doi: 10.1111/obr.12642

Obesity Comorbidity/Etiology and Pathophysiology

The cross-sectional associations between objectively measured sedentary time and cardiometabolic health markers in adults – a systematic review with meta-analysis component

C. Powell[1], M. P. Herring[1,3], K. P. Dowd[2], A. E. Donnelly[1,3†] and B. P. Carson[1,3†]

[1]Department of Physical Education and Sport Sciences, University of Limerick, Limerick, Ireland, [2]Department of Sport and Health Sciences, Athlone Institute of Technology, Athlone, Ireland, and [3]Health Research Institute, University of Limerick, Limerick, Ireland

Received 26 July 2017; revised 21 September 2017; accepted 2 October 2017

Address for correspondence: C Powell, Department of Physical Education and Sport Sciences, University of Limerick, Ireland. E-mail: cormac.powell@ul.ie

†These authors contributed equally to this research.

Summary

Sedentary time is viewed as an independent risk factor for adverse cardiometabolic health (CMH). No systematic review and meta-analysis on the cross-sectional associations between objectively measured sedentary time and CMH markers has been conducted. PubMed, Scopus and Web of Science Core Collection were searched for papers that examined the cross-sectional association between objectively measured sedentary time and CMH markers in adults. Forty-six papers met the inclusion criteria. The included papers had a combined sample size of 70,576 and an age range of 18–87 years. To examine the effect of increased levels of sedentary time on CMH markers, data on effect sizes and moderators were extracted, where pos-sible. By pooling the unadjusted data from the included papers, increased sedentary time was shown to have a significant detrimental association with fasting glucose (= 0.12, 95% confidence interval [CI]: 0.02, 0.23), fasting insulin (= 0.19, 95% CI: 0.06, 0.32), triglycerides (= 0.25, 95% CI: 0.14, 0.37), high-density li-poprotein cholesterol (= 0.20, 95% CI: 0.28, 0.13) and waist circumference (= 0.25, 95% CI: 0.15, 0.35). How sedentary time was quantified and the device used to measure sedentary time significantly influence the size of the effect reported. Future interventions focused on both decreasing sedentary time and increasing physical activity may be the most effective strategy to improve CMH.

Keywords: cardiometabolic health, meta-analysis, sedentary time, systematic review.

Introduction

Benefits of physical activity (PA) include primary and secondary prevention of chronic diseases (1). Specific guide-lines exist regarding how much moderate-to-vigorous PA (MVPA) adults should engage in daily to elicit health bene-fits (2). However, the modern lifestyle does not promote regular PA (3), with a large portion of waking time now spent being sedentary (4). Sedentary behaviour, defined as any waking behaviour characterized by an energy expendi-ture ≤1.5 METs while in a sitting or reclining posture (5), is distinct from physical inactivity, which is generally considered to be not meeting the MVPA guidelines, or the amount of time not engaged in PA of a predetermined inten-sity (5,6). Levels of time spent in sedentary behaviours are high, with sedentary time accounting for up to 10 h/day of waking time (7).

Increased sedentary time is associated with diabetes, cardiovascular disease and mortality (8–10). Prior reviews have predominantly employed subjective measures of sedentary time. However, the measurement of sedentary behaviour by subjective means is problematic. Self-report

measures are common but may lead to erroneous results (11), primarily because of misreporting and recall bias. The ubiquitous nature of sedentary behaviour may be a key limitation for accurately recalling and reporting the behaviour (12). Objective measurement avoids subjective biases, is more rigorous and has increased in use (12,13). Accelerometers, worn on either the hip or wrist, have been the predominant method utilized to objectively measure sedentary behaviour. The only objective measurement-orientated review to date has been conducted by Brocklebank and colleagues (14). The review focused on both the cross-sectional and prospec-tive associations between sedentary behaviour and cardio-metabolic biomarkers. Accelerometry was the only objective measure of sedentary behaviour that was in-cluded in the review.

Accelerometers, worn predominantly on either the hip or wrist, have addressed some self-report limitations; however, the traditional method of applying count-based thresholds to accelerometry data cannot distinguish between postures (12). Consequently, periods of quiet standing may be misclassified as sitting time, or vice versa (15). This may have important health consequences, as physiological differ-ences exist between sitting and standing (16–18). To over-come this issue, the use of postural measurement devices, such as the activPAL device (worn on the anterior aspect of the thigh), has increased, owing to both their greater ac-curacy for measuring sedentary time (19) and their ability to correctly differentiate between sitting and standing (20). Other less commonly used objective measurement modali-ties include heart rate monitors, movement sensors and multi-site/sensor devices (12). As no review to date has in-cluded sedentary time measured by all of the previously mentioned objective methods, a review focusing on all ob-jective measurement modalities is warranted to help under-stand the associations between sedentary time and cardiometabolic health (CMH) markers.

The primary aim of this review was to provide an in-depth review of the cross-sectional associations between objectively measured sedentary time, measured by any ob-jective means, and CMH markers in adults. Additionally, the overall population association between objectively measured sedentary time and CMH markers was esti-mated using meta-analysis of available unadjusted data. Potential significant sources of variability were explored using meta-regression. To complement the detailed review of cross-sectional associations, prospective studies that have also examined the association between objectively measured sedentary time and CMH markers in adults were summarized and discussed. As a large number of bio-markers have been examined relative to sedentary behaviour (21), only well-studied markers and/or markers with well-established associations with sedentary behaviour were included.

Methods

Data sources and searches

This systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (22). Articles published before 13 February 2017 were located by C. P. through searches of PubMed, Scopus and Web of Science Core Collection databases, using combinations of search terms related to the behaviour (sedentary, sitting), measure-ment (acceleromet*, objective*, activPAL, ActiGraph, SenseWear) and health (blood pressure, BMI, body mass in-dex, cardio metabolic, cardiometabolic, cardiovascular, cholesterol, CVD, diabetes, glucose, HDL-C, hypertension, insulin, LDL-C, metabolic, metabolism, obes*, triglycerides, waist and weight). The full search strategy is available on-line (File S1). Reference lists of included papers and previ-ously published systematic reviews were searched manually (8,14,23,24).

Paper selection

Inclusion criteria included (i) English language publication; (ii) cross-sectional study design; (iii) objec-tively measured sedentary time; (iv) measurement of ≥1 CMH marker; (v) participants aged ≥18 years; and, (vi) participants had to be free from any specific diseases and/or conditions (e.g. type II diabetes and cancer), as per the included articles' inclusion criteria. Retrieved arti-cles were reviewed by two authors (C. P. and B. C.); any disagreement regarding eligibility was resolved by discus-sion until consensus. Fig. 1 presents a flowchart of paper selection.

Data extraction and quality assessment

Data were extracted from included articles by C. P. and B. C., and statistical data for the meta-analytic component were cross-checked for accuracy by M. P. H. Extracted data included participant and study characteristics, test statistics and significance information (as reported by authors of in-cluded papers) for cross-sectional associations between sed-entary time and the CMH markers and, where data permitted, unadjusted means and standard deviation (SD) for health outcomes by sedentary time. Papers that reported p-trend values were deemed non-significant, as they may not necessarily become a significant finding with an increase in sample size (25). Study quality was assessed using an amended version of a tool developed by Brocklebank and colleagues (14) based on the Newcastle–Ottawa Scale (26) and the Strengthening the Reporting of Observational stud-ies in Epidemiology statement (27). The total score available was 6 points (Table 1). Two authors (C. P. and B. C.)

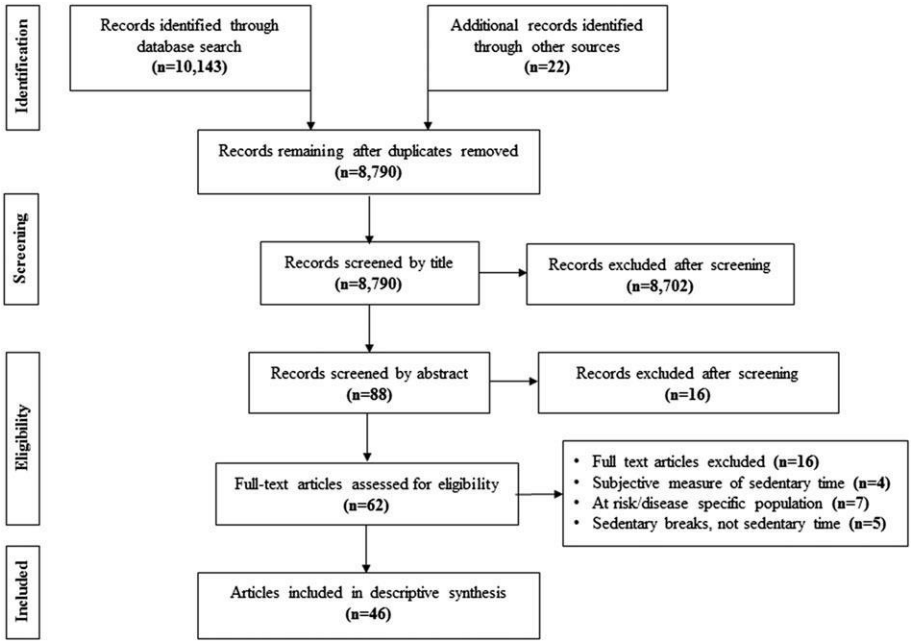

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart illustrating the inclusion and exclusion criteria used in the systematic review.

independently rated papers; discrepancies were resolved by consensus. A score of 0–2 was considered low quality, 3–4 moderate quality and 5–6 high quality.

Paper characteristics

The search identified 10,143 papers (46 of which were included). Because of the large variation in health outcomes and statistical analyses performed in these 46 papers, the meta-analysis was performed on five common CMH markers: fasting glucose, fasting insulin, triglycerides, high-density lipoprotein cholesterol (HDL-C) and waist cir-cumference. Fifteen papers provided unadjusted data for waist circumference, from which 31 effects were derived. Eight papers provided unadjusted data for fasting glucose, from which 19 effects were derived. For fasting insulin, four papers provided unadjusted data, from which 11 effects were derived. Fifteen papers provided unadjusted data for HDL-C, from which 31 effects were derived. For triglycer-ides, 11 papers provided unadjusted data, from which 25 ef-fects were derived. The ActiGraph accelerometer was the most commonly used, with 31 papers defining sedentary time as <100 counts per minute. Of the included papers, some of the authors used data from larger studies. Specifi-cally, 10 articles used data from the National Health and Nutrition Examination Survey (NHANES) (7,28–36), three from the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) (37–39), three from the Whitehall II Study (40– 42), two from the Health Survey England (HSE) (43,44) and two from the European Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study (45,46). Each one of the articles was treated as a separate study owing to the differences in participant inclusion criteria and methods being employed to process and analyse data. Previous reviews that have included multiple articles from the same study (8,14) have also treated them as individual data for review and analysis.

Effect size calculation

For papers that provided unadjusted mean and SD for health outcomes by sedentary time (29,33,35,43,47–50), standardized mean difference (d) was calculated for each increasing level of sedentary time compared to the lowest level of sedentary time by subtracting the mean of the lowest level of sedentary time from the mean of each in-creasing level of sedentary time and dividing by the pooled SD (51–53). When SDs were not provided, SD was esti-mated from standard error (SE) (33,35,43,48,49) or 95% confidence interval (CI) (29,50). When exact means were not provided, standard mean difference was converted from unadjusted correlation coefficients and estimated SE_r (41,42,54–59) or converted from unadjusted odds ra-tio and estimated SE_{OR} (36,60) according to accepted methods (51–53). Increased values of each health outcome compared to the lowest level of sedentary time resulted in a positive effect size. Accordingly, for HDL-C, effect sizes below zero represent a worsening of HDL-C with increas-ing sedentary time.

Table 1 Descriptive information of included papers

Study	Year	Population	N	Male (N)	Age	Device	Sedentary definition	Quantification of sedentary time	Measurement days	Quality score	Quality
Aadland et al.	2013	Norway	78	33	18–60	ActiGraph GT1M and GT3X+	<100 cpm	Time spent sedentary	7	3	Moderate
Alkahtani et al.*	2015	Saudi	84	84	37.6	ActiGraph wGT3X-BT	<100 cpm	Time spent sedentary	7	3	Moderate
Bakrania et al.*	2016	England (HSE)	2,131	981	50.8	ActiGraph GT1M	Sedentary behaviour (<100 cpm) to light-intensity PA ratio	Sedentary status (sedentary behaviour/ LIPA)	7	5	High
Balkau et al.	2008	Europe (RISC)	801	346	30–60	ActiGraph 7164	<100 cpm	% of wear time spent sedentary	8	4	Moderate
Bankoski et al.	2011	USA (NHANES)	1,367	601	71	ActiGraph 7164	<100 cpm	Time spent sedentary	7	6	High
Barone Gibbs et al.	2015	USA	2,027	862	38–50	ActiGraph 7164	<100 cpm	Time spent sedentary	7	6	High
Buman et al.	2014	USA (NHANES)	2,185	1,157	46.6	ActiGraph 7164	<100 cpm	Time spent sedentary	7	4	Moderate
Carson et al.	2014	Canada (CHMS)	4,935	3,677	20–79	Actical	<100 cpm	Time spent sedentary	7	5	High
Celis-Morales et al.*	2012	Chile	317	140	37.5	ActiTrainer	<100 cpm	Time spent sedentary	7	4	Moderate
Chase et al.	2014	Canada	50	23	71.5	SenseWear Pro	<1.5 METs	Time spent sedentary	7	3	Moderate
Dyck et al.	2015	Belgium, Brazil, Colombia, Czech Republic, Denmark, China, Mexico, Spain, United Kingdom and the USA (IPEN)	5,712	2,685	18–65	ActiGraph: 7164, GT1M, ActiTrainer and GT3X models	<100 cpm	Time spent sedentary	7	3	Moderate
Ekblom et al.	2015	Sweden (SCPIS)	930	445	57.7	ActiGraph GT3X and GT3X+	Uniaxial <100 cpm	Time spent sedentary	7	5	High
Garcia-Hermoso et al.*	2015	Spain (EVIDENT)	1,122	427	55	ActiGraph GT3X	<100 cpm	Time spent sedentary	7	6	High
Gennuso et al.	2013	USA (NHANES)	1,914	995	74.6	ActiGraph 7164	<100 cpm	Time spent sedentary	7	5	High
Gennuso et al.	2015	USA (NHANES)	5,076	2,319	43.8	ActiGraph 7164	<100 cpm	Time spent sedentary	7	6	High
Green et al.*	2014	USA	50	0	24	ActiGraph GT3X+	<150 cpm	Time spent sedentary	7	3	Moderate
Gupta et al.	2016	Denmark (NOMAD)	205	120	44.8	ActiGraph GT3X+	Sitting time	Sitting time	4	4	Moderate
Halloway et al.	2016	USA (Latino population)	147	46	66	ActiGraph GT1M	<100 cpm	Time spent sedentary	7	4	Moderate
Hamer et al.	2014	England (Whitehall II Study)	445	223	66	ActiGraph GT3X	<1.5 METs, <200 cpm	Time spent sedentary	7	4	Moderate
Hamer et al.*	2012	England (Whitehall II Study)	443	265	66	ActiGraph GT3X	<1.5 METs, <200 cpm	Time spent sedentary	7	4	Moderate
Hamer et al.*	2012	England (Whitehall II Study)	446	224	66	ActiGraph GT3X	<1.5 METs, <200 cpm	Time spent sedentary	7	3	Moderate
Healy et al.	2015	Australia (AusDiab)	698	314	57.3	activPAL3	Postural classification	Sitting time	7	5	High
Healy et al.*	2011	USA (NHANES)	4,757	2,398	46.5	ActiGraph 7164	<100 cpm	Time spent sedentary	7	5	High
Healy et al.	2008	Australia (AusDiab)	169	67	53.4	ActiGraph 7164	<100 cpm	Time spent sedentary	7	4	Moderate

(Continues)

Table 1 (Continued)

Study	Year	Population	N	Male (N)	Age	Device	Sedentary definition	Quantification of sedentary time	Measurement days	Quality score	Quality
Healy et al.	2007	Australia (AusDiab)	173	67	53.3	ActiGraph 7164	<100 cpm	Time spent sedentary	7	6	High
Honda et al.	2014	Japan	661	516	43	Active Style Pro HJA 350-IT	≤1.5 METs	Time spent sedentary	10	5	High
Keating et al.*	2016	Australia	82	49	40.1	SenseWear	<1.6 METs	Time spent sedentary	4	2	Low
Kim et al.	2013	Japan	483	179	47.9	Active Style Pro HJA 350-IT	≤1.5 METs	Time spent sedentary	7	5	High
Knaeps et al.*	2016	Belgium (LLSLFH)	341	207	53.8	SenseWear Pro3	≤1.5 METs	Time spent sedentary	7	5	High
Lahjibi et al.	2013	Europe (RISC)	727	313	30–60	ActiGraph 7164	<100 cpm	Time spent sedentary	8	5	High
Maher et al.	2013	USA (NHANES)	5,083	2,623	20–60+	ActiGraph 7164	<100 cpm	Time spent sedentary	7	4	Moderate
Myers et al.	2016	England	71	13	37.4	SenseWear Armband	<1.5 METs	% of wear time spent sedentary	7–8	4	Moderate
Peterson et al.*	2014	USA (NHANES)	5,268	2,597	20–85	ActiGraph 7164	<100 cpm	Time spent sedentary	7	4	Moderate
Qi et al.*	2015	USA (HCHS/SOL)	12,083	5,771	18–74	Actical B1	<100 cpm	Time spent sedentary	7	6	High
Ryde et al.	2013	Australia	105	37	40.9	Sitting pad	Amount of time spent sitting at work desk	Sitting time	/	3	Moderate
Saleh and Janssen*	2014	USA (NHANES)	1,371	768	49	ActiGraph 7164	<100 cpm	% of wear time spent sedentary	7	5	High
Sandbakk et al.	2016	Norway (Generation 100 Study)	874	379	70–77	ActiGraph GT3X+	<100 cpm	Time spent sedentary	7	5	High
Scheers et al.*	2013	Belgium	370	177	41.7	SenseWear Pro3	≤1.5 METs	Time spent sedentary	7	5	High
Scheers et al.	2013	Belgium	391	188	41.4	SenseWear Pro3	≤1.8 METs	Time spent sedentary	7	4	Moderate
Smith et al.	2014	England	12	0	30.9	activPAL	Postural classification	Time spent sedentary	7	4	Moderate
Stamatakis et al.	2011	England (HSE)	649	—	60+	ActiGraph GT1M	<100 cpm (<1.5 METs)	Time spent sedentary	7	5	High
Swartz et al.*	2012	USA	232	56	64.3	ActiGraph 7164	<100 cpm	% of wear time spent sedentary	7	3	Moderate
Tigbe et al.*	2017	Scotland	111	96	40	activPAL	Postural classification	Time spent sedentary	7	6	High
Velde et al.*	2015	USA (NHANES)	543	299	32	ActiGraph 7164	<100 cpm	% of wear time spent sedentary	7	6	Moderate
Wanner et al.	2017	USA (NHANES)	4,794	2,368	44.3	ActiGraph 7164	<100 cpm	Time spent sedentary	7	5	Moderate
Wilson et al.*	2015	Siberia	63	32	51.32	ActiGraph GT3X	<100 cpm	Time spent sedentary	2	2	Low

For the quality assessment, 1 point if analysis adjusted for moderate-to-vigorous PA, PA, exercise or activity levels; 1 point if analysis adjusted for body mass index and/or waist circumference; 1 point if analysis adjusted for sex; 1 point for an objective measure of the health outcome(s); 1 point for a measurement period of 7 days or more; and 1 point for an adequate description of the population (N, gender distribution, age, nationality, etc.). Two papers (4%) were considered to be of low quality, 23 papers (51%) moderate quality and 21 papers (46%) high quality. *Data from this paper included in the meta-analysis component.

AusDiab, Australian Diabetes, Obesity and Lifestyle Study; CHMS, Canadian Health Measures Survey; HSE, Health Survey England; IPEN, International Physical Activity and the Environment Network Adult Study; NHANES, National Health and Nutrition Examination Survey; NOMAD, New Method for Objective Measurements of Physical Activity in Daily Living; PA, physical activity; RISC, Relationship between Insulin Sen-sitivity and Cardiovascular Risk; (SCPIS)Swedish CArdioPulmonary bioImage Study.

Data synthesis and analysis

Using SPSS macros (SPSS MeanES and SPSS MetaReg), random-effects models were used to aggregate mean effect size delta ( ) and to test variation in the effects according to potential moderators (51,52). Heterogeneity was examined with the Q statistic and I^2 (52,61). Heterogeneity was indicated if Q_{Total} reached a significance level of $p \leq 0.05$ and the sampling error accounted for less than 75% of the observed variance (52).

Moderators

When data permitted, mean effects and associated 95% CIs were calculated for each level of potential moderators, including age, sex, how sedentary time was quantified and the device used to measure sedentary time. When possible and appropriate, each of the moderators was coded accord-ing to contrasts among its levels and tested with univariate meta-regression analysis with maximum likelihood (62).

Results

Details of the 46 included papers are presented in Table 1. There was agreement on the quality of 41 of the included papers (89%), with five papers (11%) requiring consensus. The included articles had a combined sample size of 70,576 and an age range of 18–87 years. From the included papers, 10 came from NHANES (7,28–36), three from AusDiab (37–39), three from the Whitehall II Study (40– 42), two from HSE (43,44), two from RISC study (45,46) and one each from the Generation 100 Study (63), EVI-DENT study (49), Leuven Longitudinal Study on Lifestyle, Fitness and Health (LLSLFH) (55), Swedish CArdioPulmo-nary bioImage Study (SCPIS) (64), International Physical Activity and the Environment Network Adult Study (65), New Method for Objective Measurements of Physical Ac-tivity in Daily Living study (66), Hispanic Community Health Study/Study of Latinos (50) and Canadian Health Measures Survey (67). The remaining 16 papers were all individual/stand-alone studies (11,47,48,56–60,68–75). For the meta-analysis, the aggregated sample size and mean age (n, years) for the five included health markers were fasting glucose (25,356, 41.6), fasting insulin (10,474, 37.0), triglycerides (26,562, 42.4), HDL-C (29,582, 46.1) and waist circumference (16,842, 44.6). Twenty-three of 31 effects (74.2%) for waist circumference were greater than zero. Twelve of the 19 effects (63.2%) for fasting glu-cose were greater than zero. Nine of 11 effects (81.8%) for fasting insulin were greater than zero. Nineteen of 25 effects were greater than zero. Twenty-four of 31 effects (77.4%) for HDL-C were less than zero. Mean effect and associ-ated 95% CI are presented in Table 2 for each level of each moderator variable across all outcomes included in the meta-analysis. A summary of the following results are available online (File S2).

Body mass and body composition measures

One paper reported a positive association between seden-tary time and body mass (71), which was reduced to non-significance following adjustment for MVPA. Three other papers reported no significant association between seden-tary time and body mass (32,46,58). No associations were reported for either fat mass (71) or lean mass (71). Seden-tary time was positively associated with body mass index (BMI) in 10 papers (39–42,44,48,56,57,71,75) (six did not adjust for any PA (40,41,48,56,57,75) and three became non-significant following adjustment for MVPA (39,42,71)). Fourteen papers reported no association between sedentary time and BMI (11,28,31– 33,35,43,46,47,49,65,66,73,74). Sedentary time had a positive association with waist circumference in 15 papers (29,35–37,39,44,48,55–58,60,68,71,75) (four did not ad-just for any PA (36,37,48,57) and four associations became non-significant following adjustment for MVPA (39,60,71) and cardiorespiratory fitness (55)). Peterson and colleagues found an association in only the moderate MVPA group (35), between those with high sedentary time and low sed-entary time. Fifteen papers reported no significant associa-tion between sedentary time and waist circumference (11,28,30,32–34,43,46,47,49,54,59,66,67,73). The associ-ation between sedentary time and percentage body fat was positive in three papers (48,57,69) (two did not adjust for PA (48,57) and one was reduced to non-significance follow-ing adjustment for MVPA (69)). Four papers (28,35,46,66) reported no significant association between sedentary time and percentage body fat.

Increased sedentary time resulted in a small but statisti-cally significant mean increase in waist circumference (= 0.25, 95% CI: 0.15, 0.35; z = 4.94, $p < 0.001$). The ef-fect was heterogeneous ($Q_{30} = 231.81$, $p < 0.001$; $I^2 = 87\%$, 95% CI: 86%, 89%). Sedentary time quantifica-tion ($\beta = 0.11$) was significantly associated with the over-all mean effect. There was no significant difference in the effect of increased sedentary time on waist circumference between papers in which sedentary time was quantified as time spent sedentary (= 0.21, k = 15) compared to the combination of papers in which sedentary time was quanti-fied as percent time spent sedentary, percent wear time spent sedentary and sedentary behaviour-to-light-intensity PA ratio (= 0.28, k = 16; z = 0.59, $p > 0.55$).

Markers of glucose control

Seven papers reported a positive association with fasting glu-cose (34,36,38,39,48,68,76) (two did not make any adjust-ments for PA (36,48) and two became non-significant

Table 2 Summary of univariate moderator analyses

Effect moderator	Contrast weights	Effects (k)		95% confidence interval	Contrast p value
Fasting glucose (aggregated n = 25,356, mean age = 41.6)					
Study nationality					
USA		13	0.12	0.01 to 0.25	
South America		3	0.22	0.02 to 0.41	
Australia		1	0.215	0.21 to 0.22	
Asia		1	0.20	0.21 to 0.19	
Europe		1	0.06	0.0598 to 0.0603	
Device type					
ActiGraph		14	0.11	0.02 to 0.23	
ActiTrainer		3	0.22	0.02 to 0.41	
SenseWear		2	0.09	0.10 to 0.28	
Sedentary time quantification					
Time spent sedentary		7	0.11	0.01 to 0.24	
Percent wear time spent sedentary		9	0.20	0.05 to 0.35	
Percent Time Spent Sedentary		3	0.11	0.25 to 0.03	
Fasting insulin (aggregated n = 10,474, mean age = 37.0)					
Study nationality					
USA		7	0.03	0.02 to 0.09	
South America		3	0.68	0.18 to 1.17	
Australia		1	0.219	0.214 to 0.224	
Device type					
ActiGraph	1	7	0.03	0.02 to 0.09	
ActiTrainer	0.5	3	0.68	0.18 to 1.17	
SenseWear	0.5	1	0.219	0.214 to 0.224	
Sedentary time quantification					
Time spent sedentary	1	5	0.55	0.19 to 0.91	<0.001
Percent wear time spent sedentary	1	6	0.03	0.03 to 0.09	
HDL-C (aggregated n = 26,562, mean age = 42.4)					
Sample sex					
Mixed sex		25	0.23	0.32 to 0.15	
Female only		3	0.11	0.24 to 0.02	
Male only		3	0.01	0.17 to 0.15	
Study nationality					
Asia		4	0.29	0.41 to 0.17	
USA		13	0.08	0.15 to 0.01	
Europe		10	0.25	0.38 to 0.12	
South America		3	0.59	1.03 to 0.15	
Australia		1	0.16	0.153 to 0.163	
Device type					
ActiGraph		23	0.12	0.19 to 0.06	
ActiTrainer		3	0.59	1.03 to 0.15	
Active Style Pro		2	0.31	0.45 to 0.18	
SenseWear		2	0.23	0.93 to 0.48	
activPAL		1	0.82	0.827 to 0.817	
Sedentary time quantification					
Time spent sedentary	1	17	0.28	0.40 to 0.16	
Percent wear time spent sedentary	0.33	9	0.08	0.17 to 0.005	≤0.04
Percent time spent sedentary	0.33	3	0.11	0.27 to 0.05	
Sedentary behaviour-to-light-intensity physical activity ratio	0.33	2	0.25	0.59 to 0.09	
Triglycerides (aggregated n = 29,582, mean age = 46.1)					
Sample sex					
Mixed sex		19	0.30	0.16 to 0.44	
Female only		3	0.20	0.07 to 0.34	
Male only		3	0.05	0.22 to 0.11	
Study nationality					
Asia		2	0.29	0.15 to 0.72	
USA		13	0.26	0.10 to 0.42	
Europe		6	0.13	0.02 to 0.27	

(Continues)

Table 2 (Continued)

Effect moderator	Contrast weights	Effects (k)		95% confidence interval	Contrast p value
South America		3	0.61	0.41 to 0.80	
Australia		1	0.25	0.259 to 0.248	
Device type					
ActiGraph	1	19	0.21	0.09 to 0.34	
ActiTrainer	0.33	3	0.61	0.41 to 0.80	>0.92
SenseWear	0.33	2	0.01	0.37 to 0.34	
activPAL	0.33	1	0.63	0.625 to 0.633	
Sedentary time quantification					
Time spent sedentary	1	13	0.26	0.10 to 0.42	
Percent wear time spent sedentary	0.5	9	0.27	0.08 to 0.47	>0.89
Percent time spent sedentary	0.5	3	0.17	0.04 to 0.31	
Waist circumference (aggregated n = 16,842, mean age = 44.6)					
Sample sex					
Mixed sex		25	0.29	0.18 to 0.41	
Female only		3	0.07	0.06 to 0.21	
Male only		3	0.007	0.16 to 0.17	
Study nationality					
Asia		4	0.14	0.05 to 0.32	
USA		14	0.28	0.11 to 0.44	
Europe		8	0.21	0.07 to 0.36	
South America		3	0.36	0.09 to 0.63	
Australia		2	0.30	0.26 to 0.85	
Device type					
ActiGraph		22	0.21	0.09 to 0.33	
ActiTrainer		3	0.36	0.09 to 0.63	
SenseWear		2	0.33	0.28 to 0.93	
activPAL		1	0.583	0.579 to 0.587	
Sitting pad		1	0.55	0.28 to 0.83	
Sedentary time quantification					
Time spent sedentary	1	15	0.21	0.09 to 0.33	
Percent wear time spent sedentary	0.33	10	0.35	0.15 to 0.55	>0.55
Percent time spent sedentary	0.33	3	0.009	0.13 to 0.15	
Sedentary behaviour-to-light-intensity physical activity ratio	0.33	2	0.22	0.02 to 0.45	

following adjustment for MVPA (38,76)). No significant association between sedentary time and fasting glucose was reported in 16 papers (11,29,30,32,33,35,37,46,50,54– 56,58–60,67). Sedentary time and 2-h glucose had a positive association in three papers (38,39,76) (two papers were reduced to non-significance after MVPA adjustment (39,76)), but a further three papers reported no significant association (29,46,50). No included paper reported a significant association between sedentary time and glycated haemoglobin (32,39–44,76). Sedentary time was positively associated with fasting insulin in six papers (29,30,35,48,67,76) (two were not adjusted for PA (30,48)). Peterson and colleagues reported a significant association between high-sedentary-time and low-sedentary-time groups within the high-MVPA group (35). Three papers found no significant association between sedentary time and insulin (46,54,56). No signifi-cant association was found for 2-h insulin or insulin secre-tion index (46). Sedentary time was shown to be significantly associated with insulin sensitivity (29,30,45) (one paper did not adjust for PA (30)) and insulin resistance (35,48,76) (two papers did not adjust for PA (35,48)) in three papers each. Non-significant associations were reported for one paper on insulin sensitivity (46) and three on insulin resistance (46,50,54). Sedentary time was positively associated with beta cell function in two papers (29,30) (one did not adjust for PA (30)).

Increased sedentary time resulted in a small but significant mean increase in fasting glucose (= 0.12, 95% CI: 0.02, 0.23, $z = 2.30$, $p \leq 0.021$). The overall effect was heteroge-neous ($Q_{18} = 99.56$, $p < 0.001$; $I^2 = 83\%$, 95% CI: 79%, 86%). The distribution of effects across levels of each moderator variable did not permit statistical differences between levels to be tested, but effects were larger for effects derived from papers that used the ActiTrainer (= 0.22; $k = 4$) and from papers in which sedentary time was quanti-fied as percent wear time spent sedentary (= 0.20, $k = 9$).

Increased sedentary time resulted in a small but signifi-cant mean increase in fasting insulin (= 0.19, 95% CI: 0.06, 0.32, $z = 2.88$, $p \leq 0.004$). The overall effect was het-erogeneous ($Q_{10} = 64.20$, $p < 0.001$; $I^2 = 86\%$, 95%CI: 82%, 89%). Device type ($\beta = 0.78$) and sedentary time quantification ($\beta = 0.79$) were significantly associated with overall effect size, such that significantly larger in-creases in fasting insulin were derived from papers that used

the ActiTrainer or SenseWear (= 0.57, k = 4) compared to papers that used the ActiGraph (= 0.03, k = 7, z = 5.66, p < 0.001) and from papers in which sedentary time was quantified as time spent sedentary (= 0.55, k = 5) compared to percent wear time spent sedentary (= 0.03, k = 6, z = 5.77, p < 0.001).

Lipid profiles

Thirteen papers reported a negative association between sedentary time and HDL-C (11,29,34,39–43,48,55,58,60,68) (three papers did not adjust for PA (40,41,48) and two became non-significant following ad-justment for MVPA (42,60)). Fifteen papers reported no sig-nificant association between sedentary time and HDL-C (30,32,33,35–37,46,47,49,50,54,56,59,67,72). Sedentary time and low-density lipoprotein cholesterol (LDL-C) were positively associated in two papers (48,70), neither of which was adjusted for PA. Twelve papers found no significant as-sociation between sedentary time and LDL-C (11,30,32,39,41,42,46,50,54,58,67,72). The association between sedentary time and total cholesterol was positive in one paper (48); however, no adjustment was made for PA. Eight papers reported no significant association be-tween sedentary time and total cholesterol (32,35,41–43,46,54,72). Fifteen papers found a positive association between sedentary time and triglycerides (11,29,30,34,36,37,39,48,49,54,58–60,68,72) (almost half of the significant positive papers did not adjust for PA (30,36,37,48,54,59,72) and one paper became non-significant following adjustment for MVPA (60)). The positive association reported by Garcia-Hermoso and col-leagues was seen only in female participants (49). Ten pa-pers found no significant association between sedentary time and triglycerides (32,33,35,40,46,47,50,55,56,67). Kim and colleagues reported a positive association with dyslipidaemia, after adjustment for MVPA (68).

Increased sedentary time resulted in a small but statisti-cally significant mean reduction in HDL-C (= 0.20, 95% CI: 0.28, 0.13, z = 5.22, p < 0.001). The effect was heterogeneous (Q_{30} = 132.56, p < 0.001; I^2 = 78%, 95% CI: 74%, 82%). Sedentary time quantification was significantly associated with overall effect size (β = 0.32), such that significantly larger decreases in HDL-C were de-rived from papers in which sedentary time was quantified as time spent sedentary (= 0.28, k = 17) compared to the combination of percent wear time spent sedentary, per-cent time spent sedentary and sedentary behaviour-to-light-intensity PA ratio (= 0.12, k = 14, z = 2.05, p ≤ 0.04).

Increased sedentary time resulted in a small but statisti-cally significant mean increase in triglycerides (= 0.25, 95% CI: 0.14, 0.37, z = 4.34, p < 0.001). The effect was heterogeneous (Q_{24} = 193.72, p < 0.001; I^2 = 88%, 95% CI: 86%, 90%). Neither device type (β = 0.02) nor seden-tary time quantification (β = 0.03) was significantly associ-ated with the overall mean effect. There was no significant difference in the effect of increased sedentary time on tri-glycerides between papers that used the ActiGraph (= 0.21, k = 19) and papers that used the ActiTrainer, SenseWear, or activPAL (= 0.39, k = 6; z = 0.09, p > 0.92) or between papers that quantified sedentary time as time spent sedentary (= 0.26, k = 13) and the combina-tion of effects from papers that quantified sedentary time as percent wear time spent sedentary or percent time spent sed-entary (= 0.25, k = 12; z = 0.14, p > 0.89).

Blood pressure

Associations between sedentary time and systolic blood pressure (SBP) and diastolic blood pressure (DBP) are mixed in the current literature. One paper reported a positive asso-ciation between sedentary time and blood pressure with no adjustment for PA (36). No significant association was re-ported between sedentary time and blood pressure in three papers (41,42,58) or hypertension in one paper (68). A pos-itive association between sedentary time and SBP was re-ported in four papers (29,48,55,60), with a negative association reported in two papers (30,56). The positive as-sociation reported by Scheers and colleagues was non-significant after adjustment for MVPA (60). Of the signifi-cant papers, one positive (48) and two negative papers (56) did not adjust for PA. Thirteen papers found no signif-icant association between sedentary time and SBP (11,32,33,35,37,39,46,50,54,59,67,68,73). Three papers reported a positive association between sedentary time and DBP (48,55,60), with one paper reporting a negative associ-ation (67). One positive association became non-significant after adjusting for MVPA (60). One of the positive papers did not adjust for PA (48). Fifteen papers reported no signif-icant association between sedentary time and DBP (11,29,30,32,33,35,37,39,46,50,54,56,59,68,73). Gennuso and colleagues reported inconsistent associations for ele-vated blood pressure when examining the influence of sed-entary time stratified by weekly amount of MVPA (34).

Other

Positive associations between sedentary time and the meta-bolic syndrome were reported in five papers (34,36,60,63,64,68) (one became non-significant after ad-justment for MVPA (60)). Ekblom and colleagues measured sedentary time with both a uniaxial accelerometer and a tri-axial accelerometer (64). The positive association remained after adjusting for MVPA and cardiorespiratory fitness in the uniaxial models, but not the triaxial models. Two papers reported no significant association between sedentary time and the metabolic syndrome (7,59). Of the three papers that

examined the association between sedentary time and a clustered metabolic risk score, two reported significant positive associations (37,68), one paper did not adjust for PA (37) and the remaining paper reported no significant association (55).

Prospective studies

While this review focused on the cross-sectional associations between objectively measured sedentary time and CMH markers, it is important to acknowledge the limitations associated with cross-sectional analyses, pri-marily the inability to determine causality. Prospective studies are the most methodologically rigorous observa-tional studies in the absence of randomized controlled tri-als. To the authors' knowledge, <10 prospective studies using any objective measurement of sedentary time that also examined markers of CMH have been conducted among healthy adults (46,76–81). To supplement the in-depth cross-sectional findings reported herein, the subse-quent section briefly summarizes the prospective findings to date.

Of the prospective studies identified, two used heart rate FLEX to measure sedentary time (79,81), with the remain-ing studies employing accelerometry (46,76–78,80). Follow-up periods ranged from 2 (80) to 5.8 (78) years, with sample sizes ranging from 376 (79) to 2,027 (76) par-ticipants. Sedentary time at baseline was not significantly associated with BMI (46,78,81), fat mass (81), waist cir-cumference (46,81), SBP and DBP (46), lipid profile markers (total cholesterol, HDL-C, LDL-C and triglycer-ides) (46), glucose measures (fasting glucose, 2-h glucose and HbA1C) (46,76), development of the metabolic syn-drome (77) and the majority of insulin measures (2-h insu-lin, insulin sensitivity and insulin resistance) (46,76). Contrasting results were reported for fasting insulin (46,76,79). Most studies that examined body mass reported no association (46,78,81), except for the work by Dugas et al. (80), who found baseline sedentary time to be associ-ated with body mass of Ghanaian male and female partici-pants, positively and negatively, respectively. The same authors reported no associations for participants from South Africa, Jamaica, Seychelles and the USA. Taken col-lectively, the prospective studies would suggest that baseline sedentary time is not a significant predictor/contributor to a host of CMH markers at follow-up. However, caution must be exercised because of the small number of prospective studies that have been conducted (e.g. one study has exam-ined lipid profile markers). Additionally, the use of heart rate (12) and accelerometry (15,82) for measuring sedentary time has known limitations. The use of postural monitors (e.g. activPAL), which have been shown to be valid for mea-suring sedentary time, should be incorporated into future prospective studies.

Discussion

This review and meta-analysis showed that the findings of individual studies are ambiguous, but when unadjusted data are aggregated, increased objectively measured sedentary time results in significant differences in fasting glucose, fasting insulin, triglycerides, waist circumference and HDL-C. Specifically, the aggregated effects approximate dif-ferences of 3.35% (HDL-C), 3.98% (triglycerides), 1.79% (waist circumference), 6.56% (fasting insulin) and 0.81% (fasting glucose). These overall change values represent an increase in sedentary time above the lowest quartile of sed-entary time. These values are comparable to the benefits that have been reported in PA research. For example, the magnitude of decrease in HDL-C with increased sedentary time is comparable to the increase expected following 20 weeks of aerobic training (83) (4.6% increase). Similarly, there were a 3.7% decrease in triglycerides after 12+ weeks of aerobic exercise (83), 1.95- to 2.12-cm decrease in waist circumference (the 1.79% increase we report equates to a 1.69-cm increase) after 6+ months of aerobic exercise (84), 6.33%+ decrease in fasting insulin after 6 months of aerobic exercise (85) and a 1.06% decrease in fasting glucose after 6 months of aerobic exercise (86). Thus, the mean effects re-ported here are clinically meaningful and support that in-creased sedentary time negatively affects CMH.

This is the first systematic review of cross-sectional asso-ciations between sedentary time and CMH markers in adults that has included all objective measurements of sed-entary time. Only one previous review is comparable to this work; however, Brocklebank and colleagues only included accelerometry as an objective measure (14). Fifteen papers (and nine CMH markers) were common to the previous re-view and ours. Brocklebank (14) reported insufficient evi-dence regarding associations between sedentary time and fasting glucose, total cholesterol and LDL-C. However, they did report associations for fasting insulin, 2-h glucose, insu-lin resistance, insulin sensitivity and triglycerides. These dif-fering conclusions may be due to the limiting of the previous review to include only accelerometry data and the total number of included papers (28 vs 46 here). Other reviews that have examined the associations between sedentary time and CMH markers have predominately included subjective measures of sedentary time (8–10), making comparisons difficult, as these measurement methods may not be measur-ing the same construct (15,48).

We examined potential sources of variability in the asso-ciations between sedentary time and the CMH markers in-cluded in the meta-analysis. The device used and how sedentary time was quantified appeared to be influential. For fasting insulin, significantly larger changes were derived from papers that used ActiTrainer and SenseWear devices, compared to those that used ActiGraph devices. Addition-ally, quantifying sedentary time as total time spent

sedentary was also associated with larger changes in fasting glucose compared to other quantification. Sedentary time quantification was also associated with significant changes in HDL-C and waist circumference. Effects on HDL-C were influenced by quantifying sedentary time as total time spent sedentary, and waist circumference effects were non-significantly different when quantifying sedentary time as percent time spent sedentary, percent wear time spent sedentary or sedentary behaviour-to-light PA ratio. With several sedentary time quantifications commonly used, no clear consensus exists concerning which quantification is best to use. From the quantitative synthesis presented in this review, sedentary time quantification was shown to be a significant source of variability. Understanding the complex associa-tion between sedentary time and CMH is dependent on the activity data being accurately measured, appropriately processed and correctly analysed.

There is growing evidence that the activPAL device is the gold standard for quantifying sedentary time (19,20,87,88). For measuring sitting time, the activPAL has demonstrated high agreement levels with direct obser-vation: $r^2 = 0.94$ ($r = 0.96$) (19) and ICC = 0.990 (87). Im-portantly, the device is sensitive enough to detect changes in sedentary breaks (i.e. transitions from sitting to stand-ing) (19,20,87), which has become an important measure-ment criterion when examining sedentary behaviour (owing to the possibility of quiet standing being misclassified as sedentary time by other objective measure-ment modalities (15)). Papers included in the meta-analysis that used an activPAL device reported greater mean changes in HDL-C (0.82), triglycerides (0.63), and waist circumference (0.583) compared to other devices. Al-though this is based on less effects (k) than the other de-vices, potentially the increased accuracy of the activPAL device for measuring sedentary time, as well as being able to accurately differentiate between sitting and standing, may make it more suitable for quantifying associations be-tween sedentary time and CMH markers.

This review has solely focused on objective measures of sedentary time. While objective measures deliver accurate data, they do not provide researchers with domain-specific information regarding an individual's sedentary behaviour. Subjective measures of sedentary behaviour can potentially provide a comprehensive measure of activity behaviours across a range of contexts, including occupational, trans-port, household and leisure (48). This contextual informa-tion may be important when designing appropriate interventions, as research has indicated that 77% of occupa-tional hours are spent sedentary, with almost half of this time spent in prolonged sedentary bouts of 20 min or more (89). Combining highly accurate objective measurements of sedentary time with appropriate contextual information could allow both domain-specific interventions and recom-mendations to be developed.

While a detailed insight into the underlying mechanisms explaining the influence of increased sedentary time on the CMH markers examined in the quantitative synthesis is be-yond the scope of this review, some of the potential detri-mental effects are consistent with current thinking. The metabolic risks associated with increased sedentary time fo-cus on the activity of the skeletal muscle enzyme, lipoprotein lipase (LPL) (90). This enzyme plays an essential role in the hydrolysis of the triglycerides contained in the lipoproteins (17), with increases in sedentary behaviour resulting in de-creased LPL activity (91). Reductions in LPL have been as-sociated with blunted plasma triglyceride uptake (92) and lower HDL-C levels (93), while LPL may also have an influ-ence on the metabolic syndrome (94). While the links be-tween LPL and sedentary behaviour are primarily based on rodent studies (90,91,95), it does offer some insight into the potential mechanisms at play.

Strengths and limitations

The inclusion/exclusion criteria ensured that only papers that utilized objective measures to quantify cross-sectional associations between sedentary time and CMH markers were included. The inclusion of meta-analysis is an addi-tional strength that allowed the first quantitative synthesis of associations between sedentary time and five CMH markers. Moreover, analysis of plausible sources of vari-ability in the overall association between sedentary time and CMH markers highlighted that the device and the method of quantification of sedentary time influence associ-ations between sedentary time and CMH markers, findings that may critically inform future research.

One limitation to the meta-analysis was the type of data, and the reporting of data in the literature. The included studies adjusted data using different models; thus, only pa-pers that reported unadjusted associations were included in the meta-analysis. However, the decision to only use un-adjusted data is guided by the lack of a common set of ad-justments between any two papers included in the review. It is inappropriate to aggregate data that have been adjusted using different covariates in the quantitative synthesis, hence the inclusion of unadjusted data only. Future research would be strengthened through increased reporting of unad-justed values and determination of standard covariate ad-justments to increase transparency and to facilitate direct quantitative comparison and integration of available data. It should be noted that for this review, authors of the in-cluded papers were not contacted for unadjusted data. A full-scale meta-analysis was not the primary objective of this review. Rather, a quantitative synthesis of available unad-justed data was included to both strengthen the conclusions that could be made from existing literature and aid in hy-pothesis generation for future large-scale studies. A further potential limitation to this review is that multiple included

papers have used data from large-scale studies. Of the 46 included papers, 20 (43.47%) used data from larger studies, 10 (21.73%) from NHANES, three (6.52%) each from AusDiab and the Whitehall II Study and two (4.34%) each from HSE and RISC. This potentially may bias some of the results.

Conclusions

Notwithstanding the aforementioned potential limitations, this is the first review of cross-sectional associations be-tween all objective measures of sedentary time and CMH markers that quantified associations between increased sed-entary time and fasting glucose, fasting insulin, triglycer-ides, HDL-C and waist circumference through aggregation of unadjusted data. Based on appraisal of individual studies, there was no consistent significant association between sed-entary time and BMI, fasting glucose, glycated haemoglobin/HbA1c, LDL-C, total cholesterol, SBP and DBP. Associations between sedentary time and waist cir-cumference, HDL-C and triglycerides were ambiguous. Ag-gregation of unadjusted data revealed that increased time spent sedentary was associated with clinically meaningful increases in fasting glucose, fasting insulin, triglycerides and waist circumference and a decrease in HDL-C. Several weeks of structured aerobic training is potentially required to offset these negative health consequences. These findings support that increased sedentary time is detrimental to CMH. While the benefits of, and recommendations for, MVPA are well known (2), the adherence rates to these guidelines are poor (96). Interventions aimed at reducing sedentary time, while increasing PA, may provide effective strategies for improving CMH.

While this review has aggregated unadjusted data at a study level, aggregating individual participant data could potentially offer an even more detailed look into the associations between sedentary time and CMH. Recent work by Ekelund and colleagues provides insight into ag-gregating individual-level data (97), whereby data from in-dividual participants, from identified studies, were reprocessed and harmonized to give the authors individual data on over one million participants. Applying this to sedentary behaviour and health data is warranted in future research.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

This research was supported by a University of Limerick Physical Education and Sport Sciences Postgraduate Scholarship (2013–2017). In addition, the authors would like to thank Ms Grannie Hayes (BSc) for her assistance in both the data extraction and quality assessments.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. https://doi.org/10.1111/obr.12642

File S1. Full search strategy
File S2. Summary of the associations reported for each CMH marker

References

1. Warburton DE, Nicol CW, Bredin SS. Health benefits of physi-cal activity: the evidence. CMAJ. 2006; 174: 801–809.
2. Haskell WL, Lee IM, Pate RR et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007; 39: 1423–1434.
3. Lanningham-Foster L, Nysse LJ, Levine JA. Labor saved, calo-ries lost: the energetic impact of domestic labor-saving devices. Obesity Res. 2003; 11: 1178–1181.
4. Loyen A, Verloigne M, Van Hecke L et al. Variation in population levels of sedentary time in European adults according to cross-European studies: a systematic literature review within DEDIPAC. Int J Behav Nutr Phys Act. 2016; 13: 71.
5. Sedentary Behaviour Research Network. Letter to the editor: standardized use of the terms 'sedentary' and 'sedentary behav-iours'. Appl Physiol Nutr Metab. 2012; 37: 540–542.
6. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. Appl Physiol Nutr Metab. 2010; 35: 725–740.
7. Bankoski A, Harris TB, McClain JJ et al. Sedentary activity associated with metabolic syndrome independent of physical activity. Diabetes Care. 2011; 34: 497–503.
8. de Rezende LF, Rey-Lopez JP, Matsudo VK, do Carmo Luiz O. Sedentary behavior and health outcomes among older adults: a systematic review. BMC Public Health. 2014; 14: 333.
9. Wilmot EG, Edwardson CL, Achana FA et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia 2012; 55: 2895–2905.
10. Biswas A, Oh PI, Faulkner GE et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 2015; 162: 123–132.
11. Honda T, Chen S, Kishimoto H, Narazaki K, Kumagai S. Identifying associations between sedentary time and cardio-metabolic risk factors in working adults using objective and subjective measures: a cross-sectional analysis. BMC Public Health. 2014; 14: 1307.
12. Atkin AJ, Gorely T, Clemes SA et al. Methods of measurement in epidemiology: sedentary behaviour. Int J Epidemiol. 2012; 41: 1460–1471.
13. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev. 2010; 38: 105–113.
14. Brocklebank LA, Falconer CL, Page AS, Perry R, Cooper AR. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. Prev Med. 2015; 76: 92–102.

15. Hart TL, Ainsworth BE, Tudor-Locke C. Objective and subjective measures of sedentary behavior and physical activity. Med Sci Sports Exerc. 2011; 43: 449–456.
16. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes. 2007; 56: 2655–2667.
17. Hamilton MT, Hamilton DG, Zderic TW. Exercise physiology versus inactivity physiology: an essential concept for understanding lipoprotein lipase regulation. Exerc Sport Sci Rev. 2004; 32: 161–166.
18. Levine JA, Lanningham-Foster LM, McCrady SK et al. Interindividual variation in posture allocation: possible role in human obesity. Science. 2005; 307: 584–586.
19. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing seden-tary behavior. Medicine and Science in Sports and Exercise. 2011; 43: 1561–1567.
20. Lyden K, Kozey Keadle SL, Staudenmayer JW, Freedson PS. Validity of two wearable monitors to estimate breaks from seden-tary time. Med Sci Sports Exerc. 2012; 44: 2243–2252.
21. Wirth K, Klenk J, Brefka S et al. Biomarkers associated with sedentary behaviour in older adults: a systematic review. Ageing Res Rev. 2017; 35: 87–111.
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151: 264–269.
23. 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: 207–215.
24. Proper KI, Singh AS, van Mechelen W, Chinapaw MJ. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. Am J Prev Med. 2011; 40: 174–182.
25. Wood J, Freemantle N, King M, Nazareth I. Trap of trends to statistical significance: likelihood of near significant P value becoming more significant with extra data. BMJ. 2014; 348: g2215.
26. Lo CK, Mertz D, Loeb M. Newcastle–Ottawa Scale: compar-ing reviewers' to authors' assessments. BMC Med Res Methodol. 2014; 14: 45.
27. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observa-tional Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61: 344–349.
28. Wanner M, Richard A, Martin B, Faeh D, Rohrmann S. Associations between self-reported and objectively measured physical activity, sedentary behavior and overweight/obesity in NHANES 2003–2006. Int J Obes (Lond). 2017; 41: 186–193.
29. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. Eur Heart J. 2011; 32: 590–597.
30. Buman MP, Winkler EA, Kurka JM et al. Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005–2006. Am J Epidemiol. 2014; 179: 323–334.
31. Maher CA, Mire E, Harrington DM, Staiano AE, Katzmarzyk PT. The independent and combined associations of physical activity and sedentary behavior with obesity in adults: NHANES 2003–06. Obesity (Silver Spring). 2013; 21 E730-7.
32. Gennuso KP, Gangnon RE, Matthews CE, Thraen-Borowski KM, Colbert LH. Sedentary behavior, physical activity, and markers of health in older adults. Med Sci Sports Exerc. 2013; 45: 1493–1500.
33. van der Velde JH, Savelberg HH, Schaper NC, Koster A. Moderate activity and fitness, not sedentary time, are independently associated with cardio-metabolic risk in U.S. Adults aged 18–49. Int J Environ Res Public Health. 2015; 12: 2330–2343.
34. Gennuso KP, Gangnon RE, Thraen-Borowski KM, Colbert LH. Dose–response relationships between sedentary behaviour and the metabolic syndrome and its components. Diabetologia. 2015; 58: 485–492.
35. Peterson MD, Al Snih S, Stoddard J, McClain J, Lee IM. Adiposity and insufficient MVPA predict cardiometabolic abnormalities in adults. Med Sci Sports Exerc. 2014; 46: 1133–1139.
36. Saleh D, Janssen I. Interrelationships among sedentary time, sleep duration, and the metabolic syndrome in adults. BMC Public Health. 2014; 14: 666.
37. Healy GN, Wijndaele K, Dunstan DW et al. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care. 2008; 31: 369–371.
38. Healy GN, Dunstan DW, Salmon J et al. Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose. Diabetes Care. 2007; 30: 1384–1389.
39. Healy GN, Winkler EA, Owen N, Anuradha S, Dunstan DW. Replacing sitting time with standing or stepping: associations with cardio-metabolic risk biomarkers. Eur heart J. 2015; 36: 2643–2649.
40. Hamer M, Stamatakis E, Steptoe A. Effects of substituting sedentary time with physical activity on metabolic risk. Med Sci Sports Exerc. 2014.
41. Hamer M, Venuraju SM, Urbanova L, Lahiri A, Steptoe A. Physical activity, sedentary time, and pericardial fat in healthy older adults. Obesity. 2012; 20: 2113–2117.
42. Hamer M, Venuraju SM, Lahiri A, Rossi A, Steptoe A. Objectively assessed physical activity, sedentary time, and coronary artery calcification in healthy older adults. Arterioscler Thromb Vasc Biol. 2012; 32: 500–505.
43. Bakrania K, Edwardson CL, Bodicoat DH et al. Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. BMC Public Health. 2016; 16: 25.
44. Stamatakis E, Davis M, Stathi A, Hamer M. Associations between multiple indicators of objectively-measured and self-reported sedentary behaviour and cardiometabolic risk in older adults. Prev Med. 2012; 54: 82–87.
45. Balkau B, Mhamdi L, Oppert JM et al. Physical activity and insulin sensitivity: the RISC study. Diabetes. 2008; 57: 2613–2618.
46. Lahjibi E, Heude B, Dekker JM et al. Impact of objectively measured sedentary behaviour on changes in insulin resistance and secretion over 3 years in the RISC study: interaction with weight gain. Diabetes Metab. 2013; 39: 217–225.
47. Alkahtani S, Elkilany A, Alhariri M. Association between sedentary and physical activity patterns and risk factors of metabolic syndrome in Saudi men: a cross-sectional study. BMC Public Health. 2015; 15: 1234.
48. Celis-Morales CA, Perez-Bravo F, Ibanez L, Salas C, Bailey ME, Gill JM. Objective vs. self-reported physical activity and seden-tary time: effects of measurement method on relationships with risk biomarkers. PloS one. 2012; 7 e36345.
49. Garcia-Hermoso A, Martinez-Vizcaino V, Recio-Rodriguez JI, Sanchez-Lopez M, Gomez-Marcos MA, Garcia-Ortiz L. Sedentary behaviour patterns and carotid intima-media thickness in Spanish healthy adult population. Atherosclerosis. 2015; 239: 571–576.

50. Qi Q, Strizich G, Merchant G et al. Objectively measured sedentary time and cardiometabolic biomarkers in US Hispanic/Latino adults: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Circulation. 2015; 132: 1560–1569.

51. Lipsey MW, Wilson DB. Practical meta-analysis. Thousand Oaks: Sage 2001.
52. Hedges LV, Olkin I. Statistical Methods for Meta-analysis. Academic Press: Orlando, FL, 1985.
53. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell: Chichester, 2014.
54. Green AN, McGrath R, Martinez V, Taylor K, Paul DR, Vella CA. Associations of objectively measured sedentary behavior, light activity, and markers of cardiometabolic health in young women. Eur J Appl Physiol. 2014; 114: 907–919.
55. Knaeps S, Lefevre J, Wijtzes A, Charlier R, Mertens E, Bourgois JG. Independent associations between sedentary time, moderate-to-vigorous physical activity, cardiorespiratory fitness and cardiometabolic health: a cross-sectional study. PloS one. 2016; 11.

56. Keating SE, Parker HM, Pavey TG et al. Objectively quantified physical activity and sedentary behavior in predicting visceral adiposity and liver fat. J Obes. 2016; 2016 2719014.
57. Swartz AM, Tarima S, Miller NE et al. Prediction of body fat in older adults by time spent in sedentary behavior. J Ageing Phys Act. 2012; 20: 332–344.
58. Tigbe WW, Granat MH, Sattar N, Lean ME. Time spent in sedentary posture is associated with waist circumference and cardiovascular risk. Int J Obes (Lond). 2017; 41: 689–696.
59. Wilson HJ, Leonard WR, Tarskaia LA, Klimova TM, Krivoshapkin VG, Snodgrass JJ. Do physical activity and sedentary behavior relate to cardio-metabolic risk factor clustering in indigenous Siberian adults? Am J Hum Biol. 2015; 27: 149–156.
60. Scheers T, Philippaerts R, Lefevre J. SenseWear-determined physical activity and sedentary behavior and metabolic syndrome. Med Sci Sports Exerc. 2013; 45: 481–489.
61. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557–560.
62. Rosenthal R. Meta-analytic Procedures for Social Research. Sage: Newbury Park, 1991.
63. Sandbakk SB, Nauman J, Zisko N et al. Sedentary time, cardiorespiratory fitness, and cardiovascular risk factor clustering in older adults – the Generation 100 study. Mayo Clin Proc. 2016; 91: 1525–1534.
64. Ekblom O, Ekblom-Bak E, Rosengren A, Hallsten M, Bergstrom G, Borjesson M. Cardiorespiratory fitness, sedentary be-haviour and physical activity are independently associated with the metabolic syndrome, results from the SCAPIS Pilot Study. PloS One. 2015; 10 e0131586.
65. Dyck DV, Cerin E, De Bourdeaudhuij I et al. International study of objectively measured physical activity and sedentary time with body mass index and obesity: IPEN adult study. Int J Obes (Lond). 2015; 39: 199–207.
66. Gupta N, Hallman DM, Mathiassen SE, Aadahl M, Jorgensen MB, Holtermann A. Are temporal patterns of sitting associated with obesity among blue-collar workers? A cross sectional study using accelerometers. BMC Public Health. 2016; 16: 148.
67. Carson V, Wong SL, Winkler E, Healy GN, Colley RC, Tremblay MS. Patterns of sedentary time and cardiometabolic risk among Canadian adults. Prev Med. 2014; 65: 23–27.
68. Kim J, Tanabe K, Yokoyama N, Zempo H, Kuno S. Objec-tively measured light-intensity lifestyle activity and sedentary time are independently associated with metabolic syndrome: a cross-sectional study of Japanese adults. Int J Behav Nutr Phys Act. 2013; 4 10: 30.
69. Scheers T, Philippaerts R, Lefevre J. Objectively-determined intensity- and domain-specific physical activity and sedentary behavior in relation to percent body fat. Clin Nutr. 2013; 32: 999–1006.

70. Chase JM, Lockhart CK, Ashe MC, Madden KM. Accelerometer-based measures of sedentary behavior and cardio-metabolic risk in active older adults. Clin Invest Med. 2014; 37 E108.
71. Myers A, Gibbons C, Finlayson G, Blundell J. Associations among sedentary and active behaviours, body fat and appetite dysregulation: investigating the myth of physical inactivity and obesity. Br J Sports Med. 2016; 4.
72. Aadland E, Andersen JR, Anderssen SA, Kvalheim OM. Physical activity versus sedentary behavior: associations with lipoprotein particle subclass concentrations in healthy adults. PloS one. 2013; 8 e85223.
73. Halloway S, Wilbur J, Schoeny ME, Semanik PA, Marquez DX. Combined effects of sedentary behavior and moderate-to-vigorous physical activity on cardiovascular health in older, community-dwelling Latinos. J Ageing Phys Act. 2016; 24: 296–304.

74. Smith L, Thomas EL, Bell JD, Hamer M. The association between objectively measured sitting and standing with body composition: a pilot study using MRI. BMJ Open. 2014; 4 e005476.

75. Ryde GC, Brown HE, Peeters G, Gilson ND, Brown WJ. Desk-based occupational sitting patterns weight-related health outcomes. Am J Prev Med. 2013; 45: 448–452.
76. Barone Gibbs B, Pettee Gabriel K, Reis JP, Jakicic JM, Carnethon MR, Sternfeld B. Cross-sectional and longitudinal associations between objectively measured sedentary time and metabolic disease: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Diabetes Care. 2015; 38: 1835–1843.
77. Honda T, Chen S, Yonemoto K et al. Sedentary bout durations and metabolic syndrome among working adults: a prospective co-hort study. BMC Public Health. 2016; 16: 888.
78. Ekelund U, Kolle E, Steene-Johannessen J et al. Objectively measured sedentary time and physical activity and associations with body weight gain: does body weight determine a decline in moderate and vigorous intensity physical activity? Int J Obes (Lond). 2017; 4 [Epub ahead of print].
79. Helmerhorst HJ, Wijndaele K, Brage S, Wareham NJ, Ekelund U. Objectively measured sedentary time may predict insulin resis-tance independent of moderate- and vigorous-intensity physical activity. Diabetes. 2009; 58: 1776–1779.
80. Dugas LR, Kliethermes S, Plange-Rhule J et al. Accelerometer-measured physical activity is not associated with two-year weight change in African-origin adults from five diverse populations. PeerJ. 2017; 5 e2902.
81. Ekelund U, Brage S, Besson H, Sharp S, Wareham NJ. Time spent being sedentary and weight gain in healthy adults: reverse or bidirectional causality? Am J Clin Nutr. 2008; 88: 612–617.
82. Clemes SA, David BM, Zhao Y, Han X, Brown W. Validity of two self-report measures of sitting time. J Phys Act Health. 2012; 9: 533–539.
83. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. Med Sci Sports Exerc. 2001; 33: S502–S515.
84. Thorogood A, Mottillo S, Shimony A et al. Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. Am J Med. 2011; 124: 747–755.

85. Houmard JA, Tanner CJ, Slentz CA, Duscha BD, McCartney JS, Kraus WE. Effect of the volume and intensity of exercise train-ing on insulin sensitivity. J Appl Physiol (1985). 2004; 96: 101–106.

86. Young DR, Coleman KJ, Ngor E, Reynolds K, Sidell M, Sallis RE. Associations between physical activity and cardiometabolic risk factors assessed in a Southern California health care system, 2010–2012. Prev Chronic Dis. 2014; 11 E219.
87. Ryde GC, Gilson ND, Suppini A, Brown WJ. Validation of a novel, objective measure of occupational sitting. J Occup Health. 2012; 54: 383–386.
88. Pfister T, Matthews CE, Wang Q, Kopciuk KA, Courneya K, Friedenreich C. Comparison of two accelerometers for measuring physical activity and sedentary behaviour. BMJ Open Sport Exerc Med. 2017; 3 e000227.
89. Thorp AA, Healy GN, Winkler E et al. Prolonged sedentary time and physical activity in workplace and non-work contexts: a cross-sectional study of office, customer service and call centre em-ployees. Int J Behav Nutr Phys Act 2012; 9: 128.
90. Hamilton MT, Etienne J, McClure WC, Pavey BS, Holloway AK. Role of local contractile activity and muscle fiber type on LPL regulation during exercise. Am J Physiol. 1998; 275: E1016–E1022.

91. Bey L, Hamilton MT. Suppression of skeletal muscle lipopro-tein lipase activity during physical inactivity: a molecular reason to maintain daily low-intensity activity. J Physiol. 2003; 551: 673–682.
92. Herd SL, Kiens B, Boobis LH, Hardman AE. Moderate exer-cise, postprandial lipemia, and skeletal muscle lipoprotein lipase activity. Metab Clin Exp. 2001; 50: 756–762.
93. Goldberg IJ, Le NA, Ginsberg HN, Krauss RM, Lindgren FT. Lipoprotein metabolism during acute inhibition of lipoprotein li-pase in the cynomolgus monkey. J Clin Invest. 1988; 81: 561–568.

94. Komurcu-Bayrak E, Onat A, Poda M et al. The S447X vari-ant of lipoprotein lipase gene is associated with metabolic syndrome and lipid levels among Turks. Clin Chim Acta. 2007; 383: 110–115.

95. Zderic TW, Hamilton MT. Physical inactivity amplifies the sensitivity of skeletal muscle to the lipid-induced downregulation of lipoprotein lipase activity. J Appl Physiol (1985). 2006; 100: 249–257.
96. Katzmarzyk PT, Lee IM, Martin CK, Blair SN. Epidemiology of physical activity and exercise training in the United States. Prog Cardiovasc Dis. 2017; 60: 3–10.
97. Ekelund U, Steene-Johannessen J, Brown WJ et al. Does phys-ical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet. 2016; 388: 1302–1310.