Fitness moderates glycemic responses to sitting and light activity breaks

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ABSTRACT

Purpose: Regular engagement in sedentary behaviours can lead to major public health consequences. This study aimed to experimentally determine whether cardio-respiratory fitness modifies postprandial glycemia during prolonged sitting and investigated the potentially blunting influence this may have upon the benefits of interrupting postprandial sitting time with light activity breaks.

Methods: Thirty-four adult volunteers (18 female; 16 male; mean±SD age: 40±9 years, BMI: 24.5±3 kg/m²) undertook two 7.5 hour experimental conditions in a randomized order: 1) Prolonged sitting; 2) Sitting interspersed with 5 minute light walking bouts every 30 minutes. Blood samples were obtained while fasting and throughout the postprandial period following ingestion of two identical meals. Incremental Area Under the Curve (iAUC) was calculated for glucose and insulin throughout each experimental condition. Maximal exercise testing quantified VO₂ peak as a measure of cardiorespiratory fitness (CRF) prior to experimental conditions. A repeated measures ANOVA investigated whether VO₂ peak modified iAUC data between conditions. This trial is registered with ClinicalTrials.gov (Reg no. NCT0493309).

Results: Interrupting prolonged sitting time with light walking breaks reduced blood glucose iAUC from 3.89 ± 0.7 to 2.51 ± 0.7 mmol·L⁻¹·h (p = 0.015) and insulin iAUC from 241 ± 46 to 156 ± 24 mU·L⁻¹·h (p = 0.013) after adjustment for VO₂ peak and sex. A significant interaction between treatment response and VO₂ peak was observed for glucose (p = 0.035), but not insulin (p = 0.062), whereby the treatment effect reduced with higher levels of fitness. Average blood glucose iAUC responses for a man at the 25th centile of CRF (42.5 mL·kg⁻¹·min⁻¹) within our cohort went from 5.80 to 2.98 mmol·L⁻¹·h during the prolonged sitting and light walking breaks conditions respectively, whereas average responses for a man at the
75th centile of CRF (60.5 mL·kg\(^{-1}\)·min\(^{-1}\)) went from 1.99 to 1.78 mmol·L\(^{-1}\)·h. Similar trends were observed for women.

**Conclusions:** Individuals with low levels of CRF gained the most metabolic benefit from breaking prolonged sitting with regular bouts of light walking. Future interventions aimed at alleviating the deleterious impacts of sedentary behavior may be optimized by tailoring to cardio-respiratory fitness levels within the general population.

**Key words:** Sedentary Behavior – Type 2 Diabetes – Physical activity – Cardio-respiratory fitness – Postprandial metabolism
INTRODUCTION

Adults in developed western countries typically spend 50 - 70% of their waking hours sat down (30), making sedentary behavior the new reference of modern living. Greater time spent in sedentary behaviors (defined as sitting or reclining with low energy expenditure), has been associated with an increased likelihood of; metabolic syndrome (10), diabetes, cardiovascular disease (CVD) and all-cause mortality (4, 27). The evidence of which appears to be the strongest and most consistent for the risk of type 2 diabetes (T2DM) (4).

However, recent epidemiological evidence has suggested that physical activity levels and cardiorespiratory fitness (CRF) may moderate these associations, such that the association between sedentary time and markers or outcomes of health may be weaker in those with higher fitness levels (7, 23, 25), or those undertaking greater physical activity (11). This suggests that sedentary behavior may be a less important determinant of health in those with adequate CRF or those that are physically active. While experimental evidence largely confirms that breaking prolonged bouts of sitting with light-intensity walking can significantly reduce postprandial blood glucose and insulin in healthy non-obese individuals (2, 24), in those who are overweight and obese (9, 26), and in those with dysglycemia (15), no previous experimental trials have investigated whether these responses are modified by CRF or habitual physical activity levels.

CRF in particular is an important candidate for further investigation, as it is one of the strongest predictors of morbidity and mortality (19). CRF has been shown to moderate the deleterious impacts of other exposures such as body mass index (BMI), whereby obese individuals with moderate to high CRF levels have a lower risk of morbidity and mortality outcomes compared to normal weighted individuals with low CRF levels (12). It is therefore plausible that high levels of CRF may also protect against the deleterious impacts of prolonged sedentary behavior. Therefore, we hypothesized that CRF would modify the
postprandial glucose response to breaking prolonged sitting with light walking breaks with lower CRF levels being associated with greater reductions to postprandial plasma glucose.

METHODS

Study Design

All participants attended the Leicester Diabetes Centre on three separate occasions between September 2014 and September 2015. The first visit involved consent, familiarization and a fitness assessment which was followed by two experimental condition visits that were at least 7 days apart. This was a randomized cross-over trial whereby each participant took part in two experimental treatment conditions in a random order, thereby acting as their own controls. Order randomization was conducted by a statistician using an online tool. Due to the nature of the trial, participants were not blinded to their randomized order, however all outcomes including blood assays were analysed blinded to the experimental condition that they derived from. Prior to commencing, this study received ethical approval from the University of Leicester - Health Sciences department and from the local NHS Research and Development committee.

This trial was also registered with ClinicalTrials.gov (NCT0493309).

Participants

Thirty six non-obese adults (BMI <30kg/m²) aged between 25 – 55 years who worked in a predominantly seated environment were recruited from the general public via study-specific information distributed in the community, around the University of Leicester campus and University Hospitals of Leicester NHS Trust. Two individuals were withdrawn following enrollment in the study due to a change in personal circumstances (n = 2). This left 34
participants who went on to complete the remaining experimental conditions. This is detailed in Figure 1.

Exclusion from taking part in this study came under the following circumstances; an inability to communicate in spoken English, a BMI ≥30kg/m², pregnancy, steroid usage, regular smoking habits, diagnosed T2DM, CVD or psychotic illness. As our study was predicated on having a broad range of fitness levels, and considering that most of the variance in CRF is explained by habitual physical activity levels (6), we stratified recruitment by self-reported leisure time physical activity. Consequently, we enrolled 12 inactive (0 minutes of MVPA/week), 12 moderately active (≥ 75minutes - <150minutes of MVPA/week), and 12 highly active (≥150minutes of MVPA/week) individuals. (See Table S-1, Supplemental Digital Content 1, scope of CRF levels captured).

Consent, familiarisation and fitness assessment visit

On arrival, a researcher described in detail all study procedures and written informed consent was obtained. Participants were then shown the designated experimental area for the study. A venous blood sample was taken to assess HbA1c and confirm absence of T2DM (<6·5% [<47·5mmol/mol]) (29). Body weight (Tanita TBE 611: Tanita, West Drayton, U.K), waist circumference (midpoint between lower costal margin and iliac crest) and height were measured to the nearest 0·1kg, 0·5cm and 0·5cm, respectively.

In order to assess CRF, participants undertook a maximal incremental exercise test on a motor driven treadmill (Technogym Excite® 700). Following a three minute warm-up at 4km/h (0% incline), participants would walk or jog at a constant speed that they felt comfortable with (6, 8, 10, or 12km/h) while elevations in treadmill gradient occurred at a rate of 0·5% every 30 seconds. All participants received encouragement to continue this exercise for as long as possible. The test was terminated upon volitional exhaustion.
Throughout the test, gas was sampled continuously and analysed using a Metalyser 3B gas analyser (Cortex 3B, Cortex Biophysik, Leipzig, Germany). Peak oxygen consumption (VO₂ peak) was calculated using the highest ten second average throughout the testing period. Before each test, the gas analyser was calibrated according to the manufacturer’s recommendations. As a safety precaution, a 12 lead electrocardiogram was performed by a cardiac nurse for each participant at rest and during the exercise test.

Finally, participants were issued with two activity monitors; an ActiGraph GT3X+ accelerometer (Pensacola, FL) worn on the right anterior axillary line, and an activPAL3 physical activity monitor (PAL Technologies, Glasgow, UK) worn on the midline anterior portion of the right thigh. Participants were required to wear these for 7 consecutive days, allowing insight into their habitual sitting and physical activity levels.

**Experimental procedure**

Participants were asked to avoid alcohol and caffeine for the 48 hours preceding experimental treatment conditions. As the influence of an acute bout of physical activity on insulin sensitivity can persist for 48 hours (17), avoidance of moderate and vigorous physical activity for this timeframe was also instructed. Continuation in this study was subject to participants being able to confirm their compliance with these restrictions. Following an ethical amendment to the protocol during this study, a subset of participants were asked to wear an accelerometer in the 2 days leading up to each experimental condition in order to confirm adherence to the exercise restriction (See Table S-2, Supplemental Digital Content 2, activity data leading up to experimental conditions).

Participants fasted from 10pm the evening before each visit and were asked to keep a record of all food eaten during the day leading up to their first experimental condition. This could
then be replicated prior to their second experimental condition in an attempt to eliminate the potentially confounding influence of pre-experimental food intake.

Participants underwent two separate 7.5 hour experimental treatment conditions:

1) Prolonged sitting - participants sat in a designated room (occupied with a desk, books, and laptop with internet services) while minimising excessive movement. Lavatory breaks were permitted using a wheelchair to and from the lavatory in order to further reduce unnecessary movements that could otherwise confound the study.

2) Light walking breaks - participants emulated the above, but interrupted sitting time with 5 minute bouts of walking at a light intensity of 3km·hr on the treadmill (Technogym Excite® 700) every 30 minutes. These bouts were performed 12 times, totalling one hour of activity and 6.5 hours of sitting throughout the course of the experimental day.

On arrival, participants had a cannula fitted into an accessible vein from which 10mL samples were obtained throughout the day. Immediately following the two fasting samples (depicted at timepoints -1 and 0 in Figure 2), participants were given a standardized meal consisting of 8 kcal per kilogram of body weight, with a macronutrient composition reflective of co-ingestion in modern western diets (14% protein, 51% carbohydrate and 35% fat). Once consumed (within ≤15 minutes), blood sampling commenced at 30, 60, 120, and 180 minutes thereafter, enabling us to capture the postprandial period. An identical meal was then issued (time point 3 in Figure 2) and sampling continued in a similar fashion at 30, 60, 120, 180, and 210 minutes following this. Participants were supervised by study staff to ensure compliance with the protocol and were asked to wear an activPAL monitor to objectively confirm sitting and walking times during each experimental condition (See Table S-3, Supplemental Digital Content 3, sitting and walking data during experimental conditions). *Ad libitum* water consumption was also noted and made consistent between conditions.
Biochemical analysis

Glucose was analysed on the day of collection by the University Hospitals of Leicester pathology department, using standard enzymatic techniques with commercially available kits (Beckman, High Wycombe, U.K).

Centrifuged (4°C) plasma samples were stored in -80°C freezers and insulin was analysed from these collectively at the end of the trial using an electrochemiluminescence assay (Meso Scale Discovery, Maryland, USA). Each sample was ran in duplicate to ensure reliability of readings. Duplicate sample values with ≥20% variability were reanalysed. Ambient conditions of the laboratory were kept consistent in order to reduce variability between assays.

Free-living activity monitor processing

ActivPAL data were downloaded using the manufacturers software (activPAL Professional Research Edition, PAL technologies, Glasgow, UK) and ‘Event’ csv files were processed using a validated automated algorithm in STATA (StataCorp LP, Texas, USA) described in detail elsewhere (28).

Actigraph data (100Hz) were downloaded using the manufacturer’s software (ActiLife version 6·10·4, Lite Edition), reintegrated into 60 second epoch files and processed using a bespoke tool (KineSoft, version 3·3·76; KineSoft, New Brunswick, Canada [www.kinesoft.org]). Freedson cut points were used to categorize activity intensities (13). Non-wear time was defined as a minimum of 60 minutes of continuous zero counts, and when assessing habitual activity levels, days with at least 10 hours of wear time were required to be considered valid.

The minimum amount of valid days utilised for both ActivPAL and ActiGraph data was three days.
Statistical analysis

Descriptive characteristics of those who completed this study are summarised overall (n = 34) and stratified by sex (Table 1) for descriptive purposes.

Missing glucose and insulin data during the experimental conditions accounted for roughly 2% of overall required samples (34 out of 1,496) (see Table S-4, Supplemental Digital Content 4, summary of missing glucose and insulin data). These 34 missing data points were imputed using a regression model previously developed for an acute trial investigating breaking sedentary behaviour (15). This approach uses key predictors (BMI, ethnicity, age, fasting values and treatment condition) to derive a regression equation for the glucose and insulin values at each individual time point, this regression equation is then used to impute missing values.

The iAUC of glucose and insulin was calculated for each experimental condition. Total AUC was calculated by applying the trapezium rule and further subtraction of fasting levels gave a single value of iAUC for each participant. Utilising iAUC as opposed to total AUC is common practice in acute interventions where fasting levels should be unaffected by the intervention (20). Glucose iAUC was defined a priori as the primary outcome.

The effect of light walking breaks compared to continuous sitting on outcomes (glucose and insulin iAUC) and whether CRF modified this response was assessed using a repeated measures ANOVA. Treatment was entered as a within-person variable, with CRF (as a continuous variable) entered as a between-subjects covariate. Sex was also entered as a between-subjects factor. ‘Treatment by CRF’ and ‘treatment by sex’ interaction terms were investigated to assess the modifying effect of fitness and sex respectively. Sex was included in the model given that it is a strong determinant of fitness and an important potential confounder. Treatment by CRF interactions were further explored by calculating the linear
regression coefficients within each treatment condition. To highlight the direction of significant interactions, derived average glucose iAUC values for men and women at the 25th, 50th and 75th centile of the CRF distribution are shown in Figure 3.

Two-tailed $p \leq 0.05$ was considered significant. Analyses were performed with SPSS (version 24). Results are presented as mean ± SE or regression coefficient (95% CI) unless stated otherwise.

RESULTS

The key characteristics of those who successfully completed all three study visits are displayed in Table 1 (n = 34). Stratification of these characteristics for both males and females are also presented here.

Overall treatment condition effect

The average postprandial concentrations of glucose (A) and insulin (B) witnessed throughout the 7·5 hour testing periods for both experimental conditions (‘prolonged sitting’ and ‘light walking breaks’) are depicted in Figure 2. There was a significant main effect of treatment for both glucose ($F (1, 31) = 6.67, p = 0.015$) and insulin ($F (1, 31) = 7.00, p = 0.013$) iAUC after adjustment for fitness and sex. Interrupting prolonged sitting time with light walking breaks reduced blood glucose iAUC by 35% (from 3.89 ± 0.7 to 2·51 ± 0.7 mmol·L⁻¹·h) and insulin iAUC by 35% (from 241 ± 46 to 156 ± 24 mU·L⁻¹·h).

Impact of CRF and sex

There was a significant treatment by CRF interaction for glucose iAUC ($F (1, 31) = 4.89, p = 0.035$). The treatment by CRF interaction for insulin iAUC failed to reach significance ($F (1, 31) = 3.76, p = 0.062$). There was no treatment by sex interaction for glucose ($F (1, 31) = 1.77, p = 0.194$) or insulin ($F (1, 31) = 1.54, p = 0.223$) iAUC.
Stratified analysis revealed that each unit increment in CRF (per mL·kg⁻¹·min⁻¹) was associated with a lower glucose iAUC (-0.21 mmol·L⁻¹·h; 95% CI -0.38, -0.05) (p = 0.013) in the prolonged sitting condition, whereas there was no association between CRF and glucose iAUC during the light walking breaks condition (-0.07 mmol·L⁻¹·h; -0.21, 0.07) (p = 0.335). In contrast, each unit increment in CRF was associated with a lower insulin iAUC (-10.93 mU·L⁻¹·h; -19.48, -2.37) (p = 0.014) in the prolonged sitting condition and a lower insulin iAUC (-6.35 mU·L⁻¹·h; -10.90, -1.83) (p = 0.007) in the light walking breaks condition.

Figure 3 uses the derived regression coefficients to show how the predicted average difference between conditions for glucose iAUC changes as CRF increases for males and females. This demonstrates that average blood glucose iAUC response for a man at the 25th centile of CRF within our cohort went from 5.80 to 2.98 mmol·L⁻¹·h (from prolonged sitting to light walking breaks, respectively), whereas average responses for a man at the 75th centile went from 1.99 to 1.78 mmol·L⁻¹·h. Similar trends were observed for women.

DISCUSSION

This study found that interrupting prolonged sitting with regular light walking breaks reduced postprandial glucose and insulin levels in a healthy cohort. However, CRF modified the response for glucose such that individuals with lower levels of fitness received incrementally greater reductions in postprandial glucose. For example, the average response for a man at the 25th centile of CRF within our population (VO₂ peak of 42.5 mL·kg⁻¹·min⁻¹) demonstrated relatively high postprandial glucose levels during prolonged sitting (5.80 mmol·L⁻¹·h) but was able to almost half this level through employing regular light walking breaks. In contrast, the average response for a man at the 75th centile of fitness (VO₂ peak of 60.5 mL·kg⁻¹·min⁻¹) demonstrated relatively low levels of postprandial glucose during prolonged sitting.
sitting (1.99 mmol·L⁻¹·h) but only reduced this by a further 11% through employing regular light walking breaks. The same pattern was demonstrated for women. These results were supported by further analysis which demonstrated that CRF was inversely associated with postprandial glucose during prolonged sitting, whereby every unit increment in VO₂ peak (per mL·kg⁻¹·min⁻¹) was associated with an average reduction of 0.21 mmol·L⁻¹·h in glucose iAUC values. Taken together, our results suggest that having high CRF or employing regular light walking breaks in those with low CRF can both reduce postprandial levels of glucose during periods of prolonged sitting activity. Elevated postprandial glucose levels are implicated with the development of T2DM and CVD (5) and therefore strategies to promote healthy glycemic responses when sedentary are of high importance.

Our observation that those with higher CRF demonstrate less metabolic benefit from light activity breaks is consistent with previous experimental research that has tended to show relatively lower metabolic benefits of light activity breaks in healthy cohorts (1, 22) compared to both those with high risk of chronic disease (9, 15). Our findings also correspond to cross sectional research that has shown the influence of sedentary time on a cluster of cardio-metabolic issues to be significantly less pertinent in those with higher fitness levels (7, 23, 25). The concept that fitter individuals may gain less pronounced health benefits from lower levels of sitting time is supported by cross-sectional research that have stratified data by habitual MVPA level, finding that individuals with higher MVPA levels display significantly weaker associations between sedentary time with HbA₁c (3), inflammation markers (16) and all-cause mortality (11).

In contrast, a recent meta-analysis found that the association between sedentary time and health outcomes persisted in sufficiently active individuals (4). However, this pooled analysis was predominantly derived from self-reported measures of sedentary time and MVPA which are prone to bias and consequently may have been insensitive to detecting true interactions. It
should also be noted that although observational research linking sedentary behaviour to health is plentiful, the vast majority have investigated the confounding rather than the modifying influence of physical activity (4, 27) or fitness (25).

The growing observational and experimental data has supported new guidance and recommendation calling for reductions in sitting time (18). However, if the findings of the current study continue to be supported by further research, there may be reasonable grounds to embark upon a more personalized/tailored approach to T2DM prevention. Precision medicine is important given that a one size fits all recommendation is rarely effective. For example, interventions to reduce sitting time may be optimized by targeting those with poor CRF, whereas those with high CRF may be better served by interventions aimed at maintaining CRF and physical activity levels across the lifespan. However, it should be noted that median levels of CRF within our population for men and women were 50.3 and 34.0 mL·kg$^{-1}$·min$^{-1}$ respectively and that the average reductions in postprandial glucose at this level of CRF was 41%. As the majority of the general population within the age range included in this study are estimated to fall below the median levels of fitness within our population (8), the importance of interrupting sitting time with light activity breaks is likely to remain generalizable to the majority of the population.

This research also suggests that increasing CRF levels may be a viable way to protect against the potential harms of prolonged sitting. Although there are genetic contributions to fitness, the largest contributor to an individual’s fitness is their time spent in MVPA (6). Participation in regular MVPA outside of seated hours may therefore offer some protection, particularly in seated occupations such as driving.

Our observation that fitter individuals experienced less pronounced postprandial glycemic excursions during prolonged sitting may result from favourable physiological adaptations.
stemming from regular engagement in MVPA (one of the main determinants of fitness), such as increased skeletal muscle GLUT 4 protein expression (14). This would also leave less scope for further improvement, potentially explaining why the benefits of interrupting sitting time with light activity breaks appear to be blunted in those with higher fitness. However, given that CRF is determined by a mixture of both MVPA engagement and genetics (6), we cannot distinguish between behavioral and genetic mechanisms driving the results of the current study.

This study has some important limitations. Although this study provides an initial proof-of-concept from which future research can tailor to alternative study cohorts, findings should not be generalised outside the population investigated. In particular, given that the population utilised in this study were healthy, the extent to which CRF modifies responses in high risk or clinical population remains to be investigated. Our second limitation is that despite instructions to standardize food intake, and refrain from caffeine and alcohol consumption leading up to treatment conditions, we did not objectively test participant compliance and relied on self-reported adherence. In addition, fitness assessments were only conducted at one time-point, thus direct causality cannot be inferred. Future interventions that actively set out to manipulate fitness levels and assess prospective change in experimental data are required to elucidate direct causality. Another concern was that those with higher fitness in this study were predominantly men and conversely, those with lower fitness were predominantly women. However, our results were adjusted for sex and it was not found to modify the treatment effect for glucose which was in contrast to CRF. Therefore the correlation between sex and CRF is unlikely to be confounding the results of this study.

In conclusion, participants with lower fitness had worse postprandial glucose and insulin responses during prolonged sitting, and were able to gain greater metabolic benefit through breaking their sitting time with light activities compared to individuals with higher fitness.
Future interventions aimed at alleviating the deleterious metabolic impacts of sedentary behaviour may therefore be optimized by tailoring to cardio-respiratory fitness levels of the general population.

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LIST OF SUPPLEMENTAL DIGITAL CONTENT

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Supplemental Digital Content 2.doc
Supplemental Digital Content 3.doc
Supplemental Digital Content 4.doc
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FIGURE CAPTIONS:

Figure 1 - Trial CONSORT Profile

Figure 2 - Effect of treatment condition on average Blood Glucose and Insulin

Figure 3 – The effect of treatment condition on average iAUC (95% CI) for glucose categorised by fitness level by the 25th, 50th and 75th centile of the cohort.