"SCAPIS Pilot Study: Sitness, Fitness and Fatness – Is Sedentary Time Substitution by Physical Activity Equally Important for Everyone's Markers of Glucose Regulation?" by Ekblom-Bak E et al.
Journal of Physical Activity & Health

Title page

Title: The SCAPIS Pilot study: Sitness, Fitness and Fatness – Is sedentary time substitution by physical activity equally important for everyone's markers of glucose regulation?

Running head: Sedentary time substitution and glucose regulation

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Abstract

Background: Although moderate-to-vigorous physical activity (MVPA) is mainly recommended for glucose control, light physical activity (LIPA) may also have the potential to induce favorable changes. We **investigated** sedentary time (SED) substitution with equal time in LIPA and MVPA, and the association with markers of glucose regulation and insulin sensitivity after **stratification** by waist circumference, fitness and fasting glucose levels. **Methods**: A total of 654 men and women, 50-64 **years**, from the SCAPIS pilot study were included. Daily SED, LIPA and MVPA were assessed using hip-worn accelerometers. Fasting plasma glucose, insulin and HOMA-IR were determined. **Results**: Substituting 30 min of SED with LIPA was significantly associated with 3.0% lower fasting insulin values and 3.1% lower HOMA-IR values, with even lower levels when substituting SED with MVPA. Participants with lower fitness and participants with high fasting glucose levels benefited significantly more from substituting 30 min of SED with LIPA compared to participants with normal to high fitness levels and participants with normal glucose levels, respectively.**Conclusions**: LIPA, and not only MVPA, may have beneficial associations with glucose regulation. This is of great clinical and public health importance, not least because it may confer a higher compliance rate **to regular PA**.

Keywords: Isotemporal substitution; sedentary; light physical activity; moderate physical activity, insulin resistance.

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Introduction

Regular physical activity (PA) plays a major role in glucose metabolism regulation including insulin sensitivity, particularly for individuals with pre-diabetes and diabetes.[1] Moreover, **low** cardiorespiratory fitness (measured as VO_2max and hereby referred to as fitness) is significantly associated with impaired insulin response in non-diabetic individuals [2] as well as in individuals at increased risk for type-2 diabetes.[3] Increases in fitness levels over time have been shown to have beneficial effects on glucose-insulin homeostasis.[4] International exercise recommendations advocate moderate-to-vigorous PA (MVPA) for both healthy individuals and patients with diabetes mellitus.[5,6] However, this may be difficult to achieve in inactive healthy as well as in many diabetic patients, who may be overweight, unfit, suffering from concomitant diseases (i.e. coronary artery disease), or lacking sufficient motivation to participate in high-intensity activity.

On the other end of the activity spectrum, greater time spent sedentary (SED) has been shown to be related to poorer insulin sensitivity and glucose regulation.[7-9] An experimental study showed that interrupting sitting time with short (2 min) bouts of light-intensity PA (LIPA) or MVPA lowered postprandial glucose and insulin levels in overweight and obese adults.[10] Importantly, studies that have examined the relationships between objectively measured SED and MVPA (by accelerometer) and fitness are scarce, and the results equivocal regarding the independent hazards of sitting. [11,12]

Some of the disparity between the findings of previous research may in part be due to the varying extent of effects of prolonged sitting between different populations. In participants with poorer health status (overweight/obese, impaired glucose regulation, low fitness), the negative effect of greater SED may be more pronounced, while the effect may be blunted in individuals with a more favorable health profile. The **statistical** method of analysis is also of importance when investigating the relationships between SED, PA and health

outcomes. Regression based analyses with simultaneous adjustment for PA as a confounder of the relationship between SED and health outcome have commonly been used in these studies. Running isotemporal substitution analyses, rather than regression modeling, has been put forward as a suitable analysis method to examine the theoretical effect of substituting one activity, for example, SED with another, for example LIPA, while keeping total time and time in other activities fixed[13]. Previous isotemporal substitution studies, including measurements of glucose regulation and/or insulin sensitivity, have found beneficial associations with SED substitution with standing[14], LIPA[14-17] and MVPA[16,17], respectively, in healthy individuals[14,16] and those at-risk of or with type 2 diabetes.[15,17]

The aim of this paper was to expand on previous research by examining the relationships between SED substitution for LIPA or MVPA and markers of glucose regulation and insulin sensitivity, before and after stratification **of** the sample by waist circumference, fitness and fasting glucose levels in a non-diabetic population. Furthermore, we wanted to investigate the substitution of different time lengths of SED, LIPA and MVPA.

Methods and materials

This study is based on data from the pilot of the Swedish CArdioPulmonary bioImage Study (SCAPIS) conducted in 2012 in Gothenburg, Sweden. The design and methods of the SCAPIS have been presented previously.[18] A sample consisting of 2243 adults aged 50 to 64 years, from low and high socioeconomic status geographical areas, was randomly selected from the local population registry of the city of Gothenburg. Out of these 2243, 1111 (50% women) agreed to participate in the study. At the test centre, the participants were asked to complete an extensive questionnaire including items to assess general health, education**al** level, perceived psychological stress and living conditions, perform a submaximal cycle test to estimate fitness[19] and undergo extensive imaging and functional assessments of the heart,

lungs and metabolism. A fasting blood sample was also collected from the participants. For the present analyses, individuals with known diabetes (n=76) or fasting levels of HbA1c > 6.5% (48 mmol/mol)[20] (n=4) were excluded. All participants provided written informed consent. The study was approved by the ethics board at Umeå University (Dnr 2010-228-31M) and adheres to the Declaration of Helsinki.

Objective assessment of time in sedentary and physical activity

The participants were asked to wear an accelerometer (ActiGraph model GT3X and GT3X+, ActiGraph LCC, Pensacola, FL, USA) for seven days to objectively measure daily movement patterns. The two accelerometer models used have strong agreement and can be used interchangeably within the same study.[21] Participants were instructed to wear the accelerometer on an elastic belt over the right hip during all waking hours for at least seven consecutive days, except during water based activities, and to return it to the laboratory in a prepaid envelope after the wearing period. ActiLife v.6.10.1 software was used to initialise the accelerometers and to download and process the collected data. The accelerometer recorded raw data (sample rate set to 30 Hz) from all three axes, which were combined into a resulting vector, and extracted as 60 seconds epoch using low frequency extension filter. Using standard definitions, SED was defined as <200 counts per minute (cpm), LIPA as cpm from 200 to 2689, and MVPA as cpm ≥2690.[22] Non-wear time was defined as 60 or more consecutive minutes with no movement (0 cpm), with allowance for maximum two minutes of counts between 0 and 200 cpm. Wear time was calculated as 24 h minus non-wear time. A minimum of 600 minutes of valid daily wear time for at least four days was required to be included in the analyses.[23]

Biochemistry and insulin sensitivity index

A fasting venous blood sample (100 ml) was collected and was used to determine levels of plasma glucose (mmol/L) and insulin (mU/L). Insulin resistance was calculated using the formula for homeostasis model assessment- insulin resistance (HOMA-IR = fasting glucose x fasting insulin / 22.5).[24] This insulin sensitivity index based on fasting levels has been shown to be moderately associated with the gold standard hyperinsulinaemic–euglycaemic clamp method[25], and due to its simplicity, in comparison to the clamp method, is often used in large-scale epidemiological studies.

Anthropometric, fitness testing and covariates

Waist circumference was measured at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line, after normal exhalation. Cardiorespiratory fitness (VO_2max) was estimated from a submaximal cycle ergometer test[19] and expressed as mL $O_2 \cdot min^{-1} \cdot kg^{-1}$. Self-reported educatio**nal** level (as a marker for socioeconomic status) was dichotomised as having completed a university degree or not, smoking habits into current smoker or not, and perceived psychosocial stress, divided into four levels. Body mass and height were measured to the nearest 0.1 kg and cm, respectively, using standardised methods.

Statistical analysis

Linear regression was used to perform isotemporal substitution analyses, examining the theoretical effect of substituting a pre-set amount of time in one activity (in this paper SED) by the same amount of time in another activity (in this paper LIPA and MVPA). All activity variables, except the behaviour substituted (SED), were entered into the linear regression model simultaneously along with total wear time and covariates. By including the total wear time variable, time is isotemporal and hence the regression coefficients for each

activity variable in the model reflect the effect of *substituting* a bout of SED with an equal time bout of a specific activity (LIPA or MVPA). This is different from the commonly used regression based models, which express the effects of *adding* the activity type, when a total time variable is not included in the analysis. The isotemporal substitution method has previously been described in greater detail.[13]

In the first part of this study (presented in Table 2) the effect of substituting 30 min of SED with LIPA or MVPA on levels of fasting glucose, fasting insulin and HOMA-IR was studied. This was performed in the total sample as well as in subgroups after stratification of the sample by waist circumference and fitness according to conventional cut-off points for increased health risks (waist circumference ≥ 88 cm in women and ≥ 102 cm in men; fitness, VO_2max < 32 $ml \cdot min^{-1} \cdot kg^{-1}$ in women and < 35 in men) and of fasting glucose (fasting glucose > 6.0 $mmol \cdot l^{-1}$).[17] In the second part of the current study (Figures 1 to 3) we repeated the aforementioned substitution analyses with 1, 5, 10, 15, 30, 60, 90 and 120 min bouts in addition to the original 30 min bout substitution analyses. To test for interactions between the stratified isotemporal substitution analyses, the procedure described by Altman and Bland was used.[26]

The outcomes as well as the standardised residuals of the isotemporal linear regression models displayed non-normality, requiring log transformation of the glucose, insulin and HOMA-IR variables. The resulting regression coefficients were subsequently back-transformed, and presented as relative rates (RR) with 95% confidence interval (95% CI). The relative rates coefficients describe the estimated percentage shift in the mean value for the outcome for each increase in LIPA or MVPA, when substituting the same amount of SED.

The correlation between the daily minutes of SED, LIPA, MVPA and the total wear time variable was ≤ 0.6 and the tolerance value > 0.2 for all models, indicating a low

probability of multicollinearity. All analyses were adjusted for sex, age, education**al** level, smoking and perceived psychological stress. Statistical significance level was two-sided and set at $p < 0.05$. All analyses were cross-sectional and performed using IBM SPSS (Statistical Package for the Social Sciences for Windows, 14.0, 2006, SPSS Inc., Chicago IL).

Results

A total of 894 participants provided valid accelerometer data. Out of these, 24 had missing data for insulin and/or glucose and seven for other covariates, while 209 did not perform the fitness test (due **to** knee, lower back or hip pain, perceived inability to perform the test, ongoing illnesses that prevented safe completion of the test or due to malfunction of the heart rate monitors or ergometer). Participants with missing data were significantly older (59 vs. 57 years), fewer had university degree (28 vs. 42%), and a greater proportion were current smokers (26 vs. 13%). Body mass index (27.4 vs 26.3 $kg \cdot m^{-2}$), waist circumference (97 vs. 94 cm), fasting glucose (5.7 vs. 5.6 mmol/l), fasting insulin (7.9 vs. 6.2 mU/l), HOMA-IR (2.00 vs. 1.52) was higher among participants with missing data, and time in MVPA (43 vs. 49 min) was lower ($p<0.05$). However, there were no differences between the two groups in relation to sex, perceived psychosocial stress level, fitness level or daily time spent in SED or LIPA. Characteristics of the study population are presented in Table 1.

In Table 2, the RR and 95% CI for SED substitution by LIPA and MVPA are displayed. In the total sample, substituting 30 min of SED with LIPA was significantly associated with 3.0% lower fasting insulin values and 3.1% lower HOMA-IR values. Substituting 30 min of SED for MVPA was associated with 11.6% and 12.4% lower fasting insulin and HOMA values, respectively. Only MVPA substitution was associated with significantly lower fasting glucose levels (0.9%). To investigate if the substitutions associated with HOMA-IR varied between good/poor metabolic status, the sample was stratified by

waist circumference, fitness and fasting glucose. Participants with lower fitness and participants with high fasting glucose levels benefited more from substituting 30 min of SED with LIPA compared to participants with normal to high fitness levels (p for interaction = 0.054) and participants with normal glucose levels (p for interaction = 0.023), respectively. Similar interactions were not seen for MVPA substitution, nor for LIPA or MVPA after stratification by waist circumference.

A graphical representation of the substitution of SED of varying time lengths and the association with HOMA-IR level, compared in samples stratified by waist circumference, fitness and fasting glucose, is shown in Figures 1 to 3. Substitution of SED with MVPA was associated with significantly lower HOMA-IR for 5 to 120 min substitutions for participants with lower waist circumferences and across all time lengths (1 to 120 min) for participants with higher waist circumferences (Figure 1). Grouped by fitness level, participants with low fitness had significantly lower HOMA-IR levels from 1 to 120 min of substitution with LIPA, and to a greater extent with MVPA (Figure 2). MVPA substitution in more fit participants also resulted in significantly lower levels of HOMA-IR across all time bouts, albeit to a lesser extent than in the less fit participants. Substitutions in the group with high fasting glucose levels resulted in significantly lower HOMA-IR from 1 to 120 min bouts for both LIPA and MVPA (Figure 3). Similar patterns were seen for normal glucose level participants for 1 to 120 min of MVPA substitution, but only from 30 min substitution of LIPA.

Discussion

The primary finding of this study is that substituting 30 min of SED with LIPA was associated with significantly lower fasting insulin and markers of insulin resistance in non-diabetic middle-aged men and women, with even lower levels when substituting SED with MVPA. Stratification of the study population by waist circumference, fitness and glucose

levels revealed that participants with low fitness or high fasting glucose levels benefited more from substituting SED time with LIPA, compared to more fit participants and those with normal fasting glucose levels. However, there were no corresponding interactions between fitness and glucose levels after substituting SED with MVPA.

These findings are in line with results from a similar study of the 2005-2006 NHANES cohort, which reported that reallocating 30 min of SED with LIPA was associated with 2.4% lower fasting insulin and 2.3% higher HOMA-S, with even stronger associations when substituting SED for MVPA.[16] Similar dose-response patterns were also reported in individuals with an increased risk of type 2 diabetes.[17] While studies that performed isotemporal substitution in stratified samples are scarce, Yates and co-workers found that both LIPA and MVPA substitution induced higher levels of HOMA-IS in participants with impaired glucose regulation. However, in participants with normal glucose metabolism SED reallocation with MVPA only, and not LIPA, was significantly associated with higher HOMA-IS.[17]

As previous studies only have compared SED substitution of one specific time bout (most often 30 min), this is one of the first studies to compare SED substitution of different time lengths, from 1 to 120 min, in the stratified groups. These analyses provide important clinical information on the theoretical implications of manipulating both the intensity and bout length of PA in a healthy population as well as in those with certain risk factors. The implications of these findings are that in participants with low fitness, substituting 120 min of SED with equal LIPA may have about the same theoretical beneficial effect on HOMA-IR as substituting 40 min of SED for an equal duration of MVPA would have. Likewise, in participants with high fasting glucose, the potential benefits on HOMA-IR levels by substituting 120 min of SED with LIPA, is comparable to substituting 60 min of SED with an equal bout of MVPA. An interesting finding is that reallocating ≥30 min of SED with LIPA is

significantly associated with lower HOMA-IR, even in participants within normal fasting glucose levels.

One of the main mechanisms that drives the detrimental side-effects of SED is the absence of skeletal muscular contractions, leading to metabolic dysfunction, partly characterised by poor glucose metabolism.[27] As mechanical activation of glucose transporters within the skeletal muscle is an important basic function for non-insulin dependent regulation of blood glucose levels and, to an extent, insulin sensitivity, this may explain some of the beneficial associations seen by replacing SED with LIPA, despite the low intensity. The present potential benefits, found among participants having a poorer metabolic and cardiorespiratory fitness profile following LIPA substitution, further support this theory. In a recent population-based study of Australian adults aged ≥ 25years, Healy and colleagues reported that the reallocation of SED with standing, but not stepping, was significantly associated with lower fasting glucose levels. In the same study, the opposite results were seen for 2 h postload glucose.[14] This highlights a rather complex and sensitive nature of the glucose regulating mechanisms at the lower end of the activity spectrum (standing to stepping/LIPA). However, it should be highlighted that LIPA and MVPA assessed by the accelerometer, are referring to absolute intensities of activity. Hence, participants with lower performance capacity may experience both LIPA and MVPA as a relatively higher intensity.

There are strengths and limitations of this study that should be mentioned. Strengths of the study are that it includes a population-based sample of middle-aged men and women from both high and low SES, and the use of objectively obtained data on SED, LIPA and MVPA; a method highly suitable for isotemporal substitution analyses. Furthermore, the stratification by high/low waist circumference, fitness and fasting blood glucose levels enabled for the first time analyses on variation in isotemporal substitution associations between these groups for the insulin resistance marker HOMA-IR. Further, limitations of the

study include the exclusion of subjects not able to perform the submaximal fitness test. There were also some differences in characteristics between participants included in the present analyses and those with missing data, with the latter having lower educational levels, poorer metabolic status and a greater likelihood of being a smoker. However, the impact on the generalisability of SED time substitution is diminished after stratification by waist circumference, fasting glucose and fitness level, as this division was made by conventional cut-off points for increased health risks in relation to these attributes, rather than cut-offs defined by the study population (for example median value). This was particularly true for SED time substitution by LIPA, as there was no difference between participants included in the analyses and those with missing data in daily time spent in SED or LIPA. Moreover, the results of the current study of middle-aged men and women may not be applicable to younger or older age groups. The methodological limitation of the ActiGraph accelerometer is its inability to differentiate between sitting and standing, which hampers analyses of substituting sedentary time with standing time. Also, the use of absolute cut-points for different PA intensities may result in that participants with varying performance capacity may experience the defined intensity categories as differently demanding. The automated wear time estimation used should be considered, as low counts during 60 minutes may be common in this age group. A limitation of using fasting glucose as a measure of diabetes is that it should not be used in isolation to diagnose diabetes. However, it is important to note that it was not the aim of the current study to definitively diagnose participants with diabetes but rather examine fasting glucose as an outcome measurement. Finally, the cross-sectional design of the study limits any conclusions of causality, and the results could only be interpreted as effects of theoretical SED substitution.

In summary, while substituting SED with MVPA confers the greatest potential benefits for glucose balance, replacing SED with LIPA also appears to be associated with

favourable health outcomes, even in this rather active population of middle-aged men and women (on average 49 min of daily MVPA). The magnitude of the association with LIPA substitution varied, with significantly stronger associations being found in subjects with poor cardiorespiratory fitness and high fasting glucose levels. The results also expand on the current knowledge of the effects of MVPA. While MVPA is the commonly recommended PA intensity for prevention and treatment of type 2 diabetes, the compliance to PA recommendations remains low. From a clinical and public health perspective, the finding that LIPA may have beneficial effects on the glucose profile is very important. Physicians and health care personnel will have additional evidence for recommending patients with impaired glucose tolerance and low fitness, who may have difficulty adhering to current MVPA recommendations, LIPA as an alternative, conferring a higher compliance rate to regular PA. An important next step would be to use the isotemporal substitution model on longitudinal accelerometer data to examine the importance of SED time substitution over time for glucose regulation or the development of randomised controlled intervention studies of the effects of replacing SED with short bouts of PA on glucose regulation.

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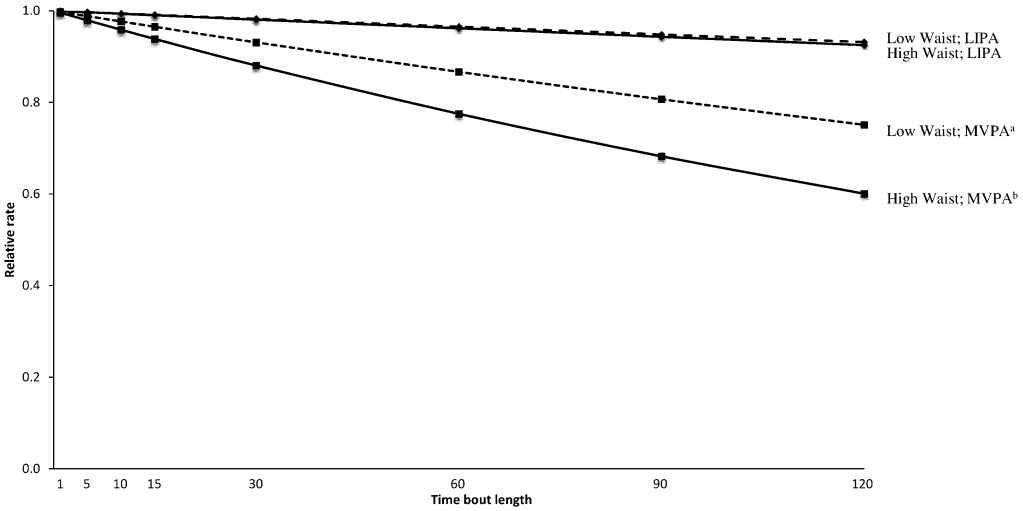

Figure 1. Relative rates (back transformed B-values) for SED time substitution with LIPA and MVPA, respectively, for HOMA-IR after stratification by high (≥88 cm in women and ≥102 cm in men) and low (<88 cm in women and <102 cm in men) waist circumference. \r\nAdjusted for sex, age, educational level, smoking and perceived psychological stress. \r\na significantly lower (p<-.05) relative rates for each 5 up to 120 min daily bout increae of MVPA. \r\nb significantly lower (p<0.05) relative rates for each 1 up to 120 min daily bout increase of MVPA.

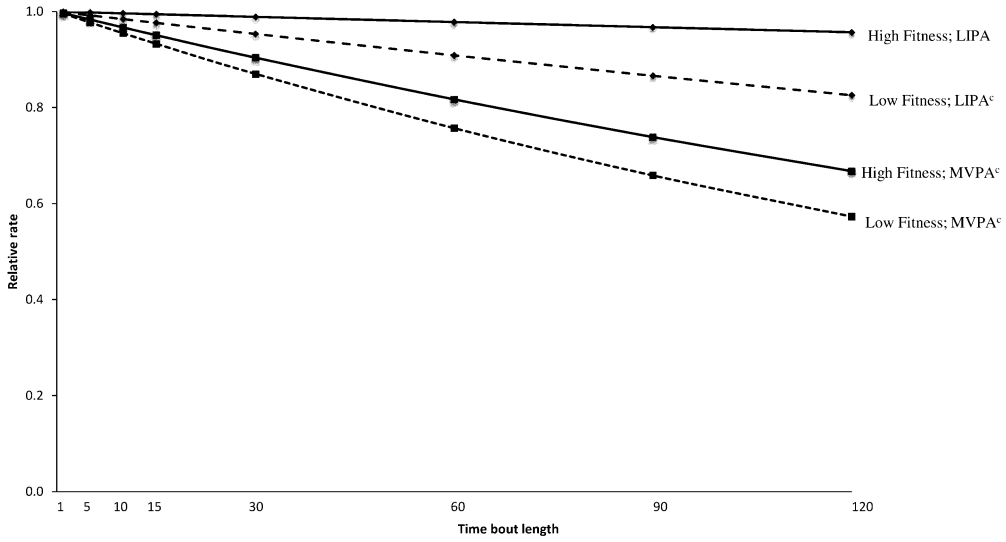

Figure 2. Relative erates (back transformed B-values) SED time substitution with LIPA and MVPA, respectively, for HOMA-IR after stratification by igh (≥32 ml·min-1·kg^{-1} in women and ≥35 in men) and low (<32 ml·min-1·kg^{-1} in women and <35 in men) cardiorespirator fitness. Adjusted for sexc, age, educationa level, smoking and perceived psychological stress. \r\nc significantly lower ($p<0.05$) relative rates for each 1 up to 120min daily bout increase of LIPA or MVPA.

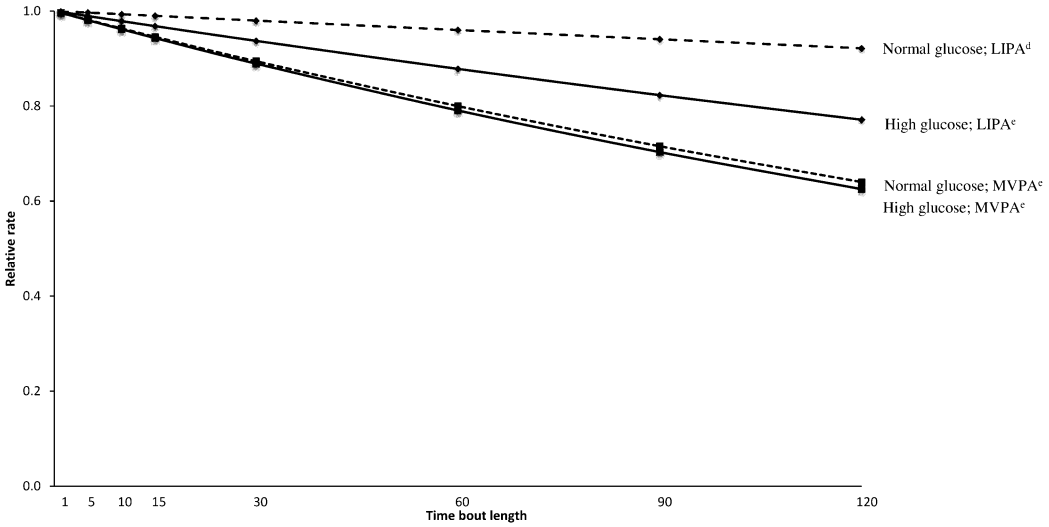

Figure 3. Relative rates (back transformed B-values) for SED time substitution with LIPA and MVPA, respectively, for HOMA-IR after stratification by high (>6.0 mmol·l^{-1}) and low ≤6.0 mmol·l^{-1}) fasting glucose levels. \r\nAdjusted for sex, age, educational level, smoking and perceived psychological stress. \r\nd significantly lower ($p<0.05$) relative rates for each 30 up to 120 min daily bout increase of LIPA. \r\ne significantly lower ($p<0.05$) relative rates for each 1 up to 120min daily bout increase of LIPA or MVPA.

Table 1 Characteristics of the study population (n=654).

	Median (Q1-Q3) or % (n)
Women	52% (341)
Age (years)	57 (54-61)
University degree	42% (378)
Current smoker	13% (83)
Constant perceived psychosocial stress the last year or longer	19% (125)
Body mass index ($kg \cdot m^{-2}$)	26.3 (24.1-28.9)
Abdominal obesity [a]	43% (278)
Fasting glucose (mmol/l)	5.6 (5.2-5.9)
Fasting insulin (mU/l)	6.2 (4.3-9.0)
HOMA-IR	1.52 (1.02-2.28)
Est. VO_2max ($ml \cdot min^{-1} \cdot kg^{-1}$)	34.4 (28.6-39.7)
Daily time in sedentary (min)	456 (393-524)
Daily time in light-intensity physical activity (min)	359 (302-415)
Daily time in moderate-to-vigorous physical activity (min)	49 (34-67)
Daily wear time (min)	871 (823-913)

[a] Waist circumference ≥ 88 in women and ≥ 102 in men

Table 2 Relative rates (back transformed B-values) and 95% CI for substitution of 30 minutes of SED by LIPA and MVPA, respectively, in the total sample for fasting glucose, fasting insulin and HOMA-IR (top) and for HOMA-IR subdivided by waist circumference, fitness and fasting glucose (bottom).

	SED to LIPA	SED to MVPA
	Relative rate (95% CI)	Relative rate (95% CI)
Fasting glucose	0.998 (0.995 – 1.001)	0.991 (0.983 – 0.999)
Fasting insulin	0.970 (0.954 – 0.987)	0.884 (0.844 – 0.927)
HOMA-IR	0.969 (0.951 – 0.987)	0.876 (0.832 – 0.923)
HOMA-IR, stratified analyses		
Waist circumference		
Women < 88 and men < 102 (n=376)	0.982 (0.962 – 1.003)	0.931 (0.878 – 0.987)
Women ≥ 88 and men ≥ 102 (n=278)	0.981 (0.954 – 1.009)	0.880 (0.816 – 0.950)
p interaction	High waist x LIPA; 0.954	High waist x MVPA; 0.250
VO_2max ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Women < 32 and men < 35 (n=285)	0.953 (0.926 – 0.982)	0.870 (0.794 – 0.953)
Women ≥ 32 and men ≥ 35 (n=369)	0.989 (0.966 – 1.013)	0.904 (0.851 – 0.960)
p interaction	Low fitness x LIPA; 0.054	Low fitness x MVPA; 0.492
Fasting glucose ($mmol \cdot l^{-1}$)		
< 6.0 (n=507)	0.980 (0.961 – 0.999)	0.894 (0.846 – 0.945)
≥ 6.0 (n=147)	0.937 (0.906 – 0.969)	0.889 (0.818 – 0.967)
p interaction	High glucose x LIPA; 0.023	High glucose x MVPA; 0.913

Adjusted for sex, age, educational level, smoking status and psychosocial stress.

The relative rates coefficients describe the estimated percentage shift in the mean value for the biomarkers of glucose regulation and insulin sensitivity for each daily 30 minutes increase in physical activity of LIPA or MVPA, while substituting the same amount of sedentary time.

SED, sedentary; LIPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; HOMA-IR, homeostasis model assessment- insulin resistance