

**Objectively measured sedentary time may predict insulin resistance,  
independent of moderate and vigorous physical activity**

**Running Title:** Sedentary time and insulin resistance

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Submitted 22 December 2008 and accepted 26 April 2009.

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*Objective:* To examine the prospective association between objectively measured time spent sedentary and insulin resistance, and whether this association is independent of moderate and vigorous physical activity (MVPA) and other relevant confounders.

*Research Design and Methods:* Population-based study (MRC Ely study) in 376 middle-aged adults (166 men, 210 women) over 5.6 years of follow-up. Physical activity and sedentary time were measured objectively by individually calibrated minute-by-minute heart rate (HR) monitoring at both baseline and follow-up. Sedentary time was calculated as the HR observations (minutes) below an individually predetermined threshold (flex HR), and expressed as a percentage of total monitored time during waking hours over 4 days. The percentage of time spent above 1.75 x resting HR represented MVPA. Fasting plasma insulin was used as a surrogate measure of insulin resistance.

*Results:* Time spent sedentary at baseline was significantly and positively associated with log fasting insulin at follow-up ( $\beta = 0.003$ , 95% CI: 0.0006 to 0.006,  $P = 0.015$ ), independent of baseline age, sex, fat mass, fasting insulin, smoking status and follow-up time. After further adjustment for MVPA, this association was somewhat strengthened ( $\beta = 0.004$ , 95% CI: 0.0009 to 0.006,  $P = 0.009$ ).

*Conclusions:* Time spent sedentary predicts higher levels of fasting insulin, independent of the amount of time spent at moderate and vigorous intensity activity levels. This highlights the importance of reducing sedentary time in order to improve metabolic health, possibly in addition to the benefits associated with a physically active lifestyle.

**I**nsulin resistance is a precursor of type 2 diabetes and a major characteristic of the metabolic syndrome (1). Hyperinsulinaemia and impaired insulin sensitivity are common clinical findings, yielding independent health risks including metabolic, cardiovascular and neoplastic disorders (2-4).

Several aetiological factors have been identified for impaired insulin sensitivity, including genotype, body composition, inflammation and lifestyle factors (5-7). Low levels of physical activity and lack of moderate and vigorous intensity physical activity (MVPA) are associated with insulin resistance (8,9).

Sedentary time has been linked to different cardio-metabolic health outcomes, sometimes independent of overall physical activity in cross-sectional analyses (10-12). As its cardio-metabolic consequences are suggested to be a unique feature in hazardous physical activity behaviour, sedentary behaviour should be considered distinctively from physical activity when examining associations with these health outcomes (13).

A recent prospective analysis suggested that MVPA but not sedentary time was associated with insulin resistance in high-risk individuals over a one year follow-up period (14). Further prospective research is needed to examine these associations and the direction of causality in normal-risk populations with longer duration of follow-up.

Therefore, the purpose of the present study was to 1) examine the prospective association between objectively measured sedentary time and fasting insulin, as a marker of insulin resistance, in healthy middle-aged Caucasians, and 2) to examine whether this association is independent of MVPA and other confounding variables.

## **RESEARCH DESIGN AND METHODS**

**Study participants:** This study is part of the Medical Research Council Ely study, a prospective population-based cohort study of the aetiology and pathogenesis of type 2 diabetes and related metabolic disorders. Data were collected in 1994-1996 (baseline) and again in 2001-2003 (median follow-up time: 5.6 years). A total of 393 participants with complete data on anthropometry, body composition and physical activity energy expenditure (PAEE) at both baseline and follow-up were initially selected (15). Participants with missing data on fasting plasma insulin, fat mass (FM), smoking status or MVPA were excluded. Therefore, the present report comprises 376 (166 male) healthy, middle-aged Caucasians. Missing data were random with respect to body composition and physical activity at baseline.

Ethical permission for the study was granted by the Cambridge Local Research Committee, and all participants provided written informed consent.

**Plasma insulin, glucose and confounding variables:** Data collection procedures have been described in detail previously (9,16). In brief, blood samples were taken after an overnight fast. Plasma insulin and glucose levels were determined using standardized protocols. Levels of fasting plasma insulin were used as a surrogate measure for insulin resistance. The HOMA-IR score was calculated as (fasting plasma insulin [ $\mu$ U/ml] x fasting plasma glucose [mmol/l])/22.5.

Anthropometry data were obtained using standardized procedures (9,16). Body composition was measured by bio-impedance (Bodystat®1500 analyzer, Bodystat, Isle of Man, UK). Information on smoking status was self-reported.

**Sedentary behaviour, physical activity and aerobic fitness:** A standard valid protocol for measuring EE was used at baseline and follow-up (17). The individual

relationship between EE and heart rate (HR) was assessed during rest and exercise according to the flex HR method (15,16,17). At baseline, individual calibration was completed through a graded cycle ergometer test using indirect calorimetry (PK Morgan oxygen analyzer). At follow-up, a sub-maximal, graded walking treadmill test was used. Oxygen consumption and carbon-dioxide production were measured by indirect calorimetry (Vista XT metabolic system, Vacumed, Ventura, CA).

HR was monitored on a minute-by-minute basis during the waking hours over 4 days of free-living (Polar Electro, Kemple, Finland). In the analysis of the free-living HR data, sedentary time was assessed as all HR observations (minutes) below the flex HR and expressed as a percentage of total monitored time. MVPA was defined as the percentage of all HR points above 1.75 times resting HR (RHR) as previously reported (9).

Aerobic fitness ( $VO_{2max}$ ) was estimated as the oxygen uptake at the age-predicted maximal HR of the extrapolated regression line for each individual's oxygen consumption and HR relationship.  $VO_{2max}$  was expressed per kg of fat free mass (FFM).

**Statistical methods:** Fasting insulin and HOMA-IR were logarithmically transformed (ln) in order to normalize their skewed distributions. Since these variables were highly correlated (Pearson's  $r = 0.99$ ) at both baseline and follow-up, and the results for HOMA-IR and for fasting insulin almost identical, results are only reported for fasting insulin.

Univariate and multivariate linear regression analysis was used to examine the associations between men and women, baseline and follow-up, and between the percentage of time spent sedentary at baseline and fasting insulin at follow-up. Confounders included in the multivariate models were baseline fasting insulin, age, sex, FM, smoking status and duration of follow-up. To

examine whether the association was independent of baseline MVPA, this variable was additionally added to the model. Collinearity was controlled for by means of the variance inflation factor. Statistical analyses were conducted using Stata/SE version 10.0 (StataCorp, College Station, Texas, USA).

## RESULTS

Table 1 shows the descriptive characteristics of the participants. Sedentary time was inversely correlated with MVPA ( $r = -0.34$ ,  $P < 0.001$ ).

Table 2 shows the associations between sedentary time and fasting insulin. No significant interaction effect (sex by sedentary time) on follow-up fasting insulin was found ( $P = 0.80$ ). Therefore, results are presented for men and women combined, adjusting for sex. Percentage of time spent sedentary at baseline was significantly and positively associated with fasting insulin at follow-up. The crude association between time spent in MVPA with fasting insulin approached statistical significance. In Model 1 (adjusting for confounders except MVPA) the association between sedentary time and fasting insulin at follow-up was attenuated but remained statistically significant. When this model was reanalyzed with substitution of FM for body fat percentage or waist circumference the results were essentially unchanged (data not shown). Model 2 (additionally adjusting for time spent in MVPA) showed virtually no change in the magnitude or direction of the association for sedentary time. To examine whether the effect of sedentary time was also independent of change in FM over the follow-up time, we added change in FM to Model 2. The association pertained in magnitude and direction after further adjustment for change in FM ( $\beta = 0.004$ , 95%CI: 0.001 to 0.006,  $P = 0.005$ ).

Baseline aerobic fitness was not associated with follow-up fasting insulin ( $P = 0.32$ ) after adjusting for baseline age, sex, FM, fasting insulin, smoking status, and follow-up time.

Adjusted geometric means of fasting insulin, stratified by quartiles of time spent sedentary are presented in Figure 1. This model accounted for 44% of the variance in fasting insulin. Sedentary time and time spent in MVPA accounted for 2.1% and 0.8% of the variance, respectively.

Excluding individuals with impaired glucose tolerance ( $n=22$ ) at baseline, did not materially change the associations (data not shown).

## **DISCUSSION**

The results from the present study showed that physiologically measured sedentary time using individual calibration was associated with hyperinsulinaemia measured 5.6 years later in healthy, middle-aged Caucasians. This association was independent of baseline confounders, including age, sex, FM, fasting insulin, smoking status, follow-up time and MVPA. Similar results were found when we modelled sedentary time as quartiles. Moreover, reliability estimates from a repeated measures sub-study of this cohort suggest that the true association between behaviour and health is likely to be twice as strong as those observed (18).

Our observations are consistent with previous cross-sectional findings using objective measurements of sedentary time suggesting that this behaviour is associated with 2h blood glucose (19) and metabolic syndrome features (11) in adults. Our results extend these previous cross-sectional observations by suggesting that sedentary time predicts higher levels of fasting insulin independent of time spent in MVPA and other confounding factors. This observation is, however, in contrast to recent prospective

observations in high-risk individuals, where accelerometry-measured MVPA and not sedentary time predicted insulin resistance at follow-up (14). Differences between studies are likely explained by different methodology for assessing sedentary time, differences in duration of follow-up and populations differences (i.e. age, diabetes risk, and obesity status). Future studies are needed to determine whether objectively measured sub-components of physical activity differentially predict insulin resistance and other metabolic outcomes due to baseline age, obesity status and diabetes risk.

The following study strengths and limitations should be considered. First, because the present study is observational the extent to which causality can be inferred is less than from a randomised controlled trial. However, our prospective study design, the relatively precise measure of our main exposure variable and the possibility to control for many confounding factors support a causal independent positive association between sedentary time and the development of insulin resistance. Second, the use of individually calibrated HR monitoring for measurement of sedentary time is likely to be more accurate compared to self-report methods. Although this method is somewhat susceptible to HR fluctuations due to external factors (environmental and emotional influences), the individually defined flex HR will greatly reduce misclassification of time spent sedentary. Our thresholds used for defining sedentary time and MVPA are somewhat arbitrary. However, these intensity thresholds are feasible when using HR monitoring in large population-based studies (9,20). Our estimate of time spent sedentary and at MVPA, based on the flex HR and RHR, is adjusted relative to the fitness level of each individual as RHR is lower in more fit individuals. This means that our results may not be directly comparable with results obtained with other objective methods such as

accelerometry. The confounding effect of aerobic fitness on our results is likely to be minimal. Indeed, additional adjustments for aerobic fitness did not change results for any of the models (data not shown). Third, the associations observed in this group of healthy, middle-aged, Caucasians may not be generalizable to other populations that differ in age and physical activity. Volunteers older than 65 years at follow-up were not included due to safety precautions for the exercise test. However, our results were unchanged after excluding those with impaired fasting glucose, suggesting that this condition did not explain our findings. Fourth, other potential confounders not accounted for in the analyses, such as genotype, dietary habits, birth weight, early growth patterns and pharmaceutical factors, may explain some of the observed associations. Also, although we adjusted for MVPA, we could not adjust for total physical activity EE because of collinearity. Finally, fasting insulin is not a direct measure of insulin resistance, but it has been shown consistently that fasting insulin is a robust surrogate for insulin resistance, and is associated with the metabolic syndrome, diabetes and their aetiology (21).

Using data from this cohort we recently showed that sedentary time at baseline was not significantly associated with a wide range of obesity indicators at follow-up; interestingly, a greater FM, waist circumference and BMI at baseline significantly predicted sedentary time at follow-up (22). This suggests that sedentary time may be differentially associated with different health outcomes and urges the need for more prospective studies using objective methods for assessing the dose-response relationships between different sub-dimensions of physical activity with obesity, insulin resistance and other chronic disease risk factors.

The results from this study may have important clinical implications. In a meta-analysis, Ruige et al. (23) reported an increased risk of 18% (8 to 29%) for cardiovascular diseases (CVD) per increment of 50 pmol/l in fasting insulin. Further, a recent meta-analysis demonstrated a linear association between fasting insulin levels and cardiovascular mortality independent of other risk factors (2).

Pathways through which inactivity can lead to insulin resistance and its co-morbidities include vascular changes. Vascular and endothelial dysfunction may contribute to reduced blood flow, decreased peripheral insulin-stimulated glucose uptake and reduced glucose-stimulated insulin secretion (24). A sedentary lifestyle also has a direct effect on inactivity induced factors including deep venous thrombosis and poor lipid metabolism (25).

In summary, this is the first study suggesting that increased time spent sedentary is prospectively associated with elevated fasting insulin levels regardless of the amount of time spent in MVPA in healthy middle-aged adults. From a public health perspective, these findings urge the need for recommendations aimed at reducing sedentary time in addition to those aimed at increasing MVPA.

#### **ACKNOWLEDGEMENTS**

We are grateful to the volunteers, who gave their time; to Susie Hennings, Sue Emms, and Ema Lucia De Rolfe, who coordinated the study and collected data; to Kate Westgate who assisted with the analysis of physical activity data; and to Stephen Sharp who provided statistical advice. The Medical Research Council (MRC), U.K. provided funding for the MRC Ely Study.

**FIGURE LEGEND**

**FIGURE 1.** Geometric means (SE) of fasting insulin (follow-up) stratified by quartiles of time spent sedentary (baseline) in healthy, middle-aged individuals (n=376). Data are adjusted for baseline age, sex, fat mass, fasting insulin, smoking status, follow-up time and time spent at moderate and vigorous intensity physical activity.

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**TABLE 1.** Descriptive characteristics of participants (n=376) at baseline and follow-up: the Medical Research Council Ely Study, 1994-2003

Characteristics	Total (n=376)		Men (n=166)		Women (n=210)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Age (years)	49.4 ± 7.7	55.0 ± 7.9*	49.6 ± 8.1	55.2 ± 8.3*	49.2 ± 7.4	54.8 ± 7.5*
Height (cm)	168.7 ± 8.7	168.5 ± 8.6†	175.7 ± 6.3	175.4 ± 6.2†	163.2 ± 6.0‡	163.1 ± 6.0‡
Weight (kg)	75.0 ± 13.7	76.3 ± 15.4*	82.8 ± 10.6	83.7 ± 12.0†	68.8 ± 12.7‡	70.3 ± 15.2*‡
BMI (kg/m <sup>2</sup> )	26.3 ± 3.9	26.7 ± 4.6*	26.8 ± 2.9	27.2 ± 3.4*	25.8 ± 4.5	26.4 ± 5.3*
Fat mass (kg)	22.2 ± 7.8	24.4 ± 9.2*	19.1 ± 5.4	21.3 ± 6.4*	24.7 ± 8.5‡	26.9 ± 10.4*‡
Fat free mass (kg)	52.8 ± 11.5	51.8 ± 11.5*	63.7 ± 6.8	62.4 ± 7.4*	44.1 ± 5.5‡	43.5 ± 6.0*‡
Waist circumference (cm)	85.9 ± 12.0	90.5 ± 13.0*	94.3 ± 8.5	98.2 ± 9.7*	79.3 ± 10.2‡	84.5 ± 12.1*‡
Current smokers (%)	16.8	-	15.1	-	18.1	-
VO <sub>2max</sub> (ml kg <sup>-1</sup> FFM min <sup>-1</sup> )	44.9 ± 11.6	56.5 ± 13.4*	46.3 ± 10.9	58.0 ± 12.2*	43.8 ± 12.0	55.4 ± 14.2*
Flex heart rate	76.1 ± 10.1	81.5 ± 11.1*	73.1 ± 9.5	77.7 ± 9.8*	78.4 ± 9.9‡	84.6 ± 11.0*‡
Time spent sedentary (% of total time)	32.9 ± 20.6	51.7 ± 22.8*	30.7 ± 19.9	47.2 ± 21.5*	34.7 ± 20.9	55.2 ± 23.2*‡
MVPA (% of total time)	1.9 ± 3.4	1.9 ± 2.2	2.2 ± 3.1	2.2 ± 2.5	1.7 ± 3.6	1.7 ± 2.8
Fasting plasma insulin (pmol/l)§	38.1 (35.9–40.4)	45.6 (42.6–48.7)*	41.7 (38.2–45.6)	52.6 (48.1–57.5)*	35.4 (32.8–38.3)	40.7 (37.0–44.7)*‡
Fasting plasma glucose (mmol/l)§	4.9 (4.8–4.9)	5.4 (5.3–5.4)*	5.0 (4.9–5.1)	5.6 (5.5–5.7)*	4.7 (4.7–4.8)‡	5.2 (5.1–5.3)*‡
HOMA-IR§	1.37 (1.28–1.46)	1.80 (1.67–1.94)*	1.54 (1.40–1.70)	2.19 (1.98–2.41)*	1.24 (1.15–1.35)‡	1.54 (1.39–1.71)*‡

Data are means ± SD or § geometric means (95% CI)

\*P &lt; 0.001, †P &lt; 0.05 for baseline vs. follow-up

‡P &lt; 0.001 for men vs. women

**TABLE 2.** Regression coefficients (95% CI) for the association between objectively measured sedentary time and moderate and vigorous physical activity time (MVPA) at baseline with fasting insulin (log pmol/l) at follow-up in healthy, middle-aged, Caucasian individuals (n=376).

	<b>B (95% CI)</b>	<b>P value</b>	<b>R<sup>2</sup></b>
<b>Crude</b>			
Sedentary (%)	0.005 (0.001; 0.008)	0.005	0.021
MVPA (%)	-0.018 (-0.04; 0.002)	0.080	0.008
<b>Model 1</b>			
Sedentary (%)	0.003 (0.0006; 0.006)	0.015	0.439
MVPA (%)	0.002 (-0.01; 0.02)	0.818	0.430
<b>Model 2</b>			
Sedentary (%)*	0.004 (0.0009; 0.006)	0.009	0.441
MVPA (%)†	0.009 (-0.007; 0.02)	0.290	0.441

Model 1 adjusted for baseline age, sex, fat mass, fasting insulin, smoking status and duration of follow-up

Model 2 additionally adjusted for MVPA(\*) or sedentary time(†)

**FIGURE 1.**

