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The Physical Effect of Exergames in Healthy Elderly—A Systematic Review

Lisbeth H. Larsen, MSc,1 Lone Schou, MSc,1 Henrik Hautop Lund, PhD,2 and Henning Langberg, DMSc, PhD1

Abstract

Exergames have been suggested as an innovative approach to enhance physical activity in the elderly. The objective of this review was to determine the effectiveness of exergames on validated quantitative physical outcomes in healthy elderly individuals. We used Centre for Review and Disseminations guidance to conduct systematic reviews. Four electronic databases were searched. We included randomized controlled trials (RCTs), the study participants were healthy elderly individuals, and the intervention of interest was exergaming. The title and abstract screening of the 1861 citations identified 36 studies as potentially eligible for this review, and an additional nine were identified from reference lists. The full text screening identified seven studies with a total of 311 participants, all reporting RCTs with low-to-moderate methodological quality. Six of the seven studies found a positive effect of exergaming on the health of the elderly. However, the variation of intervention approaches and outcome data collected limited the extent to which studies could be compared. This review demonstrates how exergames have a potential to improve physical health in the elderly. However, there is a need for additional and better-designed studies that assess the effectiveness and long-term adherence of exergames designed specifically for the elderly.

Introduction

Modern healthcare systems are currently facing major challenges as the population ages. Between 2000 and 2050, the proportion of the world’s population over 60 years of age will double from about 11 percent to 22 percent, whereas the number of people 80 years of aged and older will quadruple over the same period.1 This has a substantial impact on both the healthcare system and the society in general. With age, physical function tends to gradually deteriorate, leading to limited mobility, frailty, or other physical health problems. However, the most common reason for loss of functional capabilities in the elderly is inactivity or immobility, and it has been well established that physical activity can effectively reduce weakness and deconditioning in elderly adults.2,3 Nevertheless, physical activity behavior of most elderly people does not comply with current guidelines.4,7 For instance, in the aging European population (≥70 years) 66 percent do not participate in physical exercise or sports, and every other respondent agrees with the statement: “Being physically active does not really interest me—I would rather do other things with my spare time.”4 Other reported barriers regarding physical activity in the elderly include poor health, fear of injury, lack of companionship, lack of opportunities for sports or leisure activities, and lack of transport opportunities.4,8

Exercise adherence is a significant hurdle to overcome. However, enforcing participation requires substantial resources, and the long-term success of these interventions is questionable.10 Accessible effective strategies to encourage voluntary participation and long-term adherence to daily physical activity are needed. Recently a new approach has been proposed in order to motivate people to be physically active: A new generation of digital gaming systems with an interface that requires physical exertion to play the game. The games incorporate technology, play, and physical activity and are also referred to as, for example, exergames, exertion games, entertainment, active-play videogames, interactive computer games, or game-based technology-mediated physical activity. In this review we use the term exergames as a synonym for all of the above terms. Some of the better-known exergames are the Nintendo® (Redmond, WA) Wii™ games, “Dance Dance Revolution” (DDR) (Konami Digital Entertainment, El Segundo, CA), Playstation®2 EyeToys® (Sony Computer Entertainment America LLC, San Mateo, CA), games, and Microsoft® (Redmond) Kinect games.

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Exergames uses different types of sensors and inputs that require the players to be active to play and win the games (e.g., balance boards, dance pads, gym equipment, cameras, remote controls with accelerometers, and heart rate monitors). Thus, exergaming relies on technology that tracks body movement or reaction.

Exergaming aims at overcoming several of the reported barriers to physical activity, such as making physical activity more appealing and engaging a large audience across different age groups. The fact that exergaming allows for real-time feedback on performance has been shown to encourage participants to compete both individually and with other players. Exergames can be graded according to the player’s own ability, ensuring increased motivation to complete the physical activity and undermining the barrier “poor health.” Finally, exergames can be a convenient activity that allows for supervised activities despite geographical distances, providing physical activity in the familiar surroundings of the home, thus overcoming the difficulties of transportation for the elderly with limited mobility.

The number of publications on exergames has been increasing exponentially during the last decade. Until recently the attention has primarily focused on early-phase piloting and development work. Many of those trials have provided preliminary evidence and clinical efficacy of exergaming, and, consequently, increasing numbers of randomized controlled trials (RCTs) are being conducted. Several reviews on intervention studies of exergaming have already been published. However, the systematic reviews have focused on children, on those in a very broad age group, or on both healthy and diseased elderly participants. Several overview articles have recently been published reviewing the current status of exergaming on specifically elderly adults. However, these articles have had an explorative approach (e.g., they have not conducted a systematic literature search, and they have included different study designs). Because the gold standard for medical evidence is the RCT, stronger evidence will be necessary for exergames to be accepted as valuable interventions. Additionally, several new studies have been published since these reviews were brought forward. Thus, the aim of the current review was to assess the effect of exergames on quantitative validated physical health outcomes in healthy elderly individuals tested in a rigorous study design (i.e., RCTs).

Materials and Methods

Selection criteria

We included RCTs that compared exergames with another alternative intervention or no intervention. Study participants were healthy elderly people (>60 years). Studies exploring exergames for rehabilitation use after a specific injury or in relation to a specific disease or chronic condition were excluded, and so were studies including individuals with significant somatic or mental illness. We examined the effect on quantitative physical outcomes (e.g., aerobic fitness, muscle strength, balance, or body composition measured with validated assessment tools).

We used the definition of a game by McGonigal to specify the selection criteria for exergames, by distinguishing game-based activities from purely technology-mediated interventions that lack structured playing (e.g., computer interaction limited to graphical feedback during training). According to McGonigal, a game consists of four key elements: (1) a specific goal toward which people are willing to work, (2) rules that stimulate creativity within specified boundaries, (3) a feedback system that lets individuals know how they are doing with respect to the goal, and (4) a voluntary acceptance of the goal, rules, and feedback information. Thus, interventions that met the following definition were considered to be exergaming: “a digital game that require players to perform physical exertion to play and where the game has specific goals, rules, and a feedback mechanism such as a score.” This definition of an exergame is in line with the one used by the American Heart Association.

Search strategy

We adopted a systematic approach based on the 2009 guidelines of the Centre for Reviews and Dissemination at the University of York. A systematic search in four databases (Medline/PubMed, EMBASE, Cochrane Library, and Web of Science) based on key words was used to identify peer-reviewed journal articles in English in January 2013. The search was conducted using the following two groups of key words in various combinations: “game OR games OR gaming OR exergame OR exergames OR exergaming OR virtual reality OR active video OR game-based OR playware OR teleplay OR digital play OR computer supported collaborative sports” AND “physical training OR physical activity OR motor activity OR leisure activity OR physical fitness OR exercise OR exertion OR BMI [body mass index] OR body composition OR vo2max [maximum O2 uptake] OR vo2peak OR weight loss OR body weight OR obesity OR sports OR kinesiology OR physical education OR move OR prevention OR rehabilitation OR health promotion OR balance OR physical function OR heart rate OR musculoskeletal OR energy expenditure OR energy metabolism.” The selection of studies was done systematically based on the prespecified PICO(S) (Participants, Interventions Comparisons, Outcome, Study-design) eligibility criteria. In an attempt to identify further relevant studies, we scanned the reference list of reviews and relevant articles. Conference, proceedings, posters, and abstracts were not included as they could not be searched in the databases in a systematic way. Full details and results of the literature search can be found in Supplementary Appendix 1 (Supplementary Data are available online at www.liebertpub.com/g4h).

Data collection and management

The study selection was conducted in two stages: An initial screening of titles and abstracts against the inclusion criteria to identify potentially relevant articles (done by L.H.L.). This was followed by a screening of the full articles identified as possibly relevant in the initial screening (done by L.H.L., L.S., and H.L.). Disagreements about study eligibility were discussed among the authors and resolved by consensus after referring to the protocol.

Methodological quality of included studies was assessed independently by L.H.L., L.S., and H.L. using the Cochrane Collaborations’ risk of bias tool (see Supplementary Appendix 2). Categories assessed were as follows: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective
reporting, and other sources of bias. Risk of bias was determined to be “low risk,” “high risk,” or “unclear risk.” The reviewers compared their assessment of included studies, and any disagreements were discussed and resolved by consensus. The PRISMA checklist was used to make an attempt to report the results systematically.30

**Results**

In total, 1861 articles were identified from the search, of which 36 studies were read in full. After reading the full text of the 36 articles we identified nine additional studies in the reference list that were also included in the full-text review process. The initial screening excluded studies because of the involvement of children/young participants or patients or because of investigating different kinds of games (e.g., educational games or non-technological games). Studies that did not include quantitative validated physical outcome were also excluded. Reasons for exclusion during the second screening are documented in Figure 1 and resulted in seven RCTs meeting the eligibility criteria.

**Study characteristics**

The studies included31–37 were conducted in four different countries (Canada, France, United States, and Switzerland) and published in either 2011 or 2012. In total, 311 healthy elderly participants were included in the trials \( n = 7 \). Details on sample size, gender balance, age of participants, intervention approach, outcomes, and key findings (statistical

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**FIG. 1.** Flow diagram of the inclusion process.
<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Sample size; % male; age (years) (SD)</th>
<th>Intervention</th>
<th>Comparative</th>
<th>Duration (weeks)</th>
<th>Dropouts (%)</th>
<th>Physical outcomes</th>
<th>Key findings (statistical results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson-Hanley et al.37</td>
<td>n=79 22% I=75.7 (9.9) C=81.3 (6.2)</td>
<td>3D (cybercycle)</td>
<td>Exercise</td>
<td>12</td>
<td>16</td>
<td>Exercise effort, muscle strength, BC</td>
<td>Similar effect in both groups</td>
</tr>
<tr>
<td>Franco et al.33</td>
<td>n=38 22% I=78.27 (6) C=81.3 (6.2)</td>
<td>Wii Fit+exercise</td>
<td>Exercise or no exercise</td>
<td>3</td>
<td>16</td>
<td>BBS, POMA</td>
<td>No effect on balance in either of the groups</td>
</tr>
<tr>
<td>Pichierri et al.35</td>
<td>n=25 60% I=83.6 (3.4) C=86.2 (4.8)</td>
<td>DDR+exercise</td>
<td>No exercise</td>
<td>12</td>
<td>40</td>
<td>Step execution under single- and dual-task conditions</td>
<td>Improved voluntary step execution for I group</td>
</tr>
<tr>
<td>Pluchino et al.32</td>
<td>n=40 38% I=72.5 (8.4) C=81.3 (6.2)</td>
<td>Wii Fit</td>
<td>Tai chi or exercise</td>
<td>8</td>
<td>33</td>
<td>Field (TUG, OLS, FR, POMA), Lab (COP, DMA)</td>
<td>Similar improvements in balance for all groups</td>
</tr>
<tr>
<td>Rendon et al.31</td>
<td>n=40 35% I=85.7 (4.3) C=83.3 (6.2)</td>
<td>Wii Fit+exercise</td>
<td>No exercise</td>
<td>6</td>
<td>15</td>
<td>TUG</td>
<td>Improved functional balance for I group</td>
</tr>
<tr>
<td>Szturm et al.36</td>
<td>n=30 63% I=80.5 C=81</td>
<td>AVG</td>
<td>Exercise</td>
<td>8</td>
<td>10</td>
<td>BBS, TUG, gait parameters, CTSIB</td>
<td>Greater improved balance scores for I group</td>
</tr>
<tr>
<td>Touloute et al.34</td>
<td>n=36 38% I=75.09 (10.26)</td>
<td>Wii Fit or Wii + exercise</td>
<td>Exercise or no exercise</td>
<td>20</td>
<td>0</td>
<td>POMA, Unipedal, Wii Fit test</td>
<td>Improved static balance for all exercise groups, improved dynamic balance only for traditional exercise</td>
</tr>
</tbody>
</table>

AVG, active videogames; BBS, Berg Balance Scale; BC, body composition; C, control group; COP, center of pressure; CTSIB, clinical test of sensory interaction and balance; DDR, "Dance Dance Revolution"; DMA, dynamic motion analysis; FR, functional reach test; I, intervention group; OLS, one leg stance test; POMA, Tinetti Performance-oriented Mobility Assessment; TUG, Timed Up and Go.
results) are presented in Table 1. Participants in the studies had a mean age between 73 and 86 years.

The exergaming solutions varied in terms of software and game platform. Four studies evaluated the use of the commercial solution Wii Fit.31–34 Of these four studies, one study compared the exergaming with usual care (no exercise),31 whereas the remaining three studies were designed as three-armed trials comparing the intervention with both another type of exercise and usual care (no exercise).32–34 Another commercial exergaming solution included in this review involved the DDR solution and compared the intervention with usual care (no exercise).35 Two non-commercial exergames were included36,37: One of those studies evaluated a self-invented exergame solution using a sponge pad/pressure mat compared with a traditional exercise program,36 and the other study investigated cybercycling compared with traditional cycling.37

The most common methodological weaknesses of the studies included in this review referred to the blinding of participants, personnel, and assessors. Moreover, three studies did not conceal the allocation of participants into different intervention groups, and three studies failed to explicitly state it. In addition, only two studies used intention-to-treat analysis. Most studies that had groups that were comparable at baseline, reported between-group analyses, and had less than 20% dropouts. There was no relation between methodological quality and degree of evidence. The risk of bias of the studies included is reported in Table 2.

**Physical outcomes**

Five studies evaluated the effect of exergames on balance performance.31–33,36 Of these five studies, two studies reported an improved effect on balance of exergaming compared with, respectively, no exercise31 or exercise,36 one study found traditional exercise to be more effective than exergaming,34 one study reported similar effects,32 and one study reported no effect.33 All five studies used one or more of the following validated field tests: the Berg Balance Scale (BBS), the Tinetti Performance-oriented Mobility Assessment (POMA), or the Timed Up and Go (TUG). In addition, two of the studies combined the analyses with a laboratory test measuring static and dynamic balance through posturography. Of the two remaining studies, one reported an effect of exergaming on stepping execution compared with no exercise measured through force platforms,32 and the second study reported the same physical effect of exergaming on exercise effort, body composition, and lower limb muscle strength compared with traditional exercise measured through bike computers, dual-energy X-ray absorptiometry scanning, and dynamometers.37 It is interesting, though, that this study found an additional cognitive effect of exergaming.37

**Discussion**

The aim of this review was to determine the effect of exergames on validated quantitative physical health outcomes in healthy elderly individuals. The systematic review identified seven RCTs comparing exergaming with an alternative intervention or no intervention in healthy elderly participants. Findings in six of the seven RCTs suggest a positive effect of exergames on physical outcomes in the

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other sources of bias (other bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen-Hanley et al. (2012)</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Franco et al. (2012)</td>
<td>B</td>
<td>C15</td>
<td>C15/C15/C15/C15/C15</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C15/C15/C15/C15/C15</td>
</tr>
<tr>
<td>Pichierri et al. (2012)</td>
<td>B</td>
<td>C15</td>
<td>C15/C15/C15/C15/C15</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C15/C15/C15/C15/C15</td>
</tr>
<tr>
<td>Pluchino et al. (2012)</td>
<td>B</td>
<td>C15</td>
<td>C15/C15/C15/C15/C15</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C15/C15/C15/C15/C15</td>
</tr>
<tr>
<td>Rendon et al. (2012)</td>
<td>B</td>
<td>C15</td>
<td>C15/C15/C15/C15/C15</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C15/C15/C15/C15/C15</td>
</tr>
<tr>
<td>Szturm et al. (2011)</td>
<td>BB</td>
<td>C15</td>
<td>C15/C15</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C15/C15</td>
</tr>
<tr>
<td>Toulotte et al. (2012)</td>
<td>B</td>
<td>C15</td>
<td>C15/C15</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C15/C15</td>
</tr>
</tbody>
</table>

Bias was scored as low risk (◦), unclear (○), or high risk (●).
elderly. However, intervention approaches, outcome measures, and control groups varied, making it difficult to translate these preliminary findings into a general recommendation about the use of exergames. For example, the intervention in two of the seven RCTs combined exergaming with additional exercise and compared it with “no exercise,” making it difficult to conclude whether the beneficial effect was due to exergaming or the additional exercise. One study did not find any effect of 3 weeks of exergaming compared with “no exercise,” nor did this study find any effect of traditional exercise. However, the outcome measures—BBS and POMA—might not be sensitive enough to track changes in a short duration of 3 weeks. Furthermore, participants had a very high score in both BBS and POMA prior to the intervention, indicating that the results are characterized by the ceiling effect. Thus, selecting reliable outcome measurements responsive to improvements in the participants involved is crucial.

Four studies evaluated the Wii Fit solutions with very different outcome, but none of them reported superior effect of the intervention compared with traditional exercise. There can be several explanations for that; one might be that Wii Fit gaming is not designed for the older population over 60 years. Szturm et al. designed their own exergames solution, and they reported improved effect on balance performance of their approach compared with traditional exercise, stressing that game concepts have to be developed and tailored to the individual prerequisites of older people.

Our findings are consistent with the conclusions of earlier reviews that demonstrated that exergaming have the potential to improve physical health, but also that further research with stronger studies is required to quantify the effect of exergames. The seven studies included in this review had a low- to-moderate methodological quality. Aspects such as the binding of participants and personnel are difficult to achieve in studies involving physical interventions. However, the use of larger sample sizes based on power analysis, methods of randomization, concealment of allocation, and binding of assessors as well as intention-to-treat analysis would improve the methodological quality of the studies considerably and strengthen the evidence. Poorly designed studies make it difficult to compare and sample results and hence make it impossible to draw any conclusions. Well-designed RCTs are considered the gold standard for research aimed at identifying the causal relationship between an intervention and outcome. Therefore these studies are necessary in order to evaluate evidence consistently. Furthermore, as evidence accumulates there will be a need for exploring the long-term efficacy of using exergaming in a non-structured and self-managed manner for physical activity promotion. The studies included in this review support the beneficial effect on motivation and demonstrate that exergames are an enjoyable form of exercise. However, these findings may be due to initial increase of motivation. Further studies are needed to reveal if adherence to exergaming persists over time.

Another important factor that has received great interest is the potential cognitive benefits of exergaming. It is beyond the scope of this review to discuss this further. It is interesting that one of the studies included in this review investigated cognitive outcome, and they found similar effects on physical outcomes of exergaming compared with traditional exercise but an additional cognitive effect. Exergames do not only involve physical activity, but also require cognitive work (e.g., sensing of stimuli, paying attention, and making quick decisions). This might be very important, as a recently published systematic review recommend that a cognitive element should be part of an exercise program for elderly because falls often occur under attention-demanding circumstances.

Strengths and limitations of this review

This systematic review’s major strength is the use of the Centre for Reviews and Dissemination’s guidance (i.e., the use of prespecified PICOS eligibility criteria, a comprehensive search strategy, duplicate and independent screening, methodological quality assessment, and data extraction). Moreover, we only included RCTs using validated assessment tools, and we made an attempt to limit the heterogeneity of the included participants. We used a strict definition of exergames because we believe it is important to distinguish exergaming from other purely technology-mediated approaches in order to evaluate the effect rigorously. We are unaware of other studies that reviewed the evidence of exergames in healthy elderly individuals with the same systematic approach. However, limitations of this review should be noted. First, we have identified a limited number of studies that met all eligibility criteria. Second, the studies we did include varied in terms of type of intervention, type of control, outcome measures, and methodological quality. Third, a publication bias may have occurred, as well as language bias, given that we considered only interventions described in published studies and restricted our search to English language publications. Additionally, the identified studies are limited to our key word search, which might have been insufficient because the use of terms varies greatly in this new field. However, we tried to meet this limitation by screening the reference list of reviews and relevant articles.

Implications for research

Longer and better-designed RCTs to assess the effectiveness of exergames are needed (e.g., use of blinded assessors, allocation concealment, and intention-to-treat analysis). It is important that future studies compare exergames with the best available alternative (e.g., traditional exercise) and that exergaming is the only difference in the investigated groups. There is also a need to better report detailed description of the game (e.g., physical content, rules of the game, technological tools required) and the intervention (e.g., length of each game session, frequency of administration, associated activities), as well as the trial characteristics (e.g., whether allocation was concealed) and the analytical approach. Future studies should aim to assess relevant physical and cognitive outcomes and compliance (e.g., behavioral change) pre- and post-intervention with validated outcome measures.

Future work may wish to design exergames that are focused on the needs of the user, including appropriate content, interface design, and game demands. The games should be designed and further developed based on an interdisciplinary understanding of the respective application field. We recommend that the effect and adherence of exergaming should be explored further before conducting large-scale studies.

In conclusion, our review identified several studies that demonstrated an effect of exergaming on quantitative health parameters in the elderly. Thus, exergaming seems to have
potential for improving health in the elderly. However, there is a need for additional and better-designed studies assessing the effectiveness and long-term adherence of exergaming where the games are specifically tailored to the individual prerequisites of older people.

Acknowledgments

We are grateful for funding from the Department of Public Health, University of Copenhagen.

Author Disclosure Statement

No competing financial interests exist.

References

34. Toullette C, Tourse C, Olivier N. Wii Fit® training vs. adapted physical activities: Which one is the most appropriate to improve the balance of independent senior subjects? A randomized controlled study. Clin Rehabil 2012; 26:827–835.


Supplementary Data

Appendix 1: Search strategy

We used the following search strategy for The Cochrane Library, PubMed, Web of Science, and EMBASE:

Search Name: Review Exergame
Last Saved: 10/01/2013 12:08:25.411
Description:
ID  Search
#1  game,ti,ab,kw in Trials (Word variations have been searched)
#2  exergame in Trials (Word variations have been searched)
#3  exergaming in Trials (Word variations have been searched)
#4  exergames in Trials (Word variations have been searched)
#5  games in Trials (Word variations have been searched)
#6  gaming in Trials (Word variations have been searched)
#7  teleplay in Trials (Word variations have been searched)
#8  digital play in Trials (Word variations have been searched)
#9  virtual reality in Trials (Word variations have been searched)
#10  computer supported collaborative sports in Trials (Word variations have been searched)
#11  active video in Trials (Word variations have been searched)
#12  game-based in Trials (Word variations have been searched)
#13  #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14  physical training in Trials (Word variations have been searched)
#15  physical activity in Trials (Word variations have been searched)
#16  motor activity in Trials (Word variations have been searched)
#17  leisure activity in Trials (Word variations have been searched)
#18  physical fitness in Trials (Word variations have been searched)
#19  exercise in Trials (Word variations have been searched)
#20  exertion in Trials (Word variations have been searched)
#21  BMI in Trials (Word variations have been searched)
#22  body composition in Trials (Word variations have been searched)
#23  vo2max in Trials (Word variations have been searched)
#24  weight loss in Trials (Word variations have been searched)
#25  body weight in Trials (Word variations have been searched)
#26  obesity in Trials (Word variations have been searched)
#27  sports in Trials (Word variations have been searched)
#28  kinesiology in Trials (Word variations have been searched)
#29  physical education in Trials (Word variations have been searched)
#30  move in Trials (Word variations have been searched)
#31  prevention in Trials (Word variations have been searched)
#32  rehabilitation in Trials (Word variations have been searched)
#33  health promotion in Trials (Word variations have been searched)
#34  balance in Trials (Word variations have been searched)
#35  physical function in Trials (Word variations have been searched)
#36  heart rate in Trials (Word variations have been searched)
#37  musculoskeletal in Trials (Word variations have been searched)
#38  energy expenditure in Trials (Word variations have been searched)
#39  energy metabolism in Trials (Word variations have been searched)
#40  #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
  or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40
#41  #13 and #40

#42  #13 and #41
### Appendix 2: Cochrane risk of bias table

#### Supplementary Table S1. The Cochrane Collaboration’s Tool for Assessing Risk of Bias

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Review authors’ judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.</td>
<td>Was the allocation sequence adequately generated? Yes No Unsure</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.</td>
<td>Was allocation adequately concealed? Yes No Unsure</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Assessments should be made for each main outcome (or class of outcomes)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</td>
<td>Was knowledge of the allocated intervention adequately prevented during the study?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participants: Yes No Unsure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Personnel: Yes No Unsure</td>
</tr>
<tr>
<td>Blinding of outcome assessors</td>
<td>Assessments should be made for each main outcome (or class of outcomes)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</td>
<td>Outcome assessors: Yes No Unsure</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Assessments should be made for each main outcome (or class of outcomes).</td>
<td>Were incomplete outcome data adequately addressed? Yes No Unsure</td>
</tr>
<tr>
<td></td>
<td>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.</td>
<td></td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>State how the possibility of selective outcome reporting was examined by the review authors, and what was found</td>
<td>Are reports of the study free of suggestion of selective outcome reporting? Yes No Unsure</td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were prespecified in the review’s protocol, responses should be provided for each question/entry.</td>
<td>Any further issues that may raise concerns about the possibility of bias? Yes No Unsure</td>
</tr>
</tbody>
</table>