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Original research

Effects of reduced sedentary time on cardiometabolic health in adults with metabolic syndrome: A three-month randomized controlled trial☆

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ABSTRACT

Objectives: To investigate if reducing sedentary behavior improves cardiometabolic biomarkers in adults with metabolic syndrome.
Design: Randomized controlled trial.
Methods: Sixty-four sedentary middle-aged adults with metabolic syndrome were randomized into intervention (INT; n = 33) and control (CON; n = 31) groups. INT was guided to limit sedentary behavior by 1 h/day through increased standing and light-intensity physical activity. CON was instructed to maintain usual habits. Sedentary behavior, breaks in sedentary behavior, standing, and physical activity were measured with hip-worn accelerometers for three months. Fasting blood sampling and measurements of anthropometrics, body composition, and blood pressure were performed at baseline and at three months. Linear mixed models were used for statistical analyses.
Results: INT reduced sedentary behavior by 50 (95% CI: 24, 73) min/day by increasing light-intensity and moderate-to-vigorous physical activity (19 [8, 30] and 24 [14, 34] min/day, respectively). Standing increased also, but non-significantly (6 [−11, 23] min/day). CON maintained baseline activity levels. Significant intervention effects favoring INT occurred in fasting insulin (INT: 83.4 [68.7, 101.2] vs. CON: 102.0 [83.3, 125.0] pmol/l at three months), insulin resistance (HOMA-IR; 3.2 [2.6, 3.9] vs. 4.0 [3.2, 4.9]), HbA_{1c} (37 [36, 38] vs. 38 [37, 39] mmol/mol), and liver enzyme alanine aminotransferase (28 [24, 33] vs. 33 [28, 38] U/l).
Conclusions: Reducing sedentary behavior by 50 min/day and increasing light-intensity and moderate-to-vigorous activity showed benefits in several cardiometabolic biomarkers in adults with metabolic syndrome. Replacing some of the daily sedentary behavior with light-intensity and moderate-to-vigorous physical activity may help in cardiometabolic disease prevention in risk populations.

Practical implications

- Reduced sedentary time and increased light- and moderate-to-vigorous-intensity physical activity had beneficial effects on several cardiometabolic risk markers in adults with metabolic syndrome.
- A 50-minute reduction in daily sedentary time was not enough to prevent the worsening of all risk markers that likely occurs over time with metabolic syndrome.
- Reducing daily sedentary behavior may be an additional approach to aid in the prevention of cardiometabolic diseases in risk populations.
- Higher volume and intensity of physical activity is likely to provide greater health benefits for sedentary individuals at increased risk of cardiometabolic diseases.

Abbreviations: ALT, alanine aminotransferase; APE, angle for postural estimation; AST, aspartate aminotransferase; BP, blood pressure; CON, control group; DBP, diastolic blood pressure; FFM, fat free mass; GGT, γ-glutamyltransferase; HOMA-IR, homeostatic model assessment of insulin resistance; INT, intervention group; LPA, light-intensity physical activity; MAD, mean amplitude deviation; MET, metabolic equivalent; MetS, metabolic syndrome; MVPA, moderate-to-vigorous physical activity; PA, physical activity; SB, sedentary behavior; SBP, systolic blood pressure; WC, waist circumference.

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1. Introduction

The modern lifestyle has reduced daily physical activity (PA) demands in the recent decades, and now the majority of waking time (~8–9 h/day) is spent sitting.[1,2] Physical inactivity and sedentary behavior (SB) increase the risk of chronic diseases and mortality,[3,4] and SB has been adversely associated with cardiometabolic outcomes (e.g., waist circumference [WC], HDL-cholesterol, triglycerides and insulin).[5] Due to the accumulating observational evidence of the detrimental effects of sitting, an increasing number of interventions are targeting reductions in SB and investigating whether sitting less can improve health. As a major proportion of adults globally are insufficiently physically active,[6] reducing SB instead of increasing PA may be a more feasible method for achieving health benefits.

Recent meta-analyses have shown that SB interventions can reduce sedentary time by 24–82 min/day[7,8] and produce beneficial effects on common cardiometabolic outcomes (e.g., weight, WC, blood pressure [BP], fasting insulin, HDL).[9] However, previous interventions have mainly targeted healthy populations[7] and occupational sitting,[8] and the majority have lasted for less than three months[9] or reported attenuations in SB reductions with longer follow-ups.[7] Additionally, accelerometers are typically used only for ≤ 7 days at the beginning and end of interventions, which may not accurately reflect actual changes during the intervention or habitual behaviors. Thus, the current evidence of cardiometabolic benefits of reduced SB is limited, particularly in populations at increased cardiometabolic disease risk.

Therefore, we investigated the effects of a three-month free-living intervention aiming at 1 h/day SB reduction on cardiometabolic outcomes in inactive sedentary adults with metabolic syndrome (MetS). In contrast to previous studies, accelerometers were used continuously throughout the intervention. In addition to the traditional cardiometabolic biomarkers, we investigated the effects on liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT), which have not been studied in the context of SB reduction previously. These enzymes are markers of liver health,[10] and they can thus provide novel and valuable information to further understand the effects of SB on metabolic health. We hypothesized that reduced SB, without intentionally adding exercise and moderate-to-vigorous PA (MVPA), has beneficial effects on cardiometabolic outcomes.

2. Methods

The study design is a parallel-group randomized controlled trial. The data was collected at the Turku PET Centre (Turku, Finland) between April 2017 and November 2019, and consists of the mid-point data of a six-month trial (Clinicaltrials.gov NCT03101228). The study involved a one-month screening phase and a three-month intervention period. Baseline measurements were performed after the screening for eligible participants, who were then randomized (1:1) by a statistician into intervention (INT; n = 33) and control (CON; n = 31) groups by random permuted block randomization with stratification for sex. The randomization code was generated with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Both groups wore accelerometers continuously throughout the screening and intervention phases, and the same outcomes were assessed at baseline and at three months. Outcome assessors were blinded to group allocation. All participants gave written informed consent. The study was conducted according to good clinical practice and Declaration of Helsinki and approved by the Ethics Committee of the Hospital District of Southwest Finland (16/1810/2017).

The participants were recruited by newspaper advertisements and bulletin leaflets from the local community. The target population was sedentary and inactive working-aged adults with MetS. As previously reported,[11] the inclusion criteria were age 40–65 years; physical inactivity (< 120 min/week of self-reported MVPA); accelerometer-measured sitting time ≥ 10 h/day or 60 % of accelerometer wear time/day during screening; BMI 25–40 kg/m^2; BP < 160/100 mm Hg; fasting glucose < 7.0 mmol/l; and fulfillment of MetS criteria including three of the following: WC ≥ 94 cm (men)/≥ 80 cm (women), triglycerides ≥ 1.7 mmol/l, HDL < 1.0 mmol/l (men)/< 1.3 mmol/l (women), systolic BP (SBP) ≥ 130 and/or diastolic BP (DBP) ≥ 85 mm Hg, or fasting glucose > 5.6 mmol/l. The exclusion criteria were previous cardiac event; diagnosed diabetes; abundant alcohol consumption (according to national guidelines); use of narcotics, cigarette or snuff tobacco; depressive or bipolar disorder; and any chronic disease/condition that could endanger participant safety or study procedures or interfere with the interpretation of results. The sample size n = 64 was determined by power calculations for the primary outcome of the six-month trial (whole-body insulin sensitivity [M-value]).

The aim of the behavioral intervention was to reduce SB by 1 h/day compared to the individually determined baseline during screening. INT participants were guided by a researcher in 1-hour tailored personal counseling sessions to sit less by increasing standing and light-intensity PA (LPA), without intentionally adding exercise or MVPA. Ways to increase standing and LPA were discussed individually according to participants' preferences, and could include e.g., use of sit-stand desks, standing during phone calls and taking stairs instead of elevators. CON was guided to maintain usual habits. Throughout the whole three-month intervention, both groups used accelerometers connected via a cloud system to an interactive ExSed-smartphone application (UKK Terveyspalvelut Oy, Tampere, Finland) described in detail elsewhere.[12] Daily SB and PA goals were set in the application individually for each participant: for INT 1 h was subtracted from baseline SB and equivalent time added to standing and LPA, whereas for CON the application reflected the baseline values. The application provided a graphical illustration of daily SB and PA accumulation, enabling self-monitoring. INT participants were contacted 2–3 times during the intervention via phone, and they visited the research center at least once to receive support with the goals and to assure devices were working properly.

To determine the baseline values during screening, SB, breaks in SB, standing, and PA were assessed in both groups for one month during waking hours (except when exposed to water) with hip-worn triaxial accelerometers (UKK AM30, UKK Institute, Tampere, Finland) with a digital acceleration sensor (ADXL345, Analog Devices, Norwood, MA, USA). Thereafter, throughout the three-month intervention period both groups used interactive hip-worn triaxial accelerometers (Movesense, Suunto, Vantaa, Finland using ExSed algorithms) during waking hours together with the ExSed-application. Wear time 10–19 h/day and ≥ 7 days was considered valid. Wear time was determined as periods when the accelerometer was worn on the hip, and non-wear time consisted of periods during which the acceleration of each of the three measurement axes remained within 187.5 mg range for ≥ 30 min (at least 180,000 measured values within 187.5 mg range for each axis had to be recorded).[13] Data collection was initialized again if the absolute value of difference between accelerometer inactivity and the incident acceleration of any axis exceeded 187.5 mg instantaneously and 500 mg within the next 5 seconds (requires only a 0.01-second movement); if not, the accelerometer returned to inactive state. Daily measurement ≥ 19 h likely indicates that the accelerometer was worn also while sleeping; therefore, the exceeding hours were subtracted from SB on the days with wear time ≥ 19 h. The accelerometer data was analyzed in six-second epochs by validated mean amplitude deviation (MAD) and angle for posture estimation (APE) methods, as described previously.[14–16] SB and standing were defined as ≤ 1.5 METs, LPA as 1.5–2.9 METs, and MVPA as ≥ 3.0 METs. Moderate and vigorous activities are combined as MVPA, as the amount of vigorous activity was negligible.

Venous blood samples were drawn after fasting ≥ 10 h and analyzed at the Turku University Hospital Laboratory. Plasma glucose was determined by an enzymatic reference method with hexokinase GLUC3; plasma triglycerides, cholesterol (total, LDL, HDL) and GGT by enzymatic colorimetric tests; and ALT and AST by the photometric IFCC method (Cobas 8000 c702). Plasma insulin was measured by electrochemiluminescence immunoassay (Cobas 8000 e801), and HbA_{1c} by turbidimetric inhibition immunoassay (Cobas 6000 c501); all analyzers by Roche Diagnostics GmbH, Mannheim, Germany. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated with formula: insulin (mU/ml) × glucose (mmol/l) / 22.5.

Weight, body fat %, fat mass and fat free mass (FFM) were measured with air displacement plethysmography (Bod Pod, COSMED USA, Inc., Concord, CA, USA) after fasting ≥ 4 h. Height was measured with a stadiometer. BMI was calculated as kg/m^2. WC was measured midway between the iliac crest and the lowest rib. BP was measured by a digital monitor (Apteq AE701f, Rossmax International Ltd, Taipei, Taiwan) after resting ≥ 5 min.

Descriptive statistics including mean (SD) or median (Q1, Q3, range) were calculated. A linear mixed model for repeated measurements including each outcome individually, time as a within-factor, group as a between-factor, and group × time-interaction was used to estimate the intervention effects and changes within and between groups. Sex was included as a variable in all models, and models with accelerometer variables included accelerometer wear time as a covariate. A compound symmetry covariance structure was used for time, and multiple comparisons were adjusted with the Tukey–Kramer method. Normality of distribution was determined by visual evaluation of residuals, and log10 transformations were performed as required. The intervention effects are reported as model-based means (95 % CI). For accelerometer outcomes, the value at three months indicates daily mean (95 % CI) of continuous accelerometer measurement throughout the three-month intervention. For non-normally distributed outcomes, back-transformed geometric means in original scale and ratios of population geometric means (INT/CON) are presented in tables and figures for ease of interpretation. Correlations between changes (Δ) during the intervention in INT were analyzed with Spearman's rank correlation and missing data was handled by pairwise deletion. Statistical significance was set at $p < 0.05$ (two-tailed). Correlation analyses were performed with IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA), and all other analyses with SAS 9.4. Figures were created with GraphPad Prism 5.01 (GraphPad Software, San Diego, CA, USA).

3. Results

A total of 263 people volunteered, of which 155 were screened to fulfill the target of 64 eligible participants. Sixty-three participants completed the three-month intervention period (mean duration 3.2 [0.6] months). Only one participant dropped out (personal reasons) (Supplementary file A online). The mean age was 58 (SD 7) years, and 37 participants (58 %) were women. Forty-one % of the participants were overweight and 59 % obese. At baseline, the participants spent 10.04 (SD 1.01) h/day sedentary, 1.79 (0.59) h/day standing, 1.74 (0.44) h/day in LPA, and 0.97 (0.32) h/day in MVPA and took 5149 (1825) steps and 29 (8) breaks in SB daily (Supplementary Table A.1 online).

Valid accelerometer data from the intervention period is available for 50 participants (78 %; n = 25 in both groups); missing data is due to data transfer issues between the accelerometers and the cloud system. The median of valid accelerometer days was 61 (Q1 37, Q3 73, range 7–99), and the accelerometers were worn for 15.11 (SD 0.75) h/day during the intervention. Wear time was ~35 min/day longer during the intervention compared to the screening in both groups. In SB, LPA, MVPA, standing time and steps/day the mean changes from baseline to three months were significantly different between groups (Fig. 1). In more detail, INT reduced SB by ~50 min/day (95 % CI: 24, 73; 8 % of daily baseline SB) primarily by increasing LPA (19 [8, 30] min/day) and MVPA (24 [14, 34] min/day). CON did not significantly change SB, LPA, or MVPA. Standing time increased slightly and not statistically significantly in INT (6 [−11, 23] min/day) and decreased in CON (−13 [−30, 5] min/day). Both groups increased steps/day, but the increase was greater in INT compared to CON: 3800 (2685, 4195) vs. 1918 (801, 3036) steps/day. Breaks in SB did not significantly change in either group.

Significant intervention effects favoring INT were seen in fasting insulin, HOMA-IR, HbA_{1c} (Fig. 2), triglycerides, ALT, and resting heart rate (Table 1). The effects mainly occurred due to increases from baseline to three months in CON that exceeded any changes in INT. In triglycerides and heart rate, within-group changes were non-significant despite significant overall intervention effects.

WC, body fat %, fat mass, SBP and DBP (Table 1) decreased slightly during the intervention with no difference between groups. Fasting glucose (Fig. 2); FFM; total, LDL- and HDL-cholesterol; AST; and GGT (Table 1) increased similarly in both groups. Weight or BMI did not change in either group (Table 1).

Changes in standing time were inversely correlated with weight and BMI changes, and changes in the number of steps/day correlated inversely with WC changes. Changes in MVPA correlated positively with HDL changes. Changes in weight and BMI correlated positively with changes in triglycerides and BP, and changes in WC also correlated positively with changes in BP. Changes in FFM correlated inversely with changes in fasting glucose (Supplementary Table A.2 online).

4. Discussion

Our results indicate benefits in several cardiometabolic outcomes with reduced SB in sedentary adults with MetS. A 50 min/day reduction in SB and subsequent increases in LPA and MVPA (consisting mainly of moderate-intensity PA) had beneficial effects on fasting insulin, HOMA-IR, HbA_{1c} and ALT, but it was not able to prevent worsening in all biomarkers. Reducing daily SB may be helpful in cardiometabolic disease prevention in risk populations, but a more substantial SB reduction and/or higher volume and intensity of PA is likely needed for sedentary individuals to achieve greater health benefits. To our knowledge, this is the first study to measure SB and PA with accelerometers continuously throughout the three-month intervention, and to investigate the health effects of SB reduction in sedentary and inactive, middle-aged adults with MetS. Compared to a population-based sample of Finnish adults of similar age, our participants spent 1,5 h more sedentary and had ~1 h less LPA and ~30 min less MVPA daily.[17]

The effects of free-living SB interventions on cardiometabolic health have been recently synthesized in two meta-analyses.[9,18] Hadgraft et al. reported improvements in anthropometrics, BP, insulin and lipids in healthy populations, but SB changes were not analyzed.[9] In clinical populations (overweight/obesity; type 2 diabetes; cardiovascular, neurological/cognitive and musculoskeletal diseases) ~1-hour SB reduction improved HbA_{1c}, body fat % and WC.[18] Similar to our findings, others have also reported benefits in HbA_{1c},[19] fasting insulin and HOMA-IR[20] following SB interventions. SB reduction may also improve fasting glucose,[21] total cholesterol,[22] body fat %,[23] WC,[20] and clustered cardiometabolic risk score.[21] On the other hand, not all interventions have been effective in reducing SB, or improving cardiometabolic outcomes despite SB reductions.[24,25]

Our study complements and extends this limited and inconsistent evidence. It seems that sitting less may be beneficial particularly from type 2 diabetes prevention perspective, as we found benefits in markers of glucose metabolism and diabetes risk (i.e., fasting insulin, HOMA-IR, HbA_{1c}), in line with previous findings. In addition to the traditional cardiometabolic biomarkers, the intervention effect favoring INT on liver enzyme ALT is a novel finding that, to our knowledge, has not been reported previously. The intervention effects on liver enzymes AST and GGT also were near-significant (group × time p = 0.057 and p = 0.071, respectively). These enzymes are markers of liver dysfunction or injury, and are most often elevated due to non-alcoholic fatty liver disease, which is considered the hepatic expression of MetS.[10] SB has been associated with fatty liver,[26] but SB interventions have not studied effects on liver health markers. Elevated ALT and AST are

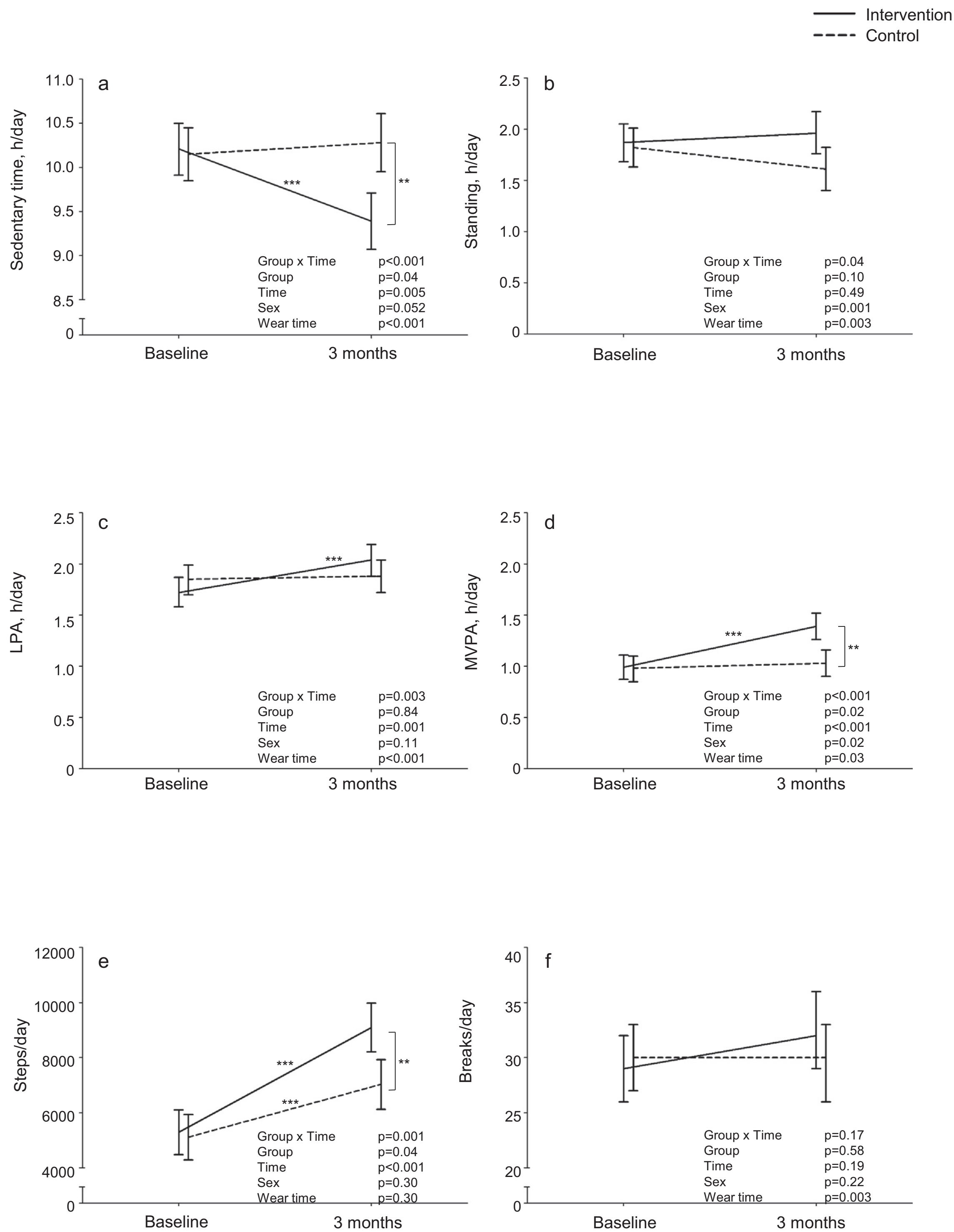

Fig. 1. The intervention effects on activity outcomes. a) Sedentary time (h/day), b) standing (h/day), c) light-intensity physical activity (h/day), d) moderate-to-vigorous physical activity (h/day), e) steps/day, and f) breaks in sedentary time/day at baseline and throughout the 3-month intervention in sedentary, inactive adults with metabolic syndrome. Baseline indicates daily mean (95 % CI) of a continuous 1-month screening accelerometer measurement, and value at three months indicates daily mean (95 % CI) of continuous accelerometer measurement throughout the 3-month intervention. Solid line represents the intervention group and dashed line the control group. ** = Tukey's $p < 0.01$; *** = Tukey's $p < 0.001$.

associated with obesity and dyslipidemia,[27] and they independently predict type 2 diabetes.[28] It may have an important impact on public health and disease prevention in risk populations if benefits in several diabetes risk markers can be achieved with SB reductions.

In addition to the intervention effects, changes in several outcomes with no difference between groups were observed during the intervention. Despite CON also improving WC, fat mass, SBP and HDL, the improvements were greater in INT. Total cholesterol, LDL and fasting glucose, on the other hand, increased similarly in both groups. However, participation effect and confounding factors not controlled for (e.g., dietary habits) can affect the results, and they should therefore be interpreted cautiously.

Although the intervention aimed to reduce SB primarily by increasing standing and LPA, both LPA and MVPA increased. Standing time also

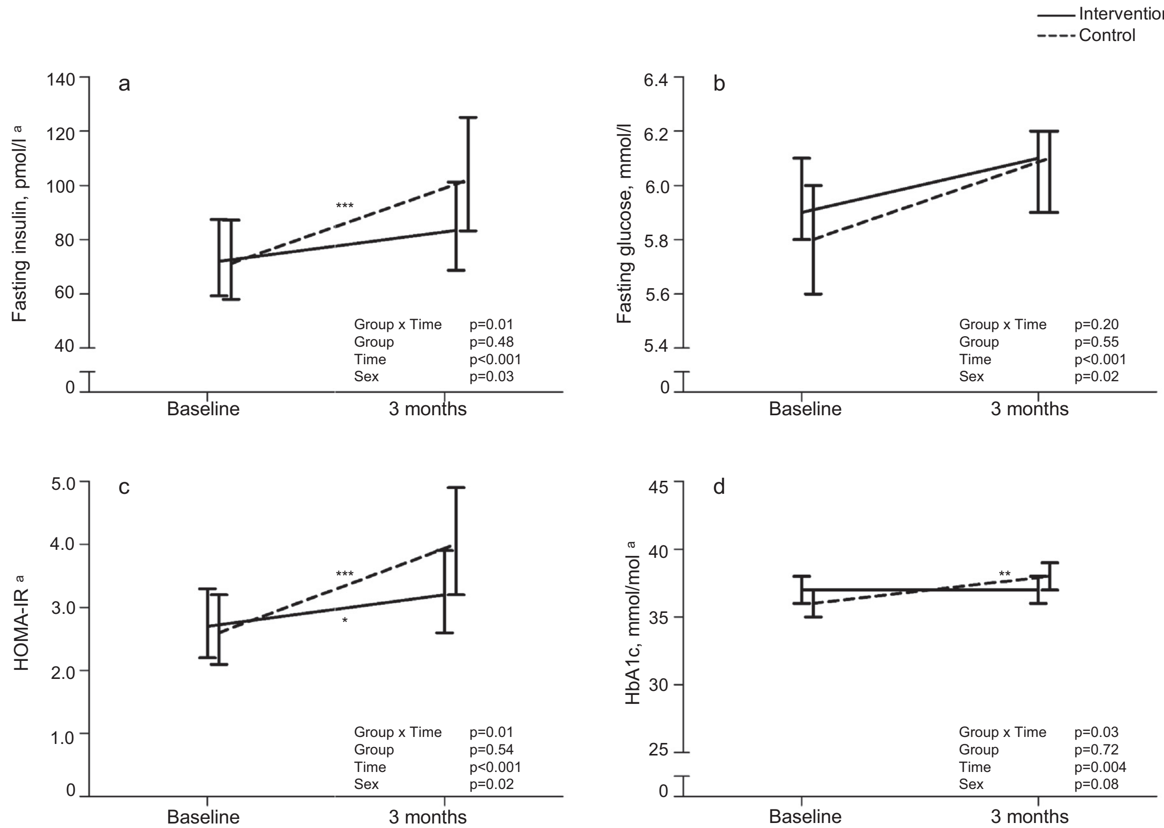

Fig. 2. The intervention effects on glycemic outcomes. Mean (95 % CI) a) fasting insulin (pmol/l), b) fasting glucose (mmol/l), c) HOMA-IR, and d) HbA_{1c} (mmol/mol) at baseline and at three months in sedentary, inactive adults with metabolic syndrome. Solid line represents the intervention group and dashed line the control group. [a] = log10 transformed; means are back-transformed geometric model-based means (95 % CI) * = Tukey's $p < 0.05$; ** = Tukey's $p < 0.01$; *** = Tukey's $p < 0.001$.

increased slightly (6 min/day), but non-significantly. A recent meta-analysis of free-living interventions in clinical populations reported a comparable ~60 min/day SB reduction, but in contrast to our study SB was mainly replaced by standing and low-intensity walking, with no change in MVPA.[18] It is noteworthy, however, that the MVPA amount is dependent on analysis methods.[13] In our study, the total MVPA

Table 1
The intervention effects on cardiometabolic outcomes within and between groups from baseline to 3 months.

	Intervention (n = 33)		Control (n = 31)		Difference between groups (95 % CI) from baseline to 3 months	p-values[a]		
	Baseline[b]	3 months[b]	Baseline[b]	3 months[b]		Group	Time	Group × time
Body weight, kg	92.8 (87.6, 98.0)	92.3 (87.1, 97.5)	93.7 (88.4, 99.1)	93.7 (88.3, 99.1)	−0.5 (−1.6, 0.6)	0.76	0.29	0.34
BMI, kg/m^2	31.5 (30.0, 33.0)	31.3 (29.8, 32.8)	31.7 (30.2, 33.3)	31.7 (30.1, 33.3)	−0.2 (−0.5, 0.2)	0.78	0.22	0.35
Waist circumference, cm	111.3 (107.5, 115)	109.7 (105.9, 113.5)	110.3 (106.5, 114.2)	109.5 (105.6, 113.4)	−0.7 (−2.6, 1.1)	0.83	**0.01**	0.42
Body fat, %	42.8 (40.6, 44.9)	41.8 (39.6, 43.9)	43.4 (41.1, 45.6)	42.4 (40.1, 44.6)	0.0 (−1.3, 1.3)	0.70	**0.004**	0.99
Fat mass, kg	39.7 (36.0, 43.5)	38.6 (34.8, 42.4)	40.9 (37.1, 44.8)	40.0 (36.2, 43.9)	−0.2 (−1.7, 1.3)	0.62	**0.01**	0.78
FFM, kg	53.1 (50.8, 55.5)	53.7 (51.4, 56.0)	52.8 (50.4, 55.2)	53.7 (51.2, 56.1)	−0.3 (−1.5, 0.9)	0.91	**0.02**	0.61
SBP, mm Hg	146 (140, 152)	141 (136, 147)	139 (133, 145)	136 (130, 142)	−2 (−9, 6)	0.11	**0.03**	0.64
DBP, mm Hg	89 (86, 92)	87 (84, 90)	88 (85, 91)	84 (81, 87)	1 (−3, 5)	0.22	**0.008**	0.51
Resting heart rate, bpm[c]	68 (65, 71)	67 (64, 70)	66 (63, 69)	68 (65, 72)	0.95 (0.90, 1.00)	0.82	0.49	**0.03**
Total cholesterol, mmol/l[c]	4.7 (4.4, 5.0)	5.0 (4.7, 5.3)	4.6 (4.3, 4.9)	5.0 (4.7, 5.3)	0.98 (0.93, 1.03)	0.71	**<0.001**	0.51
LDL-cholesterol, mmol/l[c]	3.0 (2.7, 3.3)	3.2 (2.9, 3.5)	2.9 (2.7, 3.2)	3.3 (3.0, 3.6)	0.97 (0.92, 1.03)	0.91	**<0.001**	0.37
HDL-cholesterol, mmol/l	1.31 (1.19, 1.43)	1.44 (1.32, 1.56)	1.39 (1.27, 1.52)	1.49 (1.36, 1.61)	0.03 (−0.06, 0.13)	0.45	**<0.001**	0.47
Triglycerides, mmol/l[c]	1.4 (1.2, 1.6)	1.4 (1.2, 1.6)	1.0 (0.9, 1.2)	1.2 (1.1, 1.5)	0.82 (0.68, 0.99)	0.06	0.10	**0.04**
ALT, U/l[c]	28 (24, 33)	28 (24, 33)	27 (23, 31)	33** (28, 38)	0.81 (0.69, 0.95)	0.67	**0.02**	**0.008**
AST, U/l[c]	25 (23, 28)	28 (25, 31)	25 (22, 27)	30 (27, 34)	0.90 (0.81, 1.00)	0.66	**<0.001**	0.06
GGT, U/l[c]	29 (23, 35)	29 (24, 36)	26 (21, 32)	31 (25, 38)	0.87 (0.74, 1.01)	0.89	**0.03**	0.07

FFM = fat free mass; SBP = systolic blood pressure; DBP = diastolic blood pressure; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyltransferase.
[a] Group: the main effect of group differences; time: the main effect of time; group × time: the interaction between the two main effects. Bolded p-values indicate statistical significance ($p < 0.05$).
[b] Model-based means (95% CI).
[c] Log10 transformed; means are back-transformed geometric model-based means (95% CI); difference is the ratio of geometric population means (95% CI) (intervention/control).
** Tukey's $p < 0.01$ between baseline and 3 months.

amount also includes short and sporadic MVPA bouts as we analyzed the accelerometer data in only six-second epochs. Steps increased in our study as well, and the increase correlated with the MVPA increase (Supplementary Table A.2 online), suggesting that the participants may have found it easier to reduce SB by walking at a moderate pace than by standing and incorporating LPA into daily activities. Reallocating SB to different behaviors, and the composition of behaviors across the 24-h day, affects health outcomes differently. Replacing SB with standing has been shown to improve glycemic outcomes[18,29] and fat mass,[29] while reallocating SB to LPA or MVPA appears beneficial for glycemic outcomes, lipids and WC.[30] Although replacing SB with any intensity PA is beneficial, the greatest benefits are achieved with the reallocation of SB to MVPA.

The intervention effects in our study appeared to mainly occur due to increases in CON that exceeded any changes in INT. The seemingly rapid worsening rate of biomarkers in CON should be interpreted cautiously, however, as it may be inflated due to a statistical phenomenon or e.g., seasonal/spontaneous variation. Nevertheless, the overall trend indicating increases in CON was consistent across the majority of studied biomarkers. It is noteworthy that these changes took place despite a significant increase in daily steps also in CON. These results suggest that the biomarker levels in adults with MetS rise steadily over time as MetS precedes the development of cardiometabolic diseases, and SB reduction alone without exercise/PA component might not be enough to prevent this. It seems that in a highly sedentary and inactive risk population a substantial increase in volume and intensity of PA might be needed to improve risk markers.

The key strengths include the randomized controlled trial design in free-living setting and the three-month accelerometer measurement. These likely provide a more truthful representation of daily activity and behavior than short measurement periods that are often used, or controlled laboratory trials. Good participant retention is also a strength. However, due to technical challenges, valid accelerometer data is not available for all participants who completed the intervention, which can be considered a limitation.

Other limitations include possible confounding factors (e.g., dietary intake), and a relatively small sample size. The participants were instructed to not change their diets during the intervention, but dietary data was not evaluated at this timepoint of the study. Additionally, lack of follow-up data beyond three months currently prevents investigation of the sustainability of changes in behavior and health outcomes. Generalizability may be limited to sedentary, white middle-aged adults with MetS, but given the prevalence of obesity and inactive lifestyles, the results are likely applicable to wider populations in developed countries.

5. Conclusion

Reducing daily SB by 50 min and increasing LPA and MVPA resulted in beneficial effects in several cardiometabolic risk markers in adults with MetS in three months, but it was not enough to prevent increases in all biomarkers. More substantial reduction in SB and/or structured exercise may be needed for sedentary individuals to achieve greater health benefits. However, sitting less may provide an additional approach to aid in chronic disease prevention in high-risk populations.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsams.2022.04.002.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J.K. received consultancy fees from GE Healthcare and AstraZeneca and speaker fees from GE Healthcare, Bayer, Lundbeck, Boehringer-Ingelheim and Merck, outside of the submitted work. The other authors report no competing interests.

Confirmation of ethical compliance

All participants gave written informed consent. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (16/1810/2017), and good clinical practice and the Declaration of Helsinki were followed.

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References

1. Matthews CE, Chen KY, Freedson PS et al. Amount of time spent in sedentary behaviors in the United States, 2003–2004. *Am J Epidemiol* 2008;167(7):875-881. doi:10.1093/aje/kwm390.
2. Loyen A, Clarke-Cornwell AM, Anderssen SA et al. Sedentary time and physical activity surveillance through accelerometer pooling in four European countries. *Sports Med* 2017;47(7):1421-1435. doi:10.1007/s40279-016-0658-y.
3. Lee IM, Shiroma EJ, Lobelo F et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012;380(9838):219-229. doi:10.1016/S0140-6736(12)61031-9.
4. Dempsey P, Strain T, Khaw KT et al. Prospective associations of accelerometer-measured physical activity and sedentary time with incident cardiovascular disease, cancer, and all-cause mortality. *Circulation* 2020;141(13):1113-1115. doi:10.1161/CIRCULATIONAHA.119.043030.
5. Healy GN, Matthews CE, Dunstan DW et al. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. *Eur Heart J* 2011;32(5):590-597. doi:10.1093/eurheartj/ehq451.
6. Guthold R, Stevens GA, Riley LM et al. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *Lancet Glob Health* 2018;6(10):e1077-e1086.
7. Peachey MM, Richardson J, Tang A AV et al. Environmental, behavioural and multicomponent interventions to reduce adults' sitting time: a systematic review and meta-analysis. *Br J Sports Med* 2020;54(6):315-325. doi:10.1136/bjsports-2017-098968.
8. Shrestha N, Kukkonen-Harjula KT, Verbeek JH et al. Workplace interventions for reducing sitting at work. *Cochrane Database Syst Rev* 2018(12):CD010912. doi:10.1002/14651858.CD010912.pub5.
9. Hadgraft NT, Winkler E, Climie RE et al. Effects of sedentary behaviour interventions on biomarkers of cardiometabolic risk in adults: systematic review with meta-analyses. *Br J Sports Med* 2021;55(3):144-154. doi:10.1136/bjsports-2019-101154.
10. Oh RC, Hustead TR, Ali SM et al. Mildly elevated liver transaminase levels: causes and evaluation. *Am Fam Physician* 2017;96(11):709-715.
11. Garthwaite T, Sjöros T, Koivumäki M et al. Standing is associated with insulin sensitivity in adults with metabolic syndrome. *J Sci Med Sport* 2021;24(12):1255-1260. doi:10.1016/j.jsams.2021.08.009.
12. Vasankari V, Halonen J, Husu P et al. Personalised eHealth intervention to increase physical activity and reduce sedentary behaviour in rehabilitation after cardiac operations: study protocol for the PACO randomised controlled trial (NCT03470246). *BMJ Open Sport Exerc Med* 2019;5(1):e000539. doi:10.1136/bmjsem-2019-000539.
13. Vähä-Ypyä H, Sievänen H, Husu P et al. Intensity paradox-low-fit people are physically most active in terms of their fitness. *Sensors* 2021;21(6):2063. doi:10.3390/s21062063.
14. Sjöros T, Vähä-Ypyä H, Laine S et al. Both sedentary time and physical activity are associated with cardiometabolic health in overweight adults in a 1 month accelerometer measurement. *Sci Rep* 2020;10:20578. doi:10.1038/s41598-020-77637-3.

15. Vähä-Ypyä H, Vasankari T, Husu P et al. Validation of cut-points for evaluating the intensity of physical activity with accelerometry-based mean amplitude deviation (MAD). *PLoS One* 2015;10(8):e0134813. doi:10.1371/journal.pone.0134813.
16. Vähä-Ypyä H, Husu P, Suni J et al. Reliable recognition of lying, sitting, and standing with a hip-worn accelerometer. *Scand J Med Sci Sports* 2018;28(3):1092-1102. doi:10.1111/sms.13017.
17. Husu P, Suni J, Vähä-Ypyä H et al. Objectively measured sedentary behavior and physical activity in a sample of Finnish adults: a cross-sectional study. *BMC Public Health* 2016;16(1):920. doi:10.1186/s12889-016-3591-y.
18. Nieste I, Franssen WMA, Spaas J et al. Lifestyle interventions to reduce sedentary behaviour in clinical populations: a systematic review and meta-analysis of different strategies and effects on cardiometabolic health. *Prev Med* 2021;148:106593. doi:10.1016/j.ypmed.2021.106593.
19. Balducci S, D'Errico V, Haxhi J et al. Effect of a behavioral intervention strategy for adoption and maintenance of a physically active lifestyle: the Italian Diabetes and Exercise Study 2 (IDES_2): a randomized controlled trial. *Diabetes Care* 2017;40(11):1444-1452. doi:10.2337/dc17-0594.
20. Aadahl M, Linneberg A, Moller TC et al. Motivational counseling to reduce sitting time: a community-based randomized controlled trial in adults. *Am J Prev Med* 2014;47(5):576-586. doi:10.1016/j.amepre.2014.06.020.
21. Healy GN, Winkler EAH, Eakin EG et al. A cluster RCT to reduce workers' sitting time: impact on cardiometabolic biomarkers. *Med Sci Sports Exerc* 2017;49(10):2032-2039. doi:10.1249/MSS.0000000000001328.
22. Graves LEF, Murphy RC, Shepherd SO et al. Evaluation of sit-stand workstations in an office setting: a randomised controlled trial. *BMC Public Health* 2015;15:1145-1148. doi:10.1186/s12889-015-2469-8.
23. Danquah IH, Kloster S, Holtermann A et al. Take a Stand!-a multi-component intervention aimed at reducing sitting time among office workers-a cluster randomized trial. *Int J Epidemiol* 2017;46(1):128-140. doi:10.1093/ije/dyw009.
24. Miyamoto T, Fukuda K, Oshima Y et al. Non-locomotive physical activity intervention using a tri-axial accelerometer reduces sedentary time in type 2 diabetes. *Phys Sportsmed* 2017;45(3):245-251. doi:10.1080/00913847.2017.1350084.
25. Schuna JM, Swift DL, Hendrick CA et al. Evaluation of a workplace treadmill desk intervention: a randomized controlled trial. *J Occup Environ Med* 2014;56(12):1266-1276. doi:10.1097/JOM.0000000000000336.
26. Helajarvi H, Pahkala K, Heinonen OJ et al. Television viewing and fatty liver in early midlife. The Cardiovascular Risk in Young Finns Study. *Ann Med* 2015;47(6):519-526. doi:10.3109/07853890.2015.1077989.
27. Chalasani N, Younossi Z, Lavine JE et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012;142(7):1592-1609. doi:10.1053/j.gastro.2012.04.001.
28. Hanley AJ, Williams K, Festa A et al. Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 2004;53(10):2623-2632. doi:10.2337/diabetes.53.10.2623.
29. Saeidifard F, Medina-Inojosa JR, Supervia M et al. The effect of replacing sitting with standing on cardiovascular risk factors: a systematic review and meta-analysis. *Mayo Clin Proc Innov Qual Outcomes* 2020;4(6):611-626. doi:10.1016/j.mayocpiqo.2020.07.017.
30. del Pozo-Cruz J, García-Hermoso A, Alfonso-Rosa RM et al. Replacing sedentary time: meta-analysis of objective-assessment studies. *Am J Prev Med* 2018;55(3):395-402. doi:10.1016/j.amepre.2018.04.042.