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Associations of Objective Physical Activity with Insulin Sensitivity and Circulating Adipokine Profile: The Framingham Heart Study

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Abstract

Purpose—To explore the relation of physical activity (PA) and sedentary time (SED) to insulin sensitivity and adipokines.

Methods—We assessed PA and SED using Actical accelerometers and insulin resistance (HOMA-IR) in 2109 participants (free of type 1 and 2 diabetes mellitus) from Framingham Generation 3 and Omni 2 cohorts (mean age 46y, 54% women). Systemic inflammation (C-reactive protein [CRP]), and circulating adipokines were measured six years earlier. Steps/day, moderate to vigorous PA (MVPA), and SED/wear time (%SED) were predictor variables in multivariable regression analyses, with HOMA-IR, CRP, and circulating adipokines as outcome measures.

Results—Higher MVPA and more steps/day were associated with lower HOMA-IR, adjusting for %SED (β= −0.036, p=0.002; β= −0.041, p=0.005). Steps were inversely associated with CRP, but were directly associated with insulin-like growth factor (IGF)-1 levels (β= −0.111, p=0.002; β=3.293, p=0.007). %SED was positively associated with HOMA-IR (β=0.033, p<0.0001), but

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Competing Interests

The authors declare no conflicts of interest.

nonsignificant after adjusting for MVPA (p=0.13). %SED was associated with higher ratio of leptin/ leptin receptor (sOB-R) and higher adipocyte fatty acid-binding protein (FABP)4 (β=0.096, p<0.0001; β=0.593, p=0.002).

Conclusions—Our findings suggest differential influences of PA versus SED on metabolic pathways, with PA modulating insulin resistance and inflammation, whereas SED influences fatty acid binding proteins.

Keywords

exercise; inflammation; c-reactive protein; insulin-like growth factor; leptin; epidemiology

Introduction

Greater physical activity (PA) is associated with lower risk of metabolic diseases including obesity[1] and diabetes mellitus (DM).[2] In contrast, excess sedentary time (SED) is associated with the release of inflammatory markers and adipokines,[3] and contributes to greater insulin resistance.[4] However, the relations between adipokine release and insulin resistance as a result of changes in the balance between PA and SED may be more complex than a simple result of concomitant changes in body weight or adiposity.

Much of what is known about the effect of PA on insulin sensitivity, inflammation and adipokines has been observed through exercise intervention studies, especially in populations at high risk for developing DM. Evidence from these exercise intervention studies suggest that long term adaptations to increased PA is associated with a more favorable anti-inflammatory and adipokine profile, promoting insulin sensitivity,[5] and resulting in lower development of DM over 12-year follow-up,[6] even in individuals not meeting weight loss goals. During the adaptation to chronic exercise, insulin-like growth factor (IGF)-1 signaling is also increased,[7] which may further promote insulin sensitivity.[8] Adiponectin, an adipokine that has been associated with lower burden of atherosclerosis,[9] may also increase following exercise training, possibly mediated by weight loss.[10] In contrast, SED promotes the storage of fatty acids in the adipose tissue, and the release of inflammatory markers (such as C-reactive protein [CRP]) and proinflammatory adipokines (leptin, adipocyte fatty acid binding protein [FABP]4, and retinol binding protein [RBP]4). The latter biomarkers have been demonstrated to decrease in response to exercise training programs in short-term intervention studies,[11–13] albeit inconsistently.[14] Prior studies are limited by small sample sizes, lack of adjustment for body mass index (BMI), and measurement error introduced in studies using self-reported measures of PA.

Another layer of complexity in the relation of PA to insulin sensitivity is whether PA of any intensity (total PA) provides the same insulin-sensitizing benefits as that resulting from moderate-to-vigorous PA (MVPA), defined as any activity that expends greater than or equal to three times the amount of energy that a person expends at rest (≥3 metabolic equivalents of task, MET). Accelerometers are now able to distinguish among different intensities and forms of activity (light PA, MVPA, and accumulation of steps), compared to their original use which was to simply report total activity or energy expended over the course of a day. Additionally, SED has emerged as an independent factor for cardiometabolic risk that is

distinct from PA.[15] The PA Guidelines for Americans suggests 150 minutes of MVPA per week for adults,[16] but does not include specific recommendations for the number of steps per day to strive for or how much to limit SED. Thus, different intensities of PA and SED may be potentially synergistic in terms of their impact on cardiometabolic risk, yet may have differential relations with key biological markers of cardiometabolic risk. The present investigation was designed to determine comprehensively whether PA and SED are related to insulin sensitivity and to circulating levels of a panel of adipokines in a large community-based sample.

Materials and Methods

Study Population

The Framingham Heart Study enrolled participants for its Generation 3 cohort (containing participants predominantly of European descent) and Omni 2 cohort (a multi-ethnic cohort) during the period 2002–2005.[17] Blood was collected after overnight fasting during the first examination cycle (2002–2005) for the measurement of adipokines and inflammatory cytokines and blood was also collected during the second examination cycles (2008–2011) to measure glucose and insulin levels for the evaluation of insulin resistance (HOMA-IR). During the second examination, we also assessed PA using accelerometry and questionnaires. For this investigation, we included participants who attended both examination cycles 1 and 2 (n=3732). Participants without valid accelerometry data (described below, n=956) or other PA questionnaires (n=87) were excluded. We also excluded participants with type 1 or type 2 DM (n=141; defined as fasting blood glucose of ≥126 mg/dl or taking hypoglycemic medications at any time during 2002–2011) to remove the potential influence of hypoglycemic medications on our outcome measures.[18] Additionally, participants were excluded if they were missing data on blood glucose, insulin, adipokines or other covariates (n=439). The final sample was 2109 participants. All participants provided written informed consent, and the institutional review board at Boston University Medical Center approved the study protocols.

Physical Activity Accelerometry

During the second examination cycle, all participants were asked to wear an omnidirectional accelerometer (Actical model no. 198-0200-00; Philips Respironics) on the hip for 8 days during all hours throughout the day and night (except when bathing).[19] This accelerometer records signals within 0.5–3 Hz and accelerations/decelerations within 0.05–2 g. Recorded signals were grouped into “counts” or “steps” and collected at 30 second intervals. For analysis, signals were averaged over 1 minute intervals. Data were analyzed at the Framingham Heart Study using customized software (Kinesoft, version 3.3.63) and a predefined protocol for quality control.[19]

Accelerometer data was considered valid if the device was worn for ≥10 hours per day for at least 4 days, not including the first day of wear (which was not included in any analysis). Non-wear time was defined as 60 consecutive minutes of zero counts, allowing for 2-minute interruption periods. Non-wear bouts were removed during data processing. SED was defined as <200 counts per minute, a threshold validated in overweight and obese

individuals,[20] who make up a large proportion of our study participants, n=1417/2109. SED was only considered during wear time occurring between 6 AM-10 PM and was reported as a percentage of wear time (%SED), a customary practice that standardizes SED to a 16 hour day.[15] MVPA was considered during any time of the day and was defined as >1486 counts per minute by weighting results from two validation studies.[2122] Total steps were also considered during any time of the day. In regression models including MVPA or steps, we adjusted for wear time. Furthermore, regression models including SED, MVPA, or steps were additionally adjusted for "overnight wear," a dichotomous variable defined by ≥30 minutes of movement (non-zero counts) during the hours of 2AM–3AM on ≥3 nights, a definition of restless sleepers. If any restless sleepers went to sleep earlier than 10PM and/or slept later than 6AM, their sleep time may be misclassified as SED. Despite the fact that we removed any sedentary movement (<200 counts/minute) that could be accumulated during the night, our adjustment for "overnight wear" represents an attempt to consider potentially higher SED accumulated by restless sleepers.

Sensitivity Analysis using MVPA Composite Score—Accelerometry does not capture select PA such as cycling or swimming. Therefore, to estimate total PA, we supplemented accelerometry data with questionnaire-based assessment of PA as detailed below. During the second examination, participants were asked to report the amount of time spent in different activities. First, they were asked how many months they performed a specific activity, then, how many times per month, and finally, how many minutes each time that activity was performed. Using reported times, average time per day was calculated for each activity. For example, the total average times reported for bicycling, swimming and weight lifting (activities not well captured by the accelerometer)[23] was 9 minutes (±15 minutes), with 38% of participants reporting no time spent in these activities over the last year. An MVPA composite score was calculated by adding the average time per day reported bicycling, swimming, and weight lifting to the accelerometer-determined MVPA.

Insulin Sensitivity

At examination cycle 2, participants underwent measurement of blood glucose and insulin after an overnight fast. Insulin was measured using an immunoassay (Roche Diagnostics, Mannheim, Germany), with an intra-assay coefficient of variation (CV) of 2.0% and interassay CV of 4.5%. The homeostasis model assessment of insulin resistance (HOMA-IR) measurement was calculated as glucose (mg/dl) * insulin (μU/ml) / 405.[24]

Adipokines and metabolic factors

Serum and plasma were drawn after an overnight fast at examination cycle 1 and stored at −80 C until assay without previous thawing. Serum high-sensitive (hs)CRP was assessed using an immunonephelometry assay (Dade Behring, now Siemens Healthcare).[25] Serum RBP4[25] and IGF-1[26] and plasma adiponectin,[27] leptin and soluble leptin receptor (sOb-R)[28] were all assayed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Inc., Minneapolis, MN). Serum FABP4[25] was measured using a kit from Biovendor (Candler, NC). All interassay CVs were <9.7% as reported previously.[25–28]

Statistical Analysis

Separate multivariable regression models were used to relate each of the following dependent variables: HOMA-IR, adipokines, and other metabolic factors to predictor variables: MVPA, steps, and %SED. Beta estimates were generated per: 4000 steps/day, 20 MVPA minutes/day, and 5% increase in %SED roughly equivalent to 1 SD of each PA variable. HOMA-IR, hsCRP, adiponectin, leptin, sOb-R, and leptin/sOb-R were natural logarithmically transformed to normalize their skewed distributions. Analyses were performed with adjustment for the following variables at examination cycle 2: age, sex, BMI, prevalent CVD, hypertension, current smoking, cohort, season of examination, residence in New England versus other, overnight wear, and total wear time. Secondary models were additionally adjusted for MVPA when %SED was the exposure of interest. Likewise, models with MVPA or steps as the predictor of interest were additionally adjusted for %SED in secondary models. Associations with $p<0.01$ level were considered statistically significant (a priori). P-values of 0.01–0.05 should be observed with caution because the multiple testing performed in this investigation increases the chance of finding a value $p<0.05$ when no true association exists.

We also note that analysis to detect the associations of the proportion of time spent in light activity (%Light) with insulin resistance, inflammation and adipokines were not performed because %SED and %Light PA had variance inflation factor (VIF) values of 7.70 and 7.63, respectively, in collinearity analysis. While these VIF values are lower than 10, they do suggest a moderate amount of collinearity. Additionally, a principal component analysis (PCA) yielded a condition index of 5.46 for component 14 and over 95% of the variance of %SED and %Light is explained by this component. The combination of the VIF and PCA results give us concern about the collinearity between %SED and %Light, thus we chose to pursue a model that contained only one component (%SED) and not the other (%Light).

Results

Study sample characteristics

Average accelerometer wear time was 13 hours and 36 minutes per day, ±77 minutes (during the designated hours of 6 AM–10 PM) (Table 1). During those hours, on average, participants spent >80% of the time as SED. Overall, 49% of participants met the PA Guidelines (≥150 minutes per week MVPA), with a higher proportion of men (n=537/977) meeting the guidelines than women (n=498/1132). Overweight and obese participants spent less time in MVPA ($p<0.0001$), but on average, spent a similar proportion of their monitor wear time in SED (displayed as %SED) compared to participants with BMI<25 ($p=0.14$) (Supplemental Table 1). Demographic characteristics of excluded participants are shown in Supplemental Table 2.

Relations of physical activity to insulin resistance and adipokines

Higher MVPA and more steps per day were associated with lower HOMA-IR, even after adjustment for %SED ($\beta = -0.036, \pm 0.012, p < 0.0001$; and $\beta = -0.041, \pm 0.014, p = 0.005$, respectively, Table 2, Figure 1A and 1B). More steps per day were also associated with lower serum hsCRP but higher IGF-1 levels ($\beta = -0.111, \pm 0.036, p = 0.002$; and $\beta =$

3.293, ± 1.218, p = 0.007, respectively, Table 2, Figure 1C and 1D). An MVPA composite score (accelerometer-determined MVPA + self-reported time spent bicycling, swimming and weight lifting) performed similarly to pure accelerometer-determined MVPA (data not shown).

Relations of sedentary time to insulin resistance and adipokines

%SED was positively associated with HOMA-IR (β = 0.033, ± 0.008, p < 0.0001, Table 3), but this relation was not significant after adjusting for MVPA (β = 0.015, ± 0.010, p = 0.13). %SED was also associated with higher circulating concentrations of leptin, lower leptin receptor (sOB-R), higher leptin/sOB-R ratio, and higher FABP4 (β = 0.061, ± 0.014, p < 0.0001; β = −0.035, ± 0.010, p = 0.0003; β = 0.096, ± 0.018, p < 0.0001; and β = 0.593, ± 0.186, p = 0.002, respectively, Table 3, Figure 1E and 1F). Sensitivity analysis was performed using raw SED (hours/day), showing a consistent lack of association of SED with HOMA-IR in the multivariable model additionally adjusting for MVPA and wear time (p = 0.52).

Discussion

The present investigation of Framingham Heart Study participants demonstrated that PA and SED were associated with insulin sensitivity and with circulating adipokine concentrations even after adjusting for important confounders, including BMI. Higher PA was associated with higher insulin sensitivity whereas SED was positively associated with leptin levels and FA binding protein concentrations. Furthermore, we observed a positive association of steps per day with IGF-1 levels and an inverse association with serum hsCRP concentration. Of note, neither MVPA nor SED were associated with IGF-1 levels or serum concentrations of hsCRP. These findings may provide clues linking PA and SED to cardiometabolic risk by influencing distinct biological pathways.

Associations of physical activity and sedentary time with insulin sensitivity

Insulin sensitivity improves in response to exercise training programs, but it is unclear whether this response is entirely due to changes in body composition,[5] or related to the potential role of SED in determining insulin sensitivity. Our results demonstrated that higher MVPA and a greater number of steps were associated with lower insulin resistance, after adjusting for BMI and %SED, among other covariates. Yet, %SED was not significantly associated with insulin resistance after adjustment for BMI and MVPA.

Our results support evidence from the European Relationship between Insulin Sensitivity and Cardiovascular risk (RISC) study, in which investigators reported that after accounting for PA and BMI, %SED was not related to insulin sensitivity (using a variable capturing percent of total wear time as SED, similar to our %SED variable).[29] Other cross-sectional studies have reported associations of SED with HOMA-IR but not after adjustment for BMI; and still other studies have reported no relations between SED and HOMA-IR, as recently reviewed by Brocklebank et al.[30] In contrast, there have been three recent studies (Coronary Artery Risk Development in Young Adults [CARDIA];[31] Hispanic Community Health

Study/Study of Latinos (HCHS/SOL),[15] and a study based in Chile[32]) that reported associations of SED with HOMA-IR after adjustment for MVPA and BMI.

Racial differences may have contributed to the different findings of these three studies compared to ours. In CARDIA and the Chilean study, the relation of SED to HOMA-IR was weaker in individuals of European descent compared to blacks or indigenous Chileans;[3132] but associations were consistent across Hispanic/Latino background groups in HCHS/SOL.[15] Racial homogeneity of our study, consisting mostly of white individuals of European descent, may have contributed to our results.

Another potential factor contributing to differences among our studies is the use of different devices, which may have contributed to differences in SED. In CARDIA, 76% of participants averaged less than 10 hours/day SED, whereas our study participants averaged 11 hours/day SED, despite lower wear time (due to our removal of data captured between 10PM–6AM as obligate non-wear time). Moreover, investigators from CARDIA and the Chilean study analyzed the effect of raw SED, by hours per day (adjusting for wear time in the model), HCHS/SOL used a residual approach to standardize SED to wear time, whereas we used the percentage of wear time spent in SED. Inconsistent PA and SED variable definitions among different cohort studies is a major limitation within the field of PA research, which may exaggerate inconsistent findings across these cohorts. However, sensitivity analyses performed in our study and CARDIA suggest that the use of SED versus %SED variables did not impact the relations between SED and HOMA-IR in either study.

Another factor that may have contributed to different findings with the HCHS/SOL study was their inclusion of participants with DM (in which 7–12% of the study population were taking medications affecting glucose metabolism). Participants with DM were excluded from analysis in CARDIA, the Chilean study, and our study. Therefore, we are unable to completely explain why our studies (with similar sample sizes between our study and CARDIA) reported different results, although differences in racial composition may have contributed.

A major perceived barrier to PA interventions is the inability/unwillingness to increase the volume of PA to levels required for weight loss (often recommended as >150 minutes/week for modest weight loss or 225–420 minutes/week for substantial results).[33] Our display of HOMA-IR by tertiles of MVPA (Figure 1A) may reflect insulin-sensitizing effects of even modest amounts of PA (<150 minutes/week). Additionally, similar strength of associations for 20 minutes MVPA or 4000 steps (each approximately equivalent to 1SD) with HOMA-IR suggest that the intensity of PA may not be as important as volume of PA in contributing to greater insulin sensitivity. Our association results suggest that higher volume of PA may also be the significant factor relating to IGF-1 concentrations, previously reported to be positively associated with self-reported walking,[34] but not related to self-reported vigorous activities.[35] Greater IGF-1 levels are associated with better insulin sensitivity and lower levels of systemic inflammation.[36]

Associations of physical activity with systemic inflammation (as measured by serum C-reactive protein concentrations)

CRP is a systemic inflammatory biomarker that has been associated with greater body fat and insulin resistance.[37] There is strong evidence demonstrating that exercise training programs lower blood CRP levels.[38] At the population level, two studies using data from the same National Health and Nutrition Examination Survey (NHANES), 2003–2004 study reported slightly different results, due to how they represented the MVPA variable.[3940] One study showed that being in the lowest tertile of either weighted mean accelerometry counts or MVPA bouts (or not meeting the Physical Activity Guidelines for MVPA) was associated with higher circulating CRP, without adjusting for wear time.[39] Another study reported that %MVPA (MVPA as a percentage of wear time) was not significantly related to CRP levels.[40] As we previously discussed, decisions about how to define PA variables can influence interpretation of results across studies. Since MVPA makes up <1% of daily activities, this variable may not be greatly influenced by wear time. Therefore, we reported raw MVPA minutes/day, not as a percentage of wear time. We demonstrated that MVPA and steps were associated with lower serum CRP levels, after adjustments for wear time, BMI, and %SED, among other covariates. Thus, the difference between our results and different NHANES results on how MVPA relates to CRP levels may simply be caused by our differences in MVPA variable definition.

Associations of total physical activity and sedentary time with leptin and adiponectin

Circulating leptin and adiponectin levels, on the other hand, were not associated with MVPA after accounting for other covariates, supporting previous evidence that short, acute bouts of MVPA do not impact circulating leptin or adiponectin in healthy subjects.[4142] Instead our results support a relation between total energy expenditure (the balance between total steps and SED) and blood leptin levels. In participants expending greater amounts of total energy (measured by steps), circulating leptin levels were lower, but there was no significant relation to sOb-R, the circulating leptin receptor. Blood leptin and sOb-R levels appeared to be related most to %SED. In participants that spent more time in sedentary activities, circulating leptin was higher and circulating sOb-R was lower, likely leaving higher free circulating leptin concentrations available to communicate a satiety signal to the brain. However, in leptin resistant individuals, the leptin satiety signal may not be received by the brain effectively, thus uncoupling energy balance from appetite and leading to weight gain.[43] It is unclear whether leptin resistance is impacted by PA and SED, since only peripheral (circulating) leptin and sOb-R concentrations were available in our sample. The lack of association of adiponectin with PA or SED variables in our study (after adjustment for BMI and other covariates) was not surprising because previous studies have reported that the association of PA with adiponectin may be driven by body composition.[42]

Associations of sedentary time with fatty acid binding proteins

The present investigation identified a relation between SED and circulating FABP4 concentrations. FABP4 is higher in obese individuals and has been associated with insulin resistance and dyslipidemia.[25] RBP4 is not as clearly linked to adiposity, but evidence suggests it lays on a causal pathway to insulin resistance.[44] Both binding proteins have been

shown to decrease in response to exercise training,[1145] but RBP4 decreased only in individuals in whom insulin resistance decreased.[45] We did not identify any relation between PA and these binding proteins, but our observed association of SED with FABP4 (after adjusting for BMI and MVPA) may provide clues about how SED influences insulin resistance.

Strengths and Limitations

The strengths of our study are the availability of accelerometry-determined PA and SED, and a comprehensive panel of standard and novel adipokines in a large community-based sample of healthy adults. As an estimate of total energy expenditure, accelerometer-determined PA is more precise and less biased than PA assessed by self-report.[46] Unlike the "gold standard" measures of energy expenditure (doubly labeled water), accelerometers also provide information about time spent in activities of different intensities, including SED. We acknowledge that our study design, limiting the processing of wear time data between 6AM and 10PM, may potential decrease in the reliability of our measurement of wear time, but alternative algorithms may cause inclusion of significant periods of SED during "sleep" time for some individuals, which was a greater concern. Additionally, we acknowledge that our decision to use the <200 counts/min cutpoint to classify SED (as validated in overweight and obese individuals)[20] may misclassify some light activity and SED, just as there are limitations to decisions to use any cutpoint. Another limitation of accelerometer-determined measure of PA is that it does not capture MVPA accumulated during certain activities (specifically bicycling, swimming, and lifting heavy objects). In the current investigation, the addition of self-reported time spent in these activities into the MVPA composite score did not influence the observed relations between PA and insulin sensitivity. We also minimized the influence of wear time by reporting SED as a proportion of wear time.

Our observations were made predominantly on white individuals of European ancestry, which limits the generalizability of our findings to other ethnicities. Given the cross-sectional design of our investigation of the relations of PA to insulin resistance, both measured during the same examination cycle (and the non-contemporaneous design of our analysis relating PA to adipokines and inflammatory markers, measured at different examination cycles), we are unable to make causal inferences about any of the observed associations. Despite this non-contemporaneous design, the analysis can be viewed generally as cross-sectional because of evidence to suggest the relative stability of PA over short time periods.[47] In a longitudinal Swedish cohort of middle-aged adults, in a similar age range as our study, MVPA and total activity (total counts/minute) were not significantly different between baseline and 6-year follow-up.[47] There was, however, a 5% increase in SED during that time period, suggesting that SED may change modestly over the 6-year time period. Additionally, any 'noise' created by using non-contemporaneous biomarker values would bias us towards the null hypothesis of no association of PA/SED with adipokines/inflammation, or create regression dilution bias, resulting in underestimation of the true strength of the observed relationships; however, we do acknowledge that the non-contemporaneous measurements do limit the translational relevance of this investigation.

We also did not ask participants to refrain from exercise the morning of the blood draw, so acute exercise may have influenced the adipokine profile in a number of participants. Furthermore, adjustment for BMI may only partly capture body composition and residual confounding by body composition, dietary intake, or medication use may remain. Finally, due to the exploratory nature of this investigation we made only a modest adjustment for multiple statistical testing. Additional studies are warranted to replicate our observations. Of note, several reported associations would withstand a conservative Bonferroni correction (0.05/21 or 0.002 [for relating 3 measures to 7 biomarker levels]).

Conclusion

Our cross-sectional study of a large community-based sample demonstrated associations of PA and SED with insulin resistance and circulating concentrations of several adipokines, even after adjusting for BMI. These findings may provide clues linking cardiometabolic risk to PA by influencing insulin resistance and systemic inflammation, and to SED by potentially modulating circulating concentrations of FA binding proteins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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All authors took part in the design of the study, interpretation of the results and contributed to writing the manuscript. M.D.S. conducted the statistical analysis. N.L.S. wrote the manuscript. R.S.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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What is already known about this subject

- Physical activity and sedentary time are associated with cardiometabolic risk.
- Previous research suggests that physical activity may be associated with a favorable adipokine profile and insulin sensitivity, but these relations have not been explored extensively in large cohort studies.

What this study adds

- This study suggests that there may be differential influences of low physical activity versus sedentary behavior on metabolic factors.
- Further understanding of the relations of lifestyle behaviors to metabolic factors could have implications for clinical prevention and treatment of metabolic diseases.

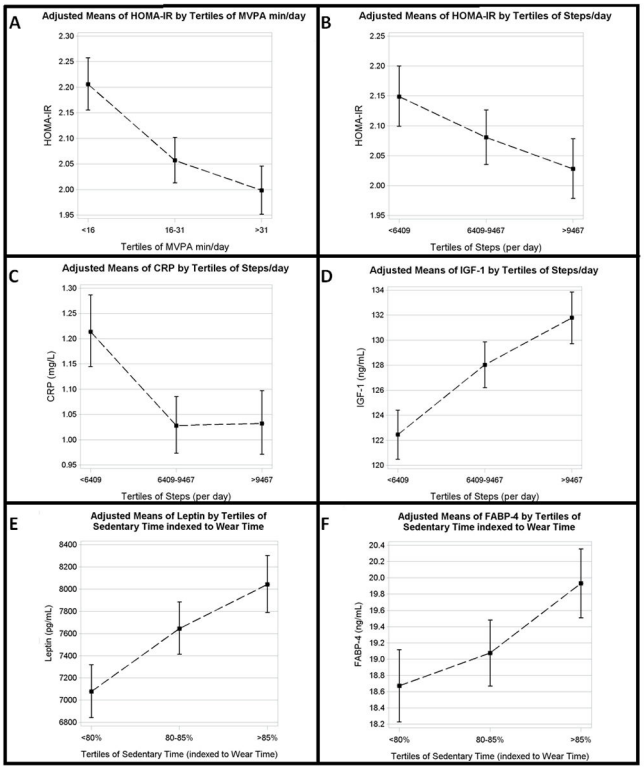

Figure 1. Relations of biomarkers to physical activity variables

Least Square Means (±SE) of homeostatic model of insulin resistance (HOMA-IR) to tertiles of moderate-to-vigorous physical activity (MVPA) (Figure 1A) and steps/day (Figure 1B), c-reactive protein (CRP) (Figure 1C) and to insulin-like growth factor (IGF)-1 (Figure 1D) to tertiles of steps/day, leptin (Figure 1D) and fatty acid binding protein (FABP)-4 (Figure 1E) to the percent of wear time spent as sedentary time. All models were adjusted for the following potential confounders: age, sex, body mass index, prevalent cardiovascular disease, hypertension, current smoking, cohort, season of exam, residence in New England or other, and overnight wear. Figures 1A–C were additionally adjusted for total wear time, and the percent of wear time spent as sedentary time. Figures 1D and E were additionally adjusted for moderate-to-vigorous physical activity.

Table 1

Characteristics of the Study Population

Study Characteristics*	Women (n=1132)	Men (n=977)	Overall (n=2109)
Age, years	46.3 ± 9.0	46.3 ± 8.7	46.3 ± 8.9
Race (% White)	95%	95%	95%
BMI	26.8 ± 5.7	28.8 ± 4.5	27.7 ± 5.3
HOMA-IR	2.1 ± 1.6	2.6 ± 1.6	2.3 ± 1.6
Current Smoking (%)	6%	9%	8%
Hypertension (%)	16%	25%	20%
Cardiovascular Disease (%)	1%	3%	2%
Adipokines †			
IGF-1 (ng/mL)	131 ± 43	129 ± 38	130 ± 41
hsCRP (mg/L)	2.8 ± 4.6	2.0 ± 3.8	2.4 ± 4.2
Adiponectin (ng/mL)	10809 ± 5513	5846 ± 3651	8510 ± 5349
Leptin (pg/mL)	18084 ± 16684	5762 ± 4956	12376±14089
sOB-R (ng/mL)	18.5 ± 8.3	17.7 ± 7.7	18.2 ± 8.0
Leptin/sOB-R	1311 ± 1763	417 ± 445	897 ± 1399
FABP4 (ng/mL)	20.9 ± 11.9	16.2 ± 7.9	18.7 ± 10.5
RBP4 (μg/mL)	37.5 ± 10.3	43.4 ± 9.9	40.2 ± 10.6
Accelerometer-Determined Physical Activity and Sedentary Time *			
Wear Time (min wear time/day) ‡	816 ± 73	814 ± 81	815 ± 77
SED (min/day) ‡	668 ± 66	656 ± 72	662 ± 69
%SED (min SED/min wear time/day) ‡	82.0 ± 5.6	80.8 ± 6.7	81.4 ± 6.2
Light (min/day) ‡	124 ± 43	130 ± 52	126 ± 48
%Light (min/min wear time/day) ‡	15.0 ± 4.7	15.7 ± 5.6	15.4 ± 5.2
Steps (per day)	8153 ± 3585	8794 ± 4109	8450 ± 3849
MVPA (min/day)	25.6 ± 20.4	29.5 ± 21.1	27.4 ± 20.8
Achieved MVPA Guidelines (>150 min/week) (%)	44%	55%	49%

Abbreviations: Body mass index (BMI); homeostatic model assessment of insulin resistance (HOMA-IR); sedentary time (SED); percent of wear time spent as sedentary time (%SED); moderate-to-vigorous physical activity (MVPA); minutes (min).

All continuous numbers are presented as mean ± SD.

*Measured at examination 2

†Measured at examination 1

‡only recorded during the hours of 6AM-10PM

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Table 2

Relations of physical activity to insulin resistance and circulating adipokines

		MVPA per 20 min/day		Steps per 4000 steps/day	
Biomarker	**Model**	**β est. (SE)**	**p-value**	**β est. (SE)**	**p-value**
HOMA-IR	Multivariable	**−0.046 (0.010)**	**<0.0001**	**−0.050 (0.011)**	**<0.0001**
	+ % SED	**−0.036 (0.012)**	**0.002**	**−0.041 (0.014)**	**0.005**
IGF-1 (ng/mL)	Multivariable	−0.480 (0.830)	0.56	0.669 (0.902)	0.46
	+ % SED	0.556 (1.001)	0.58	**3.293 (1.218)**	**0.007**
hsCRP (mg/L)	Multivariable	−0.056 (0.025)	0.022	−0.069 (0.027)	0.010
	+ % SED	−0.072 (0.030)	0.015	**−0.111 (0.036)**	**0.002**
Adiponectin (ng/mL)	Multivariable	0.016 (0.013)	0.21	0.028 (0.014)	0.048
	+ % SED	0.002 (0.015)	0.92	0.015 (0.019)	0.44
Leptin (pg/mL)	Multivariable	−0.035 (0.014)	0.013	**−0.071 (0.015)**	**<0.0001**
	+ % SED	0.0007 (0.017)	0.97	−0.046 (0.021)	0.024
sOb-R (ng/mL)	Multivariable	−0.0009 (0.010)	0.93	0.027 (0.010)	0.011
	+ % SED	−0.023 (0.012)	0.050	0.013 (0.014)	0.34
Leptin/sOb-R	Multivariable	−0.034 (0.018)	0.061	**−0.098 (0.020)**	**<0.0001**
	+ % SED	0.023 (0.022)	0.28	−0.060 (0.026)	0.023
FABP4 (ng/mL)	Multivariable	−0.287 (0.186)	0.12	**−0.574 (0.202)**	**0.004**
	+ % SED	0.104 (0.224)	0.64	−0.193 (0.273)	0.48
RBP4 (μg/mL)	Multivariable	0.028 (0.217)	0.90	0.021 (0.236)	0.93
	+ % SED	0.286 (0.262)	0.28	0.441 (0.319)	0.17

Abbreviations: Moderate-to-vigorous physical activity (MVPA); percent of wear time spent as sedentary time (%SED); homeostatic model assessment of insulin resistance (HOMA-IR); insulin-like growth factor (IGF)-1; high sensitivity C-reactive protein (hsCRP); adipocyte fatty acid-binding protein (FABP)4; retinol binding protein (RBP)4.

HOMA-IR, hsCRP, adiponectin, leptin, sOb-R, and leptin/sOb-R were natural log (ln) transformed.

Multivariable model: adjusted for cohort, age, sex, body mass index, cardiovascular disease, hypertension, current smoking, season of exam, residence in New England or other, overnight wear, and wear time.

Associations considered significant ($p < 0.01$) were bolded for emphasis.

Table 3

Relations of sedentary time to insulin resistance and circulating adipokines

		% SED per 5% increment	
Biomarker	**Model**	**β est. (SE)**	**p-value**
HOMA-IR	Multivariable	**0.033 (0.008)**	**<0.0001**
	+ MVPA	0.015 (0.010)	0.13
IGF-1 (ng/mL)	Multivariable	1.274 (0.675)	0.060
	+ MVPA	1.550 (0.834)	0.063
hsCRP (mg/L)	Multivariable	0.016 (0.020)	0.43
	+ MVPA	−0.020 (0.025)	0.41
Adiponectin (ng/mL)	Multivariable	−0.019 (0.010)	0.069
	+ MVPA	−0.019 (0.013)	0.15
Leptin (pg/mL)	Multivariable	**0.062 (0.011)**	**<0.0001**
	+ MVPA	**0.061 (0.014)**	**<0.0001**
sOb-R (ng/mL)	Multivariable	**−0.024 (0.008)**	**0.002**
	+ MVPA	**−0.035 (0.010)**	**0.0003**
Leptin/sOb-R	Multivariable	**0.086 (0.015)**	**<0.0001**
	+ MVPA	**0.096 (0.018)**	**<0.0001**
FABP4 (ng/mL)	Multivariable	**0.542 (0.151)**	**0.0003**
	+ MVPA	**0.593 (0.186)**	**0.002**
RBP4 (μg/mL)	Multivariable	0.352 (0.177)	0.047
	+ MVPA	0.479 (0.218)	0.028

Abbreviations: Moderate-to-vigorous physical activity (MVPA); percent of wear time spent as sedentary time (%SED); homeostatic model assessment of insulin resistance (HOMA-IR); insulin-like growth factor (IGF)-1; high sensitivity C-reactive protein (hsCRP); adipocyte fatty acid-binding protein (FABP)4; retinol binding protein (RBP)4.

HOMA-IR, hsCRP, adiponectin, leptin, sOb-R, and leptin/sOb-R were natural log (ln) transformed.

Multivariable model: adjusted for cohort, age, sex, body mass index, cardiovascular disease, hypertension, current smoking, season of exam, residence in New England or other, and overnight wear.

Associations considered significant ($p < 0.01$) were bolded for emphasis.