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

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/m²) 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 HbA₁c) and outcomes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], prediabetes by HbA₁c, 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 HbA₁c, 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.
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 HbA1c. 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 accelerometer-derived ST with continuous metabolic variables (fasting glucose, fasting insulin, 2-h postchallenge glucose, HOMA of insulin resistance [HOMA-IR], and HbA1c) and metabolic outcomes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], prediabetes by HbA1c, 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 ≥4 days with ≥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. HbA1c 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 HbA1c, 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 ≥60 consecutive minutes. Accelerometry data were considered valid if participants had ≥4 days of monitoring with ≥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 (≥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 ≥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) 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 ± SDs of %ST were 54 ± 12%, 55 ± 10%, 56 ± 9%, 55 ± 10%, and 55 ± 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. HbA1c 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) \times fasting glucose (mmol/L)]/22.5) (16). Diabetes was defined as either self-reported use of diabetes medications, HbA1c \geq 6.5\% \text{ or} \geq 47.5 \text{ mmol/mol}, fasting glucose \geq 100 \text{ mg/dL}, or 2-h glucose \geq 200 \text{ 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 \geq 140–199 \text{ mg/dL}, IFG was defined as a fasting glucose of 100–125 \text{ mg/dL}, and prediabetes from HbA1c was defined as an HbA1c of 5.7–6.4\% (39 to \approx 47.5 \text{ 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 \geq 140 \text{ mmHg}, diastolic blood pressure \geq 90 \text{ mmHg}, or antihypertensive medication use. Height and weight were measured without shoes and in light clothing. BMI was calculated as kg/m². Total cholesterol was measured using an enzymatic assay.

Statistical Methods

All variables were checked for normality and transformed or analyzed using non-parametric methods. Baseline characteristics were compared across ST categories by testing for linear trends or chi-squared 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 HbA1c. Logistic regression evaluated whether categorical ST was associated with prevalent IFG, IGT, prediabetes by HbA1c, 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 IGF, IGT, prediabetes by HbA1c, 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 accelerometer 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 \times 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 \leq 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 HbA1c 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 HbA1c 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 accelerometer data did not influence relationships with metabolic parameters (data not shown for %SB or
SB/LA ratio). For example, when adjusting for MVPA cross-sectionally and similar to the results in Table 2, only fasting insulin \( (P \text{ for trend } = 0.005) \) and HOMA-IR \( (P \text{ for trend } = 0.012) \) 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 \( \times \) 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 \( (\beta \text{ [blacks] } = 3.7%, P = 0.011; \beta \text{ [whites] } = 1.4%, P = 0.205) \) and HOMA-IR \( (\beta \text{ [blacks] } = 4.5%, P = 0.009; \beta \text{ [whites] } = 1.4%, P = 0.274) \).

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

| Category | Age (years) | Sex | Race | Education (years) | Total family income ($/year) | BMI (kg/m²) | Alcohol consumption (drinks/day) | Hypertension (%) | Total cholesterol (mg/dL) | Accelerometer wear time (h/day) | MVPA, median min/day (IQR)† | Average cpm, median (IQR)† | %ST | Sedentary–to–light-activity ratio (IQR)† |
|----------|-------------|-----|------|------------------|-------------------------------|-------------|--------------------------------|-----------------|--------------------------|-------------------------------|-----------------------------|-----------------------------|------|----------------------------------|
| <6 h/day | 44.6 ± 3.6  | 137 (64%) | 116 (54%) | 14 ± 2 | 49 (23%) | 28.7 ± 6.3 | 2.0 | Year 20 | 183 ± 32 | 13.7 ± 1.6 | 38 [23, 58] | 0.7 [0.6, 0.8] |
| 6 to <8 h/day | 45.2 ± 3.7 | 441 (61%) | 319 (44%) | 15 ± 2 | 104 (14%) | 29.2 ± 6.6 | 3.5 | Year 25* | 196 ± 37 | 14.3 ± 1.2 | 30 [17, 48] | 1.1 [0.9, 1.3] |
| 8 to <10 h/day | 45.5 ± 3.5 | 464 (56%) | 296 (36%) | 16 ± 3 | 71 (9%) | 28.8 ± 7.6 | 2.3 | Change (year 25 – year 20)* | 194 ± 34 | 15.0 ± 1.1 | 26 [16, 41] | 1.6 [1.4, 1.9] |
| ≥10 h/day | 45.5 ± 3.3 | 123 (46%) | 107 (40%) | 16 ± 3 | 312 (44%) | 29.1 ± 6.7 | 2.5 | | 193 (73%) | 24 [16, 41] | 2.3 [1.9, 2.6] |

† log transformed for analysis.

Note: Boldface type denotes statistically significant differences across groups. * \( n = 1,718 \) included in analysis of 5-year follow-up data; † log transformed for analysis.

Association Between ST and IFG, IGT, Prediabetes by HbaA1c, 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. 1C). 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. 1D). ST category was not significantly related to prevalent IFG, prevalent prediabetes by HbaA1c, or 5-year incidence of IGT, IGT, prediabetes by HbaA1c, or diabetes (all \( P > 0.05 \)) (Fig. 1A, 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)* | 0.9 <0.001                  | 0.28 0.368                | 0.28 0.368                    |
| Model 1: demographics and lifestyle  | 0.6 0.228                  | 0.45 0.192                | 0.45 0.192                    |
| Model 2: +MVPA               | −0.1 0.561                 | 0.14 0.446                | 0.14 0.446                    |
| 2-h glucose (mg/dL)**       | 1.5 <0.001                 | 0.21 0.721                | 0.21 0.721                    |
| Model 1: demographics and lifestyle  | 0.3 0.542                  | −0.24 0.708               | −0.24 0.708                    |
| Model 2: +MVPA               | 0.0 0.932                  | −0.39 0.461               | −0.39 0.461                    |
| Fasting insulin (mU/dL)*    | 4.8 <0.001                 | 0.14 0.183                | 0.14 0.183                    |
| Model 1: demographics and lifestyle  | 2.8 0.005                  | 0.10 0.398                | 0.10 0.398                    |
| Model 2: +MVPA               | 2.0 0.007                  | 0.04 0.708                | 0.04 0.708                    |
| HOMA-IR*                    | 5.8 <0.001                 | 0.04 0.182                | 0.04 0.182                    |
| Model 1: demographics and lifestyle  | 2.8 0.006                  | 0.04 0.237                | 0.04 0.237                    |
| Model 2: +MVPA               | 1.9 0.021                  | 0.02 0.399                | 0.02 0.399                    |
| HbA1c (%)††                | 0.3 0.094                  | 0.01 0.099                | 0.01 0.099                    |
| Model 1: demographics and lifestyle  | 0.1 0.591                  | 0.01 0.058                | 0.01 0.058                    |
| Model 2: +MVPA               | −0.2 0.176                 | 0.01 0.059                | 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.

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 R² 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 HbA1c.

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 = 0.700). Again, adjusted R² 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 HbA1c 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 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 HbA1c or 5-year incidence of IFG, IGT, prediabetes by HbA1c, or diabetes (Supplementary Table 4).
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 ≥ 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...
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 R²). 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

| 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 | R² | Cpm* % difference | P value | R² |
| 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% |
| HbA1c (%)¶ | | | | | | | |
| 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% |

| 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 | <0.001 | −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% |
| HbA1c (%)¶ | | | | | | | |
| 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% |

* 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; §missing in 400 participants; ¶missing in 401 participants; ‡missing in 244 participants.

Model 2 adjusted for demographics, lifestyle, accelerometers wear time, and log-transformed MVPA (total minutes); model 3 adjusted for the same as model 2 + 8M, hypertension, diabetes, and total cholesterol (+5-year change in longitudinal model). Boldface type denotes statistically significant associations. Std, standardized.
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 1 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, and diabetes by HbA1c, 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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References

1. Solomon TP, Thyfault JP. Type 2 diabetes sits in a chair. Diabetes Obes Metab 2013;15:987–992
2. Dempsey PC, Owen N, Biddle SJ, Dunstan DW. Managing sedentary behavior to reduce the risk of diabetes and cardiovascular disease. Curr Diab Rep 2014;14:522
3. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia 2012;55:2895–2905
4. Sugiyama T, Healy GN, Dunstan DW, Salmon J, Owen N. Is television viewing time a marker of a broader pattern of sedentary behavior? Ann Behav Med 2008;35:245–250
5. Gibbs BB, Hergenroeder AL, Katzmarzyk PT, Lee IM, Jakicic JM. Definition, measurement, and health risks associated with sedentary behavior. Med Sci Sports Exerc 2015;47:1295–1300
6. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardiometabolic biomarkers in US adults: NHANES 2003–06. Eur Heart J 2011;32:590–597
7. Henson J, Yates T, Biddle SJ, et al. Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. Diabetologia 2013;56:1012–1020
8. Helmerhorst HJ, Wijndaele K, Brage S, Wareham NJ, Ekelund U. Objectively measured sedentary time may predict insulin resistance independent of moderate- and vigorous-intensity physical activity. Diabetes 2009;58:1776–1779
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. Diabet Care 2009;32:1081–1086
10. Wijndaele K, Orrow G, Ekelund U, et al. Increasing objectively measured sedentary time increases clustered cardiometabolic risk: a 6 year analysis of the ProActive study. Diabetologia 2014;57:305–312
11. Stamatakis E, Hamer M, Tilling K, Lawlor DA. Sedentary time in relation to cardio-metabolic risk factors: differential associations for self-report vs accelerometry in working age adults. Int J Epidemiol 2012;41:1328–1337
12. McGuire KA, Ross R. Sedentary behavior is not associated with cardiometabolic risk in adults with abdominal obesity. PLoS One 2011;6:e20503
13. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41:1105–1116
14. Troiano RP, Berrigan D, Dodd KW, Mäeše LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–188
15. Chau JY, Grunseit AC, Chey T, et al. Daily sitting time and all-cause mortality: a meta-analysis. PLoS One 2013;8:e80000
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
17. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama 2003;289:2506–2572
18. Stamatakis E, Davis M, Stathi A, Hamer M. Associations between multiple indicators of objectively measured and self-reported...
sedentary behaviour and cardiometabolic risk in older adults. Prev Med 2012;54:82–87
19. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care 2009;32:791–796
20. 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
21. 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
22. Wolff DL, Fitzhugh EC, Bassett DR, Churilla JR. Total activity counts and bouted minutes of moderate-to-vigorous physical activity: Relationships with cardiometabolic biomarkers using 2003-2006 NHANES. J Phys Act Health. 7 August 2014 [Epub ahead of print]
23. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. Metabolism 2011;60:941–949
24. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes 2007;56:2655–2667
25. Thosar SS, Johnson BD, Johnston JD, Wallace JP. Sitting and endothelial dysfunction: the role of shear stress. Med Sci Monit 2012;18:RA173–RA180
26. Thyfault JP, Du M, Kraus BE, Levine JA, Booth FW. Physiology of sedentary behavior and its relationship to health outcomes. Med Sci Sports Exerc 2015;47:1301–1305
27. Buckley JP, Mellor DD, Morris M, Joseph F. Standing-based office work shows encouraging signs of attenuating post-prandial glycaemic excursion. Occup Environ Med 2014;71:109–111
28. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking up prolonged sitting reduces post-prandial glucose and insulin responses. Diabetes Care 2012;35:976–983
29. Thorp AA, Kingwell BA, Sethi P, Hammond L, Owen N, Dunstan DW. Alternating bouts of sitting and standing attenuate postprandial glucose responses. Med Sci Sports Exerc 2014;46:2053–2061
30. Atkin AJ, Gorely T, Clemes SA, et al. Methods of measurement in epidemiology: sedentary behaviour. Int J Epidemiol 2012;41:1460–1471