The effects of frequency, intensity, duration and volume of walking interventions on CVD risk factors: A systematic review and meta-regression analysis of randomized controlled trials among inactive healthy adults

Pekka Oja, Paul Kelly, Elaine Murtagh, Marie Murphy, Charlie Foster, Sylvia Titze

Corresponding author: Pekka Oja

UKK Institute, P.O.Box 30, 33501 Tampere, Finland
pekka.oja@uta.fi
phone: +358-503394593

Other authors:
Paul Kelly: Physical Activity for Health Research Centre, Institute of Sport, Physical Education and Health Sciences, University of Edinburgh, Edinburgh, UK
Elaine Murtagh: Department of Arts Education and Physical Education, Mary Immaculate College, Limerick, Ireland
Marie Murphy: Centre for Physical Activity and Health Research, Ulster University, Belfast, UK
Charlie Foster: Centre for Exercise, Nutrition & Health Sciences, Bristol University, Bristol, UK
Sylvia Titze: Institute of Sport Sciences, University of Graz, Graz, Austria

Key words: walking, cardiovascular disease risk factors, health, dose-response, meta-analysis

Word count: abstract 250, main text xxxx (without tables and references)

61 references, 4 tables, 3 supplementary tables, supplementary file, 1 figure
The effects of frequency, intensity, duration and volume of walking interventions on CVD risk factors: A systematic review and meta-regression analysis of randomized controlled trials among inactive healthy adults

Pekka Oja, Paul Kelly, Elaine Murtagh, Marie Murphy, Charlie Foster, Sylvia Titze

Abstract

Objective. Walking interventions in healthy populations show clinically relevant improvements for many cardiovascular disease (CVD) risk factors. We aimed to assess the changes in CVD risk factors and the dose-response relationship between frequency, intensity, duration and volume of walking based on randomized controlled trials (RCTs).

Design. A systematic review with meta-analysis and meta-regression.

Data sources. Four electronic databases searched from January 1971 to April 2017.

Eligibility criteria. Walking RCTs reporting one or more CVD risk factor outcomes; trials including at least one group with walking intervention and a no-walking control group; duration ≥8 weeks; participants ≥18 years old, inactive but healthy; risk factors assessed pre- and post-intervention; English language articles in peer-reviewed journals.

Results. Thirty-seven RCTs, involving 2001 participants (81% women), and assessing 13 CVD risk factors were identified. Pooled meta-analysis showed favorable effects (p<0.05) of walking intervention for seven CVD risk factors (body mass, BMI, body fat, systolic and diastolic blood pressure, and fasting glucose, and VO2 max). There were no significant effects (p>0.05) for waist circumference, waist-to-hip ratio, and four blood lipid variables.

Despite testing 91 possible dose-response relationships, linear meta-regression analysis adjusted for age indicated just 7 (or 7.7%) statistically significant findings.

Summary/conclusion. Walking interventions benefit a number of CVD risk factors. Despite multiple studies and tested metrics only a few dose-response relationships were identified and the possibility of chance findings cannot be ruled out. There is insufficient evidence to quantify the frequency, length, bout duration, intensity, and volume of the walking required to improve CVD risk factors.

word count: 250
INTRODUCTION

Non-communicable diseases (NCD) are a major burden worldwide. It has been estimated that elimination of physical inactivity would remove between 6% and 10% of the major NCDs of coronary heart disease (CHD), type 2 diabetes, and breast and colon cancers, and increase life expectancy. One key approach to increase population levels of physical activity is to promote safe, accessible, and environmentally friendly activity options for all citizens, including improved infrastructure for walking and cycling for transport and recreation.

Walking is the ideal physical activity intervention to improve health across the population. A recent systematic review of 32 randomized controlled trials by Murtagh et al. (reference) showed that walking increases aerobic capacity and reduces blood pressure, waist circumference, body weight, percent body fat and body mass index. Another systematic review (Hanson and Jones 2015) reported similar health benefits of recreational walking including reduced systolic and diastolic blood pressure, resting heart rate, body fat, body mass index and total cholesterol, and increased VO2max, physical functioning and the distance covered in a 6-min walk-test.

National physical activity recommendations are based on summative volumes of different intensities of physical activity over a week, with walking as the cornerstone of health promotion efforts. However, walking can vary considerably in terms of the frequency, intensity, daily/weekly duration, and total volume. Specific evidence on the dose-response relationships could increase health professionals' effectiveness in promoting physical activity, and specifically walking for health benefits.

Observational data indicate some dose response relationships at a population level. In a systematic review of epidemiological studies with all-cause mortality as the endpoint Hamer et al. (2008) found that walking pace was a stronger independent predictor than walking volume. Through meta-analysis Kelly et al. showed an increased reduction in the risk of all-cause mortality for higher walking volumes (in MET-hours per week). Also randomized controlled walking trials have found some dose-response relationships. Asikainen et al. (2002a) searched for the minimum dose of walking for health benefits and found that a weekly dose of 1000 to 1500 kcal of walking improved the aerobic power and body composition of previously sedentary non-obese post-menopausal women. Recently anson and Jones noted based on their systematic review of randomized controlled walking trials that there is insufficient evidence to suggest any conclusions about the dose-response between the volume and intensity of walking and the health outcomes.

CVD risk factor reduction via walking promotion must be based not only on evidence of effectiveness but also on being able to identify the effects of variations in different characteristics of walking, potentially offering more options for walking. Based on the updated data of Murtagh et al (reference) our systematic review aimed to (1) update the evidence for the effects of walking interventions on CVD risk factors and in particular to (2) study the dose-response relationships.
between the frequency, intensity, duration and volume of walking interventions and CVD risk factors in healthy inactive adults.

METHODS

Registration

This study is registered in PROSPERO as CRD42016039409.

Data search

Studies (1971-2012) included in an earlier systematic review, were supplemented by electronic searches (January 2012 – April 2017) of 4 databases: Cochrane Central Register for Controlled Trials, Medline, Web of Science and SPORTDiscus. The following search terms were used in both searches (1) walking, (2) exercise, (3) health, (4) cardiovascular risk. The full search strategy for the 2012-2017 search is enclosed as "Supplementary file". Reference lists from review and original articles were hand-searched for additional studies.

Eligibility criteria

Studies were selected based on the following inclusion/exclusion criteria: randomized controlled trials (RCTs) studying the effects of walking on one or more CVD risk factors; trials with at least one group completing walking as the only intervention; intervention duration at least 8 weeks; control group with no walking intervention; participants aged 18 years or older who were insufficiently active but otherwise healthy and capable of unaided walking (otherwise no other age limit); CVD risk factors assessed pre- and post-training (or change from pre- to post-intervention reported); English language articles published in peer-reviewed journals between January 1971 and April 2017.

Study selection

eligibility by two authors (PO, ST and PO, PK). Disagreements were resolved by jointly reassessing the studies against the eligibility criteria.

Data extraction

Two authors (PO, PK) extracted participant characteristics and outcome measures data independently and a third author (ST) checked the extracted data of all included studies. Disagreements were resolved by consensus. Dose attributes were defined as frequency, intensity, duration and total volume of walking, and the health outcomes for CVD risk factors as measures of cardio-metabolic fitness, adiposity and blood lipid profile. Intervention dose metrics were extracted by one author (PO) and cross-checked by a second author (ST). Missing information was sought from the authors of twelve studies 10-21.

Intervention dose metrics were: frequency (sessions per week), duration of the intervention (weeks), bout duration (minutes per session), intensity as METs and %VO2max, and volume as MET-minutes per week, and total MET-hours. The outcome measures were: aerobic fitness expressed as VO2max (ml*kg⁻¹*min⁻¹), body mass (kg), body fat (%), body mass index (weight in kilograms divided by height in meters²), waist circumference (cm), waist-to-hip-ratio, systolic and diastolic blood pressure (mmHg), total cholesterol (mmol*L⁻¹), HDL cholesterol (mmol*L⁻¹), LDL cholesterol (mmol*L⁻¹), triglycerides (mmol*L⁻¹), and fasting glucose(mmol*L⁻¹). Outcomes for insulin resistance and inflammation-related serum cytokines, blood flow in lower extremities, arterial stiffness, postural stability, bone mineral density, and biomarkers of endothelial function were not included in the meta-analyses because of insufficient number of comparisons (<10) (see ref 29).

Assessment of the risk of bias

Risk of bias of individual studies was assessed by the Cochrane Collaboration tool 29. Two authors (PO, EM) assessed studies independently for sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity. Divergent ratings were re-assessed independently by a third author (MM) to reach consensus.

Synthesis of results

The software “Comprehensive Meta-Analysis” was used for all statistical analyses 30. For each CVD risk factor outcome, standardized mean difference (SMD) (defined as the raw difference between the mean change in the intervention group and the mean change in the control group divided by pooled post standard deviation (SD)) was used as the summary measure. When these data were not reported, we used the reported findings as follows. For the studies by Butcher et al. 19,
Murphy et al. \(^{18}\), and Tully et al. \(^{15} 16\) we used mean change and its SD and the number of participants in each group to calculate SMD. For the study of Hamdorf et al. \(^{31}\) we used pre and post means and the number of participants in each group and F for the difference between changes. For body mass in the study by Hinkleman et al. \(^{32}\) the number of participants in each group and F for difference between the changes were used in the formula.

Eleven studies included more than one walking intervention group. The results for each group compared to the control were treated as independent studies. The number of participants in the control group was divided by the number of intervention groups \(^{29}\). The effect direction was set negative for studies where a decrease represented an improvement in the health risk factor compared to the control group, and the effect direction was set positive for HDL cholesterol and VO\(_{2}\)max as an increase represents an improvement in health risk. The following Q statistics were used to identify and quantify the heterogeneity in effect sizes for each CVD outcome: (1) the estimated standard deviation of the true effect size (Tau); (2) the ratio of true heterogeneity to total variation in observed effects (I\(^2\)), which can range from 0% to 100%; and (3) the p-value to test the null-hypothesis that all studies share a common effect size \(^{30}\). Publication bias was assessed by visual inspection of funnel plots. If a publication bias was assumed cumulative forest plots \(^{30}\) were used for confirmation.

Effect sizes were expressed in the original units of the outcome variables by multiplying SMD by a population representative standard deviation for the outcome \(^{29}\). Representative standard deviations were obtained from the MONICA Population Survey data \(^{33}\) for body mass, BMI, waist circumference, systolic and diastolic blood pressure and total and HDL cholesterol. For VO\(_{2}\)max the SD was taken from a Norwegian study of 3816 participants \(^{34}\), and for percent body fat from the FINN RISK 2007 study \(^{35}\).

All analyses were adjusted for age. Sex was not considered a confounder because only two studies were male only. Further adjustment for sex indicated that there was no difference in the effect sizes between subgroups with females only, males only, mixed and no information.

**Dose-response by walking characteristics**

We conducted random-effects univariate meta-regression analysis with adjustment for age using continuous walking intervention characteristics as the covariates to test linear as well as curvilinear relationships. The dependent variable was the SMD for each CVD-outcome. In the regression models the study’s weight was the inverse of the total variance for each CVD-outcome.

Meta regression results are reported as the linear β-coefficient with 95% CI and p-values. The curvilinear regressions between the MET-related doses and the outcomes were analysed by creating two variables (dose minus mean and dose minus mean squared) and testing if the interaction was significant. The Bonferroni correction (Field 2012) was applied to interpret the multiple comparison p-values.
RESULTS

Selection of studies

We searched four electronic databases from 2012 – April 2017 to update the data of the previous systematic review (Murtagh et al 2015). The search resulted in a total of 7862 records. The screening of the titles and abstracts yielded 37 papers for potential inclusion. These were supplemented by 28 papers from the previous review and one paper was identified by hand searching. The full-text versions of 70 papers were then screened. Thirty-two papers were excluded due to the following reasons: mixed training content (7), non- or group-randomized design (8), non-healthy participants (8), no no-walking control group (3), incomplete outcome data (4), and unclear intervention (2). Thirty-eight eligible studies were included in the analyses. This included 28 studies from the previous review and 10 new studies. Where studies reported results using the same participants in more than one article these were combined to represent one study in the meta-analysis. Study selection is depicted in Figure 1.
Study characteristics

Participant characteristics, study characteristics and walking intervention characteristics (session duration, frequency, and intensity as well as length of the intervention) for all 37 included studies are shown in supplementary table 1. In brief, 22 studies 18 20 25-38 31 32 36-40 43 44 48 52-56 58 included only women, three studies 13 14 17 only men, and 14 studies 12 15 16 19 21 41 42 45-47 49-51 57 both sexes as participants. The mean age of participants ranged from 30 to 72 years. The studies included 55 walking intervention groups. Thirty studies prescribed ordinary walking, four studies treadmill walking, two studies utilized Nordic walking, and one “trekking” intervention.

Exposure metrics

Intervention dose characteristics varied considerably (Supplementary table 1 and 2): total duration 8 to 52 weeks, session duration 10 to 90 minutes, number of sessions per week 1 to 15.4, weekly duration 10 to 325 minutes, intensity 1.7 to 5.8 METs, total weekly volume 27 to 1300 MET-minutes per week, total walking duration 130 to 10192 minutes, and total intervention volume 5.85 to 576 MET-hours.

Twenty studies reported walking intensity as either percentage of maximum heart rate (range: 50-86 % HRmax) 13 14 17 18 36 37 44 50-52 55 57, percentage of VO2max (range 45-65%) 25 32 38 39 47 54 or percentage heart rate reserve (range 54-85 %) 42 53 56. Four studies reported that walking was “self-paced” 19 41 48 49 and seven studies noted that walking intensity was at a “brisk pace” 12 15 16 21 27 43 45. Additionally two studies measured the intensity as walking speed 46 58, and one study as HR 31, MET 26, RPE 20, and ventilator threshold 28, each.

In ten studies 19 20 25 31 34-38 52-55 56 the intensity in METs could not be derived from the information provided, therefore intensity data are missing for these studies.

Outcome data

Our pooled data included sufficient number (≥10) of comparisons in the meta-analyses for body mass (40), BMI (28), body fat (28), waist circumference (18), waist-to-hip ratio (13), systolic blood pressure (34), diastolic blood pressure (32), total cholesterol (37), HDL cholesterol (35), LDL cholesterol (34), triglycerides (34), fasting glucose (16), and VO2max (31). Overall, both the meta-analyses and the meta-regression analyses included 13 or more comparisons.
Risk of bias

Results of the assessment of the risk of bias according to the Cochrane Collaboration assessment tool are shown in the Supplementary table 3. Among the 37 studies only two studies were assessed as being at low risk of bias across all domains \textsuperscript{12,15}.

Meta-analysis

Pooled meta-analysis results (SMD, 95% confidence intervals, p-value) are shown in Table 1. Significant favorable effects (p<0.05) were seen for body mass, BMI, body fat, systolic and diastolic blood pressure, fasting glucose, and VO$_2$max. Estimated effect sizes were: body mass -1.6 kg, BMI -0.60 kg*(m$^2$)$^{-1}$, systolic blood pressure -4.05 mmHg, diastolic blood pressure -1.76 mmHg, and VO$_2$max 4.86 ml*kg$^{-1}$*min$^{-1}$.

Heterogeneity, as indicated by $I^2$, was 0% for all outcomes except for systolic (17%) and diastolic (6%) blood pressure, total cholesterol (16%), and fasting glucose (23%).
Table 1. Meta-analysis on the effects of walking interventions on biomedical indices of health

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Effect size</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SDM</td>
<td>95% CI</td>
</tr>
<tr>
<td>Body mass</td>
<td>42</td>
<td>-0.134</td>
<td>-0.233 to -0.034</td>
</tr>
<tr>
<td>BMI</td>
<td>29</td>
<td>-0.142</td>
<td>-0.257 to -0.027</td>
</tr>
<tr>
<td>Body fat</td>
<td>29</td>
<td>-0.216</td>
<td>-0.336 to -0.096</td>
</tr>
<tr>
<td>WC</td>
<td>18</td>
<td>-0.104</td>
<td>-0.265 to 0.058</td>
</tr>
<tr>
<td>WHR</td>
<td>13</td>
<td>-0.165</td>
<td>-0.340 to 0.009</td>
</tr>
<tr>
<td>SBP</td>
<td>35</td>
<td>-0.213</td>
<td>-0.344 to -0.082</td>
</tr>
<tr>
<td>DBP</td>
<td>33</td>
<td>-0.166</td>
<td>-0.285 to -0.047</td>
</tr>
<tr>
<td>TC</td>
<td>38</td>
<td>-0.123</td>
<td>-0.242 to 0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>36</td>
<td>0.035</td>
<td>-0.080 to 0.150</td>
</tr>
<tr>
<td>LDL-C</td>
<td>35</td>
<td>0.030</td>
<td>-0.089 to 0.148</td>
</tr>
<tr>
<td>TG</td>
<td>35</td>
<td>-0.084</td>
<td>-0.201 to 0.033</td>
</tr>
<tr>
<td>FG</td>
<td>17</td>
<td>-0.211</td>
<td>-0.401 to -0.022</td>
</tr>
<tr>
<td>VO₂max</td>
<td>31</td>
<td>0.528</td>
<td>0.391 to 0.664</td>
</tr>
</tbody>
</table>

All estimates are from the meta-analysis using the random-effects model comparing an intervention group (walking) with a control group (no intervention)

n = number of comparisons
body mass (kg), BMI = body mass index (kg/m²), SBP = systolic blood pressure (mmol*L⁻¹), DBP = diastolic blood pressure (mmol*L⁻¹), TC = total cholesterol (mmol*L⁻¹), HDL-C = high-density lipoprotein cholesterol (mmol*L⁻¹), LDL-C = low-density lipoprotein cholesterol (mmol*L⁻¹), TG = triglycerides (mmol*L⁻¹), FG = fasting glucose (mmol*L⁻¹), VO₂max = maximal oxygen uptake

SDM = standardized difference in means, CI = confidence interval, p-value for SDM (test of the null hypothesis that the effect is zero), T = Tau (estimate of the standard deviation in true effect sizes), I² = heterogeneity (ratio of true heterogeneity to total observed variation), p-value (test of the null hypothesis that all studies in the analysis share a common effect size)

Funnel plots for the outcomes showed symmetric patterns suggesting non-significant publication bias except those for body fat and LDL (see supplementary file 1). Cumulative forest plots of these outcomes (see supplementary file 1) showed symmetric pattern of the effect sizes even with the
Meta regression and dose-response by walking dose characteristics

The linear meta-regression analyses for (i) walking frequency (number of session per week), (ii) intervention duration (weeks) and (iii) session duration (minutes) showed three significant (p≤0.05) positive associations from 39 possible dose-response relationships [intervention duration with LDL-cholesterol (p=0.001) and VO₂max (p=0.018), and session duration with triglycerides (p=0.029)], and one inverse association [session duration with systolic blood pressure (p=0.050)] (table 2).
Table 2. Meta regression analysis: frequency, intervention duration, session duration (adjusted model$^a$)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency, sessions per week</th>
<th>Duration of intervention, weeks</th>
<th>Duration of session, minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>β</td>
<td>95% Cl</td>
</tr>
<tr>
<td>Body mass</td>
<td>42</td>
<td>-0.0020</td>
<td>-0.0390 to 0.0429</td>
</tr>
<tr>
<td>BMI</td>
<td>29</td>
<td>-0.0068</td>
<td>-0.0552 to 0.0417</td>
</tr>
<tr>
<td>Body fat</td>
<td>29</td>
<td>0.0136</td>
<td>-0.0542 to 0.0815</td>
</tr>
<tr>
<td>WC</td>
<td>18</td>
<td>0.0041</td>
<td>-0.0523 to 0.0604</td>
</tr>
<tr>
<td>WHR</td>
<td>14</td>
<td>0.0046</td>
<td>-0.1122 to 0.1215</td>
</tr>
<tr>
<td>SBP</td>
<td>35</td>
<td>0.0418</td>
<td>-0.0058 to 0.0885</td>
</tr>
<tr>
<td>DPB</td>
<td>33</td>
<td>-0.0247</td>
<td>-0.0743 to 0.0249</td>
</tr>
<tr>
<td>TC</td>
<td>38</td>
<td>0.0393</td>
<td>-0.0163 to 0.0950</td>
</tr>
<tr>
<td>HDL-C</td>
<td>36</td>
<td>0.0035</td>
<td>-0.0492 to 0.0562</td>
</tr>
<tr>
<td>LDL-C</td>
<td>35</td>
<td>0.0367</td>
<td>-0.0172 to 0.0905</td>
</tr>
<tr>
<td>TG</td>
<td>33</td>
<td>-0.0004</td>
<td>-0.0534 to 0.0526</td>
</tr>
<tr>
<td>FG</td>
<td>17</td>
<td>-0.0420</td>
<td>-0.1372 to 0.0533</td>
</tr>
<tr>
<td>VO$_{2max}$</td>
<td>31</td>
<td>-0.0125</td>
<td>-0.0639 to 0.0389</td>
</tr>
</tbody>
</table>

# adjusted for age

n = number of comparisons

β = linear regression coefficient, CI = confidence interval,

Body mass (kg), BMI = body mass index (kg*(m$^2$)$^{-1}$), body fat (%), WC = waist circumferences (cm), WHR = waist to hip ratio, SBP = systolic blood pressure (mm Hg), DBP = diastolic blood pressure (mm Hg), TC = total cholesterol (mmol*L$^{-1}$), HDL-C = high-density lipoprotein cholesterol (mmol*L$^{-1}$), LDL-C = low-density lipoprotein cholesterol (mmol*L$^{-1}$), TG = triglycerides (mmol*L$^{-1}$), FG = fasting glucose (mmol*L$^{-1}$), VO$_{2max}$ = maximal oxygen uptake (ml*kg$^{-1}$*min$^{-1}$)
The linear meta-regression analysis between the three MET related metrics (METs, MET-minutes per week, total MET-hours) and the outcomes resulted in three positive associations from a possible 39: METs with VO₂max (p=0.049), MET-min per week with triglycerides (p=0.009), and total MET-hours with LDL-cholesterol (p=0.007) (Table 3). We found one positive relationships to be significantly curvilinear after adjustment for multiple testing: intensity in METs with LDL-cholesterol (results not shown).

Respective linear analysis with the relative intensity dose (%VO₂max) yielded one inverse association: %VO₂max with diastolic blood pressure (p=0.020) (Table 4).
Table 3. Meta regression analysis: MET-related doses (adjusted model#)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>METs β</th>
<th>95% CI</th>
<th>p</th>
<th>MET-minutes per week β</th>
<th>95% CI</th>
<th>p</th>
<th>MET-hours total β</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td>34</td>
<td>-0.0613</td>
<td>-0.1979</td>
<td>0.378</td>
<td>-0.0002</td>
<td>-0.0005</td>
<td>0.337</td>
<td>-0.0002</td>
<td>-0.0008</td>
<td>0.640</td>
</tr>
<tr>
<td>BMI</td>
<td>24</td>
<td>-0.0265</td>
<td>-0.2147</td>
<td>0.782</td>
<td>-0.0000</td>
<td>-0.0004</td>
<td>0.937</td>
<td>-0.0000</td>
<td>-0.0007</td>
<td>0.961</td>
</tr>
<tr>
<td>Body fat</td>
<td>23</td>
<td>-0.1309</td>
<td>-0.2927</td>
<td>0.113</td>
<td>-0.0003</td>
<td>-0.0007</td>
<td>0.163</td>
<td>-0.0002</td>
<td>-0.0009</td>
<td>0.518</td>
</tr>
<tr>
<td>WC</td>
<td>14</td>
<td>-0.1696</td>
<td>-0.4420</td>
<td>0.222</td>
<td>-0.0003</td>
<td>-0.0011</td>
<td>0.499</td>
<td>-0.0004</td>
<td>-0.0013</td>
<td>0.572</td>
</tr>
<tr>
<td>WHR</td>
<td>13</td>
<td>-0.0231</td>
<td>-0.3677</td>
<td>0.896</td>
<td>0.0001</td>
<td>-0.0008</td>
<td>0.763</td>
<td>0.0002</td>
<td>-0.0007</td>
<td>0.678</td>
</tr>
<tr>
<td>SBP</td>
<td>28</td>
<td>-0.0254</td>
<td>-0.2027</td>
<td>0.779</td>
<td>0.0003</td>
<td>-0.0001</td>
<td>0.154</td>
<td>0.0006</td>
<td>-0.0005</td>
<td>0.270</td>
</tr>
<tr>
<td>DBP</td>
<td>26</td>
<td>-0.1528</td>
<td>-0.3185</td>
<td>0.071</td>
<td>-0.0001</td>
<td>-0.0006</td>
<td>0.544</td>
<td>-0.0000</td>
<td>-0.0010</td>
<td>0.988</td>
</tr>
<tr>
<td>TC</td>
<td>33</td>
<td>0.1390</td>
<td>-0.0432</td>
<td>0.135</td>
<td>0.0003</td>
<td>-0.0001</td>
<td>0.148</td>
<td>0.0006</td>
<td>-0.0002</td>
<td>0.133</td>
</tr>
<tr>
<td>HDL-C</td>
<td>32</td>
<td>0.0391</td>
<td>-0.1233</td>
<td>0.637</td>
<td>0.0001</td>
<td>-0.0003</td>
<td>0.722</td>
<td>0.0001</td>
<td>-0.0006</td>
<td>0.737</td>
</tr>
<tr>
<td>LDL-C</td>
<td>32</td>
<td>0.1124</td>
<td>-0.0503</td>
<td>0.176</td>
<td>0.0002</td>
<td>-0.0002</td>
<td>0.292</td>
<td>0.0010</td>
<td>0.0003</td>
<td>0.0017</td>
</tr>
<tr>
<td>TG</td>
<td>23</td>
<td>0.1251</td>
<td>-0.0384</td>
<td>0.134</td>
<td>0.0005</td>
<td>0.0001</td>
<td>0.009</td>
<td>0.0008</td>
<td>-0.0001</td>
<td>0.086</td>
</tr>
<tr>
<td>FG</td>
<td>14</td>
<td>-0.1564</td>
<td>-0.4049</td>
<td>0.217</td>
<td>-0.0005</td>
<td>-0.0011</td>
<td>0.064</td>
<td>-0.0010</td>
<td>-0.0025</td>
<td>0.185</td>
</tr>
<tr>
<td>VO2max</td>
<td>29</td>
<td>0.1612</td>
<td>0.0006</td>
<td>0.3218</td>
<td>0.049</td>
<td>0.0000</td>
<td>0.115</td>
<td>0.0009</td>
<td>-0.0002</td>
<td>0.106</td>
</tr>
</tbody>
</table>

# adjusted for age

n = number of comparisons

β = linear regression coefficient, CI = confidence interval,

Body mass (kg), BMI = body mass index (kg/m²), body fat (%), WC = waist circumferences (cm), WHR = waist to hip ratio, SBP = systolic blood pressure (mm Hg), DBP = diastolic blood pressure (mm Hg), TC = total cholesterol (mmol*L⁻¹), HDL = high-density lipoprotein cholesterol (mmol*L⁻¹), LDL = low-density lipoprotein cholesterol (mmol*L⁻¹), TG = triglycerides (mmol*L⁻¹), FG = fasting glucose (mmol*L⁻¹), VO2max = maximal oxygen uptake (ml*kg⁻¹*min⁻¹)
Table 4. Meta regression analysis: %VO$_2$ max dose (adjusted model*)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>%VO$_2$ max dose</th>
<th>ß</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td>23</td>
<td></td>
<td>-0.0051</td>
<td>-0.0228 to 0.0126</td>
<td>0.574</td>
</tr>
<tr>
<td>BMI</td>
<td>14</td>
<td></td>
<td>-0.0073</td>
<td>-0.0362 to 0.0216</td>
<td>0.620</td>
</tr>
<tr>
<td>Body fat</td>
<td>14</td>
<td></td>
<td>-0.0080</td>
<td>0.0318 to 0.0157</td>
<td>0.506</td>
</tr>
<tr>
<td>WC</td>
<td>8</td>
<td></td>
<td>0.0180</td>
<td>-0.0338 to 0.0698</td>
<td>0.496</td>
</tr>
<tr>
<td>WHR</td>
<td>5</td>
<td></td>
<td>0.0316</td>
<td>-0.0357 to 0.0989</td>
<td>0.357</td>
</tr>
<tr>
<td>SBP</td>
<td>19</td>
<td></td>
<td>-0.0197</td>
<td>-0.0409 to 0.0015</td>
<td>0.068</td>
</tr>
<tr>
<td>DBP</td>
<td>17</td>
<td></td>
<td>-0.0235</td>
<td>-0.0433 to -0.0037</td>
<td>0.020</td>
</tr>
<tr>
<td>TC</td>
<td>19</td>
<td></td>
<td>0.0032</td>
<td>-0.0193 to 0.0257</td>
<td>0.781</td>
</tr>
<tr>
<td>HDL-C</td>
<td>18</td>
<td></td>
<td>-0.0027</td>
<td>-0.0252 to 0.0197</td>
<td>0.812</td>
</tr>
<tr>
<td>LDL-C</td>
<td>19</td>
<td></td>
<td>0.0017</td>
<td>-0.0223 to 0.0256</td>
<td>0.892</td>
</tr>
<tr>
<td>TG</td>
<td>18</td>
<td></td>
<td>0.0068</td>
<td>-0.0158 to 0.0294</td>
<td>0.555</td>
</tr>
<tr>
<td>FG</td>
<td>8</td>
<td></td>
<td>-0.0252</td>
<td>-0.0570 to 0.0066</td>
<td>0.120</td>
</tr>
<tr>
<td>VO$_2$max</td>
<td>24</td>
<td></td>
<td>0.0161</td>
<td>-0.0019 to 0.0342</td>
<td>0.080</td>
</tr>
</tbody>
</table>

* adjusted for age

n = number of comparisons

ß = linear regression coefficient, CI = confidence interval,

Body mass (kg), BMI = body mass index, body fat (%), WC = waist circumferences (cm), WHR = waist to hip ratio, SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), TC = total cholesterol (mmol*L$^{-1}$), HDL = high-density lipoprotein cholesterol (mmol*L$^{-1}$), LDL = low-density lipoprotein cholesterol (mmol*L$^{-1}$), TG = Triglycerides (mmol*L$^{-1}$), FG = fasting glucose (mmol*L$^{-1}$), VO$_2$max = maximal oxygen uptake (ml*kg$^{-1}$*min$^{-1}$)
DISCUSSION

Despite multiple studies and tested metrics only a few significant dose-response relationships between the walking doses and the CVD outcomes were identified and the possibility of chance findings cannot be ruled out. This review suggests that there is insufficient evidence to quantify the frequency, length, bout duration, intensity, and volume of the walking required to improve CVD risk profile.

Our meta-analysis showed significant positive impact of walking on seven CVD risk factors; body mass, BMI, body fat, systolic and diastolic blood pressure, fasting glucose, and VO\textsubscript{2}max. These findings are consistent with those of Murtagh et al. \textsuperscript{7} except that of waist circumference, for which they found a statistically significant effect but we did not, and the new finding of decreased fasting glucose in the present review.

Murtagh et al. (2015) evaluated the clinical significance of their findings and concluded that the found increase in VO\textsubscript{2}max would account for 15% reduction in mortality, the decreased systolic and diastolic blood pressure for ten and seven % reduction in mortality, respectively, and the decreased in BMI for ?? reduction in ???. As the found impacts in the current analyses were of greater magnitude than reported by Murtagh et al\textsuperscript{7}(2015), and there was the additional decrease of fasting glucose, the found changes in the CVD risk factors can be considered clinically substantial.

There was no indication of publication bias in the cumulative Funnel Plots but the quality of studies was variable. Due to incomplete reporting the risk of bias in sequence generation, allocation concealment, and blinding could not be assessed for the majority (76 to 84 %) of studies. In contrast low risk of bias for outcome analysis and reporting, and for other potential sources of bias was assessed for the majority (65 to 95 %) of the included studies. These observations highlight the need for careful execution and full reporting of future walking trials according to the current quality criteria to ensure the validity of the findings.

Adherence to the exercise protocol may have an impact on the reported outcome results. Actual adherence is likely to be smaller than intended, especially in long lasting interventions, and the difference may lead to overestimation of the dose needed for changes. In our data of 37 studies 22 studies reported adherence rate and 15 did not. The reported adherence rates varied between 67\% and 100\% with 17 studies reporting over 80\% adherence. While it is possible that the non-reporting studies had lower adherence the high rates in the majority of the studies suggest that the possible overestimation of the dose may not substantial. We performed post-hoc sub-group and mixed-effect analyses comparing studies with adherence rates over and below 90\% for all study outcomes. The results indicated no statistically significant differences in any of the outcomes.
Sufficient sample sizes are needed for reliable results. We examined our data from this perspective by conducting post-hoc sub-group and mixed-effects analyses comparing study group sizes over and below 20 (per study arm) for all outcome variables. The sub-group analysis indicated statistically significant differences between the two sample sizes for fasting glucose, systolic blood pressure and LDL-Cholesterol. Subsequent mixed-effects analyses showed no differences between the two groups for LDL-Cholesterol, and statistically significant differences for fasting glucose and systolic blood pressure. Overall the sample size affected only two of the 13 outcomes, which may also be due to the multiple comparisons.

In our study we have attempted to explore the dose-response between walking characteristics and CVD risk factors using meta-regression analysis. One assumption for the use of meta-regression is sufficient heterogeneity in the outcome effects, i.e. some of the variance across the included studies is real. We found some (4-23%) heterogeneity as measured by the statistic $I^2$ in four and no heterogeneity in nine outcomes. This low level of heterogeneity may explain the fact that we found only a few statistically significant dose-response associations.

Moreover, as the meta-regression analyses included multiple comparisons between the dose and the outcomes (each 13 comparisons) there is a risk of overestimating the statistical significance. A more conservative p-value for our multiple testing would be between $p<0.004$ to 0.002 according to Bonferroni. All but one (weeks of intervention with LDL) of the found p-values for the regressions were greater than this. We therefore did not find any evidence that the response of the CVD risk factors is associated with the walking dose characteristics used in this study.

The dose of walking in METs represents the absolute intensity, which confers different levels of relative physiological load across individuals with different capacity. Thus a dose of 5 METs may mean 50% of the capacity of a person with good cardiorespiratory fitness and 80% of the capacity of a person with low fitness. This means that the METs intensity is only an estimate of the absolute but not the relative physiological stimulus. Physiological load relative to maximum is likely to be the key stimulus for many of the alterations in health outcomes being considered. We found one significant positive response ($V_O^{\text{max}}$, $p=0.049$) for the METs dose. Maximal oxygen uptake is the gold standard for aerobic fitness. The percent level of $V_O^{\text{max}}$ of training represents a good measure of the relative physiological training stimulus. We had 20 studies with %$V_O^{\text{max}}$ intensity (reported or converted). In all these studies the training intensity was determined by individual heart rate monitoring (19 studies) or walking speed (1 study) derived from laboratory assessment. Thus the relative intensity dose was physiologically controlled at the group level. The regression analysis (Table 4) resulted in a significant ($p=0.020$) inverse association between the %$V_O^{\max}$ dose and diastolic blood pressure. As this p-value does not reach the conservative significance p-level of 0.004, the response of the CVD risk factors is likely to be independent also of the relative intensity dose.
In order to put our findings in the context of current physical activity recommendations we can use MET-minutes per week dose, which combines the frequency, bout duration and intensity, as the bases. WHO recommends 150 minutes of moderate-intensity aerobic physical activity per week for health benefits. Applying 3 METs as the lower limit of moderate-intensity activity, the weekly minimum recommended dose is 450 MET-minutes. Our results indicate that walking within the range of approximately 100 to 1300 MET-min per week can benefit CVD risk factors. Thus according to our results even less than the recommended amount of weekly walking (e.g. 450 MET-minutes) may be health-promoting for inactive middle-aged and older people. This is in line with a recent evidence summary, which suggests that approximately 200 MET-min per week is sufficient for health benefits.

Strengths and weaknesses

Our systematic review including 38 studies published between 1971 and 2017 identified a large number of randomized controlled walking trials conducted according to a standard set of quantitative criteria. The data set consisted of 28 studies from a previous review (Murtagh et al. 2015) and ten new studies. This data set included 2001 participants and 55 comparisons between intervention and control groups and a commonly accepted set of the most important CVD risk factors, allowing for rigorous meta-analysis of the main effects of walking, and yielding robust effect sizes in several outcomes. Extraction of clearly defined walking dose characteristics enabled unique meta-regression analysis for the dose-response between walking attributes and health outcomes. In addition, both the linear and the curvilinear relationships were tested. To our knowledge this is the first attempt to explore the dose-response patterns with meta-regression analysis of data from randomized controlled walking trials.

The study is not without weaknesses. We were not able to perform an individual participant data analysis using the primary data for each study but relied on aggregated data across studies resulting in increasing intra and inter study heterogeneity, and potentially regression to the mean. The low level of heterogeneity of the changes in the outcomes across the studies may have limited the power to detect dose-response relationships. The used dose metrics had to be converted from a variety of respective measures leading in several cases to estimated levels of the dose. The quality of the included studies was variable. In particular the sequence generation, allocation concealment and blinding in the trials was less than adequate in many studies. This may attenuate the precision of the effect sizes, although the direction of the observed effects was consistent. Another weakness concerns the generalizability of the findings. Participants in the studies were mostly healthy but inactive women so direct applicability to men and individuals with pre-existing chronic disease may be questioned. However, based on recent evidence on the effects of PA on health and on the resulting PA recommendations there appears very few differences between women and men. Moreover, as 35 of the 38 studies came from Europe, United states, Canada and Australia the findings may not be applicable to lower and middle income countries.
SUMMARY AND CONCLUSIONS

Meta-analysis of data from 37 randomized controlled walking trials revealed significant improvements in seven CVD risk factors: decreases in body mass, BMI, body fat, systolic and diastolic blood pressure, fasting glucose, and an increase in VO2max. The effect sizes indicate clinically important improvements in CVD risk profile. There were non-significant effects on six CVD risk factors: waist-hip ratio and waist circumference, and in total-, HDL-, and LDL-cholesterol and triglycerides.

Our meta-regression analyses did not find associations between the observed effects on the CVD risk factors and the frequency, length, bout duration, intensity and volume of the walking training. These results suggest that any walking exposure within the dose range of the included studies is likely to be beneficial for cardiovascular health. Current practice, population health promotion and exercise referral should reflect this. As these controlled intervention studies were designed and implemented for healthy but inactive middle-aged and older women and men, the findings demonstrate the health potential of everyday walking for large segments of populations. Walking still remains firmly a “best buy” for public health.

REFERENCES


Figure 1

Records from electronic search 2012-2017 7862

Irrelevant records excluded 7825

Potentially included papers 37

Papers from Murtagh 2015 32

Hand-search papers 1

Full papers screened 70

Papers excluded 32
- mixed training content 7
- non- or group-randomized design 8
- participants not healthy 8
- no no-walking control group 3
- incomplete outcome data 4
- unclear intervention 2

Eligible studies 38
Figure caption: Selection of studies.