Sedentary time and MRI derived measures of adiposity in active vs. inactive individuals

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What is already known about the subject?

- Sedentary behaviour is a distinct risk factor for several health outcomes; including obesity and type 2 diabetes
- Regular MVPA (>150 minutes per week) is one of the cornerstone interventions for the prevention of T2DM
- Although the positive effects of MVPA on regional fat deposition have been well documented, the effects of sedentary behaviour and the mediating role of MVPA remains equivocal

What does your study add?

- For individuals at high risk of T2DM, sedentary time is detrimentally associated with liver, visceral and total abdominal fat, independent of MVPA.
- Associations between sedentary time, liver, visceral and total abdominal fat are stronger in those who do not reach the current exercise recommendations for health (<150 minutes per week).
- The manner in which sedentary time is accumulated may influence the strength of the associations with markers of MRI derived adiposity.

Objective: To examine cross-sectional associations between objectively measured sedentary time and MRI assessed adiposity in a population at high risk of type 2 diabetes (T2DM) and to determine whether associations are modified by the recommended levels of moderate-to-vigorous physical activity (MVPA).

Methods: Sedentary time and MVPA were measured objectively using accelerometers. Linear regression models examined the association of sedentary time with liver, visceral, subcutaneous and total abdominal fat (quantified using magnetic resonance imaging (MRI)). Interaction terms determined whether results were consistent across activity categories (active (>150 minutes of MVPA per week) vs. inactive (<150 minutes of MVPA per week)).

Results: 124 participants (age=64.0±7.1years; male=65.3%; BMI= 31.8±5.6kg/m²) were included. Following adjustment, each 60 minutes of sedentary time was associated with 1.74L higher total abdominal, 0.62L higher visceral, 1.14L higher subcutaneous and 1.86% higher liver fat. When results were stratified by MVPA (active vs. inactive), sedentary time was associated with greater liver, visceral and total abdominal fat in the inactive group only.

Conclusions: These findings suggest that sedentary time is associated with higher levels of inter- and intra-organ fat but associations with liver, visceral and total abdominal fat were stronger in those who do not reach the current exercise recommendations for health.

Introduction

It has been well documented that obesity and physical inactivity predispose individuals to insulin resistance and type 2 diabetes (T2DM) (1, 2). More specifically, evidence suggests that the distribution of excess fat is an important determinant of metabolic, cardiovascular and mortality risk with a predominance of android rather than gynoid being a key contributor (3-5). In particular, ectopic fat, defined as the deposition of triglycerides within locations not classically associated with adipose storage, particularly within the intra- and inter-abdominal organs, appear to confer a higher metabolic risk than total abdominal fat per se (6, 7).

Physical activity is known to be one of the cornerstone interventions for the prevention of T2DM, and it has been well documented that individuals who regularly engage in the recommended levels of moderate-to-vigorous physical activity (MVPA), typically 150 minutes per week, manifest a myriad of physiological benefits (including reduced visceral fat) and experience reduced risk of chronic disease and premature mortality (8, 9). Conversely, sedentary time (defined as any sitting/reclining activity with a low energy expenditure (10)) has been shown to be detrimentally associated with HOMA-IR, insulin, insulin sensitivity, T2DM and mortality (2, 11-13). The evidence appears particularly compelling for those at high risk of, or diagnosed, T2DM. Objectively measured sedentary behaviour quantified using an accelerometer is strongly associated with markers of insulin resistance (14-16), Interleukin-6 (IL-6) (17) and markers of regional adiposity, assessed by MRI (18). Importantly, the majority of these observations persist after further adjustment for body mass index (BMI)/total fat mass and MVPA (15, 17, 18).

Despite these findings, there is emerging evidence that levels of fitness or physical activity may modify the association between sedentary time and health, with stronger associations seen in those who are inactive or unfit (15, 17, 19, 20). Others have also demonstrated that in comparison to

adults who are physically inactive with high sedentary time, those who are physically active have a more desirable health profile across multiple cardio-metabolic markers (BMI, A1c and HDL-cholesterol) (19). In addition, cross-sectional analyses in individuals at high risk of T2DM have demonstrated that after stratifying by MVPA, the detrimental effects of sedentary time on interleukin-6 (IL-6) are stronger in those who were classed as inactive (17). More recently, a harmonised meta-analysis also found that high levels of moderate physical activity (60-75 minutes/day) largely negated the increased risk of mortality associated with high sitting time (12).

Taken together, these studies begin to suggest that the effects of sedentary time may be more relevant in those individuals who do not engage in sufficient levels of MVPA. However, these findings have yet to be explored beyond traditional markers of adiposity (BMI and waist circumference). The way in which sedentary time is accumulated may also influence health outcomes. For example, sedentary time that occurs in long periods without interruption, may be more detrimental to health than shorter bouts (21). Moreover, previous research has shown that breaks in sedentary time are strongly associated with traditional measures of adiposity (14). Therefore, the aim of this study was to examine the associations between objectively measured sedentary time (total and prolonged bouts), breaks in sedentary time and MRI assessed body composition in a population at high risk of T2DM and to determine whether associations are mediated by the recommended levels of MVPA.

Methods

Subjects

This was a nested study within a randomised controlled trial (RCT) for a subset of participants. Individuals were recruited from the Walking Away from Type 2 Diabetes trial, reported in detail

previously (22). Participants at increased risk of T2DM were recruited through 10 primary care practices in Leicestershire, UK, in 2010–2011. Individuals with an increased risk of impaired glucose regulation (IGR; any combination of impaired glucose tolerance (IGT) and/or impaired fasting glycaemia (IFG) or undiagnosed T2DM) were identified using a modified version of the Leicester Risk Score (23). Individuals were unaware of their diabetes risk status before entering the study. At baseline, individuals were randomised to usual care or the Walking Away structured education programme (24). There was no difference between groups in levels of MVPA, sedentary behaviour or markers of metabolic health at 12 months (25). Therefore, this paper reports cross-sectional data at 12-months from a sample of 124 participants, collected during 2011. Ethical approval was obtained from the Nottingham Research Ethics Committee, UK. Informed consent was obtained from all individual participants included in the study.

Quantification of sedentary time (total and bouts), breaks in sedentary time and MVPA

All eligible participants were asked to wear an accelerometer at their 12 month visit (Actigraph GT3X, Pensacola, FL, USA), for seven consecutive days during waking hours. Data were collected in 15 second epochs and re-integrated into 60 second epochs for the purposes of this study. Freedson cut-points were used to categorise an epoch as sedentary (<100 counts per 60 seconds) or MVPA (≥ 1952 counts per 60 seconds) (26). Breaks in sedentary time were defined as a transition from a sedentary (<100 counts per 60 seconds) to an active state (≥ 100 counts per 60 seconds). Bouts of sedentary behaviour were categorised into either 0-30 minute, 30-60 minute or 60+ minutes time periods (27). Non-wear time was defined as a minimum of 60 minutes of continuous zero counts and days with at least 600 minutes of wear time were considered valid (28). In order to be included in the analysis, participants were required to have a minimum of four valid days (29). In order for individuals to be classed as active, they needed to have undertaken an average of at least 150 minutes of MVPA (30).

A data analysis tool (KineSoft version 3.3.76, Kinesoft, Loughborough, UK; www.kinesoft.org) was used to process the accelerometer data.

MRI derived measures of adiposity

At the 12-month follow-up measurement, participants were invited to undergo an MRI scan in addition to their other study assessments. MRI scans were performed at Glenfield Hospital, Leicester, UK, where liver, visceral, subcutaneous and total abdominal fat (includes liver, subcutaneous and visceral fat) was quantified. MRI is a reliable modality for the assessment of adipose tissue and is capable of measuring fat distribution with a high spatial resolution (31, 32).

Scanning was performed using a 1.5 Tesla Avanto system (Siemens Medical, Erlangen, Germany). Flexible body array coils were applied to the thorax and abdomen for signal reception.. For lipid volume quantification, a 2-point Dixon gradient-echo pulse sequence was used to separate tissue water signal from lipid signal. With this technique, two images are acquired: in the first, the fat and water signals are aligned in-phase; in the second the fat and water signals have opposed phase directions. After correction of phase distortions due to magnetic field inhomogeneity, algebraic addition of the two images produces an image containing signal largely from water, while subtraction produces an image containing signal largely from fat (33). 3-D images were acquired axially with 5 mm slice thickness and in-plane resolution of 1.56 mm, interpolated to 0.78 mm. The field of view was 500 mm (left-right) by 375 mm (anterior-posterior). Images were acquired in three contiguous blocks, covering the thoracic, abdominal and pelvic regions, with each block acquired in a breath-hold at full inspiration to minimise motion-related artefacts and to negate changes in slice position. The acquisition time for each block was 18s. All scans were performed by the same team of trained staff according to standardised procedures.

Analysis of the MR images was performed by a trained individual using Java Image Manipulation analysis software (Version 7; Xinapse Systems, West Bergholt, UK; www.xinapse.com). All analysis was undertaken by the same researcher who was blinded to the clinical, anthropometric and accelerometer data.

For analysis, the 'fat' and 'water' images were algebraically combined to create a 'fat percentage' image. Fat-containing voxels were then defined as those with an intensity between 51% and 99% (100% being due to image artefact). In order to expedite the analysis, the images were then down sampled in the slice direction into 15 mm thick contiguous slices, from the top of the pulmonary trunk extending to the bottom of the symphysis pubis. Volumes of interest for total abdominal fat were created by outlining the perimeter of the body on each relevant slice using a mouse-controlled pointer and excluding those voxels outside the structures.

The visceral (and retroperitoneal) fat was further separated, by outlining the abdominal and chest wall muscles and excluding the voxels for subcutaneous fat. The fat volume was calculated automatically by multiplying the cross-sectional areas of the fat-containing voxels, summed over all slices on which the tissue was outlined, by the slice thickness. This created two fat volumes: total abdominal fat and visceral fat (from the top of the pulmonary trunk to the bottom of the symphysis pubis). Subcutaneous fat volume was calculated by subtracting visceral fat from total abdominal fat. The liver fat percentage was also measured using a representative region of interest (1000 sq mm) placed in the right lobe of liver avoiding the main portal veins.

Covariates

Information on ethnicity (coded according to census criteria), current smoking status and lipid lowering medication use was obtained following an interview-administered questionnaire with a health care professional. Height and weight (Tanita TBE 611, Tanita, West Drayton, UK) were obtained by trained staff according to standard operating procedures and the subsequent values used to compute BMI (kg/m^2). Social deprivation was determined by assigning an index of multiple deprivation (IMD) score to the participant's resident area (based on postcode). IMD scores are publicly available continuous measures of compound social and material deprivation linked to health outcomes (including; income, employment, education, living environment and health). The dietary habits of participants were assessed using the Dietary Instrument for Nutrition Education (DINE) food frequency questionnaire; a method of measuring fibre, fat and unsaturated fat intake in primary care (34). Only self-reported dietary fat intake is reported within this paper.

Statistical Analysis

IBM SPSS Statistics v24.0 (Chicago, IL, USA) was used to conduct all statistical analyses. Linear regression analysis was used to examine the independent association of total, bouts and breaks in sedentary time with liver, subcutaneous, visceral and total abdominal fat. We display the main results per 60 minutes of sedentary time for ease of interpretation.

Model 1 was adjusted for age (continuous), sex, ethnicity (white European/south Asian/other), social deprivation (continuous), smoking status (current/ex/never smoked), lipid lowering medication (yes/no), study arm (intervention/control), dietary fat intake and time accelerometer worn (average number of minutes per day). Model 2 was additionally adjusted for MVPA or sedentary time and

MVPA (breaks). In order to examine the extent to which total adiposity attenuated these relationships, model 3 was further adjusted for BMI. Models were assessed for normality and multi co-linearity was assessed through the variance inflation factor (VIF).

Significant observations in Model 3 were followed up with interaction terms to assess whether associations between total sedentary time and adiposity were modified by levels of MVPA (active vs. inactive) or sex (male vs. female). Analysis was further stratified by MVPA status to show the direction of significant interactions.

Two-tailed p values of 0.05 or less were considered statistically significant for main effects. $p < 0.1$ was considered significant for interactions. Results of the generalised linear regression analysis are presented as the unstandardised beta co-efficient (β ; 95% confidence interval (CI) per 60 minutes of sedentary time). Adjustment was not made for multiple comparisons, therefore data were viewed with caution and in relation to the overall pattern of results.

Results

In total, 124 participants (age=64.0 $\pm$ 7.1 years; male=65.3%) (of a possible 141) had valid measures of objective activity, MRI and covariate data. There were no significant differences ($p > 0.05$) in anthropometric, metabolic, and demographic measures between participants who were included in this analysis vs. those not included. Table 1 displays the demographic, anthropometric, MRI-derived and accelerometer characteristics of all included participants, and when stratified by MVPA levels.

Total sedentary time

Following adjustment for age, sex, ethnicity, social deprivation, smoking status, lipid lowering medication, randomisation arm, dietary fat intake and time accelerometer worn, each 60 minutes of sedentary time was associated with higher liver (1.86%; CI (1.14, 2.52)), visceral (0.62L (0.32, 0.92)), subcutaneous (1.14L (0.54, 1.74)) and total abdominal fat (1.74L (0.96, 2.46)). Results are displayed in Table 2. All associations persisted after further adjustment for MVPA. Association of sedentary time with visceral and liver fat remained after additional adjustment for BMI.

Bouts of prolonged sedentary time

Results for bouts and breaks are displayed in Table S1. In the fully adjusted model, there were no significant associations between 0-30 minute bouts of sedentary time and MRI outcomes. Continuous 30-60 minute bouts of prolonged sedentary time were significantly associated with liver (1.44% (0.18, 2.70)), visceral (0.78L (0.36, 1.26)), subcutaneous (1.08L (0.12, 2.04)) and total abdominal fat (1.86L (0.66, 3.12)). When further adjusted for BMI, the results remained significant for visceral fat (0.48L (0.18, 0.78)).

A similar pattern was observed for continuous 60+ minute bouts. In the fully adjusted model, continuous 60+ minute bouts of sedentary time were significantly associated with liver (1.44% (0.66, 2.22)), visceral (0.66L (0.24, 1.08)) and total abdominal fat 2.88L (1.62, 4.08)) (not additionally adjusted for BMI).

Breaks in sedentary time

The number of breaks in sedentary time were significantly inversely associated with visceral (-0.06L (-0.85, -0.26)), subcutaneous (-0.68L (-1.35, -0.01)) and total abdominal fat (-0.12L (-0.21, -0.04)) in model 1. However, all associations were attenuated once adjusted for total sedentary time, MVPA and BMI.

Interaction analysis

Interaction analyses indicated MVPA status modified some associations, with inactive individuals displaying stronger associations of total sedentary time with liver, visceral and total abdominal fat, interaction values shown in Table S2. After stratification, no significant associations were found in active individuals. Conversely, each 60 minutes of sedentary time in the inactive cohort was associated with 2.16% higher liver (1.08, 3.30), 0.54L (0.12L, 0.96L) higher visceral and 1.80L (0.54L, 3.06L) higher total abdominal fat (results displayed in Table 3). There were no significant interactions for bout length or breaks in sedentary time (all $p > 0.1$; data not shown).

Figure 1 displays fat percentage images (from the bottom of the symphysis pubis to the top of liver) depicting total abdominal fat in two male participants with similar sedentary time, but different amounts of MVPA. Figure 2 displays the multiple linear regression coefficients for 0-30minutes, 30-60minutes and 60+ minute bouts of sedentary time (95% CI) with MRI derived measures of adiposity.

Discussion

This study demonstrates that for individuals at high risk of T2DM, sedentary time is detrimentally associated with liver, visceral and total abdominal fat, independent of important confounders (including MVPA). These findings extend previous cross-sectional results observed in the general population (35) and in those at high risk of T2DM (18) by showing that associations between sedentary time liver, visceral and total abdominal fat are stronger in those who do not reach the current exercise recommendations for health (<150 minutes per week); whereas no significant associations were observed in the active (>150 minutes per week) cohort. Furthermore, the bout length of sedentary time influenced the strength of the association.

To our knowledge this study is the first to look at the modifying influence of MVPA on associations between sedentary time and MRI derived fat distribution. The finding that the association between sedentary time and visceral fat is stronger in the inactive cohort is intriguing and lends credence to the proposition that physical activity levels may be an important determinant in the accrual of adipose tissue (9). Broadly, visceral fat has been associated with incident CVD, cancer and mortality after adjustment for clinical risk factors and generalised adiposity . In particular, it has been suggested to be an important link between cardio-respiratory fitness (with its high correlation with MVPA) and markers of the metabolic syndrome (36, 37), with exercise training studies showing inverse associations between visceral fat and insulin sensitivity in obese subjects (38). Furthermore, regular MVPA may induce selective reductions in visceral abdominal adipose tissue and other region specific fat deposits (subcutaneous) that would not necessarily be apparent when using more traditional measures to quantify body mass/adiposity (e.g. BMI and waist circumference).

Similarly, the observation that liver fat is strongly associated with sedentary time in the inactive cohort is a novel finding, which may be partially explained by excess visceral fat, where non-esterified fatty acids (NEFA), glycerol and hormones released from adipose tissue within the visceral

peritoneum are drained into the hepatic portal vein that feeds directly to the liver (39). Sustained exposure of the liver to an increased flux of NEFA via the portal circulation is the antecedent to many of the disturbances in glucose and lipids, thus predisposing an individual to peripheral insulin resistance, hyperlipidaemia and hypertension (40). This process may be further exacerbated by high levels of sedentary time and low levels of physical activity. Indeed, it has been shown that a prolonged bout of sitting (7.5 hours) elicits a less favourable NEFA postprandial response when compared to breaking sitting with either standing or walking (5 minutes every 30 minutes), which may reflect an increase in the lipolysis of triglycerides stored in adipose tissue in order to supply the working muscle (27).

Our observations for a modifying effect of MVPA status on the association of sedentary time with visceral, liver and total abdominal fat broadly corroborates other cross-sectional research which demonstrates that those who are physically active have a more desirable cardio-metabolic and inflammatory profile, even when combined with high sedentary time (17, 19). Similar results have also been shown in individuals recently diagnosed with T2DM where results were suggestive of a stronger association between sedentary time and subcomponents of metabolic risk among individuals below the median for cardiorespiratory fitness (15). This hypothesis appears to extend beyond traditional markers of health as a recent meta-analysis, which included more than 1 million people and used self-reported data, found that when compared to the referent group (<4h of sitting per day, ~60-75 minutes of moderate intensity activity per day; 9.0% of the cohort) there was no increased risk of mortality during follow-up in those who sat for more than 8 hours per day but also engaged in ~60-75 minutes of activity (HR 1.04, 95% CI 0.99-1.10; 4.4% of the cohort). However, this high activity levels was shown to attenuate, rather than eliminate, the association with mortality of those watching 5 hours or more of TV per day (1.15; 1.05, 1.29) (12).

The aforementioned observational findings have also been explored in an experimental context, which showed that individuals with higher fitness levels demonstrated a lower incremental area under the curve response for glucose and insulin when subjected to 7.5 hours of prolonged sitting (40). Similarly, they also accrued less of a metabolic benefit from breaking sitting time with light walking, when compared to those with lower fitness levels, although small benefits were still seen for reduction in insulin levels in individuals with higher fitness. Taken together, the experimental and cross-sectional literature imply that sedentary time may not be as pertinent in individuals with a relatively high fitness level or in those who engage in recommended levels of MVPA.

We found no significant associations between overall breaks in sedentary time and MRI outcomes. However, our findings do reinforce previous studies which have demonstrated that prolonged bouts of sedentary time are detrimental to health, particularly when examining markers of cardio-metabolic health (21). We found that as the prolonged sedentary bout length increased (from 0-30 minutes to 30-60 minutes to 60+ minutes), so did the strength of the association with MRI derived markers. This further reiterates the importance of targeting prolonged sitting time as well as MVPA in future disease prevention interventions.

Our study has multiple strengths. Most notably, it provides novel evidence of the modifying effect of MVPA on MRI derived adiposity in a sedentary, high risk of T2DM population. Secondly, we used gold standard measures in order to quantify regional fat deposition and physical activity levels. All measurements (including MRI scans) were also performed by the same team of trained staff, following identical standard operating procedures. Thirdly, participants were recruited from a multi-ethnic community.

Limitations include the cross-sectional design, thus limiting inference about the direction of causality between sedentary time and markers of MRI derived adiposity; as such, reverse causality remains a

possibility. It is also plausible that unmeasured lifestyle variables (i.e. alcohol intake) and residual confounding may have influenced the observed relationships. Exposures were only carried out at one time-point (up to 7 days), which precludes the drawing of causal inferences and may not be an accurate reflection of habitual activity. Finally, accelerometers rely on categorising movement (acceleration), as opposed to distinguishing between specific postures (sitting, lying and standing behaviours), which may lead to an under-estimation of the true association between sedentary time and markers of adiposity.

Conclusion

These novel findings from a high risk of T2DM cohort suggest that the deleterious associations of objectively measured sedentary time with visceral, liver and total abdominal fat, may be particularly pertinent for those individuals who do not undertake sufficient amounts of MVPA. Moreover, the manner in which sedentary time is accumulated may influence the strength of the associations with markers of MRI derived adiposity.

	All	Inactive	Active	P for difference
Characteristics	(N=124)	(N=66)	(N=58)	
Age (years)	64.0 ± 7.1	64.4 ± 7.1	62.4 ± 6.9	0.087
Male	81 (65.3)	37 (56.1)	44 (75.9)	<0.001
Current smokers	8 (6.5)	4 (6.1)	4 (6.9)	0.851
IMD score	21.8 ± 16.1	23.5 ± 15.9	19.9 ± 16.1	0.212
<i>Cardio-metabolic variables</i>				
BMI (kg/m ²)	31.8 ± 5.6	32.8 ± 6.0	30.8 ± 5.0	0.034
Waist circumference (cm)	105.4 ± 13.2	107.7 ± 14.5	103.0 ± 11.3	0.032
Weight (kg)	90.1 ± 17.3	91.3 ± 19.3	88.8 ± 15.1	0.495
<i>MRI-derived variables</i>				
Visceral fat (L)	6.6 ± 2.4	6.9 ± 2.5	6.4 ± 2.3	0.323
Liver fat (%)	10.6 ± 5.7	11.9 ± 6.1	9.0 ± 4.9	0.005
Subcutaneous fat (L)	13.1 ± 0.6	14.3 ± 5.9	11.9 ± 5.4	0.007
Total abdominal fat (L)	19.7 ± 6.7	21.2 ± 7.0	18.3 ± 6.0	0.007
<i>Ethnicity</i>				
White European	113 (91.1)	58 (87.9)	55 (94.8)	0.216
South Asian	8 (6.5)	7 (10.6)	1 (1.7)	0.045
Other	3 (2.4)	1 (1.5)	2 (3.4)	0.485
<i>Diagnosis</i>				
Normal glucose tolerance	96 (77.4)	48 (72.7)	48 (82.8)	0.183
Isolated impaired fasting glycaemia (IFG)	5 (4.0)	2 (3.0)	3 (5.2)	0.545
Isolated impaired glucose tolerance (IGT)	15 (12.1)	11 (16.7)	4 (6.8)	0.096
Both	8 (6.5)	5 (7.6)	3 (5.2)	0.587
All (impaired glucose regulation (IGR))	28 (22.6)	18 (27.3)	10 (17.2)	0.183
Dietary fat intake	26.4 ± 12.7	25.1 ± 13.2	27.8 ± 12.1	0.223
<i>Accelerometer variables</i>				
Time accelerometer worn (minutes per day)	858 ± 96	855 ± 98	861 ± 96	0.977
Sedentary Time (minutes per day)	546 ± 114	576 ± 120	516 ± 96	0.002
Sporadic 0-30 minute bout (minutes per day)	364.7 ± 75.9	373.9 ± 78.7	354.2 ± 71.9	0.149
Continuous 30-60 minute bout (minutes per day)	120.3 ± 57.4	132.3 ± 64.4	106.7 ± 45.0	0.013
Continuous 60+ minute bout (minutes per day)	61.4 ± 51.9	70.0 ± 58.1	51.6 ± 42.4	0.045
Light activity (minutes per day)	284 ± 80	270 ± 84	299 ± 72	0.042
Moderate-to-vigorous physical activity (minutes per day)	20.2 (12.5-39.8)	12.5 (6.1-16.7)	39.5 (28.3-55.1)	<0.001
Breaks in sedentary time (average per day)	80 ± 16	80 ± 15	80 ± 17	0.837
Total physical activity counts (x 1000·day)	229 (175-333)	176 (145-212)	330 (253-382)	<0.001
Steps per day	6802 ± 2940	4937 ± 1866	8731 ± 2856	<0.001

Table 1. Participant characteristics

Sedentary time = <100 counts per 60s; MVPA= ≥1952 counts per 60s; Total physical activity counts = the summation of counts within each epoch. Continuous parametric results as mean±standard deviation (SD), number (column percentage) and continuous non-parametric results as median

(interquartile range). IMD= Index of multiple deprivation. Inactive = <150 minutes per week of MVPA; Active = ≥ 150 minutes per week of MVPA

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Table 2: Associations per 60 minutes of sedentary time with markers of MRI-derived regional fat distribution

Model 1		
	Sedentary time β (95% CI)	<i>p</i>
Liver fat (%)	1.86 (1.14, 2.52)	<0.001
Visceral fat (L)	0.62 (0.32, 0.92)	<0.001
Subcutaneous fat (L)	1.14 (0.54, 1.74)	<0.001
Total abdominal fat (L)	1.74 (0.96, 2.46)	<0.001
Model 2		
Liver fat (%)	1.80 (0.96, 2.58)	<0.001
Visceral fat (L)	0.60 (0.30, 0.90)	<0.001
Subcutaneous fat (L)	0.96 (0.30, 1.62)	0.006
Total abdominal fat (L)	1.56 (0.72, 2.40)	0.001
Model 3		
Liver fat (%)	1.44 (0.66, 2.22)	<0.001
Visceral fat (L)	0.36 (0.06, 0.60)	0.013
Subcutaneous fat (L)	0.18 (-0.24, 0.66)	0.348
Model 1 adjusted for age, sex, ethnicity, social deprivation, smoking status, lipid lowering medication, arm (control/intervention), dietary fat intake and time accelerometer worn		
Model 2 adjusted for the above covariates and MVPA		
Model 3 adjusted for the above covariates and BMI. Total abdominal fat was not additionally adjusted for BMI due to multicollinearity.		

Table 3. Associations per 60 minutes of sedentary time with markers of MRI-derived regional fat distribution (Inactive vs. Active)

	Inactive (n=66)			Active (n=58)	
	Sedentary time β (95% CI)	p		Sedentary time β (95% CI)	p
Liver fat (%)	2.16 (1.08, 3.30)	<0.001		0.60 (-0.72, 1.92)	0.364
Visceral fat (L)	0.54 (0.12, 0.96)	0.014		0.30 (-0.30, 0.84)	0.348
Total abdominal fat (L)	1.80 (0.54, 3.06)	0.005		0.18 (-1.26, 1.62)	0.817
Adjusted for age, sex, ethnicity, social deprivation, smoking status, lipid lowering medication, arm (control/intervention), dietary fat intake, time accelerometer worn, sedentary time, MVPA, interaction term and BMI (not for total abdominal fat)					

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Figure legends

Figure 1. Fat percentage images (from the bottom of the symphysis pubis (top left) to the top of liver (bottom right)) depicting total abdominal fat in two male participants with similar sedentary time, but different amounts of MVPA. Colours represent the magnitude of adipose tissue density; from blue (0%) through to red (100%)

A. Sedentary time = 65.9%; MVPA = 5.5% (344 minutes per week) - **ACTIVE**

B. Sedentary time = 66.6%; MVPA = 0.2% (11 minutes per week) - **INACTIVE**

Figure 2. Multiple linear regression coefficients for sporadic (0-30minutes) and continuous (30-60minutes and 60+ minutes) bouts of sedentary time (95% CI) Adjusted for age, sex, ethnicity, social deprivation, smoking status, lipid lowering medication, arm (control/intervention), dietary fat intake, MVPA and time accelerometer worn.

CI: Confidence Interval

MVPA: Moderate-to-vigorous physical activity

Results for visceral and liver fat remained significant after further adjustment for BMI. Total abdominal fat was significant but not additionally adjusted for BMI due to multicollinearity.

Figure1a

401x151mm (96 x 96 DPI)

Accepted A

Figure1b

406x156mm (96 x 96 DPI)

Accepted A

179x162mm (300 x 300 DPI)

Acc

Table S1. Multiple linear regression models for continuous bouts of sedentary time (0-30 minutes, 30-60 minutes and 60+ minutes) and breaks in sedentary time with MRI derived measures of adiposity.

Model 1								
	Sporadic 0-30 minutes ^a β (95% CI)	p	Continuous 30-60 minutes ^a β (95% CI)	p	Continuous 60+ minutes ^a β (95% CI)	p	Breaks ^b β (95% CI)	p
Liver fat (%)	1.02 (-0.06, 2.10)	0.065	1.80 (0.54, 3.00)	0.005	1.98 (0.84, 3.12)	0.001	-0.08 (-1.62, 0.01)	0.067
Visceral fat (L)	0.54 (0.12, 0.96)	0.011	0.84 (0.42, 1.26)	<0.001	1.08 (0.66, 1.56)	<0.001	-0.06 (-0.85, -0.26)	<0.001
Subcutaneous fat (L)	0.72 (-0.18, 1.68)	0.120	1.38 (0.42, 2.34)	0.004	2.04 (1.08, 3.00)	<0.001	-0.68 (-1.35, -0.01)	0.047
Total abdominal fat (L)	1.32 (0.12, 2.52)	0.035	2.22 (1.02, 3.42)	<0.001	3.12 (1.92, 4.32)	<0.001	-0.12 (-0.21, -0.04)	0.005
Model 2								
Liver fat (%)	0.84 (-0.36, 1.98)	0.166	1.44 (0.18, 2.70)	0.023	1.62 (0.48, 2.82)	0.007	-0.03 (-0.10, 0.04)	0.287
Visceral fat (L)	0.42 (0.01, 0.84)	0.042	0.78 (0.36, 1.26)	<0.001	1.08 (0.66, 1.50)	<0.001	-0.04 (-0.08, 0.01)	0.053
Subcutaneous fat (L)	0.36 (-0.54, 1.32)	0.435	1.08 (0.12, 2.04)	0.029	1.80 (0.84, 2.76)	<0.001	-0.03 (-0.11, -0.06)	0.558
Total abdominal fat (L)	0.84 (-0.42, 2.04)	0.188	1.86 (0.66, 3.12)	0.003	2.88 (1.62, 4.08)	<0.001	-0.06 (-0.17, -0.04)	0.250
Model 3								
Liver fat (%)	0.54 (-0.66, 1.68)	0.367	0.66 (-0.54, 1.92)	0.284	1.44 (0.66, 2.22)	0.048	-0.01 (-0.04, 0.03)	0.831
Visceral fat (L)	0.30 (-0.06, 0.66)	0.082	0.48 (0.18, 0.78)	0.020	0.66 (0.24, 1.08)	0.001	-0.02 (-0.05, 0.02)	0.295
Subcutaneous fat (L)	0.06 (-0.60, 0.54)	0.967	0.06 (-0.60, 0.72)	0.939	0.48 (-0.18, 1.14)	0.145	-0.01 (-0.09, 0.07)	0.798
Model 1 adjusted for age, sex, ethnicity, social deprivation, smoking status, lipid lowering medication, arm (control/intervention), dietary fat intake and time accelerometer worn								
Model 2 adjusted for the above covariates and MVPA ^a or MVPA and sedentary time ^b								
Model 3 adjusted for the above covariates and BMI. Total abdominal fat was not additionally adjusted for BMI due to multicollinearity.								

Table S2. Interaction values for the modifying effects of MVPA status (inactive vs. active) on associations between sedentary time and liver fat, visceral fat and total abdominal fat.

	<i>p</i>
Liver fat (%)	0.028
Visceral fat (L)	0.019
Subcutaneous fat (L)	0.381
Total abdominal fat (L)	0.051
Adjusted for age, sex, ethnicity, social deprivation, smoking status, lipid lowering medication, arm (control/intervention), dietary fat intake, time accelerometer worn, sedentary time, MVPA, interaction term and BMI (not for total abdominal fat)	

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