027 Coronary Artery Risk Development in Young Adults (CARDIA) study participants (aged 38–50 years, 57% female, and mean BMI of 29.0 ± 7.0 kg/m^2) with accelerometry data (≥4 days with ≥10 h/day) measured at the year 20 follow-up exam (2005–2006). Metabolic variables (fasting glucose, fasting insulin, 2-h postchallenge glucose, HOMA of insulin resistance [HOMA-IR], and HbA_{1c}) and outcomes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], prediabetes by HbA_{1c}, and diabetes) were assessed concurrently and 5 years later.

RESULTS

Average ST was 8.1 ± 1.7 h/day or 55 ± 10% of wear time. Each additional hour per day of ST was cross-sectionally associated with a 3% higher fasting insulin and HOMA-IR (both $P < 0.01$) but not 5-year changes in metabolic parameters. Having ≥10 h/day vs. <6 h/day of ST was associated with an odds ratio (OR) = 2.74 (95% CI 1.13, 6.62) for IGT and an OR = 3.80 (95% CI 1.39, 10.35) for diabetes. ST was not associated with prevalent IFG, prevalent prediabetes by HbA_{1c}, or 5-year incidence of any metabolic outcomes (all $P > 0.05$).

CONCLUSIONS

ST was independently related to insulin, HOMA-IR, and prevalent diabetes and IGT but did not predict 5-year changes in metabolic parameters or incidence of metabolic outcomes. These results suggest that higher ST may not be a risk factor for future metabolic outcomes, but more research with repeated ST measurement and longer follow-up is needed.

[1]Department of Health and Physical Activity, University of Pittsburgh, Pittsburgh, PA
[2]Division of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center at Houston, School of Public Health Austin Regional Campus, Austin, TX
[3]National Heart, Lung, and Blood Institute, Bethesda, MD
[4]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL
[5]Department of Research, Kaiser Permanente Northern California, Oakland, CA

Corresponding author: Bethany Barone Gibbs, bbarone@pitt.edu.

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Accumulating evidence suggests that prolonged sedentary time (ST), at the expense of light-intensity physical activity and moderate- to vigorous-intensity physical activity (MVPA), is contributing to the current diabetes epidemic (1,2). A recent meta-analysis of 10 studies found that higher levels of sedentary behavior were associated with a twofold increase in the risk of incident diabetes (3). However, in each of the included studies, self-reported television time was used as a surrogate for overall ST. Extrapolation of television viewing time to ST is problematic because of the error in self-report, the imperfect relationship between television viewing and overall sedentary behavior (4), and the potential for residual confounding. Indeed, a need for better observational evidence with objectively measured ST and longitudinal follow-up of adverse outcomes has recently been identified as a top priority in sedentary behavior research (5).

A growing number of cross-sectional and fewer longitudinal studies have also evaluated associations of objectively measured ST with fasting and postchallenge glucose, fasting insulin, insulin sensitivity, and HbA_{1c}. These studies have used various study populations and have yielded mixed results, with some studies finding that individuals engaging in a higher amount versus a lower amount of ST have worse metabolic health (6–8) and others finding no associations (9–12). One contributor to the inconsistent results could be different methods for defining ST based on objective activity monitoring data (e.g., total minutes or percentage of time spent sedentary [%ST]), although the influence of alternative sedentary behavior metrics is yet unclear (5). Thus, more longitudinal studies comparing various definitions are needed to clarify the impact of sedentary behavior on the development of metabolic impairment.

The objective of the current study was to investigate associations of accelerometry-derived ST with continuous metabolic variables (fasting glucose, fasting insulin, 2-h postchallenge glucose, HOMA of insulin resistance [HOMA-IR], and HbA_{1c}) and metabolic outcomes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], prediabetes by HbA_{1c}, and diabetes) both cross-sectionally and after 5 years of follow-up in a well-characterized, population-based cohort of middle-aged adults. We hypothesized that higher amounts of ST would be associated with worse metabolic variables and a higher prevalence and incidence of outcomes. A secondary objective was to evaluate the influence of alternative definitions of sedentary behavior and overall physical activity measured via accelerometry.

RESEARCH DESIGN AND METHODS

Participants

The Coronary Artery Risk Development in Young Adults (CARDIA) study enrolled 5,115 black and white adults aged 18–30 years in 1985 and 1986 in Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA, to study the development and determinants of cardiovascular disease beginning in young adulthood (13). Follow-up examinations of the cohort have been conducted approximately every 2 to 5 years. For the current study, baseline data were collected in 2005–2006 (CARDIA year 20; retention rate 72% of the surviving cohort), and 5-year follow-up data were collected in 2010–2011 (CARDIA year 25; retention rate 72%). The sample for the current report includes participants enrolled in the CARDIA year 20 Fitness substudy and who had $\geq$4 days with $\geq$10 h of accelerometry data (n = 2,049). Of these, 22 were excluded for missing covariates, resulting in n = 2,027 for cross-sectional analyses. For 5-year longitudinal analyses, the sample size was n = 1,718 after excluding n = 162 with prevalent diabetes at baseline, n = 144 who did not complete the follow-up exam, and n = 3 for missing covariate data. HbA_{1c} was also measured in a subset of participants (CARDIA ancillary study, Young Adult Longitudinal Trends in Antioxidants) and 2-h oral glucose tolerance tests (2-h glucose) were only measured in participants meeting eligibility criteria. Thus, for baseline and 5-year follow-up, sample sizes were n = 1,766 and n = 1,474 for HbA_{1c} and n = 1,627 and n = 1,317 for 2-h glucose.

ST and Physical Activity

Daily activity was measured using a uniaxial accelerometer (model 7164; ActiGraph, Pensacola, FL) during the baseline exam only (not included in the 5-year follow-up exam). Participants were instructed to wear the device around the waist for 7 days during all waking hours, except while bathing or during other water activities. The epoch was set at 1 min. Total wear time was calculated for each 24-h period by subtracting nonwear time, which was defined as time intervals with 0 counts per minute (cpm) for $\geq$60 consecutive minutes. Accelerometry data were considered valid if participants had $\geq$4 days of monitoring with $\geq$10 h/day. Average cpm was calculated as the total accelerometer counts divided by the total wear time. National Health and Nutrition Examination Survey (NHANES) cut points were used to classify total duration of sedentary behavior (0–99 cpm), light-intensity activity (100–2,019 cpm), and MVPA ($\geq$2,020 cpm) (14).

ST was considered as a continuous variable (hours/day) and categorized as $<$6.0, 6.0 to $<$8.0, 8 to $<$10.0, or $\geq$10 h/day. Categories were chosen based on literature using 10 h/day as the upper limit (15) but also to have an adequate sample size in each category. Because wear time could influence ST, we evaluated the hypothesis that absolute and relative (%) ST would be different across quintiles of wear time. We found that absolute ST differed significantly across quintiles of wear time ($F = 141.98$, $P < 0.001$), but %ST did not vary across quintile of ST ($F = 1.85$, $P = 0.11$). In order of ascending quintiles of wear time, the means $\pm$ SDs of %ST were 54 $\pm$ 12%, 55 $\pm$ 10%, 56 $\pm$ 9%, 55 $\pm$ 10%, and 55 $\pm$ 10%, suggesting that adjustment for sedentary behavior as a covariate was appropriate. Thus, all regression analyses were adjusted for wear time. %ST and the ratio of ST divided by light-intensity activity (ST/LA ratio) were also calculated to be used in sensitivity analyses.

Metabolic Variables and Outcomes

Metabolic variables and outcomes were measured at baseline and 5-year follow-up. Standardized protocols for data collection were used across study centers and examinations. Participants were instructed to fast for at least 12 h before each examination and to avoid smoking or engaging in heavy physical activity for at least 2 h. Blood samples were collected at field sites using standard protocols at baseline and 5-year follow-up and were processed by a central laboratory. Plasma glucose was assayed using

the hexokinase-ultraviolet method, and insulin was measured by radioimmunoassay. HbA_{1c} was measured by the high-performance liquid chromatography method. The HOMA-IR index was used as a surrogate measure for insulin resistance and calculated as [fasting insulin (mU/mL) × fasting glucose (mmol/L)]/22.5 (16). Diabetes was defined as either self-reported use of diabetes medications, HbA_{1c} ≥6.5% (≥47.5 mmol/mol), fasting glucose ≥126 mg/dL, or 2-h glucose ≥200 mg/dL. Although we did not have information on type of diabetes, only n = 9 and n = 11 cases of diabetes were present at the CARDIA exams occurring when subjects were 18–30 and 23–35 years old, suggesting few (~5% of total cases) might have had type 1 diabetes. Among those without diabetes, IGT was defined as a 2-h glucose ≥140–199 mg/dL, IFG was defined as a fasting glucose of 100–125 mg/dL, and prediabetes from HbA_{1c} was defined as an HbA_{1c} of 5.7–6.4% (39 to <47.5 mmol/mol).

Other Covariates

Demographic characteristics, smoking, and alcohol were measured at baseline by standardized questionnaires. Systolic and diastolic blood pressures were the average of the second and third automated measurements taken after 5 min of quiet sitting (HEM-907XL; Omron Healthcare, Inc., Lake Forest, IL) (17). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or antihypertensive medication use. Height and weight were measured without shoes and in light clothing. BMI was calculated as kg/m^2. Total cholesterol was measured using an enzymatic assay.

Statistical Methods

All variables were checked for normality and transformed or analyzed using nonparametric methods. Baseline characteristics were compared across ST categories by testing for linear trends or χ^2 tests.

For cross-sectional analyses, linear regression was used to evaluate whether continuous ST was associated with fasting glucose, 2-h glucose, fasting insulin, HOMA-IR, or HbA_{1c}. Logistic regression evaluated whether categorical ST was associated with prevalent IFG, IGT, prediabetes by HbA_{1c}, or diabetes. Progressive models were used as follows. Model 1 adjusted for demographics (age, race, center, sex, education, and income), smoking, alcohol, and accelerometer wear time; model 2 added minutes of MVPA; and model 3 added diabetes (linear regression models only) and BMI, hypertension, and total cholesterol (both linear and logistic regression models). The covariates in model 3 were not considered as confounding but rather potentially explanatory of the relationship between ST and metabolic outcomes. Sensitivity analyses evaluated the influence of alternative ST definitions by repeating all analyses with ST defined as a continuous variable, categories, %ST, and ST/LA ratio. Also, models with metabolic parameter outcomes were repeated after excluding participants using diabetes medications.

For longitudinal analyses, participants with diabetes at baseline were excluded. Associations between baseline continuous ST and 5-year changes (follow-up − baseline value) in metabolic variables were evaluated with the progressive linear regression models described above but with the addition of baseline value as a covariate in all models and baseline, and change in BMI, hypertension, and total cholesterol were included in model 3. Similar logistic regression models with progressive adjustment evaluated the relationship between categorical ST at baseline and incident IFG, IGT, prediabetes by HbA_{1c}, and diabetes, after the exclusion of baseline cases for each outcome. Again, analyses were repeated using alternative definitions of sedentary behavior and after excluding participants on diabetes medications.

Last, linear regression models at baseline and 5-year follow-up were refit using average accelerometry cpm rather than separate ST and MVPA. To facilitate comparison, adjusted R^2 and standardized coefficients for average cpm were compared with otherwise similar models but with standardized coefficients for ST and MVPA.

We tested for interaction terms in regression models adjusting for demographics, lifestyle, and MVPA for each outcome. No statistically significant interactions were identified for ST (continuous) with MVPA (P values ranged from 0.10 to 0.99), race (P values ranged from 0.10 to 0.98), or sex (P values ranged from 0.11 to 0.89). Thus, physical activity was modeled as an independent covariate and race and sex groups were combined for the primary report. However, because race × sedentary behavior interactions for metabolic parameters have been previously reported (6), we repeated these analyses after stratification by race.

Stata version 13.1 (College Station, TX) was used for all analyses. A P value of <0.05 was considered statistically significant.

RESULTS

Most participants (76%) spent 6 to <10 h per day sedentary (Table 1). Higher ST was associated with older age, male sex, white race, more education, and higher income (all $P < 0.01$). The lowest ST category had the greatest proportion of former smokers and the least current or never smokers ($P < 0.001$). Higher ST was also associated with less MVPA and lower accelerometer cpm along with higher %ST and ST/LA ratio (all $P < 0.001$).

Association Between ST and Continuous Metabolic Variables

Cross-sectionally, having a higher amount of ST was associated with a higher fasting glucose, 2-h glucose, fasting insulin, and HOMA-IR in models adjusted for demographics and lifestyle variables (Table 2). In model 1, each additional hour of ST was associated with a 0.9% higher fasting glucose level ($P < 0.001$), 1.5% higher 2-h glucose ($P < 0.001$), 4.8% higher fasting insulin ($P < 0.001$), and 5.8% higher HOMA-IR level ($P < 0.001$). Associations persisted after further adjustment (MVPA in model 2 and then comorbidities in model 3) for fasting insulin and HOMA-IR only. ST was not significantly associated with HbA_{1c} levels.

Longitudinally, baseline ST was not significantly related to 5-year changes in the metabolic parameters (all $P > 0.05$), although the relationship with change in HbA_{1c} approached statistical significance in adjusted models (P = 0.06) (Table 2).

Results in subsequent analyses were similar when ST was considered as categories, %SB, or SB/LA ratio, indicating that differences in operationalizing ST from accelerometry data did not influence relationships with metabolic parameters (data not shown for %SB or

Table 1—Participant characteristics across categories of ST (*n* = 2,027)

	<6 h/day (*n* = 214)	6 to <8 h/day (*n* = 722)	8 to <10 h/day (*n* = 825)	≥10 h/day (*n* = 266)	*P* for trend
Age (years)	**44.6 ± 3.6**	**45.2 ± 3.7**	**45.5 ± 3.5**	**45.5 ± 3.3**	**0.002**
Sex					**<0.001**
Female, *n* (%)	**137 (64%)**	**441 (61%)**	**464 (56%)**	**123 (46%)**	
Male, *n* (%)	**77 (36%)**	**281 (39%)**	**361 (44%)**	**143 (54%)**	
Race					**<0.001**
Black, *n* (%)	**116 (54%)**	**319 (44%)**	**296 (36%)**	**107 (40%)**	
White, *n* (%)	**98 (46%)**	**403 (56%)**	**529 (64%)**	**159 (60%)**	
Education (years)	**14 ± 2**	**15 ± 2**	**16 ± 3**	**16 ± 3**	**<0.001**
Total family income ($/year)					**<0.001**
<20,000	**49 (23%)**	**104 (14%)**	**71 (9%)**	**31 (12%)**	
20,000–49,999	**26 (12%)**	**50 (7%)**	**50 (6%)**	**18 (7%)**	
50,000–99,999	**28 (13%)**	**102 (14%)**	**98 (12%)**	**24 (9%)**	
≥100,000	**111 (52%)**	**466 (65%)**	**606 (74%)**	**193 (73%)**	
BMI (kg/m^2)					
Year 20	28.7 ± 6.3	29.2 ± 6.6	28.8 ± 7.6	29.1 ± 6.7	0.830
Year 25*	29.1 ± 6.3	29.0 ± 6.4	28.9 ± 7.9	29.0 ± 6.5	0.762
Change (year 25 − year 20)*	0.5 ± 2.5	0.5 ± 2.3	0.7 ± 2.5	0.5 ± 2.5	0.452
Smoking					**<0.001**
Current, *n* (%)	**45 (21%)**	**156 (22%)**	**173 (21%)**	**62 (23%)**	
Former, *n* (%)	**63 (29%)**	**124 (17%)**	**112 (14%)**	**33 (12%)**	
Never, *n* (%)	**106 (50%)**	**442 (61%)**	**540 (66%)**	**171 (64%)**	
Alcohol consumption (drinks/day)					0.314
0	87 (42%)	309 (44%)	374 (46%)	118 (45%)	
0.1–1.9	72 (35%)	248 (35%)	290 (36%)	99 (38%)	
≥2.0	47 (22%)	153 (21%)	147 (18%)	46 (17%)	
Hypertension (%)					
Year 20	52 (24%)	191 (27%)	194 (23%)	70 (26%)	0.555
Year 25*	61 (32%)	198 (33%)	204 (29%)	74 (34%)	0.322
Change (year 25 − year 20)*	21 (11%)	57 (9%)	69 (10%)	24 (11%)	0.862
Total cholesterol (mg/dL)					
Year 20	183 ± 32	188 ± 35	186 ± 35	191 ± 34	0.080
Year 25*	192 ± 34	196 ± 37	194 ± 34	195 ± 34	0.850
Change (year 25 − year 20)*	10 ± 26	8 ± 31	7 ± 30	4 ± 33	0.050
Accelerometer wear time (h/day)	**13.7 ± 1.6**	**14.3 ± 1.2**	**15.0 ± 1.1**	**16.3 ± 1.7**	**<0.001**
MVPA, median min/day [IQR]†	**38 [23, 58]**	**30 [17, 48]**	**26 [16, 41]**	**22 [14, 36]**	**<0.001**
Average cpm, median [IQR]†	**506 [421, 624]**	**386 [319, 483]**	**317 [252, 391]**	**246 [206, 318]**	**<0.001**
%ST	**38**	**50**	**60**	**67**	**<0.001**
Sedentary–to–light-activity ratio [IQR]†	**0.7 [0.6, 0.8]**	**1.1 [0.9, 1.3]**	**1.6 [1.4, 1.9]**	**2.3 [1.9, 2.6]**	**<0.001**

IQR, interquartile range. Boldface type denotes statistically significant differences across groups. **n* = 1,718 included in analysis of 5-year follow-up data; †log transformed for analysis.

SB/LA ratio). For example, when adjusting for MVPA cross-sectionally and similar to the results in Table 2, only fasting insulin (*P* for trend = 0.005) and HOMA-IR (*P* for trend = 0.012) increased across increasing categories of ST (Supplementary Table 1). When adjusting for MVPA in 5-year change models, no statistically significant trends (all $P > 0.10$) were observed for any continuous metabolic parameter across ST categories (Supplementary Table 2). Results did not differ when we excluded subjects reporting the use of diabetes medications at baseline or follow-up (data not shown).

Last, since previous studies have reported race × sedentary behavior interactions for metabolic variables (6), we stratified the sample by race and repeated analyses (Supplementary Table 3). Although formal tests for interaction were not statistically significant ($P \geq 0.10$), cross-sectional relationships were observed in blacks and not whites for insulin (β [blacks] = 3.7%, $P = 0.011$; β [whites] = 1.4%, $P = 0.205$) and HOMA-IR (β [blacks] = 4.5%, $P = 0.009$; β [whites] = 1.4%, $P = 0.274$).

Association Between ST and IFG, IGT, Prediabetes by HbA_{1c}, and Diabetes

Cross-sectionally, compared with <6 h per day, ≥10 h of ST per day was associated with 2.74 times greater odds ($P = 0.026$) of IGT (Fig. 1*C*). Each category above <6 h per day was associated with a greater odds of prevalent diabetes, with ≥10 vs. <6 h of ST per day having 3.8 times greater odds ($P = 0.009$) (Fig. 1*G*). ST category was not significantly related to prevalent IFG, prevalent prediabetes by HbA_{1c}, or 5-year incidence of IFG, IGT, prediabetes by HbA_{1c}, or diabetes (all $P > 0.05$) (Fig. 1*A*, *B*, *D*, *E*, *F*, and *H*). Prevalence and 5-year incidence of metabolic outcomes can be found in Supplementary Table 4.

Cross-sectionally, each additional hour of continuous ST was positively associated with prevalent IGT in models adjusted for demographics and lifestyle

Table 2—Cross-sectional and 5-year longitudinal relationships between ST and continuous metabolic variables

	Cross-sectional (n = 2,027)		5-Year change (n = 1,718)	
	β (% difference per hour ST)*	P value	β (5-year change per hour ST)	P value
Fasting glucose (mg/dL)*				
Model 1: demographics and lifestyle	**0.9**	**<0.001**	0.28	0.368
Model 2: +MVPA	0.6	0.228	0.45	0.192
Model 3: +comorbidities	−0.1	0.561	0.14	0.446
2-h glucose (mg/dL)*†				
Model 1: demographics and lifestyle	**1.5**	**<0.001**	0.21	0.721
Model 2: +MVPA	0.3	0.542	−0.24	0.708
Model 3: +comorbidities	0.0	0.932	−0.39	0.461
Fasting insulin (mU/dL)*				
Model 1: demographics and lifestyle	**4.8**	**<0.001**	0.14	0.183
Model 2: +MVPA	**2.8**	**0.005**	0.10	0.398
Model 3: +comorbidities	**2.0**	**0.007**	0.04	0.708
HOMA-IR*				
Model 1: demographics and lifestyle	**5.8**	**<0.001**	0.04	0.182
Model 2: +MVPA	**2.8**	**0.006**	0.04	0.237
Model 3: +comorbidities	**1.9**	**0.021**	0.02	0.399
HbA_{1c} (%)*‡				
Model 1: demographics and lifestyle	0.3	0.094	0.01	0.099
Model 2: +MVPA	0.1	0.591	0.01	0.058
Model 3: +comorbidities	−0.2	0.176	0.01	0.059

Model 1 adjusted for age, center, race, sex, education, income, smoking, alcohol, wear time, and baseline value (longitudinal model only); model 2 adjusted for same as model 1 + log-transformed MVPA (total minutes); model 3 adjusted for same as model 2 + BMI, hypertension, and diabetes and total cholesterol (+5-year change in longitudinal model). Boldface type denotes statistically significant associations. *Dependent variables were log transformed in cross-sectional models; thus, β is presented as the percent difference associated with each additional 1 h increase in ST; †missing in 400 participants at baseline and 401 participants at 5-year follow-up; ‡missing in 261 participants at baseline and 244 participants at 5-year follow-up.

factors (odds ratio [OR] = 1.20, P = 0.003), but this relationship was not independent of MVPA (OR = 1.11, P = 0.121). Continuous ST was associated with prevalent diabetes, even in fully adjusted models, with the odds of diabetes increasing by 22% for each additional hour of ST (P = 0.006). Baseline ST was not significantly associated with prevalent IFG or prediabetes by HbA_{1c}, or 5-year incidence of IFG, IGT, prediabetes by HbA_{1c}, or diabetes (Supplementary Table 4).

Comparison of ST and MVPA Versus Average Accelerometer Counts per Minute

Table 3 displays results from linear regression models with either MVPA and ST or average cpm as independent variables. MVPA and average cpm were highly correlated (log-transformed variables, r = 0.84, $P < 0.001$). The partial correlation between ST and log-transformed average cpm, after adjusting for wear time, was also high ($r_{partial} = -0.73$, $P < 0.001$). Standardized coefficients were calculated to facilitate comparison across variables. Since MVPA and average cpm were log transformed, these were scaled to an SD of the log-transformed variable, which was roughly a doubling of MVPA minutes (e.g., 30 vs. 60 min) and a 50% increase in average cpm (e.g., 400 vs. 600 cpm). Coefficients for ST were scaled to the SD of 1.75 h.

In cross-sectional models, in model 2, each doubling of MVPA minutes was associated with a 7.5% lower fasting insulin ($P < 0.001$); each additional 1.75 h of ST was associated with a 4.4% higher fasting insulin (P = 0.005); and each 50% higher average cpm was associated with a 9.5% lower fasting insulin ($P < 0.001$). As evidenced by the similar adjusted R^2 values, the choice of activity metric (ST + MVPA or average cpm) explained a similar amount of variance. Associations followed a pattern where if MVPA was statistically significant, then so too was average cpm in the comparable model. However, models separating MVPA and ST offered distinct information about patterns of activity associated with better metabolic health. Specifically, MVPA and ST were each independently associated with fasting insulin and HOMA-IR, but only MVPA was associated with fasting glucose, 2-h glucose, and HbA_{1c}.

In longitudinal models, in model 2, each doubling of minutes of baseline MVPA was associated with a 2.66 mg/dL lower change in 2-h glucose change (P = 0.005). Although other coefficients were nonsignificant and would thus be considered null associations, mathematical interpretations of other covariates would be as follows: each additional 1.75 h of baseline ST was nonsignificantly associated with a 1.06 mg/dL lower change in 2-h glucose (P = 0.708) and each 50% higher average baseline cpm was nonsignificantly associated with a 1.46 mg/dL lower change in 2-h glucose (P = 0.070). Again, adjusted R^2 values were similar in models using MVPA + ST or average cpm. However, only MVPA was predictive of any changes (2-h glucose in model 2; fasting glucose and HbA_{1c} in model 3).

CONCLUSIONS

The principal findings of the current study are that individuals with more versus less objectively measured ST had higher fasting insulin, HOMA-IR, and prevalent IGT and diabetes cross-sectionally, even after adjustment for MVPA and related comorbidities. However, in the same cohort, baseline ST did not predict 5-year changes in any metabolic variables or incidence of metabolic disease. A reassuring finding from the current study is that operationalizing

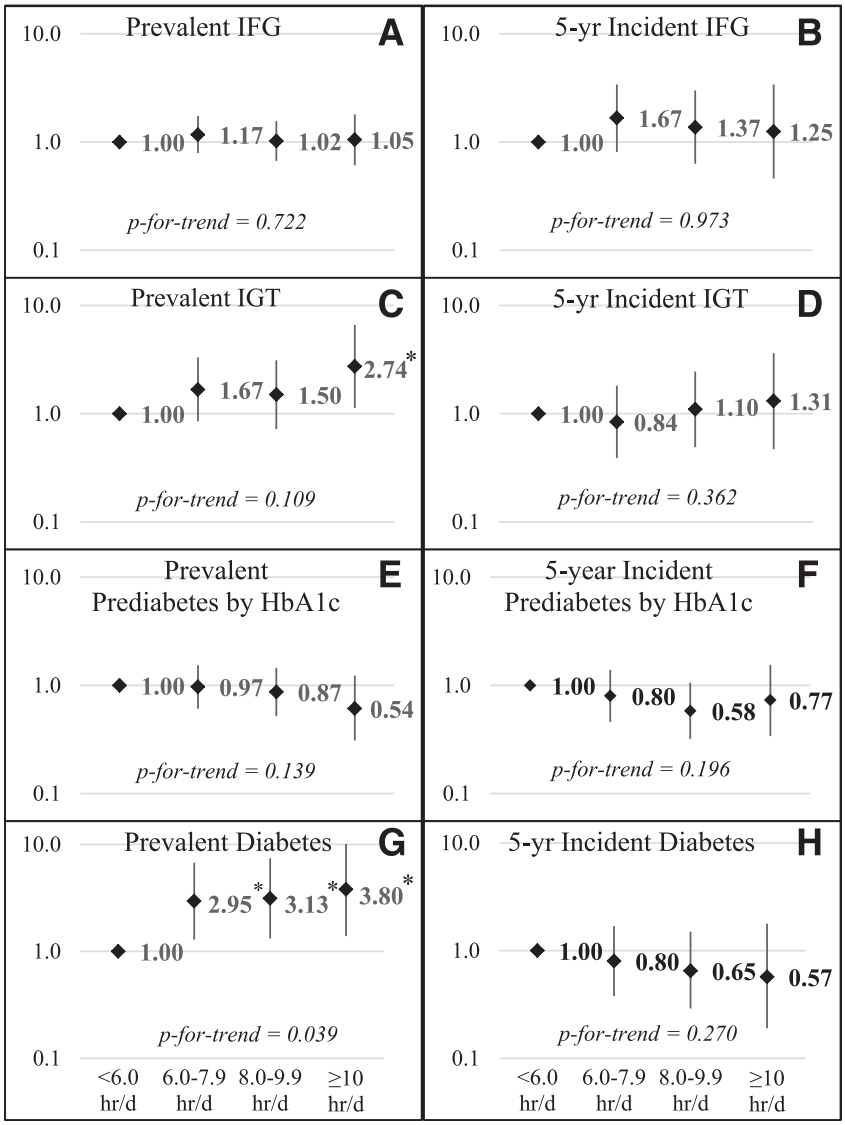

Figure 1—Adjusted cross-sectional and longitudinal ORs of IFG (*A* and *B*), IGT (*C* and *D*), prediabetes by HbA_{1c} (*E* and *F*), and diabetes (*G* and *H*) by increasing category of ST (<6 h/day, 6 to <8 h/day, 8 to <10 h/day, and ≥10 h/day). Adjusted for age, center, race, sex, education, income, smoking, alcohol, wear time, and log-transformed MVPA. d, day; hr, hour. *$P < 0.05$.

accelerometry data as absolute ST adjusted for wear time, categorical ST, %ST, or ST/LA ratio yielded similar relationships with outcomes. Further, we found that using average cpm rather than absolute time spent in MVPA or sedentary behaviors was often equivalent for explaining variability in metabolic parameters but sometimes resulted in a loss of information about relevant patterns of activity accumulation that were associated with outcomes.

Our cross-sectional results are consistent with several other studies. In NHANES 2003–2006, a higher amount of ST was associated with higher fasting insulin and HOMA-IR and was not related to fasting glucose or 2-h glucose (6). Direct associations of ST with fasting insulin and HOMA-IR were also observed in a study of 878 adults at risk for diabetes (7). Other studies have found that ST was not cross-sectionally associated with fasting insulin or HOMA-IR, but these results may be limited by small sample sizes and lower statistical power (9,12).

Data from NHANES (6) also exhibited a significant race interaction where higher amounts of ST were related to higher fasting insulin and lower HOMA-IR in whites, with no association in blacks (P for interaction <0.01). CARDIA has large samples of black and white participants, but no significant race interactions ($P \geq 0.10$) were present. Additionally, stratification revealed slightly stronger associations in blacks versus whites (Supplementary Table 3). Thus, results from the current study do not support that associations between ST and metabolic parameters are stronger in whites versus blacks.

Longitudinally, baseline ST did not predict 5-year changes in metabolic parameters. This is consistent with results from the ProActive UK trial in high-risk adults, which found that baseline ST measured by accelerometry did not predict 1-year changes in fasting insulin or HOMA-IR (9) (n = 192), and, over 6 years of follow-up, change in objectively measured ST was not associated with changes in fasting glucose or fasting insulin (n = 171) (10). In contrast, the Medical Research Council Ely Study (n = 376) found that baseline ST predicted follow-up fasting insulin measured, on average, 5.6 years later (P for trend = 0.012) (8). Although the reasons for the disparate results are not entirely clear, a notable difference is that the Medical Research Council Ely Study used a heart rate monitor to indirectly estimate sedentary behavior.

Although self-reported ST or TV time measured at baseline has been associated with prevalent and incident diabetes in other studies (3,18,19), fewer studies have investigated these relationships with objective measures of ST. In contrast to our findings that each additional hour of ST was cross-sectionally associated with ~20% higher odds of diabetes, a study of n = 649 older adults in the Health Survey for England found that objectively measured ST was not related to prevalent diabetes (OR = 1.05 for each 30 min, P = 0.49) (18). Although this study was also population based, the different results could be attributed to differences in study population (i.e., age and race). We are unaware of other prospective studies of incident IGT, IFG, or diabetes with objectively measured sedentary behavior, highlighting the contribution of this study and a need for more research. Taken together, when sedentary behavior is objectively measured, there is little evidence that sedentary behavior contributes to future metabolic disease risk. Thus, it may be premature to

Table 3—Comparison across activity variables of associations and model fit in cross-sectional and longitudinal models

	MVPA + ST					Average cpm		
	MVPA* % difference	*P* value	ST† % difference	*P* value	R^2	Cpm* % difference	*P* value	R^2
Cross-sectional (*n* = 2,027)								
Fasting glucose (mg/dL)‡								
Model 2	**−2.2**	**<0.001**	0.6	0.228	7.6%	**−2.3**	**<0.001**	7.7%
Model 3	**−1.3**	**<0.001**	−0.2	0.561	45.6%	**−0.9**	**<0.001**	45.5%
2-h glucose (mg/dL)‡§								
Model 2	**−4.1**	**<0.001**	0.6	0.542	7.4%	**−4.0**	**<0.001**	7.4%
Model 3	**−3.2**	**<0.001**	−0.1	0.932	29.2%	**−2.8**	**<0.001**	29.1%
Fasting insulin (mU/L)‡								
Model 2	**−7.5**	**<0.001**	**4.4**	**0.005**	10.2%	**−9.5**	**<0.001**	10.5%
Model 3	**−3.9**	**0.001**	**3.5**	**0.007**	36.2%	**−5.6**	**<0.001**	36.3%
HOMA-IR‡								
Model 2	**−9.5**	**<0.001**	**5.0**	**0.006**	11.4%	**−11.6**	**<0.001**	11.7%
Model 3	**−5.1**	**<0.001**	**3.3**	**0.021**	43.5%	**−6.5**	**<0.001**	43.5%
HbA_{1c} (%)‡‖								
Model 2	**−0.8**	**0.028**	0.2	0.646	9.2%	**−0.9**	**0.002**	9.4%
Model 3	−0.2	0.525	−0.2	0.176	49.0%	0.1	0.616	49.0%
	MVPA + ST					Average cpm		
	Std β MVPA*	*P* value	Std β ST†	*P* value	R^2	Std β cpm*	*P* value	R^2
5-year change (*n* = 1,718)								
Fasting glucose (mg/dL)								
Model 2	0.49	0.173	0.38	0.192	7.9%	0.07	0.803	7.9%
Model 3	**0.71**	**0.019**	0.25	0.446	34.9%	0.32	0.201	34.8%
2-h glucose (mg/dL)¶								
Model 2	**−2.66**	**0.005**	−1.06	0.708	17.7%	−1.46	0.070	17.5%
Model 3	−1.58	0.068	−0.67	0.548	33.5%	−0.83	0.256	33.4%
Fasting insulin (mU/L)								
Model 2	−0.10	0.608	0.21	0.164	15.4%	−0.19	0.250	15.4%
Model 3	−0.12	0.470	0.07	0.708	23.1%	−0.13	0.363	23.2%
HOMA-IR								
Model 2	0.01	0.889	0.08	0.128	11.8%	−0.04	0.427	11.8%
Model 3	0.01	0.853	0.04	0.399	27.0%	−0.02	0.632	27.1%
HbA_{1c} (%)#								
Model 2	0.01	0.351	0.02	0.063	2.7%	−0.01	0.390	2.5%
Model 3	**0.02**	**0.047**	0.02	0.058	37.0%	0.00	0.912	36.8%

Model 2 adjusted for demographics, lifestyle, accelerometers wear time, and log-transformed MVPA (total minutes); model 3 adjusted for the same as model 2 + BMI, hypertension, diabetes, and total cholesterol (+5-year change in longitudinal model). Boldface type denotes statistically significant associations. Std, standardized. *MVPA and cpm were log transformed. The standardized β coefficients presented are based on the SD of the independent variable and represent the difference that would be expected with an approximate doubling of MVPA (e.g., 60 vs. 120 min) and an ∼50% increase in cpm (e.g., 400 vs. 600 cpm); †the standardized β coefficients are based on the SD of ST in this sample and represent the difference that would be expected with a 1-h and 45-min difference in ST; ‡dependent variables were log transformed in cross-sectional models; thus, the β presented is the percent difference associated with each additional standardized increase in MVPA, ST, or average cpm; §missing in 400 participants; ‖missing in 261 participants; ¶missing in 401 participants; #missing for 244 participants.

consider prolonged sedentary behavior as a risk factor for metabolic disease.

Some researchers have suggested that total physical activity (average cpm), rather than ST and MVPA considered separately, could be the important determinant of metabolic disease (20–22). In a cross-sectional analysis of 801 healthy adults from the European Relationship between Insulin Sensitivity and Cardiovascular risk (RISC) study, when added concurrently, average cpm ($P < 0.001$) but not ST% ($P = 0.8$) was significantly associated with insulin sensitivity measured by euglycemic clamp (20). Significant colinearity of average cpm with both ST and MVPA prevented us from adding all of these variables together into the same model. Rather, average cpm was investigated as an alternative metric in regression models. This comparison revealed that average cpm might be equivalent to MVPA and ST when adjusting for activity as a confounder (i.e., similar adjusted R^2). However, models including only average cpm sometimes lost information about whether just MVPA or MVPA and sedentary behavior independently had relationships with metabolic parameters. Thus, separation of ST and MVPA may still be important for understanding the patterns of activity associated with better metabolic health.

Sedentary behavior is thought to contribute to the development of metabolic disease acutely through infrequent muscle contractions and reduced shear stress, which could lead to impairment of glucose disposal (23), suppression of lipoprotein lipase (24), and decreased bioavailability of nitric oxide (25). These mechanisms have been observed in short-term and laboratory studies (23,26–29). This research is consistent with our cross-sectional findings that support associations with insulin sensitivity and prevalent metabolic disease. Sedentary behavior could also potentially contribute to the development of metabolic disease through an effect on

weight, body composition, or dyslipidemia (6), although prospective studies providing evidence that objectively measured sedentary behavior leads to these risk factors are also limited (5).

Less clear is why baseline ST did not predict metabolic outcomes 5 years later as we hypothesized, but several explanations are possible. Follow-up may not have been long enough, with post hoc power calculations suggesting that ORs of ~1.3 could be detected at 80% power for each one SD increase in ST. Also, ST, although objective, was only measured at baseline and for 1 week. Although 1 week of measurement is standard and has been found to produce reliable estimates of sedentary behavior (30), individual variability over time is possible and a repeated measure of ST at the 5-year follow-up was not collected. Considering the evidence that sedentary behavior can acutely influence metabolic parameters (23,26–29), recent exposure to sedentary behavior may be more important for some metabolic outcomes, and this could explain the presence of cross-sectional and not longitudinal relationships. Reverse causality, where metabolic disease could lead to sedentary behavior, is another possible explanation for the cross-sectional and not longitudinal associations. These limitations underscore the importance of continuing to study longitudinal relationships between ST and health outcomes in order to better understand the temporal nature of these relationships.

This study has several strengths, including the large, well-characterized sample able to evaluate race (black vs. white) and sex interactions; objective activity assessment; laboratory-based outcome definitions for IFG, IGT, prediabetes by HbA_{1c}, and diabetes; the investigation of cross-sectional and longitudinal associations in the same cohort; and consideration of multiple sedentary behavior definitions. Aside from the short follow-up and single assessment of objective ST as previously described, other limitations include the limited age range and lack of other racial/ethnic groups in the study population, which may limit the generalizability of the findings. Last, ST was measured by an accelerometer in the current study, which provides an estimate of time spent not moving (i.e., generating <100 cpm) but does not specifically measure posture (i.e., standing vs. sitting). Thus, the results of this study reflect a definition of sedentary behavior that does not include posture (5).

Summary

Individuals with a higher amount of ST had worse metabolic parameters and were more likely to have prevalent IGT and diabetes as compared with individuals with less ST. However, higher amounts of baseline ST did not predict 5-year changes or incidence of metabolic disease. The findings of the current study do not support that sedentary behavior is a lifestyle target for lowering the risk of developing metabolic disease, although more studies with repeated assessment of objective ST and longer follow-up are needed.

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