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ARTICLE

Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health

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Abstract
Aims/hypothesis The study aimed to examine the associations between objectively measured sedentary time, breaks in sedentary time, moderate-to-vigorous physical activity (MVPA) and total physical activity with markers of cardiometabolic health in a population with known risk factors for type 2 diabetes mellitus.
Methods This study reports data from two ongoing diabetes prevention programmes. Participants with known risk factors were recruited from primary care practices located within the East Midlands, UK, over the period 2010–2011. ActiGraph GT3X accelerometers (15 s epochs) were used to assess sedentary time (<25 counts per 15 s), MVPA (≥488 counts per 15 s) and total physical activity (total counts). A break was considered as any interruption in sedentary time (≥25 counts per 15 s). Linear regression examined the independent association of sedentary time, breaks in sedentary time, MVPA and total physical activity with markers of cardiometabolic health.
Results The sample comprised 878 participants; 153 from Project STAND (Sedentary Time And Diabetes) (age 32.9±5.6 years, 28.8% male) and 725 from Walking Away from Diabetes (age 63.7±7.8 years, 64.8% male). Following adjustment for various covariates, including MVPA and BMI, there were detrimental linear associations of sedentary time with 2 h plasma glucose (standardised beta coefficient) (β=0.220, p<0.001), triacylglycerol (β=0.206, p=0.001) and HDL-cholesterol (β=−0.123, p=0.029). Breaks in sedentary time, total physical activity and MVPA were significantly inversely associated with measures of adiposity, but not with any other cardiometabolic variables after adjustment for sedentary time and BMI.
Conclusions/interpretation In adults at high risk of type 2 diabetes mellitus, time spent sedentary is strongly and

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adversely associated with cardiometabolic health and may be a more important indicator of poor health than MVPA.

Keywords Breaks in sedentary time · High risk · Physical activity · Primary care · Sedentary behaviour · Type 2 diabetes mellitus

Abbreviations

CVD	Cardiovascular disease
FPG	Fasting plasma glucose
IFG	Impaired fasting glycaemia
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IMD	Index of multiple deprivation
MVPA	Moderate-to-vigorous physical activity
MET	Metabolic equivalent
STAND	Sedentary Time and Diabetes
WA	Walking Away from Type 2 Diabetes

Introduction

Sedentary behaviour has previously been characterised as ≤1.5 metabolic equivalents (METs) [1, 2]. METs are the energy cost of physical activity and are expressed as multiples of resting metabolic rate, where one MET (or 3.5 ml $min^{-1}kg^{-1}$) is equivalent to a typical metabolism at rest. Given the fact it is impractical to measure energy expenditure in most studies and there are limited behaviours that involve both sitting and energy expenditure (>1.5 METs), a more operational behavioural interpretation has been recommended whereby sedentary behaviour is defined as any non-exercise sitting time [3]. Over the last decade, sedentary behaviour has emerged as a distinctive behavioural paradigm with detrimental effects on chronic disease risk, independent of moderate-to-vigorous intensity physical activity (MVPA) [4–8]. This new paradigm is conceptualised around two constructs: total time spent sedentary and the number of breaks in sedentary time (e.g. rising from a sitting/lying position to a more active state, including standing). Both expressions show strong associations with markers of cardiometabolic health independent of each other and other lifestyle behaviours [4–6, 8, 9].

Traditionally, epidemiological evidence examining the effect of sedentary time on health has tended to focus on self-report measures [6, 10–12], but these are prone to bias and have poor levels of validity [13]. Although more recent studies employing objective measures of sedentary behaviour have been reported, the effect of age on the association between sedentary time and cardiometabolic risk remains unclear, and most studies have been conducted in the general population without reference to specific risk factors [4, 5, 8, 14, 15]. It is therefore unclear to what extent the reported associations are generalisable to those at high risk of chronic disease. This is an important limitation as international recommendations and policies specify that chronic disease prevention strategies should include targeted interventions aimed at the identification and management of high-risk individuals [16–18]. Therefore, the importance of sedentary behaviour in this group needs to be better understood in order to inform the content and structure of prevention programmes.

In this study, we examined the extent to which sedentary time, breaks in sedentary time, MVPA and total physical activity are independently associated with cardiometabolic risk factors in a population with known risk factors for type 2 diabetes mellitus. We hypothesised that all four constructs would be independently associated with health in both younger and older adults.

Methods

Participants This study used combined baseline data from two prevention studies, the Walking Away from Type 2 Diabetes Study (WA; ISRCTN31392913) and Project STAND (Sedentary Time And Diabetes; ISRCTN08434554), 2010–2011. Both trial protocols have been published elsewhere [19, 20]. Briefly, WA is a randomised controlled trial investigating whether a lifestyle intervention programme can promote behaviour change in those identified as being at high risk of type 2 diabetes mellitus. Similarly, Project STAND is a randomised controlled trial investigating the effect of structured education and self-monitoring on reducing sedentary time in young adults with known risk factors for type 2 diabetes mellitus.

Individuals were unaware of their diabetes risk status before entering the two studies, and all participants were excluded if they had known type 2 diabetes mellitus or were taking steroids. Baseline measurements across both studies were performed before treatment allocation by the same team of trained staff, who followed identical standard operating procedures. Informed consent was obtained from all eligible participants, and both studies gained full ethical approval from the Nottingham Research Ethics Committee.

Walking Away from Type 2 Diabetes Study Middle-aged and older adults (aged up to 74 years) were recruited from ten primary care practices within Leicestershire, UK. Individuals at high risk of impaired glucose regulation (IGR; a composite of impaired glucose tolerance [IGT] and/or impaired fasting glycaemia [IFG] or type 2 diabetes mellitus) were identified using a modified version of the automated Leicester Risk Score, specifically designed to be

administered in primary care [21]. An automated platform using medical records was used to rank individuals for diabetes risk using predefined weighted variables (age, sex, BMI, family history of type 2 diabetes mellitus and use of antihypertensive medication). Those scoring within the 90th percentile in each practice were invited to take part in the study. This approach has been shown to have reasonable sensitivity and specificity for identifying participants with a high risk of IGR [21].

Project STAND Young adults who were at risk of developing type 2 diabetes mellitus from across Leicestershire and the South East Midlands region were recruited from primary care practices. Practice databases were searched for participants meeting the following inclusion criteria: (1) aged 18–40 years with a BMI in the obese range (≥30 kg/m^2; ≥27.5 kg/m^2 for south Asian participants) or (2) aged 18–40 years with a BMI in the overweight range ≥25 kg/m^2 (≥23 kg/m^2 for south Asian participants) plus one additional risk factor; a family history of type 2 diabetes mellitus or cardiovascular disease (CVD), previous gestational diabetes, polycystic ovarian syndrome, HbA_{1c} ≥5.8% (40 mmol/mol) or IGR [22].

Cardiovascular, metabolic and anthropometric outcomes Markers of metabolic and cardiovascular health were measured, including fasting plasma glucose (FPG) and 2 h plasma glucose (via an OGTT), HbA_{1c}, total cholesterol, HDL-cholesterol and triacylglycerol. Venous blood samples were obtained following an overnight fast and all assays were measured in the same laboratory located within the Leicester Royal Infirmary, UK. Analysis was conducted by individuals blinded to the patients' identity, using stable methodologies, standardised to external quality assurance values. Plasma glucose was analysed in venous samples via the hexokinase method. HbA_{1c} was analysed using the Bio-Rad Variant II HPLC system (Bio-Rad Clinical Diagnostics, Hemel Hempstead, UK). HDL-cholesterol and triacylglycerol were measured using standard enzymatic techniques.

Body weight (Tanita TBE 611; Tanita, West Drayton, UK) and waist circumference (midpoint between the lower costal margin and iliac crest) were measured to the nearest 0.1 kg and 0.5 cm, respectively. Information on current smoking status, medication and ethnicity was obtained following an interview administered protocol with a healthcare professional. Social deprivation was determined by assigning an Index of Multiple Deprivation (IMD) score to the participant's resident area [23]. IMD scores are publicly available continuous measures of compound social and material deprivation that are calculated using a variety of data, including current income, employment, education and housing.

Accelerometer measures Participants were asked to wear a triaxial accelerometer (ActiGraph GT3X, Pensacola, FL, USA) on the right midaxillary line of the hip (attached via a waistband), for a minimum of seven consecutive days during waking hours. These accelerometers translate raw accelerations into activity counts. Accelerometers were initialised to record activity in 5 s epochs in the STAND cohort and 15 s epochs in the WA cohort. During each sampling interval (5 s or 15 s), all registered activity counts were summed and stored in the monitor memory. In order to allow for direct comparison, all data from the STAND cohort were reintegrated into 15 s epochs. Freedson cut-points were used to categorise each epoch as sedentary (<25 counts per 15 s), light-intensity physical activity (≥25 to <488 counts per 15 s) or MVPA (≥488 counts per 15 s) [24]. Breaks in sedentary time were defined as a transition from a sedentary (<25 counts per 15 s) to an active state (≥25 counts per 15 s) [4, 8]. Total physical activity counts represented the summation of counts within each epoch.

Non-wear time was defined as a minimum of 60 min of continuous zero counts and days with at least 600 min wear time were considered valid [4, 5, 14]. In order for data to be included in the analysis, participants required at least four valid days of measurement [25].

All accelerometer-derived variables (sedentary time, MVPA, breaks in sedentary time and total counts) were computed by summing the values over all valid days and calculating the mean value per valid day.

An accelerometer data analysis tool (ActiSci, Hadleigh, UK) was used to process the accelerometer data.

Statistical analysis Statistical analyses were performed using PASW Statistics v18.0 (Chicago, IL, USA). Due to their skewed distribution, FPG, 2 h glucose, HDL-cholesterol, triacylglycerol and total:HDL cholesterol ratio were log-transformed (log_{10}).

Forced-entry linear regression analysis was used on the combined study cohorts to examine the independent associations of sedentary time, total physical activity, breaks in sedentary time and MVPA with markers of metabolic (FPG, 2 h glucose, HbA_{1c}, waist circumference, BMI) and cardiovascular health (triacylglycerol, HDL-cholesterol and total: HDL cholesterol ratio).

Model 1 was adjusted for age, sex, smoking status, ethnicity, social deprivation, lipid lowering and beta-blocker medication, family history of type 2 diabetes mellitus and time the accelerometer was worn (average min/day). Model 2 was additionally adjusted for MVPA time (min/day), and the associations for breaks, MVPA and total physical activity were examined having also adjusted for sedentary time (min/day). In order to examine the extent to which adiposity may attenuate these relationships, model 3 was further adjusted for BMI.

Significant associations were followed up with interaction terms to assess differences in the strength of the associations between sedentary time, breaks in sedentary time, total physical activity and MVPA by study group and sex, adjusted for the covariates listed in model 2. To further represent the strength of sedentary time and breaks in sedentary time with cardiometabolic markers, variables were also examined as tertiles using analysis of covariance procedures.

In order to enable direct comparison to previous published studies, a sensitivity analysis was conducted to investigate whether results were affected by integrating the measure of sedentary time to 60 s epochs.

Two-tailed $p \leq 0.05$ or less were considered statistically significant for main effects. Adjustment was not made for multiple comparisons; therefore data were viewed with caution and in relation to the overall pattern of results. A value $p<0.1$ was considered significant for interactions. Due to log-transformation, and to allow for direct comparisons across cardiometabolic markers, results of the linear regression analysis are presented as the standardised beta coefficient (β)±SE.

Results

In total, 153 younger participants from Project STAND (age 32.9±5.6 years, 28.8% male) and 725 older participants from WA (age 63.7±7.8 years, 64.8% male) had valid measures of both objective activity and biochemical variables. This equated to 87% of the combined cohort. The majority of excluded participants failed to meet the minimum accelerometer wear time requirement. Those included in this analysis had a similar ethnic breakdown and social deprivation score compared with those who did not reach the minimum accelerometer criteria. However, those excluded were more likely to be younger (51.3±14.6 vs 58.4±13.8 years; $p<0.001$) and have a larger waist circumference (105.4±15.4 vs 101.6±12.0 cm; $p<0.001$) and higher BMI (34.6±6.7 vs 32.5±5.2 kg/m^2; $p<0.001$). Table 1 reports the demographic, cardiometabolic, anthropometric and accelerometer characteristics of included participants.

Accelerometer wear time (Project STAND 14.5±1.4 vs WA 14.4±1.4 h/day) and sedentary time (10.3±1.5 vs 10.3±1.5 h/day) were similar between study cohorts. The younger Project STAND cohort spent a longer time engaged in MVPA (interquartile range; 0.7 [0.4–0.9] vs 0.5 [0.3–0.9] h/day).

Overall sedentary time showed a moderate inverse correlation with total physical activity ($r=-0.34$, $p<0.001$) and MVPA ($r_s=-0.36$, $p<0.001$) and a small inverse correlation with breaks ($r=-0.111$, $p=0.001$). MVPA had a small association with breaks ($r=0.23$, $p<0.001$) and was strongly correlated with total physical activity ($r=0.88$, $p<0.001$). Furthermore, total physical activity displayed a moderate correlation with the number of breaks ($r=0.31$, $p<0.001$)

Table 2 displays the adjusted associations in the combined cohort of sedentary time, total physical activity, MVPA and number of breaks in sedentary time with biomedical and anthropometric markers.

Sedentary time After adjustments for known confounders, including MVPA and BMI, sedentary time showed a detrimental association with 2 h glucose (β=0.220±0.060, $p<0.001$), HDL-cholesterol (β=−0.123±0.056, $p=0.029$) and triacylglycerol (β=0.206±0.061, $p=0.001$).

Total physical activity Total physical activity was inversely associated with a multitude of cardiometabolic factors, including 2 h glucose (β=−0.164±0.035, $p<0.001$), waist circumference (β=−0.270±0.032, $p<0.001$), BMI (β=−0.281±0.051, $p<0.001$), triacylglycerol (β=−0.173±0.036, $p<0.001$), total:HDL cholesterol ratio (β=−0.126±0.034, $p<0.001$) and HDL-cholesterol (β=0.160±0.033, $p<0.001$). Associations with biochemical factors were weakened after further adjustment for sedentary time, with only the association with HDL-cholesterol remaining significant. However, associations between total physical activity and measures of adiposity were largely unaffected by adjustment for sedentary time.

MVPA Time in MVPA was significantly inversely associated with 2 h glucose (β=−0.121±0.035, $p<0.001$), triacylglycerol (β=−0.149±0.036, $p<0.001$), total:HDL cholesterol ratio (β=−0.124±0.034, $p<0.001$), HDL-cholesterol (β=0.150±0.033, $p<0.001$), BMI (β=−0.241±0.031, $p<0.001$) and waist circumference (β=−0.270±0.033, $p<0.001$). However, after adjustment for sedentary time, only BMI (β=−0.215±0.041, $p<0.001$) and waist circumference (β=−0.228±0.043, $p<0.001$) remained significant.

Breaks in sedentary time Independent of known confounders (including sedentary time), breaks in sedentary time were significantly inversely associated with 2 h glucose (β=−0.111±0.055, $p=0.046$) waist circumference (β=−0.215±0.051, $p<0.001$) and BMI (β=−0.151±0.049, $p=0.003$). However, further adjustment for BMI attenuated the association with 2 h glucose.

All results reported above were unaffected if waist circumference rather than BMI was used in model 3.

Figure 1 illustrates the associations between sedentary time and 2 h glucose, triacylglycerol and HDL-cholesterol when examined as tertiles. Figure 2 shows the association of breaks with waist circumference and BMI.

Interaction analyses indicated a significant effect for study cohort, with the older cohort demonstrating greater

Table 1 Demographics, metabolic, anthropometric and accelerometer characteristics of participants

Characteristics	STAND (n=153)	Walking Away (n=725)	All (n=878)
Age (years)	32.9±5.6	63.7±7.8	58.4±13.8
Male	44	470	514
Current smokers	57 (37.3)	62 (8.6)	119 (13.6)
Family history of diabetes (first degree)	100 (65.4)	261 (36.0)	361 (41.1)
Cardiometabolic variables			
BMI (kg/m^2)	34.6±4.8	31.2±5.3	32.5±5.2
Waist circumference (cm)	102.9±13.5	101.3±11.7	101.6±12.0
Weight (kg)	98.3±17.3	91.5±16.5	92.7±16.9
FPG (mmol/l)	4.8 (4.5–5.1)	5.2 (4.9–5.6)	5.1 (4.8–5.5)
2 h plasma glucose (mmol/l)	5.3 (4.5–6.4)	6.1 (4.9–7.8)	5.9 (4.8–7.5)
Body fat (%)	40.5±7.2	35.6±8.7	36.5±8.6
Total cholesterol (mmol/l)	4.8 (4.2–5.4)	5.1 (4.3–5.9)	5.0 (4.3–5.8)
HDL-cholesterol (mmol/l)	1.2 (1.0–1.4)	1.4 (1.1–1.6)	1.3 (1.1–1.6)
Total:HDL cholesterol ratio (mmol/l)	3.9 (3.2–4.7)	3.7 (3.0–4.4)	3.8 (3.0–4.5)
Triacylglycerol (mmol/l)	1.30 (0.90–1.70)	1.30 (1.00–1.80)	1.30 (1.00–1.80)
Lipid-lowering medication	1 (0.7)	240 (33.1)	241 (27.4)
Beta-blockers	2 (1.3)	127 (17.5)	129 (14.7)
HbA_{1c} (%)	5.6 (5.3–5.8)	5.9 (5.6–6.1)	5.8 (5.6–6.1)
HbA_{1c} (mmol/mol)	38 (34–40)	41 (38–43)	40 (38–43)
Ethnicity			
White European	128 (83.7)	645 (89.0)	773 (88.0)
South Asian	15 (9.8)	53 (7.3)	68 (7.8)
Other	10 (6.5)	27 (3.7)	37 (4.2)
Diagnosis			
Normal glucose tolerance	137 (89.6)	512 (70.6)	649 (73.9)
Isolated IFG	3 (2.0)	38 (5.2)	41 (4.7)
Isolated IGT	11 (7.2)	124 (17.1)	135 (15.4)
Both	1 (0.7)	31 (4.3)	32 (3.6)
Type 2 diabetes mellitus	1 (0.7)	20 (2.8)	21 (2.4)
All (IGR)	16 (10.5)	214 (29.5)	230 (26.2)
Accelerometer variables (h/day)			
Time accelerometer worn	14.5±1.4	14.4±1.4	14.4±1.4
Sedentary time	10.3±1.5	10.3±1.5	10.3±1.5
Light-intensity activity	3.5±0.9	3.5±0.9	3.5±0.9
MVPA	0.7 (0.4–0.9)	0.5 (0.3–0.9)	0.6 (0.3–0.9)
Accelerometer variables (percentage at each activity level)			
Sedentary time	70.5±7.6	71.5±7.8	71.0±8.0
Light-intensity activity	24.3±6.5	24.3±6.3	24.3±6.4
MVPA	4.7 (2.8–6.2)	3.7 (2.1–5.9)	3.9 (2.3–6.0)
Breaks per day	297±68	273±60	277±62
Total physical activity counts (×1,000/day)	274±109	253±126	257±123
Average steps per day	7,153±2,954	6,993±3,384	7,016±3,313

Continuous parametric results as mean±SD, number (column percentage) and continuous non-parametric results as median (interquartile range)

Sedentary time=<25 counts per 15 s, light-intensity activity ≥25 to <488 counts per 15 s, and MVPA ≥488 counts per 15 s

associations of MVPA and total physical activity with BMI (p for interaction <0.001) and waist circumference (p for interaction <0.001). For breaks in sedentary time, the same pattern was observed, with the older cohort achieving a stronger association for waist circumference (p for interaction <0.001) and BMI (p for interaction <0.001). No other significant interactions were observed for the effect of study group. In addition, there were no significant interactions for sex in the results for sedentary time, total physical activity, MVPA or breaks.

Table 2 Multiple linear regression models for sedentary time, total physical activity, MVPA and breaks in sedentary time with cardiometabolic variables

Variable	Sedentary time (<25 counts per 15 s) β (SE)[a]	*p* value	Total physical activity (cpm) β (SE)[b]	*p* value	MVPA (≥488 counts per 15 s) β (SE)[b]	*p* value	Breaks β (SE)[c]	*p* value
Model 1								
2 h glucose (mmol/l)	0.238 (0.045)	<0.001	−0.164 (0.035)	<0.001	−0.121 (0.035)	<0.001	−0.180 (0.038)	<0.001
Waist circumference (cm)	0.250 (0.043)	<0.001	−0.270 (0.032)	<0.001	−0.270 (0.033)	<0.001	−0.198 (0.037)	<0.001
BMI (kg/m^2)	0.210 (0.041)	<0.001	−0.281 (0.051)	<0.001	−0.241 (0.031)	<0.001	−0.148 (0.035)	<0.001
Triacylglycerol (mmol/l)	0.217 (0.045)	<0.001	−0.173 (0.036)	<0.001	−0.149 (0.036)	<0.001	−0.150 (0.040)	<0.001
Fasting glucose (mmol/l)	0.046 (0.045)	0.308	−0.068 (0.058)	0.248	−0.033 (0.036)	0.488	−0.024 (0.038)	0.777
Total:HDL cholesterol ratio	0.130 (0.043)	0.003	−0.126 (0.034)	<0.001	−0.124 (0.034)	<0.001	−0.114 (0.037)	0.003
HDL-cholesterol (mmol/l)	−0.187 (0.042)	<0.001	0.160 (0.033)	<0.001	0.150 (0.033)	<0.001	0.130 (0.036)	<0.001
HbA_{1c} (%)	0.035 (0.050)	0.489	0.031 (0.035)	0.379	−0.034 (0.046)	0.464	−0.021 (0.038)	0.590
Model 2								
2 h glucose (mmol/l)	0.235 (0.060)	<0.001	−0.038 (0.073)	0.494	−0.033 (0.047)	0.473	−0.111 (0.055)	0.046
Waist circumference (cm)	0.091 (0.057)	0.113	−0.259 (0.070)	<0.001	−0.228 (0.043)	<0.001	−0.215 (0.051)	<0.001
BMI (kg/m^2)	0.054 (0.053)	0.327	−0.247 (0.055)	<0.001	−0.215 (0.041)	<0.001	−0.151 (0.049)	0.003
Triacylglycerol (mmol/l)	0.214 (0.062)	0.001	−0.067 (0.060)	0.266	−0.042 (0.048)	0.385	−0.046 (0.056)	0.418
Fasting glucose (mmol/l)	0.023 (0.062)	0.714	−0.040 (0.035)	0.257	−0.021 (0.048)	0.662	−0.011 (0.038)	0.903
Total:HDL cholesterol ratio	0.101 (0.058)	0.085	−0.085 (0.070)	0.120	−0.075 (0.045)	0.096	−0.075 (0.054)	0.167
HDL-cholesterol (mmol/l)	−0.137 (0.056)	0.016	0.120 (0.052)	0.022	0.083 (0.044)	0.060	0.071 (0.052)	0.175
HbA_{1c} (%)	0.014 (0.051)	0.836	0.024 (0.056)	0.670	−0.013 (0.036)	0.725	−0.035 (0.056)	0.537
Model 3								
2 h glucose (mmol/l)	0.220 (0.060)	<0.001	−0.017 (0.057)	0.766	−0.019 (0.055)	0.678	−0.095 (0.056)	0.091
Triacylglycerol (mmol/l)	0.206 (0.061)	0.001	−0.021 (0.061)	0.732	−0.011 (0.050)	0.826	−0.019 (0.056)	0.736
Fasting glucose (mmol/l)	0.011 (0.063)	0.857	−0.023 (0.033)	0.694	−0.009 (0.047)	0.850	0.000 (0.050)	0.993
Total:HDL cholesterol ratio	0.090 (0.057)	0.120	−0.033 (0.055)	0.547	−0.037 (0.045)	0.412	−0.044 (0.053)	0.408
HDL-cholesterol (mmol/l)	−0.123 (0.056)	0.029	0.063 (0.052)	0.228	0.041 (0.043)	0.344	0.035 (0.051)	0.495
HbA_{1c} (%)	0.008 (0.062)	0.898	0.064 (0.067)	0.260	−0.010 (0.046)	0.828	−0.022 (0.054)	0.689

Model 1 was adjusted for age, sex, smoking status, ethnicity, social deprivation, family history, beta-blockers, lipid-lowering medication and time accelerometer worn

Model 2 was adjusted for the above covariates and [a] MVPA, [b] sedentary time or [c] sedentary time and MVPA

Model 3 was adjusted for the same covariates as model 2 and BMI

The pattern of results and significance levels were unaffected if the data were analysed at 60 s epochs. However, standardised beta-coefficients were consistently around 10% lower, reflecting the less sensitive nature of the data for longer epochs (data available on request).

Discussion

This study demonstrates that for individuals with known risk factors for type 2 diabetes mellitus recruited from primary care, sedentary time was detrimentally associated with 2 h glucose, triacylglycerol and HDL-cholesterol, independent of measured confounders. These results remained significant after further adjustment for measures of adiposity. Furthermore, the findings for biochemical factors were consistent across groups with diverse age ranges, providing evidence that the deleterious consequences of excess sedentary time exist across young to old adults. Interestingly, sedentary time was shown to have stronger associations with several important cardiometabolic markers (2 h glucose, triacylglycerol and HDL-cholesterol) compared with total physical activity and MVPA, after adjustment for each other and other important confounders. Associations of breaks in sedentary time with markers of health, independent of overall time spent sedentary and in MVPA, were less consistent, although beneficial associations were observed with measures of adiposity. To our knowledge, this is the first study to examine the effect of sedentary time and breaks on markers of cardiometabolic health in a primary care population with known risk factors for type 2 diabetes mellitus.

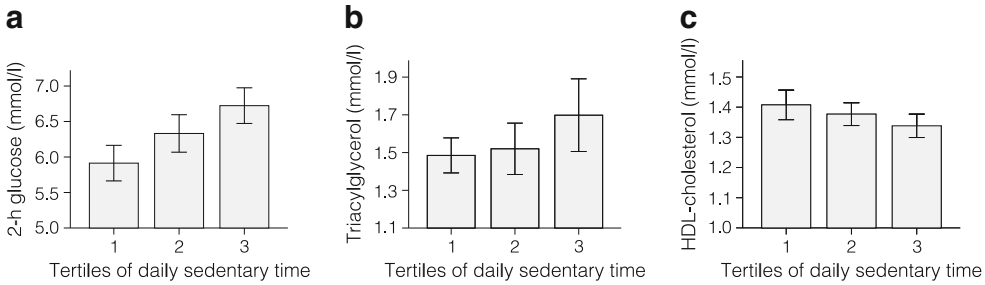

Fig. 1 Tertiles of sedentary time with 2 h glucose (**a**), triacylglycerol (**b**) and HDL-cholesterol (**c**). Estimated marginal means are adjusted for age, sex, ethnicity, IMD score, smoking status, family history of type 2 diabetes mellitus, lipid-lowering medication, beta-blockers, time accelerometer worn, time spent in MVPA and BMI. Tertile cut-points for sedentary time were 9.6 and 10.9 h/day. Medians and ranges for tertile 1=8.7 h (2.9–9.5); tertile 2=10.3 h (9.6–10.9); tertile 3=11.7 h (11.0–15.8). $p<0.001$ for trend (**a**), $p<0.05$ for trend (**b**, **c**)

Our study has multiple strengths. Most notably, it provides novel evidence in a high-risk population recruited through primary care using an objective measure of sedentary time, across a wide age range. Furthermore, all participants were from the same geographical location, with similar risk profiles, and measurements across both studies were performed by the same team of trained staff, following identical standard operating procedures. In addition, participants were rigorously phenotyped with traditional markers of cardiometabolic health using standardised biochemical procedures.

Limitations include the cross-sectional design, thus limiting inference about the direction of causality between the sedentary variables, physical activity and markers of cardiometabolic health; reverse causality remains a possibility. Despite allowing for more robust assessments of sedentary behaviour compared with self-report, accelerometers are not without limitations. For example, they rely on categorising movement (acceleration) strength, rather than directly distinguishing between sitting, lying and standing behaviours. Furthermore, they may underestimate overall physical activity as they are unable to accurately quantify certain non-step-based activities (e.g. cycling).

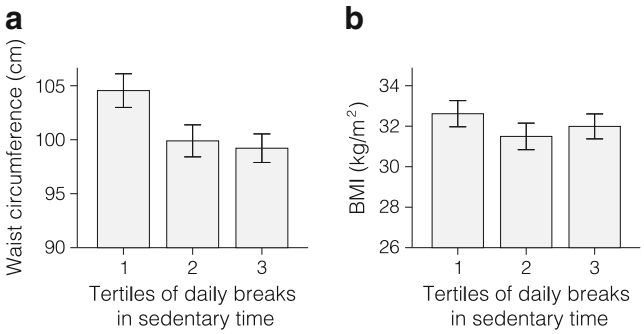

Fig. 2 Tertiles of breaks in sedentary time with waist circumference (**a**) and BMI (**b**). Estimated marginal means are adjusted for age, sex, ethnicity, IMD score, smoking status, family history of type 2 diabetes mellitus, lipid-lowering medication, beta-blockers, time accelerometer worn and time spent in sedentary and MVPA. Cut-points for daily breaks in sedentary time were 234 and 285. Medians and ranges for tertile 1=215 (33–234); tertile 2=268 (235–284); tertile 3=329 (285–487). $p<0.001$ for trend (**a**), $p<0.01$ for trend (**b**)

Our results extend those from other studies that have used both self-reported and objective measures of sedentary time and MVPA with cardiometabolic variables in the general population. Self-reported sedentary behaviour in the form of television viewing time has been positively associated with a multitude of cardiometabolic risk factors [6, 26–28], including 2 h glucose [26, 27]. Similarly, recent reviews also report that self-reported sedentary time is consistently associated with an increased risk of diabetes [9] and metabolic syndrome [29].

Several studies have examined the joint effect of sedentary behaviour and physical activity on health outcomes [5, 30, 31]. In contrast to our observations, most have concluded that physical activity is a stronger predictor of metabolic risk [30] and insulin resistance [31]. This discrepancy in findings may be due to differences in study populations, as our participants had several known risk factors for type 2 diabetes mellitus and were largely obese. Indeed, our results are consistent with previous findings in a similar population, showing that sedentary time has stronger associations with various markers of cardiometabolic health compared with MVPA [32]. This is particularly important as our population is representative of those who are likely to be identified as being at high risk of type 2 diabetes mellitus within routine care and referred on to available prevention programmes. As such, these studies provide preliminary evidence that sedentary behaviour may be a more effective paradigm to target in the prevention of type 2 diabetes mellitus, rather than solely focusing on MVPA. Moreover, sedentary time occupies large portions of the day, unlike MVPA.

Despite a trend for higher levels of breaks to be associated with lower 2 h glucose levels, our study was not able to corroborate a previous finding that breaks in sedentary time were independently associated with glucose regulation and triacylglycerol [8]. This discrepancy may be partly explained

by the fact that our participants spent longer in sedentary pursuits. Nevertheless, our findings are broadly consistent with other studies conducted in the general population and in those with type 2 diabetes that have shown no associations between breaks in sedentary time and measures of insulin resistance and lipid variables [4, 32]. However, as with the present study, strong associations between breaks in sedentary time and measures of adiposity were observed. Consequently, this study further suggests that breaks in sedentary time, rather than total sedentary time per se may be an important factor in the regulation of body weight. This is consistent with a small intervention study suggesting that regular variations in posture allocation may be an influential factor in the regulation of energy homeostasis [33].

The non-significant associations observed for FPG and HbA_{1c} across all measures of sedentary behaviour and physical activity are consistent with previous research [4, 14, 34] and reflect the different pathophysiological process underlying 2 h and FPG regulation, with 2 h glucose largely influenced by peripheral insulin resistance [34, 35]. Our findings, therefore, highlight the importance of using 2 h glucose level as the primary outcome variable when assessing the impact of sedentary time on cardiometabolic risk.

Animal models have begun to elucidate the potential biological mechanisms that may underlie the relationship between sedentary behaviour and cardiometabolic risk. Previous laboratory work has identified that distinctive physiological pathways are activated with increased sedentary behaviour, particularly around the metabolism of lipoprotein lipase, which remains largely unaffected by MVPA [36]. Lipoprotein lipase is a key regulator of lipid metabolism and is causally linked to CVD [37]. In addition, sedentary behaviour may also reduce glucose transporter protein content, thus exacerbating insulin resistance [38]. Nevertheless, published experimental research in humans is largely lacking and the underlying mechanisms are likely to be multifarious.

In addition, there is a need to accumulate supplementary data from prospective studies and new evidence from human experimental work and intervention trials. To date, only one experimental study focused specifically on sedentary behaviour in middle-aged adults has been published. Nineteen overweight/obese adults showed large reductions in the area under the glucose and insulin curve when sitting time was regularly punctuated with short periods of both light and moderate intensity activity [39]. Surprisingly, there was no difference between the effect sizes found for the light or moderate intensity profiles. Although encouraging, the findings from this study need to be confirmed in different populations in order to establish a causal link between sedentary behaviour and cardiometabolic dysfunction.

In conclusion, the findings from this study may have important methodological and public health implications. This study provides novel objective evidence that, in individuals at high risk of type 2 diabetes mellitus, sedentary time may be a more important indicator of cardiometabolic health than MVPA. This may raise questions regarding the prescription of optimal daily human movement for health. As such, diabetes and cardiovascular prevention programmes concentrating solely on MVPA may overlook an area that is of fundamental importance to cardiometabolic health. Along with messages related to accumulating at least 150 min/week of MVPA, which form the cornerstone of diabetes prevention programmes [40], such interventions may be more effective if individuals are further encouraged to simply sit less and move more, regardless of the intensity level. This is an innovative approach that requires a paradigm shift, so that individuals think about the balance of sedentary behaviour and activity in all aspects of daily life. Nevertheless, given the limitations, this study should not be used to confirm a direct link between sitting time and metabolic health, but should act as a stimulus for tightly controlled experimental studies in different populations in order to influence future physical activity and sedentary behaviour interventions and public health initiatives aimed at disease prevention.

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Contribution statement JH and TY had the original idea for the analysis. JH wrote the first draft of the article. JH, TY, SJHB, KK, EGW, MAN and MJD made substantial contributions to conception and design. JH and CLE carried out acquisition of data. JH, CLE and TG processed raw accelerometer files. JH, TY and LJG carried out analysis and interpretation of the data. All authors reviewed/edited the manuscript and gave final approval of the version to be published.

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