ORIGINAL RESEARCH

Associations of Accelerometer-Measured Sedentary Time and Physical Activity With Prospectively Assessed Cardiometabolic Risk Factors: The CARDIA Study

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***Background*—**Isotemporal substitution examines the effect on health outcomes of replacing sedentary time with light-intensity physical activity or moderate-to-vigorous intensity physical activity; however, existing studies are limited by cross-sectional study designs.

***Methods and Results*—**Participants were 1922 adults from the CARDIA (Coronary Artery Risk Development in Young Adults) study. Linear regression examined the associations of sedentary, light-intensity physical activity, and moderate-to-vigorous intensity physical activity at year 20 (2005–2006) with waist circumference, blood pressure, glucose, insulin, triglycerides, high-density lipoprotein cholesterol, and a composite risk score at year 30 (2015–2016). Models then examined change in activity with change in cardiometabolic risk over the same 10-year period. Replacing 30 min/day of sedentary time with 30 min/day of light-intensity physical activity at year 20 was associated with a lower composite risk score (−0.01 SD [95% CI, −0.02, −0.00]) at year 30, characterized by lower waist circumference (0.15 cm [95% CI, −0.27, 0.02]), insulin (0.20 μU/mL [95% CI, −0.35, −0.04]), and higher high-density lipoprotein cholesterol (0.20 mg/dL [95% CI, 0.00, 0.40]; all $P<0.05$). An increase of 30 min/day in MVPA from year 20 to year 30, when replacing an equivalent increase in sedentary time, was associated with a decrease in the composite risk score (−0.08 [95% CI, −0.13, −0.04]) over the same 10 years, characterized by a decrease in waist circumference (1.52 cm [95% CI, −2.21, −0.84]), insulin (−1.13 μU/mL [95% CI, −1.95, −0.31]), triglycerides (−6.92 mg/dL [95% CI, −11.69, −2.15]), and an increase in high-density lipoprotein cholesterol (1.59 mg/dL [95% CI, 0.45, 2.73]; all $P<0.05$).

***Conclusions*—**Replacement of sedentary time with light-intensity physical activity or moderate-to-vigorous intensity physical activity is associated with improved cardiometabolic health 10 years later. **(*J Am Heart Assoc*. 2019;8:e010212. DOI: 10.1161/JAHA.118.010212)**

Key Words: cardiometabolic risk • epidemiology • isotemporal substitution • physical activity • sedentary time

High prevalence of sedentary behaviors in today's society is a growing public health concern. Excess sedentary time is associated with many markers of cardiometabolic risk, including larger waist circumference and higher blood pressure, glucose, insulin, triglycerides, and lower high-density lipoprotein cholesterol (HDL-C).[1–5] Evidence suggests that meeting guidelines for physical activity may not be sufficient for chronic disease prevention if accompanied by

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Clinical Perspective

What Is New?

- Few large, epidemiological studies have repeated measures of accelerometer-measured sedentary time, light-intensity physical activity, and moderate-to-vigorous intensity physical activity (MVPA), which allows for more-accurate quantification of the rest-activity behavioral profile compared with self-reported questionnaires.
- Using isotemporal substitution, this study examined longitudinal associations of accelerometer-measured sedentary time, light-intensity physical activity, and moderate-to-vigorous intensity physical activity in 2005–2006 with cardiometabolic risk factors assessed in 2015–2016, as well as change in activity with change in cardiometabolic risk factors over the same 10-year period.

What Are the Clinical Implications?

- Study findings indicate that replacement of sedentary time with light-intensity physical activity or moderate-to-vigorous intensity physical activity is associated with improved cardiometabolic health 10 years later.
- In addition to promoting moderate-to-vigorous intensity physical activity, clinicians and public health practitioners should consider encouraging patients to replace sedentary time with light-intensity physical activity for cardiometabolic benefit, which may be a more-feasible lifestyle modification strategy for highly sedentary adults.

high levels of sedentary time.[6] Given that the number of hours in a day is fixed, participation in 1 activity means that a different activity is displaced, and each activity may have differential associations with cardiometabolic risk factors depending on the type of activity displaced. For example, replacing sedentary time with light-intensity physical activity (LPA) may have heterogeneous effects on cardiometabolic risk factors as compared with replacing sedentary time with moderate-to-vigorous intensity physical activity (MVPA). It is therefore important to assess the associations of substituting sedentary time with physical activity of various intensity levels to better inform health promotion efforts.

Isotemporal substitution has been used to examine the associations of alternating allocations of time in 1 behavior with another while holding total time constant.[7] This approach was originally developed for nutritional epidemiology and has recently been used in the physical activity literature to examine associations when replacing sedentary time with physical activities of varying types and intensities across a variety of outcomes, including self-rated health,[8–10] cardiometabolic risk factors,[7,11–20] and all-cause mortality.[21–24] Although there has been increasing use of the isotemporal substitution method, these studies are largely limited by their cross-sectional study designs. A small number of studies haves used isotemporal substitution to examine the associations of physical activity and sedentary behaviors with prospective measures of health outcomes. However, to our knowledge, the isotemporal substitution method has not been used to examine change in objectively measured physical activity with concurrent change in cardiometabolic risk factors.

The CARDIA (Coronary Artery Risk Development in Young Adults) Fitness and Activity ancillary studies provide an opportunity to fill this existing gap in knowledge, as a subset of participants wore an ActiGraph accelerometer for 7 consecutive days in early (ages 38–50 years) and late (ages 48–60 years) midlife, corresponding to the year 20 and 30 CARDIA exams. The objective of this study was to examine the associations of time spent in accelerometer-measured activity (sedentary, LPA, and MVPA) at year 20 with a composite cardiometabolic risk score (primary outcome) and each individual cardiometabolic risk factor (secondary outcomes: waist circumference, blood pressure, glucose, insulin, triglycerides, and HDL-C) at year 30, using the isotemporal substitution method. We then examined associations between change in time spent in accelerometer-measured activity from year 20 to year 30, with change in the composite risk score and individual risk factors from year 20 to year 30. We hypothesized that replacing sedentary time with LPA or MVPA at year 20 will result in more-favorable cardiometabolic risk factors at year 30, and that an increase in LPA or MVPA from year 20 to year 30, when substituted for sedentary time, will be associated with more-favorable 10-year changes in cardiometabolic risk factors.

Methods

Requests to access the data set, analytical methods, and study materials may be sent to the CARDIA Coordinating Center. Contact information can be found on the CARDIA website.[25]

Study Participants

The CARDIA study is an ongoing longitudinal cohort of 5115 black and white men and women, aged 18 to 30 years, who completed an in-person clinical examination in 1985–1986 (year 0) from 1 of 4 field centers: Birmingham, Alabama; Minneapolis, MN; Chicago, IL; or Oakland, CA. Additional in-person clinic examinations were held approximately every 2 to 5 years, including a year 20 (2005–2006) and 30 (2015–2016) exam, with 72% and 71% participant retention, respectively. Details on eligibility criteria, methods of participant selection, and follow-up have been previously reported.[26]

All ambulatory participants in the core study were invited to take part in the ancillary CARDIA Fitness Study during the year 20 exam, where physical activity was measured for 7 days with the ActiGraph 7164 (N=2332). As previously described, individuals who did not take part in the year 20 CARDIA Fitness Study for medical or nonmedical reasons had a higher risk of cardiovascular events and/or all-cause mortality as compared with those who took part in the Fitness Study.[27] At year 30, all ambulatory participants were again invited to take part in the CARDIA Activity Study, where physical activity was measured using the ActiGraph wGT3X-BT (N=1397). For the present study, participants were excluded if they had unreasonably high values for MVPA (>14 h/day, N=3, all 7164 devices), or were missing data on the cardiometabolic risk factors of interest at the year 20 (N=25) or year 30 examinations (N=318), or were missing data on potential confounders of interest from year 20 (N=64), resulting in a final sample of 1922 for the analyses examining associations of year 20 physical activity with year 30 cardiometabolic outcomes. Participants who were excluded from analyses because of missing data on cardiometabolic risk factors or other covariates (N=410) were more likely to be black, with less years of education, without health insurance, reporting medication use, and were also more likely to be current smokers as compared with those included in the analyses (see Table 1). Of the 1922 participants included in analyses, 913 also had accelerometer data from the year 30 examination and were included in the analyses examining change in activity and cardiometabolic risk from years 20 to 30. The smaller sample with accelerometer data at year 30 was primarily the result of a shortened data collection period (because of funding mechanism) that began approximately midway through the year 30 exam. The institutional review board at each center approved all study protocols for the primary CARDIA exam, as well as the CARDIA Fitness and Activity studies. The institutional review boards at the University of Alabama at Birmingham, Northwestern University, University of Minnesota, and Kaiser Permanente approved the study. Written informed consent was obtained at each exam, separately for the primary and ancillary studies.

Table 1. Characteristics of CARDIA Participants Included and Excluded From Analyses

Characteristics	Included Participants (N=1922)	Excluded Participants (N=410)*	*P* Value†
Age, y	45.3±3.5	45.2±3.8	0.509
Female, n (%)	1123 (58.4)	221 (54.0)	0.102
White, n (%)	1143 (59.5)	215 (52.4)	0.009
Education, y	15.3±2.6	14.6±2.6	<0.001
Unemployment, n (%)	206 (10.7)	56 (13.8)	0.072
Health insurance, n (%)	1716 (89.3)	333 (81.4)	<0.001
Medication use, n (%)‡	375 (19.5)	106 (25.9)	0.004
Smoking status, n (%)			<0.001
Current	282 (14.7)	92 (23.4)	
Former	411 (21.4)	17 (18.1)	
Never	1229 (63.9)	230 (58.5)	
Alcohol consumption, mL/day	2.4 (14.5)	0.0 (13.6)	0.117
Body mass index, kg/m^2	28.8±6.4	29.6±9.0	0.101
Accelerometer measured activity, min/day§			
Total wear time	886.5±86.9	878.4±100.7	0.093
Sedentary	490.1±102.4	472.1±112.8	0.003
LPA	360.9±86.3	360.5±89.3	0.938
MVPA	29.8 (29.8)	30.7 (33.7)	0.916

Data presented as mean±SD or median (interquartile range), unless otherwise specified. CARDIA indicates Coronary Artery Risk Development in Young Adults; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity.

*Participants excluded because of unreasonably high values for MVPA (N=3), or if they were missing data on the cardiometabolic risk factors of interest at the year 20 (N=25) or year 30 examinations (N=318), or were missing data on potential confounders of interest from year 20 (N=64).

†*P*-value testing for differences among those who were included vs excluded from analyses using independent samples *t* tests, Wilcoxon–Mann–Whitney tests, or chi-square tests, as appropriate.

‡Self-reported medication use for blood pressure, cholesterol, or diabetes mellitus.

§Freedson cut point thresholds defined sedentary time in counts/minute as <100, LPA as 100–1951, and MVPA as ≥1952.

Physical Activity and Sedentary Behavior

The ActiGraph 7164 (Year 20) and ActiGraph wGT3X-BT (Year 30) were initialized to start collecting data at 12:00 AM on the day following the in-person examination and were worn on an elastic belt during waking hours. The 7164 model was initialized to collect data in 60-second epochs, and for the wGT3X-BT devices, raw triaxial data were sampled at 40 Hz. Data from both monitors were processed using ActiLife6 software, and raw data from the wGT3X-BT were reintegrated to a 60-second epoch (with the low-frequency extension applied). Files from both devices were screened for wear time using the Troiano algorithm.[28] Weekly summary physical activity and sedentary behavior estimates were averaged across days for all participants with at least 4 valid days of ≥10 hours of wear time based on criteria established for (National Health and Nutrition Examination Survey 2003–2004 and 2005–2006 cycles.[28] Total and average accelerometer counts per day were calculated using summed counts detected over wear periods and time (ie, minutes) spent in different intensity levels using standardized cut-point threshold values.[28–30] Freedson cut-point threshold values were selected given their broad use in physical activity research; sedentary time was defined as ≤100 counts per minute,

LPA as 101 to 1951 counts per minute, and MVPA as 1952+ counts per minute.[30] We chose to combine moderate-intensity physical activity and vigorous-intensity physical activity because of the low prevalence of vigorous activity detected in this cohort.

Given that different monitors were used in the 2 exams, we examined the comparability of the 7164 and wGT3X-BT models by having a subset of participants (N=100) wear both monitors simultaneously during the year 30 examination.[31] There were significant differences between monitors for sedentary, LPA, and MVPA. Therefore, to allow for data harmonization between the 2 monitors, we developed and applied a calibration factor to the wGT3X-BT values. After calibration, no differences were observed between the 7164 and wGT3X-BT in min/day for sedentary (513.2±93.6 versus 509.6±98.6; P=0.23), LPA (335.3±81.5 versus 338.7±81.1; P=0.22), or MVPA (33.1±24.6 versus 32.0±26.0; P=0.13). For the present analyses, we report the calibrated values for the wGT3X-BT; no correction was applied to the 7164 values.

Cardiometabolic Risk Factors

The same protocols and procedures for all cardiometabolic risk factors were used at both the year 20 and year 30 examinations. Participants were asked to fast for at least 12 hours before the study examination and refrain from smoking or engaging in vigorous physical activities for at least 2 hours earlier. Waist circumference was measured in duplicate to the nearest 0.5 cm at the minimal abdominal girth and then averaged. Blood pressure was measured 3 times on the right arm using an automated sphygmomanometer (Omron HEM907XL) in 1-minute intervals after the participant was seated for 5 minutes. The average of the second and third blood pressure readings were used for analysis. Serum glucose was obtained from fasting venous blood samples and assessed in the Molecular Epidemiology and Biochemistry Research Laboratory (Minneapolis, MN) with quality control using standards from the National Institute of Standards and Technology. Fasting insulin was measured using radioimmunoassay by Linco Research (St. Louis, MO), and triglycerides and HDL-C were measured using an enzymatic assay by Northwest Lipids Research Laboratory (Seattle, WA).

Composite risk score was estimated separately at year 20 and year 30 by standardizing and summing the following variables: waist circumference, average blood pressure ([systolic+diastolic]/2), fasting blood glucose, insulin, triglycerides, negative HDL-C, then dividing by 6 to create a z-score, as previously reported in the literature, so that higher scores represent poorer cardiometabolic status.[32–35] Before standardization, log transformations were performed on glucose, insulin, and triglycerides because of skewed distributions. Standardization was done by subtracting the sample mean from the individual mean and dividing by the SD of the sample mean. Sex-specific standardizations were performed for waist circumference and HDL-C. Both the year 20 and 30 composite scores were standardized using the sample mean and SD of the year 20 variables to better illustrate the change in score over 10 years, and to reduce random error and improve regression estimate precision.

Covariates

Study covariates from the year 20 examination included field center and self-reported age, sex, race (black/white), years of education completed, employment status (yes/no), health insurance for the past 2 years (yes/no), and medication use for blood pressure, cholesterol, or diabetes mellitus (yes/no). Smoking status was obtained from a tobacco-use questionnaire that has previously been validated by a study using serum cotinine levels[36] and categorized as never, former, or current. Alcohol consumption was calculated in milliliters per day using self-reported intake of wine, beer, and hard liquor. Body mass index (BMI) was calculated using measured height and weight (kg/m^2).

Statistical Analyses

Descriptive statistics were calculated and stratified by year 20 physical activity quartiles, standardized to total wear time. Quartile cut points were similar for men and women; therefore, the same cut points were used for both sexes. Means and SDs or medians and interquartile ranges were calculated for accelerometer measures and cardiometabolic risk factors at the year 20 and year 30 examinations. Differences between exam years were examined using paired samples t tests or Wilcoxon signed-ranks test. Spearman correlations were used to examine bivariate associations for continuous variables between accelerometer measures at year 20 with cardiometabolic risk factors at year 30.

Multivariable linear regression isotemporal substitution models were used to examine how accelerometer-measured activity at the year 20 exam (sedentary, LPA, and MVPA) was associated with cardiometabolic risk factors 10 years later, during the year 30 exam. We then repeated this process, examining how changes in accelerometer-measured activity between the 2 exams (eg, Δsedentary=year 30 sedentary−year 20 sedentary) were associated with changes in the dependent variable, or change in cardiometabolic risk factors, from the same 10-year period (eg, Δrisk score=year 30 risk score−year 20 risks core). Isotemporal substitution models estimated the effect of replacing time from 1 activity for an equal amount of time from another activity. This was done by entering all variables that collectively characterize total (wear) time (sedentary+LPA+MVPA or Δsedentary+ΔLPA+ΔMVPA) and

the individual activity categories to the models simultaneously, while dropping the specific activity of interest from the model. These models represent the effect of replacing the dropped activity variable with the other variables in the model. Inclusion of a total time variable (or change in total time) in the model constrains time and allows for direct comparison between activities and their impact on cardiometabolic risk score. Before entry in the models, all activity categories were divided by 30, such that a unit increase in the activity represented an increase of 30 min/day within the given category, as commonly reported in the isotemporal literature.[8,11,20,22,24] For example, if sedentary time is dropped from the model, then the interpretation of the beta coefficient for LPA is the effect on the cardiometabolic risk factor of substituting 30 min/day of sedentary time with 30 minutes of LPA.

All models were adjusted for year 20 demographics (center, sex, race, age, education, employment status, health insurance, self-reported medication use for blood pressure, cholesterol, or diabetes mellitus), lifestyle behaviors (smoking status, alcohol consumption, and BMI), and the year 20 cardiometabolic risk factor of interest, to account for differences in baseline risk. In the models examining change in activity with change in cardiometabolic risk, we additionally adjusted for year 20 sedentary time and MVPA to account for differences in baseline activity. BMI was not included in the waist circumference or composite risk score model because of the high correlation with waist circumference (r=0.87). Because of skewed distributions, we examined the glucose, insulin, and triglyceride models using both original and log-transformed data. Findings did not materially differ; therefore, to facilitate interpretation, we report the results using the original data only. All models were tested for multicollinearity (variance inflation factor <2.0).

In sensitivity analyses, we also adjusted for an overall diet-quality score assessed at the year 20 exam.[37] Results were unchanged, and because of the high level of missing data (N=205), we report findings without adjustment for diet. A second set of sensitivity analyses was also conducted where individuals with past cardiovascular disease, self-reported at the year 20 exam, including history of myocardial infarction, angina, peripheral vascular disease, stroke, or transient ischemic attack at year 20, were excluded (N=45). Results again did not materially differ; therefore, we present results with the full study sample. In a third set of sensitivity analyses, we additionally adjusted for year 20 cardiorespiratory fitness, assessed using a maximal graded exercise treadmill test. Finally, we tested for interactions between physical activity and sex as well as physical activity and race; none were statistically significant, and therefore we only present models adjusted for sex and race. All statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Inc, Cary, NC). All tests were 2-sided, with statistical significance set at P<0.05.

Results

Participant characteristics at the year 20 exam, stratified by quartiles of accelerometer-measured physical activity are shown in Table 2. There were significant differences across physical activity quartiles by sex, race, education, smoking status, alcohol consumption, and BMI. Percentages of women and whites decreased across quartiles of physical activity, as did years of education and BMI, whereas alcohol consumption was positively associated with activity quartiles. Cardiometabolic risk factors were generally more favorable across physical activity quartiles, with waist circumference, diastolic blood pressure, glucose, insulin, triglycerides, and the composite risk score going down and HDL-C going up across activity groups.

Accelerometer wear time did not significantly differ between the year 20 and year 30 exams (see Table 3). Sedentary min/day increased, on average, by 36.8 min/day between the 2 exams. LPA and MVPA decreased, on average, by 29.6 and 5.4 minutes, respectively (all P<0.001). There were also significant differences observed in cardiometabolic risk factors across the 2 exams (Table 4). Waist circumference, systolic blood pressure, diastolic blood pressure, glucose, insulin, and the composite risk score were significantly higher at the year 30 exam compared with the year 20 exam, indicating adverse changes over time. HDL-C increased over time, indicating a health improvement, which has been previously described in the CARDIA.[38] The increase in HDL-C was observed in both men and women, and persisted after excluding individuals who reported cholesterol medication use at either exam (data not shown). There were no differences between the 2 exams in triglycerides.

Correlations between the year 20 accelerometer measures and year 30 cardiometabolic risk factors are presented in Table 5. Sedentary time at year 20 was positively associated with year 30 waist circumference, glucose, insulin, triglycerides, and the composite risk score and inversely associated with HDL-C. LPA and MVPA were inversely associated with waist circumference, average blood pressure (MVPA only), glucose, insulin, triglycerides, HDL-C (LPA only), and the composite risk score.

Isotemporal substitution models examining associations of physical activity at year 20 with cardiometabolic risk factors from year 30 are presented in Table 6. Replacing 30 minutes of sedentary time with 30 minutes of LPA resulted in a 0.15 cm lower waist circumference, a 0.20 μU/mL lower insulin, a 0.20 mg/dL higher HDL-C, and a −0.01 SD lower composite risk score. Replacing the same duration of sedentary time with MVPA resulted in a 0.73 μU/mL lower insulin and a 4.57 mg/dL lower triglycerides. Replacing LPA with MVPA resulted in a 0.54 μU/mL lower insulin and a 4.51 mg/dL lower triglycerides. In sensitivity analyses with additional adjustment for year 20 cardiorespiratory fitness

Table 2. Participant Characteristics at Year 20 by Physical Activity Quartiles, the CARDIA Study, 2005–2006 (N=1922)

Characteristics	Quartiles of Physical Activity*				*P* Value†
	Q1 ≤333 Min/Day (N=480)	Q2 334 to 391 Min/Day (N=481)	Q3 392 to 454 Min/Day (N=481)	Q4 ≥455 Min/Day (N=480)	
Age, y	45.5±3.5	45.3±3.7	45.2±3.4	45.2±3.5	0.100
Female, n (%)	250 (52.1)	191 (39.7)	155 (32.2)	203 (42.3)	<0.001
White, n (%)	313 (65.2)	277 (57.6)	305 (63.4)	248 (51.7)	<0.001
Education, y	15.8±2.5	15.5±2.5	15.4±2.6	14.5±2.4	<0.001
Unemployment, n (%)	55 (11.5)	48 (10.0)	49 (10.2)	54 (11.3)	0.842
Health insurance, n (%)	432 (90.0)	437 (90.9)	433 (90.0)	414 (86.3)	0.094
Medication use, n (%)‡	99 (20.6)	96 (20.0)	89 (18.5)	91 (18.0)	0.839
Smoking status, n (%)					<0.001
Current	58 (12.1)	63 (13.1)	59 (12.3)	102 (21.3)	
Former	103 (21.5)	93 (19.3)	119 (24.7)	96 (20.0)	
Never	319 (66.5)	325 (67.6)	303 (63.0)	282 (58.5)	
Alcohol consumption, mL/day	2.4 (12.4)	2.4 (12.7)	2.7 (14.3)	4.9 (17.0)	0.011
Body mass index, kg/m^2	29.5±6.7	29.0±6.5	28.3±6.3	28.5±6.1	0.009
Accelerometer measured activity, min/day§					
Total wear time	887.6±89.8	895.4±86.3	890.5±83.7	872.6±86.3	0.005
Sedentary	597.1±68.0	528.2±54.2	468.0±45.0	367.2±62.4	<0.001
LPA	264.6±44.4	335.2±40.2	385.9±44.9	457.7±65.5	<0.001
MVPA	21.6 (22.6)	27.3 (27.8)	31.0 (28.1)	41.4 (38.1)	<0.001
Cardiometabolic risk factors					
Waist circumference, cm	93.7±15.7	90.6±14.4	88.0±14.1	89.7±13.5	<0.001
Systolic blood pressure, mm Hg	115.4±13.3	113.7±13.1	113.5±15.1	114.8±13.6	0.446
Diastolic blood pressure, mm Hg	72.2±10.5	70.9±10.1	70.5±11.0	70.8±10.5	0.038
Glucose, mg/dL	95.6 (12.7)	95.6 (11.7)	94.6 (11.7)	94.6 (12.7)	0.008
Insulin, μU/mL	8.9 (6.6)	8.9 (5.9)	7.6 (5.2)	7.6 (5.2)	<0.001
Triglycerides, mg/dL	93.0 (74.5)	84.0 (72.0)	84.0 (59.0)	83.0 (61.0)	<0.001
HDL-C, mg/dL	51.2±15.4	54.8±16.4	57.4±16.7	55.1±16.2	<0.001
Composite risk score‖	0.14±0.70	0.02±0.66	−0.09±0.66	−0.07±0.62	<0.001

Data presented as mean±SD or median (interquartile range), unless otherwise specified. CARDIA indicates Coronary Artery Risk Development in Young Adults; HDL-C, high-density lipoprotein cholesterol; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity.

*Accelerometer measured light-, moderate-, and vigorous-intensity physical activity, standardized for total wear time.

†*P*-value testing for differences across quartiles of physical activity using chi-square test, 1-way ANOVA, or Kruskal–Wallis test, as appropriate.

‡Self-reported medication use for blood pressure, cholesterol, or diabetes mellitus.

§Freedson cut-point thresholds defined sedentary time in counts/min as <100, LPA as 100 to 1951, and MVPA as ≥1952.

‖Composite risk score was calculated by standardizing and summing waist circumference, average blood pressure ([systolic+diastolic]/2), log glucose, log insulin, log triglycerides, and negative HDL-C, then dividing by 6 to create a *z*-score.

(data not shown), the observed associations were unchanged with 3 exceptions; replacement of sedentary time with LPA was no longer associated with HDL-C (0.18 mg/dL; *P*=0.08), and replacement of sedentary time with MVPA, and LPA with MVPA, was no longer associated with insulin (−0.48 μU/mL, *P*=0.07; and −0.27 μU/mL, *P*=0.35, respectively), although associations remained in the expected direction.

Isotemporal substitution models examining change in physical activity with change in the cardiometabolic risk factors from year 20 to year 30 are shown in Table 7. A 30-minute increase in MVPA, when replacing a 30-minute increase in sedentary time, was associated with a 1.52-cm decrease in waist circumference, a 1.13-μU/mL decrease in insulin, a 6.92-mg/dL decrease in triglycerides, a 1.59-mg/dL increase in HDL-C, and a 0.08-SD decrease in the composite risk score. Similarly, a 30-minute increase in MVPA, when replacing an increase in LPA, was associated with a 1.47-cm decrease in waist circumference, a 0.93-μU/mL decrease in

Table 3. Accelerometer-Measured Total Wear Time, Sedentary, Light-, and Moderate-to-Vigorous Intensity Physical Activity by Examination Year, the CARDIA Study, 2005–2016

Accelerometer Measures, Min/Day*	Year 20 2005–2006 (N=1922)	Year 30 2015–2016 (N=913)	Year 30−20 Difference (N=913)	*P* Value†
Total wear time	886.5±86.9	894.1±87.8	0.2±101.3	0.961
Sedentary	490.1±102.4	532.3±102.7	36.8±110.6	<0.001
LPA	360.9±86.3	332.4±84.2	−29.6±85.2	<0.001
MVPA	29.8 (29.8)	24.1 (28.8)	−5.4 (23.3)	<0.001

Data presented as mean±SD or median (interquartile range). CARDIA indicates Coronary Artery Risk Development in Young Adults; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity.

*Freedson cut-point thresholds defined sedentary time in counts/min as <100, LPA as 100 to 1951, and MVPA as ≥1952.

†*P*-value testing for differences between year 20 and year 30 accelerometer measures using paired samples *t* tests or Wilcoxon signed-ranks test.

insulin, a 6.52-mg/dL decrease in triglycerides, a 1.35-mg/dL increase in HDL-C, and a 0.08-SD decrease in the composite risk score. There were no significant associations when replacing a 30-minute increase in LPA with the same duration of sedentary time. With additional adjustment for cardiorespiratory fitness (data not shown), the findings were unchanged with 1 exception: replacement of LPA with MVPA was no longer associated with a decrease in insulin, although the direction of the association was unchanged (−0.71 μU/mL; *P*=0.12).

Discussion

The primary finding of this population-based cohort study is that substituting sedentary time with LPA in early midlife (ages 38–50 years, CARDIA year 20) was associated with a significantly lower composite cardiometabolic risk score in late midlife (ages 48–60 years, CARDIA year 30), which was primarily characterized by lower waist circumference and insulin and higher HDL-C. Additionally, an increase in MVPA from early to late midlife, when replacing an equivalent increase in sedentary time or LPA, was associated with a significant decrease in the composite cardiometabolic risk score from the same 10-year period. This decrease in cardiometabolic risk was characterized by a corresponding decrease in waist circumference, insulin, and triglycerides and an increase in HDL-C. These associations were largely robust after adjustment for baseline (year 20) demographics, lifestyle behaviors, the cardiometabolic risk factor of interest, activity level (in the change models), and cardiorespiratory fitness. This study contributes to the existing literature by using isotemporal substitution to examine the associations of accelerometer-measured physical activity with a prospective assessment of cardiometabolic risk. Furthermore, this study is novel for using the isotemporal substitution paradigm to examine change in activity with change in cardiometabolic risk.

The majority of studies in the isotemporal literature examining cardiometabolic outcomes have focused on individual risk factors, whereas few have additionally included a composite or clustered cardiometabolic risk score. Nilsson et al examined whether sedentary behavior, when replaced with LPA or MVPA, influenced a composite risk score (including waist

Table 4. Cardiometabolic Risk Factors by Examination Year, the CARDIA Study, 2005–2016 (N=1922)

Cardiometabolic Risk Factors	Year 20 2005–2006	Year 30 2015–2016	Year 30−20 Difference	*P* Value*
Waist circumference, cm	90.5±14.6	94.7±15.6	4.2±7.2	<0.001
Systolic blood pressure, mm Hg	114.3±13.8	119.7±16.1	5.4±15.1	<0.001
Diastolic blood pressure, mm Hg	71.1±10.6	73.3±10.6	2.2±10.3	<0.001
Glucose, mg/dL	94.6 (12.7)	95.0 (14.0)	0.4 (12.6)	0.034
Insulin, μU/mL	8.3 (5.2)	9.7 (9.3)	1.1 (6.6)	<0.001
Triglycerides, mg/dL	86.0 (67.0)	86.0 (60.0)	1.0 (47.0)	0.409
HDL-C, mg/dL	54.6±16.3	60.4±18.9	5.7±11.6	<0.001
Composite risk score†	−0.00±0.66	0.11±0.77	0.11±0.50	<0.001

Data presented as mean±SD or median (interquartile range). CARDIA indicates Coronary Artery Risk Development in Young Adults; HDL-C, high-density lipoprotein cholesterol.

**P*-value testing for differences between year 20 and year 30 cardiometabolic risk factors using paired samples *t* tests or Wilcoxon signed-ranks test.

†Composite risk score was calculated by standardizing and summing waist circumference, average blood pressure ([systolic+diastolic]/2), log glucose, log insulin, log triglycerides, and negative HDL-C, then dividing by 6 to create a *z*-score.

Table 5. Spearman Correlations of Accelerometer-Measured Activity at Year 20 and Cardiometabolic Risk Factors at Year 30, the CARDIA Study, 2005–2016 (N=1922)

	Accelerometer Measured Activity			Cardiometabolic Risk Factors					
	Sedentary	LPA	MVPA	Waist	BP	Glucose	Insulin	Triglycerides	HDL
Accelerometer measured activity									
LPA	−0.608*								
MVPA	−0.187*	0.157*							
Cardiometabolic risk factors									
Waist	0.073*	−0.101*	−0.131*						
BP	0.004	0.002	−0.088*	0.276*					
Glucose	0.045*	−0.048*	−0.085*	0.472*	0.205*				
Insulin	0.068*	−0.090*	−0.209*	0.675*	0.250*	0.503*			
Triglycerides	0.064*	−0.096*	−0.066*	0.430*	0.186*	0.357*	0.466*		
HDL-C	−0.101*	0.108*	0.016	−0.543*	−0.102*	−0.349*	−0.473*	−0.532*	
Composite score	0.070*	−0.096*	−0.193*	0.777*	0.462*	0.638*	0.829*	0.680*	−0.667*

BP indicates average blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; HDL, high-density lipoprotein cholesterol; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity.
*Statistically significant ($P<0.05$).

circumference, blood pressure, glucose, HDL-C, and triglycerides) in 120 women aged 65 to 70 years.[18] They found that replacing 10 min/day of sedentary time or LPA with MVPA was associated with a decrease in the composite risk score; however, associations were attenuated after adjustment for total accelerometer wear time. Knaeps et al also examined the theoretical substitution of sedentary time with LPA and MVPA on a composite risk score among 410 Flemish adults, using the same risk factors as Nilsson et al. The investigators found that replacing 30 min/day of sedentary time or LPA with MVPA resulted in a significantly lower composite risk score. There was no observed benefit of replacing sedentary time with LPA, which differs from our study findings. However, Ekblom-Bak et al found that replacing 10 minutes of sedentary time with LPA, MPA, or VPA was associated with significantly lower metabolic syndrome prevalence among 836 participants from the Swedish Cardiopulmonary Bioimage Study, with lower odds in a dose-response manner with higher physical activity intensity.[14] Across studies, health benefits were observed when replacing sedentary time with physical activity, with the

Table 6. Replacing 30 Min/Day in Sedentary and LPA With 30 Min/Day in LPA or MVPA at Year 20 With Cardiometabolic Risk Factors at Year 30, the CARDIA Study, 2005–2016 (N=1922)

	Replace Sedentary With LPA			Replace Sedentary With MVPA			Replace LPA With MVPA		
Cardiometabolic Risk Factors	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
Waist circumference, cm	−0.15*	−0.27, −0.02*	0.020*	−0.36	−0.77, 0.05	0.084	−0.21	−0.65, 0.23	0.347
Average blood pressure, mm Hg	−0.08	−0.27, 0.11	0.404	−0.36	−0.97, 0.26	0.254	−0.28	−0.94, 0.39	0.414
Glucose, mg/dL	−0.42	−0.85, 0.03	0.065	0.66	−0.78, 2.10	0.369	1.08	−0.49, 2.64	0.177
Insulin, μU/mL	−0.20*	−0.35, −0.04*	0.012*	−0.73*	−1.23, −0.24*	0.004*	−0.54*	−1.08, −0.00*	0.049*
Triglycerides, mg/dL	−0.06	−1.04, 0.91	0.900	−4.57*	−7.75, −1.39*	0.005*	−4.51*	−7.96, −1.06*	0.010*
HDL-C, mg/dL	0.20*	0.00, 0.40*	0.045*	−0.21	−0.85, 0.44	0.528	−0.41	−1.11, 0.29	0.252
Composite risk score†	−0.01*	−0.02, −0.00*	0.020*	−0.03	−0.05, 0.00	0.070	−0.02	−0.05, 0.02	0.307

CARDIA indicates Coronary Artery Risk Development in Young Adults; HDL-C, high-density lipoprotein cholesterol; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity.
*Statistically significant ($P<0.05$). Models adjust for year 20 center, age, race, sex, employment, health insurance, medication use, smoking status, alcohol consumption, body mass index (excluding waist circumference and composite risk score models), total wear time, and the cardiometabolic risk factor of interest (eg, model predicting change in waist circumference is adjusted for year 20 waist circumference).
†Composite risk score was calculated by standardizing and summing waist circumference, average blood pressure ([systolic+diastolic]/2), log glucose, log insulin, log triglycerides, and negative HDL-C, then dividing by 6 to create a *z*-score.

Table 7. Replacing a 30 Min/Day Increase in Sedentary and LPA With a 30 Min/Day Increase in LPA or MVPA From Year 20 to Year 30 on Change in Individual Cardiometabolic Risk Factors From Year 20 to Year 30, the CARDIA Study, 2005–2016 (N=913)

	Replace ΔSedentary With ΔLPA			Replace ΔSedentary With ΔMVPA			Replace ΔLPA With ΔMVPA		
Change in Cardiometabolic Risk Factors	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
ΔWaist circumference, cm	−0.06	−0.25, 0.13	0.557	−1.52*	−2.21, −0.84*	<0.001*	−1.47*	−2.19, −0.74*	<0.001*
ΔAverage blood pressure, mm Hg	0.05	−0.24, 0.33	0.751	0.68	−0.34, 1.70	0.188	0.64	−0.45, 1.72	0.249
ΔGlucose, mg/dL	0.18	−0.45, 0.81	0.573	−1.18	−3.43, 1.07	0.304	−1.36	−3.75, 1.03	0.265
ΔInsulin, μU/mL	−0.19	−0.42, 0.04	0.098	−1.13*	−1.95, −0.31*	0.007*	−0.93*	−1.80, −0.06*	0.035*
ΔTriglycerides, mg/dL	−0.40	−1.73, 0.94	0.559	−6.92*	−11.69, −2.15*	0.005*	−6.52*	−11.6, −1.45*	0.012*
ΔHDL-C, mg/dL	0.25	−0.07, 0.56	0.133	1.59*	0.45, 2.73*	0.006*	1.35*	0.13, 2.56*	0.030*
ΔComposite risk score†	−0.01	−0.02, 0.01	0.352	−0.08*	−0.13, −0.04*	<0.001*	−0.08*	−0.12, −0.03*	0.002*

CARDIA indicates Coronary Artery Risk Development in Young Adults; HDL-C indicates high-density lipoprotein cholesterol; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity.

*Statistically significant ($P<0.05$). Models adjust for year 20 center, age, race, sex, employment, health insurance, medication use, smoking status, alcohol consumption, body mass index (excluding waist circumference and composite risk score models), sedentary time, MVPA, change in total wear time, and the cardiometabolic risk factor of interest (eg, model predicting change in waist circumference is adjusted for year 20 waist circumference).

†Composite risk score was calculated by standardizing and summing waist circumference, average blood pressure ([systolic+diastolic]/2), log glucose, log insulin, log triglycerides, and negative HDL-C, then dividing by 6 to create a *z*-score.

strongest associations found for MVPA. However, these studies are limited by their cross-sectional study design. The present analysis contributes to the literature by using the isotemporal substitution paradigm to examine associations of physical activity with an assessment of cardiometabolic risk 10 years later.

In addition to prospectively assessing cardiometabolic risk factors, we examined whether change in activity was associated with change in cardiometabolic risk factors over the same 10-year period. A 30 min/day increase in MVPA over 10 years, when replacing a 30 min/day increase in sedentary behavior or LPA, was associated with a significant decrease in the composite risk score. In our sample, we observed an average increase in sedentary time of ≈40 min/day and a concurrent decrease in MVPA of ≈5 min/day from early to late midlife. Furthermore, we observed adverse changes in the majority of the cardiometabolic risk factors over the same 10-year period. Our findings indicate that if we replace the traditional increase in sedentary time with an increase in MVPA, we can prevent the usual decline in cardiometabolic health observed over time. This supports the notion that even in midlife, it is not too late to become physically activity to improve cardiometabolic health.

When examining the individual cardiometabolic risk factors, we observed a greater health benefit for insulin and triglycerides when replacing sedentary time with MVPA, as compared with replacing sedentary time with LPA, which is consistent with the existing literature.[11,12,14,16,20] However, when replacing sedentary time with LPA, we observed significant reductions in waist circumference and insulin, and a significant increase in HDL-C 10 years later, illustrating the importance of LPA for future cardiometabolic risk reduction. In comparison to MVPA, less is known about the role of LPA on health outcomes.[39] Our findings add to the growing body of evidence regarding the health benefits of lower-intensity physical activity. This prospective study extends the work of LaMonte et al, who recently reported favorable cross-sectional associations between accelerometer-measured LPA with many markers of cardiometabolic risk, including HDL-C, triglycerides, glucose, C-reactive protein, BMI, and waist circumference among 4832 women enrolled in the Objective Physical Activity and Cardiovascular Health Study.[40] The investigators also found that LPA was favorably associated with the Reynolds Risk Score, which predicts 10-year cardiovascular disease risk.[41,42] Taken together, our findings have important implications for health promotion efforts given that individuals may be more willing to increase LPA as compared with MVPA. However, it is important to note that the lack of a dose-response relationship (significant findings for the year 30 composite risk score when replacing sedentary time with LPA, but not when replacing sedentary time with MVPA) raises concerns about biological plausibility, and thus findings should be interpreted with caution.

Strengths of this study include the use of objectively measured physical activity and cardiometabolic risk factors at 2 time points, when participants were in early and late midlife, and the use of a relatively large biracial sample. This study is also novel for using isotemporal substitution to examine change in physical activity with change in cardiometabolic risk factors. This provides the opportunity to present a novel methodological approach that should be considered in other longitudinal physical activity studies. However, there are several study limitations that should be noted. First, isotemporal substitution is a statistical model that does not reflect real-time reallocation. Second, we were unable to account for sleep duration or quality

in the analyses, as done in several previous studies.[11,20,21,43] Isotemporal substitution does not require representation from the full 24-hour day; therefore, omission of sleep is acceptable within this statistical framework. However, this does not eliminate the possibility of confounding attributed to differences in sleep duration or quality across individuals. Third, with any observational study, there is a potential for residual confounding. However, this possibility is minimized through use of the well-characterized CARDIA data set. Last, this study was limited to black and white adults, and therefore findings may not be generalizable to individuals of other races/ethnicities and different age groups.

In conclusion, this study provides evidence that replacing sedentary behaviors with LPA is associated with a lower cardiometabolic risk score 10 years later. This study also makes a novel contribution to the isotemporal literature by examining the associations of change in activity with change in cardiometabolic risk over a 10-year period. We found that an increase in MVPA from early to late midlife, when replacing an increase in sedentary time or LPA, was associated with a significant decrease in the cardiometabolic risk score over the same time period. Our findings illustrate that improvements in cardiometabolic health may be possible as one ages from early to late midlife by reallocating sedentary time to LPA or MVPA. Clinicians and public health practitioners should consider the potential benefits to cardiometabolic health of encouraging LPA in addition to MVPA among midlife adults.

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