Nutrition, Metabolism & Cardiovascular Diseases (2014) xx, 1–7

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes

C.L. Falconer [a,b,*], A.R. Cooper [a,b], J.P. Walhin [c], D. Thompson [c], A.S. Page [a], T.J. Peters [d], A.A. Montgomery [e,f], D.J. Sharp [f], C.M. Dayan [g], R.C. Andrews [d]

[a] Centre for Exercise, Nutrition and Health Sciences, School for Policy Studies, University of Bristol, UK
[b] National Institute for Health Research Bristol Biomedical Research Unit in Nutrition, Diet and Lifestyle, University of Bristol, UK
[c] Department for Health, University of Bath, Bath, UK
[d] School of Clinical Sciences, University of Bristol, Bristol, UK
[e] Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK
[f] School of Social and Community Medicine, University of Bristol, Bristol, UK
[g] Institute of Clinical Diabetes and Metabolism, Cardiff University School of Medicine, Cardiff, UK

Received 26 November 2013; received in revised form 18 March 2014; accepted 20 March 2014
Available online ■ ■ ■

KEYWORDS
Sedentary time;
Type 2 diabetes;
Breaks in sedentary time;
Inflammation

Abstract *Background and aims:* We investigated whether objectively measured sedentary time was associated with markers of inflammation in adults with newly diagnosed type 2 diabetes.
Methods and results: We studied 285 adults (184 men, 101 women, mean age 59.0 ± 9.7) who had been recruited to the Early ACTivity in Diabetes (Early ACTID) randomised controlled trial. C-reactive protein (CRP), adiponectin, soluble intracellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), and accelerometer-determined sedentary time and moderate-vigorous physical activity (MVPA) were measured at baseline and after six-months. Linear regression analysis was used to investigate the independent cross-sectional and longitudinal associations of sedentary time with markers of inflammation.

At baseline, associations between sedentary time and IL-6 were observed in men and women, an association that was attenuated following adjustment for waist circumference. After 6 months of follow-up, sedentary time was reduced by 0.4 ± 1.2 h per day in women, with the change in sedentary time predicting CRP at follow-up. Every hour decrease in sedentary time between baseline and six-months was associated with 24% (1, 48) lower CRP. No changes in sedentary time between baseline and 6 months were seen in men.
Conclusions: Higher sedentary time is associated with IL-6 in men and women with type 2 diabetes, and reducing sedentary time is associated with improved levels of CRP in women. Interventions to reduce sedentary time may help to reduce inflammation in women with type 2 diabetes.

Introduction

Type 2 diabetes is one of the most prevalent chronic diseases worldwide, contributing significantly to the global burden of disease [1]. Diabetes is an independent risk factor for cardiovascular disease (CVD) and in people with CVD, the presence of diabetes worsens prognosis [2]. Chronic inflammation is implicated in the pathogenesis of type 2 diabetes and in the development of CVD and other

* Corresponding author. NIHR Biomedical Research Unit in Nutrition, Diet and Lifestyle, Level 3, University Hospitals Bristol Education Centre, Upper Maudlin Street, Bristol BS2 8AE, UK. Tel.: +44 1173421759.
E-mail address: Catherine.falconer@bristol.ac.uk (C.L. Falconer).

0939-4753/$ - see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2014.03.009

diabetic complications including diabetic retinopathy [3]. Inflammatory cytokines secreted by adipose tissue are involved in the regulation of glucose metabolism and insulin resistance, and also in other inflammatory processes linked to an increased CVD risk [4]. For example, high levels of C-reactive protein (CRP) are related to risk of future CVD in people with type 2 diabetes [5]. The inflammatory nature of type 2 diabetes is partly mediated through increased adiposity [6], with hepatic CRP secretion suggested to increase in response to an adiposity-related increase in another inflammatory cytokine, interleukin-6 (IL-6). Adiposity is also associated with reduced levels of adiponectin [7], an anti-inflammatory cytokine with anti-atherogenic properties. Other, non-adipose, markers of inflammation such as soluble intracellular adhesion molecule-1 (sICAM-1), are independently associated with risk of CVD and provide information on the inflammatory state of the vasculature [8].

Regular physical activity is a cornerstone in the prevention and treatment of type 2 diabetes due to its actions on glucose control, and blood pressure [9] and is also known to reduce inflammation in people with type 2 diabetes [10], therefore providing a potential avenue for intervention to reduce CVD risk. However, people with type 2 diabetes have low levels of physical activity with few meeting physical activity recommendations of 30 min moderate to vigorous physical activity (MVPA) on five days of the week [11]. There is increasing interest in the role that sedentary behaviours may play in adult health. Higher levels of time spent sedentary are associated with an increased risk of type 2 diabetes, cardiovascular disease, and cardiovascular and all-cause mortality [12,13], independently of levels of physical activity. In addition, detrimental cross-sectional associations between sedentary time objectively measured with accelerometers and waist circumference, HDL-cholesterol and insulin resistance have been shown in both healthy individuals [14] and those with type 2 diabetes [15]. In adults with newly diagnosed type 2 diabetes, MVPA accounts for 3.2% of the day in contrast to 61.5% of the day spent sedentary [15], and reducing sedentary time may thus provide an alternative approach to managing health status in such individuals.

There is evidence that prolonged sedentary time may impact upon inflammation [16,17]. However, the mechanism by which this occurs and how much of the effect is mediated through differences in MVPA and adiposity is not well understood. Studies in healthy individuals or those at risk of type 2 diabetes have demonstrated higher levels of objectively measured sedentary time to be associated with CRP, independently of MVPA [14,18,19], and one study reported evidence of a sex difference, with self-reported sitting time associated with inflammation in women, but not men [20]. However, all associations were attenuated when adjusted for BMI [20]. To date, no studies have investigated the independent associations of objectively measured sedentary time with inflammatory biomarkers in individuals with type 2 diabetes.

Therefore, the aim of the present study was to investigate the sex-specific associations of objectively measured sedentary time with selected inflammatory biomarkers in individuals with newly diagnosed type 2 diabetes. If such associations are present, they may indicate an alternative route to improve health in people with type 2 diabetes.

Methods

Participants

This paper presents a secondary data analysis from the Early ACTivity in Diabetes (Early ACTID) study, a randomised controlled trial of physical activity and diet in the management of type 2 diabetes. This study has been described in detail previously [21]. Briefly, participants with newly diagnosed type 2 diabetes were recruited through primary care in the South West of England. Eligible participants had a clinical diagnosis of type 2 diabetes in the previous 6 months and were aged 30–80 years at diagnosis. Participants were excluded on the basis of uncontrolled diabetes (HbA1c $>$ 10% [85.8 mmol/mol]), blood pressure $>$ 180/100 mmHg, LDL-cholesterol $>$4 mmol/l, and body mass index (BMI) $<$ 25 kg/m^2 or body weight $>$180 kg. Telephone screening was performed on 1634 participants, of whom 712 were eligible for face-to-face screening and 593 were enrolled in the study. All participants provided written informed consent prior to participation and ethical approval was obtained from the Bath Hospital Research Ethics Committee (05/Q2001/5). This study is registered (number ISRCTN92162869).

Metabolic and anthropometric outcomes

Venous blood samples were obtained following an overnight fast and analysis was conducted by individuals blinded to the patient's identity. Serum was analysed for IL-6, sICAM-1 and adiponectin using commercially available solid phase ELISAs (Quantikine, R and D Systems Inc., Abingdon; US). High sensitivity serum CRP was determined using an automated high sensitivity immunoturbidimetric assay and RX Daytona clinical chemistry analyser (Randox Laboratories Ltd., UK). Average intra- and inter-assay coefficient of variation (CV) was established from the repeated analysis of 20–60 samples at different concentrations. The intra-assay CV was 3%, 5%, 6% and 9% for CRP, adiponectin, sICAM-1 and IL-6, respectively. The inter-assay coefficient of variation was 6–7% for all assays except IL-6 which was 16%. Body weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively with participants wearing light, indoor clothing and without shoes. Waist circumference was measured at the midpoint between the lowest rib and anterior iliac. Social deprivation was measured using the Index of Multiple Deprivation (IMD) score, a measure of local area deprivation that takes into account income, employment, health and disability, education and training, housing and services, living environment and crime, based on

Please cite this article in press as: Falconer CL, et al., Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes, Nutrition, Metabolism & Cardiovascular Diseases (2014), http://dx.doi.org/10.1016/j.numecd.2014.03.009

respondent's postcode [22]. Information on current smoking status, ethnicity and medication were obtained by the research nurse.

Physical activity and sedentary time

Participants wore an uni-axial accelerometer (Actigraph GT1M; Actigraph LLC, Pensacola, FL, USA) set to record data every minute on a waist-worn belt for seven days during waking hours except when swimming or bathing. Accelerometer data were downloaded using Actilife software (version 1.0.52 Actigraph LLC) and data were processed using Kinesoft (version 3.3.62; Kinesoft, Saskatoon, SK, Canada) to generate outcome variables (mean daily physical activity, accelerometer counts per minute (cpm), and daily minutes of MVPA and sedentary time). For comparison with other studies, thresholds of $\geq$1952 cpm for MVPA and $<$100 cpm for sedentary time were used to compute the average number of minutes spent in each behaviour [14,23]. Non-wear time was defined as a period of $\geq$20 min with continuous zero values, and days with at least 10 h of measurement were considered valid. For inclusion in the analyses, participants were required to record at least three valid days of accelerometer data [15]. Medication was held constant between the baseline and 6 month assessments.

Statistical analyses

Since the Early ACTID intervention was not designed to influence sedentary behaviour, data were treated as a cohort and not analysed by trial arm. Descriptive characteristics are summarised as mean and SD, unless otherwise stated. Due to their skewed distribution, inflammatory marker variables were log transformed and are presented as geometric means. Sex differences in demographic, physical activity and inflammatory variables were explored using *t*-tests for continuous variables and the chi-squared test for differences for categorical data. Paired sample *t*-tests were used to describe differences in mean values of continuous variables between baseline and 6 months. Linear regression analyses were used to explore cross-sectional associations between sedentary time and inflammatory variables at baseline. Regressions were performed separately in males and females. Linear regression models were built with total sedentary time as the exposure and each inflammatory variable in turn as the outcome. Model 1 was adjusted for age, current smoking (yes/no), trial arm (diet, diet plus activity or usual care), deprivation score, lipid, blood pressure or diabetes-lowering medication (dichotomised as medication yes/no), accelerometer wear time, and MVPA. Model 2 was additionally adjusted for waist circumference. Linear regression was used to examine whether a change in sedentary time between baseline and 6 months predicted the inflammatory variables at follow-up. Models were adjusted as before, and also included baseline values of sedentary time, change in MVPA and the baseline inflammatory variable under investigation. Interaction terms were used to test differences in the effect of sedentary time by sex. CRP can be influenced by acute infection and therefore a sensitivity analysis was conducted to explore whether excluding high values ($>$10 mg/L) influenced the outcome. All analyses were conducted using STATA 12 (College Station, TX; StataCorp). The significance level was set as $p < 0.05$ for all analysis and $p < 0.1$ for interaction terms.

Results

A total of 593 patients were randomised to the Early-ACTID study. Of these, 285 (48%) fulfilled the accelerometer inclusion criteria, had complete inflammatory marker profiles at baseline and 6 months and were included in the present analyses. Participants who were included in the analysis tended to be younger than those who had incomplete data (58.9 $\pm$ 9.7 years compared to 60.9 $\pm$ 10.5 years) but there were no other differences in terms of BMI, HbA1c, MVPA or sedentary time.

The baseline demographic, metabolic, inflammatory and physical activity characteristics of the participants are shown in Table 1 (n = 285), overall and for each sex separately. Men were more physically active than women. No sex-related differences in total sedentary time were observed. Females tended to be more obese and had higher levels of sICAM-1, CRP and adiponectin than males.

Table 2 shows the regression coefficients for the cross-sectional baseline associations between sedentary time with markers of inflammation, adjusting for medication status, trial arm, age, smoking, deprivation, accelerometer wear time and MVPA. An association was seen between IL-6 and sedentary time in both men and women. For every increased hour spent sedentary, IL-6 was lower by 8% (95% CI 0, 15) in men and 12% (95% CI 0, 24) in women. These associations were attenuated following adjustment for waist circumference. No other associations between sedentary time and inflammatory markers were seen. Removing MVPA from the models did not substantially change the coefficients and all models were unaffected by replacement of BMI for waist circumference. No associations between MVPA and markers of inflammation were observed following adjustment for confounders.

Changes in sedentary time and inflammatory markers between baseline and 6 months are shown in Table 1. Sedentary time was reduced in women only, decreasing by 0.4 $\pm$ 1.2 h per day between baseline and 6 months. In women, sICAM-1 had reduced by 7.9% (95% CI $-$14.3, $-$1.1) after 6 months and reductions of 42.0% (95% CI $-$56.9, $-$22.1) in CRP were also seen. In men, the only inflammatory cytokine to change was adiponectin increasing by 23.6% (95% CI 12.4, 36.0) after 6 months. Daily MVPA increased by 3.8 $\pm$ 22.9 min between baseline and follow-up in men, while no changes were seen in women.

Table 3 shows the longitudinal associations between sedentary time and inflammatory outcomes at follow-up. A change in sedentary time from baseline to 6 months

Please cite this article in press as: Falconer CL, et al., Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes, Nutrition, Metabolism & Cardiovascular Diseases (2014), http://dx.doi.org/10.1016/j.numecd.2014.03.009

Table 1 Demographic, metabolic and inflammatory characteristics of participants at baseline and 6 months.

Characteristic	Men	Women	Total	*P* Value[a]
n	*184*	*101*	*285*	
Age (years)	59.8 ± 9.3	57.5 ± 10.3	59.0 ± 9.7	0.064
BMI (kg/m^2)	30.6 ± 4.8	33.5 ± 7.0	31.6 ± 5.8	<0.001
Waist circumference (cm)	107.6 ± 11.4	105.0 ± 14.9	106.7 ± 12.8	0.103
Ethnicity (% white)	97.8	96.0	97.2	0.382
Family history diabetes (%)	45.1	64.4	51.9	0.002
Current smoker (%)	5.0	8.2	7.0	0.311
Deprivation index	14.3 ± 10.0	16.9 ± 12.6	16.5 ± 15.2	0.052
Time since diagnosis (days)	147.0 ± 52.4	145.0 ± 49.4	146.3 ± 51.3	0.747
HbA1c (%)	6.6 ± 1.0	6.8 ± 1.1	6.7 ± 1.0	0.086
On diabetes medication (%)	33.7	41.6	36.5	0.186
On lipid medication (%)	66.3	51.5	61.1	0.014
On BP medication (%)	59.8	64.4	61.4	0.448
Inflammatory markers[b]				
sICAM-1 (ng/ml)				
Baseline	240.4 (232.9, 248.2)	266.3 (254.3, 278.4)	253,5 (246.5, 260.7)	0.005
6 months	238.8 (229.3, 248.8)	239.2 (227.0, 251.9)	248.6 (239.4, 257.7)	0.968
Difference	0.7 (5.0, 4.4)	−7.9 (−14.3, −1.1)	−3.3 (−7.2, 0.7)	
IL-6 (pg/ml)				
Baseline	2.4 (2.0, 2.9)	2.4 (2.1, 2.7)	2.4 (2.1, 2.7)	
6 months	2.0 (1.8, 2.2)	2.0 (1.8, 2.2)	2.0 (1.9, 2.2)	0.658
Difference	−4.8 (−17.7, 33.4)	1.3 (−14.6, 20.1)	4.9 (−4.8, 15.4)	0.792
CRP (mg/L)				
Baseline	1.6 (1.4, 1.9)	3.2 (2.6, 3.9)	3.7 (3.2, 4.3)	
6 months	1.7 (1.4, 2.0)	1.8 (1.5, 2.3)	1.7 (1.5, 2.0)	<0.001
Difference	6.9 (5.0, 20.1)	−42.0 (−56.9, 22.1)	−15.1 (−29.7, 2.7)	0.552
Adiponectin (μg/ml)				
Baseline	4.4 (4.1, 4.7)	5.9 (5.3, 6.5)	5.5 (5.2, 5.9)	<0.001
6 months	5.4 (5.1, 5.9)	5.2 (4.7, 5.8)	5.4 (5.1, 5.7)	0.557
Difference	23.6 (12.4, 36.0)	−10.4 (−21.9, 2.6)	10.4 (1.9, 19.5)	
Physical activity				
MVPA (min/day)				
Baseline	29.6 ± 20.7	20.7 ± 16.4	26.4 ± 19.7	<0.001
6 months	33.4 ± 24.1	21.3 ± 18.6	29.1 ± 23.0	<0.001
Difference	3.8 ± 22.9	0.64 ± 14.3	2.7 ± 20.3	
Sedentary time (h/day)				
Baseline	7.9 ± 1.3	8.1 ± 1.1	8.0 ± 1.2	
6 months	7.7 ± 1.5	7.6 ± 1.2	7.7 ± 1.4	0.315
Difference	−0.2 ± 1.5	−0.4 ± 1.2	−0.3 ± 1.4	0.640
Accelerometer wear time (days)				
Baseline	4.5 ± 0.7	4.6 ± 0.6	4.5 ± 0.67	0.093
6 months	4.4 ± 0.8	4.5 ± 0.7	4.4 ± 0.8	0.425
Accelerometer wear time (hours/day)				
Baseline	12.9 ± 1.0	13.0 ± 1.0	12.9 ± 1.0	0.398
6 months	12.6 ± 1.1	12.6 ± 0.9	12.6 ± 1.0	0.776

Results are presented as means ± SD, and number (column percentages).
[a] *P* value for differences between men and women. Significance level, $p < 0.05$.
[b] Inflammatory markers are displayed as geometric means ± SD with differences between baseline and 6 months are presented as ratios of the geometric means.

predicted CRP at follow-up in women, with a reduction of 1 h in sedentary time being associated with a 24% (95% CI 1.0, 48.0) reduction in CRP in women, with no associations seen in men.

Regression models containing appropriate interaction terms provided some evidence that any associations between sedentary time and CRP differed for men and women (Table 2). There was also evidence of an interaction by sex for the relationship between a change in sedentary time and CRP (Table 3). All results were unaffected if participants with a CRP >10 mg/L ($n = 17$) were excluded from the analysis, data not shown.

Discussion

This study investigated the cross-sectional and longitudinal associations between total sedentary time and markers of inflammation in a sample of adults with newly diagnosed type 2 diabetes enrolled in the Early ACTID diet and lifestyle randomised controlled trial. Independent cross-sectional associations between total sedentary time and IL-6 were seen in men and women; however, all associations were attenuated following adjustment for waist circumference. At 6 months follow-up, adiponectin had increased in men compared to baseline and sICAM-1 and

Please cite this article in press as: Falconer CL, et al., Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes, Nutrition, Metabolism & Cardiovascular Diseases (2014), http://dx.doi.org/10.1016/j.numecd.2014.03.009

Table 2 Cross-sectional linear regression analysis of the associations of sedentary time with inflammatory variables in the full baseline sample.

	Sedentary time				Interaction terms	
	Men (n = 184)		Women (n = 101)		B (95% CI)	P value
	β (95% CI)	P value	β (95% CI)	P value		
Log sICAM-1 (ng/ml)[a]						
Model 1	0.01 (−0.04, 0.02)	0.642	−0.01 (−0.05, 0.04)	0.751		
Model 2	−0.01 (−0.04, 0.02)	0.336	−0.02 (−0.07, 0.03)	0.409	0.03 (−0.01, 0.08)	0.171
Log IL-6 (pg/ml)[a]						
Model 1	0.08 (0.00, 0.15)	0.049	0.12 (0.00, 0.24)	0.043		
Model 2	0.07 (−0.01, 0.14)	0.097	0.08 (−0.05, 0.20)	0.228	−0.04 (−0.17, 0.08)	0.483
Log CRP (mg/L)[a]						
Model 1	0.05 (−0.09, 0.19)	0.485	0.16 (−0.05, 0.36)	0.129		
Model 2	0.02 (−0.11, 0.16)	0.768	0.06 (−0.14, 0.27)	0.537	−0.25 (−0.47, −0.03)	0.025
Log adiponectin (μg/ml)[a]						
Model 1	0.00 (−0.07, 0.06)	0.937	−0.08 (−0.17, 0.02)	0.110		
Model 2	0.00 (−0.06, 0.07)	0.979	−0.05 (−0.15, 0.05)	0.322	0.02 (−0.08, 0.11)	0.724

Regression results are presented as unstandardized coefficients (β) (95% CI) All models are adjusted for age, trial arm, smoking, deprivation score, lipid, glucose or blood pressure lowering medication, accelerometer wear time and MVPA. Model 2 is additionally adjusted for waist circumference. Interaction terms were performed on model 2.

[a] Indicates exponentiated regression coefficients interpreted as proportionate change in outcome for 1 unit change in sed time.

CRP were reduced in women. Lifestyle behaviours were also changed with men increasing MVPA and women reducing sedentary time. Longitudinal associations were demonstrated between a change in sedentary time and follow-up CRP in women. All associations were independent of MVPA. Our results build on accumulating evidence to show the detrimental health effects of prolonged sedentary time [15,18]. To our knowledge, these results are the first to show the harmful effects of sedentary time on inflammation in adults with newly diagnosed type 2 diabetes.

This study has several strengths. The study included a relatively large number of adults with newly diagnosed type 2 diabetes. A range of outcome measures including metabolic health, lifestyle behaviours, inflammatory markers and potential confounders including medication status, smoking, and age were collected. Sedentary time was measured objectively using accelerometers. There are also limitations within this study. The observational nature of the analysis means causality cannot be inferred and there is a possibility of residual confounding by other factors, for example dietary intake while sedentary. The analysis was performed separately by sex to allow for differences in the sedentary behaviours as a result of the intervention. There was a suggestion of a possible sex-by-sedentary time interaction for CRP with women exhibiting a greater increase in CRP per unit increase in sedentary time. However, the large discrepancy in sample size between males and females makes meaningful comparisons between sexes difficult.

Although accelerometers offer increased accuracy compared to self-report, they have a number of limitations for the measurement of sedentary time. Whilst the thresholds used to define MVPA measured with the Actigraph accelerometer in adults are well defined, a range of thresholds have been used to define sedentary time [18,20,23]. In addition, the criteria used in data reduction procedures to discard continuous periods of zero values, generally interpreted as time when the accelerometer has been removed, commonly range between 20 and 60 min. Since sedentary time is defined as <100 cpm, and estimates therefore include zero as a 'real' value, these decisions may impact upon the measured volume of sedentary time. Such methodological differences limit the potential for comparisons across studies. The thresholds for sedentary time and handling of zero values used in the current study were selected to allow comparison with the AusDiab data [23]. A further limitation of waist-worn

Table 3 Longitudinal linear regression analysis of the association of sedentary time with inflammatory variables.

Variable	Δ SED between 0 and 6 months				Interaction terms	
	Men B (95% CI)	P value	Women B (95% CI)	P value	β	P value
sICAM-1 (ng/ml)	0.02 (−0.01, 0.06)	0.220	0.01 (−0.05, 0.01)	0.723	−0.01 (−0.06, 0.05)	0.795
IL-6 (pg/ml)	0.07 (0.00, 0.16)	0.081	0.08 (−0.03, 0.20)	0.155	−0.02 (−0.14, 0.11)	0.801
CRP (mg/L)	0.05 (−0.11, 0.21)	0.541	0.24 (0.01, 0.48)	0.043	−0.23 (−0.47, 0.00)	0.054
Adiponectin (μg/ml)	0.03 (−0.04, 0.09)	0.397	0.02 (−0.10, 0.13)	0.740	0.01 (−0.10, 0.11)	0.890

Regression results are presented as unstandardized coefficients (B) (95% CI). All models are adjusted for age, trial arm, smoking, deprivation score, WC, relevant lipid, glucose or blood pressure lowering medication, baseline sedentary time, change in accelerometer wear time, and change in MVPA.

Please cite this article in press as: Falconer CL, et al., Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes, Nutrition, Metabolism & Cardiovascular Diseases (2014), http://dx.doi.org/10.1016/j.numecd.2014.03.009

accelerometers in the measurement of sedentary time is their inability to differentiate between postures, and potential for misclassifying standing time as sedentary, since sedentary behaviour is defined as "any waking behaviour characterised by an energy expenditure of less than or equal to 1.5 metabolic equivalents *while in a sitting or reclining posture*" [24]. To quantify the association between sedentary time and health outcomes precisely, more accurate measurement of sedentary time is required.

The inflammatory profiles of participants in the present study were indicative of low-grade inflammation [25]. Women had heightened inflammation, as indicated by elevated CRP, sICAM-1 and IL-6 compared to men. This is in agreement with previous studies who have also observed associations between sedentary time and adverse health outcomes in women only [20,26]. Previous studies have suggested that the physical activity patterns of men, who tend to do more MVPA than women, may offer protection against the detrimental health effects of sedentary time [20]. Poor dietary behaviours such as snacking are known to co-vary with time spent sedentary, and there are suggestions of a more consistent association in women [27]. More research is needed to understand the dietary implications of prolonged sedentary time, and how these might vary by sex.

The Early ACTID intervention did not specifically target sedentary behaviours. However, women in the cohort achieved an average reduction of sedentary time of 24 min/day after 6 months follow-up and furthermore the change in sedentary time was associated with CRP such that for every hour reduction in sedentary time, CRP was reduced by 24%. It has been suggested that improvements in IL-6 and CRP following lifestyle intervention are dependent upon increases in MVPA [28], or reductions in weight [29]. However, CRP was reduced at 6 months compared to baseline in women, despite no changes in MVPA and the addition of change in MVPA or weight into the regression model did not attenuate the observed associations. This finding further strengthens the cross-sectional associations between breaks in sedentary time and CRP observed in the NHANES cohort that were independent of time spent in MVPA [14]. The health benefits of MVPA are well documented and for people with type 2 diabetes include beneficial effects on lipid profiles, glucose control and inflammation [9]. However, people with type 2 diabetes commonly exhibit low levels of physical activity and interventions to increase MVPA often fail to achieve levels suggested to confer metabolic benefits [21]. In the current study, sedentary behaviour accounted for over 60% of the participants waking day [21], and plausible physiological mechanisms exist to explain the association between prolonged sedentary time and CRP [30]. The accumulating evidence of the detrimental health effects of prolonged sedentary time suggest targeting sedentary time may be an alternative strategy for improving the health of people with type 2 diabetes. These types of interventions may be particularly beneficial for women, who have a heightened state of inflammation and CVD risk and who may find increasing MVPA more difficult.

In conclusion, our data suggest that in women with newly diagnosed type 2 diabetes, sedentary behaviour can have a harmful effect on markers of inflammation which may be important for future risk of CVD. Inflammatory profiles were improved following 6 months of lifestyle intervention, with a change in sedentary time predictive of a change in CRP for the women only, a finding that warrants further investigation. These findings suggest that interventions to reduce sedentary time should be explored as potential ways to reduce chronic inflammation in women with type 2 diabetes. The incorporation of recommendations for reducing sedentary time into national guidelines would provide further impetus for the development of interventions to reduce sedentary time.

Funding source

The research was supported by the National Institute for Health Research (NIHR) Bristol Nutrition Biomedical Research Unit based at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

References

[1] Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 2011;8(4):228–36.
[2] Monesi L, Tettamanti M, Cortesi L, Baviera M, Marzona I, Avanzini F, et al. Elevated risk of death and major cardiovascular events in subjects with newly diagnosed diabetes: findings from an administrative database. Nutrition, metabolism, and cardiovascular diseases. Nutr Metab Cardiovasc Dis 2014;24(3):263–70.
[3] Williams M, Nadler J. Inflammatory mechanisms of diabetic complications. Curr Diab Rep 2007/06/01;7(3):242–8 [in English].
[4] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation January 28, 2003;107(3):499–511.
[5] Yu HI, Sheu WHH, Song YM, Liu HC, Lee WJ, Chen YT. C-reactive protein and risk factors for peripheral vascular disease in subjects with type 2 diabetes mellitus. Diabet Med 2004;21(4):336–41.
[6] Kriketos AD, Greenfield JR, Peake PW, Furler SM, Denyer GS, Charlesworth JA, et al. Inflammation, insulin resistance, and adiposity: a study of first-degree relatives of type 2 diabetic subjects. Diabetes Care August 1, 2004;27(8):2033–40.
[7] Silha J, Krsek M, Skrha J, Sucharda P, Nyomba B, Murphy L. Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. Eur J Endocrinol October 1, 2003;149(4):331–5.
[8] Jenny NS, Arnold AM, Kuller LH, Sharrett AR, Fried LP, Psaty BM, et al. Soluble intracellular adhesion molecule-1 is associated with cardiovascular disease risk and mortality in older adults. J Thromb Haemost 2006;4(1):107–13.
[9] Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint

position statement. Diabetes Care December 1, 2010;33(12):e147–67.
[10] Lee I-M, Sesso HD, Ridker PM, Mouton CP, Stefanick ML, Manson JE. Physical activity and inflammation in a multiethnic cohort of women. Med Sci Sports Exerc 2012;44(6):1088–96.
[11] Jakicic JM, Gregg E, Knowler W, Kelley DE, Lang W, Miller GD, et al. Activity patterns of obese adults with type 2 diabetes in the look AHEAD study. Med Sci Sports Exerc 2010;42(11):1995.
[12] Katzmarzyk P, Church T, Craig C, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Med Sci Sports Exerc 2009;41(5):998–1005.
[13] Thorp AA, Owen N, Neuhaus M, Dunstan DW. Sedentary behaviors and subsequent health outcomes in adults: a systematic review of longitudinal studies, 1996–2011. Am J Prev Med 2011;41(2):207–15.
[14] Healy GN, Matthews CE, Dunstan DW, Winkler EAH, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. Eur Heart J March 1, 2011;32(5):590–7.
[15] Cooper AR, Sebire S, Montgomery AA, Peters TJ, Sharp DJ, Jackson N, et al. Sedentary time, breaks in sedentary time and metabolic variables in people with newly diagnosed type 2 diabetes. Diabetologia 2012/03/01;55(3):589–99 [in English].
[16] Healy G, Matthews C, Dunstan D, Winkler E, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. Eur Heart J 2011;32(5):590–7.
[17] Allison MA, Jensky NE, Marshall SJ, Bertoni AG, Cushman M. Sedentary behavior and adiposity-associated inflammation: the multiethnic study of atherosclerosis. Am J Prev Med 2012;42(1):8–13.
[18] Henson J, Yates T, Biddle SJH, Edwardson CL, Khunti K, Wilmot EG, et al. Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. Diabetologia; 2013/03/01:1–9 [in English].
[19] Henson J, Yates T, Edwardson CL, Khunti K, Talbot D, Gray LJ, et al. Sedentary time and markers of chronic low-grade inflammation in a high risk population. PLoS One 2013;8(10):e78350.
[20] Yates T, Khunti K, Wilmot EG, Brady E, Webb D, Srinivasan B, et al. Self-reported sitting time and markers of inflammation, insulin resistance, and adiposity. Am J Prev Med 2012;42(1):1–7.
[21] Andrews RC, Cooper AR, Montgomery AA, Norcross AJ, Peters TJ, Sharp DJ, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the early ACTID randomised controlled trial. Lancet 2011;378(9786):129–39.
[22] The English indices of deprivation: summary 2007 [11 January 2012]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf.
[23] Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in Sedentary Time: beneficial associations with metabolic risk. Diabetes Care April 2008;31(4):661–6.
[24] Network SBR. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". Appl Physiol Nutr Metab 2012;37:540–2. http://dx.doi.org/10.1139/h2012-024. PubMed PMID.
[25] Leinonen E, Hurt-Camejo E, Wiklund O, Hultén LM, Hiukka A, Taskinen M-R. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. Atherosclerosis 2003;166(2):387–94.
[26] Stamatakis E, Chau JY, Pedisic Z, Bauman A, Macniven R, Coombs N, et al. Are sitting occupations associated with increased all-cause, cancer, and cardiovascular disease mortality risk? A pooled analysis of seven British population cohorts. PLoS One 2013;8(9):e73753.
[27] Pearson N, Biddle SJH. Sedentary behavior and dietary intake in children, adolescents, and adults: a systematic review. Am J Prev Med 2011;41(2):178–88.
[28] Herder C, Peltonen M, Koenig W, Sütfels K, Lindström J, Martin S, et al. Anti-inflammatory effect of lifestyle changes in the Finnish Diabetes Prevention Study. Diabetologia 2009/03/01;52(3):433–42 [in English].
[29] Church TS, Earnest CP, Thompson AM, Priest E, Rodarte RQ, Sanders T, et al. Exercise without weight loss does not reduce C-reactive protein: the INFLAME study. Med Sci Sports Exerc 2010;42(4):708.
[30] Bey L, Hamilton MT. Suppression of skeletal muscle lipoprotein lipase activity during physical inactivity: a molecular reason to maintain daily low-intensity activity. J Physiol September 1, 2003;551(2):673–82.

Please cite this article in press as: Falconer CL, et al., Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes, Nutrition, Metabolism & Cardiovascular Diseases (2014), http://dx.doi.org/10.1016/j.numecd.2014.03.009