Association of Habitual Daily Physical Activity With Glucose Tolerance and β-Cell Function in Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes From the Restoring Insulin Secretion (RISE) Study

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OBJECTIVE

We examined the relationship between habitual daily physical activity and measures of glucose tolerance, insulin sensitivity, and β-cell responses in adults with impaired glucose tolerance (IGT) or drug-naive, recently diagnosed type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants included 230 adults (mean ± SD age 54.5 ± 8.5 years, BMI 35 ± 5.5 kg/m^2; 42.6% women) who underwent a 3-h oral glucose tolerance test (OGTT) and hyperglycemic clamp. Wrist accelerometers worn for 7 consecutive days measured total physical activity counts (TAC) (daily mean 233,460 [~50th percentile for age]). We evaluated whether TAC was associated with fasting plasma glucose, OGTT 2-h plasma glucose or glucose incremental area under the curve (G-iAUC), hyperglycemic clamp measures of insulin sensitivity (steady-state glucose infusion rate/insulin [M/I]) and β-cell responses (acute C-peptide response to glucose, steady-state C-peptide, and maximal β-cell response), and OGTT C-peptide index (ΔC-peptide$_{0–30}$/Δglucose$_{0–30}$).

RESULTS

After adjustments for confounders, there was no association of TAC with fasting plasma glucose, 2-h glucose, or G-iAUC. Higher TAC was associated with higher insulin sensitivity (M/I). After adjusting for M/I, higher TAC was not associated with measures of β-cell response.

CONCLUSIONS

In adults with IGT or drug-naive, recently diagnosed type 2 diabetes, higher levels of habitual physical activity are associated with higher insulin sensitivity. Further studies are needed to understand why higher levels of physical activity are not associated with better β-cell response.

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**A complete list of the RISE Consortium Investigators can be found in the Supplementary Data online.*

It is estimated that more than 30 million people in the U.S. have diabetes, with an additional 84 million having prediabetes (1). Included in the risk factors for developing diabetes, as well as for developing complications, is physical inactivity. Physical activity is a key modifiable risk factor shown to improve glucose tolerance (2–4), insulin sensitivity (5,6), β-cell function (5), and durability of glycemic control (7). In addition, large clinical trials have shown that increased physical activity can lower diabetes risk in individuals with impaired glucose tolerance (8–10). It has been estimated that physical inactivity is responsible for 7% of the burden of disease of type 2 diabetes (11).

A variety of methods are available to assess physical activity. One method is to rely on self-report using validated questionnaires. Another is to use intensity-specific cut points to group physical activity into bouts, including light, moderate, moderate to vigorous, and vigorous physical activity. More recently, it has been shown that using total physical activity counts per day (TAC) is a better indicator of total volume of physical activity (12–14) because TAC also captures data on light physical activity, thereby incorporating the full continuum of intensities of physical activity. Further, TAC is an important variable for assessing total daily physical activity because it takes into account frequency, intensity, and duration of various activity bouts and condenses them into one single value.

There is a limited amount of research about the metabolic impact of physical activity in individuals with impaired glucose tolerance (IGT) or those with recently diagnosed, untreated type 2 diabetes under free-living conditions. TAC has been shown to have a stronger association with insulin and other biomarkers of endocrine function (11,13) than self-reported minutes of moderate to vigorous physical activity. Results vary between studies, however, and some studies are limited to fasting measures for assessing insulin sensitivity. The primary purpose of this study, therefore, was to examine the relationships between habitual daily physical activity (TAC) and measures of glucose tolerance, insulin sensitivity, and β-cell responses in adults with IGT or drug-naive, recently diagnosed type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants

We performed a cross-sectional analysis of data obtained during the run-in and baseline phase of the Restoring Insulin Secretion (RISE) Adult Medication Study, a randomized controlled trial. Between 2013 and 2017, participants were recruited from the active patient populations and communities at three RISE adult centers: *1*) University of Chicago and Jesse Brown Veterans Affairs (VA) Medical Center, *2*) Indiana University, and *3*) VA Puget Sound Health Care System and the University of Washington. Individuals at high risk for IGT and type 2 diabetes who met other study inclusion/exclusion criteria were screened with a 75-g oral glucose tolerance test (OGTT) and HbA_{1c} measurement. Those with fasting plasma glucose 5.3–6.9 mmol/L (95–125 mg/dL) plus elevated 2-h glucose ($\geq$7.8 mmol/L [$\geq$140 mg/dL]) and HbA_{1c} $\leq$7.0% (53 mmol/mol) were eligible. Individuals with self-reported diabetes who were diagnosed for $<$1 year and drug-naive were also eligible. Additional details on participant recruitment and eligibility criteria have been described elsewhere (15), and detailed information is available on the RISE website (https://rise.bsc.gwu.edu/web/rise/collaborators).

For this analysis, we included a subset of all participants in the adult medication study who completed all baseline procedures (n = 267) and who also had 7 days of wrist actigraphy (n = 230). Classification of glucose tolerance was based on the American Diabetes Association OGTT criteria for fasting and 2-h glucose (16).

All participants gave written informed consent, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board.

Anthropometric Measurements

Anthropometric measurements were performed with participants wearing light clothing without shoes. Height was measured in a fully vertical position with the heels together using a calibrated stadiometer. Weight was measured using a calibrated electronic scale, zeroed before each measurement. Both measurements were performed twice (three times if the first two values differed too widely), and the average value was reported. From these measurements, BMI was calculated as weight (kg)/[height (m)]^2. Waist and hip circumferences were measured using a fiberglass (nonstretching) tape, with waist measured at the midpoint between the top of the iliac crest and the bottom of the costal margin in the midaxillary line, in a horizontal plane. Hip circumference was measured in a horizontal plane encompassing the greater femoral trochanters.

Blood pressure was measured using calibrated automated devices, with appropriately sized arm cuffs. Pressure was measured in a seated position with feet touching the floor or otherwise supported after at least 5 min rest in a quiet room, with outer clothing removed and sleeves rolled loosely to the shoulder. The cuff was placed at heart level, with two measurements taken 5 min apart. The second measurement was used as the value of record.

Procedures

Following a 10-h overnight fast, a 75-g OGTT was performed. Blood samples were collected through an indwelling intravenous catheter 10 and 5 min prior to and 10, 20, 30, 60, 90, 120, 150, and 180 min after glucose ingestion (15,17).

A two-stage hyperglycemic clamp was performed on a different day following a 10-h overnight fast with goal glucose levels of 11.1 and $>$25 mmol/L (200 and $>$450 mg/dL, respectively), the latter including administration of the nonglucose secretagogue arginine. These target glucose levels were achieved using boluses and a variable-rate intravenous infusion of dextrose, the rate being determined by a computerized algorithm developed by the RISE Consortium (15,18,19), combined with bedside glucose monitoring. A full description of this method has been published previously (19).

For both procedures, all blood samples were collected on ice and immediately thereafter were separated and frozen at −80°C. All frozen samples were then shipped to the central biochemistry laboratory at the University of Washington for subsequent measurement of plasma glucose, C-peptide, and insulin.

Assays

Glucose was measured by the glucose hexokinase method using Roche reagent on a c501 autoanalyzer (Roche). C-peptide and insulin were measured by a two-site immunoenzymometric

assay performed on the Tosoh 2000 autoanalyzer (Tosoh Bioscience, Inc., South San Francisco, CA). The interassay coefficients of variation on quality control samples with low, medium, medium-high, and high concentrations were 2.0% for glucose, 4.3% for C-peptide, and 3.5% for insulin. Further details on these assays have been published (19). All measures are presented in Système International units. These can be converted to conventional units using standard conversion factors with the exception of insulin, for which 0.134 should be used.

Calculations for OGTT-Derived Measurements

The inverse of fasting insulin was used as a surrogate estimate of insulin sensitivity (20). The C-peptide index (CPI) (ΔC-peptide$_{0–30}$/Δglucose$_{0–30}$) and insulinogenic index (IGI) (Δinsulin$_{0–30}$/Δglucose$_{0–30}$) were calculated using the 0- and 30-min samples from the OGTT (21,22). Individuals were classified as having IGT or type 2 diabetes based on the 2-h glucose concentration at the screening visit (16). The incremental glucose area under the curve (G-iAUC) response above the fasting concentration over the 3-h sampling period was calculated using the trapezoidal method and used as a measure of glucose tolerance.

Calculations for Clamp-Derived Measurements

Insulin sensitivity (M/I) was quantified as the mean of the glucose infusion rate (M) at 100, 110, and 120 min of the glucose clamp procedure, expressed per kilogram of body weight and corrected for urinary glucose loss, divided by the mean steady-state plasma insulin concentration at these same time points (I) (23–25).

Acute (first-phase) C-peptide response to glucose (ACPR$_g$) was calculated as the mean incremental response above baseline (average of −10 and −5 min) from samples drawn at 2, 4, 6, 8, and 10 min after intravenous dextrose administration (20). Steady-state (second-phase) C-peptide concentration was calculated as the mean of the respective measurements at 100, 110, and 120 min of the hyperglycemic clamp (24). Acute C-peptide response to arginine at maximal glycemic potentiation (>25 mmol/L [>450 mg/dL]) (ACPR$_{max}$) was calculated as the mean concentration in samples drawn 2, 3, 4, and 5 min after arginine injection minus the average concentration of the samples drawn 1 and 5 min prior to arginine (26).

Accelerometer Measurements

All participants wore the Actiwatch Spectrum (Philips Respironics, Murrysville, PA) on their wrist for 7 consecutive days. The Actiwatch Spectrum is an uniaxial, omnidirectional piezoelectric, water-resistant accelerometer used to measure sleep and physical activity patterns (27). It continuously collects acceleration/deceleration data at a sampling rate of 32 Hz; data are then averaged over intervals called "epochs" and recorded as an activity "count." If no physical activity occurs during the epoch, such as during sleep or rest, "0" is recorded as the activity count for that epoch. Participants were instructed to wear the device on their nondominant wrist, and to not remove the device for the duration of the 7 days, except for lengthy water activities (e.g., swimming) and for bathing if they preferred. They were instructed in the use of the event marker on the actigraph and were asked to press the marker upon getting into or out of bed. In addition, participants were instructed to continue their "usual" sleep and activities while wearing the device. They also completed a sleep diary upon awakening each morning, in which they documented time to bed, latency to sleep, time awake, time out of bed, and any naps taken.

Actigraphs were preprogrammed centrally at the University of Chicago core reading center to collect physical activity and light intensity in 30-s epochs. Upon return of the actigraph and sleep diary to the reading center, data were downloaded for subsequent analysis. Data were preprocessed using the Actiware (Philips Respironics, Murrysville, PA) software available from the manufacturer (27). Nonwear time was automatically excluded using a built-in galvanic sensor that identified when the device was worn. Rest and wake intervals were manually determined using a previously published standardized actigraphy scoring algorithm based on four inputs: event markers, sleep diary, white light intensity, and physical activity in order of importance, respectively (28). Wake intervals were exclusive of the daily major rest interval and were used to determine daily TAC. An epoch was scored as "immobile" if there were two or less activity counts during that 30-s period. %Immobility is the percentage of all epochs during the wake interval that were scored as "immobile." All studies were scored by one of the study investigators (B.M.), who was blinded to the results of OGTT and hyperglycemic clamps. Actiwatch accelerometer counts are moderately and significantly correlated with indirect calorimetry-measured energy expenditure during routine physical activity in adults (29–31).

Statistical Analysis

Data were stored and managed centrally, and analyses were performed according to a prespecified analytic plan. All analyses were cross-sectional. Outcomes of interest were HbA_{1c}; parameters from the OGTT including fasting glucose, fasting insulin, fasting C-peptide, 2-h glucose, and G-iAUC from 0–180 min; measures of β-cell response from the OGTT including IGI and CPI; measures of β-cell response from the hyperglycemic clamp including ACPR$_g$, ACPR$_{max}$, and steady-state C-peptide; and measures of insulin sensitivity including M/I from the hyperglycemic clamp and the inverse of fasting insulin from the OGTT. Descriptive statistics are presented as percentages, mean ± SD, or geometric means and 95% CIs for nonnormally distributed data; for the geometric means, *P* values from the log-transformed data were calculated. Comparisons between groups were computed using ANOVA for continuous variables and χ^2 tests for categorical variables. Except where noted, *P* values <0.05 were considered nominally statistically significant, with no adjustments made for multiple tests.

Linear regression models were used to explore the relationship between physical activity parameters (TAC and %Immobility) and measures of glycemia, insulin sensitivity, and β-cell responses from the hyperglycemic clamp and OGTT. Linear regression models were adjusted for age, sex, race/ethnicity, BMI, and waist circumference. Measures of β-cell response were also adjusted for M/I (clamp-derived insulin sensitivity). Models used natural logarithmically transformed M/I and β-cell response variables owing to the skewed distribution of these data. Prior to taking logs, we added a constant of 1.06 to the ACPR$_g$

because of negative values in this β-cell response variable.

Quartiles of physical activity based on the TAC were defined among the study sample. Least square means and 95% CIs for each physical activity quartile adjusted for age, sex, race/ethnicity, BMI, and waist circumference were calculated. Measures of β-cell response were also adjusted for log M/I, the clamp-derived measure of insulin sensitivity. *P* values for the linear trend of the quartiles are presented. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 230 adults completed 7 days of wrist actigraphy and all baseline testing in the RISE Study. This cohort comprised 98 (42.6%) women and 132 (57.4%) men, with 169 (73.5%) having IGT and 61 (26.5%) having recently diagnosed, drug-naive type 2 diabetes at screening. The mean ± SD age was 54.5 ± 8.5 years, BMI was 35.0 ± 5.5 kg/m^2, and TAC was 233,460 ± 76,748 (Tables 1 and 2).

Across the quartiles of TAC, there was no significant difference in age, BMI, sex, or race/ethnicity. Weight ($P = 0.020$) and waist circumference ($P = 0.006$) were significantly different across the four quartiles, with the least active quartile having the highest weight and waist circumference (Table 1).

Across the quartiles of TAC, objectively measured sleep duration by actigraphy did not differ significantly. In contrast, total immobility time and %Immobility were significantly different across the quartiles ($P < 0.001$), with the greatest amount of immobility (29.6%) in the least active quartile and the lowest amount of immobility (12.2%) in the most active quartile.

Table 2 summarizes the unadjusted metabolic measures from the OGTT and hyperglycemic clamp across the quartiles of TAC. In an unadjusted comparison, fasting glucose, 2-h glucose, and G-iAUC did not differ across TAC quartiles. Fasting insulin differed significantly across quartiles when sampled with the OGTT ($P = 0.033$) and the clamp ($P = 0.009$), with the highest levels of insulin (126.47 and 119.10 pmol/L, respectively) in the quartile with the lowest physical activity. Fasting C-peptide similarly differed significantly in samples from both the OGTT ($P = 0.033$) and the clamp ($P = 0.032$), with the highest levels of C-peptide (1.40 and 1.32 nmol/L, respectively) in the quartile with the lowest physical activity. Insulin sensitivity, as assessed by 1/fasting insulin ($P = 0.033$) with the OGTT and by M/I ($P = 0.0002$) from the clamp, was significantly different across the quartiles of TAC, with the lowest insulin sensitivity seen in the quartile with the lowest physical activity.

In unadjusted analyses, the IGI did not differ across the quartiles of TAC ($P = 0.111$), but the CPI trended toward a relationship with TAC ($P = 0.053$), with the lowest CPI being seen with higher physical activity (Table 2). The relationship of TAC with insulin and C-peptide responses measured during the clamp varied. Clamp-derived steady-state insulin ($P = 0.012$) and C-peptide ($P = 0.002$) were lowest in the quartile with the highest level of physical activity (512.86 pmol/L and 3.46 nmol/L, respectively), concordant with the OGTT-derived CPI observation. Neither $ACPR_g$ nor $ACPR_{max}$ differed across quartiles of TAC (Table 2).

Adjusted associations of TAC and %Immobility as continuous variables with measures of glycemia, insulin sensitivity, and β-cell responses are shown in Table 3. In linear regression models adjusting for age, sex, race/ethnicity, BMI, and waist circumference, both higher TAC and lower %Immobility were associated with increased insulin sensitivity (M/I) ($P = 0.0210$ and $P = 0.010$, respectively).

Table 1—Select baseline physical and demographic characteristics by quartiles of TAC

	All (n = 230)	First quartile (least active) (n = 57)	Second quartile (n = 58)	Third quartile (n = 57)	Fourth quartile (most active) (n = 58)	P value
Demographics						
Age (years)	54.5 ± 8.5	56.1 ± 7.8	55.2 ± 8.7	53.7 ± 8.5	53.2 ± 9.0	0.237
Female	98 (42.6)	16 (28.1)	26 (44.8)	26 (44.8)	30 (52.6)	0.058
Race/ethnicity						0.064
White	126 (54.8)	36 (63.2)	33 (56.9)	34 (58.6)	23 (40.4)	
Black	75 (32.6)	18 (31.6)	15 (25.9)	17 (29.3)	25 (43.9)	
Hispanic (any race)	13 (5.7)	1 (1.8)	7 (12.1)	3 (5.2)	2 (3.5)	
Other	16 (7.0)	2 (3.5)	3 (5.2)	4 (6.9)	7 (12.3)	
Weight (kg)	102.3 ± 18.4	108.3 ± 18.7	97.8 ± 14.7	101.1 ± 18.9	102.0 ± 19.8	0.020
Waist circumference (cm)	112.3 ± 13.1	116.3 ± 13.6	108.3 ± 11.7	110.6 ± 11.6	114.0 ± 14.2	0.006
BMI (kg/m^2)	35.0 ± 5.5	36.1 ± 6.0	34.1 ± 5.0	34.4 ± 4.9	35.3 ± 5.9	0.170
Hip circumference (cm)	116.7 ± 11.0	119.5 ± 11.3	114.2 ± 9.7	115.6 ± 10.0	117.6 ± 12.3	0.053
Systolic BP (mmHg)	126.7 ± 13.5	127.4 ± 12.3	128.8 ± 13.1	125.3 ± 13.0	125.2 ± 15.6	0.431
Diastolic BP (mmHg)	77.19 ± 10.65	76.98 ± 11.25	78.84 ± 9.61	77.28 ± 9.82	75.63 ± 11.81	0.452
Actigraphy measurements						
Sleep time (min)	394.29 ± 57.71	407.81 ± 60.27	393.14 ± 56.81	396.67 ± 61.05	379.53 ± 49.93	0.072
Activity duration (min)	995.55 ± 110.00	962.07 ± 55.89	994.21 ± 68.71	1,017.72 ± 170.49	1,007.83 ± 100.79	0.038
Immobile time (min)	197.87 ± 87.35	284.48 ± 66.35	224.25 ± 63.57	160.69 ± 65.43	122.25 ± 52.18	<0.001
%Immobility	20.13 ± 8.78	29.63 ± 6.65	22.77 ± 6.31	15.93 ± 5.04	12.23 ± 4.90	<0.001
TAC	233,460 ± 76,748	144,718 ± 22,954	198,476 ± 16,871	251,579 ± 16,984	339,364 ± 44,015	<0.001
Activity counts/min	235.28 ± 77.27	150.50 ± 24.34	199.45 ± 18.69	251.83 ± 27.50	339.68 ± 51.71	<0.001

Data are n (%) or mean ± SD. "Other" for race/ethnicity includes mixed, Asian, American Indian, and other. Actigraphy measurements are the daily average over 7 days of use. *P* values represent comparisons across the four quartiles by ANOVA, using native scale data for normally distributed variables or log-transformed data otherwise. BP, blood pressure.

Table 2—Baseline measures of glycemic parameters, insulin sensitivity, and β-cell responses from the hyperglycemic clamp and OGTT by quartiles of TAC

	All (n = 230)	First quartile (least active) (n = 57)	Second quartile (n = 58)	Third quartile (n = 57)	Fourth quartile (most active) (n = 58)	P value
Glycemic characteristics						
Diabetes at screening						0.116
Diabetes	61 (26.5)	11 (19.3)	22 (37.9)	13 (22.4)	15 (26.3)	
IGT	169 (73.5)	46 (80.7)	36 (62.1)	45 (77.6)	42 (73.7)	
HbA_{1c} (%)	5.76 ± 0.40	5.69 ± 0.40	5.82 ± 0.42	5.77 ± 0.41	5.77 ± 0.35	0.372
HbA_{1c} (mmol/mol)	39.49 ± 4.35	38.72 ± 4.36	40.16 ± 4.64	39.52 ± 4.53	39.53 ± 3.79	0.372
OGTT parameters						
Fasting glucose (mg/dL)	111.29 ± 11.64	109.47 ± 13.47	112.23 ± 13.04	111.53 ± 9.07	111.90 ± 10.54	0.585
Fasting glucose (mmol/L)	6.18 ± 0.65	6.08 ± 0.75	6.23 ± 0.72	6.19 ± 0.50	6.21 ± 0.59	0.585
2-h glucose (mg/dL)	181.18 ± 39.98	173.63 ± 36.81	190.81 ± 44.82	179.69 ± 37.49	180.46 ± 39.35	0.138
2-h glucose (mmol/L)	10.06 ± 2.22	9.64 ± 2.04	10.59 ± 2.49	9.97 ± 2.08	10.02 ± 2.18	0.138
Fasting insulin (pmol/L)	107.77 [35.96, 322.98]	126.47 [35.37, 452.14]	105.64 [31.34, 356.1]	108.85 [46.86, 252.85]	92.76 [35.5, 242.35]	0.033
Fasting C-peptide (nmol/L)	1.26 ± 0.52	1.40 ± 0.70	1.30 ± 0.49	1.21 ± 0.38	1.13 ± 0.43	0.033
1/Fasting insulin ($\times 10^{-3}$ 1/[pmol/L])	9.30 [3.10, 27.87]	7.92 [2.22, 28.33]	9.39 [2.79, 31.66]	9.12 [3.92, 21.17]	10.80 [4.14, 28.23]	0.033
IGI (pmol/mmol)	113.3 [28.17, 455.59]	135.64 [30.58, 601.6]	111.05 [27.62, 446.57]	113.3 [40.89, 313.94]	97.51 [20.33, 467.78]	0.111
CPI (nmol/mmol)	0.41 [0.14, 1.19]	0.5 [0.16, 1.52]	0.41 [0.14, 1.19]	0.41 [0.19, 0.89]	0.37 [0.11, 1.26]	0.053
G-iAUC (mg/dL · min)	10,788.88 ± 4,365.34	9,923.13 ± 4,100.54	11,977.89 ± 4,958.50	10,757.19 ± 4,062.26	10,454.87 ± 4,097.72	0.076
G-iAUC (mmol/L · min)	599.38 ± 242.52	551.28 ± 227.81	665.44 ± 275.47	597.62 ± 225.68	580.83 ± 227.65	0.076
Clamp variables						
Fasting glucose (mg/dL)	110.02 ± 10.13	109.15 ± 10.19	110.54 ± 11.11	109.56 ± 10.70	110.81 ± 8.46	0.794
Fasting glucose (mmol/L)	6.11 ± 0.56	6.06 ± 0.57	6.14 ± 0.62	6.08 ± 0.59	6.15 ± 0.47	0.794
Fasting insulin (pmol/L)	103.54 [35.93, 298.39]	119.1 [43.83, 323.63]	106.7 [34.91, 326.1]	106.7 [41.65, 273.36]	85.63 [29.14, 251.64]	0.009
Fasting C-peptide (nmol/L)	1.22 ± 0.47	1.32 ± 0.42	1.29 ± 0.57	1.19 ± 0.40	1.08 ± 0.45	0.032
Steady-state insulin (pmol/L)	632.7 [157.34, 2,544.27]	788.4 [233.88, 2,657.66]	601.85 [161.87, 2,237.69]	651.97 [213.32, 1,992.61]	512.86 [91.4, 2,877.85]	0.012
Steady-state C-peptide (nmol/L)	3.9 [1.92, 7.89]	4.44 [2.42, 8.15]	3.9 [1.96, 7.74]	3.9 [2.12, 7.15]	3.46 [1.52, 7.87]	0.002
M/I ($\times 10^{-5}$ mmol/kg/min per pmol/L)	3.00 [0.72, 12.56]	2.32 [0.61, 8.78]	3.03 [0.71, 12.94]	3.03 [0.9, 10.23]	3.90 [0.8, 19.06]	0.002
$ACPR_g$ (nmol/L)	1.73 [0.98, 3.06]	1.84 [1.02, 3.31]	1.67 [0.91, 3.06]	1.72 [1.09, 2.69]	1.68 [0.9, 3.15]	0.241
$ACPR_{max}$ (nmol/L)	4.81 [2.03, 11.39]	5.05 [2.05, 12.45]	4.81 [2.03, 11.39]	4.85 [2.13, 11.06]	4.48 [1.82, 11.04]	0.566

Data are n (%), mean ± SD, or geometric mean [95% CI] for nonnormally distributed data. P values represent comparisons across the four quartiles by ANOVA, using native scale data for normally distributed variables or log-transformed data otherwise.

Table 3—Adjusted relationships of activity parameters as continuous variables with measures of glycemia, insulin sensitivity, and β-cell responses from the hyperglycemic clamp and OGTT

Association	β coefficients	SE	*P* value
Effect of TAC (per 10,000 counts)			
HbA_{1c} (mmol/mol)	0.0048	0.0368	0.8964
Fasting glucose (mmol/L)	0.0098	0.0057	0.0893
2-h glucose (mmol/L)	0.0105	0.0203	0.6037
Log fasting insulin (pmol/L)	−0.0085	0.0048	0.0747
Fasting C-peptide (nmol/L)	−0.0059	0.0045	0.1860
Log IGI† (pmol/mmol)	−0.0103	0.0053	0.0547
Log CPI† (nmol/mmol)	−0.0089	0.0046	0.0549
G-iAUC (0–180 min) (mmol/L · min)	−0.6352	2.2339	0.7764
Log M/I ($\times 10^{-5}$ mmol/kg/min per pmol/L)	0.0139	0.0060	0.0210*
Log 1/fasting insulin [$\times 10^{-3}$ 1/(pmol/L)]	0.0085	0.0048	0.0747
Log $ACPR_{max}$† (nmol/L)	−0.0010	0.0038	0.7959
Log $ACPR_g$† (nmol/L)	−0.0013	0.0025	0.6167
Log steady-state C-peptide† (nmol/L)	−0.0018	0.0022	0.4212
Percent time immobile (per 1%)			
HbA_{1c} (mmol/mol)	0.0044	0.0315	0.8882
Fasting glucose (mmol/L)	−0.0069	0.0049	0.1619
2-h glucose (mmol/L)	−0.0115	0.0174	0.5092
Log fasting insulin (pmol/L)	0.0067	0.0041	0.1046
Fasting C-peptide (nmol/L)	0.0063	0.0038	0.0990
Log IGI index† (pmol/mmol)	0.0071	0.0046	0.1262
Log CPI† (nmol/mmol)	0.0060	0.0040	0.1332
G-iAUC (0–180 min) (mmol/L · min)	0.0483	1.8802	0.9795
Log M/I ($\times 10^{-5}$ mmol/kg/min per pmol/L)	−0.0132	0.0051	0.0105*
Log 1/fasting insulin ($\times 10^{-3}$ 1/[pmol/L])	−0.0067	0.0041	0.1046
Log $ACPR_{max}$† (nmol/L)	−0.0007	0.0032	0.8195
Log $ACPR_g$† (nmol/L)	0.0007	0.0022	0.7512
Log steady-state C-peptide† (nmol/L)	0.0010	0.0019	0.6014

Linear regression models adjusted for age, sex, race/ethnicity, BMI, and waist circumference. †Measures of β-cell response are adjusted for age, sex, race/ethnicity, BMI, waist circumference, and M/I (insulin sensitivity). *$P < 0.05$.

There was no association of HbA_{1c}, fasting glucose, 2-h glucose, G-iAUC, or fasting C-peptide with either TAC or %Immobility.

In order to more fully assess associations of TAC and %Immobility with measures of β-cell response, we performed linear regression models adjusting for M/I and also adjusting for age, sex, race/ethnicity, BMI, and waist circumference (Table 3). There was no significant association of TAC or %Immobility with IGI, CPI, steady-state C-peptide, $ACPR_g$, or $ACPR_{max}$.

Figure 1 illustrates the adjusted means with 95% CIs by quartile of TAC for selected outcome measures. There was no difference in TAC across the quartiles for HbA_{1c}, 2-h glucose, or G-iAUC (data not shown). Insulin sensitivity as measured by M/I was significantly increased with higher TAC ($P = 0.005$). Looking at quartiles of TAC, no linear trend was seen for IGI, CPI, steady-state C-peptide, $ACPR_g$, or $ACPR_{max}$.

CONCLUSIONS

In this cross-sectional analysis of adults with either IGT or drug-naive, recently diagnosed type 2 diabetes, we demonstrated that higher levels of physical activity and lower levels of %Immobility were associated with higher levels of insulin sensitivity after controlling for age, sex, race/ethnicity, BMI, and waist circumference. We further showed that with added adjustment for M/I (insulin sensitivity), higher TAC was not associated with measures of β-cell response.

Several studies have illustrated the usefulness of TAC as a valid and objective measure of daily physical activity (12–14). TAC provides a better estimate of total daily physical activity volume because it includes light physical activity as well as higher intensity physical activity. Our cohort had a mean TAC of 233,460 ± 76,748, which is similar to that shown in other population-based studies (14) and is at approximately the 50th percentile for age compared with data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES) (13).

A study that looked at the impact of physical activity on insulin sensitivity in patients with newly diagnosed type 2 diabetes showed that the number of footsteps per day and the amount of moderate to vigorous physical activity were positively associated with insulin sensitivity (6). Using the 2003–2006 NHANES data, Wolff-Hughes et al. (32) showed a strong inverse association of TAC with fasting plasma glucose, insulin, and C-peptide. Boyer et al. (13) examined this group further and determined that surrogate measures of insulin sensitivity (HOMA of insulin resistance and quantitative insulin sensitivity check index) showed a significant inverse association with TAC, which was much stronger than the association with moderate to vigorous physical activity.

In our cohort, the association of TAC was more robust with M/I than with fasting insulin, in keeping with M/I being a more precise measure of insulin sensitivity. While adjusted fasting insulin levels were 19.8% lower in the highest quartile of TAC versus the lowest quartile, adjusted insulin sensitivity (M/I) was 31.5% higher. After adjusting for insulin sensitivity (M/I), we did not see any difference in OGTT and clamp-based measures of β-cell response (IGI, CPI, steady-state C-peptide, $ACPR_g$, and $ACPR_{max}$). This observation is in keeping with the changes in β-cell responses being the result of those in insulin sensitivity and thereby reflecting no overall change in β-cell function (33). To date it remains unclear why exercise and/or physical activity can improve insulin sensitivity without significantly improving β-cell function.

Several studies looking at the effect of exercise training (34) as well as the relationship with total physical activity (5,6,13,35) have shown that increased physical activity is related to enhanced insulin sensitivity. A few studies, including a randomized clinical trial, however, have shown that neither increased physical activity nor exercise directly increase β-cell response (6,34). In older subjects without known diabetes, 6 months of exercise training improved insulin sensitivity; however, glucose tolerance did not change because of reciprocal changes in β-cell responses and

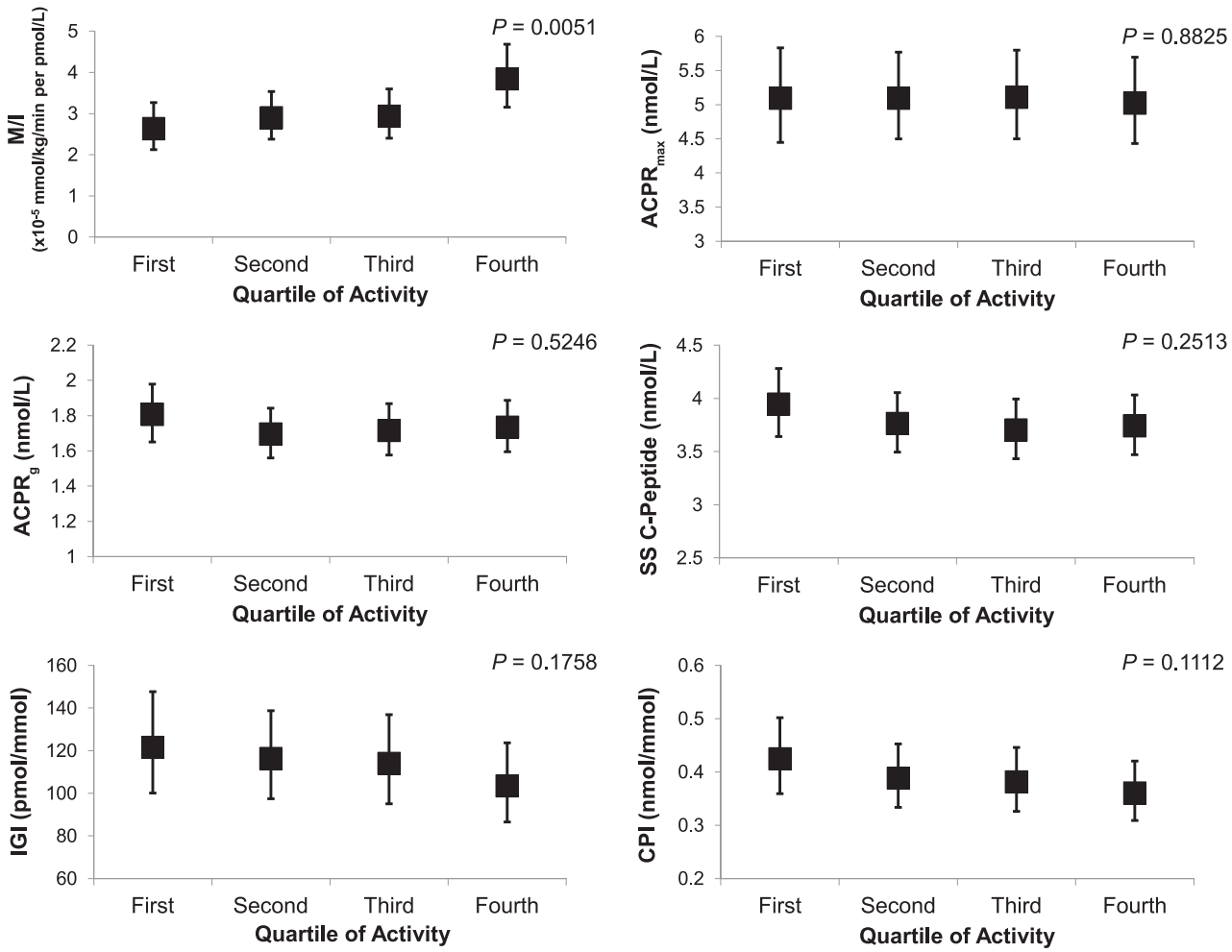

Figure 1—Adjusted means by quartiles of TAC. Relationship of log-transformed dependent variables with independent variables (TAC). Data shown are least square means and 95% CI for each activity quartile adjusted for age, sex, race/ethnicity, BMI, and waist circumference. Steady-state (SS) C-peptide, $ACPR_g$, $ACPR_{max}$, IGI, and CPI are also adjusted for log M/I (insulin sensitivity). *P* values for linear trend.

thus no change in β-cell function (36,37). The Resistance Versus Aerobic Exercise in Type 2 Diabetes (RAED2) trial (34) examined the effect of either aerobic training or resistance training upon insulin sensitivity and β-cell function in participants with type 2 diabetes. Both aerobic and resistance training led to similar reductions in HbA_{1c} levels and increased insulin sensitivity but had no effect on β-cell function. The Verona Newly Diagnosed Type 2 Diabetes Study (VNDS) (6) looked at free-living physical activity measures in individuals with newly diagnosed type 2 diabetes. Daily physical activity and accompanying energy expenditure improved insulin sensitivity but had no effect on β-cell function. Conversely, Færch et al. (5) demonstrated that in individuals with prediabetes, an increase in self-reported moderate to vigorous physical activity over 5 years was associated with a concordant increase in fasting insulin sensitivity (S) as measured by HOMA-S, as well as a decrease in fasting β-cell function (β) as measured by HOMA-β. Another study looking at self-reported physical activity in Mexican American adults showed that higher levels of physical activity were significantly associated with lower fasting insulin levels and increased β-cell function, as measured by the disposition index (35).

Our study has several noteworthy strengths. Our cohort was ethnically diverse and participants were recruited from different regions in the U.S. The use of TAC is an important strength because it provides a continuous measure of physical activity that weights each 30-s epoch according to the frequency and intensity of the movement, allowing it to serve as a proxy for total volume of physical activity over multiple days. To reduce variability, actigraphy scoring was performed centrally following a standardized actigraphy scoring algorithm (28). Several studies have shown that TAC has the strongest association with biomarkers of endocrine function, including glucose and insulin (13,14,32,38). Another strength of this study is the use of sophisticated and quantitative methodologies, such as the 3-h OGTT and hyperglycemic clamp, to assess insulin sensitivity, glucose tolerance, and β-cell responses. Further, the biochemical assays were all performed in a central laboratory, allowing for direct comparison of insulin sensitivity and β-cell function across all study participants.

Our study has some limitations. The cross-sectional nature of the study limits any potential inferences regarding causality. We chose a relatively conservative

physical activity count cutoff of two activity counts per 30-s epoch to detect immobile time, representing a small portion of total sedentary time. A less conservative estimate of immobile or sedentary time might show a relationship of %Immobility to measures of glycemia, insulin sensitivity, or β-cell response. It is possible that a larger sample size might find a significant association between physical activity and clamp- or OGTT-based measures of β-cell response. Our study design did not include individuals with normal glucose tolerance. As a result, we are limited in assessing whether increased physical activity would have a similar effect in these individuals, and therefore our results are not generalizable across all populations. Lastly, although TAC appears to be the best measure to assess total volume of physical activity in free-living conditions, total physical activity may still be underestimated because accelerometers cannot capture data on nonambulatory movements such as resistance training and swimming.

In conclusion, our results indicate that higher TAC in a population with IGT or recently diagnosed, drug-naive type 2 diabetes is associated with better insulin sensitivity. These data complement those from other studies that looked at the impact of physical activity on insulin sensitivity. Taken together, our data emphasize the potential for physical activity as an adjunct to weight loss to prevent or delay the onset of type 2 diabetes or its complications.

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Author Contributions. Members of the RISE Consortium recruited participants and collected study data. K.A.T. and B.M. proposed the analysis. A.H.T. and S.L.E. performed the analysis. K.A.T. interpreted the data and wrote the first draft, which was also reviewed and edited by A.H.T., K.M.A., E.B., T.S.H., K.J.M., K.M.U., S.L.E., D.A.E., and B.M. The RISE Steering Committee reviewed and edited the manuscript and approved its submission. A.H.T., S.L.E., and B.M. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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