Sedentary Time Is Independently Related to Adipose Tissue Insulin Resistance in Adults With or at Risk of Type 2 Diabetes

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ABSTRACT

ENGIN, B., S. A. WILLIS, S. MALAIKAH, J. A. SARGEANT, G. J. H. BIDDLE, C. RAZIEH, S. ARGYRIDOU, C. L. EDWARDSON, C. JELLEYMAN, D. J. STENSEL, J. HENSON, A. V. ROWLANDS, M. J. DAVIES, T. YATES, and J. A. KING. Sedentary Time Is Independently Related to Adipose Tissue Insulin Resistance in Adults With or at Risk of Type 2 Diabetes. *Med. Sci. Sports Exerc.*, Vol. 55, No. 9, pp. 1548–1554, 2023. **Introduction:** This cross-sectional study examined associations of device-measured sedentary time and moderate-to-vigorous physical activity (MVPA) with adipose tissue insulin resistance in people with or at high risk of type 2 diabetes (T2DM). **Method:** Data were combined from six previous experimental studies (within our group) involving patients with T2DM or primary risk factors (median (interquartile range) age, 66.2 (66.0–70.8) yr; body mass index (BMI), 31.1 (28.0–34.4) $kg \cdot m^{-2}$; 62% male; $n = 179$). Adipose tissue insulin resistance was calculated as the product of fasted circulating insulin and nonesterified fatty acids (ADIPO-IR), whereas sedentary time and MVPA were determined from wrist-worn accelerometery. Generalized linear models examined associations of sedentary time and MVPA with ADIPO-IR with interaction terms added to explore the moderating influence of ethnicity (White European vs South Asian), BMI, age, and sex. **Results:** In finally adjusted models, sedentary time was positively associated with ADIPO-IR, with every 30 min of sedentary time associated with a 1.80-unit (95% confidence interval, 0.51–3.06; $P = 0.006$) higher ADIPO-IR. This relationship strengthened as BMI increased ($\beta = 3.48$ (95% confidence interval, 1.50–5.46), $P = 0.005$ in the upper BMI tertile (≥ 33.2 $kg \cdot m^{-2}$)). MVPA was unrelated to ADIPO-IR. These results were consistent in sensitivity analyses that excluded participants taking statins and/or metformin ($n = 126$) and when separated into the participants with T2DM ($n = 32$) and those at high risk ($n = 147$). **Conclusions:** Sedentary time is positively related to adipose tissue insulin sensitivity in people with or at high risk of T2DM. This relationship strengthens as BMI increases and may help explain established relationships between greater sedentary time, ectopic lipid, and hyperglycemia. **Key Words:** PHYSICAL ACTIVITY, INSULIN SENSITIVITY, LIPOLYSIS, LIPOGENESIS, OBESITY

Insulin resistance is central to the pathophysiology of numerous obesity-related conditions, including type 2 diabetes (T2DM) (1) and nonalcoholic fatty liver disease (2). The metabolic consequences of insulin resistance are tissue-specific, and although the metabolic sequelae of insulin resistance in skeletal muscle and the liver is well defined, evidence relating to adipose tissue insulin resistance is less established. Adipose tissue insulin resistance typically develops with obesity, once adipocytes become enlarged and inflamed (3). A diminished antilipolytic response to insulin ensues, resulting in elevated circulating nonesterified fatty acids (NEFA) and exaggerated lipid deposition in the liver, pancreas, and skeletal muscle (4). These ectopic lipid deposits directly impair insulin signaling, glucose, and lipid metabolism (5).

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The gold-standard technique for measuring adipose tissue insulin sensitivity in humans requires a multistep hyperinsulinemic–euglycemic clamp with stable-isotope tracer (glycerol and/or palmitate) (6). However, issues relating to cost, practicality, and technical expertise limit its utility. Alternatively, the adipose tissue insulin resistance index (ADIPO-IR), calculated as the product of fasting insulin and NEFA concentrations, provides a simple estimate of adipose tissue insulin resistance. Although being a "static" metric, the ADIPO-IR has been validated against clamp-based assessments (7,8) of adipose tissue insulin sensitivity, confirming that the index adequately represents the dynamic interaction between insulin/hyperinsulinemia, circulating NEFA, and/or lipolysis. *In vitro* studies also show that the ADIPO-IR provides a valid representation of antilipolysis and lipogenesis (9).

In cross-sectional studies, ADIPO-IR is positively related to obesity (10–12) and indices of glycemic control (13,14), with evidence of dose–response. Positive associations of ADIPO-IR with biomarkers of chronic inflammation have also been observed (13). An inverse association has been identified between ADIPO-IR and pancreatic beta-cell function (15), likely reflecting the lipotoxic effect of elevated circulating NEFA. Moreover, baseline ADIPO-IR was associated with a greater risk (odds ratio, 1.59 per SD) of developing dysglycemia (i.e., the onset of impaired fasting glucose, impaired glucose tolerance or T2DM) over 9 yr, independent of anthropometric and cardiometabolic biomarkers (16). Recently, ADIPO-IR was shown to predict the severity of liver fibrosis in patients with nonalcoholic fatty liver disease and T2DM (17). These findings, along with others (18,19), have prompted the suggestion that ADIPO-IR is a valid marker of adipose tissue dysfunction, which in itself is a more prognostic biomarker of metabolic health than adiposity *per se*.

The therapeutic potential of improving adipose tissue insulin sensitivity has been recognized (20), with the glucose-lowering effect of thiazolidinediones ascribed specifically to enhanced adipogenesis in more "metabolically friendly" lipid depots (11). Our recent meta-analysis demonstrated that formal exercise training can improve adipose tissue insulin sensitivity, when measured via ADIPO-IR or clamp-based techniques (21). Importantly, however, this analysis focused solely on formal exercise training regimens within clinical trials. It did not examine incidental movement behaviors with more translational relevance. Despite established links between sedentary time and chronic inflammation (22) and dysregulated glucolipid metabolism (23), the relationship between habitual sedentary time and adipose tissue insulin sensitivity has received minimal attention.

Using a pooled data set of adults with or at high risk of T2DM (derived from experimental trials in our group), this study examined associations between physical activity and sedentary time (device-measured) with adipose tissue insulin resistance. A secondary aim was to explore whether relevant demographic and biological factors mediated these associations. We hypothesized that sedentary time would be positively associated with ADIPO-IR, whereas physical activity would be inversely related. Furthermore, because aging, adipocyte size, and South Asian ethnicity have each been linked with greater adipose tissue insulin resistance (24–26), we hypothesized that associations of sedentary time and physical activity with ADIPO-IR would be stronger in individuals who were older, had higher body mass index (BMI) values, and were of South Asian ethnicity (compared with White European).

METHODS

Ethical approval. This cross-sectional analysis pooled baseline data from previous experimental studies conducted within the National Institute for Health and Care Research Leicester Biomedical Research Centre (see Supplemental Table 1, Supplemental Digital Content, Summary of included studies, http://links.lww.com/MSS/C854; clinical trials: NCT02453204, ISRCTN12337078, NCT03315988, NCT03482596, NCT04004273, NCT03549390). All studies obtained ethical approval from local National Health Service research ethics committees (REC reference: 14-EM-1217, 15-EM-0259, 17-WS-0184, 18-EM-0006, 18-EM-0161, 18-EM-0185) and were conducted in accordance with the Declaration of Helsinki (2013). Written informed consent was obtained for each participant before their participation.

Participants. Overall, data for 179 volunteers (111 men, 68 women) were included in the present analysis. Figure 1 describes the sample reduction process. Primary care services, community events, poster advertisement, existing research databases, and word-of-mouth were used to recruit study volunteers. Participants were aged between 28 and 80 yr and were classified as either having T2DM or being at high risk of T2DM because of obesity, elevated hepatic steatosis, and/or non-diabetic hyperglycemia. Female participants were either postmenopausal (for at least 12 months) or were not pregnant

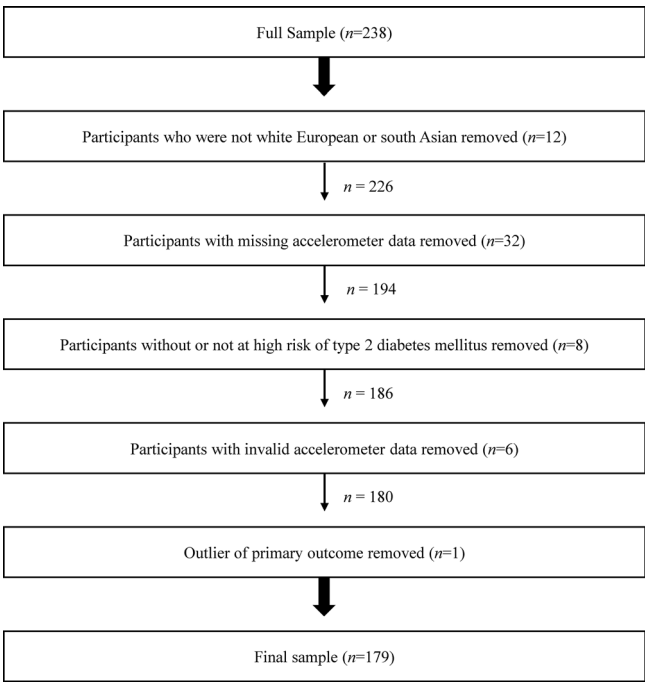

FIGURE 1—Study sample reduction process.

or lactating (self-reported). The exclusion criteria of the primary studies were as follows: those undertaking a weight loss dietary intervention (with the purpose of reducing body mass), those engaging in regular purposeful exercise (see Supplemental Table 1, Supplemental Digital Content, for the definition used in each study, http://links.lww.com/MSS/C854), and those exhibiting weight instability within the last 3 months (≥3 kg weight change). In the present analysis, participants who were not from a White European or South Asian ethnic background were excluded (n = 10).

Study procedures. All data were collected between April 2015 and July 2022 from study screening and/or baseline assessment visits. Identical research techniques and standard operating procedures were used between studies for each outcome in this analysis. The exception was body fat percentage, which was measured via dual-energy x-ray absorptiometry in one study (27) (NCT03315988; n = 16) and via bioelectrical impedance analysis in all other studies (n = 163). Participants were instructed to avoid alcohol, caffeine, and structured exercise in the 24 h before study visits. Information on participants' demographics, medical history, and medication use was obtained by a healthcare professional.

Anthropometric measurements. Height was measured to the nearest 0.5 cm using a stadiometer, whereas body weight was measured to the nearest 0.1 kg using integrated weighing scales (Tanita TBE 611; Tanita, West Drayton, United Kingdom). These values were then used to calculate participants' BMI (in kilograms per meter squared). Body fat percentage was measured by bioelectrical impedance analysis (Tanita TBE 611; Tanita) or dual-energy x-ray absorptiometry (Lunar Prodigy; GE Corporation, Chicago, IL).

Device-measured physical activity and sedentary time. To assess physical activity and sedentary time, participants were requested to wear a wrist-worn triaxial accelerometer (GENEActiv; ActivInsights Ltd, Kimbolton, United Kingdom) after their baseline assessment visit for at least 6 d. Participants were instructed to continue their daily activities as usual and wear the device on their non-dominant wrist at all times, if possible. A log was provided to record any periods where the device was removed, along with participants' wake and sleep times for each date of accelerometer wear. Data were recorded at 100 Hz, downloaded using GENEActiv PC software (version 3.2, GENEActiv; ActivInsights Ltd), and processed using an R-package GGIR (28) (http://cran.r-project.org). Data were extracted, and the average magnitude of dynamic acceleration was corrected for gravity (Euclidean Norm minus 1g)) averaged over 5-s epochs and expressed in milligravitational units (mg). Files were excluded if they showed postcalibration error greater than (10 mg) or did not contain at least 4 valid days of measurement, each consisting of ≥16 h of wear time. The duration of the sleep window was calculated using automated sleep detection (28) (HDCZA sleep detection algorithm [29]). Physical activity variables, calculated as average minutes per day, were classified as time spent sedentary (<40 mg excluding the sleep period) (30), in light physical activity (LPA; 40–100 mg), moderate physical activity (MPA; 100–400 mg vigorous physical activity (VPA; >400 mg) (31), and moderate-to-vigorous physical activity (MVPA; >100 mg). MVPA data were expressed in bouts of ≥1 min (where 80% of the activity was above the threshold) to avoid capturing very short incidental activity (31).

Blood sampling and biochemical analysis. Venous blood samples were taken from an antecubital vein in the fasted state on the morning of study visits. Blood samples were drawn into chilled EDTA monovettes (Sarstedt, Leicester, United Kingdom) and centrifuged immediately at 3500 rpm for 10 min at 4°C. Plasma supernatant was then removed, aliquoted, and stored at −80°C for later analysis.

A semi-automated clinical chemistry benchtop analyzer (Pentra 400; Horiba Medical, Montpellier, France) was used to determine plasma concentrations of glucose (Horiba Medical) and NEFA (Randox Laboratories Ltd, County Antrim, United Kingdom) using colorimetric methods. Plasma insulin concentrations were measured by an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). The coefficient of variation for the glucose, NEFA, and insulin analyses were 0.57%, 0.64%, and 4.61%, respectively. The adipose tissue insulin resistance index (ADIPO-IR) was calculated as fasting plasma NEFA ($mmol \cdot L^{-1}$) × fasting plasma insulin ($pmol \cdot L^{-1}$) (7).

Statistical analysis. Statistical analyses were performed using SPSS version 27.0 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov tests were performed to check the distribution of the data. Participant characteristics are shown as mean ± SD for normally distributed data, median (interquartile range) for non-normally distributed data, and number (percentage) for categorical data. Generalized linear models with a normal distribution and identity link function were used to assess the independent associations of physical activity and sedentary time (exposure variables) with ADIPO-IR (outcome variable). Three models were ran as follows: 1) basic model adjusted for study and waking hours (continuous); 2) adjusted for the previous variables plus age (continuous), sex (men/women), and ethnicity (White European/South Asian); and 3) adjusted for the previous variables plus BMI (continuous). LPA and VPA were not considered separately in the analysis because of multicollinearity between LPA and sedentary time, whereas median VPA was less than 1 min per day. Where significant associations were observed, interaction terms were subsequently added to model 3 to assess whether these associations were moderated by ethnicity, sex, age, and BMI. To facilitate interpretation, significant interactions between continuous variables were stratified into tertiles to describe the direction of the interaction. Statistical significance was considered $P < 0.05$ for main effects and $P < 0.10$ for interactions (given that interaction analyses have lower statistical power).

Sensitivity analysis. Because some participants were taking statins only (n = 36), metformin only (n = 5), or both (n = 10) (which lower circulating NEFA [32] and glucose), we performed a sensitivity analysis by removing individuals taking these medications (n = 126) to determine whether their use impacted the associations of physical activity and sedentary time with ADIPO-IR. Furthermore, given that our sample included both participants with T2DM (n = 32) and those at

TABLE 1. Participant characteristics (all cohort and stratified by sex).

	All (n = 179)	Male (n = 111)	Female (n = 68)
Demographic variables			
Age, yr	66.2 (66.0–70.8)	66.0 (58.1–71.0)	66.4 (62.0–70.6)
Ethnicity (White European), %	122 [68.2]	76 [68.5]	46 [67.6]
BMI, kg·m^{-2}	31.1 (28.0–34.4)	31.7 (28.0–34.3)	30.9 (28.0–34.7)
Body fat (n = 176), %	36.4 ± 8.0	32.8 ± 7.3	42.2 ± 5.1
No. participants diagnosed with T2DM, %	32 [17.9]	32 [28.8]	0 [0]
Metformin use (no statins; n = 177), %	5 [2.8]	5 [4.5]	0 [0]
Statin use (no metformin; n = 177), %	36 [20.2]	24 [21.6]	12 [17.6]
Metformin and statin use (n = 177), %	10 [5.6]	10 [9]	0 [0]
Fasted metabolic variables			
Glucose, mmol·L^{-1}	5.2 (4.4–5.9)	5.6 (5.0–6.4)	5.0 (4.7–5.4)
Insulin, pmol·L^{-1}	75.4 (52.8–103.5)	77.4 (56.9–107.5)	68.1 (45.9–93.2)
NEFA, mmol·L^{-1}	0.52 (0.38–0.68)	0.50 (0.36–0.67)	0.54 (0.40–0.78)
HOMA-IR, AU	3.43 ± 1.93	3.83 ± 2.05	2.80 ± 1.55
ADIPO-IR, AU	43.0 ± 26.6	43.6 ± 26.4	42.1 ± 27.3
Physical activity variables			
Waking hours, min·d^{-1}	968 ± 76	971 ± 75	964 ± 77
Sedentary time, min·d^{-1}	670 ± 99	677 ± 97	659 ± 103
Light PA, min·d^{-1}	225 ± 72	219 ± 75	233 ± 65
Vigorous PA, min·d^{-1}	0.9 (0.2–2.0)	0.9 (0.2–2.2)	0.9 (0.4–1.8)
1-min bouted MVPA, min·d^{-1}	24 (11–43)	27 (13–49)	18 (10–37)

Data are presented as mean ± SD, median (interquartile range), or number [column percentage].
HOMA-IR, homeostatic assessment for insulin resistance; PA, physical activity.

high risk (n = 147), we also examined associations of physical activity and sedentary time with ADIPO-IR within these individual groups. Independent-sample t-tests for normally distributed and Mann–Whitney U tests for non-normally distributed data were used to assess differences in participant characteristics between the whole cohort and the sensitivity cohort (i.e., with those taking statins and/or metformin removed). For the sensitivity analysis, identical generalized linear models and interaction terms were subsequently run in the sensitivity cohort. Additional models were also run to confirm whether the main results were consistent when body fat percentage was included as a covariate in place of BMI.

RESULTS

Participant characteristics. The demographic, metabolic, and physical activity characteristics of all participants are presented in Table 1. A total of 179 participants (median age, 66.2 (66.0–70.8) yr; 62.0% male) with valid physical activity data were pooled in this analysis. All participants were classified as either having or being at high risk of T2DM (with either overweight or obesity (median BMI, 31.1 kg·m^{-2}; interquartile range, 28.0–34.4 kg·m^{-2}), elevated hepatic steatosis, and/or non-diabetic hyperglycemia). Furthermore n = 5 (2.8%) were taking metformin only (no statins), n = 36 (20.2%) were taking statins only (no metformin), and n = 10 (5.6%) were taking both metformin and statins. On average, participants were sedentary for 670 min (11 h 10 min) per day and were performing 24 min of MVPA per day.

The participant characteristics of the cohort stratified by either White European (n = 122 (68.2%); median age, 66.6 yr; 62.3% male) or South Asian ethnicity (n = 57 (31.8%); median age, 66.0 yr; 61.4% male) are shown in Supplemental Table 2 (see Supplemental Digital Content, Participant characteristics stratified by ethnicity, http://links.lww.com/MSS/C854). BMI and body fat percentage were significantly higher in White Europeans compared with South Asians (all P < 0.05), whereas vigorous physical activity levels were significantly lower (P = 0.003). All other demographic, metabolic, and physical activity variables were similar between ethnicities.

Sedentary time. Table 2 shows the associations of device-assessed sedentary time with ADIPO-IR. In model 1, sedentary time (per 30 min) was positively associated with ADIPO-IR (2.34 (1.02–3.66) arbitrary unit (AU)). After further adjustments for demographics (model 2) and BMI (model 3), the positive association remained such that each 30 min of sedentary time was associated with a 1.80 (0.51–3.06) AU higher ADIPO-IR. To explore whether this association was independent of participants' MVPA levels, we conducted an additional model that was further adjusted for MVPA. This model revealed that sedentary time was positively associated with ADIPO-IR independent of MVPA (2.52 (1.05–3.96) AU; P < 0.001).

Moderate-to-vigorous physical activity. Associations between device-assessed MVPA and ADIPO-IR are

TABLE 2. Associations of device-measured sedentary time and physical activity with ADIPO-IR

	Sedentary Time (Per Minute)		Sedentary Time (Per 30 min)		1-min Bouted MVPA (Per Minute)		1-min Bouted MVPA (Per 10 min)	
n = 179	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Model 1 ADIPO-IR	0.078 (0.034 to 0.122)	**<0.001**	2.34 (1.02 to 3.66)	**<0.001**	−0.065 (−0.192 to 0.062)	0.315	−0.65 (−1.92 to 0.63)	0.315
Model 2 ADIPO-IR	0.079 (0.034 to 0.123)	**<0.001**	2.37 (1.02 to 3.69)	**<0.001**	−0.060 (−0.191 to 0.071)	0.372	−0.60 (−1.91 to 0.71)	0.372
Model 3 ADIPO-IR	0.060 (0.017 to 0.102)	**0.006**	1.80 (0.51 to 3.06)	**0.006**	0.023 (−0.104 to 0.150)	0.718	0.23 (−1.04 to 1.50)	0.718

Model 1: adjusted for study and waking hours. Model 2: adjusted for model 1 + age, sex, and ethnicity. Model 3: adjusted for model 2 + BMI.
Values in bold font indicate statistical significance (P < 0.05).

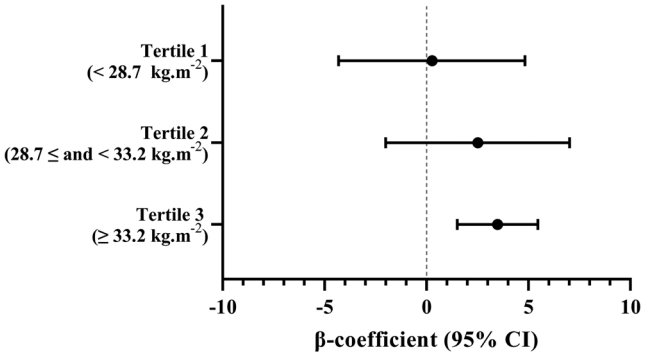

FIGURE 2—Forest plot showing the interaction of BMI within the association between device-measured sedentary time (per 30 min) and ADIPO-IR (n = 179).

presented in Table 2. In models 1–3, MVPA was not significantly associated with ADIPO-IR.

Interaction analyses. Interaction analyses found that associations were not modified by ethnicity (P = 0.894), sex (P = 0.415), or age (P = 0.171). However, results were modified by BMI (P = 0.005; Fig. 2). Across BMI tertiles, the association between sedentary time and ADIPO-IR strengthened at higher BMIs, with the most pronounced relationship seen with BMI values ≥33.2 kg·m^{-2} (tertile 3).

Sensitivity analyses. After the removal of participants taking statins and/or metformin, a total of 126 participants were included in a sensitivity analyses. No significant differences in participant characteristics were evident between this cohort and the whole study cohort ($P \geq 0.072$; see Supplemental Table 3, Supplemental Digital Content, Participant characteristics for whole study cohort vs those not taking statins and/or metformin, http://links.lww.com/MSS/C854). For this sensitivity cohort, Supplemental Table 4 shows the generalized linear model analyses examining associations of sedentary time and MVPA with ADIPO-IR, whereas Supplemental Table 5 details the related interaction analyses (see Supplemental Digital Content, http://links.lww.com/MSS/C854). Overall, the pattern of results in this sensitivity cohort was similar to those reported for the full cohort. In the other sensitivity analysis, we examined associations between our exposure and outcome variables separately in those with (n = 32) and at high risk of T2DM (n = 147) (see Supplemental Table 6, Supplemental Digital Content, Participant characteristics for participants not diagnosed with T2DM vs those diagnosed with T2DM, http://links.lww.com/MSS/C854). Again, the pattern of results was similar to the combined (full) cohort; however, the P values approached statistical significance in the smaller T2DM cohort (see Supplemental Tables 7 and 8, Supplemental Digital Content, Associations of device-measured sedentary time and physical activity with ADIPO-IR on those not diagnosed with T2DM and on those diagnosed with T2DM, http://links.lww.com/MSS/C854). Furthermore, the results of the main study analysis remained consistent when models were adjusted for body fat percentage in place of BMI (see Supplemental Tables 9 and 10, Supplemental Digital Content, Associations of device-measured sedentary time and physical activity with ADIPO-IR, and Interaction analyses with ethnicity, sex, age, and body fat percentage for device-measured sedentary time, http://links.lww.com/MSS/C854).

DISCUSSION

Our primary finding is that sedentary time is positively associated with ADIPO-IR, independent of MVPA and other confounding variables. This association remained evident in sensitivity analyses excluding participants taking glucose- and lipid-lowering medications and was particularly strong in those with higher BMI values. Conversely, no associations were seen between MVPA and ADIPO-IR.

Adipose tissue insulin resistance is defined as an impaired cellular (adipocyte) response to insulin, resulting in exaggerated lipolysis and/or impaired lipogenesis (3). It manifests in response to adipocyte stress, commonly associated with obesity, adipocyte hypertrophy, and low-grade inflammation (3). Our analyses demonstrate that sedentary time is positively related to ADIPO-IR, with every 30 min of device-measured sedentary time associated with a 2.5-unit higher ADIPO-IR. Importantly, this relationship is independent of key confounding variables. To contextualize the magnitude of this association, our previous meta-regression (21) identified an opposing yet similar strength association whereby each kilogram of exercise-induced weight loss was associated with a 2.7-unit lower ADIPO-IR. Adipose tissue inflammation may mechanistically link sedentary time and adipose tissue insulin resistance, with numerous studies showing that greater volumes of sedentary time are positively related to biomarkers of chronic inflammation (22). Given the pathophysiological link between exaggerated adipose lipolysis, ectopic lipid deposition (skeletal muscle, liver, pancreas) (16), and insulin resistance, impaired adipose tissue insulin sensitivity may mechanistically link excess sedentary time with hyperglycemia and cardiovascular disease risk.

Accumulating evidence suggests that sedentary time and MVPA are independent behaviors with distinct metabolic health impacts (33). Our data support this notion as the association between sedentary time and ADIPO-IR remained after statistically controlling for MVPA. Although our observational data cannot elucidate mechanisms, our findings are supported by data from bedrest studies that provide an extreme physiological model of sedentary behavior (34). Specifically, formal exercise training is unable to overcome many adverse metabolic effects, including alterations to lipid metabolism and ectopic fat deposition (34). Our data imply that chronic low-level muscle contraction is necessary for the maintenance of adipocyte sensitivity to insulin, although experimental trials are needed to confirm this notion and identify responsible mechanisms.

Within our analyses, we explored whether BMI, age, sex, and ethnicity moderated associations between activity behaviors and ADIPO-IR (24–26). These variables were chosen *a priori* given that each influences body composition, fat localization, and metabolic characteristics of adipocytes. BMI

was found to moderate the relationship between sedentary time and ADIPO-IR, with stronger associations seen in those with higher levels of BMI. It is possible that the more deleterious cardiometabolic profile typically seen in those with higher BMI values, including higher circulating insulin and NEFA concentrations, provided a greater scope for sedentary time to influence ADIPO-IR. The lack of mediating influence of ethnicity (White European vs South Asian) was unexpected in our study as South Asians have been found to be more insulin resistant than White Europeans when adiposity is normalized (35). This notion was evident within our data set whereby South Asians had a similar ADIPO-IR despite a lower BMI and body fat percentage. Furthermore, ethnic-based differences in adipocyte structure and function have been reported (36), prompting our hypothesis that stronger associations between activity behaviors and ADIPO-IR would be seen in South Asians than in White Europeans.

Within our study, we conducted sensitivity analyses that 1) excluded participants who were taking statins or metformin (~30% of the study cohort) and 2) assessed associations between our exposure and outcome variables separately in participants with T2DM (18% of the cohort) and those at high risk (82% of the cohort). The first analysis was necessary as statins lower circulating NEFA concentrations (32), while metformin improves glucose regulation in people with impaired glycemic control. The second analysis was also warranted given that people with T2DM exhibit a more severe metabolic profile, and many were also taking metformin. Overall, these sensitivity analyses demonstrated that the independent association between sedentary time and ADIPO-IR was consistent across our primary and sensitivity analyses, albeit with marginally weaker β-coefficients in the non-medicated sample as well as the group composed solely of individuals with T2DM. However, it should be noted that the small sample sizes in these groups may have contributed to the weaker effect in the latter analyses. One difference between the whole cohort and sensitivity cohort (non-medicated sample) was that BMI moderated the association between sedentary time and ADIPO-IR in the former but not the latter. Given that the β-coefficients within interaction analyses were similar between cohorts across tertiles of BMI, reduced statistical power with the smaller sample size may similarly explain the absence of the BMI interaction in the sensitivity cohort.

In our analyses, MVPA was unrelated to ADIPO-IR, in the both the whole study and sensitivity cohorts. Based on our recent systematic review and meta-analysis (21), this outcome was somewhat unexpected. Specifically, although limited to pre-to-post intervention analyses (without non-exercise control groups), we previously found that structured exercise training reduced ADIPO-IR. Furthermore, many observational studies have documented inverse associations between MVPA and indices of whole-body insulin sensitivity (including fasting insulin) (37,38), whereas insulin sensitivity is typically improved in response to physical activity interventions in healthy individuals and those with insulin resistance/hyperglycemia (39,40). Given that our sample had notably raised circulating insulin concentrations, with circulating NEFA modestly elevated, it is not clear why an inverse association between MVPA and ADIPO-IR was not apparent. It may be relevant that vigorous-intensity physical activity was negligible in our sample, whereas participants' moderate-intensity physical activity would primarily derive from incidental movement behaviors given our study exclusion criteria prohibiting regular, purposeful exercise. Consequently, the intensity of these behaviors may have been insufficient to influence the components of ADIPO-IR.

Key strengths of this study include the 24-h assessment of physical activity/movement behaviors with highly sensitive accelerometery and the diversity of the sample, which permitted interaction analyses. Limitations include the indirect measurement of adipose tissue insulin resistance via ADIPO-IR, rather than direct measurement through an insulin-clamp with stable-isotope tracer (glycerol and/or palmitate tracer). Participants' VPA totaled less than 1 $min \cdot d^{-1}$, meaning that specific relationships with this movement behavior could not be assessed; therefore, further analyses are required in cohorts exhibiting a greater range of times spent in VPA. Furthermore, the causal nature of these findings cannot be determined from our cross-sectional analyses, with intervention studies needed to confirm our findings. Alternative compositional approaches such as isotemporal substitution and compositional data analysis could be used to provide some insight. However, given the cross-sectional (observational) nature of our data, the current approach was adopted to avoid overstating the implications of our findings and should be interpreted simply as hypothesis-generating with which to inform future prospective studies.

CONCLUSIONS

In a population with or at high risk of T2DM, this study has shown that sedentary time is positively associated with adipose tissue insulin resistance, independent of MVPA, with stronger associations seen in people with higher BMIs. Conversely, MVPA was unrelated to adipose tissue insulin resistance. Our observational findings suggest that greater sedentary time may impair the ability of insulin to regulate adipose tissue lipolysis and/or lipogenesis, which may potentially contribute to ectopic lipid deposition, insulin resistance, and heightened cardiometabolic risk.

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