Home-based cardiac rehabilitation: Development and evaluation of a novel intervention with telemonitoring guidance and wearable sensors

Kraal, J.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
Chapter 2

The influence of training characteristics on the effect of exercise training in patients with coronary artery disease:

Systematic review and meta-regression analysis
Abstract

Although exercise-based cardiac rehabilitation improves exercise capacity of patients with coronary artery disease, it is unclear which characteristics of the exercise programme determine the improvement in exercise capacity. Both total energy expenditure and its constituent training characteristics (training intensity, session frequency, session duration and programme length) vary considerably in clinical studies, making it hard to compare studies directly. Therefore, we performed a systematic review and meta-regression analysis to assess the effect of total energy expenditure and individual training characteristics of aerobic exercise programmes on exercise capacity. We identified randomised controlled trials comparing continuous aerobic exercise training with usual care for patients with coronary artery disease. Studies were included when 1) the exercise programme was described in terms of training intensity, session frequency, session duration and programme length, and 2) improvement in exercise capacity was reported as peak oxygen uptake. Total energy expenditure of each exercise programme was calculated from the four training characteristics. The effect of the training characteristics and total energy expenditure on exercise capacity was determined using mixed effects linear regression analyses. The analyses were performed with and without total energy expenditure as covariate. Twelve studies were included in the analyses. Whereas total energy expenditure was significantly related to the improvement of exercise capacity, no effect was found for its constituent training characteristics after adjustment for total energy expenditure. This suggests that the design of an exercise programme should primarily be aimed at total energy expenditure rather than on one specific training characteristic. Therefore, exercise programmes can be tailored to patients’ preferences without losing its effectiveness.

Introduction

Exercise-based cardiac rehabilitation (ECR) improves exercise capacity and quality of life, and decreases cardiovascular mortality and morbidity in patients with coronary artery disease (CAD) [1–3]. Exercise training is therefore considered a crucial component of cardiac rehabilitation and is highly recommended in both European and American clinical guidelines [4,5]. Furthermore, ECR is widely accepted and implemented in daily practice for CAD patients. Because exercise capacity is strongly associated with morbidity and mortality in CAD patients, it is important to understand which factors determine the beneficial effects of exercise. Moreover, if we understand which training characteristics are the strongest determinants of improvement in exercise capacity after exercise training, the most effective exercise programme can be prescribed [6].
Studies with healthy adults showed that the effects of exercise training improve when total energy expenditure of an exercise programme increases [7]. Recently, two systematic reviews confirmed that total energy expenditure was the strongest predictor of improvement in exercise capacity in chronic heart failure patients [8,9]. Total energy expenditure of an exercise programme is determined by session frequency, session duration, training intensity and programme length. Although practice guidelines describe the content of an exercise programme, the individual characteristics of an exercise programme vary considerably in practice and between training studies [1,10,11]. Therefore, the individual effect of the training characteristics remains under debate.

Vanhees et al. showed in a retrospective cohort study that session frequency and training intensity were strong predictors for the improvement in exercise capacity [12]. Other studies indicated that although a minimum energy expenditure was required for the improvement in exercise capacity, adjustments to individual characteristics above a certain cut-off value (e.g. session duration of 30 minutes, session frequency of twice a week) did not influence the improvement in exercise capacity [13,14]. However, those studies did not adjust for total energy expenditure of the exercise programmes. Since energy expenditure is comprised by the four training characteristics, a correction for energy expenditure is necessary to identify the individual effect of the training characteristics. Therefore, studies comparing training protocols to determine the effect of a training characteristic should therefore perform an isocaloric comparison (i.e. a comparison in which energy expenditure of both exercise programmes are matched).

Previous studies with isocaloric comparisons but dissimilar session frequency and/or programme length in the exercise programmes showed that the improvement in exercise capacity was similar [15,16]. In addition, the effect of training intensity appears inconclusive. Whereas two systematic reviews showed a superior effect on exercise capacity after high intensity training compared to moderate intensity training [17,18], other studies comparing isocaloric programmes showed no differences between the exercise programmes [19–21]. However interpretation of the results of these studies is hampered, as exercise programmes in those studies did not only differed with respect to training intensity but also to training modality. High intensity training is performed using an interval protocol, whereas moderate intensity training is performed using a continuous training protocol. Therefore, the individual effect of the training characteristics remains unknown.

With large sets of exercise data, regression analyses can be used to explore the individual effect of the training characteristics on the improvement of exercise capacity. In addition, a correction for energy expenditure can be performed in the analyses. Therefore, the objective of this systematic review and meta-regression analysis was to investigate which training characteristics determine the improvement of exercise capacity after ECR in CAD patients, correcting for total energy expenditure of the exercise programme.
Methods

Literature search strategy
We conducted a systematic literature search in the database of EMBASE and MEDLINE to find papers published between 1st of April 2007 and 1st of April 2015, addressing aerobic exercise training after cardiac rehabilitation for CAD patients. In the search strategy, which involved a mix of MeSH-terms and free text terms, we combined synonyms on three topics: population and diagnosis (i.e. coronary artery disease, cardiac patients, myocardial infarction), therapy (i.e. cardiac rehabilitation, secondary prevention, exercise training, physical training) and outcome (i.e. physical function, exercise capacity, exercise tolerance). The search was limited to randomised controlled trials published between 01-04-2007 and 01-04-2015 and written in English. The complete search strategy is described in appendix A. The protocol of this systematic review and meta-regression analysis is published in the Prospero database (http://www.crd.york.ac.uk/prospero) with registration number CRD42014014846. The search strategy and methodology of this meta-analysis is based on a similar meta-analysis with chronic heart failure patients published elsewhere [9].

Study Selection
We included randomised controlled trials comparing continuous aerobic exercise programmes with usual care in CAD patients. Only studies reporting change in peakVO₂ to evaluate training effects were included. Studies evaluating interval training, resistance training or cardiac rehabilitation modalities not affecting exercise capacity (e.g. cognitive therapy, stress-management) were excluded. Studies that reported the results of a combination of aerobic exercise with strength training were excluded as well. All included studies were required to describe the aerobic exercise programme in detail, with at least information concerning session frequency, session duration, programme length and training intensity (% of peak heart rate, peakVO₂ or maximum workload). When important data concerning the exercise programme or outcome parameter were missing, authors were contacted to retrieve the missing data.

Data collection process
Four couples of researchers screened the titles and abstracts using the abovementioned inclusion and exclusion criteria. Both researchers in each couple performed the screening independently. Afterwards, they compared the results and reached consensus. The full papers of the selected articles were screened by three couples of researchers to make a final decision on inclusion in a similar procedure. When no consensus was reached between the two researchers, a third researcher decided whether the article was included. Data concerning patient characteristics, exercise programme, outcome measures, and risk of bias of the included studies were extracted from the full texts and stored in a Microsoft Access database.
Energy expenditure

We calculated energy expenditure (J.kg⁻¹) for all interventions by multiplying total training time (i.e. session frequency*session duration*programme length) with training intensity. First, training intensity was converted to a percentage of peakVO₂ using a conversion table from the American College of Sports Medicine [22]. Second, the oxygen consumption (VO₂ ml.min⁻¹.kg⁻¹) per intervention was calculated using pre-training exercise capacity (peakVO₂) multiplied with training intensity (% of peakVO₂), and total programme length in minutes. Finally, total oxygen uptake (in ml.min⁻¹.kg⁻¹) was converted to Joules per kg under the assumption that consumption of one liter oxygen equals 20.93 Joule [22].

Risk of bias quality assessment

The methodological quality of the included articles was assessed using the Cochrane Collaboration’s tool for assessing risk of bias [23]. The tool identifies seven potential sources of bias in randomised trials (i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other forms of bias). Two independent researchers classified each potential risk of bias as ‘low’, ‘high’ or ‘unclear’, with the last category indicating either lack of information or uncertainty concerning the potential bias.

Synthesis of results

The relationship between training characteristics and exercise-related changes in exercise capacity (peakVO₂) was determined using mixed-effects linear regression analyses. First, a linear regression analysis was used to assess differences in exercise capacity between exercise training and usual care. Second, the effect of energy expenditure and the four training characteristics was assessed separately by five univariate analyses. Subsequently, the effect of the four training characteristics (i.e. session frequency, session duration, training intensity and programme length) was assessed by four multivariate regression analyses with total energy expenditure as a covariate. Model fit was assessed using residual deviance and I², which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Large values of I² indicate inconsistency in the result of the underlying studies. The effect of training characteristics was assessed by their Z-score. Because of the large number of statistical comparisons we considered p-values below 0.01 as significant. When heterogeneity (i.e. I²) was high and sufficient data were available, the analysis was repeated without outliers. Baseline differences between groups were tested using an independent student t-test with a significance level of 0.05.
Results

Study selection
We identified 812 unique studies from the EMBASE and MEDLINE databases. Figure 1 provides an overview of the search and selection studies records. Through screening of titles and abstract we excluded 539 studies, and 188 studies were excluded after full-paper review. From the remaining 29 studies, 17 were included in an analysis for chronic heart failure patients published elsewhere [9] and 12 were included in this review. One study randomised their participants in two intervention groups (i.e. high intensity training and moderate intensity training) and one control group [24]. Therefore, we included this study as two separate comparisons with the same control group.

Figure 1: Inclusion flowchart of the selected studies
Study characteristics
An overview of the baseline characteristics is provided in Table 1. Median sample size of the included studies was 46 patients, ranging from 20 to 118 included patients. A total number of 367 patients were randomised to aerobic exercise training, and 326 patients received usual care. In the control group, median age was 57.0 (range 52.0 to 69.1) and 84% were male. In the training group, median age was 54.3 (range 52.0 to 71.1) and 87% were male. There were no significant differences between groups at baseline.

Table 1: Baseline characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N, #</th>
<th>N, #</th>
<th>Male, # (%)</th>
<th>Male, # (%)</th>
<th>Age, #</th>
<th>Age, #</th>
<th>Peak VO₂ (ml.min⁻¹.kg⁻¹)</th>
<th>Peak VO₂ (ml.min⁻¹.kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aamot 2010 [25]</td>
<td>20</td>
<td>19</td>
<td>15 (75)</td>
<td>14 (74)</td>
<td>61</td>
<td>58</td>
<td>30.6 ± 6.7</td>
<td>29.8 ± 6.1</td>
</tr>
<tr>
<td>Balen 2008 [26]</td>
<td>30</td>
<td>30</td>
<td>21 (70)</td>
<td>23 (77)</td>
<td>59</td>
<td>61</td>
<td>20 ± 4.4</td>
<td>17.9 ± 4.6</td>
</tr>
<tr>
<td>Benetti 2010a [24]</td>
<td>29</td>
<td>29</td>
<td>29 (100)</td>
<td>29 (100)</td>
<td>-</td>
<td>-</td>
<td>29.2 ± 2.2</td>
<td>31.6 ± 3.9</td>
</tr>
<tr>
<td>Benetti 2010b [24]</td>
<td>29</td>
<td>29</td>
<td>29 (100)</td>
<td>29 (100)</td>
<td>-</td>
<td>-</td>
<td>32 ± 5.3</td>
<td>31.6 ± 3.9</td>
</tr>
<tr>
<td>Bilinska 2010 [27]</td>
<td>59</td>
<td>59</td>
<td>29 (49)</td>
<td>29 (49)</td>
<td>54</td>
<td>54</td>
<td>24.3 ± 4.5</td>
<td>24.7 ± 4.3</td>
</tr>
<tr>
<td>Giallauria 2011 [28]</td>
<td>37</td>
<td>38</td>
<td>28 (76)</td>
<td>32 (84)</td>
<td>61</td>
<td>60</td>
<td>16.4 ± 1.5</td>
<td>16.7 ± 2.2</td>
</tr>
<tr>
<td>Giallauria 2012 [29]</td>
<td>24</td>
<td>26</td>
<td>23 (96)</td>
<td>23 (88)</td>
<td>54</td>
<td>52</td>
<td>13 ± 3</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>Giallauria 2013 [30]</td>
<td>25</td>
<td>21</td>
<td>22 (88)</td>
<td>18 (86)</td>
<td>54</td>
<td>54</td>
<td>14 ± 3</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Lee 2009 [31]</td>
<td>20</td>
<td>19</td>
<td>20 (100)</td>
<td>19 (100)</td>
<td>52</td>
<td>52</td>
<td>22.2 ± 3.9</td>
<td>22.7 ± 3.1</td>
</tr>
<tr>
<td>Mameletzi 2011 [32]</td>
<td>10</td>
<td>10</td>
<td>10 (100)</td>
<td>10 (100)</td>
<td>69</td>
<td>71</td>
<td>22 ± 3.9</td>
<td>21 ± 4.2</td>
</tr>
<tr>
<td>Oliveira 2014 [33]</td>
<td>47</td>
<td>45</td>
<td>40 (85)</td>
<td>37 (45)</td>
<td>55</td>
<td>59</td>
<td>27.6 ± 7.3</td>
<td>26.9 ± 5.6</td>
</tr>
<tr>
<td>Ribeiro 2012 [34]</td>
<td>20</td>
<td>18</td>
<td>18 (90)</td>
<td>13 (72)</td>
<td>54</td>
<td>57</td>
<td>30.8 ± 7.8</td>
<td>32.6 ± 5.8</td>
</tr>
<tr>
<td>Su 2011 [35]</td>
<td>17</td>
<td>12</td>
<td>17 (100)</td>
<td>12 (100)</td>
<td>52</td>
<td>52</td>
<td>22.5 ± 3.7</td>
<td>21.2 ± 2.1</td>
</tr>
</tbody>
</table>

Data provided as mean ± standard deviation, unless stated otherwise.
INT=intervention; CON=control; peakVO₂=maximal oxygen consumption
Programme characteristics

Training intensity was described as %HRmax in six studies and as %peakVO₂ in six studies. Median programme length was 12 weeks (range 3 to 28) with a median of 3 sessions per week (range 2 to 5). Session duration varied from 20 to 60 minutes, with a median of 30 minutes. Median training intensity was 65% of peakVO₂ (range 45% to 79% of peakVO₂). Total training time varied from 260 to 2700 minutes, with a median of 1080 minutes, and total energy expenditure varied from 74 to 1300 J.kg⁻¹ with a median of 364 J.kg⁻¹. The programme characteristics of the included studies are described in Table 2.

Table 2: Exercise programme characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Program length (weeks)</th>
<th>Session Frequency (n/week)</th>
<th>Session Duration (min)</th>
<th>Intensity (% peakVO₂)</th>
<th>Total training volume (min)</th>
<th>EE total (Joule.kg⁻¹)</th>
<th>EE week (Joule.kg⁻¹)</th>
<th>Δ Peak VO₂ (ml.min⁻¹.kg⁻¹)</th>
<th>Δ Peak VO₂ (ml.min⁻¹.kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aamot 2010 [25]</td>
<td>4</td>
<td>2</td>
<td>32.5</td>
<td>44.5</td>
<td>260</td>
<td>74.0</td>
<td>18.5</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Balen 2008 [26]</td>
<td>3</td>
<td>5</td>
<td>45</td>
<td>55</td>
<td>675</td>
<td>155.2</td>
<td>51.7</td>
<td>3.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Benetti 2010a [24]</td>
<td>12</td>
<td>5</td>
<td>45</td>
<td>78.9</td>
<td>2700</td>
<td>1300.1</td>
<td>108.3</td>
<td>12.4</td>
<td>-2.4</td>
</tr>
<tr>
<td>Benetti 2010b [24]</td>
<td>12</td>
<td>5</td>
<td>45</td>
<td>66.3</td>
<td>2700</td>
<td>1197.2</td>
<td>99.8</td>
<td>5.9</td>
<td>0</td>
</tr>
<tr>
<td>Bilinska 2010 [27]</td>
<td>6</td>
<td>3</td>
<td>60</td>
<td>66.3</td>
<td>1080</td>
<td>363.7</td>
<td>60.6</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Giallauria 2011 [28]</td>
<td>26</td>
<td>3</td>
<td>30</td>
<td>68.4</td>
<td>2340</td>
<td>548.6</td>
<td>21.1</td>
<td>4.6</td>
<td>-0.4</td>
</tr>
<tr>
<td>Giallauria 2012 [29]</td>
<td>26</td>
<td>3</td>
<td>30</td>
<td>65</td>
<td>2340</td>
<td>413.3</td>
<td>15.9</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Giallauria 2013 [30]</td>
<td>26</td>
<td>3</td>
<td>30</td>
<td>65</td>
<td>2340</td>
<td>445.0</td>
<td>17.1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Lee 2009 [31]</td>
<td>12</td>
<td>3</td>
<td>20</td>
<td>62.5</td>
<td>720</td>
<td>208.8</td>
<td>17.4</td>
<td>2.8</td>
<td>-0.3</td>
</tr>
<tr>
<td>Mameletzi 2011 [32]</td>
<td>28</td>
<td>3</td>
<td>30</td>
<td>60</td>
<td>2520</td>
<td>663.6</td>
<td>23.7</td>
<td>4.6</td>
<td>-0.9</td>
</tr>
<tr>
<td>Oliveira 2014 [33]</td>
<td>8</td>
<td>3</td>
<td>30</td>
<td>69</td>
<td>720</td>
<td>288.5</td>
<td>36.1</td>
<td>2.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>Ribeiro 2012 [34]</td>
<td>8</td>
<td>3</td>
<td>35</td>
<td>60</td>
<td>840</td>
<td>324.4</td>
<td>40.6</td>
<td>3.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Su 2011 [35]</td>
<td>12</td>
<td>3</td>
<td>20</td>
<td>62.5</td>
<td>720</td>
<td>211.6</td>
<td>17.6</td>
<td>2.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Data provided as mean ± standard deviation, unless stated otherwise.
INT=intervention; CON=control; peakVO₂=maximal oxygen consumption; EE=energy expenditure
**Effect of training characteristics**

The mean difference in improvement peakVO\_2 between the intervention group and control group was 4.19 ml.min\(^{-1}\).kg\(^{-1}\) (p<0.01, 95% CI 1.90 to 6.48, figure 2). Table 3 presents the results from univariate regression and multivariate regression analyses. Total energy expenditure was significantly associated with improvement of exercise capacity, showing that an increase of energy expenditure of 100 J.kg\(^{-1}\) was associated with a peakVO\_2 improvement of 0.91 ml.min\(^{-1}\).kg\(^{-1}\) (p<0.01, 95% CI 0.77 to 1.05). All other training characteristics were significantly associated with improvement of peakVO\_2 in the univariate analyses. Although heterogeneity for energy expenditure was low (I\(^2\)=17%), it was high for all individual training characteristics (I\(^2\) ranging from 79% to 89%). When adjusting for total energy expenditure, none of the individual training characteristics was significantly associated with improvement of peakVO\_2. After the adjustment, heterogeneity was low for all characteristics (I\(^2\) ranging from 0% to 22%). Detailed results of the regression analyses are provided in Appendix B.

**Table 3: Results of regression analyses, with and without correction for energy expenditure**

<table>
<thead>
<tr>
<th>Training characteristics</th>
<th>Effect scale</th>
<th>Effect Size (ml.min(^{-1}).kg(^{-1}))</th>
<th>95% CI (ml.min(^{-1}).kg(^{-1}))</th>
<th>p-value</th>
<th>I(^2)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate regression analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total EE 100 Joule.kg(^{-1})</td>
<td>0.91</td>
<td>0.77-1.05</td>
<td>&lt;0.001*</td>
<td>16.9</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>Session frequency 1 session/week</td>
<td>1.36</td>
<td>0.85-1.88</td>
<td>&lt;0.001*</td>
<td>78.5</td>
<td>67.1</td>
<td></td>
</tr>
<tr>
<td>Training intensity 10% peakVO_2</td>
<td>0.70</td>
<td>0.37-1.03</td>
<td>&lt;0.001*</td>
<td>83.5</td>
<td>69.7</td>
<td></td>
</tr>
<tr>
<td>Session duration 10 minutes</td>
<td>1.15</td>
<td>0.51-1.79</td>
<td>&lt;0.001*</td>
<td>87.3</td>
<td>71.5</td>
<td></td>
</tr>
<tr>
<td>Programme length 2 weeks</td>
<td>0.47</td>
<td>0.15-0.78</td>
<td>0.003*</td>
<td>88.6</td>
<td>73.3</td>
<td></td>
</tr>
<tr>
<td><strong>Multivariate regression analyses, correcting for energy expenditure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session duration 10 minutes</td>
<td>-0.40</td>
<td>-0.81-0.01</td>
<td>0.058</td>
<td>0.0</td>
<td>49.8</td>
<td></td>
</tr>
<tr>
<td>Training intensity 10% peakVO_2</td>
<td>-0.17</td>
<td>-0.40-0.17</td>
<td>0.422</td>
<td>18.3</td>
<td>51.6</td>
<td></td>
</tr>
<tr>
<td>Session frequency 1 session/week</td>
<td>-0.15</td>
<td>-0.77-0.47</td>
<td>0.633</td>
<td>21.3</td>
<td>51.8</td>
<td></td>
</tr>
<tr>
<td>Programme length 2 weeks</td>
<td>-0.05</td>
<td>-0.21-0.11</td>
<td>0.579</td>
<td>22.0</td>
<td>52.0</td>
<td></td>
</tr>
</tbody>
</table>

Effect size is given as change in peakVO\_2

I\(^2\)=residual heterogeneity; AIC=Akaike’s information coefficient (model fit); peakVO\_2=maximal oxygen consumption; EE=energy expenditure; * = significant at p<0.01
<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Mean difference</th>
<th>MD</th>
<th>95%−CI</th>
<th>W (fixed)</th>
<th>W (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aamot IL et al.</td>
<td>20</td>
<td>0.1</td>
<td>8.952653</td>
<td>19</td>
<td>0.9</td>
<td>8.562126</td>
<td></td>
<td>−0.80</td>
<td>[−6.30; 4.70]</td>
<td>2.0%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Balen S et al.</td>
<td>30</td>
<td>3.2</td>
<td>7.429670</td>
<td>30</td>
<td>0.6</td>
<td>6.936137</td>
<td></td>
<td>2.60</td>
<td>[−1.04; 6.24]</td>
<td>4.5%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Benetti M et al.</td>
<td>29</td>
<td>12.4</td>
<td>4.568370</td>
<td>29</td>
<td>−2.4</td>
<td>5.537147</td>
<td></td>
<td>14.80</td>
<td>[12.19; 17.41]</td>
<td>8.7%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Benetti M et al.</td>
<td>29</td>
<td>5.9</td>
<td>6.307139</td>
<td>29</td>
<td>−2.4</td>
<td>5.537147</td>
<td></td>
<td>8.30</td>
<td>[5.25; 11.35]</td>
<td>6.4%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Bilinska M et al.</td>
<td>59</td>
<td>1.8</td>
<td>6.301587</td>
<td>59</td>
<td>1.1</td>
<td>6.601515</td>
<td></td>
<td>0.70</td>
<td>[−1.63; 3.03]</td>
<td>11.0%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Giallauria F et al.</td>
<td>24</td>
<td>4.0</td>
<td>4.979960</td>
<td>26</td>
<td>1.0</td>
<td>5.513620</td>
<td></td>
<td>3.00</td>
<td>[0.09; 5.91]</td>
<td>7.0%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Giallauria F et al.</td>
<td>37</td>
<td>4.6</td>
<td>2.882707</td>
<td>38</td>
<td>−0.4</td>
<td>2.607681</td>
<td></td>
<td>5.00</td>
<td>[3.75; 6.25]</td>
<td>38.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Giallauria F et al.</td>
<td>25</td>
<td>4.0</td>
<td>4.979960</td>
<td>21</td>
<td>1.0</td>
<td>6.928203</td>
<td></td>
<td>3.00</td>
<td>[−0.55; 6.55]</td>
<td>4.7%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Lee BC et al.</td>
<td>20</td>
<td>2.8</td>
<td>6.304760</td>
<td>19</td>
<td>−0.3</td>
<td>4.155719</td>
<td></td>
<td>3.10</td>
<td>[−0.24; 6.44]</td>
<td>5.3%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Mameletzi et al.</td>
<td>10</td>
<td>4.6</td>
<td>5.715768</td>
<td>10</td>
<td>−0.9</td>
<td>5.290558</td>
<td></td>
<td>5.50</td>
<td>[0.67; 10.33]</td>
<td>2.6%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Oliveira et al.</td>
<td>47</td>
<td>2.1</td>
<td>11.371455</td>
<td>45</td>
<td>−0.1</td>
<td>8.174962</td>
<td></td>
<td>2.20</td>
<td>[−1.83; 6.23]</td>
<td>3.7%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Ribeiro F et al.</td>
<td>20</td>
<td>3.1</td>
<td>11.274307</td>
<td>18</td>
<td>0.3</td>
<td>9.363760</td>
<td></td>
<td>2.80</td>
<td>[−3.77; 9.37]</td>
<td>1.4%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Su MY et al.</td>
<td>17</td>
<td>2.6</td>
<td>6.652819</td>
<td>12</td>
<td>0.6</td>
<td>3.290897</td>
<td></td>
<td>2.00</td>
<td>[−1.67; 5.67]</td>
<td>4.4%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

**Fixed effect model** 367 355

**Random effects model**

Heterogeneity: $I^2$-squared=86.1%, $\tau^2$-squared=14.19, $p<0.0001$

**Figure 2:** Forest plot describing the effect of exercise training on peakVO2
As appears from Figure 2, the study by Benetti et al. found a much larger effect on peakVO$_2$ than the other included studies, and was probably causing high heterogeneity in the meta-regression. We therefore performed a sensitivity analysis without this study. The sensitivity analysis showed that heterogeneity improved for all univariate and multivariate analyses (Table 4). Energy expenditure and all four characteristics remained significantly associated with improvement of exercise capacity in the univariate analyses, and none of the characteristics were significantly associated with improvement of exercise capacity after adjustment for energy expenditure. Detailed results of the regression analyses are provided in Appendix C.

### Table 4: Results of the sensitivity analysis, with and without correction for energy expenditure

<table>
<thead>
<tr>
<th>Training characteristics</th>
<th>Effect scale</th>
<th>Effect Size (ml.min$^{-1}$.kg$^{-1}$)</th>
<th>95% CI (ml.min$^{-1}$.kg$^{-1}$)</th>
<th>p-value</th>
<th>I$^2$</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate regression analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total EE</td>
<td>100 Joule.kg$^{-1}$</td>
<td>0.83</td>
<td>0.64-1.01</td>
<td>&lt;0.001*</td>
<td>0.0</td>
<td>40.7</td>
</tr>
<tr>
<td>Programme length</td>
<td>2 weeks</td>
<td>0.36</td>
<td>0.28-0.43</td>
<td>&lt;0.001*</td>
<td>0.0</td>
<td>39.4</td>
</tr>
<tr>
<td>Training intensity</td>
<td>10% peakVO$_2$</td>
<td>0.47</td>
<td>0.30-0.65</td>
<td>&lt;0.001*</td>
<td>26.7</td>
<td>44.7</td>
</tr>
<tr>
<td>Session frequency</td>
<td>1 session/week</td>
<td>0.90</td>
<td>0.50-1.31</td>
<td>&lt;0.001*</td>
<td>41.9</td>
<td>45.6</td>
</tr>
<tr>
<td>Session duration</td>
<td>10 minutes</td>
<td>0.67</td>
<td>0.18-1.17</td>
<td>0.008*</td>
<td>69.7</td>
<td>50.2</td>
</tr>
<tr>
<td><strong>Multivariate regression analyses, correcting for energy expenditure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session duration</td>
<td>10 minutes</td>
<td>-0.36</td>
<td>-0.85-0.14</td>
<td>0.160</td>
<td>0.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Programme length</td>
<td>2 weeks</td>
<td>0.23</td>
<td>-0.10-0.57</td>
<td>0.176</td>
<td>0.0</td>
<td>38.2</td>
</tr>
<tr>
<td>Session frequency</td>
<td>1 session/week</td>
<td>0.04</td>
<td>-0.64-0.72</td>
<td>0.907</td>
<td>0.0</td>
<td>39.7</td>
</tr>
<tr>
<td>Training intensity</td>
<td>10% peakVO$_2$</td>
<td>-0.07</td>
<td>-0.22-0.35</td>
<td>0.653</td>
<td>0.0</td>
<td>42.8</td>
</tr>
</tbody>
</table>

*Effect size is given as change in peakVO$_2$.*

$I^2$ = residual heterogeneity; AIC = Akaike’s information coefficient (model fit); peakVO$_2$ = maximal oxygen consumption; EE = energy expenditure. * = significant at $p<0.01$.

As appears from Figure 2, the study by Benetti et al. found a much larger effect on peakVO$_2$ than the other included studies, and was probably causing high heterogeneity in the meta-regression. We therefore performed a sensitivity analysis without this study. The sensitivity analysis showed that heterogeneity improved for all univariate and multivariate analyses (Table 4). Energy expenditure and all four characteristics remained significantly associated with improvement of exercise capacity in the univariate analyses, and none of the characteristics were significantly associated with improvement of exercise capacity after adjustment for energy expenditure. Detailed results of the regression analyses are provided in Appendix C.

### Others (risk of bias, publication bias)

Results of the risk of bias analysis (Appendix A) showed that overall methodological quality was good. Differences in quality between studies were small. The funnel plots (Appendix A) showed little evidence for publication bias.
Discussion

The present study showed that total energy expenditure of exercise programmes is a strong determinant of the effect of ECR on exercise capacity in CAD patients. Whereas the meta-regression analysis showed that the four constituent parameters of total energy expenditure (i.e. session duration, session frequency, training intensity and programme length) were all related to the improvement in exercise capacity, no independent effect of any of the four training characteristics was observed after correction for total energy expenditure.

Although the beneficial effects of exercise training on exercise capacity have already been established in prior clinical trials and meta-analyses [3,36], the effect of individual training characteristics on improvement in exercise capacity was not well established. Results from our meta-analysis indicate that total energy expenditure is an important determinant of improvement in exercise capacity, and that the effects of the individual training characteristics disappear when we adjust for energy expenditure. This is in line with studies comparing individual training characteristics using isocaloric exercise programmes [15,16,21]. Therefore, we recommend that ECR programmes should be aimed at a high total energy expenditure without specific preference for a high training intensity or other training characteristics.

The results from our regression analyses provide additional information compared to the systematic reviews and randomised controlled trials previously performed. The regression analysis calculates an effect size for each individual training characteristic. The effect sizes illustrate how we can enhance the effect of the exercise programme if energy expenditure is not taken into account. If we assume that the range of the included studies determines practice variation, a maximum improvement of 1.60 ml.min\(^{-1}\).kg\(^{-1}\) peakVO\(_2\) can be achieved by increasing intensity from 45 to 79\% of peakVO\(_2\). Similarly, according to the results of the sensitivity analysis, an improvement of 2.71 ml.min\(^{-1}\).kg\(^{-1}\) is achieved by an increase in session frequency from 2 to 5 sessions per week, while an improvement of 2.69 ml.min\(^{-1}\).kg\(^{-1}\) peakVO\(_2\) is achieved by increasing session duration from 20 to 60 minutes per session and 4.45 ml.min\(^{-1}\).kg\(^{-1}\) peakVO\(_2\) by increasing programme length from 3 to 28 weeks. However, these results are based on the assumption that there is a linear dose-response relationship for exercise training. Previous studies indicated that the beneficial effects of exercise deteriorate with vigorous exercise [7]. Therefore, the results are primarily applicable within the range described in this review.

In our first analysis, all training characteristics were significantly related to improvement in exercise capacity. However, these effects were absent after correction for total energy expenditure. This implies that prescription of an exercise programme should primarily be focused on total energy expenditure rather than on one specific training characteristic. Therefore, factors such as training adherence, patients’ preference and determinants of sustainability of training effects should be taken into account when designing an exercise programme. First, a high...
training adherence improves the effectiveness of ECR [37]. Previous studies indicated that a high training intensity can reduce training adherence, whereas an increase in session frequency or session duration are not associated with a reduction in adherence [38–40]. Second, an exercise programme aligned with the preferences of a patient (e.g. training type, training characteristics, location) improves motivation and training adherence, indirectly influencing the improvement in exercise capacity [38,41]. In view of the abovementioned facts, an exercise programme can be translated to the home-environment for patients that prefer exercise training at home. For instance, patients with little time available for exercise can perform training sessions with a short duration and high session frequency. Similarly, as a high training intensity is difficult to reach and control in a home environment without fitness equipment, endured walking or biking sessions at a moderate training intensity can be performed. Furthermore, the development of telemonitoring opportunities to sustain guidance in the home environment (i.e. wearable sensors and increased connectivity) provides an opportunity to design a feasible and effective home-based training programme that can induce an optimal short-term and long-term training effect [42,43].

Limitations
First, due to strict criteria in the inclusion and exclusion procedure, sample size and variation in training characteristics among the included studies was low. Studies that lacked information concerning the training characteristics were excluded from the analyses. Consequently, the unaccounted variability in the univariate regression analyses was high, indicating a low model fit. Therefore, the results must be interpreted with cause. Second, we assumed a linear dose-response relationship in exercise training. However, previous literature showed that excessive exercise may hamper the improvement in exercise capacity [44]. Therefore, our results can only be interpreted with respect to the variance of training characteristics in the included studies. Because the variance of the included studies is within the borders of a regular ECR programme, we expect that our results and recommendations are applicable to ECR programmes. Third, our analyses were based on the exercise programme reported in the included studies. However, the actual exercise performed during the programme often deviates from the prescribed exercise programme, which is reported in the study. Conraads et al. showed that the actual training intensity in a high intensity training group was lower than prescribed in the exercise programme, while the actual intensity of the moderate intensity training group was higher than prescribed [21]. They discussed that this could be an important factor influencing the improvement in exercise capacity in both groups, and suggested that the adherence to the prescribed programme should be measured during the exercise programme and reported in the study. Because our analyses are based on the prescribed exercise programmes, the results could be different when both the performed exercise programmes and the prescribed exercise programmes were reported and included in the analyses. Finally, several studies reported no standard deviation of the change from baseline in peakVO₂. Therefore, a correlation between baseline and follow-up assessment of peakVO₂ was assumed at p=0.7. This could have affected the results.
Conclusion
This study showed that total energy expenditure of an exercise programme is the main determinant of improvement in exercise capacity in CAD patients. To increase total energy expenditure, all four training characteristics appear suitable to adjust. To optimise the effectiveness of ECR, we recommend to take into account other factors determining the sustainability of exercise training, like patient preference and adherence.

Acknowledgements
We want to thank Rutger Brouwers, Anne-Marieke Mulder-Wiggers and Mariette van Engen-Verheul for their help during the screening of records. Dr. Gerben ter Riet and Dr. Gert Valkenhoef are acknowledged for their help in constructing the methodological framework and analyses.
References

4) A.S. Leon, B. a Franklin, F. Costa, et al., Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nut, Circulation. 111 (2005) 369–76.


Appendix A

Medline search strategy


#5 ("2007/31/03"[PDat] : "2015/01/04"[PDat]) AND (English[lang]) AND (Randomised Controlled Trial[ptyp])

#6 #1 AND #2 AND #3 AND #5 NOT #4
Appendix A, figure 1: Funnel-plot

Appendix A, figure 2: Funnel-plot of sensitivity analyses
Appendix A, figure 3: Risk of bias
Appendix B

Results from the multivariate regressions analyses

Session frequency

Mixed-Effects Model ($k = 13$; $\tau^2$ estimator: DL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau^2$</td>
<td>0.5925 (SE = 1.2155)</td>
</tr>
<tr>
<td>$\tau$ (square root of estimated $\tau^2$ value)</td>
<td>0.7697</td>
</tr>
<tr>
<td>$I^2$ (residual heterogeneity / unaccounted variability)</td>
<td>21.29%</td>
</tr>
<tr>
<td>$H^2$ (unaccounted variability / sampling variability)</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Test for Residual Heterogeneity: $QE(df = 1) = 13.9758$, $p-val = 0.2343$

Test of Moderators (coefficient(s) 1,2): $QM(df = 2) = 147.1148$, $p-val < .0001$

Model Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq</td>
<td>-0.1514</td>
<td>0.3175</td>
<td>-0.4769</td>
<td>0.6334</td>
<td>-0.7737</td>
</tr>
<tr>
<td>expend</td>
<td>0.0098</td>
<td>0.0017</td>
<td>5.6583</td>
<td>&lt;.0001</td>
<td>0.0064</td>
</tr>
</tbody>
</table>

---

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Training intensity

Mixed-Effects Model ($k = 13$; $\tau^2$ estimator: DL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau^2$</td>
<td>0.5192 (SE = 1.2306)</td>
</tr>
<tr>
<td>$\tau$ (square root of estimated $\tau^2$ value)</td>
<td>0.7206</td>
</tr>
<tr>
<td>$I^2$ (residual heterogeneity / unaccounted variability)</td>
<td>18.27%</td>
</tr>
<tr>
<td>$H^2$ (unaccounted variability / sampling variability)</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Test for Residual Heterogeneity: $QE(df = 11) = 13.4584$, $p-val = 0.2644$

Test of Moderators (coefficient(s) 1,2): $QM(df = 2) = 153.0276$, $p-val < .0001$

Model Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intensity</td>
<td>-1.1677</td>
<td>1.4530</td>
<td>-0.8036</td>
<td>0.4216</td>
<td>-4.0156</td>
</tr>
<tr>
<td>expend</td>
<td>0.0101</td>
<td>0.0015</td>
<td>6.8293</td>
<td>&lt;.0001</td>
<td>0.0072</td>
</tr>
</tbody>
</table>

---

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
### Session duration

**Mixed-Effects Model (k = 13; tau^2 estimator: DL)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau^2) (estimated amount of residual heterogeneity)</td>
<td>0 (SE = 0.9659)</td>
</tr>
<tr>
<td>(\tau) (square root of estimated (\tau^2) value)</td>
<td>0</td>
</tr>
<tr>
<td>(I^2) (residual heterogeneity / unaccounted variability)</td>
<td>0.00%</td>
</tr>
<tr>
<td>(H^2) (unaccounted variability / sampling variability)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Test for Residual Heterogeneity:** \(QE(df = 11) = 10.8527, \) \(p-val = 0.4557\)

**Test of Moderators (coefficient(s) 1,2):** \(QM(df = 2) = 223.2415, \) \(p-val < .0001\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>duration</td>
<td>-0.0396</td>
<td>-1.8920</td>
<td>0.0585</td>
<td>-0.0806</td>
<td>0.0014</td>
</tr>
<tr>
<td>expend</td>
<td>0.0111</td>
<td>9.1473</td>
<td>&lt;.0001</td>
<td>0.0087</td>
<td>0.0134</td>
</tr>
</tbody>
</table>

---

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 1

### Programme length

**Mixed-Effects Model (k = 13; tau^2 estimator: DL)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau^2) (estimated amount of residual heterogeneity)</td>
<td>0.7430 (SE = 1.4602)</td>
</tr>
<tr>
<td>(\tau) (square root of estimated (\tau^2) value)</td>
<td>0.8620</td>
</tr>
<tr>
<td>(I^2) (residual heterogeneity / unaccounted variability)</td>
<td>21.96%</td>
</tr>
<tr>
<td>(H^2) (unaccounted variability / sampling variability)</td>
<td>1.28</td>
</tr>
</tbody>
</table>

**Test for Residual Heterogeneity:** \(QE(df = 11) = 14.0949, \) \(p-val = 0.2278\)

**Test of Moderators (coefficient(s) 1,2):** \(QM(df = 2) = 137.3016, \) \(p-val < .0001\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>-0.0234</td>
<td>-0.5544</td>
<td>0.5793</td>
<td>-0.1060</td>
<td>0.0593</td>
</tr>
<tr>
<td>expend</td>
<td>0.0095</td>
<td>8.0662</td>
<td>&lt;.0001</td>
<td>0.0072</td>
<td>0.0119</td>
</tr>
</tbody>
</table>

---

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 1
Results from the univariate regression analyses

Total energy expenditure

Mixed-Effects Model (k = 13; tau^2 estimator: DL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau^2 ) (estimated amount of residual heterogeneity):</td>
<td>0.4494 (SE = 1.1052)</td>
</tr>
<tr>
<td>( \tau ) (square root of estimated ( \tau^2 ) value):</td>
<td>0.6703</td>
</tr>
<tr>
<td>( I^2 ) (residual heterogeneity / unaccounted variability):</td>
<td>16.85%</td>
</tr>
<tr>
<td>( H^2 ) (unaccounted variability / sampling variability):</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Test for Residual Heterogeneity: \( QE(df = 12) = 14.4325, p-val = 0.2739 \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>expend</td>
<td>0.0091</td>
<td>0.0007</td>
<td>12.5754</td>
<td>&lt;.0001</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

---

Session frequency

Mixed-Effects Model (k = 13; tau^2 estimator: DL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau^2 ) (estimated amount of residual heterogeneity):</td>
<td>8.0447 (SE = 5.3651)</td>
</tr>
<tr>
<td>( \tau ) (square root of estimated ( \tau^2 ) value):</td>
<td>2.8363</td>
</tr>
<tr>
<td>( I^2 ) (residual heterogeneity / unaccounted variability):</td>
<td>78.47%</td>
</tr>
<tr>
<td>( H^2 ) (unaccounted variability / sampling variability):</td>
<td>4.64</td>
</tr>
</tbody>
</table>

Test for Residual Heterogeneity: \( QE(df = 12) = 55.7314, p-val < .0001 \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq</td>
<td>1.3603</td>
<td>0.2627</td>
<td>5.1781</td>
<td>&lt;.0001</td>
<td>0.8454</td>
</tr>
</tbody>
</table>

---

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1  ‘ ’ 1
Training intensity

Mixed-Effects Model (k = 13; tau^2 estimator: DL)

- \(\tau^2\) (estimated amount of residual heterogeneity): 11.7245 (SE = 7.2598)
- \(\tau\) (square root of estimated \(\tau^2\) value): 3.4241
- \(I^2\) (residual heterogeneity / unaccounted variability): 83.55%
- \(H^2\) (unaccounted variability / sampling variability): 6.08

Test for Residual Heterogeneity: \(QE(df = 12) = 72.9434\), \(p\)-val < .0001

Model Results:

<table>
<thead>
<tr>
<th></th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intensity</td>
<td>6.9781</td>
<td>1.6753</td>
<td>4.1652</td>
<td>&lt;.0001</td>
<td>3.6945</td>
</tr>
</tbody>
</table>

---

Signif. codes: 0 ‘***’ 0.001 ** 0.01 * 0.05 ‘.’ 0.1 ‘ ’ 1

Session duration

Mixed-Effects Model (k = 13; tau^2 estimator: DL)

- \(\tau^2\) (estimated amount of residual heterogeneity): 15.1383 (SE = 9.6789)
- \(\tau\) (square root of estimated \(\tau^2\) value): 3.8908
- \(I^2\) (residual heterogeneity / unaccounted variability): 87.31%
- \(H^2\) (unaccounted variability / sampling variability): 7.88

Test for Residual Heterogeneity: \(QE(df = 12) = 94.5254\), \(p\)-val < .0001

Model Results:

<table>
<thead>
<tr>
<th></th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>duration</td>
<td>0.1149</td>
<td>0.0325</td>
<td>3.5311</td>
<td>0.0004</td>
<td>0.0511</td>
</tr>
</tbody>
</table>

---

Signif. codes: 0 ‘***’ 0.001 ** 0.01 * 0.05 ‘.’ 0.1 ‘ ’ 1
**Programme length**

**Mixed-Effects Model (k = 13; tau^2 estimator: DL)**

- \( \tau^2 \) (estimated amount of residual heterogeneity): 19.7574 (SE = 10.7283)
- \( \tau \) (square root of estimated \( \tau^2 \) value): 4.4449
- \( I^2 \) (residual heterogeneity / unaccounted variability): 88.62%
- \( H^2 \) (unaccounted variability / sampling variability): 8.78

**Test for Residual Heterogeneity:** \( QE(df = 12) = 105.4172, \) \( p-val < .0001 \)

**Model Results:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
<th>Signif. codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>0.2331</td>
<td>0.0798</td>
<td>2.9225</td>
<td>0.0035</td>
<td>0.0768</td>
<td>0.3895 **</td>
</tr>
</tbody>
</table>

*Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1*
Appendix C

Results of the sensitivity analysis, multivariate regression analysis

Session frequency

Mixed-Effects Model (k = 12; tau^2 estimator: DL)

<table>
<thead>
<tr>
<th></th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq</td>
<td>0.1445</td>
<td>0.3132</td>
<td>0.4613</td>
<td>-0.4694</td>
<td>0.7584</td>
</tr>
<tr>
<td>expend</td>
<td>0.0070</td>
<td>0.0019</td>
<td>3.6611</td>
<td>0.0003</td>
<td>0.0108</td>
</tr>
</tbody>
</table>

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Training intensity

Mixed-Effects Model (k = 12; tau^2 estimator: DL)

<table>
<thead>
<tr>
<th></th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intensity</td>
<td>0.6592</td>
<td>1.4674</td>
<td>0.4492</td>
<td>0.6533</td>
<td>-2.2169</td>
</tr>
<tr>
<td>expend</td>
<td>0.0071</td>
<td>0.0018</td>
<td>3.9603</td>
<td>&lt;0.0001</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Session duration

Mixed-Effects Model (k = 12; tau^2 estimator: DL)

- $\tau^2$ (estimated amount of residual heterogeneity): 0 (SE = 1.1055)
- $\tau$ (square root of estimated $\tau^2$ value): 0
- $I^2$ (residual heterogeneity / unaccounted variability): 0.00%
- $H^2$ (unaccounted variability / sampling variability): 1.00

Test for Residual Heterogeneity: $QE(df = 10) = 5.8891$, $p-val = 0.8245$
Test of Moderators (coefficient(s) 1,2): $QM(df = 2) = 104.9340$, $p-val < .0001$

**Model Results:**

<table>
<thead>
<tr>
<th></th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>duration</td>
<td>-0.0200</td>
<td>0.0227</td>
<td>-0.8800</td>
<td>0.3789</td>
<td>-0.0645</td>
</tr>
<tr>
<td>expend</td>
<td>0.0090</td>
<td>0.0015</td>
<td>5.8718</td>
<td>&lt;0.0001</td>
<td>0.0060</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Programme length

Mixed-Effects Model (k = 12; tau^2 estimator: DL)

- $\tau^2$ (estimated amount of residual heterogeneity): 0 (SE = 1.2163)
- $\tau$ (square root of estimated $\tau^2$ value): 0
- $I^2$ (residual heterogeneity / unaccounted variability): 0.00%
- $H^2$ (unaccounted variability / sampling variability): 1.00

Test for Residual Heterogeneity: $QE(df = 10) = 4.7808$, $p-val = 0.9053$
Test of Moderators (coefficient(s) 1,2): $QM(df = 2) = 106.0424$, $p-val < .0001$

**Model Results:**

<table>
<thead>
<tr>
<th></th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>0.0549</td>
<td>0.0400</td>
<td>1.3721</td>
<td>0.1700</td>
<td>-0.0235</td>
</tr>
<tr>
<td>expend</td>
<td>0.0060</td>
<td>0.0015</td>
<td>3.8940</td>
<td>&lt;0.0001</td>
<td>0.0030</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Results of the sensitivity analysis, univariate regression analysis

Total energy expenditure

Mixed-Effects Model (k = 12; tau^2 estimator: DL)

| tau^2 (estimated amount of residual heterogeneity): | 0 (SE = 1.0238) |
| tau (square root of estimated tau^2 value): | 0 |
| t^2 (residual heterogeneity / unaccounted variability): | 0.00% |
| H^2 (unaccounted variability / sampling variability): | 1.00 |

Test for Residual Heterogeneity:  
QE(df = 11) = 6.6635,  
p-val = 0.8256

Model Results:  
<table>
<thead>
<tr>
<th>expend</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0078</td>
<td>0.0008</td>
<td>10.2059</td>
<td>&lt;.0001</td>
<td>0.0063</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

---

Session frequency

Mixed-Effects Model (k = 11; tau^2 estimator: DL)

| tau^2 (estimated amount of residual heterogeneity): | 1.7061 (SE = 1.9763) |
| tau (square root of estimated tau^2 value): | 1.3062 |
| t^2 (residual heterogeneity / unaccounted variability): | 41.88% |
| H^2 (unaccounted variability / sampling variability): | 1.72 |

Test for Residual Heterogeneity:  
QE(df = 10) = 17.2046,  
p-val = 0.0700

Model Results:  
<table>
<thead>
<tr>
<th>freq</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9033</td>
<td>0.2059</td>
<td>4.3869</td>
<td>&lt;.0001</td>
<td>0.4997</td>
<td>1.3069</td>
</tr>
</tbody>
</table>

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

---
Training intensity
Mixed-Effects Model (k = 11; tau^2 estimator: DL)

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tau^2 (estimated amount of residual heterogeneity):</td>
<td>0.8977 (SE = 1.5518)</td>
</tr>
<tr>
<td>tau (square root of estimated tau^2 value):</td>
<td>0.9475</td>
</tr>
<tr>
<td>I^2 (residual heterogeneity / unaccounted variability):</td>
<td>26.69%</td>
</tr>
<tr>
<td>H^2 (unaccounted variability / sampling variability):</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Test for Residual Heterogeneity: \(QE(df = 10) = 13.6398, p-val = 0.1901\)

<table>
<thead>
<tr>
<th>parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intensity</td>
<td>4.7475</td>
<td>0.8956</td>
<td>&lt;.0001</td>
<td>2.9921</td>
<td>6.5029</td>
</tr>
</tbody>
</table>

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Session duration
Mixed-Effects Model (k = 11; tau^2 estimator: DL)

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tau^2 (estimated amount of residual heterogeneity):</td>
<td>5.3000 (SE = 4.3275)</td>
</tr>
<tr>
<td>tau (square root of estimated tau^2 value):</td>
<td>2.3022</td>
</tr>
<tr>
<td>I^2 (residual heterogeneity / unaccounted variability):</td>
<td>69.66%</td>
</tr>
<tr>
<td>H^2 (unaccounted variability / sampling variability):</td>
<td>3.30</td>
</tr>
</tbody>
</table>

Test for Residual Heterogeneity: \(QE(df = 10) = 32.9593, p-val = 0.0003\)

<table>
<thead>
<tr>
<th>parameter</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>duration</td>
<td>0.0673</td>
<td>0.0252</td>
<td>2.6710</td>
<td>0.0076</td>
<td>0.0179</td>
</tr>
</tbody>
</table>

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Programme length

Mixed-Effects Model (k = 11; tau^2 estimator: DL)

- tau^2 (estimated amount of residual heterogeneity): 0 (SE = 1.2141)
- tau (square root of estimated tau^2 value): 0
- I^2 (residual heterogeneity / unaccounted variability): 0.00%
- H^2 (unaccounted variability / sampling variability): 1.00

Test for Residual Heterogeneity:  QE(df = 10) = 4.6617,  p-val = 0.9126

<table>
<thead>
<tr>
<th>Model Results:</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>0.1779</td>
<td>0.0202</td>
<td>8.8204</td>
<td>&lt;.0001</td>
<td>0.1383</td>
</tr>
</tbody>
</table>

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1