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Objective Measures of Physical Activity and Cardiometabolic and Endocrine Biomarkers

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Abstract

Purpose—Although physical activity is an established risk factor for chronic disease prevention, the specific mechanisms underlying these relationships are poorly understood. We examined the associations between total activity counts (TAC) and moderate-vigorous physical activity (MVPA) measured by accelerometer, and physical activity energy expenditure (PAEE) measured by doubly-labeled water, with plasma levels of pro-insulin, insulin, c-peptide, IGFBP-3, IGF-1, adiponectin, leptin and leptin-sR.

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Methods—We conducted a cross-sectional analysis of 526 healthy US women in the Women's Lifestyle Validation Study, 2010–2012. We performed multiple linear regression models adjusting for potential lifestyle and health-related confounders to assess the associations between physical activity, measured in quartiles (Q) and biomarkers.

Results—Participants in Q4 vs. Q1 of TAC had lower proinsulin (−20%), c-peptide (−7%), insulin (−31%) and leptin (−46%) levels, and higher adiponectin (55%), leptin-sR (25%) and IGF-1 (9.6%) levels (all P-trend≤0.05). Participants in Q4 vs Q1 of MVPA had lower proinsulin (−26%), c-peptide (−7%), insulin (−32%) and leptin (−40%) levels, and higher adiponectin (31%) and leptin-sR (22%) levels (all P-trend≤0.05). Further adjustment for body mass index attenuated these associations, but the associations with adipokines remained significant. Those in Q4 vs. Q1 of PAEE had lower leptin (−21%) and higher leptin-sR (10%) levels (all P-trend ≤0.05), after additional adjustment for body mass index. In the sensitivity analysis, the associations were similar but attenuated when physical activity was measured using the subjective physical activity questionnaire.

Conclusion—Our data suggests greater physical activity is modestly associated with favorable levels of cardiometabolic and endocrine biomarkers, where the strongest associations were found with accelerometer-measured physical activity. These associations may be only partially mediated through BMI, further supporting the role of physical activity in the reduction of cardiometabolic and endocrine disease risk, independent of adiposity.

Keywords

accelerometer; doubly-labeled water; physical activity questionnaire; cardiometabolic risk; endocrine health; exercise

INTRODUCTION

Higher levels of physical activity have been linked to lower risks of type 2 diabetes, coronary heart disease and several cancers, including breast, colon, endometrial, ovarian, colorectal, lung, prostate and possibly others (3, 8, 36). It was estimated that physical inactivity is responsible for 7% of the burden of disease of type 2 diabetes (T2D), 6% of coronary heart disease, 10% of breast cancer and 10% of colon cancer (23). Thus, physical activity is one of the main modifiable risk factors to reduce the risk of such diseases, presenting a potential opportunity for prevention. The 2008 Physical Activity Guidelines for Americans recommends at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week, or an equivalent combination, preferably spread throughout the week (47). The American Cancer Society has the same recommendation for cancer prevention (21).

Despite widespread recognition for the role of physical activity in the prevention of many chronic diseases, the underlying biological pathway(s) explaining these associations are not fully understood. Although the exact mechanisms are unknown, higher physical activity is associated with altered adipokines, which include higher adiponectin and leptin-sR and lower leptin levels (26). In addition, physical activity is hypothesized to improve insulin sensitivity and increase glucose uptake (26), and could therefore be associated with lower

glucose, insulin, proinsulin, c-peptide, and insulin growth factor-1 (IGF-1) levels. Ninety-nine percent of IGF-1 levels circulate in plasma are bound to insulin growth factor biding proteins (IGFBP) and most are bound to IGFBP-3 specifically, and it has been hypothesized these two biomarkers are associated with risks of certain cancers (13, 15). In addition, previous studies have found that exercise-induced changes in insulin sensitivity have occurred independently of the changes in body weight or body composition (5, 16, 26, 33), but that increases in adiponectin levels have mostly been observed with significant weight loss (14, 26).

Some studies have evaluated the potential biomarkers that may mediate the relationship between physical activity and cardiometabolic and endocrine diseases, but few have evaluated these associations using accelerometer-based measures as well as doubly labeled water estimates of physical activity energy expenditure. Therefore, the objective of this study was to understand further the associations between physical activity and cardiometabolic biomarkers, by evaluating the association between objectively measured total activity counts and moderate-vigorous physical activity (TAC, and MVPA, respectively) and physical activity energy expenditure (PAEE) as well as the self-reported total and moderate-vigorous physical activity measured by the physical activity questionnaire (PAQ), with cardiometabolic and endocrine biomarkers including plasma levels of pro-insulin, insulin, c-peptide, IGFBP3, IGF-1, adiponectin, leptin and leptin-sR in healthy women. This cohort provides a unique opportunity to evaluate multiple objective measures of physical activity, to give insight into the relationships between physical activity and endocrine and cardiometabolic health.

METHODS

Study population

We conducted this analysis in the Women's Lifestyle Validation Study (WLVS), one of three studies in The Multi-Cohort Eating and Activity Study for Understanding Reporting Error, designed to study the structure of measurement error associated with self-reported dietary and physical activity measures (28). The WLVS data were collected between 2010 and 2012, in a subset of participants in the Nurses' Health Study (NHS) and NHS II prospective cohort studies of female registered nurses, described in detail previously (6, 10). A random sample among a subset of the cohorts' participants who had completed the 2006/2007 questionnaire cycle and previously provided blood samples and had no history of coronary heart disease, stroke, cancer, or major neurological disease were invited to participate in the WLVS. In total, 5,509 women were invited to participate and, of these, 796 (14%) consented to participate in an intensive data collection protocol that included repeated measures of diet, physical activity, sleep, and biospecimen collections over the course of 1 year. This analysis utilized the baseline data. The sample size of participants included in our study was 453–526, depending on the biomarker. Insulin and proinsulin assays resulted in some data loss, hence the somewhat lower sample sizes for these biomarkers.

This study was approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

Assessment of physical activity measures

Accelerometer—We mailed participants an accelerometer (ActiGraph GT3X, Actigraph Corporation, Pensacola, FL), detailed instructions, and a wear time diary. They were instructed to wear the monitor on the hip for seven days during all waking hours, except when bathing or swimming, and record the days the monitor was worn. Participants then shipped the accelerometer back to the study center. We screened accelerometer data for wear time using standard methods (44, 45). For triaxial vector magnitude data, which was utilized in this study, non-wear time was defined as ≥ 60 consecutive minutes with zero accelerometer counts, allowing up to two minutes with limited movement (<200 counts/min, which is the triaxial vector magnitude threshold for sedentary time) (1, 20). Daily wear time was determined by subtracting non-wear time from 24 hours. Participants with at least 4 days with ≥10 hours of wear per day were included in the analysis (44, 45).

Doubly-labeled water—We used DLW to assess total daily energy expenditure. Bottled DLW was mailed to participants a few days before they underwent the protocol. Participants provided four urine samples, two directly before and two after (4.5 and 6 hours post-dose) the administration of the DLW dose. After 10 to 14 days, participants provided two more urine samples following the same procedures. All samples were sent to Dr. Jennifer Rood in the Mass Spectrometry Core at Pennington Biomedical Research Center to determine energy expenditure via mass spectroscopic analysis of urine specimens for deuterium and oxygen-18 (38, 39). To estimate physical activity energy expenditure (PAEE), we subtracted resting metabolic rate and thermic effect of food from total daily energy expenditure (9). We estimated resting metabolic rate as described by Mifflin et al. (27, 49). For the thermic effect of food, we used a constant 10% of total energy (9).

Assessment of biomarkers

Participants received a sample collection kit containing collection supplies. Blood was drawn by the participant's local laboratory into glass sodium heparin collection tubes and returned to the processing facility with a cold pack via overnight courier. The biomarkers were measured from fasting blood samples using enzyme-linked immunosorbent assays (Elisa) at Dr. Michael Pollak's lab at the Cancer Prevention Research Unit of McGill University, Montreal, Canada. Proinsulin and insulin were measured by Mercodia Proinsulin or Insulin Elisa (Uppsala, Sweden). C-peptide was measured by ALPCO C-peptide Elisa (Salem, NH). Adiponectin, leptin, and leptin-sR were measured by the Quantikine Human Total Adiponectin, Leptin, or Leptin-sR Immunoassay (DRP300, DLP00, and DOBR00, respectively, R&D Systems Europe Ltd, Abingdon, UK). IGFBP-3 and IGF-1 were measured by IDS-iSYS IGFBP-3 or IGF-1 Assay (IS-4400 and IS-3900, respectively, Immunodiagnostic Systems, Boldon, England). The overall coefficients of variation (CV) were 0.2 – 3.9 % for proinsulin, 0.7 – 4.8 % for c-peptide, 0.2 – 6.0 % for insulin, 0.3 – 5.5 % for IGFBP-3, 1.2 – 4.8 % for IGF-1, 0.1 – 4.1% for adiponectin, 1.8 – 4.7 % for leptin and 2.5 – 6.9 % for leptin-sR.

Assessment of covariates

We collected demographic and anthropometric data such as age, weight and height from the baseline questionnaire, from which we calculated BMI for each participant. Information on lifestyle and reproductive factors such as smoking status, postmenopausal status and post-menopausal hormone use, age at menopause and multivitamin use was collected from the baseline blood sample collection questionnaire. We derived race, age at menarche, parity and age at first birth (AFB) and family history of cancer from the most recent main NHS or NHS II cohort questionnaires. We estimated caffeine and total fiber intakes using the 133-item semi-quantitative food frequency questionnaire at baseline using methods described previously (2). We chose to adjust for these two dietary factors specifically because they have been consistently associated with type 2 diabetes, cardiovascular disease, and cardiometabolic health in general (11, 12, 30, 40, 43).

Statistical analysis

We examined three categories of physical activity as measured by the accelerometer: total activity counts (TAC/day), moderate-to-vigorous physical activity (MVPA) (minutes/day) and total physical activity (TPA), which includes light, moderate, and vigorous physical activity (minutes/day) described below. TACs are the accelerations captured by the device that were filtered, full-wave rectified, and integrated over time, representing the intensity of ambulatory activity. We calculated TAC/day by averaging TAC/day across valid wear days. To identify MVPA minutes, we used thresholds set by Sasaki et al. to estimate the intensity of activities; (35) for MVPA: moderate intensity (3 – 5.99 Metabolic Equivalent Tasks (METs)) = 2690–6166 counts/min; and vigorous intensity (≥ 6 METs) = ≥ 6167 counts/min. Light-intensity physical activity was defined as the total number of minutes between 200 and 2690 counts/min (1). In a recent study, investigators used Artificial Neural Networks to determine separate GT3X VM cutpoints for youth, adults, and older adults. In older adults (aged 65 – 80 years), the cutpoint was 2751 for moderate activity (>3 METs) and 9359 for vigorous activity (> 6 METs) (34). As 2751 is very close to the Sasaki cutpoint of 2690 for moderate activity, we chose to use the Sasaki cutpoint as it is much more commonly used. Although the cutpoint for vigorous activity proposed by Santos-Lozano et al. (9359) was significantly higher than the Sasaki cutpoint (6167), we expected women in our study to do very little vigorous activity at the lower cutpoint, so using the higher cutpoint would have little impact on our results.

To count MVPA minutes, MVPA had to be in at least 10 minute bouts, and a bout was defined as a period of at least 10 consecutive minutes where at least 80% (e.g. 8 out of 10 minutes) of the minutes were above the moderate intensity cut-point (44, 47). To determine TPA minutes, we summed all minutes spent in light, moderate and vigorous intensities where the count met the criterion for that intensity. We estimated mean daily time in intensity-specific categories across all valid wear days.

We grouped participants into quartiles of physical activity, with the lowest quartile serving as the reference group, reducing the influence of outliers and not assuming linearity (50). Biomarker measures were standardized for batch effect as described by Rosner et al (32). ß coefficients from a linear regression model of each biomarker, with a batch indicator

variable was averaged. Then, for each specific batch, the difference between the corresponding ß coefficient from the model and the average coefficient was subtracted from the unadjusted biomarker value to create a continuous measurement that was standardized to the average batch (41).

We used multiple linear regression to evaluate the associations between physical activity measures and biomarkers. The distributions of biomarkers were assessed for normality and biomarkers with non-normal distributions were logarithmically transformed to approximate a normal distribution. We estimated the means of the log-transformed biomarkers as geometric means along with their 95% confidence intervals. Model 1 was adjusted for age (continuous), Caucasian race (yes/no), age at menopause (continuous), age at menarche (≤11, 12, 13, 14+ years), parity and AFB (nulliparous, 1–2 children at <25 y AFB, 1–2 children at 25+ y AFB, 3+ children at < 25 y AFB, 3+ children at 25+ y AFB), postmenopausal status and hormone use (premenopausal, postmenopausal – never use, postmenopausal – past use, postmenopausal - current use), smoking status (never, past, current 1–14 cigarettes/day, current 15+ cigarettes/day), alcohol intake (0, 1.0 - 4.9, 5.0 - 14.9, 15.0+ g/day), current multivitamin use (yes/no), family history of cancer (yes/no), caffeine and total fiber intake (in quartiles). Total accelerometer wear time (hours/day, continuous) was included in model 1 when the exposure was measured by accelerometer. Since BMI might be on the causal pathway between physical activity and the biomarkers, we presented models with and without adjustment for BMI.

We conducted tests for linear trends using quartiles of the physical activity exposure variable as a continuous variable by assigning the median values of the quartiles to the variable. All statistical tests were 2-sided and we considered a P-value < 0.05 statistically significant. The statistical analysis used SAS version 9.3 for UNIX (SAS Institute Inc).

RESULTS

Table 1 presents the age-adjusted characteristics of the study population according to their TAC/day measured by accelerometers. Women with higher TAC/day were younger in age, older at menopause, more likely to be Caucasian, less likely to have a family history of cancer or use multivitamins, and tended to have lower BMI levels and higher total energy intake.

Table 2 presents the multivariable-adjusted partial correlation coefficients of objective physical activity variables with biomarkers in the WLVS study population. TAC measured by accelerometer was inversely correlated with proinsulin, insulin and leptin (r=−0.20, −0.19, −0.22, respectively and P-values ≤ 0.001) and positively correlated with adiponectin and leptin-sR (r=0.20, 0.26, respectively and P-values ≤ 0.001). However, after further adjusting for BMI, TAC was attenuated but remained significantly correlated with proinsulin, adiponectin and leptin-sR (r=−0.13, 0.14, 0.17, P-value <0.05). MVPA (mins/day) measured by accelerometer was inversely correlated with proinsulin and leptin (r= −0.15, −0.19, respectively and P-values ≤ 0.01) and positively correlated with IGF-1 and leptin-sR (r=0.14, 0.21, respectively and P-values ≤ 0.01). Additionally adjusting for BMI attenuated the correlations but they remained significant between MVPA and leptin-sR and

IGF-1 (r=0.15, 0.11, respectively and P-values ≤ 0.05). PAEE (kcal/day) measured by DLW, was not correlated with any of the biomarkers, but after further adjusting for BMI, PAEE became positively correlated with leptin-sR and IGF-1 (r=0.11, 0.11, respectively and P-values < 0.05) and inversely correlated with leptin (r=−0.20, P-value < 0.001).

The multivariable-adjusted geometric means and 95% confidence intervals of the biomarkers by quartiles of TAC/day measured by accelerometer are presented in Table 3. TAC/day was inversely associated with pro-insulin, c-peptide, insulin and leptin levels (all P-trend ≤ 0.0023) and positively associated with adiponectin, IGF-1 and leptin-sR levels (P-trend ≤ 0.0235) in model 1. The associations were attenuated after further adjusting for BMI in model 2 but remained significant between TAC/day and adiponectin, leptin and leptin-sR (all P-trend ≤ 0.0001).

The associations between MVPA (mins/day), measured by accelerometer, and the 8 biomarkers are presented in Table 4. In model 1, MVPA was inversely associated with proinsulin, c-peptide, insulin and leptin (all P-trend ≤ 0.0005) and positively associated with adiponectin and leptin-sR (all P-trend ≤ 0.003). After further adjusting for BMI in model 2, all associations were attenuated but remained significant between MVPA and insulin, leptin and leptin-sR (all P-trend ≤ 0.044).

The associations between PAEE (kcal/day) measured by DLW with the biomarkers are shown in Table 5. There were no significant associations between PAEE and the biomarkers in model 1. However, after additionally adjusting for BMI in model 2, PAEE became positively associated with leptin-sR and inversely associated with leptin (P-trend =0.003 and 0.0001, respectively). In addition, further adjusting the analyses in Tables 2–5 for family history of myocardial infarction, family history of diabetes, diabetes status, diabetes medication use, and statin use did not impact the results (data not shown).

In our sensitivity analyses, we calculated the multivariable-adjusted partial correlation coefficients of total physical activity measured by accelerometer (mins/day), and both TPA and MVPA measured by the PAQ (MET-hrs/week) (see Table, Supplemental Digital Content 1, partial correlation coefficients of multiple measures of physical activity by accelerometer and PAQ). TPA measured by accelerometer was inversely correlated with proinsulin, insulin, and leptin (r=−0.12, −0.11, and −0.20 respectively and P-values ≤ 0.05) and positively correlated with leptin-sR (r=0.22, P-value ≤ 0.001). However, after further adjusting for BMI, TPA only remained significantly correlated with leptin-sR (r=0.16, P-value <0.01). TPA and MVPA measured by PAQ were positively correlated with adiponectin and inversely correlated with leptin (TPA: r=0.20 and −0.13, MVPA: r=0.18 and −0.14, respectively, all P-values <0.05). Correlations were attenuated after further adjusting for BMI, but both TPA and MVPA remained positively correlated with adiponectin (r=0.16 and 0.13, respectively, all P-values ≤ 0.01).

We also evaluated the association between TPA measured in minutes per day, rather than total activity counts, by accelerometer with the biomarkers, estimating their multivariable-adjusted geometric means and 95% confidence intervals by quartiles of TPA (see Table, Supplemental Digital Content 2, geometric means of biomarkers by quartiles of TPA

measured by accelerometer). TPA was inversely associated with proinsulin, c-peptide, insulin and leptin levels (all P-trend ≤ 0.007) and positively associated with adiponectin and leptin-sR levels (all P-trend ≤ 0.0005) in model 1. The associations were attenuated after further adjusting for BMI in model 2 but remained significant between TPA and both leptin and leptin-sR (all P-trend ≤ 0.020).

We also evaluated the associations between TPA in MET-hrs/week as measured by the baseline PAQ, which is the most widely used physical activity assessment tool in epidemiologic studies, and the biomarkers (see Table, Supplemental Digital Content 3, geometric means of biomarkers by quartiles of TPA measured by PAQ). In model 1, questionnaire-based TPA was positively associated with adiponectin and leptin-sR (P-trend=0.002, 0.044, respectively) and negatively associated with leptin (P-trend=0.047). After further adjustment for BMI, these associations diminished but remained significant between TPA and adiponectin (P-trend=0.016). We also assessed the relationships between MVPA (MET-hrs/week) measured by the PAQ with the biomarkers (see Table, Supplemental Digital Content 4, geometric means of biomarkers by quartiles of MVPA measured by PAQ). We observed that MVPA was positively associated with adiponectin and leptin-sR and inversely associated with leptin and in model 1 (P-trend=0.0006, 0.036, and 0.019, respectively). All associations were attenuated after further adjusting for BMI in model 2, but remained significant between MVPA and adiponectin (P-trend=0.007). In addition, light physical activity, measured by either accelerometer or questionnaire, was not associated with any of the eight biomarkers in model 1 and model 2, which included BMI, after including MVPA (data not shown).

DISCUSSION

In this study of the relationship between objective measures of physical activity and cardiometabolic and endocrine biomarkers among women, greater physical activity was associated with favorable profiles of these biomarkers. Higher levels of accelerometer-based TAC were associated with lower proinsulin (−20%), c-peptide (−7%), insulin (−31%), and leptin (−46%), and higher adiponectin (55%), leptin-sR (25%), and IGF-1 (9.6%) (all P-values < 0.05), comparing participants at the highest quartile with the lowest. In addition, accelerometer-based estimates of MVPA minutes/day were associated with lower proinsulin (−26%), c-peptide (−7%), insulin (−32%), and leptin (−40%) levels, and higher adiponectin (31%) and leptin-sR (22%) levels, comparing extreme quartiles. Further adjusting for BMI attenuated most associations. The associations remained significant between both TAC, MVPA and PAEE with leptin and leptin-sR, independent of BMI. The relationships between TAC and adiponectin, and MVPA and both insulin and IGF-1 also remained significant independent of BMI. This demonstrates that physical activity may beneficially impact cardiometabolic and endocrine health, independent of its effect on body weight or adiposity.

Of the six measures of physical activity in this study, including TAC, MVPA and TPA by accelerometer, PAEE by DLW, and TPA and MVPA by PAQ, TAC had the strongest associations with the biomarkers of cardiometabolic and endocrine function in this study. TAC is a measure of physical activity recently proposed as an approximate of total volume of physical activity (4). A recent study of the National Health and Nutrition Examination

Survey evaluated the relationships between TAC and MVPA and biomarkers and anthropometrics and similarly observed stronger associations for TAC than MVPA for HDL-C, triglyceride, plasma glucose, C-peptide, insulin, C-reactive protein, homocysteine, systolic blood pressure, waist circumference, triceps skinfold, and subscapular skinfold (52). DLW is deemed the “gold-standard” of measuring total energy expenditure (37), but TAC might also be a particularly useful measure of physical activity in relation to hard clinical endpoints (22). Further, individuals with a higher body mass would generate higher PAEE for the same activity as those with a lower body mass; therefore, DLW measurements also reflect confounding by body size, as well as other sources of variability in energy expenditure (e.g., resting metabolic rate). Also consistent with our findings, previous publications generally found that MVPA was more strongly associated with cardiometabolic and endocrine biomarkers than TPA, whether measured by accelerometer in minutes per day or by PAQs in MET-hrs/week (25, 42).

Although TAC was favorably associated with biomarkers evaluated in this study, it was also positively associated with IGF-1 levels before adjusting for BMI, which has been associated with greater risks of breast, colon and prostate cancers (51). However, there were inconsistent results among both intervention (29) and cross-sectional studies where the findings show that physical activity is positively (19, 24), negatively (48), or not (18, 31) associated with IGF-1 levels.

The 2008 Physical Activity Guidelines for Americans recommend at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week, or an equivalent combination, preferably spread throughout the week (47). In our study population, only 34% of women had at least 150 minute per week of moderate intensity exercise, and only 3% had at least 75 minute per week of vigorous intensity exercise. These levels of MVPA are lower than those found in a national sample of US adults, ages eighteen and above, in 2011 where more than 51% met the guidelines criteria (46). This illustrates the low MVPA levels in the US and the immense potential for improving upon this behavior for chronic disease prevention. Given TAC is a new measure of physical activity, there are no physical activity guidelines recommending specific TAC/d targets.

Several proposed mechanisms link higher physical activity with reduced cardiometabolic and endocrine risk, and some of these pathways are mediated by decreased body weight and/or adiposity. First, higher physical activity can both directly and indirectly, through reduced body weight and/or body fat, decrease insulin resistance, hyperinsulinemia and risk of T2D (7, 26). Second, physical activity can reduce systemic inflammation alone or through the reduction of adiposity, which decreases inflammatory cytokines (26). Lastly, physical activity, both independently and through reduction in adiposity, results in increased secretion of anti-inflammatory and reduces pro-inflammatory cytokines, which could decrease risk of T2D, cardiovascular disease and colon, renal, lower esophageal, thyroid, endometrial and postmenopausal breast cancers (17, 26). The magnitude of differences between the highest vs. lowest quartiles of activity varied. For example, comparing extreme quartiles of accelerometer-based TAC, we observed 7% lower c-peptide levels, while adiponectin levels were 55% greater. The clinical relevance for the magnitudes of these potential benefits of

physical activity likely varies greatly across the biomarker and chronic disease endpoint of interest.

Our study has several strengths. First, the multiple objective measures of physical activity allowed us to study physical activity with more accuracy and precision than the common PAQ. Further, data collected in the WLVS allowed us to evaluate the gold standard (DLW) alongside the more commonly used epidemiologic tools (e.g., PAQ or accelerometer). Second, having finely detailed diet and lifestyle data in the WLVS study and several decades of prior data collected by the main NHS and NHS II cohorts provided a wealth of data, which enabled control for many potential confounders. There were also some limitations to our study. First, the design was cross-sectional, which limits our ability to establish a temporal relationship between physical activity and biomarker outcomes. It is possible that some participants with unfavorable cardiometabolic risk were recently advised by their physician to increase their physical activity levels (i.e., reverse causation), which could lead to a modest underestimation of the associations between physical activity and biomarker levels. Second, measurement error in both the physical activity and the biomarkers measures have likely attenuated the true correlations, thus the true correlations are likely higher. In addition, residual confounding was likely in the use of BMI as a marker of overall adiposity, where an actual measure of percent body fat would have been ideal. Third, this study was conducted among female nurses who were older in age and predominantly Caucasian and therefore generalizability may be limited.

In summary, physical activity, especially TAC and MVPA, are modestly associated with favorable levels of pro-insulin, insulin, leptin, c-peptide, adiponectin, leptin and leptin-sR. The associations between TAC and adiponectin, leptin and leptin-sR and between MVPA and insulin, leptin and leptin-sR were attenuated but remained significant even after further adjusting for BMI, suggesting that the beneficial effects of physical activity on these biomarkers is partly mediated through body weight or adiposity. DLW was associated with a favorable leptin and leptin-SR profile, but not with the other biomarkers evaluated. Altogether, this provides further evidence on the mechanisms underlying the relationship between physical activity and cardiometabolic and endocrine health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Age-adjusted baseline characteristics of the Women's Lifestyle Validation Studies study population by quartiles of total activity counts per day measured by accelerometer, United States, 2010–2012.

	Quartiles of Total Activity Counts per Day							
	Q1 (n=138)		Q2 (n=138)		Q3 (n=123)		Q4 (n=127)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years [a]	67 (9)		65 (9)		62 (9)		60 (9)	
BMI, kg/m^2	29.2 (6.5)		27.5 (5.6)		25.2 (4.7)		24.6 (4)	
Postmenopausal women, %		83		85		81		84
Age at menopause, years [a]		47		49		49		50
Current use of postmenopausal hormones, %		6		5		3		8
Age at menarche < 12 years, % [2]		63		66		62		58
Nulliparous, %		4		7		13		13
Parity among parous	2.4 (1.1)		2.5 (1.0)		2.5 (1.0)		2.7 (1.0)	
Age at first birth, years [a]	24.5 (5.3)		25.5 (5.1)		25.2 (6.8)		24.8 (6.6)	
Caucasian, %		81		92		93		96
Family history of cancer [b], %		45		33		34		30
Family history of diabetes, %		30		16		24		14
Family history of MI, %		30		23		28		17
Current multivitamin use, %		63		59		65		54
Current smoker, %		2		1		2		3
Total energy, kcal/day	1831 (512)		1892 (541)		1990 (577)		2022 (515)	
Alcohol, g/day	8.3 (14.4)		8.1 (10.6)		9.3 (11.8)		8.6 (10.3)	
Total fiber, g/day	22 (6)		24 (6)		23 (5)		24 (6)	
Caffeine, mg/day	172 (151)		193 (139)		164 (124)		167 (130)	

Abbreviations: BMI, body mass index; SD, standard deviation.

[a] Value is not age adjusted.

[b] Ovarian, breast, colon, pancreatic, melanoma, uterine, and kidney cancers were included in deriving this variable.

Table 2

Partial correlation coefficients of objective physical activity measures and intermediate biomarkers of cardiometabolic and endocrine health in the Women's Lifestyle Validation Studies study population, Unites States, 2010–2012 (n=453–526).[a]

	Accelerometer				Doubly-labeled water	
	Total activity counts per day		Moderate-to-vigorous physical activity, minutes per day		Physical activity energy expenditure, kcal	
	Multivariable-adjusted	Multivariable and BMI - adjusted	Multivariable-adjusted	Multivariable and BMI - adjusted	Multivariable-adjusted	Multivariable and BMI - adjusted
Proinsulin	−0.20***	−0.13*	−0.15**	−0.09	0.07	0.05
C-peptide	−0.07	−0.001	−0.03	0.02	0.07	0.04
Insulin	−0.19***	−0.10	−0.11*	−0.04	0.05	0.02
IGFBP-3	0.05	0.04	0.04	0.03	0.08	0.08
IGF-1	0.10	0.07	0.14*	0.11*	0.10	0.11*
Adiponectin	0.20***	0.14**	0.10	0.05	−0.04	−0.02
Leptin	−0.22***	−0.07	−0.19***	−0.09	−0.08	−0.20***
Leptin-sR	0.26***	0.17**	0.21***	0.15**	0.06	0.11*

Abbreviations: kcal, kilocalories; BMI, body mass index; IGFBP-3, insulin-like growth factor binding protein 3; IGF-1, insulin-like growth factor 1; Leptin-sR, leptin soluble receptor.

[a]Adjusted for age (continuous), Caucasian (yes/no), age at menopause (continuous), age at menarche (<12, 12, 13, 14+ years), parity and age at first birth (nulliparous, 1–2 children at <25 y at first birth, 1–2 children at 25+ y at first birth, 3+ children at < 25 y at first birth, 3+ children at 25+ y at first birth), postmenopausal status and post-menopausal hormone use (premenopausal, never, past, current use), smoking status (never, past, current 1–14 cigs/day, current 15+ cigs/day), alcohol intake (0, 0,1 – <5, 5 – <15, 15+ g/day), multivitamin use (yes.no), family history of cancer (yes/no), caffeine intake (quartiles) and total fiber intake (quartiles). Accelerometer models were additionally adjusted for total accelerometer wear time (hours/day, continuous). BMI was adjusted for continuously (kg/m^2).

*P-value < 0.05;

**P-value ≤ 0.01;

***P-value ≤ 0.001

Table 3

Geometric means and 95% CI of cardiometabolic and endocrine biomarkers by quartiles of total activity counts per day, Women's Lifestyle Validation Studies, United States, 2010–2012.

	Quartiles of Total Activity Counts per Day								
	1 (median=387,250)		2 (median=511,739)		3 (median=624,002)		4 (median=792,067)		P-trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Pro-Insulin (pmol/L), n=470									
Model 1[a]	19.7	18.0, 21.6	19.2	17.6, 20.9	17.8	16.0, 19.8	15.7	14.1, 17.5	0.0023
Model 2[b]	18.4	16.8, 20.1	18.8	17.3, 20.4	18.5	16.7, 20.4	17.1	15.4, 19.1	0.33
C-peptide (ng/ml), n=525									
Model 1[a]	6.86	6.68, 7.04	6.69	6.53, 6.86	6.27	6.09, 6.45	6.40	6.22, 6.59	0.0003
Model 2[b]	6.72	6.54, 6.89	6.66	6.50, 6.81	6.33	6.16, 6.51	6.55	6.37, 6.74	0.13
Insulin (mU/ml), n=453									
Model 1[a]	8.09	7.18, 9.12	7.07	6.33, 7.90	6.72	5.82, 7.75	5.58	4.79, 6.50	0.0004
Model 2[b]	7.27	6.51, 8.12	7.03	6.36, 7.77	7.15	6.28, 8.14	6.26	5.44, 7.19	0.14
IGFBP-3 (ng/ml), n=524									
Model 1[a]	3.71	3.57, 3.86	3.63	3.50, 3.77	3.71	3.55, 3.88	3.87	3.70, 4.05	0.13
Model 2[b]	3.73	3.58, 3.88	3.63	3.50, 3.77	3.70	3.54, 3.87	3.86	3.69, 4.04	0.21
IGF-1 (ng/ml), n=524									
Model 1[a]	104	98, 110	100	95, 106	103	97, 110	114	107, 121	0.0235
Model 2[b]	105	99, 112	100	95, 106	103	96, 109	112	105, 120	0.11
Adiponectin (μg/ml), n=526									
Model 1[a]	10.2	9.2, 11.2	12.2	11.1, 13.4	14.3	12.8, 16.0	15.8	14.2, 17.7	<.0001
Model 2[b]	11.0	9.9, 12.1	12.5	11.4, 13.6	13.8	12.4, 15.3	14.5	13.0, 16.2	0.0004
Leptin (ng/ml), n=524									
Model 1[a]	39.6	35.6, 44.0	32.4	29.3, 35.7	27.5	24.4, 30.9	21.4	19.0, 24.1	<.0001
Model 2[b]	33.6	30.9, 36.5	31.1	28.9, 33.5	29.9	27.4, 32.7	25.5	23.3, 28	<.0001

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	Quartiles of Total Activity Counts per Day								
	1 (median=387,250)		2 (median=511,739)		3 (median=624,002)		4 (median=792,067)		P-trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Leptin-sR (ng/ml), n=524									
Model 1[a]	27.6	26.3, 28.9	28.7	27.5, 30.0	32.3	30.6, 34.0	34.4	32.7, 36.3	<.0001
Model 2[b]	29.0	27.7, 30.3	29.0	27.9, 30.2	31.5	30.1, 33.0	32.7	31.1, 34.3	0.0002

Abbreviations: IGFBP-3, insulin-like growth factor binding protein 3; IGF-1, insulin-like growth factor 1; Leptin-sR, leptin soluble receptor.

[a]Model 1: Adjusted for age (continuous), Caucasian (yes/no), age at menopause (continuous), age at menarche (<12, 12, 13, 14+ years), parity and age at first birth (nulliparous, 1–2 children at <25 y at first birth, 1–2 children at 25+ y at first birth, 3+ children at < 25 y at first birth, 3+ children at 25+ y at first birth), postmenopausal status and post-menopausal hormone use (premenopausal, never, past, current use), smoking status (never, past, current 1–14 cigs/day, current 15+ cigs/day), alcohol intake (0, 0,1 – <5, 5 – <15, 15+ g/day), multivitamin use (yes.no), family history of cancer (yes/no), caffeine intake (quartiles), total fiber intake (quartiles) and total accelerometer wear time (hours/day, continuous).

[b]Model 2: Model 1 + adjusted for body mass index (kg/m^2, continuous).

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Table 4

Geometric means and 95% CI of cardiometabolic and endocrine biomarkers by quartiles of moderate-to-vigorous physical activity measured by accelerometer (mins/day), Women's Lifestyle Validation Studies, United States, 2010–2012.

	Quartiles								
	1 (median=0)		2 (median = 5.1)		3 (median=16.0)		4 (median=37.5)		P-trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Pro-Insulin (pmol/L), n=470									
Model 1[a]	21	19.3, 22.8	17.4	15.8, 19.1	18.1	16.3, 20.1	15.6	14, 17.4	0.0004
Model 2[b]	19.6	18.1, 21.2	17.4	15.9, 19	19	17.2, 21	16.7	15, 18.5	0.07
C-peptide (ng/ml), n=525									
Model 1[a]	6.85	6.68, 7.02	6.54	6.37, 6.71	6.5	6.32, 6.7	6.34	6.15, 6.52	0.0005
Model 2[b]	6.7	6.54, 6.86	6.54	6.38, 6.7	6.59	6.41, 6.78	6.45	6.28, 6.64	0.11
Insulin (mU/ml), n=453									
Model 1[a]	8.05	7.2, 9	6.98	6.18, 7.89	6.92	6, 7.97	5.51	4.76, 6.37	0.0002
Model 2[b]	7.23	6.52, 8.01	7.06	6.33, 7.88	7.46	6.56, 8.48	6.01	5.27, 6.87	0.044
IGFBP-3 (µg/ml), n=524									
Model 1[a]	3.7	3.57, 3.83	3.68	3.54, 3.83	3.75	3.59, 3.92	3.77	3.61, 3.94	0.40
Model 2[b]	3.72	3.58, 3.86	3.68	3.54, 3.83	3.74	3.58, 3.91	3.76	3.59, 3.93	0.61
IGF-1 (ng/ml), n=524									
Model 1[a]	101	96, 106	104	98, 110	107	100, 114	109	103, 116	0.07
Model 2[b]	102	97, 108	104	98, 110	106	99, 113	108	101, 115	0.24
Adiponectin (µg/ml), n=526									
Model 1[a]	11.4	10.4, 12.6	13.1	11.9, 14.5	12.2	10.8, 13.6	14.9	13.3, 16.6	0.003
Model 2[b]	12.6	11.5, 13.7	13.1	11.9, 14.4	11.5	10.3, 12.8	13.7	12.4, 15.3	0.34
Leptin (ng/ml), n=524									
Model 1[a]	37.8	34.2, 41.8	30.3	27.2, 33.7	29.5	26.2, 33.3	22.5	19.9, 25.3	<.0001
Model 2[b]	31.5	29.1, 34	30.3	28, 32.9	32.9	30, 36	26.1	23.8, 28.5	0.004

	Quartiles								
	1 (median=0)		2 (median = 5.1)		3 (median=16.0)		4 (median=37.5)		P-trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Leptin-sR (ng/ml), n=524									
Model 1[a]	28.2	27, 29.5	29.8	28.4, 31.2	30.1	28.6, 31.8	34.3	32.6, 36.2	<.0001
Model 2[b]	29.9	28.7, 31.1	29.7	28.5, 31	29.2	27.8, 30.6	32.8	31.3, 34.4	0.003

Abbreviations: mins, minutes; IGFBP-3, insulin-like growth factor binding protein 3; IGF-1, insulin-like growth factor 1; Leptin-sR, leptin soluble receptor.

[a]Model 1: Adjusted for age (continuous), Caucasian (yes/no), age at menopause (continuous), age at menarche (<12, 12, 13, 14+ years), parity and age at first birth (nulliparous, 1–2 children at <25 y at first birth, 1–2 children at 25+ y at first birth, 3+ children at < 25 y at first birth, 3+ children at 25+ y at first birth), postmenopausal status and post-menopausal hormone use (premenopausal, never, past, current use), smoking status (never, past, current 1–14 cigs/day, current 15+ cigs/day), alcohol intake (0, 0,1 – <5, 5 – <15, 15+ g/day), multivitamin use (yes.no), family history of cancer (yes/no), caffeine intake (quartiles), total fiber intake (quartiles) and total accelerometer wear time (hours/day, continuous).

[b]Model 2: Model 1 + adjusted for body mass index (kg/m^2, continuous).

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Table 5

Geometric means and 95% CI of cardiometabolic and endocrine biomarkers by quartiles of physical activity energy expenditure measured by doubly-labeled water (kcal/day), Women's Lifestyle Validation Studies, United States, 2010–2012.

	Quartiles of Physical Activity Energy Expenditure								
	1 (median=471)		2 (median=622)		3 (median=763)		4 (median=978)		P-trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Pro-Insulin (pmol/L), n=470									
Model 1[a]	17.2	15.7, 18.9	19	17.3, 20.9	18.3	16.6, 20.2	18.8	16.9, 20.8	0.33
Model 2[b]	17.6	16.2, 19.1	19.1	17.5, 20.8	18.4	16.8, 20.1	18.1	16.5, 19.9	0.80
C-peptide (ng/ml), n=525									
Model 1[a]	6.62	6.45, 6.8	6.53	6.36, 6.7	6.55	6.37, 6.74	6.62	6.43, 6.81	0.95
Model 2[b]	6.65	6.48, 6.81	6.55	6.39, 6.71	6.56	6.4, 6.73	6.55	6.38, 6.73	0.52
Insulin (mU/ml), n=453									
Model 1[a]	6.67	5.9, 7.53	7.13	6.28, 8.1	6.82	5.99, 7.76	7.38	6.42, 8.48	0.37
Model 2[b]	6.88	6.18, 7.67	7.22	6.46, 8.08	6.95	6.20, 7.80	6.82	6.02, 7.72	0.82
IGFBP-3 (μg/ml), n=524									
Model 1[a]	3.71	3.57, 3.86	3.68	3.54, 3.82	3.7	3.56, 3.85	3.82	3.66, 3.98	0.30
Model 2[b]	3.71	3.56, 3.85	3.67	3.53, 3.82	3.7	3.55, 3.85	3.83	3.67, 3.99	0.25
IGF-1 (ng/ml), n=524									
Model 1[a]	101	95, 107	105	99, 111	107	101, 114	106	100, 113	0.21
Model 2[b]	101	95, 106	105	99, 111	107	101, 114	107	101, 114	0.13
Adiponectin (μg/ml), n=526									
Model 1[a]	12.6	11.3, 13.9	12.5	11.3, 13.9	12.9	11.6, 14.4	12.9	11.6, 14.5	0.66
Model 2[b]	12.4	11.3, 13.6	12.4	11.3, 13.6	12.8	11.6, 14.2	13.4	12.1, 14.9	0.22
Leptin (ng/ml), n=524									
Model 1[a]	33.6	30, 37.5	29.4	26.3, 32.8	27.9	24.9, 31.3	29.7	26.3, 33.6	0.15
Model 2[b]	34.6	32, 37.4	30.2	27.9, 32.7	28.3	26.1, 30.7	27.4	25.2, 29.9	0.0001

	Quartiles of Physical Activity Energy Expenditure								
	1 (median=471)		2 (median=622)		3 (median=763)		4 (median=978)		P-trend
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Leptin-sR (ng/ml), n=524									
Model 1[a]	29.1	27.7, 30.5	30.3	28.8, 31.8	31.4	29.8, 33	30.7	29.1, 32.4	0.10
Model 2[b]	28.7	27.5, 30	30.1	28.8, 31.3	31.3	29.9, 32.7	31.5	30.1, 33.0	0.003

Abbreviations: kcal, kilocalories; IGFBP-3, insulin-like growth factor binding protein 3; IGF-1, insulin-like growth factor 1; Leptin-sR, leptin soluble receptor.

[a]Model 1: Adjusted for age (continuous), Caucasian (yes/no), age at menopause (continuous), age at menarche (<12, 12, 13, 14+ years), parity and age at first birth (nulliparous, 1–2 children at <25 y at first birth, 1–2 children at 25+ y at first birth, 3+ children at < 25 y at first birth, 3+ children at 25+ y at first birth), postmenopausal status and post-menopausal hormone use (premenopausal, never, past, current use), smoking status (never, past, current 1–14 cigs/day, current 15+ cigs/day), alcohol intake (0, 0,1 – <5, 5 - <15, 15+ g/day), multivitamin use (yes.no), family history of cancer (yes/no), caffeine intake (quartiles) and total fiber intake (quartiles).

[b]Model 2: Model 1 + adjusted for body mass index (kg/m^2, continuous).