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Lifestyle interventions to reduce sedentary behaviour in clinical populations: a systematic review and meta-analysis of different strategies and effects on cardiometabolic health

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Abstract

Cardiometabolic comorbidities are highly prevalent in clinical populations, and have been associated (partly) with their sedentary lifestyle. Although lifestyle interventions targeting sedentary behaviour (SB) have been studied extensively in the general population, the effect of such strategies in clinical populations is not yet clear. Therefore, this systematic review and meta-analysis evaluated the effect of different lifestyle interventions on SB and cardiometabolic health in clinical populations.

Randomised controlled trials were collected from five bibliographic databases (PubMed, Embase, Web of Science, The Cochrane Central Register of Controlled Trials, and Scopus). Studies were eligible for inclusion if they evaluated a lifestyle intervention to reduce objectively measured SB, in comparison with a control intervention among persons with a clinical condition. Data were pooled using a random-effects meta-analysis.

In total, 7094 studies were identified. Eighteen studies met the inclusion criteria and were categorised in five population groups: overweight/obesity, type 2 diabetes mellitus, cardiovascular, neurological/cognitive and musculoskeletal diseases. Participants reduced their SB by 64 min/day (95%CI: [-91, -38]min/day; p<0.001), with larger within-group differences of multicomponent behavioural interventions including motivational counselling, self-monitoring, social facilitation and technologies (-89min/day; 95%CI: [-132, -46]min/day; p<0.001). Blood glycated haemoglobin concentration (-0.17%; 95% CI: [-0.30, -0.04]%; p=0.01), fat percentage (-0.66%; 95% CI: [-1.26, -0.06]%, p=0.03) and waist circumference (-1.52cm; 95%CI: [-2.84, -0.21]cm; p=0.02) were significantly reduced in the intervention groups compared to control groups.

Behavioural lifestyle interventions reduce SB among clinical populations and improve cardiometabolic risk markers such as waist circumference, fat percentage, and glycaemic control.

Sedentary behaviour, Cardiometabolic health, Clinical populations

1. Introduction

Cardiometabolic comorbidities, such as hypertension, dyslipidaemia and glucose tolerance are highly prevalent among populations with clinical conditions[1-5]. These comorbidities increase the hospitalization rate and often accelerate disability progression[4, 6, 7]. As such, it is crucial to explore strategies to improve the cardiometabolic health of clinical populations. Besides (epi)genetics, environmental, hormonal and medicinal factors, lifestyle is a crucial determinant for the development of cardiometabolic risk factors[8]. Lifestyle interventions have already been shown to significantly improve the cardiometabolic health of high-risk populations[9-13]. Such interventions usually combine education on risk factors such as smoking, diet, and moderate-to-vigorous physical activity (MVPA) exercise[9-13]. However, the current international physical activity (PA) guidelines, advising 150min of moderate or 75min of vigorous intensity PA per week, are not met by 23% of the general population worldwide[14]. In clinical populations, inactivity percentages are even higher. This is due to disease-specific barriers such as pain, transportation, disability, specialist availability, fatigue, health concerns, inaccessibility, comorbidities, and the time burden of treatment[15-22].

Furthermore, clinical populations spend substantially more time engaged in sedentary behaviours than the general population (8.9-10.1h/day vs 7.7h/day respectively[23]). Sedentary behaviour (SB) is defined as any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents while in a sitting, reclining or lying posture[24]. Recent evidence shows that SB is inversely related to several markers of cardiometabolic health, especially in individuals not meeting the recommended PA guidelines[25-30] and clinical populations[27, 31-34]. Reallocating SB to low-intensity non-exercise PA (NEPA) is feasible for individuals with clinical conditions[21] and positive effects on cardiometabolic health have been shown in laboratory-based interventions[35-37]. The effects of free-living SB interventions on cardiometabolic health have been investigated in the general population and are summarized in two meta-analyses[38, 39]. Martin *et al.* reported a significant SB reduction (-22min/day), but could not identify studies with SB-only interventions and cardiometabolic health[39]. Hadgraft *et al.* found significant improvements in some cardiometabolic measures (anthropometrics, blood pressure, insulin and lipids), but did not perform a pooled analysis of SB changes[38]. Furthermore, evidence in both studies was mostly based on healthy populations, limiting extrapolation to clinical populations[38, 39]. Additionally, the interpretation of intervention effects is limited by the inclusion of multifactorial interventions (SB and PA and/or diet components) and subjective SB measures[39-41]. A recent meta-analysis of Franssen *et al.* showed the ability of consumer wearable activity trackers to improve PA and cardiometabolic health in clinical populations, but SB changes were not clear[42]. Therefore, the present study aims to summarize and pool the SB and cardiometabolic effects of free-living SB interventions in clinical populations.

Environmental adaptations, education, motivational counselling, and technologies such as wearable devices and smartphones are reported to significantly reduce SB in the general population[43-45]. However, interventions are often conducted in workplace settings with low external validity regarding clinical populations who are often un- or not fully employed[46]. Moreover, disease-specific symptoms offer further challenges to reduce free-living SB from a symptom or mobility perspective and, require specific intervention components. Here, Prince *et al.* reported self-monitoring with real-time feedback, goal setting, and individual sessions to discuss barriers and facilitators to be important components. However, this was based on only two interventions[23]. Therefore, the aim of this systematic review and meta-analysis is to identify 1) intervention components that objectively reduce SB under free-living conditions in clinical populations and 2) the effect of reducing SB on cardiometabolic health, including the blood lipid profile, glycaemic control, blood pressure, and anthropometric measures.

2. Methods

This systematic review and meta-analysis was registered in the PROSPERO international prospective register of systematic reviews (registration number: CRD42020158537) and was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement.

2.1. Literature search

Studies were collected from inception until December 2019 in the PubMed, Embase, Web of Science (WoS), The Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus electronic databases. Four main concepts were combined to design the search: diseases included in the 11th Revision of the International Classification of Diseases (ICD-11), strategies to reduce SB, objective time/day in SB, and health measures. For each main concept, different synonyms, related terms and keywords were included (details in Appendix A). Inclusion of articles was restricted to the English and Dutch language.

2.2. Eligibility criteria

Inclusion criteria to select studies were: 1) Study population: adults (>18y) with diseases, disorders or injuries included in the ICD-11 (details in Appendix A); 2) Study types: peer-reviewed randomised cross-over or controlled trials on low-intensity NEPA interventions to reduce free-living SB compared to a usual care/waitlist control group. The following lifestyle interventions are included: a) environmental interventions, involving changes to a particular behaviour setting (e.g. activity-permissible workstations, TV-limiting devices, screen-based prompts), b) behavioural interventions, targeting the individual, or c) combined environmental and behavioural interventions[44]. Laboratory-based and multicomponent intervention studies including diet and/or MVPA components were excluded, except when similar MVPA or diet components were included in both the intervention and control group; 3) Primary outcome: objective SB in min/day, with no restrictions in sensor wear location or method to measure SB. To be included, a SB-focused intervention in combination with objectively measured SB as primary or secondary outcome, was mandatory; 4) Secondary outcome: PA-related outcomes (SB breaks, standing time, walking time, steps/day and time in MVPA), cardiometabolic health outcomes including systolic and diastolic blood pressure, blood lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels), glycaemic control (blood glycated haemoglobin (HbA1c), glucose and insulin levels) or systemic inflammation (C-reactive protein (CRP) levels) and anthropometric measurements (body weight, waist circumference, body mass index (BMI) or percentage fat mass).

2.3. Study selection

Duplicates were removed using the de-duplication method of Bramer *et al.*[47]. Relevant original research papers were selected based on titles and abstracts, screened and systematically excluded based on the pre-specified eligibility criteria. Review articles, conference abstracts and editorials were excluded. Studies were independently screened by two authors (I.N. and W.M.A.F.) and disagreements between authors were resolved by consensus with a third reviewer (B.O.E).

2.4. Data extraction

Data extraction was performed with the aid of a predesigned data-collection form, adapted from the Cochrane Collaboration extraction form (Appendix B). Information on study characteristics, study participants, methods and outcome variables were extracted. For studies with multiple intervention groups, data from interventions not (only) targeting SB were not included.

Continuous data, including means, standard deviations and sample size numbers were extracted. When mean differences over time were not available, authors were contacted to request additional data. When standard deviations were not provided, variances were estimated from the confidence intervals according to the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.2, chapter 7)[48]. Additionally, when data were presented as median and interquartile range, the mean and standard deviations were estimated using the formula from Hozo *et al.*[49]. Blood parameters were converted to the same unit, from mmol/l to mg/dl (triglycerides: divide by 0.0112, total cholesterol, HDL, and LDL cholesterol by 0.02586, and glucose by 0.5551)[50]. SB and PA variables were converted to min/day.

2.5. Study quality assessment

The risk of bias was evaluated using the 'Cochrane Collaboration's tool for assessing risk of bias in randomised trials'[51]. The following domains of bias were assessed: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Each of these criteria were judged and classified as either 'low risk', 'high risk' of 'unclear risk' of bias.

2.6. Statistical analysis

Statistical analyses were performed with Review Manager 5.4. For SB, PA and cardiometabolic health, baseline differences and mean post- and pre intervention differences between control and intervention groups were calculated and are presented with 95% confidence intervals. Due to the inclusion of different population groups and intervention types/components, there was a large heterogeneity among studies. As such, a random-effects meta-analysis was used to obtain the pooled effect estimates. To evaluate the effect of population group, intervention component, SB sensor, intervention duration, age, gender, and baseline SB on SB change of the intervention groups, univariate (including one predictor) random-effects meta-regression analyses (R version 3.6.0) were used. A multiple meta-regression model, including several predictors, was not used due to multicollinearity and overfitting problems. Sensitivity analyses were performed to assess robustness of the results. Publication bias was assessed using funnel plots (Appendix C). The effect of heterogeneity of each summary effect size was quantified using a chi-squared test and the I^2 statistic, in which the boundary limits 25, 50 and 75% were designated as low, moderate, and high heterogeneity values[52].

3. Results

The systematic literature search identified 13,414 potentially relevant articles, of which 7094 remained after deduplication. Nineteen full-text articles met all inclusion criteria. Because one article[53] only reports follow-up measures of another included article[54], the remainder of this review will consider 18 studies for qualitative and quantitative synthesis (Fig. 1). All included studies were published in the last 10 years (2010 to 2019), with the majority originating after 2017 (n=10). Six studies included a follow-up measure 7 to 40 weeks post-intervention[53,

[55-59]. All studies were written in the English language and could be categorised in five clinical population groups, including overweight/obesity (n=6), (pre) diabetes mellitus type 2 (T2DM, n=4), cardiovascular diseases (CVD; n=4), neurological and cognitive disorders (n = 2) and musculoskeletal disorders (n = 2). Study characteristics are presented in Table 1.

3.1. Risk of bias

The overall risk of bias in the included studies was relatively low (Fig. 2). Eight studies met either two (n: 5)[56, 57, 59-61] or one (n: 3)[55, 62, 63] of the six risk of bias criteria. However, 13 studies provided insufficient information to assess three (n: 3)[64-66], two (n: 4)[62, 67-69] and one (n: 6)[54, 55, 58, 60, 70, 71] risk of bias criteria. Although a selection bias could be precluded in all studies, five studies did not describe the concealment procedure in sufficient detail. Due to the intervention type, no study was able to blind study participants. However, this was only explicitly stated in seven of 18 studies. Only five studies blinded the outcome assessors, seven did not adequately report blinding of those assessing outcomes and six could not preclude a detection bias. Two studies had large amounts of missing data (23%[70] and 30%[55]). However, missing data were balanced in numbers and had similar reasons across groups, limiting the risk of an attrition bias[48]. The risk of a reporting bias was judged to be non-existing in all studies included in the current meta-analysis. Furthermore, no publication bias could be detected (Appendix C).

3.2. Population characteristics

The included studies evaluated a total of 1040 participants (intervention: n: 541, control: n: 499), of which the majority had T2DM (n: 342, drop-out 11%) or was overweight or obese (n: 291, drop-out 13%). One hundred and seventy participants had a musculoskeletal disorder (rheumatoid arthritis, drop-out 4%), 137 participants had a CVD (stroke, peripheral or coronary artery disease, drop-out 4%) and 100 participants had a neurological or cognitive disorder (multiple sclerosis and serious mental illness, drop-out 13%). Study participants had a mean age of 53±11 years (range: 33-67 years) and were predominantly female (66%). One study included exclusively women[68], and in two studies no information on gender was provided[57, 64].

3.3. Intervention characteristics

All study designs were randomised controlled trials, except for one study in which a randomised cross-over design was used[66]. In 10 out of 18 included articles, the duration of the intervention period comprised 12 weeks, with a mean duration of 13±5 weeks, ranging from 6 to 24 weeks. Sixteen studies implemented a behavioural intervention, one study combined behavioural and environmental (portable pedal machine) components[70] and only one intervention was environmentally based[65]. The following four behavioural components could be identified: 1) self-monitoring[63, 69], 2) education in combination with motivational counselling[54, 67, 71], where the overall goal was to increase the participant's intrinsic motivation to change[72], 3) the use of a website/app and 4) social facilitation. In six studies self-monitoring and motivational counselling were combined[55-57, 59, 64, 68] and six other studies also added the use of a website/app and/or social facilitation[58, 60-62, 66, 70]. Self-monitoring devices were mostly focused on PA (steps/day[56-59, 64, 70] or minutes of PA/day[68, 69]), whereas five studies also included prompts to interrupt SB[55, 60, 61, 63, 66].

Motivational counselling and education were provided in different formats; via the study website or app[60, 62], face-to-face sessions[59, 64], combined face-to-face and group sessions[58], phone calls, text messages or emails[61, 66, 68, 70] or

a combination of group/face-to-face sessions with follow-up phone calls, text messages or emails[54-57, 67, 71]. Social facilitation was organized by showing results of peers in the website or app with the possibility to comment or like activity[61, 62, 66] or by optional weekly walks[58]. One of 18 studies applied an environmental intervention by providing a height-adjustable desk in the office, without further additional information or prompting[65]. Excluded intervention groups[64, 68, 69] are described in Table 1.

In 14 of 18 studies the control groups consisted of usual care, in three studies a waitlist was used[61, 68, 70], and one study implemented an attention-matched control group with the message to increase calcium intake for bone health[67]. One study included general health recommendations including nutrition to both the intervention and control group[60]. The average drop-out rate among studies was 8.7% and ranged from 0%[60, 69] to 30%[55]. The average drop-out rate of follow-up measures was 11.9%. One study assessed the effect of the SB intervention on body composition and included SB as a secondary outcome[68], all other studies primarily assessed SB changes. Ten studies measured SB by activPAL3™, in which an inclinometer to assess posture and an accelerometer to assess acceleration, are combined. The remaining studies only measured acceleration with different sensors and wear locations; at the waist (Actigraph GT3X®[55-57, 68], HJA-350IT Omron[69]), wrist (GENEActiv[58]), ankle (StepWatch™ physical activity monitor[70]), or a combination of wrist, ankle and waist (wearable sensor system[66]). Three studies also evaluated the impact of reducing sitting time on anthropometrics[58, 61, 68], and 11 studies also added cardiometabolic health measures[54-56, 62-66, 69-71].

3.4. Sedentary behaviour (SB) & physical activity (PA)

All studies reported baseline SB and mean pre-post differences, expressed in min/day. Walking time[54, 59-64, 67] and time in MVPA[55-59, 63, 67, 68] were reported in eight studies, step counts in 11 studies[55-57, 60, 62-66] and nine of 10 studies using an inclinometer reported standing time[54, 55, 60, 62-65, 67]. Baseline SB was comparable between all groups (10.0±1.2h, population groups: p=0.59; intervention and control groups: p=0.38) when excluding four studies where sleeping time and SB were combined [56, 57, 61, 62]. Patients with a clinical condition or disability reduced their SB by 64 min/day following an intervention to reduce SB (95%CI: [-91,-38]min/day; p<0.001) compared to control groups without intervention (Fig. 3). Furthermore, participants of the intervention groups significantly increased their walking time (+27 [13,41]min/day; p<0.001) and step count (+1976 [785,3167]steps/day, p=0.001), but not standing time (+28 [-1,57]min/day; p=0.06) nor MVPA (+0.3 [-5,6]min/day; p=0.92; Table 3). At follow-up, only changes in walking time remained statistically significant (+13 [0,26]min/day, p=0.04), whereas sitting time, standing time, steps, and MVPA changes were not significantly different from baseline values.

3.5. Impact of population group and intervention characteristics on SB changes

Meta-regression analysis showed no significant effect of population on SB changes over time (p=0.12), indicating a similar intervention effect between population groups. The overall and subgroup analyses showed significant heterogeneity within obese/overweight persons, T2DM, neurological/cognitive, and musculoskeletal patients, but not CVD patients. Changes in SB following an intervention were not associated with the type of sensor used to measure SB (p=0.15), intervention duration (p=0.26), age (p=0.96), gender (p=0.57), or baseline SB (p=0.47). Furthermore, within-group changes for the different behavioural components showed that SB reductions were only significant when self-monitoring and motivational counselling were combined and when social facilitation and/or the use of an app/website were added to the intervention (Table 2). However, no significant difference between intervention components was found in the meta-regression analysis (p=0.30).

Table 2. Sedentary time changes in minutes per day for the behavioural intervention components

Behavioural intervention component	No. of studies	No. of participants			Mean change (95% CI)	p-value
		Int.	Con.	Drop-out		
Self-monitoring	2	31	31	3%	-42 [-83, -1]	0.36
Motivational counselling	3	104	101	3%	-53 [-159, 54]	0.33
Self-monitoring and motivational counselling	6	246	212	18%	-44 [-76, -13]	0.006
Self-monitoring and motivational counselling and website/app and /or socialization	6	145	143	9%	-89 [-132, -46.]	<0.001

Abbreviations: **Int.** intervention group, **Con.** control group, **CI** confidence interval

3.6. Cardiometabolic health

The intervention groups significantly improved their HbA1c (-0.17%; 95%CI: [-0.30,-0.04]%; p=0.01), fat percentage (-0.66%; 95%CI: [-1.26,-0.06]%, p=0.03) and waist circumference (-1.52cm; 95%CI: [-2.84,-0.21]cm; p=0.02) compared to the control groups. HbA1c and waist circumference results were substantially heterogeneous (p=0.01, I^2 = 63% and p=0.004, I^2=64%, respectively). Other cardiometabolic health measures did not significantly change (Table 3).

Table 3. Effects of sedentary behaviour interventions on activity parameters and cardiometabolic health

	No. of studies	No. of participants Int.	Con.	Baseline values (SD) Int.	Con.	Mean difference [95% CI]	p-value
Physical activity							
Standing time (min/day)	9	232	199	225 (33)	231 (35)	28 [-1, 57]	0.06
Walking time (min/day)	15	416	368	136 (116)	141 (128)	27 [13, 41]	<0.001
Steps/day	11	294	255	6176 (1790)	6098 (2163)	1976 [785, 3167]	0.001
MVPA (min/day)	8	177	209	42 (38)	35 (29)	0.27 [-5, 6]	0.92
Blood lipids[a]							
Triglycerides (mg/dl)	7	193	185	125.4 (29.5)	131 (17.4)	0.10 [-12.7, 12.5]	0.99
Total cholesterol (mg/dl)	7	165	158	185.1 (27.8)	177.5 (26.9)	1.17 [-3.0, 5.3]	0.58
HDL cholesterol (mg/dl)	6	181	172	52.8 (9.0)	52.7 (7.7)	-0.5 [-2.2, 1.2]	0.54
LDL cholesterol (mg/dl)	5	132	125	105.8 (29.1)	104.5 (27.4)	-0.4 [-6.0, 5.2]	0.89
Glycaemic control							
Fasting glucose (mg/dl)[a]	6	170	171	103.4 (13.2)	104.6 (16)	3.2 [-1.8, 8.2]	0.20
HbA1c (%)	7	211	215	6.4 (0.8)	6.4 (0.9)	-0.2 [-0.3, -0.04]	**0.01**
Blood pressure							
Systolic (mm Hg)	10	303	287	129.1 (12.7)	127.5 (11)	-0.5 [-2.1, 1.1]	0.55
Diastolic (mm Hg)	9	257	241	80.9 (3.4)	79.2 (4.8)	-0.8 [-2.0, 0.4]	0.21
Anthropometrics							
Body weight (kg)	12	341	325	85 (10.6)	84 (10.7)	-0.4 [-1, 0.2]	0.16
BMI (kg/m²)	11	325	304	30.1 (3.9)	30 (4.3)	-0.1 [-0.2, 0.1]	0.32
Body fat (%)	5	141	129	43 (2.1)	43.2 (2.5)	-0.7 [-1.3, -0.1]	**0.03**
Waist circumference (cm)	9	294	286	97.3 (9.8)	97.1 (11.4)	-1.5 [-2.8, -0.2]	**0.02**

Mean differences are pre-post differences between control and intervention groups.
Abbreviations: **Int**. intervention, **Con**. control, **CI** confidence interval, **MVPA** moderate-to-vigorous physical activity
[a]Blood parameters were converted to the same unit (from mmol/l to mg/dl)

4. Discussion

This review is, to the best of our knowledge, the first that systematically evaluated the effect of lifestyle interventions to reduce SB under free-living conditions in clinical populations. Results showed that persons with overweight/obesity, T2DM, CVD, neurological/cognitive, or musculoskeletal disorders significantly reduced their SB by 64 min/day following a lifestyle intervention targeting SB.

The SB reduction in this meta-analysis is larger than what is reported for the general population with similar behavioural interventions (-30 to -56.86 min/day)[39, 40, 44, 73]. Importantly, the inclusion of subjective SB measures in previous meta-analyses limits comparison with the current objective results. Nevertheless, clinical populations might have more opportunities to reduce SB as they are more often un- or not fully employed[46] and have higher baseline SB (current results: 10.0±1.2h vs general population: 7.7±3.2h[74]). Importantly, the largest SB reductions in the current results were found with the multicomponent behavioural interventions (Table 2), which is in line with findings in the general population[40, 75]. A previous review on behavioural interventions to reduce SB in clinical populations already reported self-monitoring and motivational counselling, including goal setting and one-to-one sessions, as important components[23]. The current findings further complement these intervention components with social facilitation and the use of technologies such as wearable devices, and smartphone/computer applications. The lack of a significant difference between the four intervention strategies is probably due to the low statistical power (post hoc analysis: 9%), as only a few single-component intervention studies could be included. Furthermore, environmental interventions in the general population are reported to have greater reductions in SB

than behavioural interventions[40, 44], but are studied to a limited extent in clinical populations. Only two interventions of the current meta-analysis included environmental adaptations, with SB reductions of larger magnitudes (114[70] and 97[65] min/day). However, no recommendations on environmental restructuring to reduce SB in clinical populations can be made.

Although all diseases of the ICD-11 were included in the current search, only five population groups could be identified, from which the majority were metabolically related. Here, the question arises whether the 'clinical disorder' of these participants is a consequence of their sedentary lifestyle or that participants become sedentary due to their clinical symptoms. However, the exact sequence of events is negligible, because a vicious inactivity circle is initiated[23]. Nonetheless, to increase the generalisability of the present results, research on SB interventions in other clinical populations is warranted. Furthermore, even though no significant differences between intervention effects across population groups were identified, the high heterogeneity in current results might indicate possible different responses per group (Fig. 3). Higgens *et al.* previously reported that moderate to considerable statistical heterogeneity is often inevitable in meta-analysis due to clinical and methodological diversity[52], but future research should take sub analyses per population group and information on disease severity and feasibility into account.

Participants replaced their SB with approximately 30min of standing and 30min of walking. MVPA did not significantly change. Previous research also shows that participants following a MVPA intervention, increase the intensity of their PA (e.g. from light to moderate/vigorous intensity), without reducing their SB[39, 43, 76]. This shows the specificity of SB and PA interventions and indicates that when SB and MVPA need to be improved simultaneously, both behaviours should be targeted. Furthermore, the extra 30min walking time corresponded with an additional 1976 steps/day, or 73 steps/min, in the intervention group. Moderate-intensity PA is associated with 100 steps/min[77], which demonstrates the low walking intensity of participants in the current review. This is however evident because most interventions aimed to specifically increase low-intensity household activities. At follow-up, walking time was the only significantly improved variable. Follow-up duration varied however largely, and only six studies included a follow-up measure of which only three could assess standing time by the means of an inclinometer. Hence, no solid conclusions can be drawn on SB changes on the longer term and, therefore, more comprehensive follow-up measures are recommended in future research.

The present results show the large window of opportunity of SB interventions in clinical populations. Moreover, previous work showed better adherence rates with lower activity intensities for sedentary adults[78], and the low drop-out rate (10%) in current results supports the feasibility of low-intensity NEPA for clinical populations. A recent meta-analysis of Hadgraft *et al*. showed positive cardiometabolic health effects of free-living SB interventions in the general population, in which clinical populations were only very limited represented[38]. The current results complement these findings for persons with a clinical condition. Here, a significant improvement in anthropometrics (fat percentage and waist circumference) and glycaemic control (HbA1c) was found following a SB reduction under free-living conditions in clinical populations. The most evident improvement was found in anthropometrics. Baseline waist circumference values indicated an increased cardiometabolic risk (men >102cm, women >88cm)[79]. According to De Koning *et al.*, the relative risk of a CVD event is reduced by 2% for every 1cm reduction in waist circumference[80]. Moreover, waist circumference and fat percentage changes were twice the magnitude of the changes in Hadgraft *et al.* (-1.52 vs -0.7cm and -0.7 vs -0.3%), implying more substantial health

benefits of light-intensity NEPA in clinical populations. Fasting glucose concentrations and HbA1c values at baseline also indicated an increased cardiometabolic risk[81] (range 87 to 134 mg/dl and 5.6 to 8.0% respectively). Although T2DM patients represented a large subsample (35%) of the total study population, risk markers remained unchanged after exclusion of the diabetic studies (HbA1c 6.1 ± 0.6%; fasting glucose 102.7 ± 8.1mg/dl). In line with findings of Hadgraft *et al.*[38], the glucose metabolism was improved after the intervention, indicated by the glycated haemoglobin measures. This effect was still present after exclusion of all studies with T2DM patients (-0.24%, 95%CI: [-0.36, -0.11] %, $p < 0.001$). The measurement of HbA1c is less subject to dietary changes of participants compared to fasting glucose variables[82], which remained unchanged in the current findings.

Blood pressure and blood lipids did not significantly change following a SB reduction of 64 min/day. It is however important to note that the included studies were not powered to detect changes in cardiometabolic health, because SB was in almost all studies the primary outcome measure. Nonetheless, the SB reduction in the current review might not be sufficient to improve these variables, as post-intervention SB of participants was still 1h higher than baseline SB of the general population[74]. Although the baseline systolic and diastolic blood pressure was within the 'high normal' spectrum according to the European Society of Cardiology guidelines, therapeutic targets of <130/80mm Hg are recommended[83]. Furthermore, a blood pressure of 120-139/80-89mm Hg is defined as prehypertension and associated with an increased risk of major CVD events[84]. In contrast with the SB interventions of Hadgraft *et al.*[38] and the activity tracking-based behaviour interventions of Franssen *et al.*[42], blood pressure did not significantly change in the current findings. This may be due to the intensity of reallocated PA minutes, as higher intensity PA is already shown to lead to superior blood pressure reductions[85]. Furthermore, interrupting sitting time with half-hourly light-intensity walking bouts is already shown to significantly improve blood pressure in previous research[37], implying a greater impact of the SB accumulation pattern and the number of SB breaks compared to the total SB per day[86]. Hence, future research should also include and report measures on PA intensity and the SB accumulation pattern. Additionally, it might be relevant to add simple resistance activities (e.g. calf-, knee raises, and squats) to interrupt SB in future interventions. Dempsey *et al.* for example found more profound effects with this approach compared to light-intensity walking bouts[37].

The blood lipid profile of participants at baseline is within the current recommendations of the American Expert Panel on Blood Cholesterol[87], except for LDL-cholesterol which is slightly elevated. This may explain why no significant improvements could be detected. Furthermore, the amount of studies including lipid measures is rather low and lipid measures are subject to standardization methods and patient adherence. However, the lack of effects on the blood lipid profile is consistent with findings in meta-analyses of laboratory-based SB interventions[88, 89] and findings of Hadgraft *et al.*, where only a significant though very small improvement on HDL-cholesterol concentration was found[38]. This seemingly contradicts our current understanding of the metabolic effects of SB or inactivity, because muscle inactivity has been linked with reduced lipoprotein lipase (LPL) activity. LPL is the rate-limiting enzyme in the breakdown of triglycerides and uptake of free fatty acids, and decreases in LPL activity have been associated with decreased HDL cholesterol and increased triglyceride levels[90]. However, this is solely based on animal or human bed rest studies, further research on the association between LPL activity and lipid measures in free-living SB (changes) is warranted.

4.1. Study limitation and strengths

An important strength of the current systematic review is that evidence is solely based on objective SB measures and randomised controlled trials. Moreover, the overall risk of bias was low. Therapist blinding is difficult in behavioural interventions and the inclusion of objective outcome measures limits the risk of a detection bias, which were the main threats of quality in this systematic review. Furthermore, SB and cardiometabolic health measures were measured simultaneously in all but four studies, allowing direct associations between SB changes and cardiometabolic health. However, several limitations were also observed. Although all SB measures were objective, different measurement methods and sensor wear locations were used, limiting comparison between studies. Sample sizes were relatively low, and while five different clinical population groups were identified, the majority of diseases was metabolically related. Furthermore, four main behavioural intervention components were distinguished, but the variation within components was still high. Frequency and means of contact for the motivational counselling (face-to-face or group sessions, telephone calls, text messages, mail), the focus of self-monitoring devices (PA or SB), and the structure of the website/app differed between studies. The social aspect was also organized differently in each intervention (optional group walks, competition/collaboration to achieve a goal). This variation in components between studies in combination with different intervention durations probably explains the high heterogeneity of SB results and limits interpretation of the independent contribution of each component. Furthermore, future research should be sufficiently powered to detect changes in cardiometabolic risk factors to explore dose-response relationships of SB reallocations to standing and walking. The accumulation pattern of SB and changes herein should also be reported[86].

5. Conclusion

The current results suggest that persons with various clinical conditions can significantly reduce their SB via behavioural interventions and that SB reductions are larger following multicomponent interventions including motivational counselling, self-monitoring, social facilitation, and technologies. Furthermore, replacing SB with one hour of light-intensity NEPA reduces the cardiometabolic risk in clinical populations, with the most evident effect on anthropometrics. Future studies are warranted to complement MVPA guidelines with appropriate low-intensity NEPA recommendations.

Declarations

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Captions

Table 1. Study characteristics

Fig. 1 PRISMA flow diagram. *Nineteen full-text articles met the inclusion criteria, but one article only reports follow-up measures of another included article, resulting in the inclusion of 18 different interventions

Fig. 2 Risk of bias graph for included studies (n = 18)

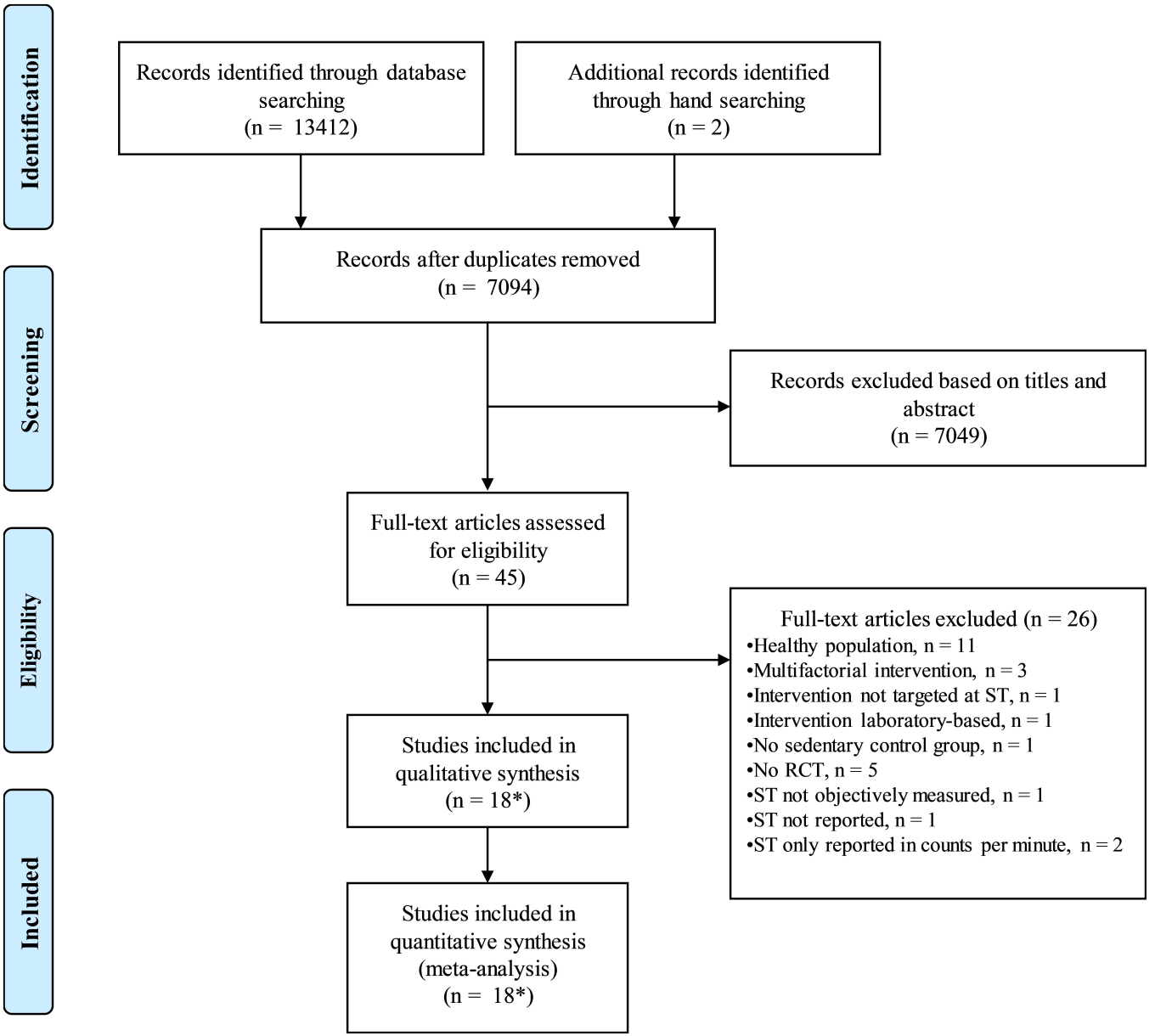
Fig. 3 Forest plot of weighted mean pre-post differences in sedentary behaviour (minutes per day) between control and intervention groups. Abbreviations: **CI** confidence interval, **I^2** variation in pooled effect size attributable to heterogeneity within that group

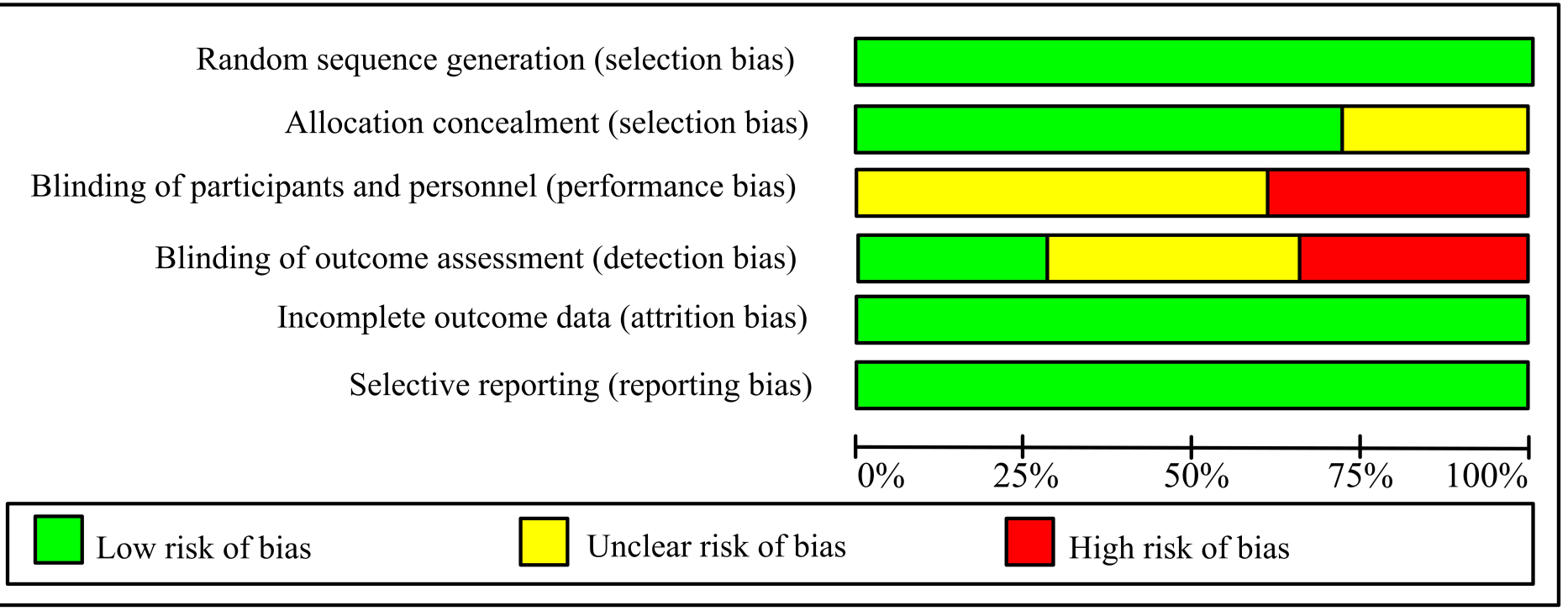
Supplementary material

Appendix A: Search strategy

Appendix B: Data extraction form

Appendix C: Funnel plots


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 13412)
Additional records identified through hand searching (n = 2)
Records after duplicates removed (n = 7094)
Records excluded based on titles and abstract (n = 7049)
Full-text articles assessed for eligibility (n = 45)
Full-text articles excluded (n = 26)
•Healthy population, n = 11
•Multifactorial intervention, n = 3
•Intervention not targeted at ST, n = 1
•Intervention laboratory-based, n = 1
•No sedentary control group, n = 1
•No RCT, n = 5
•ST not objectively measured, n = 1
•ST not reported, n = 1
•ST only reported in counts per minute, n = 2
Studies included in qualitative synthesis (n = 18*)
Studies included in quantitative synthesis (meta-analysis) (n = 18*)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

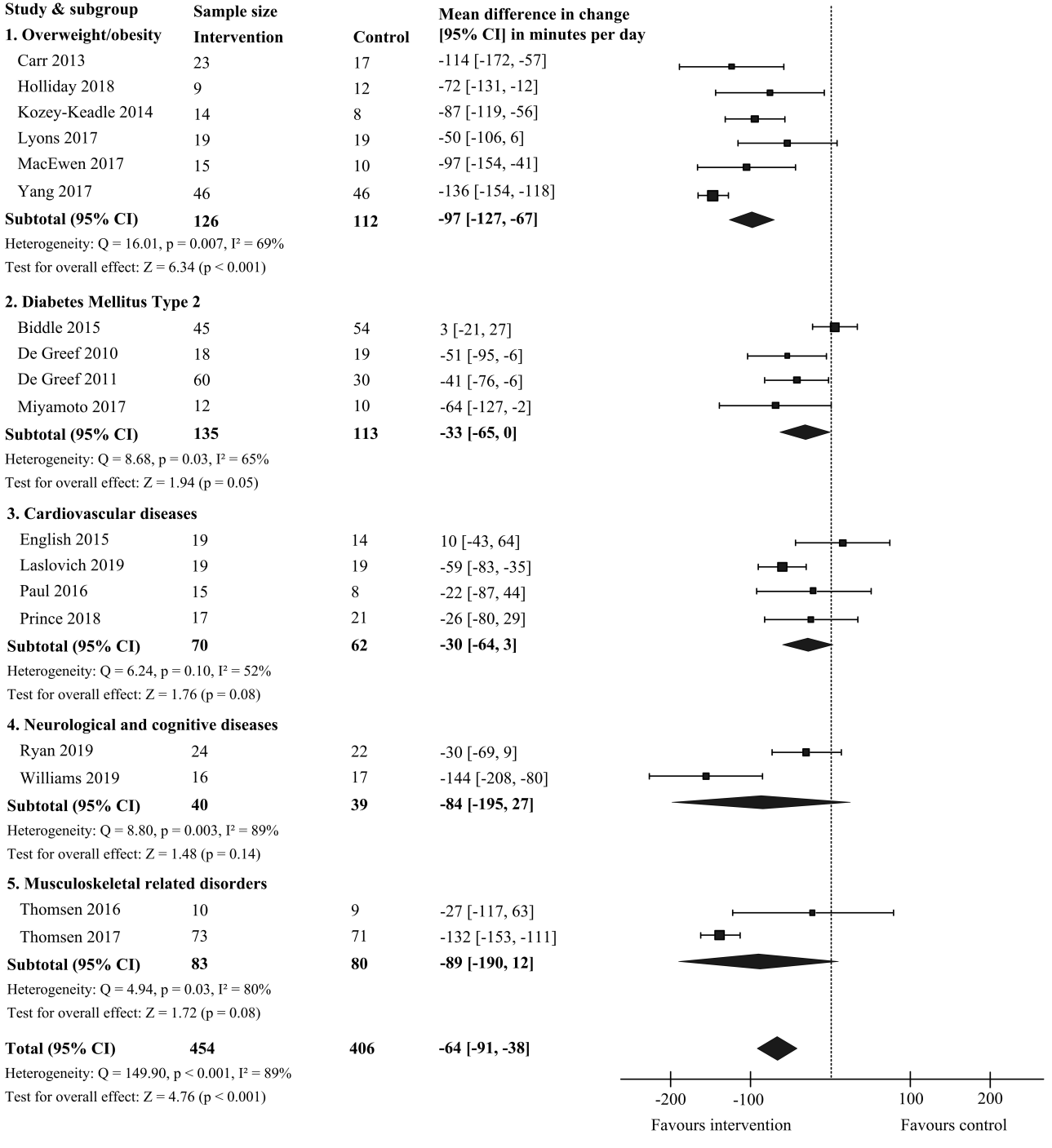

Study & subgroup
Sample size
Intervention
Control
Mean difference in change [95% CI] in minutes per day
1. Overweight/obesity
Carr 2013 23 17 -114 [-172, -57]
Holliday 2018 9 12 -72 [-131, -12]
Kozey-Keadle 2014 14 8 -87 [-119, -56]
Lyons 2017 19 19 -50 [-106, 6]
MacEwen 2017 15 10 -97 [-154, -41]
Yang 2017 46 46 -136 [-154, -118]
Subtotal (95% CI) 126 112 -97 [-127, -67]
Heterogeneity: Q = 16.01, p = 0.007, I² = 69%
Test for overall effect: Z = 6.34 (p < 0.001)
2. Diabetes Mellitus Type 2
Biddle 2015 45 54 3 [-21, 27]
De Greef 2010 18 19 -51 [-95, -6]
De Greef 2011 60 30 -41 [-76, -6]
Miyamoto 2017 12 10 -64 [-127, -2]
Subtotal (95% CI) 135 113 -33 [-65, 0]
Heterogeneity: Q = 8.68, p = 0.03, I² = 65%
Test for overall effect: Z = 1.94 (p = 0.05)
3. Cardiovascular diseases
English 2015 19 14 10 [-43, 64]
Laslovich 2019 19 19 -59 [-83, -35]
Paul 2016 15 8 -22 [-87, 44]
Prince 2018 17 21 -26 [-80, 29]
Subtotal (95% CI) 70 62 -30 [-64, 3]
Heterogeneity: Q = 6.24, p = 0.10, I² = 52%
Test for overall effect: Z = 1.76 (p = 0.08)
4. Neurological and cognitive diseases
Ryan 2019 24 22 -30 [-69, 9]
Williams 2019 16 17 -144 [-208, -80]
Subtotal (95% CI) 40 39 -84 [-195, 27]
Heterogeneity: Q = 8.80, p = 0.003, I² = 89%
Test for overall effect: Z = 1.48 (p = 0.14)
5. Musculoskeletal related disorders
Thomsen 2016 10 9 -27 [-117, 63]
Thomsen 2017 73 71 -132 [-153, -111]
Subtotal (95% CI) 83 80 -89 [-190, 12]
Heterogeneity: Q = 4.94, p = 0.03, I² = 80%
Test for overall effect: Z = 1.72 (p = 0.08)
Total (95% CI) 454 406 -64 [-91, -38]
Heterogeneity: Q = 149.90, p < 0.001, I² = 89%
Test for overall effect: Z = 4.76 (p < 0.001)
-200
-100
100
200
Favours intervention
Favours control

Table 1. Characteristics of included studies

Study	Population	Intervention duration (w)	Participants	Intervention	Outcome parameters (ST monitor; monitor time)
Biddle 2015	Adults at risk of T2DM	12 Follow-up: 52	**Intervention** N: 94 Drop-out: 30 (32%) Age: 32.4 ± 5.4y BMI: 34.6 ± 4.9 M/F: 28/66 *non-attendance at education session: 25% **Control** N: 93 Drop-out: 25 (27%) Age: 33.3 ± 5.8y BMI: 34.5 ± 5 M/F: 31/62	*Behavioural*[3] **MC:** 1 group education session (3h) targeting knowledge and perceptions of prevalent risk factors for T2DM and promoting SB change, goal setting and group discussions + 1 follow-up phone call at 6w **SM**: Gruve with vibration prompts if participant had been sitting for an extended period (feedback on ST via a computer, not real-time) Usual care	**Physical activity** (10d): - ST (AG; WT) - Standing time (AP; W+ST) - ST breaks (AP; W+ST) - Steps/day (AG; WT) - MVPA time (AG; WT) **Cardiometabolic risk:** - HbA1c - Fasting glucose - Total chol - HDL-chol - LDL-chol - Triglycerides - Systolic BP - Diastolic BP **Anthropometrics:** - Body weight - BMI - Fat% - WC
Carr 2013	Overweight/obesity	12	**Intervention** N: 17 Drop-out: 2 (12%) Age: 47.6 ± 9.9y BMI: 33.2 ± 4.5 M/F: 1/16	***Multicomponent*** *Behavioural*[4]*:* **MC:** Access to motivational website individually tailored to the local worksite with theory-based messages (content: reducing ST by both increasing active sitting through pedaling and taking breaks from sitting by means of social support, self-efficacy and discussion of perceived environment) + 3 theory-based motivational emails/week targeting goal setting, self-efficacy and perceived environment **SM:** Pedometer (Omron HJ-150) + daily mails to remind participants to self-monitor daily pedal time and steps on website **Social facilitation:** Communication via website in groups of 4-5 participants + virtual competition (groups travelled across the USA) *Environmental:*	**Physical activity** (Stepwatch Physical Activity Monitor; 7d - WT): - ST **Cardiometabolic risk:** - Total chol - HDL-chol - LDL-chol - Triglycerides - BP - Diastolic BP **Anthropometrics:** - Body weight - BMI

				portable pedal machine + PC interface with real-time feedback + suggestions for daily pedaling time and on how to set goals (no pre-specified goals)	- WC
			Control N: 23 Drop-out: 7 (30%) Age: 42.6 ± 8.9y BMI: 31.7 ± 4.9 M/F: 3/20	Wait list	
De Greef 2010	T2DM	12 Follow-up: 52	**Intervention** N: 20 Drop-out 12w: 2 (10%) Drop-out 52w: 3 (15%) Age: 61.3 ± 6.3y BMI: 29 ± 4.2 M/F: 13/7 **Control** N: 21 Drop-out 12w: 2 (9.5%) Drop-out 52w: 2 (9.5%) Age: 61.3 ± 6.9y BMI: 31.5 ± 5 M/F: 15/6	*Behavioural*[3] **MC:** 5 group sessions (90 min; week 1, week 3, week 5, week 8, week 12) + booster session (week 23). Sessions start with a motivational interviewing phase, after which lifestyle change plans are developed (the where, when and how the planned behaviour changes would take place). Afterwards pedometer results are discussed and goals reviewed and renewed. **SM:** Pedometer + pedometer diary to record physical activity in order to set goals in the context of their daily routine Usual care + single education session about T2DM and physical activity (similar to first session of intervention group), with information on the benefits of physical activity and the risks of SB and were not motivated to increase physical activity	**Physical activity** (AG; 5d - WT): - ST - Steps/day - MVPA time **Cardiometabolic risk:** - HbA1c - Total chol - Systolic BP - Diastolic BP **Anthropometrics:** - Body weight - BMI
De Greef 2011	T2DM	24 Follow-up: 52	**Intervention** N: 60 Drop-out: 2 (3%) Age: 62 ± 9.0y BMI: 30 ± 2.8	*Behavioural*[3]*:* **MC:** 1 face-to-face session (30min) and 7 telephone calls (week 2, week 4, week 8, week 12, week 16, week 20, week 24). Face-to-face session started with a motivational interviewing phase, after which lifestyle change plans were developed (the where, when and how the planned behaviour changes would take place). Phone calls were specifically structured and included counselling on goal-setting, self-monitoring, self-efficacy, benefits, decisional balance, problem-solving strategies, social support and relapse prevention. **SM:** Pedometer + pedometer diary to record physical activity. A gradual increase of steps/days starting from baseline levels was advised (increase baseline steps/day with 1500 in 3 activity goals, unless participants were	**Physical activity** (AG; 5d - WT): - ST - Steps/day - MVPA time

				already sufficiently active (>10.000 steps/day) they were encouraged to maintain that level).	
			Control N: 32 Drop-out: 2 (6%) Age: 62 ± 9.0y BMI: 30 ± 2.8 M/F: 63/29	Usual care	
English 2016	Stroke survivors (3.2 ± 3.4y since stroke, 12/33 require assistance in ADLs, 12/33 require walking aid)	7	**Intervention** N: 19 Drop-out: 0 Age: 65.4 ± 12.3y BMI: 29.3 ± 5.8 M/F: 13/6	*Behavioural[2]:* **MC:** 1 face-to-face session, 3 follow-up phone calls (week 1, 3 and 7). Main message: 'Sit less and move more' with encouragement to regularly break up sitting time with short bursts of light intensity activity (standing, walking at a comfortable peace). In first face-to-face session, feedback on baseline ST was provided, action plans, goals and strategies were elicited from participants.	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - Walking time - MVPA time
			Control N: 16 Drop-out: 2 (12.5%) Age: 67.8 ± 13.8y BMI: 27.5 ± 3 M/F: 9/7	Control group participants received the same schedule of interviews as the intervention group, with a placebo message of increasing calcium for bone health. Data from a food frequency questionnaire were used to create personalized feedback	
Holliday 2018	Overweight/ obesity	24	**Intervention** N: 24 Drop-out: 2 (8%) Age: 41 ± 2.0y BMI: 29.2 ± 3.4 M/F: 0/24 *compliance with accelerometer protocol: n = 9	*Behavioural[3]:* **MC:** Contact by telephone and email twice weekly for the first 4 weeks, and once fortnightly from weeks 4 to 12 (positive reinforcement when target points/min of SM were achieved, encouragement to persevere and if targets were not achieved, participants were reminded of the typical benefits of being more active for health and general well-being). **SM:** Points-based physical activity monitoring with table. Participants need to accumulate 30 points per week, equating to 5 × 30 min of brisk walking and are provided a table of examples of different activities, each with a points score allocated per ten-minutes of activity. Points values are derived from MET scores (-1.5METs for SB). These activities had to be additional to regular physical activity behaviour. Participants could add specific activities to the table to which points scores were assigned.	**Physical activity** (AG; 3d - WT) - ST - MVPA time **Anthropometrics:** - Body weight - BMI - Fat% - WC

			Control N: 26 Drop-out: 6 (23%) Age: 41 ± 2y BMI: 29.2 ± 3.4 M/F: 0/26 *compliance with accelerometer protocol: n = 3	Wait list **Excluded intervention group:** Structured exercise (150 min MVPA/week)	
Kozey Keadle 2014	Overweight/obesity	12	**Intervention** N: 18 Drop-out: 4 (22%) Age: 44.5 ± 9.5y BMI: 34.8 ± 4.3 **Control** N: 10 Drop-out: 2 (20%) Age: 42.7 ± 10.1y BMI: 35.3 ± 5.2	*Behavioural*[3]*:* **MC:** Education on strategies to reduce sitting time at home and at work (i.e. standing during commercials, taking 5min breaks every hour, etc.) and on benefits of NEPA + recommendation to accumulate NEPA in small bouts throughout day + weekly face-to-face meetings to discuss strategies and feedback on physical activity results **SM:** Omron pedometer + weekly goals based on baseline steps Control group participants had to maintain current levels of activity **Excluded intervention groups:** - Structured exercise (exercise 5 days/week for 40 min/session at moderate intensity) - Combination of structured exercise and SB intervention	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - Walking time - Steps/day **Cardiometabolic risk:** - Fasting glucose - Total chol - HDL-chol - Triglycerides - Systolic BP - Diastolic BP **Anthropometrics:** - Body weight - BMI - Fat%
Laslovich 2019	Asymptomatic PAD	12	**Intervention** N: 19 Drop-out: 0 Age: 68 ± 7.5y BMI: 29.5 ± 4.1 M/F: 10/9	*Behavioural*[4]*:* **MC:** 2x/month online video with health recommendations related to PAD (general PAD facts and figures, hypertension, diabetes, cardiovascular disease prevention, tobacco use, and nutrition) + instruction to walk at least 2 or more 10min bouts continuously + planning + goal setting (individualized automated goal setting features in online platform, continuously updated based on uploaded data) **SM:** Wearable activity tracker + real-time feedback (indicator bar with 5 activity levels + vibration prompts when >50min are spent sedentary) + online self-monitoring home page dashboard	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - ST - Walking time - Steps/day

			Control N: 19 Drop-out: 0 Age: 68 ± 10.6y BMI: 28.8 ± 5.2 M/F: 7/12	Control group participants received the same bimonthly videos as the intervention group	
Lyons 2017	Mid-aged and older adults with obesity	12	**Intervention** N: 20 Drop-out: 1 (5%) Age: 61.3 ± 6.0y BMI: 30 ± 2.9 M/F: 3/17	*Behavioural*[4]*:* **MC:** Orientation visit for guidance on the use of the activity tracker and app, encouragement for social interaction in app and goal-setting. Mobile phone app with individual goals and socialization + weekly telephone counselling (15-20 min, content: adverse events, technical problems, discussion of goals for steps/day and ST alerts, planning, social support, problem solving, self-rewards, relapse prevention, stress and time management) **SM:** Wearable physical activity monitor (Jawbone Up24) + prompts when > 1h is spent sedentary + tablet device **Social facilitation:** Home page in app with possibility to comment and like activity of other participants in the same cohort	**Physical activity** (AP ;7d - W+ST): - ST - Walking time - Steps/day **Anthropometrics:** - Body weight - Fat%
			Control N: 20 Drop-out: 1 (5%) Age: 61.7 ± 6.3y BMI: 30.7 ± 4.0 M/F: 3/17	Waitlist	
MacEwen 2017	Office workers with abdominal obesity	12	**Intervention** N: 15 Drop-out: 0 Age: 43.2 ± 9.7y BMI: 36.5 ± 9.0 M/F: 3/13	*Environmental* Height-adjustable desks, without any additional information or prompting. Advice to sit or stand as much as they liked.	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - ST breaks - Steps/day

			Control N: 12 Drop-out: 2 (17%) Age: 48.9 ± 11.4y BMI: 34.6 ± 7.0 M/F: 2/10	Control group participants had to continue work at seated desks with the advice to sit or stand as much as they liked	**Cardiometabolic risk:** - HbA1c[a] - Fasting glucose[a] - Total chol[a] - HDL-chol[a] - LDL-chol[a] - Triglycerides[a] - Systolic BP - Diastolic BP **Anthropometrics:** - Body weight - BMI - Fat% - WC
Miyamoto 2017	T2DM	12	**Intervention** N: 12 Drop-out: 0 Age: 60.0 ± 3.1y BMI: 25.2 ± 1.3 M/F: 9/3 **Control** N: 10 Drop-out: 0 Age: 60.2 ± 3.0y BMI: 23.9 ± 0.7 M/F: 8/2	*Behavioural[1]:* **SM:** Tri-axial accelerometer + instruction to increase non-locomotive PA (routine domestic or occupational tasks such as sit-to-stand activity or washing dishes) Usual care + accelerometer with display turned off and no instruction regarding physical activity **Excluded intervention group:** Tri-axial accelerometer + instruction to increase locomotive PA (which requires moderate-to-vigorous energy consumption)	**Physical activity** (HJA-350IT; 7d - WT): - ST **Cardiometabolic risk:** -HbA1c - Fasting glucose - Total chol - LDL-chol - Triglycerides **Anthropometrics:** - Body weight

Paul 2016	Stroke survivors (3.8 ± 2.5 - 4.9 ± 6.1y since stroke, 10/23 require walking aid)	6	**Intervention** N: 16 Drop-out: 1 (6%) Age: 56.3 ± 8.7y BMI: 24.1 ± 3.5 M/F: 7/8 **Control** N: 8 Drop-out: 0 Age: 55.3 ± 12.6y BMI: 24.8 ± 1.8 M/F: 4/4	*Behavioural[4]:* **MC:** Participants receive smartphone with 'STARFISH app' + instructions (30min) + feedback session to discuss progress after 3w. App content: Goal setting (daily step count target based on baseline period which is weekly adjusted), planning, feedback and rewards (fish, representing progress, blow bubbles when active and grow when targets are reached), social facilitation (virtual groups of 4 persons, when all persons reach targets another sea creature is added to fish tank + all participants of the group see activity of other participants (fish swims and blows bubbles) **SM:** Visual representation of fish in mobile phone app Usual care: No active rehabilitation, only appointments with health care professional as required	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - Walking time - Steps/day **Cardiometabolic risk:** - Systolic BP - Diastolic BP **Anthropometrics:** - BMI
Prince 2018	Coronary artery disease patients	6.5	**Intervention** N: 19 Drop-out: 2 (11%) Age: 62.4 ± 10.7y BMI: 28.7 ± 5.8 M/F: 10/7 **Control** N: 21 Drop-out: 0 Age: 61.5 ± 9.7y BMI: 30.5 ± 5.4 M/F: 13/8	*Behavioural[1]:* **SM:** Monitor (activPAL VTAP model) with vibration prompts when >30 consecutive minutes are spent sedentary (2min of standing/movement necessary to reset) Usual care: Cardiac rehabilitation	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - ST breaks - Walking time - Steps/day - MVPA time **Cardiometabolic risk:** - HbA1c - Fasting glucose - Total chol - HDL-chol - LDL-chol - Triglycerides - Systolic BP - Diastolic BP **Anthropometrics:** - Body weight - BMI

					- WC
Ryan 2019	Multiple sclerosis	12 Follow-up: 36	**Intervention** N: 30 Drop-out 12w: 2 (7%) Drop-out 36w: 3 (10%) Age: 56.9 ± 9.0y BMI: 25.9 ± 5.3 M/F: 13/17 **Control** N: 30 Drop-out 12w: 3 (10%) Drop-out 36w: 5 (17%) Age: 56.7 ± 9.2y BMI: 26.3 ± 5.9 M/F: 13/17	*Behavioural[3]:* **MC:** 4 face-to-face sessions (30-45min; discussion of step count, ST and goals) + behaviour change techniques + handbook (content: Pre-reading and reflection that needs to be completed prior to each session + goal setting + self-monitoring) **SM:** Yamax SW-200 digiwalker + activity diary in handbook Usual care	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - Walking time - Steps/day - MVPA time
Thomsen 2016 **Thomsen 2017, 2019**	Rheumatoid arthritis	16 Follow-up: 22	**Intervention** *2016* N: 10 Drop-out 16w: 0 Age: 64.5 ± 8.5y BMI: 28.7 ± 6.5 M/F: 4/6	*Behavioural[2]:* **MC:** 3 motivational counselling sessions (week 1, week 3, week 10, content: 4 key messages using motivational interviewing: Reduce TV viewing, substitute sitting with standing when possible at work and/or at home, break up prolonged sitting by standing up frequently, maximum 30min sitting per episode). Session 1: Monitoring and discussion of physical activity and ST (goal setting & action planning). Session 2-3:	**Physical activity** (AP; 7d - W+ST): - ST - Standing time - ST breaks - Walking time

			2017, 2019 N: 75 Drop-out 16w: 1 (1%) Drop-out 22m: 4 (5%) Age: 59.7 ± 10.7y BMI: 26.0 ± 5.5 M/F: 15/60 **Control** *2016* N: 10 Drop-out: 1 (10%) Age: 54.0 ± 14.0y BMI: 21.9 ± 4.2 M/F: 4/6 *2017, 2019* N: 75 Drop-out 16w: 2 (3%) Drop-out 22m: 11 (14.6%) Age: 59.5 ± 12.7y BMI: 26.8 ± 5.3 M/F: 14/61	Discussion and modification of goals + oral and written information about the health benefits of reducing sitting time + text messages to remind participants of their individually set behavioural goals (depending on participants' preference (max 1/day and 5/week) Usual lifestyle	**Cardiometabolic risk:** - HbA1c - Fasting glucose - Total chol[b] - HDL-chol[b] - LDL-chol[b] - Triglycerides[b] - Systolic BP - Diastolic BP **Anthropometrics:** - Body weight - BMI - WC
Williams 2019	Serious mental illness	17 Follow-up: 24	**Intervention** N: 20 Drop-out: 4 (20%) Age: 43.0 ± 18.0y M/F: 13/7 **Control** N: 20 Drop-out: 3 (15%) Age: 43.0 ± 18.0y M/F: 9/11	*Behavioural[4]:* **MC:** 1 group education session at baseline (content: Benefits of being active, harms of being sedentary, strategies to reduce and interrupt ST) + two weekly face-to-face coaching sessions (30min, content: Discussion of barriers) **SM:** Yamax digi-walker + recording on individual calendar **Social facilitation**: Optional weekly walks Usual care	**Physical activity** (Geneactiv 3d - WT): - ST - MVPA time **Anthropometrics:** - WC

Yang 2017	Overweight	12	**Intervention** N: 53 Drop-out: 5 (9%) Age: 33.9 ± 10.0y BMI: 27.2 ± 3.4 M/F: 21/32	*Behavioural*[4]*:* **MC:** Individual reminder messages (at least 1/week, content: Evidence-based health information, professional personnel counselling and constructive feedback) via Line and email. **SM:** Physical activity sensor + related smartphone app (monitors food intake, physical activity data, sleep hours, sleep efficacy) **Social facilitation:** Interactive webpage (data of smartphone app + specific targets for calories to burn, steps/day (>10.000/day), walking distance (>6.8km/day) and activity intensity (ST < 8h). Results from peer group visible and health recommendations ('good, please continue')	**Physical activity** (wearable sensor module with a neural-network-based activity classification algorithm[1]): - ST - Steps/day **Cardiometabolic risk:** - Fasting glucose - HDL cholesterol - Triglycerides - Systolic blood pressure **Anthropometrics:** - Body weight - BMI - Waist circumference
			Control N: 53 Drop-out: 2 (4%) Age: 32.4 ± 9.2y BMI: 30.3 ± 4.9 M/F: 21/32	Usual care with health education (booklet of MetS prevention published by the Health Promotion Administration of Ministry of Health and Welfare with details on 5 topics: dietary control, PA, quitting tobacco and alcohol, stress management, regular health examination)	

1. Lin CW, Yang YT, Wang JS, et al. A wearable sensor module with a neural-network-based activity classification algorithm for daily energy expenditure estimation. *IEEE transactions on information technology in biomedicine : a publication of the IEEE Engineering in Medicine and Biology Society* 2012; 16: 991-998. 2012/08/10. DOI: 10.1109/titb.2012.2206602.

Appendix A: Search strategy

	MeSH terms	PubMed: title/abstract WoS: topic Cochrane, Sopus and Embase: title/abstract/keyword
Population	OR	OR
1. Infectious or parasitic disorders	PubMed/Cochrane: - infectious disease - OR communicable disease - OR parasitic disease Embase: - 'Communicable disease'/exp - OR 'parasitosis'/exp	- bacterium OR virus OR parasit* OR fungus OR infectious OR communicable - AND diseas*
2. Neoplasms	PubMed/Cochrane: - Neoplasms Embase: - 'Neoplasm'/exp	- Neoplasm* - OR cancer
3. Diseases of the blood or blood-forming organs	PubMed/Cochrane: - Hematological disease	- (Blood OR "blood forming organs") - AND diseas*
4. Diseases of the immune system	PubMed/Cochrane: - Immune system disease Embase: - 'immunopathology'/exp	- (autoimmune OR immune) - AND (diseas* OR disorder OR dysregulation)
5. Endocrine, nutritional or metabolic diseases	PubMed/Cochrane: - Nutritional and metabolic diseases Embase: - 'metabolic disorder'/exp	- diabetes mellitus - OR "impaired glucose regulation" - OR "impaired glucose tolerance" - OR "glucose intolerance" - OR "insulin resistance" - OR dyslipid* - OR hyperlipid* - OR obes* - OR overweight - OR "metabolic syndrome" - OR metabolic* AND (unhealthy OR abnormal) - OR (metabolic* OR endocrin* OR nutrition*) AND (diseas* OR disorder)
6. Mental, behavioural or neurodevelopmental disorders	PubMed/Cochrane: - mental disorder Embase: - 'mental disease'/exp	- (mental OR behaviour* OR neurodevelopmental) - AND (diseas* OR disorder)
7. Sleep-wake disorders	PubMed/Cochrane: - Sleep wake disorders Embase: -'sleep disorder'/exp	-"sleep wake disorder"
8. Nervous system diseases	PubMed/Cochrane: - Nervous system diseases - OR paralysis Embase: - 'neurological disease'/exp - OR 'paralysis'/exp	- ((nervous OR neurologic*) - AND (diseas* OR disorder)) - OR *plegia - OR paralys* - OR "chronic fatigue syndrome"
9. Diseases of the visual system	Embase: - 'visual disorder'/exp	- Visual - AND (diseas* OR disorder)
10. Diseases of the ear or mastoid process	PubMed/Cochrane: - Ear diseases Embase: - 'ear disease'	- (ear OR mastoid process) - AND (disease* OR disorder)
11. Diseases of the circulatory system	PubMed/Cochrane: - Cardiovascular disease Embase: - 'cardiovascular disease'/exp	- ((circulat* OR cardiovascular OR cardio-vascular OR vascular OR cardiac) - AND (diseas* OR disorder))

			- OR hypertensions - OR atheroscleros*
12.	Diseases of the respiratory system	PubMed/Cochrane: - Respiratory tract diseases Embase: - 'chronic obstructive lung disease'/exp	- "chronic obstructive pulmonary disease" - respiratory AND (diseas* OR disorder)
13.	Diseases of the digestive system	PubMed/Cochrane: - Digestive system disease Embase: - 'digestive system disease'/exp	- digestive - AND (diseas* OR disorder)
14.	Diseases of the skin	PubMed/Cochrane: - Skin disease Embase: - 'skin disease'/exp	- ((skin OR dermis OR subcutaneous OR cutaneous) - AND (diseas* OR disorder))
15.	Diseases of the musculoskeletal system or connective tissue	PubMed/Cochrane: - Musculoskeletal disease - OR connective tissue disease Embase: - 'musculoskeletal disease'/exp - OR 'connective tissue disease'/exp	- musculoskeletal AND (diseas* OR disorder) - OR "mobility limitation" - OR "connective tissue" AND (diseas* OR disorder)
16.	Diseases of the genitourinary system	PubMed/Cochrane: - Male urogenital disease - OR female urogenital disease Embase: - 'urogenital tract disease'/exp	- urological OR urogenital OR genitourinary - AND (diseas* OR disorder)
17.	Conditions related to sexual health	PubMed/Cochrane: - Female genital disease - OR male genital disease Embase: - 'genital system disease'/exp	- sexual AND (dysfunction OR disorder)
18.	Certain conditions originating in the perinatal period	Embase: - 'newborn disease'/exp	- Perinatal AND (diseas* OR disorder)
19.	Developmental anomalies		- Development* AND (diseas* OR disorder OR anomal*)
20.	Not elsewhere specified	PubMed/Cochrane: - Pain - OR fibromyalgia - OR signs and symptoms Embase: - 'pain'/exp - OR 'fibromyalgia'/exp	- Clinical AND (sign OR finding) - OR fibromyalg* - OR diseas* - OR disorder - OR symptom*
21.	Injury, poisoning or certain other consequences of external causes	PubMed/Cochrane: - Wounds and injuries - OR poisoning Embase: - 'injury'/exp - OR 'intoxication'/exp	- injur* - OR poisoning - OR "maltreatment syndrome" - OR wounds
Intervention (OR)			
1.	Activity	[- Low intensity activit* - OR low intensity physical activit* - OR minimal intensity activit* - OR minimal intensity physical activit* - OR Light intensity activit* - OR light intensity physical activit* - OR light activit* - OR light physical activit* - OR "nonexercise activity" OR "non exercise activity" OR "non-exercise activity" - OR "nonexercise activities" OR "non exercise activities" OR "non-exercise activities" - OR "nonexercise physical activity" OR "non exercise physical activity" OR "non-exercise physical activity" - OR "nonexercise physical activities" OR "non exercise physical activities" OR "non-exercise physical activities"	

	- OR "non-exercise activity thermogenesis" - OR LIPA or LPA or NEPA or NEAT - OR "activity break" OR "sedentary break" - OR "sit to stand transition" - OR ((displac* OR replac* OR reallocat* OR substitut* OR reduc* OR interrupt* OR break* OR decreas* or limit* or restrain*) AND (sedentar* OR sitting OR inactiv* OR sedentary lifestyle[MeSH]))] AND - (walking[MeSH] OR walk* OR stepping OR stand* OR exercise OR "physical activit*")	
2. Article type	AND - Trial - OR intervention - OR experiment* - OR randomiz*	
Comparison		
Sedentary lifestyle	- Sedentary lifestyle [MeSH] - OR sedentar* - OR inactiv* - OR (uninterrupted or prolonged or continuous) AND (sitting OR inactiv* OR sedentar*)	
Outcome	MeSH terms	PubMed: title/abstract WoK: topic Cochrane, scopus and embase: title/abstract/keyword
	OR	OR
1. Blood pressure	PubMed/Cochrane/Embase: - blood pressure	- "blood pressure"
2. Blood lipids	PubMed/Cochrane: - Lipids - Cholesterol - Triglycerides Embase: - 'lipid level'/exp - 'lipid'/exp	- "blood lipids" - "blood lipid level" - Lipid* - cholesterol - triglycerid* - HDL* - LDL* - non-HDL*
3. Glycaemic control	PubMed/Cochrane: - Blood glucose - Glucose - glycosylated haemoglobin - insulin Embase: - 'glucose blood level'/exp - 'glucose'/exp - 'glycosylated hemoglobin'/exp - 'insulin'/exp	- "glycaemic control" - "glucose control" - "glucose tolerance" - "blood glucose" - "glucose concentration" - "glucose regulation" - "glycosylated haemoglobin" - HbA1c - glycemia - insulin - "homeostatic model assessment" AND insulin - HOMA - "C-peptide"
4. Inflammation	PubMed/Cochrane: - C reactive protein Embase: - 'inflammation'/exp	- "c reactive protein" - CRP - inflamm*
5. Cardiometabolic risk	PubMed/Cochrane: - Metabolic diseases - Cardiovascular disease - Comorbidity Embase: - 'metabolic disorder'/exp - 'cardiovascular disease'/exp - 'comorbidity'/exp	- cardiometabol* - cardio-metabol* - "metabolic diseas*" - cardiovascul* - cardio-vascul* - "vascular diseas*" - comorbid*

Abbreviations: **MeSH** Medical Subject Headings, **WoS** Web of Science

Appendix B: Data Extraction Form adapted from the Cochrane Collaboration

1. Data form completed (dd/mm/yyyy)	
2. Name/ID of person extracting data	
3. Report title (title of paper/abstract/ report that data are extracted from)	
4. Report contact details of person extracting data	
5. Publication type (e.g. full report, abstract, letter)	
6. Study ID (e.g. Surname of first author and year first full report of study was published e.g. Smith 2001)	
7. Country in which the study was performed	
8. Economic level of the country in which the study was performed (e.g. low income, lower-middle income or upper-middle income)	-
9. Study funding source	-
10. Possible conflicts of interest	
Notes:	

Study Characteristics	**Review Inclusion Criteria**	**Location in text** (page#/fig/table)
11. Type of study		
12. Population description		
13. Focused disease/condition		
14. Notes:		

Study Participants	**Description**	**Location in text** (page#/fig/table)
15. Total sample size		
16. Age		
17. Sex		
18. Country		

19. Ethnicity		
20. Notes:		

Methods	**Description**	**Location in text** (page#/fig/table)
21. Aim of the study		
22. Study design (e.g. cross-sectional study, case-control study)		
23. Duration of intervention		
24. Control group		
25. Intervention type		
26. Intervention components		
27. Intervention frequency		
28. Blinding		
29. Notes:		

Control group	**Description**	**Location in text** (page#/fig/table)
30. Components		
31. Notes:		

Interventions	**Description**	**Location in text** (page#/fig/table)
32. Total number of intervention groups		
33. Notes:		

Intervention 1	**Description**	**Location in text** (page#/fig/table)
34. Specific intervention		
35. Notes:		

Outcomes	**Description**	**Location in text** (page#/fig/table)
36. physical examination/ Self-reported outcomes		

37. Blinding		
38. Notes:		

Outcome 1	**Description**	**Location in text** (page#/fig/table)
38. Outcome definition		
39. Unit (and period) of measurement		
40. Time points measured		
41. Time points reported		
42. Statistical method used		
43. Notes:		

Outcome 2	**Description**	**Location in text** (page#/fig/table)
44. Outcome definition		
45. Unit (and period) of measurement		
46. Time points measured		
47. Time points reported		
48. Statistical method used		
49. Notes:		

Outcome 3	**Description**	**Location in text** (page#/fig/table)
50. Outcome definition		
51. Unit (and period) of measurement		
52. Time points measured		
53. Time points reported		
54. Statistical method used		
55. Notes:		

Outcome 4	Description	Location in text (page#/fig/table)
56. Outcome definition		
57. Unit (and period) of measurement		
58. Time points measured		
59. Time points reported		
60. Statistical method used		
61. Notes:		

Results	Description	Location in text (page#/fig/table)
176. Number of participants allocated to control group		
177. Number of participants allocated to each intervention group		
178. Notes:		

Outcome 1	Description as stated in paper	Location in text (page#/fig/table)
179. Outcome name		
180. Sample size		
181. Missing participants		
182. Summary data for intervention group (e.g. mean and SDs or confidence intervals)		
183. Estimate of effect with confidence interval; P value		
184. Notes:		

Outcome 2	Description as stated in paper	Location in text (page#/fig/table)
185. Outcome name		
186. Sample size		
187. Missing participants		
188. Summary data for intervention group (e.g. mean and SDs)		

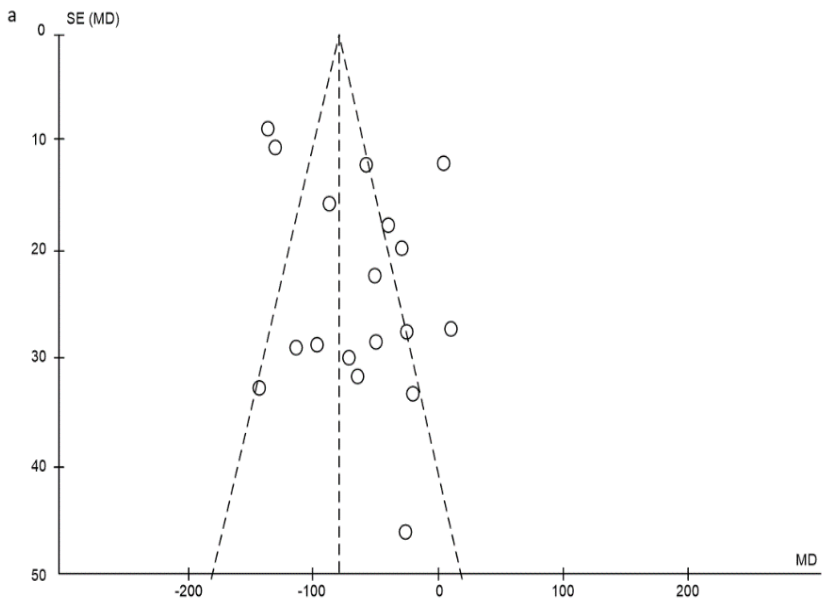
189. Estimate of effect with confidence interval; P value		
190. Notes:		

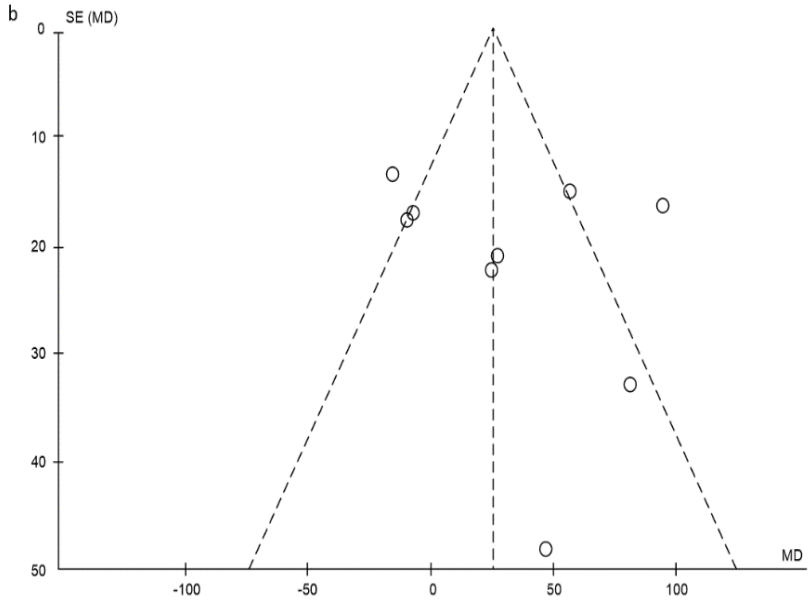
Outcome 3	**Description as stated in paper**	**Location in text** (page#/fig/table)
191. Outcome name		
192. Sample size		
193. Missing participants		
194. Summary data for intervention group (e.g. mean and SDs)		
195. Estimate of effect with confidence interval; P value		
196. Notes:		

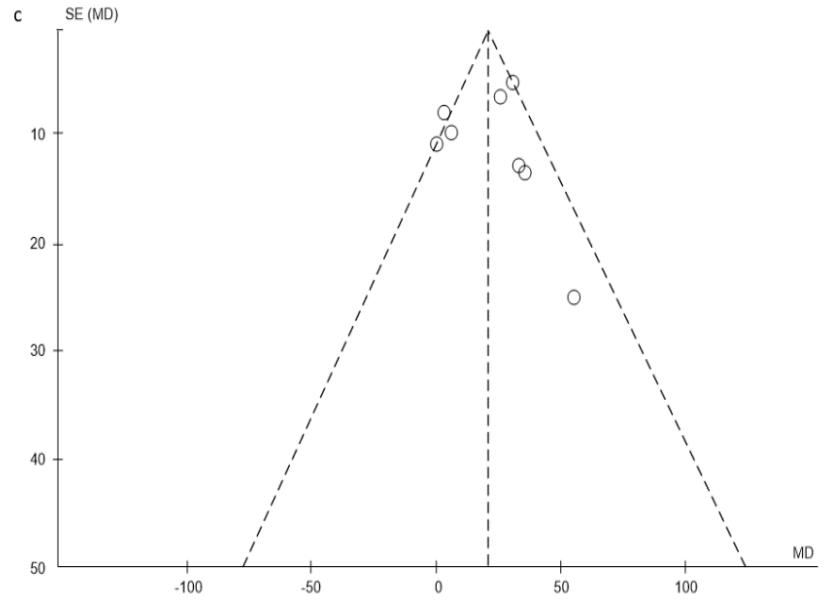
Limitations	**Description as stated in paper**	**Location in text** (page#/fig/table)
74. Strength		
75. Limitations		
76. Notes:		

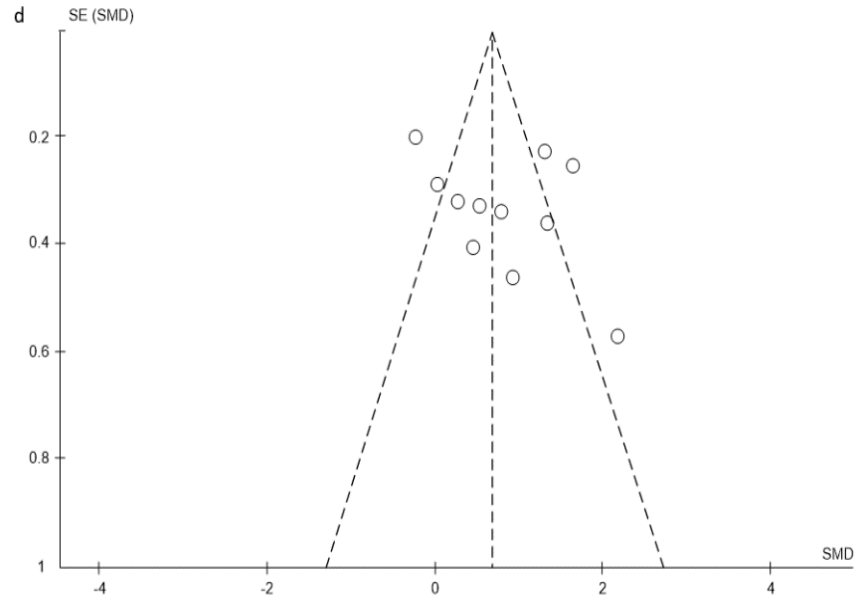
Conclusion	**Description as stated in paper**	**Location in text** (page#/fig/table)
77. Key conclusions of the study authors		
78. Notes:		

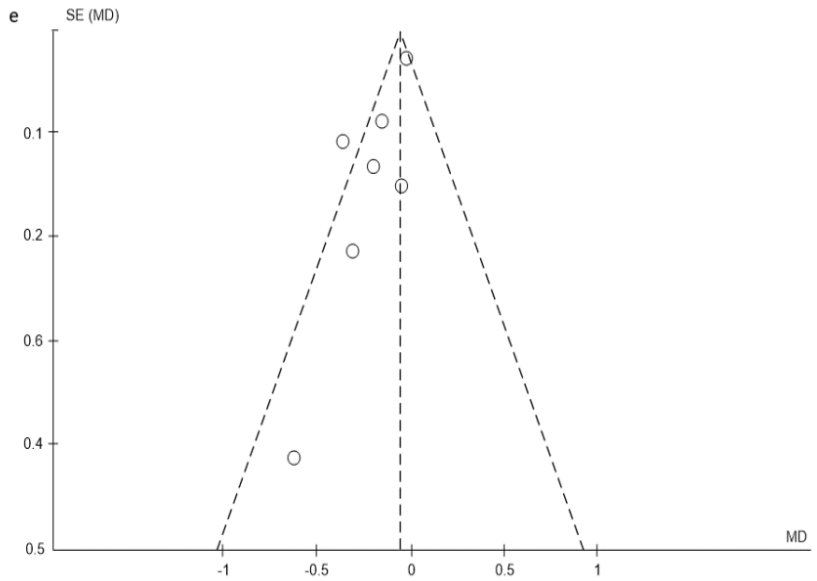
Appendix 3: Funnel plots







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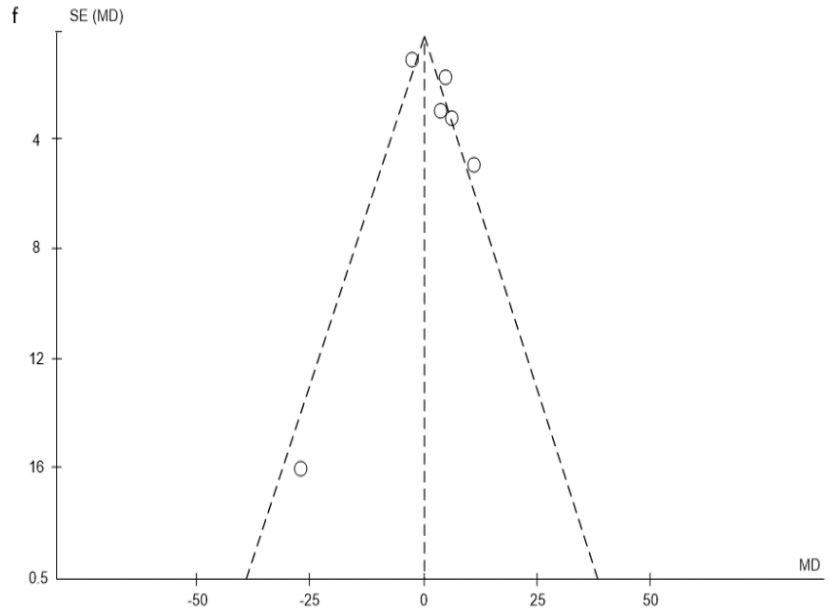
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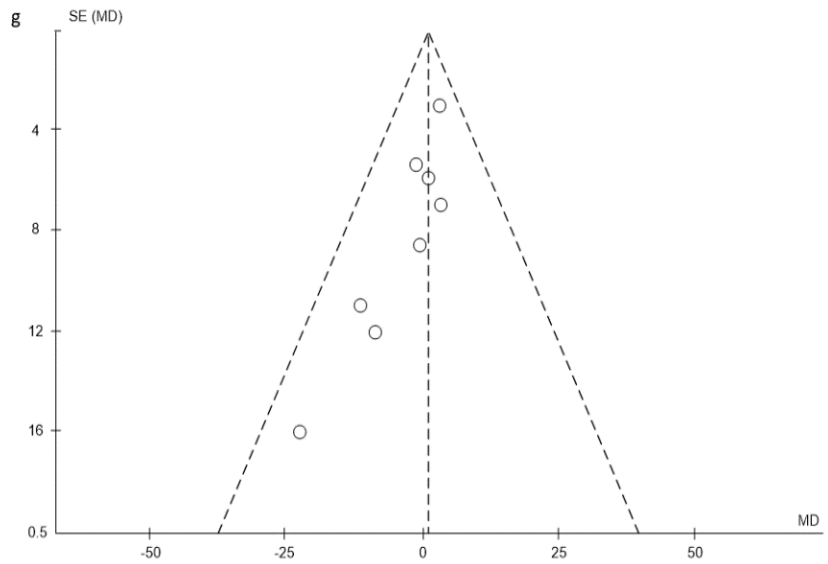
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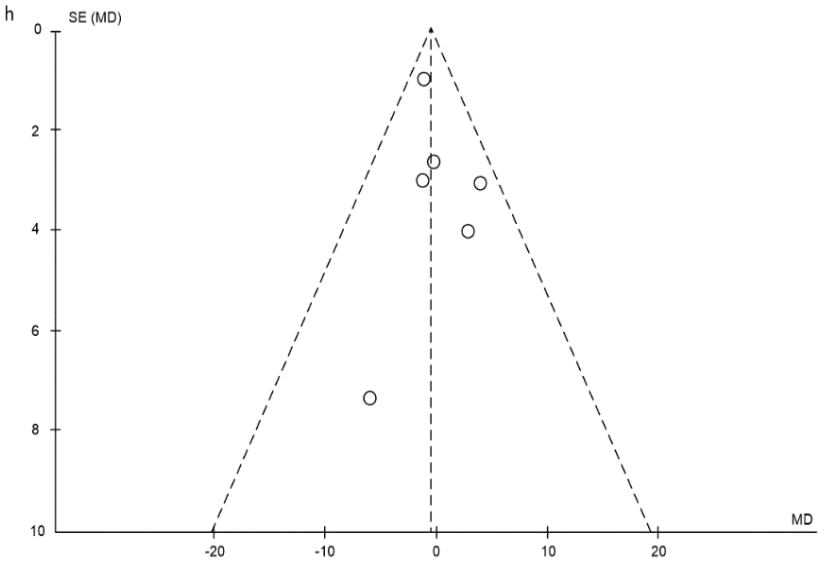
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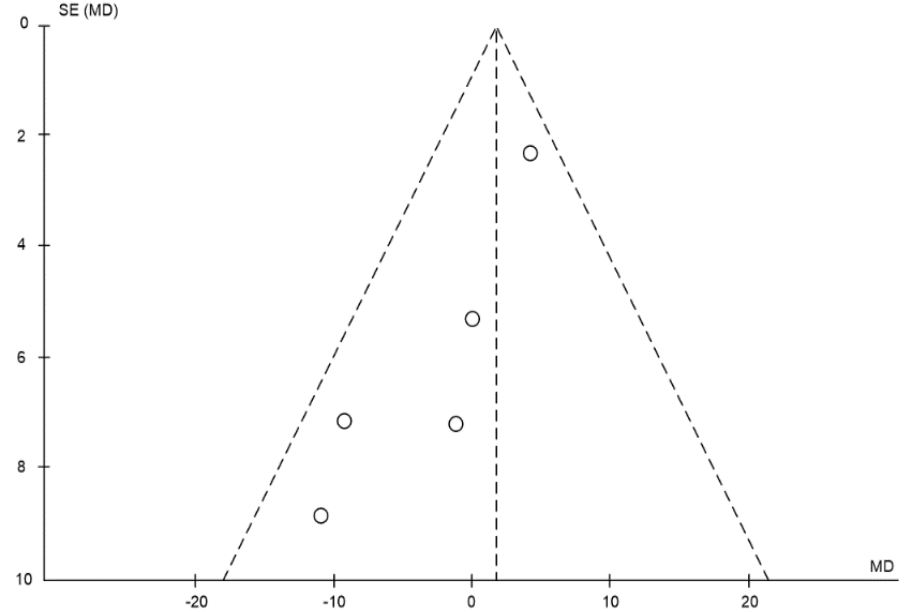
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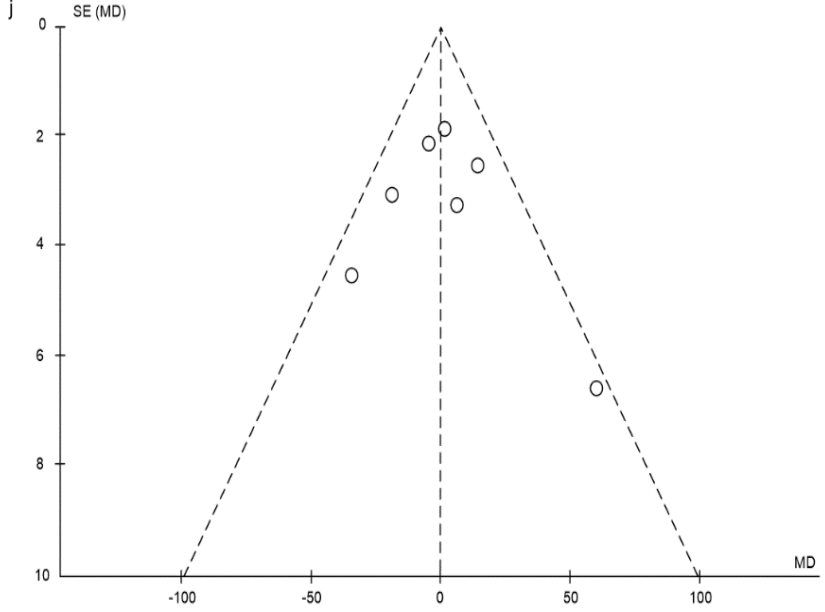
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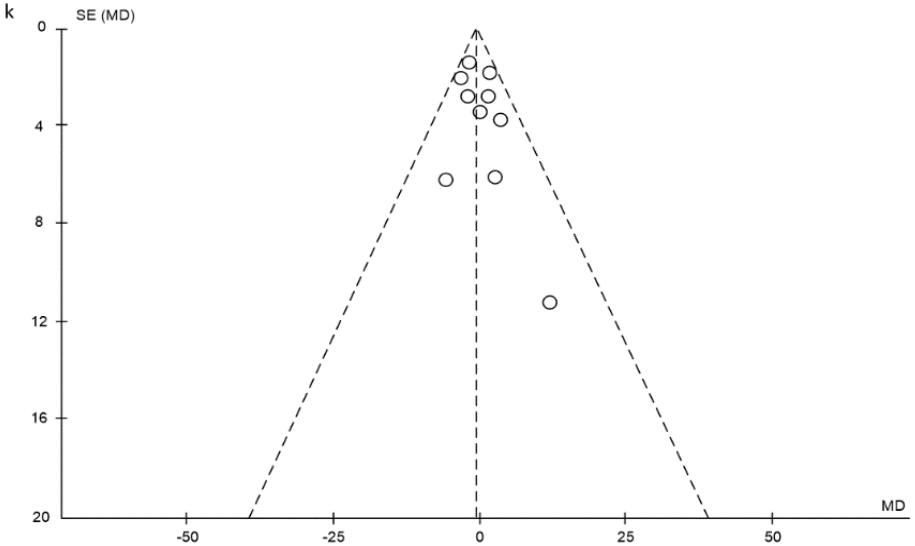
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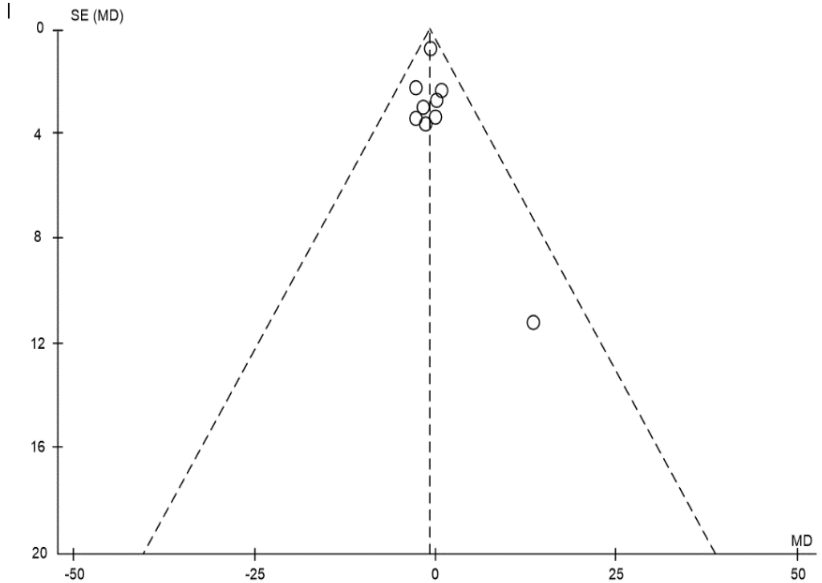
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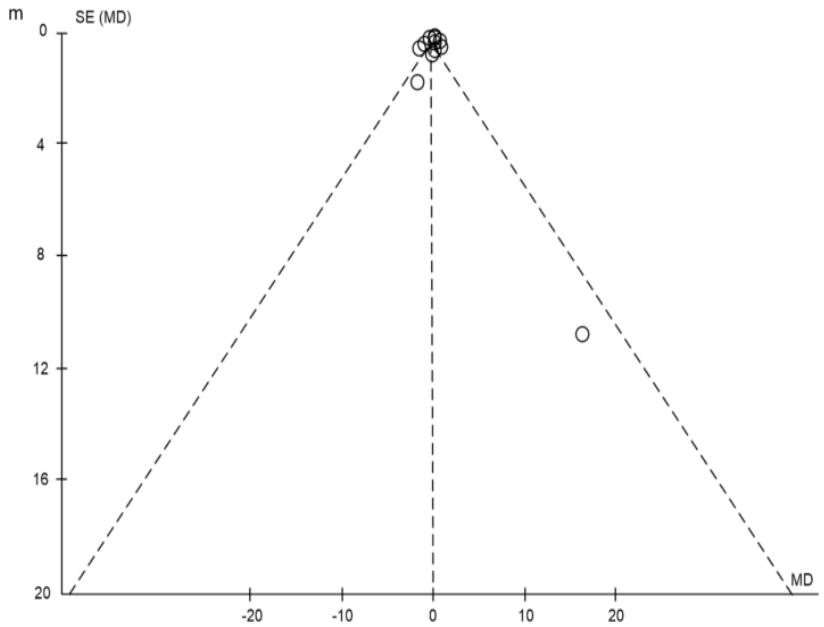
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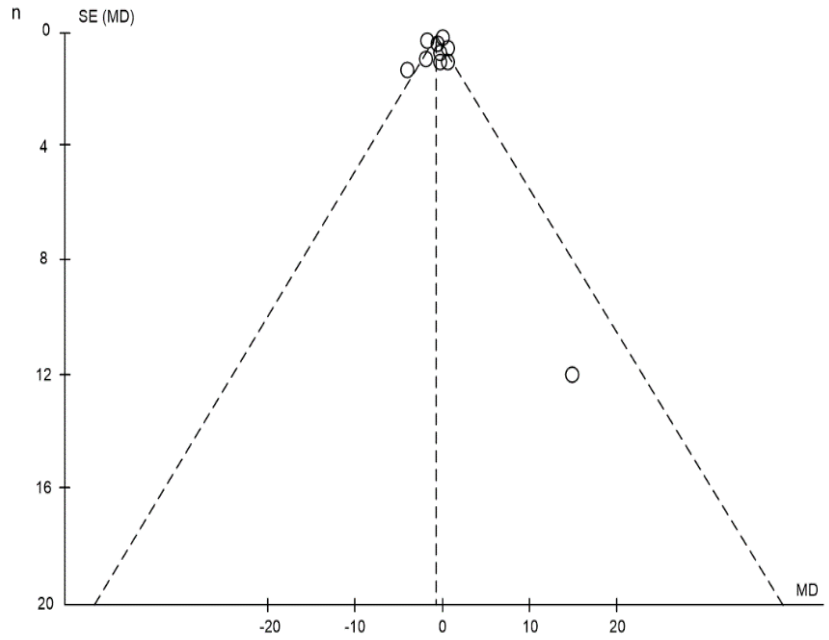
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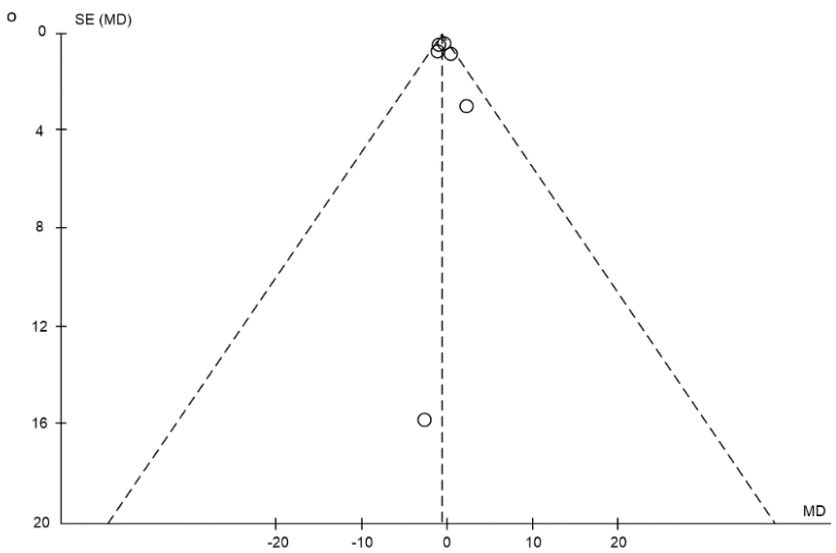
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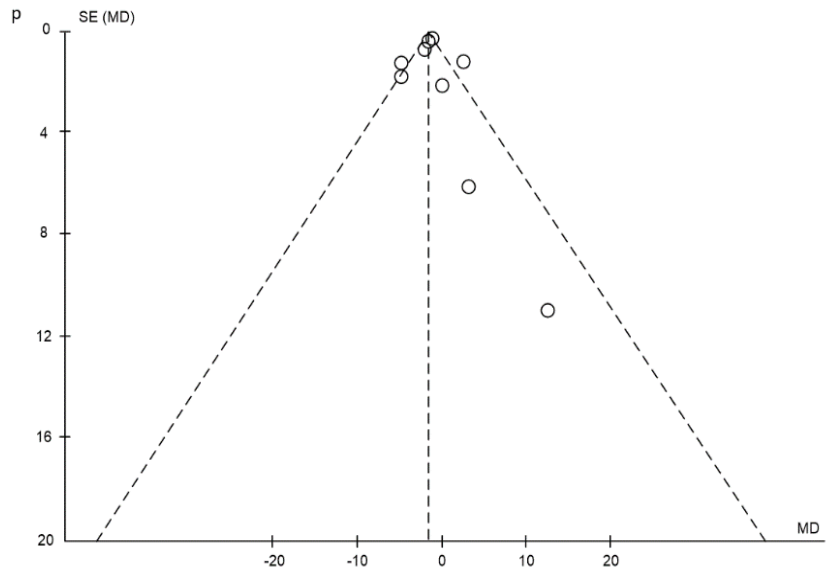
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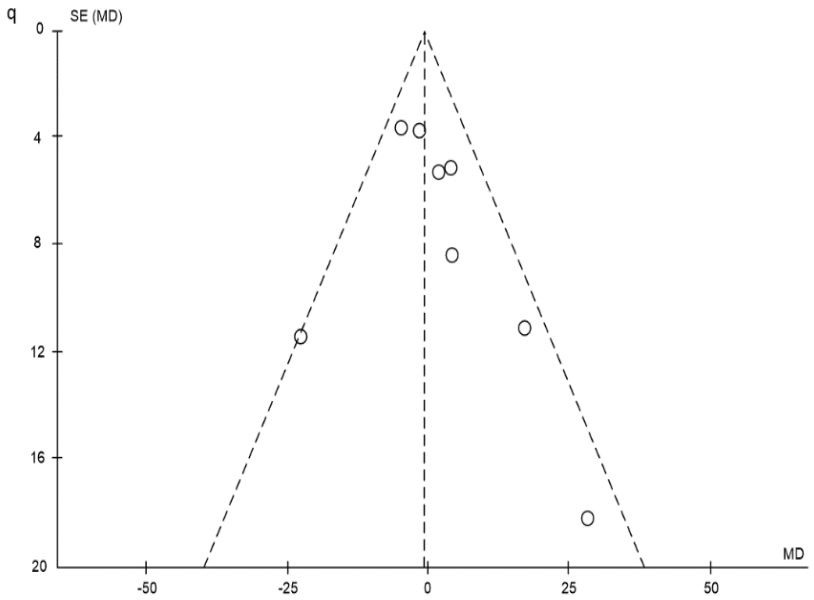

Funnel plots comparing interventions for (a) sedentary time, (b) standing time, (c) walking time, (d) steps*, (e) HbA1c, (f) fasting glucose, (g) total cholesterol, (h) HDL cholesterol, (i) LDL cholesterol, (j) triglycerides, (k) systolic blood pressure, (l) diastolic blood pressure, (m) body mass index, (n) body weight, (o) fat percentage, (p) waist circumference, (q) moderate to vigorous physical activity

*standardized mean difference