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Cross-sectional associations of device-measured sedentary behaviour and physical activity with cardio-metabolic health in the 1970 British Cohort Study

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Abstract

Aims: This study aimed to examine the cross-sectional associations of thigh accelerometry-assessed sedentary behaviour and moderate-to-vigorous physical activity (MVPA) with cardio-metabolic health markers and prevalent diabetes in a population sample of middle-aged British adults.

Methods: Participants (n = 4892) from the age-46-to-48 wave of the 1970 British Cohort Study were fitted with a waterproofed activPAL3 micro device. Total/prolonged sedentary time, breaks and MVPA were the main exposures. We dichotomized prolonged sedentary time and MVPA based on the corresponding median, generating four combinations as categorical exposures. Outcomes comprised of diabetes and seven cardio-metabolic health markers. We used logistic regression and generalized linear models to examine independent/joint associations, conducting a minimally adjusted model including demographics and contextual covariates, and further adjusted for total sedentary time and/or MVPA as applicable.

Results: Each set of 10 sedentary breaks and 1 h of prolonged sedentary time were associated with HbA_{1c} (mmol/mol) [$B = -0.18$ (−0.33, −0.03) and 2.35 (1.01, 3.69), respectively]. Each set of 10 sedentary breaks and 1 h of MVPA were favourably associated with diabetes [adjusted odds ratio (AOR): 0.80 (0.71, 0.99) and 0.42 (0.26, 0.67), respectively]. Joint analyses showed that only the low MVPA × long sedentary time combination had significantly higher odds for diabetes than the referent high MVPA × short sedentary time combination [AOR: 1.89 (1.17, 3.03)].

Conclusions: Each set of additional 10 sedentary breaks per day was associated with 20% lower odds for diabetes. A low physical activity level combined with long sedentary time might synergistically deteriorate cardio-metabolic health.

1 | INTRODUCTION

Physical inactivity is a major global health issue, causing 5.3 million deaths per year and 7% of type 2 diabetes cases.[1] Sedentary behaviour, defined as low energy expenditure (≤ 1.5 metabolic equivalents) in a sitting or reclining posture during waking times, has also been associated with cardio-metabolic health markers and elevated mortality risk.[2] Current public health guidelines suggest both increasing physical activity and decreasing sitting time to ameliorate the cardio-metabolic health burden.[3] However, the quantification of sitting guidelines has been problematic due to inconsistencies in how 'sedentary behaviour' has been measured to date[3] and the lack of evidence in particular longitudinal studies on which guidelines are based. In large cohort studies, sedentary behaviour has been routinely measured using self-reports or hip/wrist-worn devices, which are less accurate approaches to quantify sitting.[4] Self-reported measurements are subject to recall bias, and hip/wrist-worn devices struggle to differentiate between sitting and standing.[5] Ideally, sedentary time should be derived from devices with postural elements (sitting–standing–moving), such as thigh-worn accelerometry. Very few general-population epidemiological studies have examined associations between thigh-measured postures and comprehensive cardio-metabolic profiles.

Beyond total sedentary time, other aspects of sedentary behaviour, e.g. accumulation patterns such as bout duration and the number of interruptions of sedentary time with physical activity breaks (also called 'sedentary breaks'), may have an impact on cardio-metabolic health.[6] Information about accumulation patterns is limited to studies using hip/wrist-worn accelerometry. For example, a cohort study of 7985 US adults[7] suggested that longer sedentary bouts were associated with increased all-cause mortality risk over 4 years. Another recent study among 1655 older British men found no association of sedentary breaks with all-cause mortality over 5 years.[8] Neither of these studies could measure interruptions to sitting[7,8] because the current data-processing approach for hip/wrist-worn accelerometry misclassifies standing–moving transitions as sedentary breaks. Thigh-worn accelerometry overcomes this limitation.[9]

The largest (n = 2497) thigh-worn accelerometry study addressing diabetes to date suggested that total sedentary time, but not sedentary breaks or bout duration, was associated with type 2 diabetes and the metabolic syndrome.[10] Embedded in the same Maastricht Study cohort, another cross-sectional study (n = 1993) indicated that both sedentary time and moderate-to-vigorous physical activity (MVPA) were associated with both conditions.[11] However, a smaller scale (n = 678) cross-sectional analysis of the AusDiab study, found that sedentary time and sedentary breaks were not associated with glucose metabolism markers, e.g. HbA_{1c} and 2-h post-load glucose.[12] Recent meta-analyses based on self-reported measurement suggested that physical activity could ameliorate the detrimental effect of total sedentary time on cardio-metabolic disease, cancer and all-cause mortality.[13,14] To date, no large-scale epidemiological study has utilized thigh-worn accelerometry to investigate cardio-metabolic risk among people with different combination profiles of physical activity and sedentary behaviour.

What's new?

- Sedentary behaviour has been promoted as an independent (of physical activity) risk factor for cardio-metabolic diseases, but definitive data are lacking and contradictory.
- Only sedentary breaks, but not sedentary time, were associated with lower odds for prevalent diabetes. A low physical activity level combined with long sedentary time might synergistically deteriorate cardio-metabolic health.
- Beyond total sedentary time, sedentary breaks might be a plausible behavioural target in future interventions.

The aim of this study, therefore, was to cross-sectionally examine the independent and joint associations of physical activity and sedentary behaviour with biomarkers of cardio-metabolic health using thigh-worn accelerometry in an established large population-based middle-age British birth cohort. Based on prior studies, we hypothesized associations between sitting time and adverse cardio-metabolic profiles, particularly glycaemic control.

2 | PARTICIPANTS AND METHODS

2.1 | Sample and design

Data for these cross-sectional analyses were drawn from the 2016–2018 wave of the 1970 British Cohort Study (BCS70; age-46-to-48-wave), with full details described elsewhere.[15,16] In brief, BCS70 is an observational prospective population-based cohort study, following the lives of 17 287 people born in a single week of 1970 in England, Scotland and Wales. The present wave of BCS70 comprised questionnaires and interviews to collect self-reported information, an online-based dietary diary, and biomedical assessments performed by nurses. At the end of the nurse visit, participants were invited to participate in the ActivPAL sub-study. If consent was provided, a trained nurse waterproofed and fitted the device on the anterior midline of a participant's right thigh

with a medical dressing. Participants were asked to wear the device without taking it off for seven consecutive days and return it using self-addressed envelopes. This survey received ethics from NRES Committee South East Coast - Brighton & Sussex (Ref 15/LO/1446).

2.2 | Measurements

Sedentary behaviour and physical activity were measured using a thigh-worn activPAL3 micro monitor (PAL Technologies, Glasgow, UK).[17] The device is a triaxial accelerometry that provides estimated body posture (sitting/reclining/lying, standing) and stepping speed (cadence) with a sampling frequency of 20 Hz. Data were downloaded and processed using the activPAL3 software and the ProcessingPAL, a validated open-access program extracting exposure variables (https://github.com/UOL-COLS/ProcessingPAL/releases).[18] The first day of data were excluded, and subsequent days were defined as the 24 h between consecutive midnights. Only participants providing at least one valid day, defined as waking wear time more than 10 h/day, were included for further analysis.[11]

A nurse conducted anthropometric measures, blood pressure (BP) measurement and blood sampling using standard protocols.[15] Anthropometry tests included height, body mass, and body-fat percentage (based on bioelectrical impedance). BMI was derived as body mass (kg) divided by squared height (m^2). Diastolic (DBP) and systolic (SBP) blood pressure were assessed via triplicate measurements. Non-fasting blood samples were analysed for HbA_{1c}, high-density lipoprotein-cholesterol (HDL-C), total cholesterol, triglycerides (TG) and C-reactive protein (CRP). Diabetes was identified from physician diagnosis, or on blood glucose-regulating drugs, or $HbA_{1c} \geq 48$ mmol/mol (6.5%). CRP was log-transformed for normality. We calculated the total-to-HDL cholesterol ratio by dividing total cholesterol to HDL-C because this ratio has been shown to be more predictive of cardio-metabolic risk hip/wrist-worn devices.

2.3 | Data handling

Constants were added to the variables for those on current medication to reduce the potential measurement errors,[19] i.e. on lipid-lowering drugs (+25% for total cholesterol; −5% for HDL-C; +18% for TG), on BP-lowing drugs (+10 mmHg for DBP and SBP, respectively), and on oral medication for diabetes [+11 mmol/mol (3.2%) for HbA_{1c}]. Daily total sedentary time, prolonged sedentary time (accumulating in continuous bouts lasting ≥ 30 min/bout),[12] and sedentary breaks (the number of sit–stand transitions) were calculated using the program mentioned above.[17,18] Daily MVPA time was derived using a validated and well-established step cadence threshold ≥ 100 steps/min.[18,20] To perform joint association analysis, we dichotomized prolonged sedentary time and MVPA based on median cut-points (4.5 and 0.8 h, respectively) to achieve roughly equal MVPA × sedentary groups. The resulting joint variable comprised four combinations, where the combined below-median prolonged sedentary time (short sedentary) and above-median MVPA (high MVPA) served as the reference.

2.4 | Statistical analyses

Demographics and contextual covariates[15,21] were collected on sex, educational attainment, device-wearing days, self-rated general health, disability/limitations, current medication, smoking status, alcohol consumption and daily energy intake. Missing values of BMI, body fat and covariates were imputed using an established multiple imputation method.[22] Briefly, all exposures, outcomes and confounders were included as predictors. We performed linear regression-based imputation using SAS 9.4 software (SAS Institute, Cary, NC, USA) and generated 20 imputation data sets. The distribution similarity was examined by histograms, and the over 99% pooled estimation efficiency was confirmed. Table S1 provides a comparison between the present imputed data set and the observed (unimputed) data set.

We defined continuous exposures as total and prolonged sedentary time (h/day), sedentary breaks (times/day) and MVPA (h/day). Derived categorical exposures for joint analysis were four combinations of prolonged sedentary time and MVPA. Continuous outcomes included the following cardio-metabolic health markers: BMI (kg/m^2), body fat (%), HbA_{1c} (mmol/mol), TG (mmol/l), log CRP, SBP (mmHg), total-to-HDL cholesterol ratio. Binary outcomes included diabetes.

All tests were performed using SAS 9.4 software and were two-sided. In Model 1, we adjusted for demographics and contextual covariates (and body fat as applicable). A second model additionally adjusted for MVPA (Model 2). In the last model (Model 3), analyses with sedentary breaks as an exposure were adjusted mutually for Model 1, MVPA and total sedentary time; analyses with MVPA as an exposure were mutually adjusted for Model 1 and total sedentary time.

The differences in covariates and continuous exposures between thirds of the total sedentary time distribution were examined by chi-square tests, analysis of variance (ANOVA) and Kruskal–Wallis tests as applicable. We applied generalized linear models (GLM)/logistic regression to examine the association of continuous exposures (sedentary behaviour and MVPA) with continuous outcomes (health markers)/binary outcome (diabetes). For total/prolonged sedentary time and MVPA, the unit of change in the exposure variables was set as 1 h/day, whereas for sedentary breaks, the unit of

change was 10 times/day. We further used GLM to examine the joint association of derived categorical exposure (four combinations) with all the above outcomes. B coefficients, odds ratios or Bonferroni-adjusted pair-wise differences with 95% confidence interval were reported, as appropriate.

3 | RESULTS

Figure 1 describes the flow of participants in the study. Some 7439 participants were invited to participate and 6562 consented (88%). Participants with unusable accelerometry data were excluded ($n = 1670$) with 'lost in post' as the main cause ($n = 591$). A total of 4892 participants were available for multiple imputation and further analysis before exclusions due to missing biomedical data. Table 1 and Table S2 present the characteristics of participants by thirds of the total sedentary time distribution. With the exception of smoking status and daily energy intake, all covariates showed statistically significant associations with total sedentary time. No appreciable multicollinearity among exposures was detected, except for total sedentary time and prolonged sedentary time ($r = 0.80$, $P < 0.0001$) (Table S3).

3.1 | Associations of sedentary behaviour and MVPA with cardio-metabolic health markers

As shown in Table 2, after adjusting for potential confounders and MVPA, total and prolonged sedentary time were positively associated with BMI [$B = 0.20$, (0.12, 0.27) and 0.28 (0.20, 0.36), respectively], per cent body fat [$B = 0.22$ (0.11, 0.34) and 0.31 (0.19, 0.43), respectively], total-to-HDL cholesterol ratio [$B = 0.03$ (0.01, 0.05) and 0.03 (0.01, 0.05), respectively). Prolonged sedentary time was further associated with HbA_{1c} [$B = 2.35$ (1.01, 3.69)]. After adjusting for potential confounders, MVPA and total sedentary time, sedentary breaks were inversely associated with BMI [$B = -0.46$ (-0.54, -0.37)], per cent body fat [$B = -0.69$ (-0.83, -0.56)] and HbA_{1c} [$B = -0.18$ (-0.33, -0.03)].

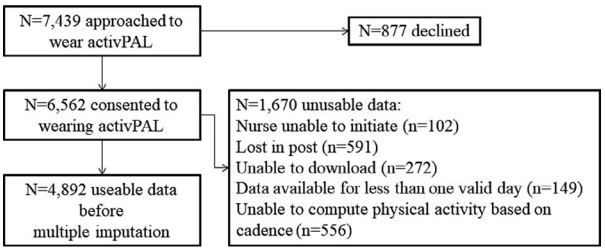

FIGURE 1 Participant recruitment flowchart

After adjusting for potential confounders and total sedentary time, MVPA was inversely associated with BMI [$B = -1.59$ (-1.95, -1.24)], per cent body fat [$B = -3.01$ (-3.56, -2.46)], log CRP [$B = -0.06$ (-0.10, -0.01)] and total-to-HDL cholesterol ratio [$B = -0.24$ (-0.34, -0.15)].

3.2 | Associations of sedentary behaviour and MVPA with prevalent diabetes

Table 3 shows associations of all continuous exposures (total/prolonged sedentary time, sedentary breaks and MVPA) with diabetes after adjusting for potential confounders. There was no association of either total or prolonged sedentary time with diabetes. Sedentary breaks and MVPA were inversely associated with odds for diabetes [adjusted odds ratio (AOR) = 0.80 (0.71, 0.90) and 0.42 (0.26, 0.67), respectively].

3.3 | Joint associations of prolonged sedentary time and MVPA with cardio-metabolic health markers and prevalent diabetes

As shown in Table 4, compared with the reference group, BMI and body fat percentage were higher in all groups, while the total-to-HDL cholesterol ratio was significantly higher in the two combinations including low MVPA. Only the low MVPA × long sedentary group showed significantly higher odds for diabetes compared to the reference [AOR = 1.89 (1.17, 3.03)]. There were no significant differences in all other measured markers between MVPA × sedentary time groups, after adjustment for potential confounders.

3.4 | Sensitivity analysis

We repeated all the above analyses in the unimputed data set, and the results showed a close agreement with the present analyses (Tables S4–S6), while the joint association of MVPA and sedentary time with diabetes were attenuated slightly [from AOR = 1.89 (1.17, 3.03) to 1.81 (0.99, 3.31)]. Because of the lack of a global definition of prolonged sitting time, we further investigated the association of prolonged sedentary time with all the outcomes by using 60 min as a cut-off for a prolonged bout using either imputed or unimputed data set.[12,16] As shown in Table S7, time spent in very long sedentary bouts resulted in a similar pattern of results in both observed and imputed data sets with the current results. We further repeated the joint analyses by removing lower-adherence participants who wore the device for < 4 days ($n = 477$, 10% of participants) (Table S8) or by dichotomizing MVPA based on 150 min/week guidelines[23] (Table S9) or

TABLE 1 Sample characteristics distribution by total sedentary time

		Tertiles of total sedentary time			
	All ($n = 4892$)	**Short (< 8.4 h/day)**	**Medium (8.4–10.1 h/day)**	**Long (> 10.1 h/day)**	***P*-value**
Sex, male	2340 (48%)	652 (40%)	749 (46%)	939 (57%)	<0.001
Degree educated[a]	1321 (27%)	342 (21%)	493 (31%)	486 (29%)	<0.001
Disability/limitation[b]	242 (5%)	39 (2%)	80 (5%)	123 (7%)	<0.001
Current smokers	874 (18%)	292 (18%)	264 (16%)	318 (19%)	0.101
Alcohol consumption[c]	1100 (23%)	323 (20%)	369 (23%)	408 (25%)	0.007
Obesity[d]	1077 (22%)	309 (19%)	346 (21%)	422 (25%)	<0.001
Diabetes[e]	176 (4%)	43 (3%)	41 (3%)	92 (6%)	<0.001
Self-rated general health (a.u.)	68.80 (21.3)	71.1 (19.9)	70.1 (20.5)	65.4 (230)	<0.001
Daily energy intake (kcal)	2093.4 (820.7)	2110.9 (807.5)	2023.3 (771.0)	2103.1 (877.6)	0.307
Device wearing days	6.2 (1.6)	6.1 (1.7)	6.3 (1.4)	6.1 (1.6)	0.004
Total sedentary time (h/day)	9.3 (2.0)	7.1 (1.1)	9.3 (0.5)	11.4 (1.1)	<0.001
Prolonged sedentary time (h/day)	4.6 (1.9)	3.0 (1.1)	4.5 (1.2)	6.4 (1.7)	<0.001
Sedentary breaks (times/day)	55 (16)	54 (16)	57 (16)	55 (16)	<0.001
MVPA (h/day)	0.9 (0.4)	1.0 (0.5)	0.9 (0.4)	0.7 (0.4)	<0.001

Note: Values are shown as *n* (%) or mean (SD) as applicable. *P*-values indicate associations between total sedentary time and measured parameters.

[a]'Degree level' or 'higher degree' academic qualification.

[b]Classified as 'severely hampered' based on the EU-Statistics on Income and Living Conditions (EU-SILC).

[c]Classified as 'increasing or higher risk drinking' based on the alcohol use disorders identification test: primary care (AUDIT-PC).

[d]Classified as 'obese' based on BMI (≥ 30 kg/m^2).

[e]Diabetes was identified from physician diagnosis, or on blood glucose-regulating drugs, or $HbA_{1c} \geq 48$ mmol/mol (6.5%).

by removing potential outliers ($n = 119$) with abnormal combinations of BMI and per cent body fat detected by Cook's distance (Table S10). In all three cases, the results were very similar to the main analyses [AOR for diabetes of low MVPA × long sedentary group: 1.94 (1.16, 3.23), 1.91 (1.22, 3.01) and 2.01 (1.22, 3.31), respectively]. Because a previous meta-analysis based on hip/waist-worn accelerometry suggested a potential non-linear association of total sedentary time and MVPA with all-cause mortality,[4] we examined the shape of the association between total sedentary time or MVPA with cardio-metabolic health markers. These analyses confirmed that associations were linear (Figures S1 and S2).

4 | DISCUSSION

Our study is the largest investigation to date to utilize thigh-worn accelerometry to examine associations of sedentary and physical activity with a comprehensive cluster of cardio-metabolic health markers. Using a postural allocation measurement method, we found that different aspects of sedentary behaviour were consistently associated with BMI and body fat percentage after adjustment for MVPA. Prolonged sedentary time and sedentary breaks were further associated with HbA_{1c}. MVPA was favourably associated with BMI, body fat percentage, CRP and total-to-HDL cholesterol ratio. Sedentary breaks and MVPA, but not sedentary time, were associated with diabetes. Joint analyses showed that only the long sedentary time × low MVPA combination showed higher odds for diabetes compared with the low sedentary time × high MVPA combination.

The health effects of sedentary time are still controversial. Our findings suggested that sedentary time, irrespective of bout duration, was adversely associated with BMI, per cent body fat, and total-to-HDL cholesterol ratio, but not with diabetes (Table 2). This is in contrast to the Maastricht Study results, which examined a similar hypothesis.[10] Van der Berg *et al.*[10] suggested that an extra hour of total sedentary time was associated with 22% higher odds for type 2 diabetes. A systematic review of cross-sectional studies using hip/wrist-worn accelerometry has shown deleterious associations with insulin and TG but not with HDL-C and blood glucose.[24] Based on prospective cohort studies with predominantly self-reported measurements, meta-analyses have shown relatively consistently deleterious associations of total sedentary time with incident type 2 diabetes.[25,26] These equivocal findings may imply that each measurement method captures different aspects of sedentary behaviour, and inconsistent results may also be explained by issues such as reverse causation and residual confounding.

TABLE 2 Multivariable association of sedentary time (h/day), sedentary breaks (times/day), MVPA (h/day) with cardio-metabolic health markers

Health marker	Model 1[a]	Model 2	Model 3
BMI (kg/m^2) ($n = 4892$)			
Total sedentary time	**0.30 (0.23, 0.37)**	**0.20 (0.12, 0.27)**	–
Prolonged sedentary time	**0.38 (0.31, 0.45)**	**0.28 (0.20, 0.36)**	–
Sedentary breaks	**−0.46 (−0.55, −0.38)**	**−0.42 (−0.50, −0.33)**	**−0.46 (−0.54, −0.37)**
MVPA	**−1.87 (−2.21, −1.54)**	–	**−1.59 (−1.95, −1.24)**
Body fat (%) ($n = 4892$)			
Total sedentary time	**0.41 (0.30, 0.52)**	**0.22 (0.11, 0.34)**	–
Prolonged sedentary time	**0.50 (0.39, 0.62)**	**0.31 (0.19, 0.43)**	–
Sedentary breaks	**−0.73 (−0.86, −0.59)**	**−0.65 (−0.78, −0.51)**	**−0.69 (−0.83, −0.56)**
MVPA	**−3.32 (−3.85, −2.80)**	–	**−3.01 (−3.56, −2.46)**
HbA_{1c}[b] (mmol/mol) (n=4,020)			
Total sedentary time	**0.14 (0.01, 0.26)**	1.19 (−0.09, 2.46)	–
Prolonged sedentary time	**0.24 (0.12, 0.37)**	**2.35 (1.01, 3.69)**	–
Sedentary breaks	**−0.17 (−0.32, −0.02)**	**−0.16 (−0.31, −0.01)**	**−0.18 (−0.33, −0.03)**
MVPA	−0.47 (−1.06, 0.12)	–	−3.09 (−9.24, 3.07)
TG (mmol/l) ($n = 2315$)			
Total sedentary time	0.02 (0.00, 0.05)	0.02 (−0.01, 0.05)	–
Prolonged sedentary time	0.00 (−0.03, 0.03)	−0.01 (−0.04, 0.02)	–
Sedentary breaks	0.03 (−0.01, 0.06)	0.03 (−0.01, 0.06)	0.03 (−0.01, 0.06)
MVPA	−0.13 (−0.27, 0.00)	–	−0.11 (−0.25, 0.03)
Log CRP ($n = 2288$)			
Total sedentary time	0.01 (0.00, 0.02)	0.01 (0.00, 0.02)	–
Prolonged sedentary time	0.01 (0.00, 0.02)	0.01 (0.00, 0.02)	–
Sedentary breaks	−0.01 (−0.02, 0.00)	−0.01 (−0.02, 0.00)	−0.01 (−0.02, 0.00)
MVPA	**−0.06 (−0.11, −0.02)**	–	**−0.06 (−0.10, −0.01)**
SBP (mmHg) ($n = 4856$)			
Total sedentary time	0.04 (−0.16, 0.24)	0.02 (−0.19, 0.23)	–
Prolonged sedentary time	−0.01 (−0.22, 0.2)	−0.04 (−0.26, 0.19)	–
Sedentary breaks	−0.12 (−0.37, 0.12)	−0.12 (−0.37, 0.13)	−0.12 (−0.37, 0.13)
MVPA	−0.38 (−1.36, 0.60)	–	−0.35 (−1.37, 0.67)
Total-to-HDL cholesterol ratio ($n = 4054$)			
Total sedentary time	**0.05 (0.03, 0.06)**	**0.03 (0.01, 0.05)**	–
Prolonged sedentary time	**0.04 (0.02, 0.06)**	**0.03 (0.01, 0.05)**	–
Sedentary breaks	−0.03 (−0.05, 0.00)	−0.02 (−0.05, 0.00)	−0.03 (−0.05, 0.00)
MVPA	**−0.29 (−0.38, −0.19)**	–	**−0.24 (−0.34, −0.15)**

Note: Values are shown as *B* coefficient and 95% confidence interval with the value in bold denoting significant differences ($P < 0.05$). For total/prolonged sedentary time and MVPA, the value represents the change in the outcome of each additional hour per day of the exposure; for sedentary breaks, the value represents the change in the outcome of each 10 additional times per day of the exposure.

[a]Model 1: adjusted for sex, education, device wearing days, self-rated health, disability/limitation, smoking, alcohol consumption, daily energy intake, and body fat (when applicable); Model 2: additionally, adjusted for MVPA; Model 3: for sedentary breaks as the exposure, Model 1 mutually adjusted for MVPA and total sedentary time; for MVPA as the exposure, Model 1 mutually adjusted for total sedentary time.

[b]A constant was added to the variable for those on current medication, i.e. on lipid-lowering drugs (+25% for total cholesterol; −5% for HDL-C; +18% for TG), on BP-lowing drugs (+10 mmHg for DBP and SBP, respectively), and on oral medication for diabetes [+11 mmol/mol (3.2%) for HbA_{1c}].

Our results support the importance of sedentary accumulating patterns, since the number of sedentary breaks, but not sedentary time, was associated with diabetes (Table 3), whereas sedentary breaks and prolonged sedentary time, but not total sedentary time, were associated with HbA_{1c} (Table 2). Cross-sectional thigh-worn accelerometry studies have

TABLE 3 Association of sedentary time (h/day), sedentary breaks (times/day), and MVPA (h/day) with the prevalence of diabetes

Disease	Model 1[a]	Model 2	Model 3
Diabetes[b] ($n = 4020$)			
Total sedentary time	0.96 (0.90, 1.03)	0.95 (0.89, 1.02)	–
Prolonged sedentary time	1.05 (0.97, 1.13)	1.02 (0.94, 1.10)	–
Sedentary breaks	**0.78 (0.70, 0.87)**	**0.80 (0.72, 0.90)**	**0.80 (0.71, 0.90)**
MVPA	**0.43 (0.27, 0.70)**	–	**0.42 (0.26, 0.67)**

Note: Values are shown as odds ratio and 95% confidence interval with the value in bold denoting significant differences ($P < 0.05$). For total/prolonged sedentary time and MVPA, the value represents the odds ratio of each one additional hour per day of the exposure; for sedentary breaks, the value represents the odds ratio of each ten additional times per day of the exposure.

[a]Model 1: adjusted for sex, education, device wearing days, self-rated health, disability/limitation, smoking, alcohol consumption, daily energy intake and body fat; Model 2: additionally, adjusted for MVPA; Model 3: for sedentary breaks, mutually adjusted for Model 1, MVPA, and total sedentary time; for MVPA, mutually adjusted for Model 1 and total sedentary time.

[b]Diabetes was identified from physician diagnosis or on blood glucose-regulating drugs and/or $HbA_{1c} \geq 48$ mmol/mol (6.5%).

generally produced inconsistent cardio-metabolic health results of sedentary behaviour.[10,12] The metric of quantifying sedentary accumulating patterns might explain the inconsistency.[27] We used sedentary time and breaks as metrics and defined accumulation at least 30 continuous minutes in a seated/reclined position as a prolonged bout. Previous studies using the same definition found no associations of prolonged sedentary time with BP and HbA_{1c},[12] and no association of the frequency of prolonged sedentary bouts with metabolic syndrome and glucose metabolism.[10] Both studies also suggested that sedentary breaks were not associated with blood glucose or HbA_{1c}. Bellettiere *et al.*[12] found that only the distribution of sedentary bouts, but not sedentary time or breaks, was associated with blood glucose. Identifying empirically what is a clinically significant prolonged sedentary bout length and what is a sensitive metric to reflect the cardio-metabolic health impact of sedentary behaviour is a key research priority.[4,27]

Our joint analyses highlighted the potentially synergistic effect of prolonged sedentary time and MVPA on cardio-metabolic health, as participants with low MVPA × long sedentary combination had significantly higher odds for diabetes. This finding supported the biggest studies investigating such a joint association based on self-reported total sedentary time and MVPA.[13,14] Ekelund *et al.*[14] found that individuals with both long sedentary time and a low physical activity level had the highest risk for all-cause mortality [hazard ratio (HR) 1.59 (1.52, 1.66)] compared with those with the combination of short sedentary time and a high physical activity level. The same authors also reported that when weekly physical activity volume was > 35.5 metabolic equivalent h/week, physical activity could eliminate the deleterious effect of total sedentary time on mortality of the cardio-metabolic disease, cancer and all-cause. The median cut-point of MVPA applied in this study(~ 50 min/day) exceeded the lowest physical activity recommendation (150 min/week) by 30 min/day on average[23] and approached the threshold mentioned above, so our joint analysis results reflect the cardio-metabolic health benefit of a high volume of MVPA. Our results also showed that independent of total sedentary time, each extra hour of MVPA was associated with 58% lower odds for diabetes. However, because wearable devices capture a more detailed physical activity profile than self-reported questionnaires,[28] comparisons with the current physical activity recommendations which are based on self-reported data[23] might be compromised. Further longitudinal studies applying device measurement with incident diabetes as an outcome are warranted to confirm our results.[4,8]

Thigh-worn accelerometry is the gold standard for differentiating between postures.[8] Other strengths of this study include the large sample size, and the continuously recorded sedentary behaviour and physical activity in free-living conditions. Compared with the largest existing study with thigh-worn measurements, our participants were in middle age before the onset of significant physical decline (this study: 46 years with 5% disability/limitations; Maastricht Study: 60 years with 17% mobility limitation),[10,11] thus allowing associations to be studied more clearly in the absence of other major comorbidities. The main limitation of the present study is its cross-sectional study design. We cannot discount the possibility of reverse causation, whereby poorer cardio-metabolic health leads to more sitting. Compared with those who did not consent to wear accelerometry in the BCS70, the sample included in our analysis tended to be healthier, which raises the possibility of self-selection bias (Table S11). Because our sample had a low prevalence of diabetes (4% vs. 25% in the Maastricht study),[11] the non-statistically significant results of sedentary behaviour and MVPA with diabetes might be attributed to the lack of statistical power due to the low disease prevalence, albeit a narrow confidence interval. We cannot rule out the possibility of residual confounding, although we were able to adjust for both dietary intake and current medication that has often been absent or poorly measured in previous studies with thigh-worn measurements.[10,11] Notably, the average energy intake (~ 2100 kcal) might reflect dietary under-reporting in the present sample. Lastly, although we have applied a conventional regression-based multivariate approach to concentrate on sedentary behaviour and MVPA, future studies based on compositional data analysis and analogous approaches will further elucidate the joint associations of these two and other time-dependent physical behaviours, such as sleep and light physical activity.

TABLE 4 Joint association of sedentary time in prolonged bouts and moderate-to-vigorous physical activity with cardio-metabolic health markers and the prevalence of diabetes

	High MVPA[a]		Low MVPA	
Health marker	**Short sedentary**	**Long sedentary**	**Short sedentary**	**Long sedentary**
BMI (kg/m^2) ($n = 4892$)	Reference	**0.86 (0.37, 1.36)**	**1.14 (0.65, 1.63)**	**2.07 (1.63, 2.51)**
Body fat (%) ($n = 4892$)		**1.28 (0.51, 2.05)**	**1.98 (1.22, 2.75)**	**3.17 (2.48, 3.86)**
HbA_{1c}[b] (mmol/mol) ($n = 4020$)		0.05 (−0.78, 0.89)	−0.34 (−1.18, 0.50)	0.61 (−0.15, 1.37)
TG (mmol/l) ($n = 2315$)		0.04 (−0.15, 0.23)	0.13 (−0.06, 0.32)	0.07 (−0.10, 0.25)
Log CRP ($n = 2288$)		0.02 (−0.04, 0.09)	0.04 (−0.02, 0.11)	0.05 (0.00, 0.11)
SBP (mmHg) ($n = 4856$)		−0.23 (−1.64, 1.19)	0.62 (−0.79, 2.03)	0.60 (−0.68, 1.88)
Total-to-HDL cholesterol ratio ($n = 4054$)		0.11 (−0.02, 0.25)	**0.15 (0.02, 0.29)**	**0.29 (0.17, 0.41)**
Diabetes[c] ($n = 4020$)		1.54 (0.87, 2.72)	1.16 (0.66, 2.05)	**1.89 (1.17, 3.03)**

Note: Values are shown in Bonferroni-adjusted pair-wise differences (BMI, body fat, HbA_{1c}, TG, log CRP, SBP, total-to-HDL cholesterol ratio) or odds ratio (diabetes) and 95% confidence interval as applicable, with the value in bold denoting significant differences ($P < 0.05$). Models were adjusted for sex, education, device-wearing days, self-rated health, disability/limitation, smoking, alcohol consumption, and daily energy intake. For HbA_{1c}, TG, log CRP, SBP, TC/HDL-C ratio, and diabetes, models were further adjusted for body fat.

[a]MVPA/prolonged sedentary time were dichotomised based on median (0.8/4.5 h/day). High MVPA × short sedentary group served as the reference group, and the significance meant different from the referent group.

[b]A constant was added to the variable for those on current medication, i.e. on lipid-lowering drugs (+25% for total cholesterol; −5% for HDL–C; +18% for TG), on BP lowing drugs (+10 mmHg for DBP and SBP, respectively), and on oral medication for diabetes [+11 mmol/mol (3.2%) for HbA_{1c}].

[c]Diabetes was identified from physician diagnosis or on blood glucose-regulating drugs and/or HbA_{1c} ≥ 48 mmol/mol (6.5%).

In conclusion, sedentary breaks, but not sedentary time, were associated with lower odds for diabetes. Sitting for prolonged periods might exaggerate the detrimental cardio-metabolic consequences of physical inactivity. To explore the detailed dose–response and direction of causality, further longitudinal studies of thigh-worn accelerometry are warranted.

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COMPETING INTERESTS

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AUTHOR CONTRIBUTIONS

B.H. performed the statistical analysis and wrote the manuscript. M.H. conceived the idea, did the preliminary set of analyses, supervised the BC70 accelerometryand biomedical data collections, and led funding acquisition, and is the corresponding author of the present study. S.C. contributed to the idea and contributed to funding acquisition. A.K. contributed to the idea and provided intellectual input on the manuscript. N.P. processed the accelerometry data and provided intellectual input on the manuscript. E.S. conceived the idea, supervised the main analysis, re-wrote parts of the manuscript, contributed to funding acquisition, and is the guarantor of the present study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplementary Material

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