Impact of objectively measured sedentary behaviour on changes in insulin resistance and secretion over 3 years in the RISC study: Interaction with weight gain


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Abstract

Aims. – The importance of reducing sedentary time is increasingly being recognized in the prevention of diabetes and cardiovascular disease. Despite this, the prospective association between sedentary time and physical activity with insulin sensitivity and cardiometabolic risk factors has been little studied.

Methods. – In an analysis of data from the European RISC study, sedentary time and time spent in activity of moderate or vigorous intensity were assessed by accelerometry at baseline in 313 men and 414 women, aged 30–60 years, with insulin sensitivity as measured by euglycaemic–hyperinsulinaemic clamp. Three years later, cardiometabolic risk factors (anthropometry, glucose, insulin, lipids) were available for 549 participants.

Results. – In cross-sectional analyses using baseline data, after adjusting for age, gender, recruitment centre and time spent in activity of moderate or vigorous intensity, significant unfavourable associations were observed between higher sedentary time with body weight, HDL cholesterol, triglycerides, clamp-measured insulin sensitivity and insulin secretion (all $P_{\text{trend}} < 0.002$). Sedentary time remained significantly associated with insulin secretion after adjusting for insulin sensitivity ($P_{\text{trend}} = 0.02$). In longitudinal analyses, higher baseline sedentary time was associated with 3-year increases in fasting glucose, fasting insulin and the HOMA insulin-resistance index score for the 50% of the study population who increased their BMI by at least 0.3 kg/m$^2$ (all $P_{\text{trend}} < 0.01$); these relationships remained significant after adjusting for time spent in activity of moderate or vigorous intensity. The 3-year increase in insulin secretion was lower in those spending more time doing activity of moderate or vigorous intensity ($P_{\text{trend}} = 0.03$).

Conclusion. – These prospective data suggest that less sedentary behaviour may partly counteract some of the negative effects of increasing body weight on glucose–insulin homeostasis.

Keywords: Cardiometabolic risk; Glucose; Insulin; Insulin resistance; Physical activity; Prospective; Sedentary time

Abbreviation: HOMA-IR, Homeostatic model assessment for insulin resistance.

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Résumé

Impact d’un comportement sédentaire sur le changement de l’insulino-résistance et l’insulino-sécrétion sur trois ans : interaction avec le gain de poids. L’étude RISC.

Objectifs. — La limitation du temps consacré à des occupations sédentaires est de plus en plus prise en compte en matière de prévention du diabète et des maladies cardiovasculaires. Cependant, l’association prospective entre comportements sédentaires et/ou l’activité physique et les facteurs de risque cardiométaboliques est mal connue.

Population étudiée et méthodes. — Le temps sédentaire et la durée d’activité physique d’intensité modérée ou élevée ont été mesurés par accéléromètres chez 313 hommes et 414 femmes, âgés de 30 à 60 ans à l’inclusion dans l’étude européenne RISC. De façon concomitante, l’insulino-sensibilité a été quantifiée par clamp euglycémiique hyperinsulinémique. Après trois ans, les facteurs de risque cardiométaboliques (anthropométrie, glycémie, insulinoémie, lipides) ont été remesurés et étaient analysables chez 549 participants de l’étude.

Résultats. — Les analyses transversales à l’inclusion, après ajustement sur l’âge, le sexe, le centre de recrutement et la durée d’activité physique d’intensité modérée ou élevée, montraient des associations défavorables entre le temps sédentaire et le poids corporel, le cholestérol-HDL, les triglycérides, l’insulino-sensibilité (mesuré par le clamp) et l’insulino-sécrétion (tous $P_{\text{trend}}<0.002$). L’association entre le temps sédentaire et l’insulino-sécrétion restait significative après ajustement pour l’insulino-sensibilité ($P_{\text{trend}}=0.02$). Les analyses longitudinales montraient que plus de temps passé sédentaire était plus, la glycémie et l’insulinoémie à jeun et l’indice HOMA d’insulino-résistance étaient augmentés, mais cela uniquement chez les individus dont l’IMC augmentait (de plus de 0,3 kg/m², médiane de sa variation sur trois ans) (tous $P_{\text{trend}}<0.01$) ; ces associations restaient significatives après ajustement additionnel sur la durée des activités physiques d’intensité modérée ou élevée. La variation sur trois ans de l’insulino-secretion était plus bas chez ceux qui passaient plus de temps dans les activités physiques d’intensité modérée ou élevée ($P_{\text{trend}}=0.03$).

Conclusions. — Les données de cette étude prospective suggèrent qu’une limitation du temps consacré aux occupations sédentaires pourrait compenser, au moins en partie, les effets négatifs d’une augmentation de poids sur l’homéostasie glucidique.

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Mots clés : Activité physique ; Comportement sédentaire ; Glycémie ; Insulinoémie ; Insulino-résistance ; Prospective ; Risque cardiométabolique

1. Introduction

In addition to the well-established role of physical activity in the prevention of chronic diseases such as type-2 diabetes [1,2], the deleterious impact of sedentary time is increasingly being documented [3,4]. In longitudinal studies, mortality and morbidity have been associated with sedentary behaviours such as television viewing [5,6], but this is only part of the time spent sedentarily [7]. In the developed countries, more than 50% of waking time, as measured by accelerometry, is spent in sedentariness [8–11]. Sedentary time as recorded by questionnaire is lower, and depends not only on the validity and reliability of questionnaires [12], but also on the questions asked and definitions used. In European countries the prevalence of sedentary time, as evaluated by the International Physical Activity Questionnaire (IPAQ) and defined as less than 3000 metabolic equivalent (MET) min/week accumulated over 7 days, ranged from 19% to 43%, while 23% to 56% of people spent more than 6 h/day sitting [13]. Thus, in Western societies a very large percentage of waking time is spent being sedentary.

While the relationship between sedentary time and morbidity and mortality has been extensively studied [3–6], only three prospective studies have investigated the impact of objectively measured sedentary time on changes in cardiometabolic risk [10,14,15]. In contrast, changes in cardiometabolic risk factors have often been studied in relation to physical activity documented both objectively [16] and by questionnaire [17–22].

On the other hand, cross-sectional studies have evaluated sedentary time and cardiometabolic risk factors, with sedentary time evaluated objectively by accelerometry [9,11,23] and by questionnaire [24–26]. It has also already been shown that insulin sensitivity is related with total activity, the intensity of activity and with sedentary time, using cross-sectional data from the Relationship between Insulin Sensitivity and Cardiovascular Disease (RISC) study, where activity was evaluated by accelerometer [8].

The present report investigated the 3-year evolution of cardiometabolic risk factors with sedentary time in participants from the RISC study [27]. The association with time spent in activities of moderate or vigorous intensity was also assessed in parallel.

2. Design and Methods

The RISC study was a 3-year observational cohort study aiming to evaluate insulin resistance and atherosclerosis development [27]; in 2002–2004, more than 1400 volunteers aged 30–60 years without diabetes, hypertension or dyslipidaemia were recruited at 20 centres in 13 European countries. Each recruitment centre had their ethics committee approval for the study, and all participants gave their written informed consent. Examinations included anthropometry, blood pressure, blood sampling, oral glucose tolerance tests (OGTTs; blood drawn at fasting and at 30, 60, 90 and 120 min) and euglycaemic–hyperinsulinaemic clamp tests. Physical activity and sedentary behaviours were monitored in all participants, who consented to wear an accelerometer. All of the above examinations, except for the euglycaemic–hyperinsulinaemic clamp and accelerometer monitoring, were repeated after 3 years.

2.1. Study population

At baseline, of the 1259 volunteers with an evaluation of insulin sensitivity, 847 had data on physical activity recorded
by accelerometry, 777 satisfied study entry criteria and 727 had data on cardiometabolic parameters. Three years later, anthropometry, blood pressure and plasma sample data were available for 549 participants.

2.2. Methods for measuring cardiometabolic risk factors

Body weight and body composition (fat-free mass, fat mass) were measured by biperadial bioelectric impedance analysis (TBF-300; Tanita International Division, Yieyslew, Middlesex, UK) with participants lightly clad, height by a clinical stadiometer and waist circumference by a measuring tape placed horizontally midway between the lowest costal margins and iliac crests in the midaxillary line. The following formula was also applied: body fat (%) = 100 × (fat mass (kg)/body weight (kg)). Sitting systolic and diastolic blood pressures were measured three times by an automated device (OMRON 705CP, OMRON Health Care Europe, The Netherlands) and the median value used in the analyses.

Biology was assayed centrally [27]. In Odense, Denmark, plasma glucose was measured by the glucose oxidase technique (COBAS INTEGRA Systems, Roche Diagnostics, Basel, Switzerland), and serum insulin by a specific time-resolved fluoroimmunoassay (AutoDELFA Insulin kit; Wallae Oy, Turku, Finland). In Dublin, Ireland, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured using colorimetric enzymatic tests (Roche cholesterol method for modular systems, Roche HDL 2nd generation method for modular systems and Roche triglycerides method for modular systems, respectively). Low-density lipoprotein (LDL) cholesterol concentration was calculated by the Friedewald formula.

At baseline the hyperinsulinaemic–euglycaemic clamp test quantified insulin sensitivity [27], and the homeostatic model assessment index for insulin resistance (HOMA-IR) was calculated at baseline and after 3 years [28]. Insulin secretion was also quantified at baseline and after 3 years using the following formula: insulin secretion index = (insulin 30 min−insulin 0 min)/glucose 30 min [29].

Physical activity and sedentary times were measured objectively by a small single-axis Actigraph accelerometer (AM7164-2.2, Computer Science and Applications, Pensacola, FL, USA) [30]. Acceleration signals were digitized by an 8-bit analogue-to-digital converter with sampling 10 times/s. Each digitized signal was summed over a 1-min interval and the total activity (counts/min) saved in the device memory. The accelerometer was secured by a belt at the small of the back and worn for up to 8 days from waking till bedtime except during water-based activities. The analysis included only those days when the accelerometer was worn for at least 10 hours and only those people who had at least 3 days’ worth of recordings. Non-wearing periods were identified as 60 minutes or more of continuous zero counts. Accelerometer data were processed by customized SAS version 9.1 software developed specifically for this project [8].

The cut-off points were less than 100 counts/min to define sedentary behavior and, for activities of moderate and vigorous intensity, 1952 to 5724 counts/min and more than 5724 counts/min, respectively [30,31]. For activity of moderate or vigorous intensity, more than 10 minutes was required, as per the recommendation for “bouts lasting 10 minutes or more” [1].

Two parameters are analyzed in the present report: sedentary time, the time spent by participants in sedentarity; and time spent in activities of either moderate or vigorous intensity.

2.3. Statistical analyses

Analyses used SAS (version 9.2) software. The following variables had non-symmetrical distributions and were logarithmically transformed: triglycerides; insulin; insulin sensitivity; HOMA-IR; and insulin secretion index. Participants’ characteristics at baseline and follow-up are described by means (SD), geometric means ([x] exp (SD log-transformed data)) or n (%), and compared men with women and those followed and not followed after 3 years, using t tests, χ² tests and, for activity variables, Wilcoxon tests. Spearman’s correlation coefficients were also calculated. Linear models were used to study both cross-sectional associations and the 3-year evolution of cardiometabolic risk factors in relation to activity variables measured at baseline; models were adjusted for age, gender and recruiting centre (included in models as a random factor). Data from men and women were also combined as there were very few interactions between gender and activity variables; gender-specific results are presented only where there was significant interaction.

To correct for the time the accelerometer was worn, residuals from gender-specific models were analyzed with time variables (either time spent sedentary or time spent in activities of moderate or vigorous intensity) regressed on the time the accelerometer was worn [23,32]. There was no analysis of time spent doing light-intensity activity (in other words, time spent in neither sedentarity nor in activity of moderate or vigorous intensity) as this was highly correlated with sedentary time (rSpearman = −0.95 and −0.98 in men and women, respectively).

Sedentary time and time spent in activity of moderate or vigorous intensity were analyzed in gender-specific quartile groups and presented as the P10 across quartile groups. As 31% of men and 34% of women participated in no activity of either moderate or vigorous intensity, this variable and sedentary time were analyzed in classes. In a sensitivity analysis, sedentary time was analyzed as a continuous variable.

Cross-sectional associations with sedentary time were further adjusted for time spent in activities of moderate or vigorous intensity, and associations with time spent in activity of moderate or vigorous intensity were further adjusted for body mass index (BMI).

The 3-year evolution of all cardiometabolic risk factors was analyzed according to baseline sedentary time and time spent in activities of moderate or vigorous intensity. Interactions were sought between sedentary time and factors that could modify the effect of sedentary time, such as baseline insulin sensitivity, baseline BMI and the 3-year change in BMI. These three factors were divided according to their medians. Significant interactions (P < 0.05) were observed only between change in BMI (median: +0.3 kg/m²) and cardiometabolic risk-factor evolution.
Table 1
Anthropometric and metabolic characteristics and accelerometer measures of activity: The RISC study.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 ± 9</td>
<td>45 ± 8</td>
<td>0.02</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82 ± 12</td>
<td>66 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8 ± 3.1</td>
<td>24.3 ± 4.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>21 ± 6</td>
<td>32 ± 7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92 ± 10</td>
<td>80 ± 11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122 ± 10</td>
<td>113 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 ± 7</td>
<td>73 ± 8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 9</td>
<td>69 ± 11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.88 ± 0.85</td>
<td>4.78 ± 0.85</td>
<td>0.10</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.28 ± 0.28</td>
<td>1.61 ± 0.40</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.07 ± 0.77</td>
<td>2.73 ± 0.78</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)²</td>
<td>1.05 x/÷ 1.57</td>
<td>0.85 x/÷ 1.56</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.2 ± 0.5</td>
<td>5.0 ± 0.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2-h glucose (mmol/L)</td>
<td>5.6 ± 1.5</td>
<td>5.8 ± 1.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>30 x/÷ 1.67</td>
<td>28 x/÷ 1.69</td>
<td>0.12</td>
</tr>
<tr>
<td>2-h insulin (pmol/L)²</td>
<td>114 x/÷ 2.46</td>
<td>155 x/÷ 2.05</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Insulin sensitivity (µmol.min⁻¹.kgFFM⁻¹.nmol/L⁻¹)²</td>
<td>121 x/÷ 1.63</td>
<td>149 x/÷ 1.50</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HOMA-IR³</td>
<td>6.92 x/÷ 1.73</td>
<td>6.23 x/÷ 1.78</td>
<td>0.01</td>
</tr>
<tr>
<td>Insulin secretion index</td>
<td>25 x/÷ 1.87</td>
<td>25 x/÷ 1.92</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Accelerometry

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days accelerometer worn</td>
<td>6 (5, 7)</td>
<td>6 (5, 7)</td>
</tr>
<tr>
<td>Wearing time (h)</td>
<td>92 (72, 105)</td>
<td>87 (70, 103)</td>
</tr>
<tr>
<td>Sedentary time (h)²</td>
<td>55 (41, 64)</td>
<td>50 (39, 60)</td>
</tr>
<tr>
<td>Percent-time</td>
<td>62%</td>
<td>59%</td>
</tr>
<tr>
<td>Moderate or vigorous intensity activity (h)²</td>
<td>0.6 (0.0, 1.8)</td>
<td>0.4 (0.0, 1.4)</td>
</tr>
<tr>
<td>Percent-time</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>No moderate or vigorous intensity activity, but not sedentary (h)²</td>
<td>30 (22, 39)</td>
<td>34 (25, 41)</td>
</tr>
<tr>
<td>Percent-time</td>
<td>37%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Data are presented as n (%), means ± SD or geometric means x/÷ (exponent of SD of the log-transformed variable), or as medians (lower quartile, upper quartile) or % (accelerometer variables).

HDL/LDL: high-density/low-density lipoprotein; HOMA-IR: homeostasis model of assessment for insulin resistance.

² Sedentary: less than 100 counts/min; moderate or vigorous intensity activity: at least 10 consecutive minutes with more than 1952 counts/min.

Sedentary time analyses were further adjusted for time spent at baseline in activities of moderate or vigorous intensity.

3. Results

3.1. Population description

The mean age at baseline of the 313 men and 414 women was 43 and 45 years, respectively, with mean BMI scores of 25.8 kg/m² and 24.3 kg/m², respectively (Table 1). Gender differences were observed for most of the body composition and metabolic variables, with men generally having a more at-risk profile than women. Also, in our study population, more than 60% of accelerometer wearing time was spent sedentarily and, on average, men spent more hours being sedentary than women (P = 0.0007). However, men also spent marginally more time in activities of moderate or vigorous intensity than women (P = 0.12). Sedentary time and time spent in activities of moderate or vigorous intensity, both adjusted for the time the accelerometer was worn, were correlated with Spearman’s correlation coefficients: r = -0.15 for men and r = -0.25 for women (both P < 0.0007).

The participants who were followed-up after 3 years were older than those who did not participate (age 45 versus 41 years; P = 0.0001), but there were no differences in other baseline variables after age adjustment.

3.2. Cross-sectional analysis of sedentary time and physical activity with cardiometabolic risk factors at baseline

Sedentary time was positively associated with body weight (but not with BMI or body fat), waist circumference, triglycerides and insulin secretion, and negatively associated with insulin sensitivity (as measured by clamp test) and HDL cholesterol after adjusting for age, gender and recruiting centre (all P<0.04; Table 2); all of these relationships were attenuated, but remained statistically significant after adjustment for time spent in activities of moderate or vigorous intensity, except...
Table 2
Cardiometabolic risk factors according to quartiles of time spent sedentary at baseline, adjusted for time wearing the accelerometer: The RISC study.

<table>
<thead>
<tr>
<th></th>
<th>Sedentary time</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile 1</td>
<td>Quartile 2</td>
<td>Quartile 3</td>
<td>Quartile 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n = 313)</td>
<td>&lt; 50.4 h (n = 78)</td>
<td>50.4–56.9 h (n = 79)</td>
<td>57.0–61.9 h (n = 78)</td>
<td>≥ 62 h (n = 78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women (n = 414)</td>
<td>&lt; 45.9 h (n = 103)</td>
<td>45.9–51.5 h (n = 104)</td>
<td>51.6–57.3 h (n = 104)</td>
<td>≥ 57.4 h (n = 103)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>71 (1.10)</td>
<td>71 (1.09)</td>
<td>74 (1.11)</td>
<td>74 (1.10)</td>
<td>0.002</td>
<td>0.006</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0 (0.30)</td>
<td>24.4 (0.30)</td>
<td>25.2 (0.30)</td>
<td>25.2 (0.30)</td>
<td>0.21</td>
<td>0.43</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>27 (0.59)</td>
<td>26 (0.58)</td>
<td>27 (0.59)</td>
<td>27 (0.59)</td>
<td>0.26</td>
<td>0.59</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85 (1.07)</td>
<td>84 (1.07)</td>
<td>86 (1.09)</td>
<td>86 (1.08)</td>
<td>0.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>116 (1.09)</td>
<td>116 (1.09)</td>
<td>117 (1.11)</td>
<td>117 (1.10)</td>
<td>0.35</td>
<td>0.48</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73 (0.72)</td>
<td>74 (0.71)</td>
<td>74 (0.73)</td>
<td>74 (0.72)</td>
<td>0.44</td>
<td>0.59</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 (1.23)</td>
<td>67 (1.23)</td>
<td>66 (1.24)</td>
<td>67 (1.24)</td>
<td>0.70</td>
<td>0.33</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.72 (0.08)</td>
<td>4.76 (0.08)</td>
<td>4.87 (0.08)</td>
<td>4.77 (0.08)</td>
<td>0.30</td>
<td>0.59</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.51 (0.03)</td>
<td>1.51 (0.03)</td>
<td>1.43 (0.03)</td>
<td>1.41 (0.03)</td>
<td>0.002</td>
<td>0.007</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.78 (0.08)</td>
<td>2.82 (0.08)</td>
<td>2.95 (0.08)</td>
<td>2.85 (0.08)</td>
<td>0.13</td>
<td>0.36</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.85 [1.04]</td>
<td>0.89 [1.04]</td>
<td>0.94 [1.04]</td>
<td>0.99 [1.04]</td>
<td>0.0004</td>
<td>0.003</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.06 (0.06)</td>
<td>5.06 (0.06)</td>
<td>5.03 (0.06)</td>
<td>5.01 (0.06)</td>
<td>0.31</td>
<td>0.29</td>
</tr>
<tr>
<td>2-h glucose (mmol/L)</td>
<td>5.67 (0.16)</td>
<td>5.73 (0.15)</td>
<td>5.46 (0.16)</td>
<td>5.78 (0.16)</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>27 [1.05]</td>
<td>28 [1.05]</td>
<td>29 [1.05]</td>
<td>29 [1.05]</td>
<td>0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>2-h insulin (pmol/L)</td>
<td>120 [1.09]</td>
<td>129 [1.09]</td>
<td>132 [1.09]</td>
<td>138 [1.09]</td>
<td>0.08</td>
<td>0.13</td>
</tr>
<tr>
<td>Insulin sensitivity (µmol·min⁻¹·kgFFM⁻¹·mmol/L⁻¹)</td>
<td>146 [1.05]</td>
<td>134 [1.05]</td>
<td>131 [1.05]</td>
<td>122 [1.05]</td>
<td>0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.11 [1.05]</td>
<td>6.30 [1.05]</td>
<td>6.50 [1.05]</td>
<td>6.54 [1.05]</td>
<td>0.20</td>
<td>0.42</td>
</tr>
<tr>
<td>Insulin secretion index</td>
<td>23 [1.06]</td>
<td>23 [1.06]</td>
<td>27 [1.06]</td>
<td>27 [1.06]</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are presented as age, gender and recruiting centre adjusted means (SE) or geometric means [SE of exponent of the log-transformed variable]. HDL/LDL: high-density/low-density lipoprotein; HOMA-IR: homoeostasis model of assessment for insulin resistance.

a For age, gender and recruiting centre.

b For age, gender, recruiting centre and time spent in activities of moderate or vigorous intensity.

for waist circumference ($P_{\text{trend}} = 0.12$). The insulin secretion index increased with sedentary time and remained significant after additional adjustment for clamp-measured insulin sensitivity ($P_{\text{trend}} = 0.02$).

When sedentary time was analyzed as a continuous variable rather than in quartiles, the relationships with higher body weight, triglycerides, insulin secretion and insulin sensitivity, and lower HDL cholesterol, remained significant; furthermore, LDL cholesterol and the 2-h insulin were positively and significantly related to sedentary time ($P_{\text{trend}} = 0.04$ and $P_{\text{trend}} = 0.008$, respectively), while fasting glucose and fasting insulin both showed marginal significance ($P_{\text{trend}} = 0.056$ and 0.054, respectively) as did waist circumference ($P_{\text{trend}} = 0.13$).

Table S1 (see supplementary material associated with this article online) shows the mean values of cardiometabolic parameters according to quartiles of time spent in activities of moderate or vigorous intensity. The anthropometric measures were strongly related to time spent in these activities (all $P_{\text{trend}} < 0.0001$), and waist circumference remained associated after adjusting for BMI. Blood pressure, heart rate, lipids, insulin and insulin sensitivity, measured by both clamp test and HOMA-IR index, as well as insulin secretion, were associated with time spent in activities of moderate or vigorous intensity (all $P_{\text{trend}} < 0.05$); glucose concentrations were not associated with these activities. After adjusting for BMI, more time spent in activities of moderate or vigorous intensity was associated with lower waist circumference, heart rate, total and LDL cholesterol, and fasting insulin, and higher HDL cholesterol concentrations. The favourable relationships seen with blood pressure, triglycerides, insulin sensitivity and insulin secretion were no longer significant after accounting for BMI.

3.3. Prospective analysis of sedentary time and physical activity with evolution of cardiometabolic risk factors

There were no relationships between either sedentary time or time spent in activities of moderate or vigorous intensity and changes in cardiometabolic risk factors, and there were no effect modification with baseline BMI or insulin sensitivity, as interactions were all non-significant. However, for the 3-year change in BMI, there were significant interactions between the two activity variables and fasting glucose, fasting insulin and HOMA-IR. In the 50% of participants who had increases in BMI of at least 0.3 kg/m² (median BMI change), baseline sedentary time and time spent in activities of moderate or vigorous intensity were associated with changes in fasting glucose, fasting insulin and HOMA-IR (Fig. 1, Fig. S1; see supplementary material associated with this article online): those with sedentary times below the lower quartile had a 0.2-mmol/L lower 3-year change in fasting glucose than those above the upper quartile. These three relationships with baseline sedentary time remained significant after controlling for time spent in activities of moderate or vigorous intensity (all $P_{\text{trend}} < 0.05$).
Changes in other cardiometabolic parameters (BMI, waist circumference, blood pressure, heart rate, total/HDL/LDL cholesterol and triglycerides and post-change glucose and insulin values) were not significantly related to either sedentary time or time spent in activities of moderate or vigorous intensity.

4. Discussion

Less sedentary time and more time spent in activities of moderate or vigorous intensity at baseline were associated with smaller increases in fasting glucose, fasting insulin and insulin resistance over the 3-year period, but only in those who had greater increases in BMI.

In cross-sectional analyses, time spent in activities of moderate or vigorous intensity was associated with lower values for anthropometric variables, whereas sedentary time was only associated with greater body weight after adjusting for time spent in activities of moderate or vigorous intensity. Sedentary time was also associated with higher triglycerides and insulin sensitivity and secretion, and lower HDL cholesterol, after adjusting for time spent in activities of moderate or vigorous intensity. Insulin secretion was still related to sedentary time after additional adjustment for clamp-measured insulin sensitivity. For participants who spent more time in activities of moderate or vigorous intensity, lower mean values after BMI adjustment were recorded for waist circumference, heart rate, total/LDL cholesterol and fasting insulin, with higher means for HDL cholesterol.

4.1. Cross-sectional relationships between cardiometabolic risk factors and objectively measured sedentary time

Our cross-sectional results are comparable to those of other studies of sedentary behaviour assessed by accelerometry [9,11,15,23]. It is noteworthy that none of these studies, however, assessed insulin sensitivity with the gold-standard clamp method. After accounting for physical activity, a small Australian study found that only waist circumference was related to sedentary time [9]; one study in the US National Health and Nutrition Examination Survey (NHANES) population showed no relationship with the metabolic syndrome [11], while another analysis of a larger NHANES population showed associations between waist circumference, HDL cholesterol, triglycerides, insulin, HOMA-IR and the HOMA insulin-secretion index [15]; in a study of newly diagnosed type 2 diabetes patients, associations were found with waist circumference, HDL cholesterol, insulin and HOMA-IR index [23].

In our present study, body weight (but not BMI or waist circumference), HDL cholesterol, triglycerides, clamp-measured insulin sensitivity (but not HOMA-IR) and insulin secretion were all associated with sedentary time after adjusting for time spent in activities of moderate or vigorous intensity. These results are in line with other studies and show the advantages of the more precise clamp assessment of insulin sensitivity over the HOMA-IR index, which was not significantly associated with sedentary time in the RISC data. Furthermore, insulin secretion remained associated with sedentary time after adjusting for clamp-measured insulin sensitivity. Both insulin sensitivity and
insulin secretion are key elements in the progression towards type-2 diabetes, and the association with sedentary time provides a rationale for targeting sedentary behaviour in diabetes prevention programmes.

4.2. Prospective relationships between changes in cardiometabolic risk factors and objectively evaluated sedentary time

In the Ely study, sedentary time was measured objectively by heart rate monitoring, and insulin sensitivity was evaluated by both fasting plasma insulin and the HOMA-IR index, in 166 men and 210 women followed for 5.6 years [10]. The percent-time spent sedentary and percent-time spent in activities of moderate or vigorous intensity were significantly associated with fasting insulin concentrations, but only sedentary time remained associated after adjusting for covariables and baseline fasting insulin in particular.

In the PROactive trial [14], 81 men and 111 women with a family history of diabetes were followed for 1 year. Physical activity was measured by accelerometry. The HOMA-IR index and fasting insulin at follow-up were only associated with time spent in activities of moderate or vigorous intensity, and not with sedentary time.

The Early Activity in Diabetes study [15], with a follow-up of 6 months, showed a significant relationship between sedentary time and HDL cholesterol even after adjusting for waist circumference ($P = 0.003$), and there were marginal relationships with waist circumference, insulin and HOMA-IR index (all $P < 0.10$); the latter two associations were greatly attenuated after adjusting for waist circumference.

Our present study found a relationship between changes in HOMA-IR index as well as in fasting glucose and insulin with sedentary time and time spent in activities of moderate or vigorous intensity — but only in the half of the population that gained more weight during the follow-up. Body weight gain over time is a recognized risk factor for type-2 diabetes [33–35] and cardiovascular disease [36], and our results show that less sedentary time and more physical activity can influence glucose homeostasis. The data reinforce the notion that efforts should be directed at limiting time spent in sedentary behaviour for maintenance of metabolic health over time and independently of physical activity, even though there were no associations with changes in lipids and blood pressure.

The 3-year change in insulin secretion was lower in those who spent more time in activities of moderate or vigorous intensity — but, as might be expected, this relationship was no longer significant after adjusting for baseline clamp-based insulin sensitivity, as greater insulin sensitivity required less insulin secretion.

4.3. Study strengths and limitations

To our knowledge, this is the first study to report on the associations between objectively measured sedentary time and its relation to changes in a panel of cardiometabolic risk factors. Our study was also able to evaluate changes in insulin sensitivity and insulin secretion.

However, one of the disadvantages of accelerometry is that it is not possible to know when people are not wearing the accelerometer, and our study (and others) have defined non-wearing periods as an arbitrary period of continuous zero counts. Thus, the sedentary time may have been overestimated when the accelerometer was not being worn and, conversely, the excluded time may have included long periods of sedentary time.

In addition, it was not possible to follow-up our entire baseline population; however, the baseline characteristics of the participants studied after 3 years were similar to those not studied.

A further limitation was the lack of a second accelerometer recording to evaluate changes in activity over the 3 years although, based on the IPAQ results [13,37], there was little change in total activity in our study population: the mean total MET-min/week increase was 5% ($P = 0.20$).

Our definition of moderate and vigorous activity required bouts of 10 minutes of such activities, which was in accordance with the current recommendations [1]. On adjusting the prospective relationship with sedentary time for total physical activity at baseline, the results were attenuated, remaining significant only for change in fasting glucose.

5. Conclusion

As summarized by Tremblay et al. [3], “sedentary behaviour, as distinct from lack of moderate to vigorous physical activity, has independent and qualitatively different effects on human metabolism, physical function, and health outcomes and thus should be treated as a separate and unique construct”. In experimental work, sedentary time has been associated with higher lipid levels (partly mediated by lipoprotein lipase activity) [37], and higher glucose and insulin resistance (perhaps mediated by muscle glucose transporter [GLUT4] protein content) [38].

In the RISC free-living population, more than 60% of time was spent in sedentarity, while less than 1% of time was spent in activity of moderate or vigorous intensity; the rest of the time was spent in ‘light activities’, which contributed to the total daily physical-activity time. While recommendations to increase activity with moderate-intensity activities such as walking are important, the promotion of less sedentary behaviour and more light activity is also important. Indeed, the changes in fasting glucose, insulin and HOMA-IR index were all attenuated after adjusting for total activity, but not for activity of moderate or vigorous intensity.

The relationships observed in our present study and by others are not strong, and the parameters shown to be associated with sedentary behaviour have not always been consistent across studies. However, changing levels of activity may have an impact on metabolic health if the intervention can induce a population shift to less sedentary time. Indeed, two recent reviews have proposed that high-quality prospective studies using device-based measures of activity may provide a better understanding of the impact of sedentary time on health outcomes [39,40].
In conclusion, these results suggest that less sedentary behaviour and more physical activity of moderate or vigorous intensity may partly counteract some of the negative effects of increasing body weight on glucose homoeostasis over time. These findings may help to target at-risk groups in health policies aiming to prevent diabetes at the population level.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Author contributions

EL and BB carried out the statistical analyses and wrote the article; BH and JMO provided advice during these two stages; JMD, KH, ML, JJN provided support and provided input to the final version of the article.

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Appendix A. Supplementary material


References


