Effects of sedentary behaviour interventions on biomarkers of cardiometabolic risk in adults: systematic review with meta-analyses

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ABSTRACT

Context/purpose Observational and acute laboratory intervention research has shown that excessive sedentary time is associated adversely with cardiometabolic biomarkers. This systematic review with meta-analyses synthesises results from free living interventions targeting reductions in sedentary behaviour alone or combined with increases in physical activity.

Methods Six electronic databases were searched up to August 2019 for sedentary behaviour interventions in adults lasting for ≥7 days publishing cardiometabolic biomarker outcomes covering body anthropology, blood pressure, glucose and lipid metabolism, and inflammation (54 studies). The pooled effectiveness of intervention net of control on 15 biomarker outcomes was evaluated using random effects meta-analyses in the studies with control groups not providing other relevant interventions (33 studies; 6–25 interventions analysed).

Results Interventions between 2 weeks and <6 months in non-clinical populations from North America, Europe and Australia comprised much of the evidence base. Pooled effects revealed small significant (p<0.05) beneficial effects on weight (= −0.6 kg), waist circumference (= −0.7 cm), percentage body fat (= −0.3 %), systolic blood pressure (= −1.1 mm Hg), insulin (= −1.4 pm) and high-density lipoprotein cholesterol (= 0.04 mM). Pooled effects on the other biomarkers (p>0.05) were also small, and beneficial in direction except for fat-free mass (= 0.0 kg). Heterogeneity ranged widely (I²=0.0–72.9).

Conclusions Our review of interventions targeting sedentary behaviour reductions alone, or combined with increases in physical activity, found evidence of effectiveness for improving some cardiometabolic risk biomarkers to a small degree. There was insufficient evidence to evaluate inflammation or vascular function. Key limitations to the underlying evidence base include a paucity of high-quality studies, interventions lasting for 12 months, sensitive biomarkers and clinical study populations (eg, type 2 diabetes).

PROSPERO trial registration number CRD42016041742

INTRODUCTION

Globally, cardiovascular diseases are the leading cause of death and a major cause of disability and lost productivity in adults.1-4 In addition, estimates from 2017 indicate that 451 million people are living with diabetes: a figure projected to rise to 693 million (=10% of the population) by 2045.3 The evidence tends to indicate that greater time spent in sedentary behaviour (ie, sitting/reclining at ≤1.5 metabolic equivalents (MET)) is adversely associated with the risk of cardiovascular disease, type 2 diabetes and some cancers,5-9 and with levels of a range of cardiometabolic risk biomarkers.9,10 A less prolonged sedentary accumulation pattern (ie, more regular breaks, shorter sedentary bouts) has also been associated with lower body mass index (BMI).11 It has largely been acute laboratory interventions (<7 days) using structured protocols providing experimental evidence that reducing or breaking up sitting can have beneficial effects on certain cardiometabolic biomarkers.9-12 For example, compared with uninterrupted sitting time, adding short bouts of light or moderate intensity activity every 20–30 min (generally over a period of 1–5 days) results in improvements to resting blood pressure,10 fasting and postprandial glucose15 16 and insulin,15 17 18 and some lipids.19

In recognition of the aforementioned evidence, several countries now, in addition to having guidelines concerning physical activity, include guidelines to reduce the quantity of sedentary behaviour and/or break it up.20-22 A variety of intervention strategies have been trialled to reduce adults’ levels of sedentary behaviour, particularly in the workplace setting.23 24 Reviews indicate these interventions are often effective for reducing sedentary behaviour, especially workplace interventions incorporating environmental modification, ideally as part of a multicomponent intervention.23 25-27 What is lacking, however, is an understanding of the nature and extent of health improvements that might be obtained when intervening to reduce sedentary behaviour over longer periods and under free-living conditions. A preliminary evaluation explored this topic (in workplace interventions only) but, having occurred prior to the emergence of several large trials of sedentary behaviour interventions, did not present any meta-analyses and could draw no firm conclusions.28

We therefore conducted a systematic review with meta-analyses aiming to synthesise the body of evidence that examined the effectiveness on biomarkers of cardiometabolic risk of ≥7 days interventions that targeted sedentary behaviour (alone or in combination with physical activity) in free-living conditions. We reviewed the evidence on...
body anthropometry, indicators of blood pressure and related haemodynamics, biomarkers relevant to the metabolism of blood glucose and lipids, and inflammatory biomarkers.

**METHODS**

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.

**Search strategy and study selection**

Six electronic databases (Ovid Medline, Ovid Embase, EBM Reviews Cochrane Central, CINAHL, Scopus, Web of Science) were searched systematically from database inception to 27 August 2019 (7 March 2017; 16 February 2018 and, 27 August 2019). A research librarian (LR) conducted an initial search for studies in Medline and Embase and used an analysis of text words and subject terms to develop the search strategies. The final searches were then executed using the appropriate specifications of each database (LR; see online supplementary table S1). Using reference management software (Endnote, Clarivate Analytics, Philadelphia, USA), records were compiled, duplicates were removed, and two authors (NTH and PCD or REC and MSG) performed title and abstract screening and reviewed each full-text article was reviewed against the inclusion criteria. Discrepancies were resolved in consultation with an independent third reviewer (EW).

**Inclusion and exclusion criteria**

Inclusion criteria, applied hierarchically, were: (1) reported intervening on sedentary behaviour for ≥7 days; (2) human study; (3) participants all aged ≥18 years; (4) English language; (5) full-length publication; (6) reported as an outcome at least one biomarker of cardiometabolic health, specifically concerning body anthropometry, glucose metabolism, lipid metabolism, blood pressure and related haemodynamics or inflammation (see online supplementary table S2); and, (7) used an intervention study design (single-group preintervention and postintervention, parallel-group design or crossover). To meet criterion (1), the intervention needed to target sedentary behaviour directly or indirectly with replacement of sedentary activity with an alternative (eg, treadmill desks), increasing ‘whole-of-day’ activity (which includes sedentary) or increasing ‘light intensity’ activity (which is almost the inverse of sedentary) or similar. Studies that only mentioned intervening on ‘physical activity’ or exercise could increase these activities at the expense of either sedentary behaviour or light activity, and therefore did not meet criterion (1). Further inclusion criteria for the meta-analyses were: (1) a no-intervention comparison arm (usual care/conditions; attention control) and (2) no other intervention that was likely to provide an appreciable impact on cardiometabolic biomarkers (eg, diet). Physical activity interventions were permitted, since reducing sedentary time very likely increases some form of physical activity as a replacement. Achievement of successful sedentary behavioural change was not considered a requirement for inclusion in the meta-analyses (to avoid potentially overstating effectiveness). Meta-analyses were conducted for each biomarker reported in at least five studies.

**Data extraction**

All data were extracted, checked and discrepancies resolved by the review team (NTH, PCD, REC and EW), using standardised rules created a priori. The rules used for regarding extraction, contacting authors for missing or questionable data are in online supplementary table S2. Study quality was assessed using the risk of bias (RoB) V2.0 tool.31

**Statistical analysis**

Analyses were performed in STATA V16 (StataCorp). Significance was set at p<0.05 (two tailed). Pooled effects were estimated based on intervention effects (mean between-groups difference, in units) for the end-of-intervention endpoint extracted from each intervention, with the standard errors multiplied by \( \sqrt{\frac{(n+1)}{2}} \) whenever there were \( n > 1 \) eligible sedentary behaviour intervention arms.32 Pooled effects were primarily estimated from random effects (Der Simoian Laird) meta-analysis models, with fixed effects results also reported, along with heterogeneity estimates (I² and Cochrane’s Q test) in the forest plots. A range of sensitivity analyses were also performed. Since Begg’s test for publication bias can be underpowered, we also reported bias-corrected estimates from Tweedie and Duval’s trim and fill method. Leave-one-out sensitivity analyses were performed to consider how dependent conclusions were to any individual study. Meta-regression models, which explored possible sources of heterogeneity, are reported in the manuscript whenever heterogeneity was significant (p<0.05) or substantial (I² >0.25), otherwise in online supplementary material. Characteristics considered were: mean participant age, mean outcome biomarker levels at baseline, degree of intervention effectiveness for sedentary behaviour (intervention effect on overall sedentary time in h/day), intervention duration (≥3 months/3–6 months /≥6 months) and study quality (RoB scores). Unadjusted and age-adjusted models were reported.

**RESULTS**

**Systematic review**

**Study inclusion**

Figure 1 shows the PRISMA flow diagram. In total, 23 976 articles were identified. Most were rejected at abstract screening, with 267 articles screened as full text. The criteria mostly excluded studies on the basis they were not ≥7 days sedentary behaviour interventions (181/218). Fifty-four studies (55 articles) were included in the systematic review.33–87

The population, design and intervention characteristics of the studies are reported in online supplementary table S3 and aggregated in table 1. Collectively, the 54 studies involved 6330 participants (48% women) with sample sizes usually <100 (k=36) and occasionally >200 (k=8), ranging between 12 and 1113. Study populations were recruited from developed nations, mostly English-speaking (table 1) usually from North America (k=20, predominantly the USA), Europe (k=19), Australia (k=10) and occasionally from Asia (k=4) or Africa (k=1). From what little and inconsistent data was reported on ethnicity, plus the study locations, we infer that most study participants were likely Caucasian or ‘white’ (variously defined) with a smaller number identifying as African American or African, Hispanic and Asian ethnicities. Study mean ages ranged from 23 years24 to 71 years.51 Typically, the studies recruited participants from the general population (k=26) or a population with a chronic disease risk factor (k=17) (generally overweight and/or obesity, occasionally in conjunction with another risk factor). Clinical conditions46 37 39 44 45 59 60 71 72 81 84 were seldom targeted for recruitment; of these only some conditions were pertinent to cardiovascular health. Many studies (k=25) used screening to recruit participants at risk for high sedentary behaviour based on their job (eg, office or desk-based work) and/or their reported...
behaviours, while 20 studies screened based on physical activity, and 11 studies screened on both behaviours.

**Interventions**

The 54 studies delivered 56 sedentary behaviour interventions, mostly in the workplace (k=27) or community (k=18) settings, with healthcare (k=9), domestic (k=1) and educational settings (k=1) being less common (Table 1, details in online supplementary table S3). Workplace interventions were about half multicomponent (k=13) and half single component (k=14), while interventions in the remaining non-workplace settings were mostly multicomponent (k=21, 72%). Workplace interventions almost all used environmental modification (k=26), commonly used counselling/education (k=13), sometimes used device self-monitoring (k=5), device-based social comparison (k=3), prompting via devices or SMS (k=6) and structured
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### Table 1  Summary of the study population, design and intervention characteristics of adult sedentary behaviour interventions ≥7 days with biomarker outcomes

#### Population / study characteristics (54 studies)

| Characteristic | Count* | Detail |
|----------------|--------|--------|
| Sample size | Median n / study | 57 | Lowest=12, highest=1113 |
| | Total n | 5217 | Female n=3065 (48.4%), male n=2252 (51.6%) |
| Location (continent and country: ISO 2-digit country codes) | | | |
| North America | 20 | USA, CA, GB |
| Europe | 19 | UK, DK, SE, ES, NL, FR, & NL & NO & PT |
| Australia | 10 | |
| Asia | 4 | TW, CN, JP |
| Africa | 1 | ZA |
| Ethnicity | >50% Caucasian / ‘white’ | 18 | |
| | <50% Caucasian / ‘white’ | 2 | |
| | Not reported | 33 | |
| Clinical population | Clinical condition | 11 | T2D 4, cancer 2, rheumatoid arthritis 2, obstructive sleep apnoea 1, intellectual disability 1, coronary artery disease 1 |
| | Clinical risk factors only | 17 | Adiposity 14, chronic disease risk (+adiposity) 3 |
| | Healthy / general | 26 | |
| Screening | Sedentary job / behaviour | 25 | 11 also screened for PA, 14 did not |
| | Physical activity (PA) | 30 | 11 also screened for PA, 19 did not |
| Study design | Randomised controlled trial | 39 | 8 cluster / 31 individually randomised |
| | Non-randomised controlled trial | 5 | 1 cluster / 4 individually allocated |
| | Multicarm (no controls) | 5 | 1 cluster randomised / 4 individually randomised |
| | Pre–post (single arm) | 5 | |
| Primary outcomes | Includes sedentary | 22 | |
| | Includes biomarker(s) | 10 | |
| | Includes both | 1 | |
| | Includes neither | 21 | PA, 8 / PA and diet 1, unstated 6, feasibility 5, fitness 1 |
| Intervention characteristics (56 interventions) | | | |
| Duration | 3 months or less | 28 | |
| | >3 to 6 months | 16 | |
| | >6 months | 12 | |
| Setting | Workplace | 27 | |
| | Community | 18 | |
| | Other | 11 | Hospital 5, primary care 4, domestic 1, education 1 |
| N components | Multicomponent | 34 | |
| | Single component | 22 | |

*Count out of 54 studies or 56 interventions as indicated in the table unless otherwise specified (eg, median).

Almost a randomised controlled trial (parallel groups) except re-enrolled some controls into the intervention on completion.

Not mutually exclusive (interventions can have multiple components, multiple messages).

T2D, type 2 diabetes.

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activity sessions (k=2). By contrast, non-workplace interventions almost always used some form of counselling/education (k=29), commonly used device self-monitoring (k=18) and occasional use of environmental modification (k=8), prompting (k=6), structured activity (k=4) and financial incentives (k=1). The extent of education or counselling was also highly variable, ranging from brief advice to theoretically grounded behavioural counselling.

The interventions varied in how they considered sedentary behaviour. Diverse behaviours were promoted as replacements for sedentary behaviour: primarily standing, walking or other stepping, but also sometimes pedalling, ‘incidental’ exercise (likely predominantly ‘light’ activities), activities of moderate or greater intensity and sometimes resistance exercise (online supplementary table S3). Sedentary behaviour targets seldom were domain specific, referenced accumulation patterns or set quantitative guidelines on sedentary time (table 1). Primary outcomes included sedentary behaviour in 23 studies, biomarkers in 11, and included neither in 20, instead being unstated (k=6), focused on feasibility (k=5) or involving physical activity with or without other outcomes (k=9).

### Evaluation of biomarker indicators of cardiovascular health

The biomarkers selected for review are shown in table 2. Biomarker outcomes nearly always included indicators of body anthropometry (k=52 studies), and often included indicators of blood pressure (k=37), lipid metabolism (k=33) and glucose metabolism (k=31). Four studies reported on C reactive protein. Other inflammatory markers, such as tumour necrosis factor α or interleukin-6, were not found among the reported outcomes.

Of the anthropometric indicators, the most commonly reported were weight (k=45) or BMI (k=39), followed by waist circumference (k=37). These were almost always collected...
### Table 2  Biomarkers reported as outcomes in 54 studies of adult sedentary behaviour interventions ≥7 days

| Outcomes                             | Studies | Detail                                    | Quality factors                              |
|--------------------------------------|---------|-------------------------------------------|----------------------------------------------|
| **Body anthropometry**                | 52      |                                           |                                              |
| Body weight*                         | 45      | 45 wt*, 39 body mass index BMI*            | Objective† / self-report: 44/1               |
| Waist circumference*                 | 37      | 37 circumference*, 2 waistch size ratio   | Objective† / self-report: 36/1               |
| Other body measurements              | 9       | 7 hip circumference, 1 neck circumference, 2 sagittal abdominal diameter |                                              |
| **Body composition**                 | 25      |                                           |                                              |
| Total fat                            | 25      | 20 percentage of body weight*, 11 mass*   | BiA: 12                                      |
| Total fat-free or lean               | 13      | 12 percentage of body weight, 1 mass*,    | DXA: 5                                       |
| Other                                | 5       | fat mass or % (4 truncal, 1 arm, 1 leg, 1 android %, 1 gynoid %); fat-free mass or % (1 arm, 1 leg); 1 skeletal muscle mass; 1 visceral fat area | BIS: 2, BADP: 3, Skinfold(s): 2, Unreported: 1 |
| **Blood pressure (BP) regulation**   | 37      |                                           |                                              |
| Resting BP *                         | 37      | 37 systolic*, 36 diastolic*, two mean arterial BP | Objective† / self-report: 36/1               |
| Ambulatory BP                        | 0       | –                                         | –                                            |
| Heart rate                           | 5       | 3 resting, 2 non-resting                 | Objective† / self-report: 5/0                |
| Detailed vascular health measures    | 3       | 1 flow mediated dilation, 1 carotid intima media thickness, 1 aortic augmentation index, 1 subendocardial variability, 1 pulse wave velocity | Objective† / self-report: 3/0                |
| **Glucose metabolism**               | 31      |                                           |                                              |
| Fasting glucose*                     | 27      |                                           | Venous / capillary: 20/7                     |
| Fasting insulin*                     | 13      |                                           |                                              |
| HOMA / HOMA-2                        | 7       | 6 HOMA-IR, 2 HOMA-%B, 1 HOMA2-%B, 1 HOMA2-%S |                                              |
| Postprandial glucose / insulin       | 4       | 4 postprandial glucose, 1 postprandial insulin, 1 insulin AUC, 1 glucose AUC, 1 C- ISI | Venous / capillary: 4/0, Duration: all 2 hours test |
| C-peptide                            | 0       | –                                         | –                                            |
| HbA1c*                               | 17      | 15 HbA1c; 2 ‘estimated average glucose’ reported as HbA1c | Venous / capillary: 15/2                     |
| **Lipid metabolism**                 | 33      |                                           |                                              |
| Cholesterol levels or ratios         | 33      | 29 total*, 28 HDL*, 24 LDL*, 1 VLDL, 1 non-LDL, 5 total/HDL, 2 LDL/HDL | Venous / capillary: 25/8, fasted / insufficient / non-fasted state: 25/1/7 |
| Triglycerides*                       | 32      | 1 cholesterol diameter; 1 lipoprotein lipase; 3 apolipoproteins (APO): 3 APO-A1, 3 APO-B, 2 APO-A1/APO-B |                                              |
| Other                                | 3       | 1 mass*                                   |                                              |
| **Inflammation**                     | 4       | 2 CRP; two high-sensitivity CRP            | Venous / capillary: 4/0, fasted / insufficient / non-fasted state: 4/0/0 |
| Other: TNF-α, IL-6                   | –       | –                                         | –                                            |

Data were extracted from the earlier paper related to this study Balducci 2017 when it was not reported in the 2019 paper (body fat percentage; fat-free mass; BMI; fasting insulin; HOMA).  
*Outcome included in the meta-analyses: was reported in >5 of the 33 studies eligible for the effectiveness meta-analyses (had control arm, no additional relevant intervention provided apart from active behaviours). †Measured objectively by research staff.  
AUC, area under the curve; BADP, body air displacement plethysmography; BiA, multifrequency bioimpedance analysis; BIS, bioelectrical impedance spectroscopy; BMI, body mass index; C- ISI, composite insulin sensitivity index; DXA, dual X-ray absorptiometry; HDL, high-density lipoprotein; HOMA-2, revised homeostatic model assessment; HOMA, homeostatic model assessment; IL-6, interleukin 6; LDL, low-density lipoprotein; TNF-α, tumour necrosis factor α; VLDL, very-low-density lipoprotein.

objectively by staff. Body composition outcomes were collected mostly using multifrequency bioimpedance analysis (k = 12) or reference-grade standards: dual X-ray absorptiometry (k = 5) or body air displacement plethysmography (k = 3). Occasionally, other methods were used (k = 4). Studies typically reported on body fat (k = 25) (most commonly as percentage of body weight), and occasionally fat-free, lean or muscle mass (k = 13). Thus, fewer studies were able to assess changes to specific tissues (eg, fat, lean tissue) or anatomical sites (eg, truncal fat, measured in four studies).

Blood pressure was generally assessed with resting blood pressure (k = 37), which was typically reported separately as systolic (k = 37) and/or diastolic blood pressure (k = 36) and as mean arterial pressure in two studies (table 2). Usually, staff measured blood pressure, with participants reporting values from home monitors in one study.  
Ambulatory blood pressure was not reported. Detailed biomarkers of vascular health (eg, endothelial dysfunction, arterial stiffness) were seldom collected. One study reported on flow mediated dilatation, carotid artery intima media thickness, aortic augmentation index and sub endocardial variability.  
Resting heart rate was collected in three studies.

Of the glucose metabolism indicators (table 2), most (k = 27) reported on fasting glucose, with only 13 reporting fasting insulin, and 7 reporting composite indicators of beta-cell function or insulin resistance (ie, measures from homeostatic model assessment, HOMA or HOMA-2). Seventeen studies reported on overall glucose control (HbA1c expressed in various forms), while four studies reported effects on postprandial glucose and/or insulin. and none reported on c-peptide. While venous blood draws were the norm for collecting fasting values (k = 20 studies), lower quality fingerstick capillary measures were occasionally used (k = 7). None of the studies reported outcomes from continuous glucose monitoring.

The most commonly reported lipid markers were: triglycerides (k = 32); total cholesterol (k = 29); high-density lipoprotein (HDL) cholesterol (k = 28) and, low-density lipoprotein (LDL)
cholesterol (k=24) (table 2). These markers are reported widely in the context of cardiovascular risk. Studies occasionally reported VLDL cholesterol, non-LDL cholesterol or cholesterol ratios. Three studies reported on apolipoproteins (APOA1, APOB and their ratio) and one reported on the diameter of various types of cholesterol. None of the studies mentioned performing detailed profiling of lipid classes or subclasses.

Study designs
Very few studies (k=5) were eligible for the meta-analyses (11 studies had provided diet intervention). For the 15 biomarkers that met the inclusion criteria, the number of studies providing data and able to be included ranged from 6 for fat mass to 25 for body weight and blood pressure, and these studies collectively represented anywhere between 724 and 2076 participants.

Risk of bias
RoB overall is reported in online supplementary table S6. To simplify reporting, criteria scored for groups of outcomes with similar concerns underlying their bias risk (eg, missing data, measurement): anthropometric and blood pressure outcomes, glucose metabolism outcomes and lipid metabolism outcomes. Overall RoB was high (≥1 criteria was ‘high’ risk) in 10 studies (30%), unclear (ie, 0 ‘high’ risk and ≥1 ‘unclear’ risk) in 17 (52%) studies and ‘low’ (ie, all ‘low’ risk) in 6 studies (18%). The most common contributor to a ‘high’ RoB rating related to the randomisation process (k=6, 18%), use of non-random methods. Four studies were also rated as ‘high’ RoB due to deviations from intended interventions (data not assessed according to intention-to-treat principles) and missing outcome data. An unclear risk level was typically assigned based on inadequate reporting of randomisation (k=12), concerns with missing outcome data (k=11) and/or bias in measurement of the outcome (k=9). Low risk was still permitted with lack of blinding, given the context (behavioural intervention) in which allocation is impossible to conceal from participants and is generally known to staff, and in which outcomes are collected objectively.

Effectiveness of sedentary behaviour interventions for biomarker outcomes
Effects on biomarkers were evaluated in the context of interventions that had displayed overall sedentary time improvements net of control that were mostly moderate (k=12, 30 to <60 min/day), otherwise strong (k=9, ≥60 min/day) or small (15 to <30 min/day, k=8) or occasionally almost zero (k=3, −15 to <15 min/day). Effects ranged from +11.3 to −132 min/day (see online supplementary table S4). Table 3 shows the pooled effects on biomarkers for the main analyses and sensitivity analyses. Begg’s tests were all p≥0.05 (online supplementary table S7).

Body weight and body composition
Consistent with the studies’ selection criteria, prior to intervention, participants had a weighted mean (±pooled SD) BMI of 25.4±3.2 kg/m², with study means ranging from 22.1 kg/m² in a workplace intervention with no weight screening criteria to 35.9 kg/m² in a treadmill intervention for overweight/obese office workers. Baseline anthropometric values are summarised in table 4 (detail in online supplementary table S4). Pooled effects showed that the sedentary behaviour interventions tended to provide small improvements (net of control) in body anthropometry outcomes (table 3). Significant pooled effects in favour of intervention were seen regarding body weight (−0.56 kg, 95% CI −0.94 to 0.17), waist circumference (−0.72 cm, 95% CI −1.21 to 0.22), body fat percentage (−0.26%, 95% CI −0.50% to 0.02%), with a tendency towards reduced fat mass (−0.33 kg, 95% CI −0.74 to 0.08) and no large or significant effect on fat-free mass (0.00 kg, 95% CI −0.52 to 0.53). Effects on BMI were in a similar direction to those for body weight, but not statistically significant (−0.07 kg/m², 95% CI −0.16 to 0.03). Forest plots for body weight and body composition are shown in online supplementary figure 1–6. Small-study effects did not lead to overstated findings, as the original findings were no more favourable than the trimmed and filled results. Also, no single study seemed to overly influence the conclusions, as improvements observed were always still present to some degree in the leave-one-out sensitivity analyses.

Body weight and body fat percentage showed little evidence of heterogeneity (I² <25%; p≥0.05) with slightly more substantial (but non-significant) heterogeneity seen for fat mass and significant heterogeneity seen for waist circumference and fat-free mass. The heterogeneity in effects on fat-free mass was completely attenuated (I²=0.0%, p=0.790) by omitting a single study. Omission of this same study partially attenuated heterogeneity in effects on waist circumference (I²=19.9%, p=0.217). Further exploration of the heterogeneity via meta-regression (table 5) did not show any significant predictors of effects on waist circumference. The largest effects and the smallest residual heterogeneity were seen for RoB scores (residual I²=22.6%, p=0.192), with effects stronger by just over 1 cm in studies with high versus low RoB. Meta-regression results for the outcomes not displaying substantial or significant heterogeneity are shown in online supplementary table S8.

Blood pressure
Prior to intervention, participants had a weighted mean (±pooled SD) blood pressure of 110.0±10.5 mm Hg systolic and 78.4±7.1 mm Hg diastolic, indicating typically healthy levels, though with some studies attracting samples with average systolic blood pressure as high as 140 mm Hg or higher (table 3 and online supplementary table S4). Pooled effects showed a small significant reduction in systolic blood pressure (−1.03 mm Hg, 95% CI −2.08 to 0.02) and a smaller non-significant reduction in diastolic blood pressure (−0.69 mm Hg, 95% CI −1.69 to 0.32; table 3). Forest plots are shown in online supplementary figure S7 and online supplementary figure 8. Corrections for small-study effects had no effect on the results and pooled effects consistently reflected tendencies towards reduced blood pressure in the leave-one-out sensitivity analyses. Heterogeneity...
was minimal for systolic blood pressure ($I^2=8.6$, $p=0.341$) but extensive for diastolic blood pressure ($I^2=52.6$, $p=0.001$), and not explained by any single study. None of the variables in the meta-regressions (Table 5) had significant associations with diastolic blood pressure or reduced the heterogeneity appreciably (residual $I^2 >50$).

### Table 3. Pooled intervention effects on biomarkers: controlled trials of 34 adult sedentary behaviour interventions ≥7 days

| Outcome                          | Main findings                              | All studies      | Pooled effect (95% CI) | Leave-one-out sensitivity analysis |
|----------------------------------|--------------------------------------------|------------------|------------------------|------------------------------------|
|                                  |                                             | $I^2$, P value   | P value                | Pooled (95% CI)                    | Least benefit (95% CI)             |
| Weight, kg                       | 25 1839 23.6%, $p=0.142$ 0.56 (−0.94 to −0.17) 0.005 n/a −0.63 (−1.03 to −0.23)† −0.47 (−0.75 to −0.18)† |
| Body mass index, kg/m²           | 24 1843 0.0%, $p=0.804$ −0.07 (−0.16 to 0.03) 0.167 −0.08 (−0.17 to 0.02) −0.10 (−0.20 to 0.01)† −0.04 (−0.14 to 0.06)§§ |
| Waist circumference, cm          | 19 2076 45.8%, $p=0.016$ −0.72 (−1.21 to −0.22) 0.004 −1.00 (−1.51 to −0.49) −0.95 (−1.38 to −0.51)§ § −0.61 (−1.20 to −0.01)†† |
| Body fat, %                      | 16 1618 5.5%, $p=0.390$ −0.26 (−0.50 to −0.02) 0.034 −0.37 (−0.65 to −0.10) −0.37 (−0.61 to −0.12) −0.17 (−0.43 to 0.09)§ § |
| Fat mass, kg                     | 6 724 26.6%, $p=0.235$ −0.33 (−0.74 to 0.08) 0.116 −0.42 (−0.73 to 0.08) −0.23 (−0.63 to 0.18)§ § |
| Fat-free mass, kg                | 7 1011 72.7%, $p=0.001$ 0.00 (−0.52 to 0.53) 0.992 0.48 (−0.02 to 0.98) 0.12 (−0.40 to 0.65)† −0.25 (−0.57 to 0.06)§§ |
| Blood pressure, mm Hg            |                                             |                 |                        |                                    |                                    |
| Systolic                         | 25 1932 8.6%, $p=0.341$ −1.05 (−2.08 to −0.02) 0.045 n/a −1.42 (−2.38 to −0.45)† −0.75 (−1.81 to 0.31)¶ ¶ |
| Diastolic                         | 25 1932 52.6%, $p=0.001$ −0.69 (−1.69 to 0.32) 0.180 n/a −0.92 (−1.86 to 0.02)††† −0.36 (−1.28 to 0.56)‡‡‡ |
| Glucose, mM                      | 19 1518 45.5%, $p=0.017$ −0.03 (−0.11 to 0.05) 0.526 −0.04 (−0.13 to 0.05) −0.05 (−0.11 to 0.02)‡‡‡ −0.01 (−0.11 to 0.09)§ § |
| Insulin, pM                       | 10 1102 64.0%, $p=0.003$ −1.42 (−2.82 to −0.02) 0.047 −1.03 (−2.48 to 0.42) −4.13 (−7.48 to −0.78)§§§ −0.45 (−1.60 to 0.69)§§ |
| HbA1c, %                          | 9 892 72.9%, $p=0.001$ 0.10 (−0.22 to 0.03) 0.129 −0.03 (−0.16 to 0.09) −0.14 (−0.29 to 0.01)¶ ¶ ¶ −0.05 (−0.17 to 0.07)§ § |

### Table 4. Average biomarker characteristics prior to intervention in controlled trials of 34 adult sedentary behaviour interventions ≥7 days with biomarker outcomes

| k | n | Weighted means pooled SD | Study means (min–max) | Study with lowest mean | Study with highest mean |
|---|---|--------------------------|-----------------------|-----------------------|------------------------|
| Weight, kg                      | 29 2456 71.3±10.6 | 62.2–99.6 | Alkhajah et al§ § | MacEwen et al§§ |
| Body mass index, kg/m²           | 34 3186 25.4±3.2 | 22.1–35.9 | Alkhajah et al§ § | Schuna et al§§ |
| Waist circumference, cm         | 21 2630 83.9±7.7 | 74.4–111.4 | Butler et al§ § | MacEwen et al§§ |
| Body fat, %                      | 18 2050 28.1±5.4 | 24.5–45.5 | Dunning et al§§ | Koze Keadle et al§ § |
| Fat mass, kg                     | 7 753 25.3±7.7 | 18.4–32.3 | Alkhajah et al§ § | Kallings et al§ § |
| Fat-free mass, kg                | 8 1252 40.0±6.7 | 44.1–56.5 | Alkhajah et al§ § | Balducci et al§ § |
| Systolic BP, mm Hg               | 25 2461 110.0±10.5 | 109–142 | Dunning et al§§ | Maxwell-Smith et al§ § |
| Diastolic BP, mm Hg              | 25 2457 68.4±6.5 | 69–86 | Peterman et al§ § | MacEwen et al§§, Maxwell-Smith et al§ § |
| Glucose, mM                      | 19 1975 4.7±1.0 | 4.1–7.6 | Peterman et al§ § | Balducci et al§ § |
| Insulin, mU                      | 11 1495 51.5±4.1 | 37.1–133.0 | Dunning et al§§ | Koze Keadle et al§ § |
| HbA1c, %                         | 11 1308 4.4±0.6 | 4.9–7.4 | Kallings et al§ § | Balducci et al§ § |
| Total cholesterol, mM           | 24 2292 4.3±0.6 | 4.0–5.5 | Peterman et al§ § | Kallings et al§ § |
| HDL cholesterol, mM             | 22 2232 1.2±0.4 | 1.1–1.8 | Peterman et al§ § | Pesola et al§ § |
| LDL cholesterol, mM             | 21 2142 2.5±0.8 | 2.5–3.3 | Peterman et al§ § | Kallings et al§ § |
| Triglycerides, mM               | 23 2202 1.1±0.5 | 0.9–1.9 | Alkhajah et al§ § | Koze Keadle et al§ § |

BP, blood pressure; HDL, high-density lipoprotein; k, number of interventions; LDL, low-density lipoprotein; n, number of participants.
### Table 5: Associations of study characteristics with intervention effects on cardiometabolic biomarkers (meta-regression)

|                      | Unadjusted                                      | Age adjusted                                     |
|----------------------|-------------------------------------------------|-------------------------------------------------|
|                      | k, n                                            | b (95% CI)                                       | P value | P value |
| Waist circumference, cm | 19, 2076                                         | −0.50 (−1.18 to 0.17)                           | 0.144    | 0.92 (−0.69 to 2.52) | 0.262   |
|                      | 19, 2076                                         | −0.01 (−0.08 to 0.09)                           | 0.856    | 0.25 (−2.28 to 1.78) | 0.809   |
| Mean baseline BMI, kg/m² | 19, 2076                                         | −0.06 (−2.25 to 1.66)                           | 0.672    | −0.02 (−0.24 to 0.22) | 0.910   |
|                      | 19, 2076                                         | 0.01 (−0.18 to 0.32)                            | 0.575    | 0.07 (−0.24 to 0.38) | 0.575   |
|                      | 19, 2076                                         | −0.02 (−1.42 to 1.40)                           | 0.127    | −1.05 (−1.96 to −0.14) | 0.023   |
| Sedentary effectiveness, h/day | 19, 2076                                         | 0.15 (−1.08 to 1.37)                           | 0.816    | −0.09 (0.05 to –0.01) | 0.004   |
|                      | 19, 2076                                         | −0.36 (−2.28 to 1.57)                           | 0.717    | −0.25 (−2.28 to 1.78) | 0.809   |
| Duration (<6 vs ≥3 months) | 19, 2076                                         | 0.098                                           | 0.212    | 0.098                                           | 0.212   |
| Risk of bias (vs high risk) | 19, 2076                                         | 0.070                                           | 0.441    | −0.52 (−2.39 to 1.34) | 0.582   |
| Low risk             | −1.47 (−3.10 to 0.16)                            | 0.077                                           | −1.36 (−3.03 to 0.31) | 0.110   |
| Fat-free mass, kg    | 7, 1011                                          | 0.72 (−0.53 to 1.98)                            | 0.258    | 1.23 (−0.73 to 3.20) | 0.219   |
|                      | 7, 1011                                          | 0.12 (−1.10 to 1.34)                            | 0.847    | 0.37 (−1.07 to 1.81) | 0.615   |
| Glucose, mM          | 19, 1518                                         | −0.01 (−0.08 to 0.07)                           | 0.891    | 0.04 (−0.24 to 0.32) | 0.769   |
|                      | 19, 1518                                         | 0.01 (−0.01 to 0.03)                            | 0.391    | −0.14 (−0.43 to 0.15) | 0.355   |
|                      | 19, 1518                                         | −0.12 (−0.37 to 0.13)                           | 0.345    | −0.14 (−0.43 to 0.15) | 0.355   |
| Risk of bias (vs high risk) | 19, 1518                                         | 0.424                                           | 0.543    | 0.424                                           | 0.543   |
| Some concerns        | 0.18 (−0.13 to 0.48)                            | 0.256                                           | 0.21 (−0.12 to 0.54) | 0.212   |
| Low risk             | 0.12 (−0.09 to 0.33)                            | 0.267                                           | 0.17 (−0.09 to 0.42) | 0.202   |
| Insulin, pM          | 10, 1102                                         | 0.76 (−2.63 to 4.15)                            | 0.660    | 1.87 (−8.64 to 12.38) | 0.728   |
|                      | 10, 1102                                         | 0.20 (−1.09 to 1.48)                            | 0.764    | 3.51 (−3.34 to 13.35) | 0.485   |
|                      | 10, 1102                                         | 0.15 (0.03 to 0.27)                             | 0.018    | 5.28 (−2.33 to 16.01) | 0.144   |
| Sedentary effectiveness, hour/day | 10, 1102                                         | 0.16 (−0.15 to 9.45)                           | 0.678    | 0.21 (−0.12 to 0.31) | <0.001 |
|                      | 10, 1102                                         | 0.01  (−0.08 to 0.09)                           | 0.565    | 0.21 (−0.12 to 0.54) | 0.212   |
| Duration (<3–6 months) | 10, 1102                                         | 2.14 (−7.20 to 11.48)                           | 0.654    | −3.10 (−11.81 to 5.62) | 0.486   |
| Risk of bias (vs high risk) | 10, 1102                                         | 7.87 (−0.21 to 15.95)                           | 0.056    | −5.60 (−11.33 to 0.14) | 0.056   |
| Some concerns        | −0.24 (−1.42 to 0.94)                           | 0.692                                           | −3.10 (−11.81 to 5.62) | 0.486   |
| Low risk             | −4.64 (−6.95 to −2.32)                          | <0.001                                         | −5.60 (−11.33 to 0.14) | 0.056   |
| HbA1c, %             | 9, 892                                           | −0.10 (−0.18 to 0.02)                           | 0.011    | 49.5% (±0.054) | −          |
|                      | 9, 892                                           | −0.01 (−0.05 to 0.03)                           | 0.599    | 76.3% (±0.001) | −          |
|                      | 9, 892                                           | −0.15 (−0.34 to 0.04)                           | 0.127    | 76.3% (±0.001) | −          |
| Sedentary effectiveness, hour/day | 9, 892                                           | 0.08 (−0.10 to 0.26)                           | 0.379    | 69.5% (±0.002) | −          |
| Duration (<3–6 months) | 9, 892                                           | 0.994                                           | 0.994    | 78.0% (±0.001) | −          |
| Risk of bias (vs high risk) | 9, 892                                           | −0.02 (−0.35 to 0.32)                           | 0.919    | 0.04 (−0.14 to 0.23) | 0.641   |
| Some concerns        | 0.30 (−0.25 to 0.85)                            | 0.287                                           | 0.28 (−0.23 to 0.79) | 0.286   |
| Low risk             | 0.50 (−0.02 to 1.02)                            | 0.058                                           | 0.40 (−0.09 to 0.89) | 0.113   |
| Diastolic blood pressure, mm Hg | 25, 1932                                         | 52.6% (±0.001)                                  | 52.6% (±0.001) | 52.6% (±0.001) |
| Mean baseline age, per 10 years | 25, 1932                                         | −0.38 (−1.30 to 0.54)                           | 0.421    | 54.4% (±0.001) | −          |
| Mean baseline BMI, kg/m² | 24, 1903                                         | −0.01 (−0.32 to 0.30)                           | 0.946    | 53.2% (±0.001) | −          |

Note: *p* values are adjusted for multiple comparisons using false discovery rate (FDR) correction. 

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Glucose metabolism

Prior to intervention, fasting glucose averaged 4.7±1.0 mM, indicating levels consistent with healthy metabolism or prediabetes rather than diabetes. However, the studies covered a diverse spectrum from 4.1 mM in a study of healthy adults to 7.6 mM in a study of type 2 diabetes patients aged 40–80 years. Baseline insulin and HbA1c levels averaged 51.5±44.1 pM and 4.4%±0.6% were also quite variable across studies (table 3 and online supplementary table S5). Pooled effects pointed to small benefits to glucose metabolism, which were statistically significant only for fasting insulin (−1.42 pM, 95% CI −2.82 to 0.02) and small non-significant tendencies towards lower fasting glucose (−0.03 mM, 95% CI −0.11 to 0.05) and HbA1c (−0.10%, 95% CI −0.22% to 0.03%). Forest plots are shown in online supplementary figure 9–11. Small-study effects may have overstated effects on insulin and HbA1c.

Glucose, insulin and HbA1c all showed substantial heterogeneity (I²=45.5 for glucose to I²=72.9 for insulin; p<0.05), which remained present in all the leave-one-out sensitivity analyses, except for glucose, where removing a single workplace study that had failed to elicit changes in sedentary behaviour markedly attenuated the heterogeneity (I²=28.4, p=0.126).

Insulin outcomes were significantly beneficially associated with lower baseline levels, shorter intervention duration and higher RoB, with limited residual heterogeneity after accounting for RoB (I²=11.9, p=0.338); however, only the association with baseline level remained significant accounting for age (residual I²=0.0, p=0.641). Higher participant age significantly predicted enhanced HbA1c outcomes, and led to lower heterogeneity (residual I²=49.5, p=0.054) while in age-adjusted models, effects were significantly beneficially associated with higher BMI, longer intervention duration and lower RoB, and a borderline association with higher baseline levels. The model with age and BMI had no residual heterogeneity (I²=0.0, p=0.454).

Lipid metabolism

Prior to intervention, baseline levels averaged 4.3±0.6 mM total cholesterol, 1.2±0.4 mM HDL, 2.5±0.8 mM LDL and 1.1±0.5 mM triglycerides, with comparatively limited variation across studies relative to other biomarkers (table 4, online supplementary table S5). Small significant improvements in response to sedentary behaviour interventions were seen in HDL cholesterol (0.04 mM, 95% CI 0.02 to 0.07) alongside...
a small, non-significant improvement in total cholesterol (−0.06 mM, 95% CI −0.16 to 0.04) and very small, non-significant effects on LDL cholesterol (−0.02 mM, 95% CI −0.07 to 0.04), and triglycerides (−0.02 mM, 95% CI −0.09 to 0.04). Forest plots for cholesterol and triglycerides are shown in online supplementary figure S12 and online supplementary figure 13–15. Small-study effects if anything limited the effects seen for lipid metabolism, with trimmed-and-filled estimates all either larger or virtually unchanged, and with a significant effect on total cholesterol emerging (−0.10 mM, 95% CI −0.20 to 0.00).

There was limited heterogeneity in outcomes concerning HDL and LDL cholesterol (I² <25, p≥0.05) and more substantial and significant heterogeneity in total cholesterol (I²=54.1, p=0.001) and triglycerides (I²=49.0, p=0.005). Removing one study markedly lowered the total cholesterol heterogeneity (I²=21.1, p=0.183) while the same was not the case for triglycerides. Meta-regressions (table 5) showed significantly greater reductions in total cholesterol were seen with higher age, and higher RoB, with limited residual heterogeneity left after accounting for age (I²=17.1, p=0.233) while in age-adjusted models, significant predictors of greater reductions were shorter study duration and higher RoB. It appears multiple factors may have contributed to the heterogeneity in triglyceride outcomes. None of the variables significantly predicted effects on triglycerides and residual heterogeneity remained high in all models (residual I²=45.1–53.6). In age-adjusted models, less effectiveness in improving sedentary behaviour outcomes significantly predicted greater reductions in triglycerides (−0.13 mM, 95% CI -0.21 to 0.05), with very limited heterogeneity left when considering both these factors simultaneously (I²=0.0, p=0.507), which also involved excluding one study due to missing data.

DISCUSSION

Several reviews have reported on sedentary behaviour interventions in relation to sedentary behaviour outcomes and found them to be effective, to varying degrees. These reviews indicated success seemed to vary depending on factors including the focus on sedentary behaviour (alone vs in combination with other lifestyle behaviours) and the type of intervention (with multicomponent workplace interventions being particularly successful). The current systematic review with meta-analyses considered these interventions in the context of their effect on biomarkers of cardiometabolic health, finding a small body of evidence. In total, 54 studies were identified, with 33 eligible for the meta-analyses, and with 6–25 controlled interventions ultimately included in meta-analyses concerning body anthropometry, blood pressure and haemodynamics, glucose metabolism and lipid metabolism.

Broadly, the meta-analyses provided some support for small improvements in selected indicators of body anthropometry, blood pressure, glucose metabolism and lipid metabolism with intervention, with none of the outcomes tending to worsen with intervention. Specifically, significant improvements were seen in body weight, waist circumference, percentage body fat, systolic blood pressure, insulin and HDL cholesterol. For some outcomes, findings varied widely from study to study, while for others they were quite consistent, with heterogeneity ranging widely (I²=0.0–72.9). It may be the case that some types of interventions are effective (and others ineffective), and/or the interventions may be effective in some populations but not others. The sensitivity analyses and meta-regressions provided some insight into potential factors underlying some of the heterogeneous results. Sometimes a single study deviating from the general pattern appeared to be the issue, while other key factors (different for each outcome) tended to be due to participant age and BMI, study duration and RoB. There were very few studies with each characteristic; consequently, the CIs around effects were quite wide, and findings should not be taken to indicate non-significant predictors in the meta-regressions were unimportant. The low number of studies was also the reason stratified analyses were not performed to inform the effectiveness of specific types of interventions, for specific populations (eg, men, women, older adults and those with clinical conditions such as type 2 diabetes). Some potential success factors not able to be explored were ethnicity (poorly reported), sex, behaviour settings and dose response. Prior findings have sometimes suggested the biological responses to sedentary time may vary depending on the setting or context in which it occurs, by ethnicity, by sex and by the activity replacing sedentary time.

The systematic review showed some key considerations for interpreting the effectiveness findings. The sedentary behaviour interventions performed were highly varied in terms of their setting, use of behavioural change components, and the degree of emphasis on sedentary behaviour; thus, the heterogeneous outcomes were not highly surprising. Also, some caution should be exerted in extrapolating findings to groups with limited or no representation in the evidence base. Evidence has mostly been collected from studies of Caucasian or ‘white’ populations (variably defined) of working age, often with overweight/obese BMI or waist circumference, with very limited representation of those with clinical conditions pertinent to cardiovascular health, such as type 2 diabetes. The short duration of most interventions may have influenced the degree of effectiveness observed in the meta-analyses; there was a paucity of studies intervening ≥12 months and including maintenance evaluations from which to consider sustainability or determine what may happen in the longer term. Previously, it has been reported that biomarker results have been more promising at 12 months compared with 3 months, despite sitting reduction being greatest at 3 months.

To overcome the limitations of the current evidence base the next logical step would be individual patient data meta-analysis, with interventions collecting ‘dose’ data regarding sedentary behaviour and the activities that may replace it in the most harmonisable way possible, even if this is only possible in a subsample of participants. Ideally, the measurement should allow both calculation of some total dose (eg, in MET hours), as well as partial out time spent sedentary and in various alternative behaviours, delineated by intensity, posture and accumulation method (eg, sedentary/sitting, standing, light movement, moderate movement, vigorous movement and bouted vs non-bouted forms of the relevant behaviours). Such an approach may help to determine the populations for which each intervention may be effective, as well as ascertain which specific behaviours (if any) may achieve the greatest biomarker improvements.

Other key features identified within the current evidence base are the type, reporting (or lack thereof) and specificity/sensitivity of biomarker outcomes collected. For example, most of the biomarkers collected (eg, blood glucose, insulin, triglycerides and blood pressure) are subject to homeostatic regulation but were only measured in fasted or resting states. It is important to also evaluate how some sensitive biomarkers (without these limitations) that have fairly consistently responded beneficially
in acute laboratory interventions lasting <7 days respond over longer intervention timeframes. Specifically, postprandial glucose, insulin, triglycerides and ambulatory blood pressure should be measured. Other understudied outcomes that are potentially useful to measure are: detailed markers of vascular haemodynamics and structure (eg, cardiovascular and cerebrovascular blood flow, flow-mediated dilatation and arterial stiffness), C-peptide; continuous glucose monitoring; postprandial lipids; lipid subclasses; site-specific tissue samples (eg, muscle, adipose tissue) and additional intermediate biomarkers (such as those related to systemic metabolic/oxidative stress and inflammation). These outcomes could be collected in all participants or in subsamples, as they represent opportunities to detect changes that might otherwise be missed, and improve our understanding of shared risk factors and potential mechanistic pathways.

There were some caveats regarding the overall quality of the evidence. Trimmed-and-filled results mostly suggested publication bias did not affect findings, but the insulin finding may be overstated and some of the lipid findings understated. Inferences were sometimes made from a very small number of studies (especially regarding biomarkers of glucose and lipid metabolism), which is especially concerning with the findings varying so much between studies. The paucity of ‘low’ RoB studies is a limitation, though importantly most studies had an ‘unclear’ rather than a ‘high’ RoB and the meta-regressions did not usually show high RoB equated to the most promising results (if anything, findings showed the opposite).

### CONCLUSIONS
This systematic review with meta-analyses synthesised the body of work concerning the effectiveness of sedentary behaviour interventions on biomarkers of cardiometabolic risk, specifically: body anthropometry; blood pressure and related haemodynamics; glucose metabolism; lipid metabolism and inflammation. Consistent with evidence from prior observational research and acute laboratory-based experiments (<7 days) linking sedentary behaviour with cardiometabolic health, the evidence from >7 days interventions in free-living conditions showed small improvements in some cardiometabolic biomarkers. These biomarker improvements definitively occurred in response to interventions targeting sedentary behaviour (alone or alongside physical activity), but how they occurred in response to sedentary reductions and increases in various forms of physical activity remains unclear. Our review indicated that studies in clinical populations, ethnicities other than Caucasian or ‘white’ in predominantly Western countries, and evaluation of biomarkers of inflammation and postprandial metabolism are key areas for future research.

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All authors reviewed the systematic review strategy. LR executed the searches. PCD, NTH, REC, MSG and EW conducted the review and screened the initial results using standardised rules created a priori. PCD, NTH, REC and EW appraised the studies and extracted data from the primary studies and EW analysed the penultimate results. PCD, NTH and EW drafted the manuscript and all authors contributed to the critical revision of the manuscript and approved the final revised version. PCD is the guarantor.

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