Effects of frequency, intensity, duration and volume of walking interventions on CVD risk factors: a systematic review and meta-regression analysis of randomised controlled trials among inactive healthy adults

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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 and cardiovascular risk factors based on randomised 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 preintervention and postintervention; 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 favourable effects (P≤0.05) of walking intervention for seven CVD risk factors (body mass, body mass index, body fat, systolic and diastolic blood pressure, fasting glucose and VO2max), here 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.

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INTRODUCTION

Non-communicable diseases (NCDs) are a major burden worldwide.1 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.2 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.3

Walking is the ideal physical activity intervention to improve health across the population.4 A recent systematic review of 32 randomised controlled trials (RCTs) by Murtagh et al5 showed that walking increases aerobic capacity and reduces blood pressure, waist circumference, body weight, per cent body fat and body mass index (BMI). Another systematic review6 reported similar health benefits of recreational walking including reduced systolic and diastolic blood pressure, resting heart rate, body fat, BMI and total cholesterol, and increased VO2 max, 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 and Chida7 found that walking pace was a stronger independent predictor than walking volume. Through meta-analysis, Kelly et al8 showed an increased reduction in the risk of all-cause mortality for higher walking volumes (in MET-hours per week). Also, randomised controlled walking trials have found some dose–response relationships. Asikainen et al 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 postmenopausal women.9 Recently, Hanson and Jones10 noted based on their systematic review of randomised 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 on evidence of effectiveness and 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., 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

Data search
Studies (1971–2012) included in an earlier systematic review were supplemented by electronic searches (January 2012 to April 2017) of four 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 and (4) cardiovascular risk. The full search strategy for the 2012–2017 search is enclosed as online supplementary file 1. 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: 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 pretraining and postraining (or change from preintervention to postintervention reported); English-language articles published in peer-reviewed journals between January 1971 and April 2017.

Study selection
Twenty-eight studies from a previous review were included in the current analyses. Two studies were excluded because of very old age of the participants and two studies because of insufficient outcome data. Screening of the previous review is described elsewhere. The updated search resulted in 10 new studies for inclusion. Titles and abstracts from the updated search were screened by three authors (PO, ST, PK). Full papers were screened independently for 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 cardiometabolic 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 12 studies.

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 (conversion formulas are indicated in the respective tables). The outcome measures were aerobic fitness expressed as VO2max (mL/kg·min), body mass (kg), body fat (%), BMI (weight in kilograms divided by height in metres squared), waist circumference (cm), waist-to-hip ratio, systolic and diastolic blood pressure (mm Hg), total cholesterol (mmol/L), high-density lipoprotein (HDL) cholesterol (mmol/L), low-density lipoprotein (LDL) cholesterol (mmol/L), triglycerides (mmol/L) and fasting glucose (mmol/L). 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 Higgins and Steiner).

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

Synthesis of results
The software ‘Comprehensive Meta-Analysis’ was used for all statistical analyses. For each CVD risk factor outcome, standardised 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-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., Murphy and Hardman and Tully et al., 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., we used pre-means 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 and Nieman, 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 with the control were treated as independent studies. The number of participants in the control group was divided by the number of intervention groups. The effect direction was set negative for studies where a decrease represented an improvement in the health risk factor compared with the control group, and the effect direction was set positive for HDL cholesterol and VO2max 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 SD of the true effect size (Tau), (2) the ratio of true heterogeneity to total variation in observed effects (I2), 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. Publication bias was assessed by visual inspection of funnel plots. If a publication bias was assumed, cumulative forest plots were used for confirmation.

Effect sizes were expressed in the original units of the outcome variables by multiplying SMD by a population representative SD.
Representative SDs were obtained from the MONICA Population Survey data for body mass, BMI, waist circumference, systolic and diastolic blood pressure, and total and HDL cholesterol. For VO₂, the SD was taken from a Norwegian study of 3816 participants and for per cent body fat from the FINRISK 2007 study. All analyses were adjusted for age. Gender was not considered a confounder because only two studies were men only. Further adjustment for gender indicated that there was no difference in the effect sizes between subgroups with women only, men only, mixed and no information (data not shown).

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 \( \beta \)-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 was applied to interpret multiple-comparison \( P \) values.

RESULTS
Selection of studies
We searched four electronic databases from 2012 to April 2017 to update the data of the previous systematic review. 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 (seven), non-randomised or group-randomised design (eight), non-healthy participants (eight), no no-walking control group (three), incomplete outcome data (four) and unclear intervention (two). 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 online supplementary table 1. In brief,
Risk of bias
Results of the assessment of the risk of bias according to the Cochrane Collaboration assessment tool are shown in online supplementary table 3. Among the 37 studies, only 2 studies were assessed as being at low risk of bias across all domains.13 31

Meta-analysis
Pooled meta-analysis results (SMD, 95% CI, P value) are shown in table 1. Significant favourable effects (P<0.05) were seen for body mass, BMI, body fat, systolic and diastolic blood pressure, fasting glucose and VO2max. Estimated effect sizes were body mass −1.6 kg, BMI −0.6 kg/m2, systolic blood pressure −4.05 mm Hg, diastolic blood pressure −1.76 mm Hg and VO2max 4.86 mL/(kg·min).

Heterogeneity, as indicated by I2, was 0% for all outcomes except for systolic (17%) and diastolic (6%) blood pressure, total cholesterol (16%) and fasting glucose (23%).

Funnel plots for the outcomes showed symmetric patterns suggesting non-significant publication bias except those for body fat and LDL (see online supplementary file 2). Cumulative forest plots of these outcomes (see online supplementary file 2) showed a symmetric pattern of the effect sizes even with the less precise studies included, thus suggesting that there is no reason to assume a publication bias.35

Meta-regression and dose–response by walking dose characteristics
The linear meta-regression analyses for (1) walking frequency (number of sessions per week), (2) intervention duration (weeks) and (3) 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).

The linear meta-regression analysis between the three MET-related metrics (METs, MET-minutes per week, total MET-hours) and

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Table 1
Meta-analysis on the effects of walking interventions on biomedical indices of health

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect size</th>
<th>Heterogeneity</th>
<th>P for I2 (%)</th>
<th>P for T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td>−0.134</td>
<td>−0.233 to −0.034</td>
<td>0.009</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.142</td>
<td>−0.257 to −0.027</td>
<td>0.015</td>
<td>0.000</td>
</tr>
<tr>
<td>Body fat</td>
<td>−0.216</td>
<td>−0.336 to −0.096</td>
<td>&lt;0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>WC</td>
<td>−0.104</td>
<td>−0.265 to 0.058</td>
<td>0.208</td>
<td>0.000</td>
</tr>
<tr>
<td>WHR</td>
<td>−0.165</td>
<td>−0.340 to 0.009</td>
<td>0.063</td>
<td>0.000</td>
</tr>
<tr>
<td>SBP</td>
<td>−0.213</td>
<td>−0.344 to −0.082</td>
<td>0.001</td>
<td>0.164</td>
</tr>
<tr>
<td>DBP</td>
<td>−0.166</td>
<td>−0.285 to −0.047</td>
<td>0.006</td>
<td>0.067</td>
</tr>
<tr>
<td>TC</td>
<td>−0.123</td>
<td>−0.242 to 0.001</td>
<td>0.052</td>
<td>0.150</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.035</td>
<td>−0.080 to 0.150</td>
<td>0.553</td>
<td>0.000</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.030</td>
<td>−0.089 to 0.148</td>
<td>0.624</td>
<td>0.000</td>
</tr>
<tr>
<td>TG</td>
<td>−0.084</td>
<td>−0.201 to 0.033</td>
<td>0.161</td>
<td>0.000</td>
</tr>
<tr>
<td>FG</td>
<td>−0.211</td>
<td>−0.401 to −0.022</td>
<td>0.029</td>
<td>0.186</td>
</tr>
<tr>
<td>VO2max</td>
<td>0.528</td>
<td>0.391 to 0.664</td>
<td>&lt;0.001</td>
<td>0.000</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).

*BMI, body mass index (kg/m2); DBP, diastolic blood pressure (mm Hg); FG, fasting glucose (mmol/L); HDL-C, high-density lipoprotein cholesterol (mmol/L); LDL-C, low-density lipoprotein cholesterol (mmol/L); n, number of comparisons; body mass index (kg); SBP, systolic blood pressure (mmol/L); SDM, standardised difference in means; T, Tau (estimate of the SD in true effect sizes); TC, total cholesterol (mmol/L); TG, triglycerides (mmol/L); VO2max, maximal oxygen uptake; WC, waist circumference (cm); WHR, waist-to-hip ratio.

P value for SDM (test of the null hypothesis that the effect is zero). 1P value (test of the null hypothesis that all studies in the analysis share a common effect size).

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22 studies included only women, 3 studies only men and 14 studies included 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 used Nordic walking and one ‘trekking’ intervention.

Exposure metrics
Intervention dose characteristics varied considerably (online supplementary tables 1 and 2): total duration 8 to 52 weeks, session duration 10 to 90 min, number of sessions per week 1 to 15.4, weekly duration 10 to 325 min, intensity 1.7 to 5.8 METs, total weekly volume 27 to 1300 MET-minutes per week, total walking duration 130 to 192 min 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), percentage of VO2max (range 45%–65%), or percentage heart rate reserve (range 54%–85%). Four studies reported that walking was ‘self-paced’ and seven studies noted that walking intensity was at a ‘brisk pace’.

In 10 studies, 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.

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Original article
the outcomes resulted in three positive associations from a possible 39: METs with VO_{max} (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 relationship 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 (\%VO_{max}) yielded one inverse association: \%VO_{max} with diastolic blood pressure (P=0.020) (table 4).

### 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_{max}. These findings are consistent with those of Murtagh et al, 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.

Blair et al evaluated the clinical significance of their findings and noted that an increase in aerobic capacity of 10% is likely to result in a 15% reduction in mortality, while Lewington et al noted that a 2 mm Hg reduction in systolic blood pressure would result in 10% lower stroke mortality and 7% lower mortality from ischaemic heart disease and other vascular causes. As the reductions in body mass, BMI and diastolic blood pressure in the current analyses were of greater magnitude than reported by Murtagh et al, and there was the additional decrease of fasting glucose, the changes found in the CVD risk factors could be considered clinically important.

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 be substantial. We performed post hoc subgroup 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 robust results. We examined our data from this perspective by conducting post hoc...
Subgroup and mixed-effects analyses comparing study group sizes over and below 20 (per study arm) for all outcome variables. The subgroup 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 2 of the 13 outcomes, which may also be due to the multiple comparisons.

In our study, we have attempted to explore the dose-response relationship 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, that is, some of the variance across the included studies is real. We found some (4%–23%) heterogeneity as measured by the statistic I² 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 $P<0.004$ and 0.002 according to Bonferroni.59 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 consistent 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 cardiopulmonary 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 training stimulus. We had 20 studies with %VO2max intensity (reported or converted). In all these studies, the training intensity was determined by individual heart rate monitoring (19 studies) or converted. In our analysis, we used the %VO2max dose (reported or converted), which is a good measure of the relative physiological training stimulus. We had 20 studies with %VO2max intensity (reported or converted). In all these studies, the training intensity was determined by individual heart rate monitoring (19 studies) or converted.

### Table 3: Meta-regression analysis: MET-related doses (adjusted model*)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
<th>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 to 0.0752</td>
<td>0.378</td>
<td>−0.0002</td>
<td>−0.0005 to 0.0002</td>
<td>0.337</td>
<td>−0.0002</td>
<td>−0.0008 to 0.0005</td>
<td>0.640</td>
</tr>
<tr>
<td>BMI</td>
<td>24</td>
<td>−0.0265</td>
<td>−0.2147 to 0.1617</td>
<td>0.782</td>
<td>−0.0000</td>
<td>−0.0004 to 0.0004</td>
<td>0.937</td>
<td>−0.0000</td>
<td>−0.0007 to 0.0007</td>
<td>0.961</td>
</tr>
<tr>
<td>Body fat</td>
<td>23</td>
<td>−0.1309</td>
<td>−0.2927 to 0.0309</td>
<td>0.113</td>
<td>−0.0003</td>
<td>−0.0007 to 0.0001</td>
<td>0.163</td>
<td>−0.0002</td>
<td>−0.0009 to 0.0005</td>
<td>0.518</td>
</tr>
<tr>
<td>WC</td>
<td>14</td>
<td>−0.1696</td>
<td>−0.4420 to 0.1023</td>
<td>0.222</td>
<td>−0.0003</td>
<td>−0.0011 to 0.0005</td>
<td>0.499</td>
<td>−0.0004</td>
<td>−0.0013 to 0.0011</td>
<td>0.572</td>
</tr>
<tr>
<td>WHR</td>
<td>13</td>
<td>−0.0231</td>
<td>−0.3677 to 0.3215</td>
<td>0.896</td>
<td>0.0001</td>
<td>−0.0008 to 0.0011</td>
<td>0.763</td>
<td>0.0002</td>
<td>−0.0007 to 0.0011</td>
<td>0.678</td>
</tr>
<tr>
<td>SBF</td>
<td>28</td>
<td>−0.0254</td>
<td>−0.2027 to 0.1519</td>
<td>0.779</td>
<td>0.0003</td>
<td>−0.0001 to 0.0007</td>
<td>0.154</td>
<td>0.0006</td>
<td>−0.0005 to 0.0016</td>
<td>0.270</td>
</tr>
<tr>
<td>DBP</td>
<td>26</td>
<td>−0.1528</td>
<td>−0.3185 to 0.0129</td>
<td>0.071</td>
<td>−0.0001</td>
<td>−0.0006 to 0.0003</td>
<td>0.544</td>
<td>−0.0000</td>
<td>−0.0010 to 0.0010</td>
<td>0.988</td>
</tr>
<tr>
<td>TC</td>
<td>33</td>
<td>0.1390</td>
<td>−0.0432 to 0.3213</td>
<td>0.135</td>
<td>0.0003</td>
<td>−0.0003 to 0.0007</td>
<td>0.148</td>
<td>0.0006</td>
<td>−0.0002 to 0.0013</td>
<td>0.133</td>
</tr>
<tr>
<td>HDL-C</td>
<td>32</td>
<td>0.0391</td>
<td>−0.1233 to 0.2014</td>
<td>0.637</td>
<td>0.0001</td>
<td>−0.0003 to 0.0004</td>
<td>0.722</td>
<td>0.0001</td>
<td>−0.0006 to 0.0008</td>
<td>0.737</td>
</tr>
<tr>
<td>LDL-C</td>
<td>32</td>
<td>0.1124</td>
<td>−0.0503 to 0.2751</td>
<td>0.176</td>
<td>0.0002</td>
<td>−0.0002 to 0.0006</td>
<td>0.292</td>
<td>0.0010</td>
<td>0.0003 to 0.0017</td>
<td>0.007</td>
</tr>
<tr>
<td>TG</td>
<td>23</td>
<td>0.1251</td>
<td>−0.0384 to 0.2886</td>
<td>0.134</td>
<td>0.0005</td>
<td>0.0001 to 0.0009</td>
<td>0.099</td>
<td>0.0009</td>
<td>−0.0001 to 0.0018</td>
<td>0.086</td>
</tr>
<tr>
<td>FG</td>
<td>14</td>
<td>−0.1564</td>
<td>−0.4049 to 0.0921</td>
<td>0.217</td>
<td>−0.0005</td>
<td>−0.0011 to 0.0000</td>
<td>0.064</td>
<td>−0.0010</td>
<td>−0.0025 to 0.0005</td>
<td>0.185</td>
</tr>
<tr>
<td>VO2max</td>
<td>29</td>
<td>0.1612</td>
<td>0.0006 to 0.3218</td>
<td>0.049</td>
<td>0.0003</td>
<td>−0.0001 to 0.0008</td>
<td>0.115</td>
<td>0.0009</td>
<td>−0.0002 to 0.0020</td>
<td>0.106</td>
</tr>
</tbody>
</table>

*Adjusted for age.

β, linear regression coefficient; BMI, body mass index (kg/m²); DBP, diastolic blood pressure; FG, fasting glucose (mmol/L); HDL-C, high-density lipoprotein cholesterol (mmol/L); LDL-C, low-density lipoprotein cholesterol (mmol/L); n, number of comparisons; SSB, systolic blood pressure (mm Hg); TC, total cholesterol (mmol/L); TG, triglycerides (mmol/L); VO2max, maximal oxygen uptake (mL/(kg·min)); WC, waist circumference (cm); WWR, waist-to-hip ratio.

### Table 4: Meta-regression analysis: %VO2max dose (adjusted model*)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td>23</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>−0.0073</td>
<td>−0.0362 to 0.0216</td>
<td>0.620</td>
</tr>
<tr>
<td>Body fat</td>
<td>14</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>0.0180</td>
<td>−0.0338 to 0.0698</td>
<td>0.496</td>
</tr>
<tr>
<td>WHR</td>
<td>5</td>
<td>0.0316</td>
<td>−0.0357 to 0.0989</td>
<td>0.357</td>
</tr>
<tr>
<td>SBF</td>
<td>19</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>−0.0235</td>
<td>−0.0433 to −0.0037</td>
<td>0.020</td>
</tr>
<tr>
<td>TC</td>
<td>19</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>−0.0027</td>
<td>−0.0252 to 0.0197</td>
<td>0.812</td>
</tr>
<tr>
<td>LDL-C</td>
<td>19</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>0.0068</td>
<td>−0.0158 to 0.0294</td>
<td>0.555</td>
</tr>
<tr>
<td>FG</td>
<td>8</td>
<td>−0.0252</td>
<td>−0.0570 to 0.0066</td>
<td>0.120</td>
</tr>
<tr>
<td>VO2max</td>
<td>24</td>
<td>0.0161</td>
<td>−0.0019 to 0.0342</td>
<td>0.080</td>
</tr>
</tbody>
</table>

*Adjusted for age.

β, linear regression coefficient; BMI, body mass index (kg/m²); DBP, diastolic blood pressure; FG, fasting glucose (mmol/L); HDL-C, high-density lipoprotein cholesterol (mmol/L); LDL-C, low-density lipoprotein cholesterol (mmol/L); n, number of comparisons; SSB, systolic blood pressure (mm Hg); TC, total cholesterol (mmol/L); TG, triglycerides (mmol/L); VO2max, maximal oxygen uptake (mL/(kg·min)); WC, waist circumference (cm); WWR, waist-to-hip ratio.
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 min 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 (eg, 450 MET-min) 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.4

Strengths and weaknesses
Our systematic review including 38 studies published between 1971 and 2017 identified a large number of randomised controlled walking trials conducted according to a standard set of quantitative criteria. The data set consisted of 28 studies from a previous review and 10 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 randomised 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 intrastudy and interstudy 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 generalisability of the findings. Participants in the studies were mostly healthy but inactive 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.

Summary and conclusions
Meta-analysis of data from 37 randomised 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-to-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.

Contributors All authors were involved in the conception or design of the work, or the acquisition, analysis or interpretation of data. PO, PK and MHM conceived the paper, ST, PK and PO carried out the statistical analysis. PO drafted the paper. All authors contributed to all drafts of the paper and approved the final manuscript.

Competing interests None declared.

Ethics approval Not applicable. Meta-analysis of data from studies that were ethically approved.

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REFERENCES


