Supplementary Online Content

de Souto Barreto P, Rolland Y,Vellas B, Maltais M. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults: a systematic review and meta-analysis [published online December 28, 2018]. *JAMA Intern Med*.
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This supplementary material has been provided by the authors to give readers additional information about their work.

Supplements

Long-term exercise for protecting against falls, fractures, hospitalizations and mortality in older adults: a systematic review and meta-analysis

Summary

Appendix 1. Study Protocol

2. Review objectives

2.1. Main objective

To assess the effects of long-term exercise training for protecting against major adverse health events in older populations.

2.2. Secondary objectives

None

3. Methods

- Firstly, information from randomised controlled trials (RCT) on the effects of exercise training (intervention) for protecting older adults against mortality, hospitalisations, falls, fractures and other major adverse health events (as defined by the authors of original investigations) will be gathered.
- Then, the content of the selected RCTs will be analysed qualitatively (the "review" part of the study).
- Finally, the effects of exercise training for protecting older adults against mortality, hospitalisations, falls, fractures and other major adverse health events will be analysed quantitatively (meta-analysis), if appropriate.

4. Criteria for considering studies for this review

4.1. Study design

- Randomised controlled trials (both cluster and parallel design) as clearly stated (or when the information is available in the reporting of the study) by the authors of the original studies. Cross-over randomised trials will be accepted, but only the first part of the trial (before cross-over) will be examined both qualitatively and quantitatively.

-For cluster RCTs, where these studies presented an estimate of effect that properly accounted for the cluster design (eg, multilevel analysis), this will be used. Where this was not the case, we will assume that the intra-cluster correlation coefficient (ICC) is the same as for other studies included in the review for that outcome. We will use an ICC from external sources if available; then, we will correct the values for each unadjusted study by the design effect (Cochrane Handbook. Chapter 16. 16.3 Cluster randomized trials. Available at: http://handbook.cochrane.org/). If an ICC from an appropriate external source is not available, we will use the raw values of the original studies.

4.2. Participants

- People 60 years-old or over. Alternatively, baseline mean age of 60 or over will also be accepted.
- Studies developed in any setting (eg, community, nursing homes, etc.) will be included. If appropriate, the potential bias related to the setting where people live will be addressed in sensitivity analysis.

4.3. Interventions

- Exercise training performed at any frequency, intensity, and session duration.
- Long-term exercise training: intervention length must be ≥ one year (or ≥12 months or ≥48 weeks). The 1-year intervention length was set in an attempt of reducing the bias related to including terminally

ill patients who might die in the first months of the study and for whom exercise would probably not influence mortality risk.

- Group-based or individually-based exercise, with or without an exercise instructor will be included.

4.4. Comparisons

- Comparisons will be made between the exercise intervention and the control group. For comparisons to be made, the only difference between experimental and control groups must be the exercise intervention; coupled interventions (co-interventions), such as, exercise training + another intervention (eg, nutritional or educational interventions) vs. usual care, for example, will be excluded from the review since it is impossible to determine the effects of the exercise intervention alone; however, if exercise + nutrition vs. nutrition alone, then the study will be included. In the case of 2 x 2 interventions (eg, exercise, nutrition, exercise + nutrition, control) only the data for the exercise group alone VS. controls will be used in meta-analysis.

- Interventions that do not have any session of exercise training but that only have educational/motivational aspects to increase physical activity levels as the core element of the intervention will be excluded (eg, when the intervention consists at one session per week or month of educative information on the benefits of physical activity).

- In RCTs that compare more than one exercise intervention to controls, the exercise program that achieves higher volumes of exercise (product of exercise frequency, intensity and session duration) will be used for the quantitative analysis. If the information available in the original studies does not provide enough information for calculating exercise volumes, the exercise group with the highest effective exercise frequency (attendance to exercise programs will be used to calculate the effective frequency of participation) will be retained for analysis. All exercise groups will be analysed qualitatively.

4.5. Outcomes

Data on the outcomes of interest for this review will come from the whole duration of the trial (between baseline and post-intervention evaluations). Data coming from an observational follow-up period after the end of the intervention will not be used.

4.5.1. Main outcome

-Mortality: binary variable with the number of people who died per study group

-Hospitalisations: binary variable with the number of people who have been admitted to the hospital (inpatient hospitalisation or ≥24hr hospitalisation) per study group. Complementarily, the total number of hospitalisations per study group will also be searched and recorded when available.

-Falls: binary variable with the number of people who have fallen (according to the definition used by original investigators) per study group. Complementarily, the total number of falls per study group will also be searched and recorded when available.

-Fractures: binary variable with the number of people who have had a fracture per study group. Complementarily, the total number of fractures per study group will also be searched and recorded when available.

-All major adverse events: binary variable with the number of people who have had at least one major adverse health event per study group. Major adverse health events are: death, hospitalisation, fall, fracture and any other event defined by original investigators as “major” or “severe”. Complementarily, the total number of major adverse events per study group will also be searched and recorded when available.

4.6. Language issues

- No language limitations will be set in the electronic search strategy.

5. Eligibility criteria (summary)

-RCTs comparing the effects of one or more exercise interventions to a control group for protecting older adults against mortality, hospitalisations, falls, fractures and other major adverse health events.

6. Dealing with changes in the procedures of the review

- Any change to this protocol will be addressed by performing sensitivity analysis (when appropriate) to assess the impact of changes on the review findings.

7. General aspects of the Review Protocol

7.1. Electronic search

-Electronic searches will be performed by one of the review authors using standard procedures. The protocol for the electronic searches (including search terms and databases) was previously validated by all the authors.

7.2. Assessment of eligibility of studies

-After performing the electronic searches, duplicate publications will be removed. Then, articles’ titles and abstracts will be screened independently by two authors (this procedure will permit to exclude studies completely out of scope) to establish their potential eligibility.

-Divergences with regards to eligibility will be discussed in an in-person meeting between the two raters. If no consensus is obtained, the articles will be included in the next phase of the review process (full-text articles assessed for eligibility).

-Full-text articles of pre-screened studies will then be assessed for eligibility. At least two authors will do this work independently; they will use a standard form to guide them to correctly assign articles as “eligible”, “not eligible” or “needing further information”. Reasons for excluding articles will be recorded.

-Divergences with regards to eligibility will be discussed with a third author.

-Studies will not be excluded systematically only because they did not report any information on the outcomes of this review. Indeed, it is possible that outcomes have been assessed in a given study but, for several reasons, authors did not report them (selective reporting bias); in such a case, authors of the original studies may be contacted to provide information on the outcomes. If the outcomes were not assessed, then the study will be excluded.

7.3. Data extraction

-This will be done independently by two authors using a standard form specifically developed for this review. The data collection form was previously validated by all the authors.

-We will carefully examine the reports and the data to try to detect potential duplicate publication (multiple reports from the same study). If uncertainties remain about duplicate publication, we will contact (by e-mail) the authors of the original studies to solve any doubts.

-When methodological procedures (for the purposes of evaluating risk of bias) or data (for the purposes of performing a meta-analysis) are insufficiently reported, we may contact authors of the original studies. For complimentary information, we may consider to examine trial registries (eg, ClinicalTrials.gov).

7.4. Other issues related to the "risk of bias" assessment

- Since exercise behaviour is hard to maintain in the long-term and since we are focusing on long-term interventions (≥ 1 year), we expect to find high attrition rates. For the same reasons we also expect to find low compliance rates. Therefore, particular attention will be paid to potential bias related to Attrition/Exclusions and very low effective frequency of exercise. RCTs for which > 40% of exercisers have missing data on the outcomes, when review authors judge that imbalance in missing data across study's arms are extremely important, or where the reasons for these missing data differ across study's arms and differences are likely to introduce bias, will be considered as "High Risk" due to attrition. These studies will not make part of the Primary Analysis in meta-analysis, but will be integrated in sensitivity analysis.

- RCTs for which the effective frequency of exercise was < 1x/week will be considered as at High Risk of "Other Bias" because this weekly frequency is unlikely to promote the benefits of exercise (especially, when considering physiological benefits). These studies will not make part of the Primary Analysis in meta-analysis, but will be integrated in sensitivity analysis.

-Sensitivity analysis in the meta-analysis will be performed by opposing studies with low risk of bias regarding attrition and exercise frequency to those with a high risk of bias.

-If bias related to selective reporting of the outcomes is detected, review authors will systematically contact the authors of the original studies to require information needed for doing meta-analysis (eg, if authors reported to have assessed hospitalisations in the Methods section of the article, but only indicated that "differences between groups for hospitalisations were not significant" (with no data) in the results section).

8. Pre-planned quantitative analyses (meta-analysis)

- For the binary outcomes, we will combine the estimates for each study using risk ratio (RR). Discrete/continuous variables will be combined using the mean difference approach. Because we expected to find high heterogeneity across studies, we will use DerSimonian and Laird's random effects model (DerSimonian and Laird, 1986) for analysis of all outcomes (Mantel-Haenszel method for binary outcomes). The degree of heterogeneity will be assessed by visual inspection, and by the I^2 method (I^2> 50% will be considered as substantial heterogeneity) (Higgins et al.,2003); when I^2< 50%, a fixed-effect model will be performed as a sensitivity analysis. Small-study effects will be evaluated using the Egger's

test (regression of estimates against their standard error), with $p < 0.1$ indicating substantial asymmetry. When the Egger's test shows evidence of asymmetry, a funnel plot will be computed for visual input.

- Subgroup analysis will be done: (1) studies with high risk of bias *VS*. studies with low risk of bias (especially regarding Attrition); (2) effective exercise frequency ≥ 1x/week *VS*. < 1x/week; (3) studies for disease-specific populations (eg, people with dementia/diabetes/heart disease) *VS*. non-disease specific.

-If the number of RCTs allow, we will consider performing meta-regressions to examine whether exercise characteristics (eg, frequency, intensity, session duration, and type (eg, aerobic exercise, strength training, or their combination – the so-called multicomponent training)) are associated with the outcomes.

Appendix 2. Electronic searches

1. Pubmed

Date searched: 20.02.2018
Dates of publication of retrieved articles: from July-August 1976 to present
Number of studies retrieved: 597

Search	Query	Items found
#1	Elder* [Title/Abstract]	230631
#2	“older adults” [Title/Abstract]	57233
#3	“older adult” [Title/Abstract]	5838
#4	“older population”[Title/Abstract]	3934
#5	“very old”[Title/Abstract]	3877
#6	“oldest old”[Title/Abstract]	2009
#7	aged[Title/Abstract]	491677
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	720745
#9	“exercis*”[Title/Abstract]	261053
#10	“physical activity”[Title/Abstract]	87920
#11	“physical therapy”[Title/Abstract]	17682
#12	“walk*”[Title/Abstract]	99515
#13	“aerobic program”[Title/Abstract]	28
#14	exercise[MeSH Terms]	163973
#15	“strength program”[Title/Abstract]	34
#16	resistance training[MeSH Terms]	6351
#17	"training"[Title/Abstract]	339581
#18	“physical rehabilitation”[Title/Abstract]	1587
#19	sport*[Title/Abstract]	64036
#20	aerobic exercise[MeSH Terms]	163973
#21	strength training[MeSH Terms]	6351
#22	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	788748
#23	"randomized controlled trial"[Publication Type]	458885
#24	death*[Title/Abstract]	717059
#25	died[Title/Abstract]	217918
#26	mortality[Title/Abstract]	643238
#27	hospitali*[Title/Abstract]	208554
#28	"Adverse event”[Title/Abstract]	21251
#29	“Adverse events”[Title/Abstract]	112947
#30	#24 OR #25 OR #26 OR #27 OR #28 OR #29	1592617
#31	**#8 AND #22 AND #23 AND #30**	**597**

2. Cochrane

Date searched: 01.03.2018
Dates of publication of retrieved articles: from July-August 1976 to present
Number of studies retrieved: 1633

ID	Search
#1	elder*:ti,ab,kw (Word variations have been searched)
#2	older adult*:ti,ab,kw (Word variations have been searched)
#3	very old:ti,ab,kw (Word variations have been searched)
#4	older population or oldest old:ti,ab,kw (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	exercis*:ti,ab,kw, “physical activity”:ti,ab,kw or “training”: ti,ab,kw, or physical therapy: ti,ab,kw, or walk*: ti,ab,kw (Word variations have been searched)
#7	aerobic program:ti,ab,kw, or strength program: ti,ab,kw, or physical rehabilitation: ti,ab,kw or sport: ti,ab,kw (Word variations have been searched)
#8	MeSH descriptor: [Exercise] explode all trees
#9	MeSH descriptor: [Resistance Training] explode all trees
#10	#6 or #7 or #8 or #9
#11	death*:ti,ab,kw or "death":ti,ab,kw or died:ti,ab,kw or "mortality":ti,ab,kw or hospitali*:ti,ab,kw
#12	adverse event*:ti,ab,kw
#13	#11 or #12
#14	"randomised clinical trial":pt
#15	randomized controlled trial:ti,ab,kw or random*:ti,ab,kw or trial:ti,ab,kw or randomised controlled trial:ti,ab,kw
#16	#5 and #10 and #13
#17	#16 and #15

3. SportDiscus

Date searched: 20.02.2018
Dates of publication of retrieved articles: from March 1990 to present
Number of studies retrieved: 291

Search	Query	Items found
S1	TI elder* OR AB elder* OR TI older adult* OR AB older adult* OR TI older population OR TI age* OR AB age* or TI oldest old OR AB oldest old OR TI old* OR AB old*	197,841
S2	TI very old OR AB very old	164
S3	S1 OR S2	197,841
S4	TI exercis* OR AB exercis* OR TI physical activity OR AB physical activity OR TI training OR AB training OR TI physical therapy OR AB physical therapy OR TI walk* OR AB walk* OR TI aerobic program OR AB aerobic program	294,496
S5	TI aerobic training OR AB aerobic training OR TI aerobic* OR AB aerobic* OR TI strength program OR AB strength program or TI strength training OR AB strength training OR TI physical rehabilitation OR AB physical rehabilitation OR TI sport* OR AB sport*	320,150
S6	TI resistance training OR AB resistance training	6,041
S7	S4 OR S5 OR S6	540,799
S8	TI death, OR AB death OR TI died OR AB died OR TI hospitali* OR AB hospitali* OR TI mortality OR AB mortality OR TI adverse event* OR AB adverse event*	35,021
S9	TI randomi#ed controlled trial* OR AB randomi#ed controlled trial* OR TI clinical trial OR AB clinical trial OR TI random* OR AB random* OR TI trial or AB trial	66,496
S10	**S3 AND S7 AND S8 AND S9**	**291**

4. PsychInfo

Date searched: 20.02.2018
Number of studies retrieved: 1,371

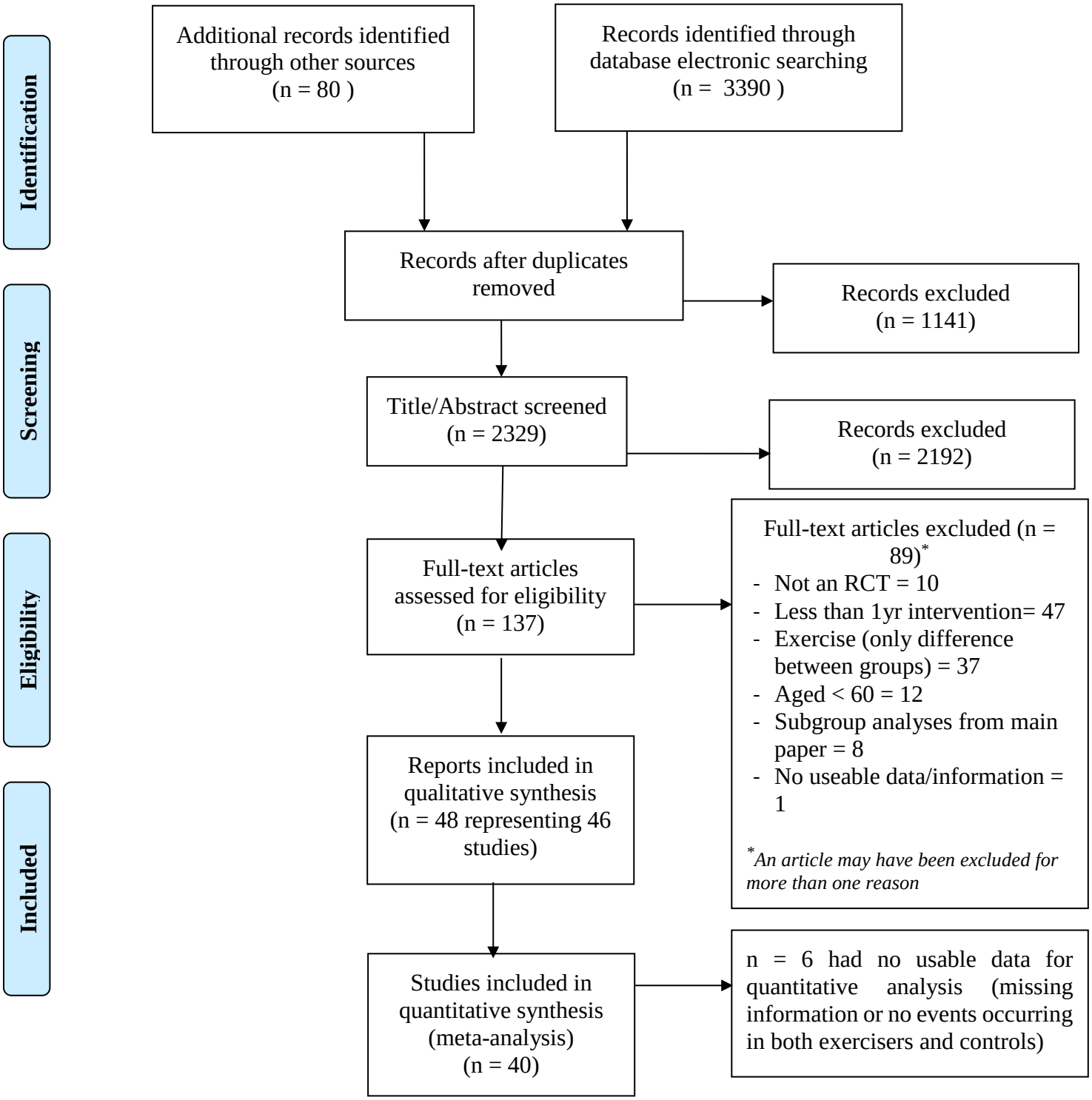
Search	Query	Items found
S1	MR clinical trial OR AB randomi#ed controlled trial* OR TI randomi#ed controlled trial* OR TI randomi#ed or AB randomi#ed OR TI random* OR AB random* OR TI trial* OR AB trial*	281,752
S2	TI sport* OR AB sport* or TI physical* OR AB physical* OR AB exercise* or TI exercise* OR AB aerobic exercise OR TI aerobic exercise OR TI resistance exercise OR AB resistance exercise or TI resistance training OR AB resistance training	292,676
S3	TI walk* OR AB walk* OR TI physical rehabilitation OR AB physical rehabilitation OR AB training OR TI training OR AB physical activity OR TI physical activity	293,195
S4	S2 OR S3	520,416
S5	TI mortality OR AB mortality OR TI died OR AB died OR AB death OR TI death OR TI hospital* OR AB hospital* OR TI adverse event* OR AB adverse event*	250,285
S6	TI age* OR AB age* OR TI elder* OR AB elder* OR TI old* OR AB old* OR TI older adult* OR AB older adult* OR AB oldest old OR TI oldest old OR TI older population OR AB older population	1,029,828
S7	**(TI age* OR AB age* OR TI elder* OR AB elder* OR TI old* OR AB old* OR TI older adult* OR AB older adult* OR TI oldest old OR AB oldest old OR TI older population OR AB older population) AND (S1 AND S4 AND S5 AND S6)**	**1,371**

5. Ageline

Date searched: 05.03.2018
Number of studies retrieved: 105

Search	Query	Items found
S1	TI elder* OR AB elder* OR TI “older adult” OR AB “older adult” OR TI “older population” OR AB “older population” OR TI “very old” OR AB “very old” OR TI “oldest old” OR AB “oldest old” OR TI aged OR AB aged	84,287
S2	TI exercis* OR AB exercis* OR TI “physical activity” or AB “physical activity” OR TI training OR AB training OR TI “physical therapy” OR AB “physical therapy” OR TI walk* OR AB walk* OR TI “aerobic program” OR AB “aerobic program”	19.304
S3	TI “strength program” OR AB “strength program” OR TI “physical rehabilitation” OR AB “physical rehabilitation” OR TI sport* OR AB sport* OR TI “aerobic exercise” or AB “aerobic exercise” OR TI “strength training” OR AB “strength training” OR TI “resistance training” OR AB “resistance training”	1,304
S4	TI death* OR AB death* OR TI died OR AB died OR TI mortality OR AB mortality OR TI hospitali* OR AB hospitali* OR TI “adverse event” OR AB “adverse event”	16,195
S5	TI random* OR AB random* OR TI randomized controlled trial* OR AB randomized controlled trial*	7,647
S6	S2 OR S3	19,682
S7	**S1 AND S4 AND S5 AND S6**	**105**

Appendix 3. Flow chart of study selection



Appendix 4. Risk of bias

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessement	Incomplete outcome data	Selective reporting	Other sources of bias
Belardinelli 2012							
Barnett 2003							
Bunout 2005							
O'Connor 2009/Blumenthal 2012							
Campbell 1997							
Dangour2011							
El-Khoury 2015							
Galvao 2014							
Gianoudis 2014							
Hambrecht 2004							
Hewitt 2018							
Karinkanta 2007							
Kemmler 2010							
King 2002							
Kovacs 2013							
Lam 2012							
Lam 2015							
Lord 1995							
Lord 2003							
Liu-Ambrose 2011							
MacRae 1994							

Merom 2015							
Messier 2004							
Messier 2013							
Munro 2004							
Muscari 2010							
Mustata 2011							
Nowalk 2001							
Pahor 2006							
Pahor 2014 / Gill 2016-BMJ / Marsh 2016							
Park 2008							
Patil 2015/Uusi 2015							
Pitkala 2013							
Prescott 2008							
Reinsch 1992							
Rejeski 2017							
Rolland 2007							
Sherrington 2014							
Suzuki 2012							
Underwood 2013							
Van Uffelen 2008							
Villareal 2011							
von Stengel 2011							
Voukelatos 2015							
Winters-Stone 2011							
Wolf 2003							
Woo 2007							

Legend: Low risk Unclear risk High risk

Appendix 5. Description of the exercise interventions

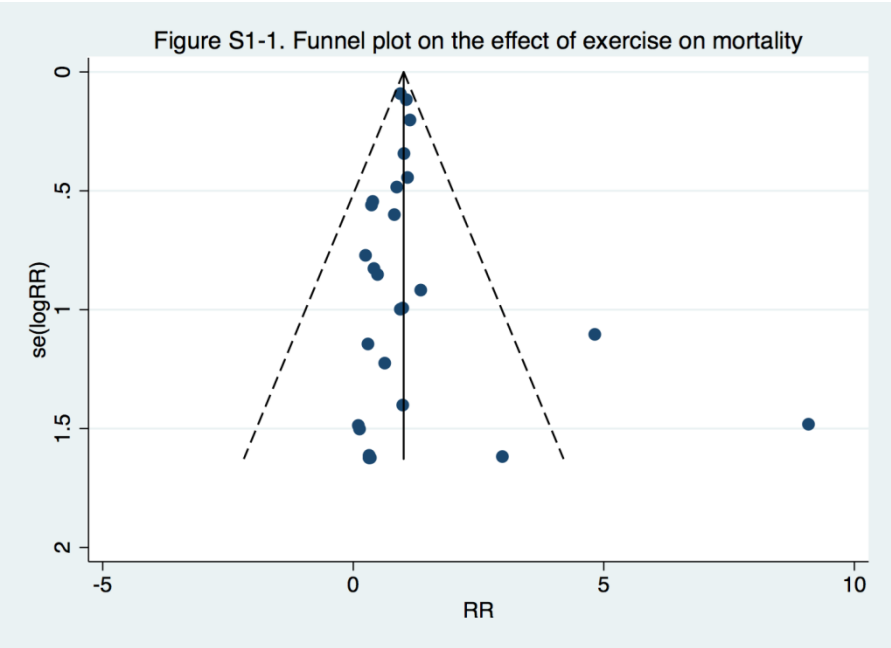
Study	Exercise Intervention Used for Comparisons	Exercise Frequency (times/week)/intensity	Exercise Compliance (%)	Exercise session duration (min)	Control group used for comparisons
Belardinelli 2012	Aerobic	3x/week Moderate intensity	88	60	Attention control
Barnett 2003	Multicomponent (RT, aerobic, balance and coordination)	2x per week Moderate intensity	62	60	Usual care
Bunout 2005	Multicomponent (RT and aerobic)	2x per week Moderate intensity	52	60	Unclear (but probably usual care)
O'Connor 2009	Aerobic	5x per week Moderate intensity	Unclear	40	Usual care
Campbell 1997	Multicomponent (RT and balance exercise)	3x per week Moderate intensity	Unclear	30	Attention control
Dangour 2011	Resistance training	2x per week Moderate intensity	38	60	Usual care
El-Khoury 2015	Multicomponent (RT, balance exercise and behavioural changes)	2x per week Moderate intensity	46.6	60	Active control
Galvao 2014	Multicomponent (aerobic exercise + RT)	4x/week Moderate intensity	77	>20	Active control
Gianoudis 2014	Multicomponent (RT and balance)	3x per week Vigorous intensity	59	Unclear	Usual care
Hambrecht 2004	Aerobic	5x per week Moderate intensity	70	28	Stent angioplasty
Hewitt 2018	Resistance training	2x per week Moderate intensity	60	45	Usual care
Karinkanta 2007	Resistance training	3x per week Vigorous intensity	74	45	Usual care
Kemmler 2010	Multicomponent (RT, aerobic and balance)	4x per week Vigorous intensity	59	40	Active control
King 2012	Aerobic	4x per week Moderate intensity	73.4	30-40	Nutrition education
Kovacs 2013	Multicomponent (RT, aerobic and balance)	3x per week Moderate intensity	Unclear	Unclear	Usual care
Lam 2012	Tai-Chi	3x per week Moderate intensity	Unclear	30	Active control
Lam 2015	Multicomponent (stretching, aerobic, Tai-Chi)	3x per week Moderate intensity	75	60	Active control
Lord 1995	Multicomponent (RT, aerobic, flexibility, hand-eye coordination and balance)	2x per week Unclear intensity	73.2	60	Unclear, probably usual care
Lord 2003	Multicomponent (RT, aerobic, flexibility, hand-	2x per week Moderate intensity	42.3	60	Usual care and active control

	eye coordination and balance)				
Liu-Ambrose 2010	Resistance training	2x per week Vigorous intensity	70.3	60	Active control
MacRae 1994	Multicomponent (RT and balance)	3x per week Moderate intensity	Unclear	60	Attention control
Merom 2015	Dance	2x per week Unclear intensity	56	60	Usual care
Messier 2013	Multicomponent (aerobic + RT) with diet	3x per week Moderate intensity	58	60	Active control
Munro 2004	Multicomponent (RT, aerobic, joint mobility, balance flexibility and coordination)	2x per week Moderate intensity	Unclear	45	Usual care
Muscari 2010	Aerobic	3x per week Moderate intensity	Unclear	60	Active control
Mustata 2011	Aerobic	4x week Unclear intensity	Unclear	60	Usual care
Nowalk 2001	Multicomponent (RT, aerobic and flexibility)	3x per week Unclear intensity	45	Unclear	Active control
Pahor 2006	Multicomponent (RT, aerobic and balance)	4.7x per week Moderate intensity	78.7	50	Active control
Pahor 2014	Multicomponent (RT, aerobic and balance)	5x per week Moderate intensity	63	50	Active control
Park 2008	Multicomponent (RT, aerobic and balance)	3x per week Moderate intensity	Unclear	60	Usual care
Patil 2015	Multicomponent (RT, balance and mobility)	1.5x per week Moderate intensity	73	Unclear	Usual care
Pitkala 2013	Multicomponent (Individual needs for improvement in mobility)	2x per week Moderate intensity	81	60	Usual care
Prescott 2008	Multicomponent (aerobic + RT)	Unclear Moderate intensity	Unclear	Unclear	Usual care
Reinsch 1992	Multicomponent (RT and balance)	3x per week Moderate intensity	Unclear	60	Attention control
Rejeski 2017	Resistance training	4x per week Vigorous intensity	85.7	45	Active control
Rolland 2007	Multicomponent (RT, aerobic, balance and flexibility)	2x per week Moderate intensity	33.2	60	Usual care
Sherrington 2014	Multicomponent (RT and balance)	6x per week Unclear intensity	58.3	25	Active control
Suzuki 2012	Multicomponent (RT, aerobic and balance)	2x per week Moderate intensity	79.2	90	Active control
Underwood 2013	Multicomponent (aerobic + RT)	2x per week Moderate intensity	54	45	Active control
Van Uffelen 2008	Aerobic (walking program)	2x per week Moderate intensity	63	60	Active control

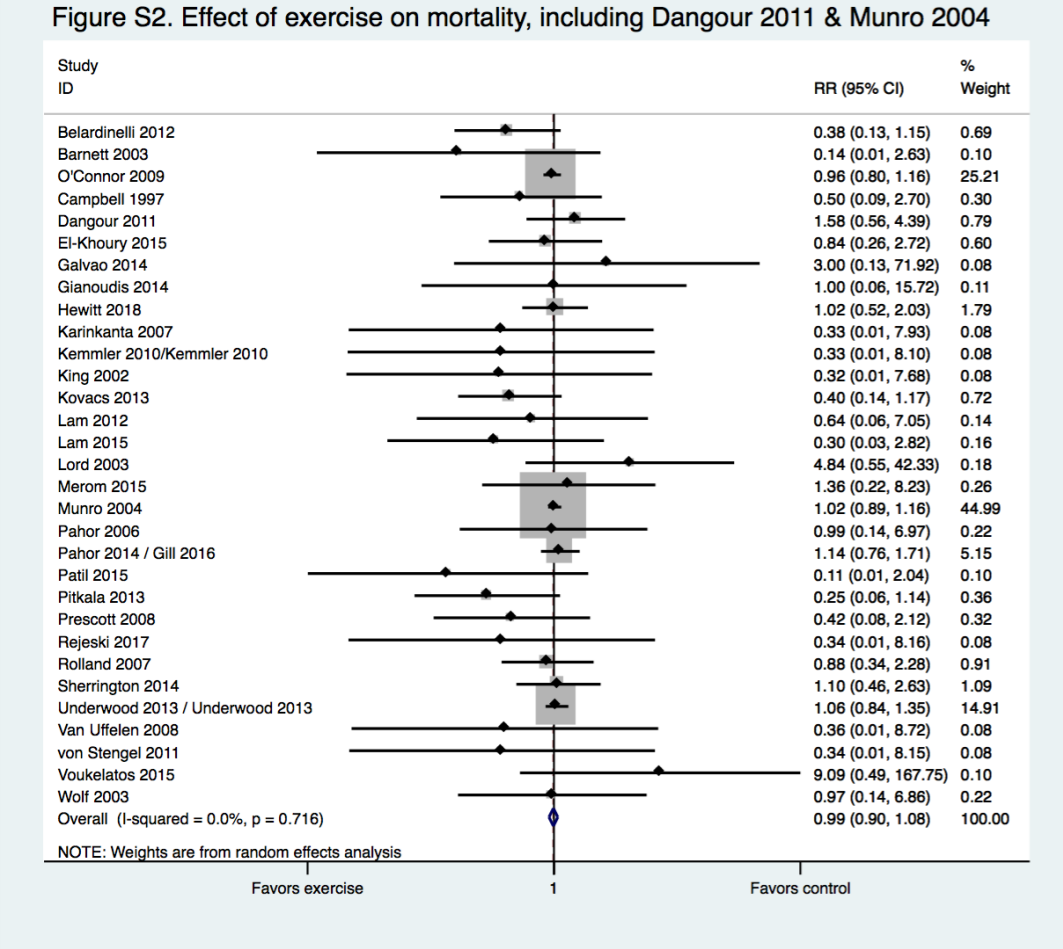
Villareal 2011	Multicomponent (aerobic +RT + flexibility)	3x per week Moderate intensity aerobic Vigorous intensity for RT	88	90	Active control
Von Stengel 2011	Multicomponent (aerobic + RT)	4x per week Vigorous intensity	59	35	Active control
Voukelatos 2015	Aerobic (walking)	Unclear Moderate intensity	Unclear	150 min/week	Attention control
Winter-Stone 2011	Resistance training	3x per week Moderate intensity	57	52.5	Active control
Wolf 2003	Tai-chi	2x per week Moderate intensity	76	30	Active controls
Woo 2007	Tai-chi	3x per week Moderate intensity	81	Unclear	Usual care

Appendix 6. Meta-analyses and meta-regressions for the outcome “Mortality”

Funnel Plot

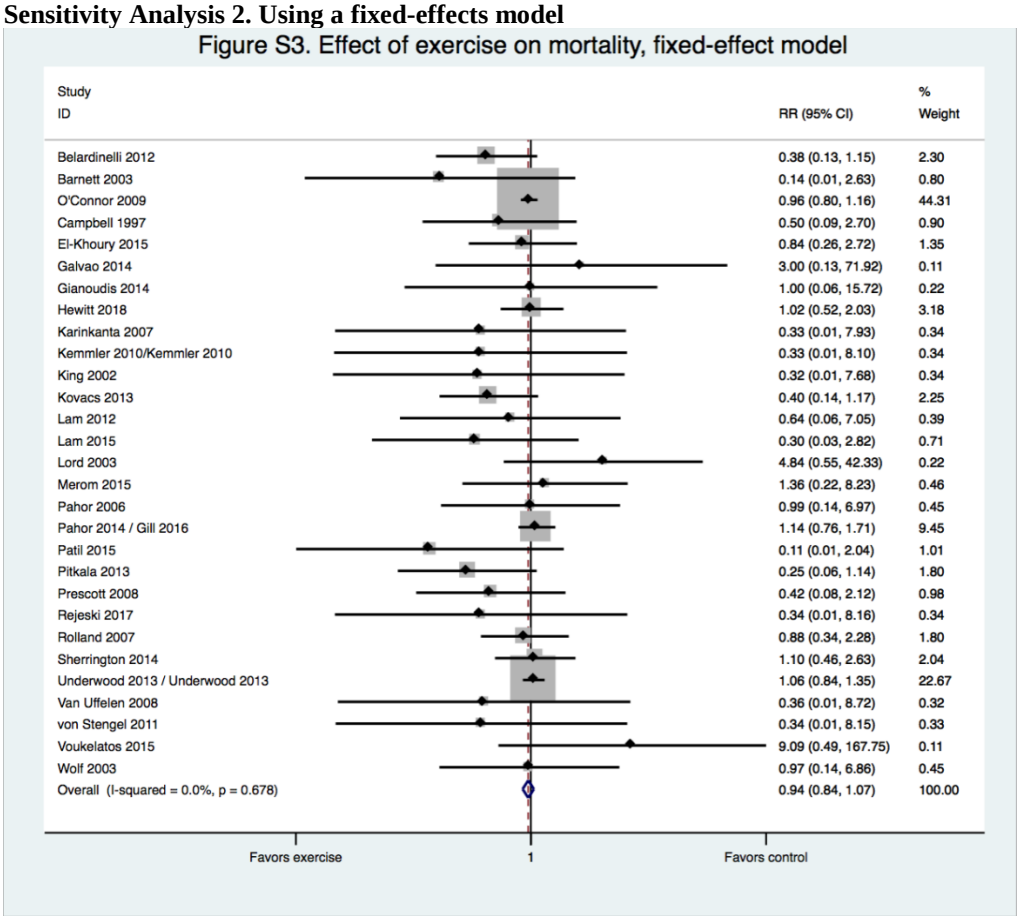


Sensitivity Analysis 1. Including studies with very low exercise compliance



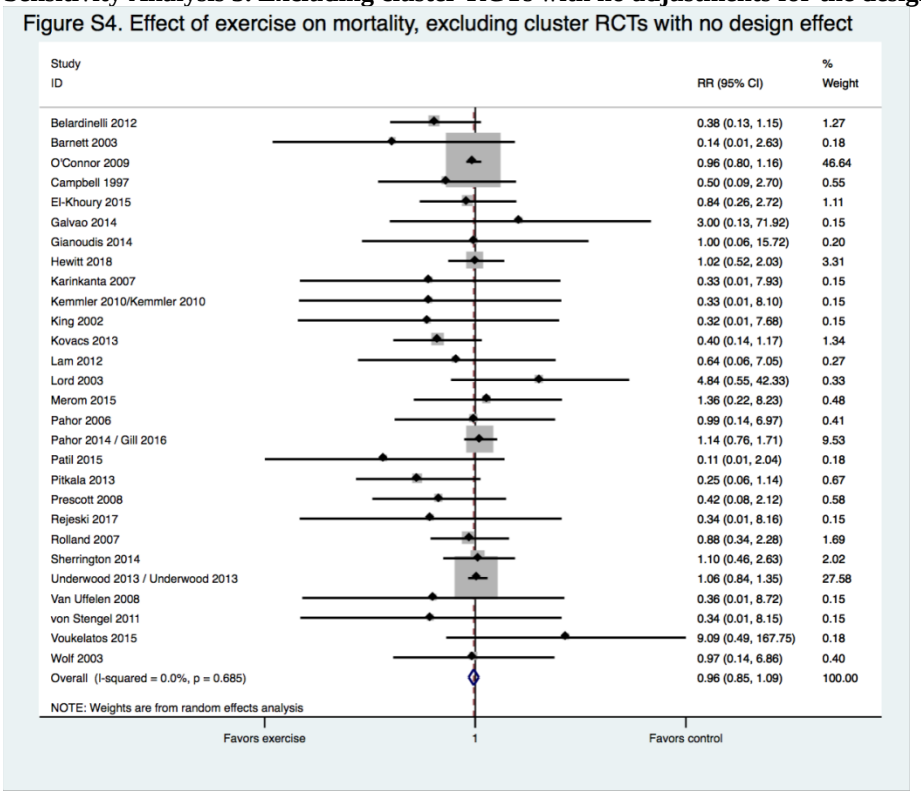
RR (95% CI): 0.988 (0.90-1.08), p=0.799
I^2=0.0%

Sensitivity Analysis 2. Using a fixed-effects model



RR (95% CI): 0.945 (0.84-1.07), p=0.365
I^2=0.0%

Sensitivity Analysis 3. Excluding cluster-RCTs with no adjustments for the design effect

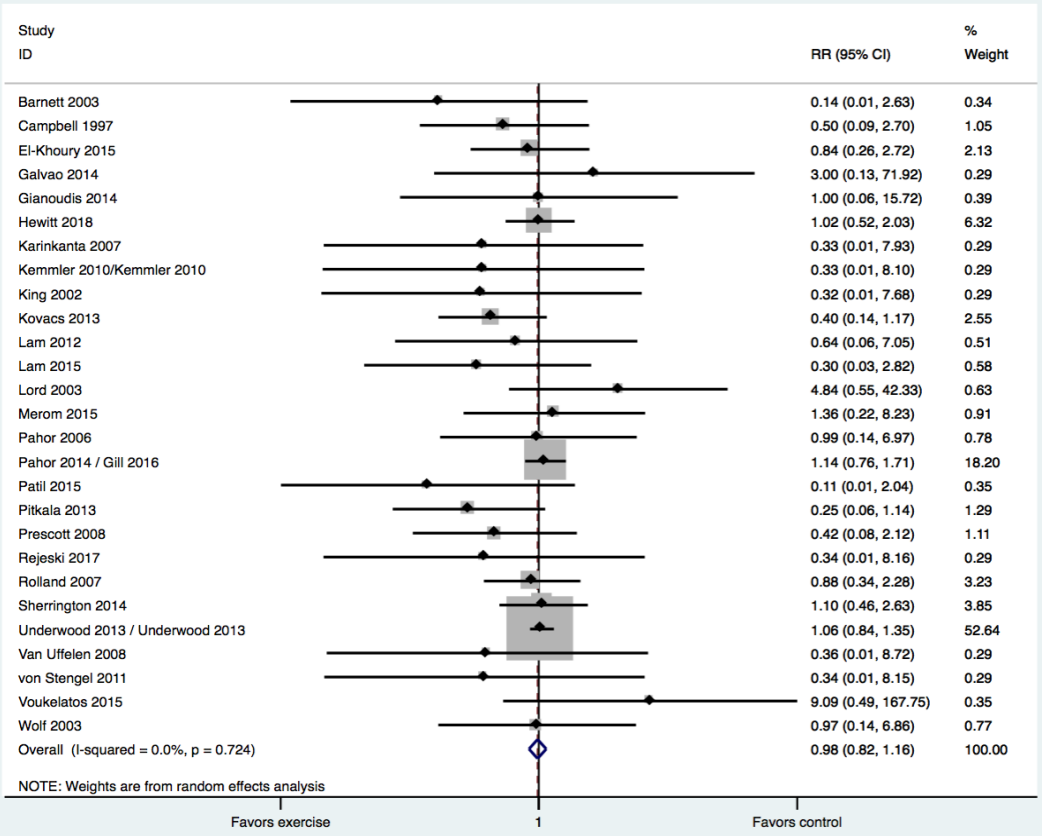


RR (95% CI): 0.963 (0.85-1.09), p=0.552

I^2=0.0%

Sensitivity Analysis 4. Excluding studies in which the population had a mean age < 60 years

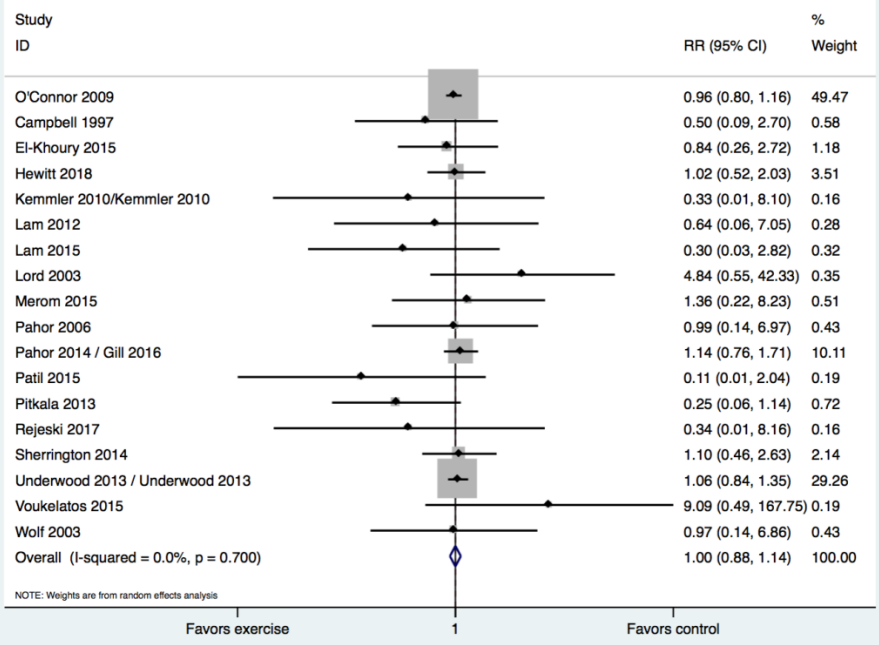
Figure S5. Effect of exercise on mortality in studies including people aged ≥60 years old



RR (95% CI): 0.977 (0.82-1.16), p=0.789
I^2=0.0%

Sensitivity Analysis 5. Restricted to studies larger than the median (>203 participants)

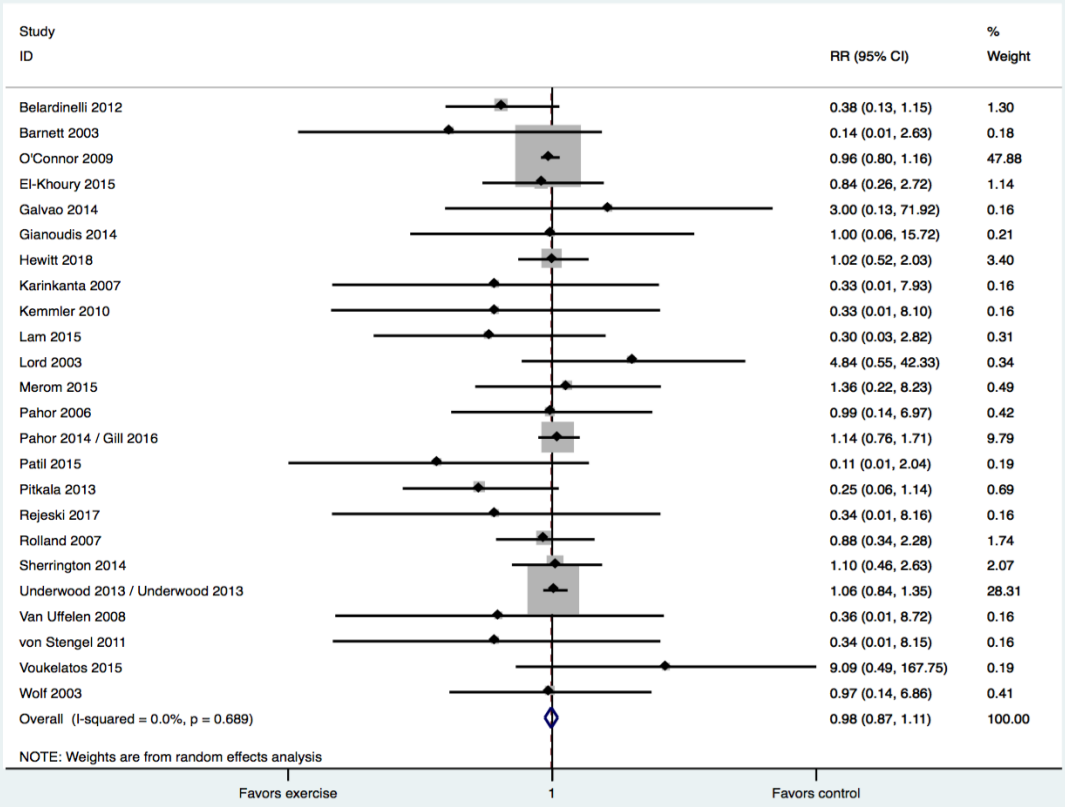
Figure S6. Effect of exercise on mortality in studies with >203 subjects



RR (95% CI): 0.999 (0.88-1.14), p=0.986
I^2=0.0%

Sensitivity Analysis 6. Restricted to studies with a low risk of attrition bias

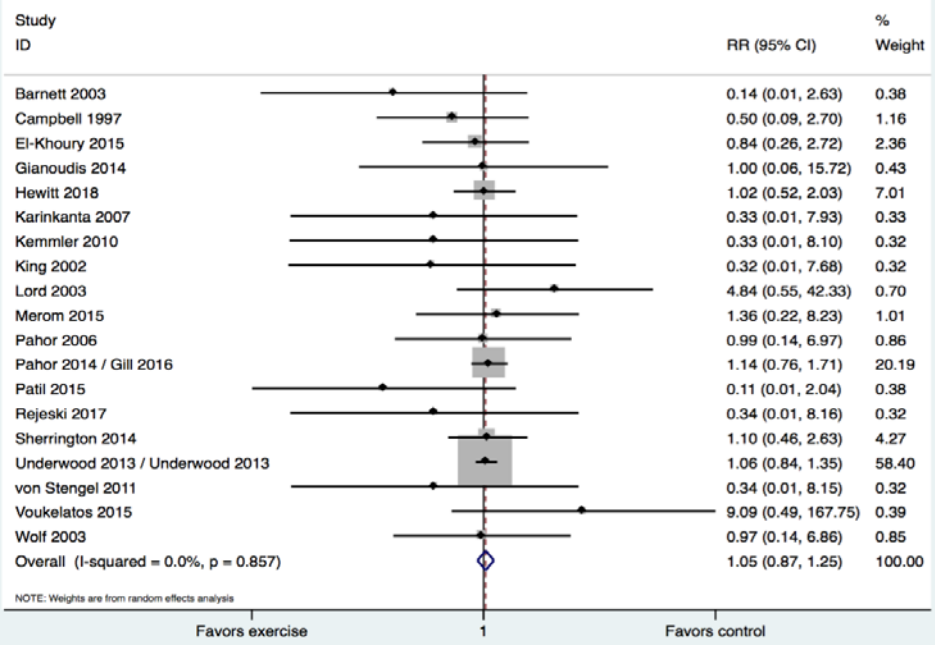
Figure S7. Effect of exercise on mortality in studies with low risk of attrition



RR (95% CI): 0.982 (0.87-1.11), p=0.781
I^2=0.0%

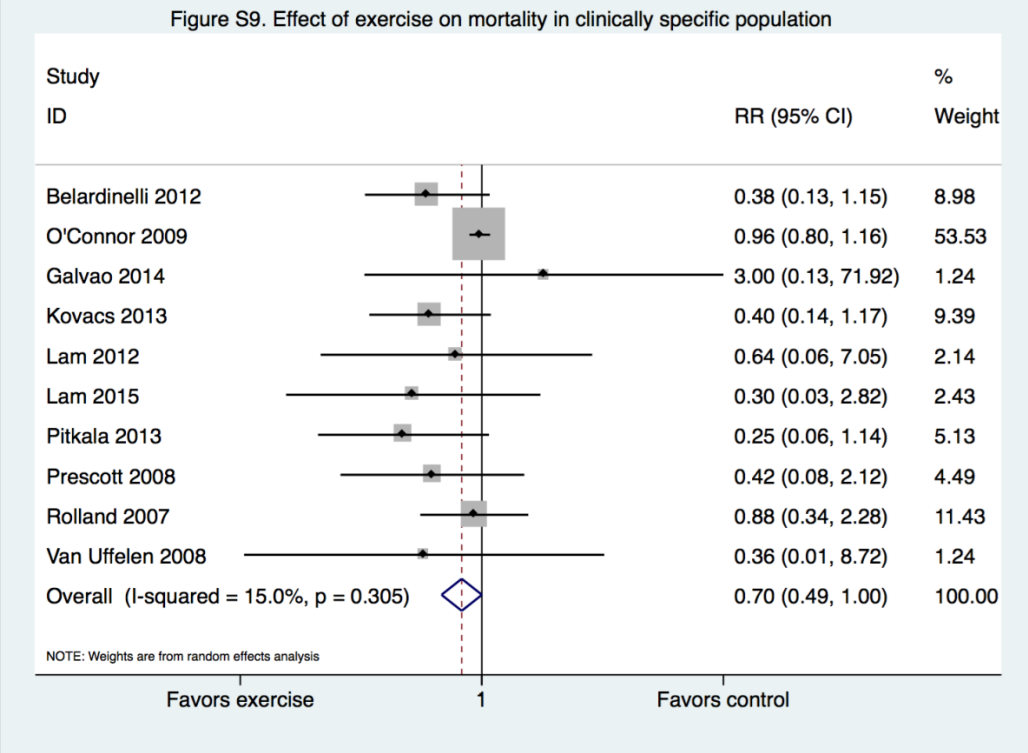
Sub-group Analysis 1. Restricted to non-clinically/disease-specific studies

Figure S8. Effect of exercise on mortality in non-clinically specific population



RR (95% CI): 1.05 (0.87-1.25), p=0.623
I^2=0.0%

Sub-group Analysis 2. Restricted to clinically/disease-specific studies



RR (95% CI): 0.701 (0.49-1.00), p=0.051
I^2=15.0%

Table S-1. Meta-regression on the association between mortality and exercise-related variables

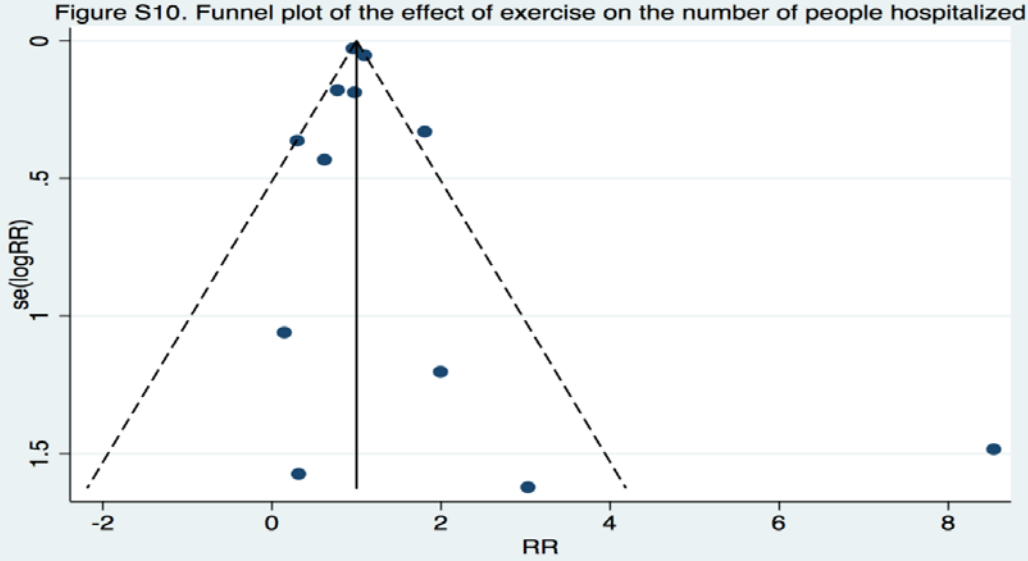
Meta-regression	Categories	Exp (b) (SE)	*p*-value
Exercise frequency (n=29)	<2x/week (ref) 3x/week >3x/week	 0.42 (0.14) 0.98 (0.13)	 0.015 0.88
Effective frequency (n=23)	<2x/week (ref) Between 2-3x/week >3x/week	 0.35 (0.16) 1.12 (0.23)	 0.028 0.60
Exercise volume (n=25)	<120/min/week (ref) Between 120-179 min/week ≥180 min/week	 0.80 (0.21) 0.92 (0.13)	 0.41 0.56
Effective volume (n=21)	≤60 min/week (ref) Between 61-120 min/week >120 min/week	 0.65 (0.21) 0.91 (0.19)	 0.20 0.65
Exercise intensity (n=27)	Moderate (ref) Vigorous intensity	 0.46 (0.32)	 0.28
Exercise type (multicomponent only as reference) (n=29)	Multicomponent (ref) Aerobic Strength Others (tai-chi and dance)	 0.96 (0.76) 0.34 (0.39) 1.03 (0.62)	 0.76 0.36 0.96
Exercise type (others vs. multicomponent + balance) (n=29)	Others (ref) Multicomponent + balance	 0.92 (0.14)	 0.58

Legend: Exp: exponential, SE: standard error

Appendix 7. Meta-analyses and meta-regressions for the outcome “Number of people hospitalized”

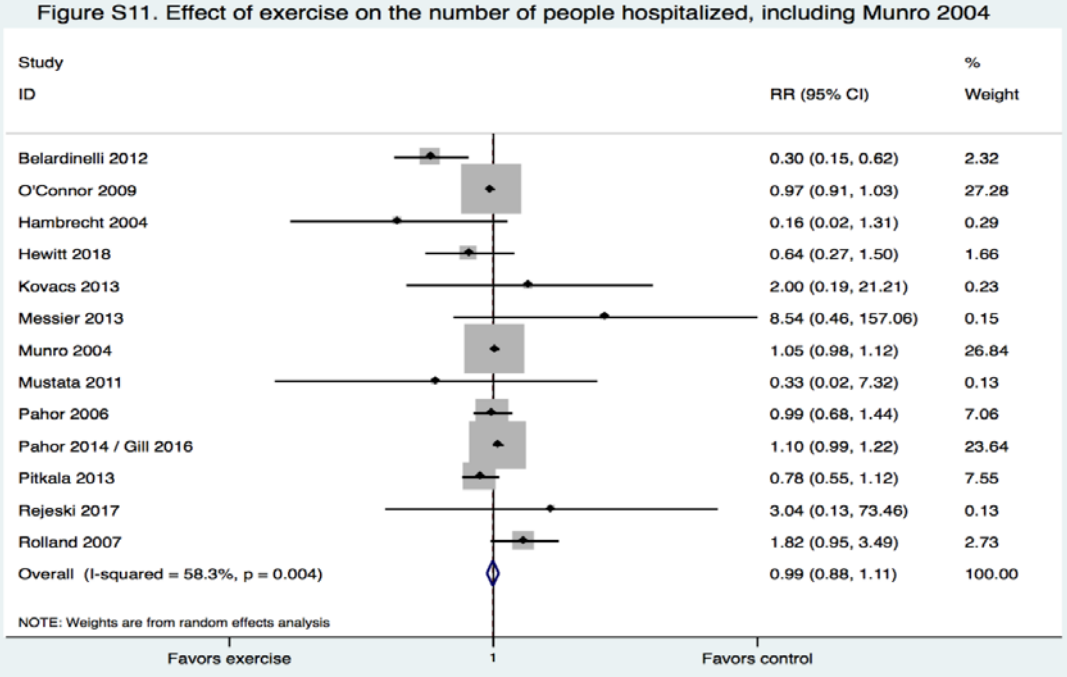
Funnel Plot

Figure S10. Funnel plot of the effect of exercise on the number of people hospitalized



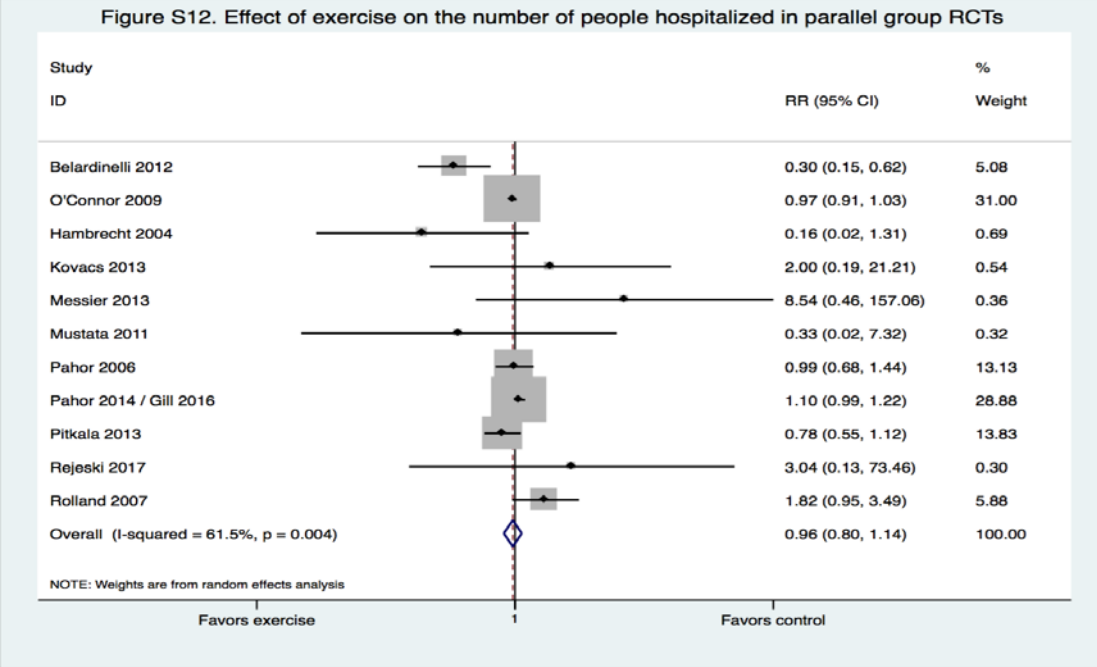
Sensitivity Analysis 1. Including studies with very low exercise compliance

Figure S11. Effect of exercise on the number of people hospitalized, including Munro 2004



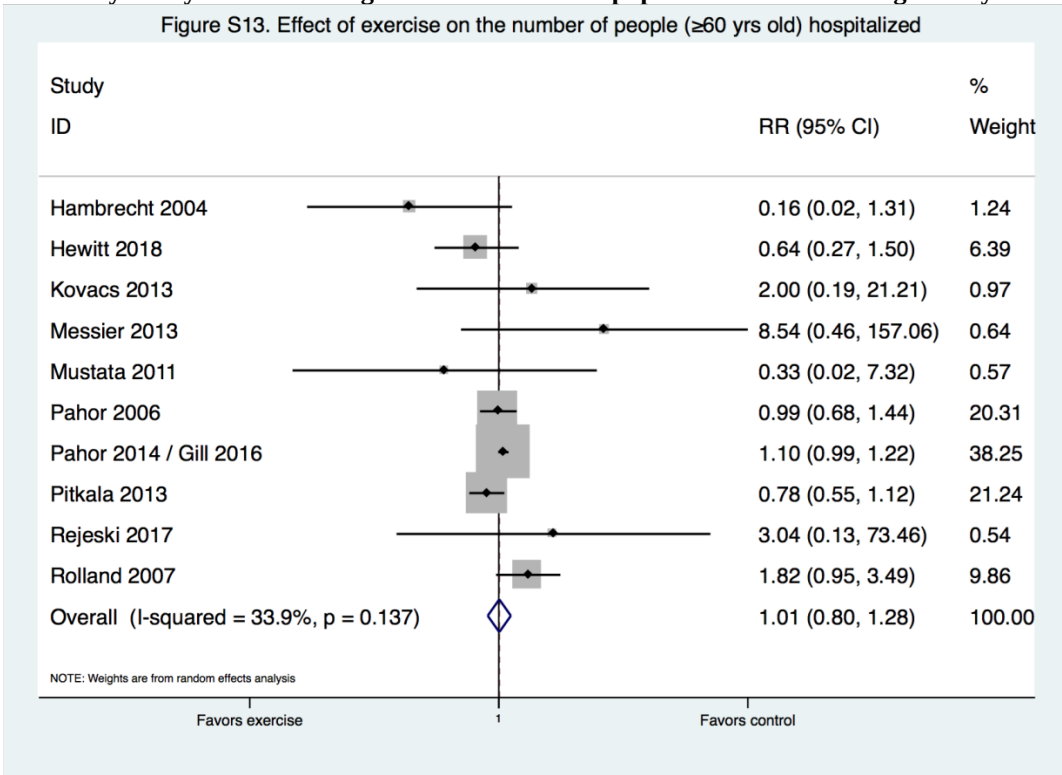
RR (95% CI): 0.989 (0.88-1.11), p=0.842
I^2=58.3%

Sensitivity Analysis 3. Excluding cluster-RCTs with no adjustments for the design effect



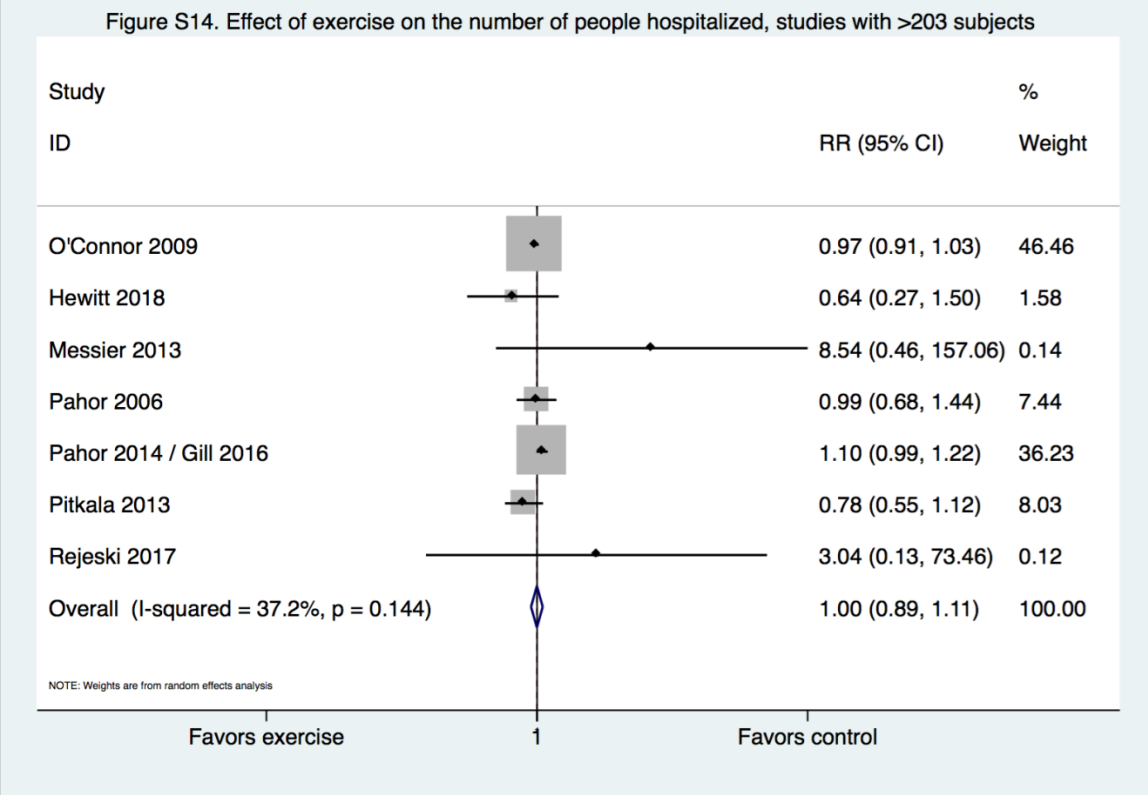
RR (95% CI): 0.957 (0.80-1.14), p=0.625
I^2=61.5%

Sensitivity Analysis 4. Excluding studies in which the population had a mean age < 60 years



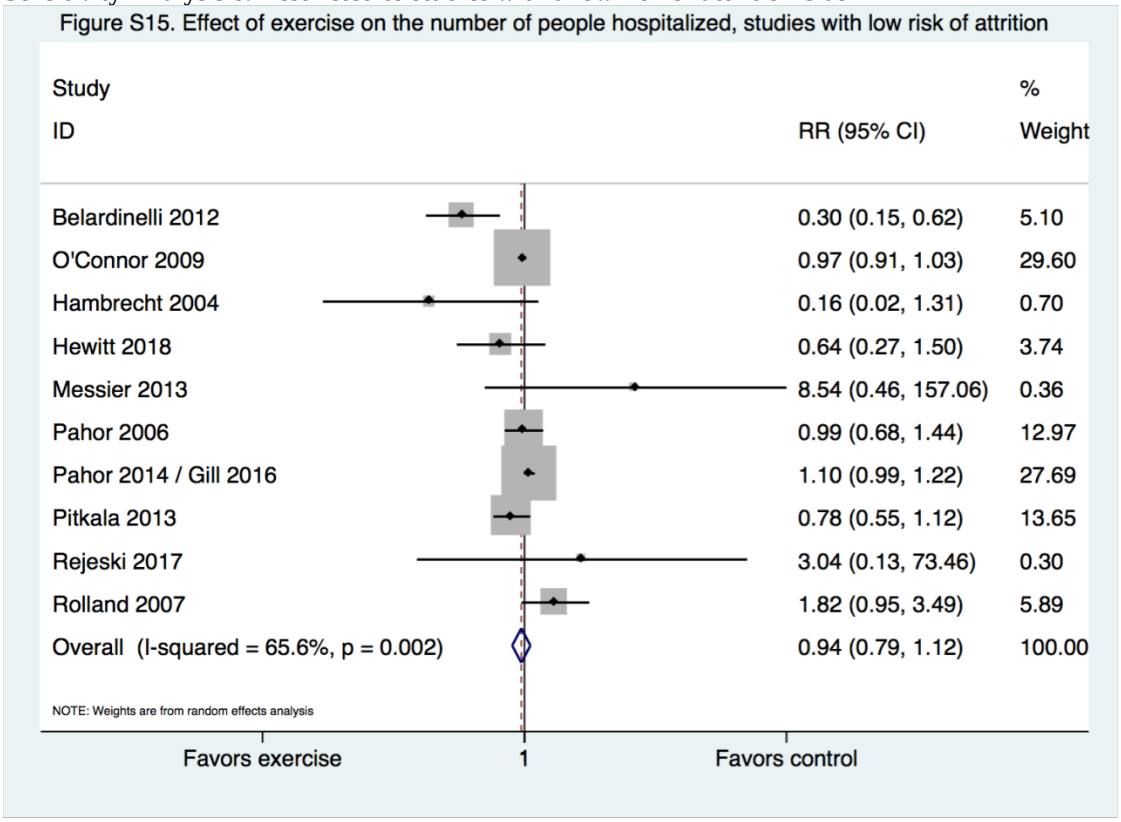
RR (95% CI): 1.01 (0.80-1.28), p=0.932
I^2=33.9%

Sensitivity Analysis 5. Restricted to studies larger than the median (>203 participants)



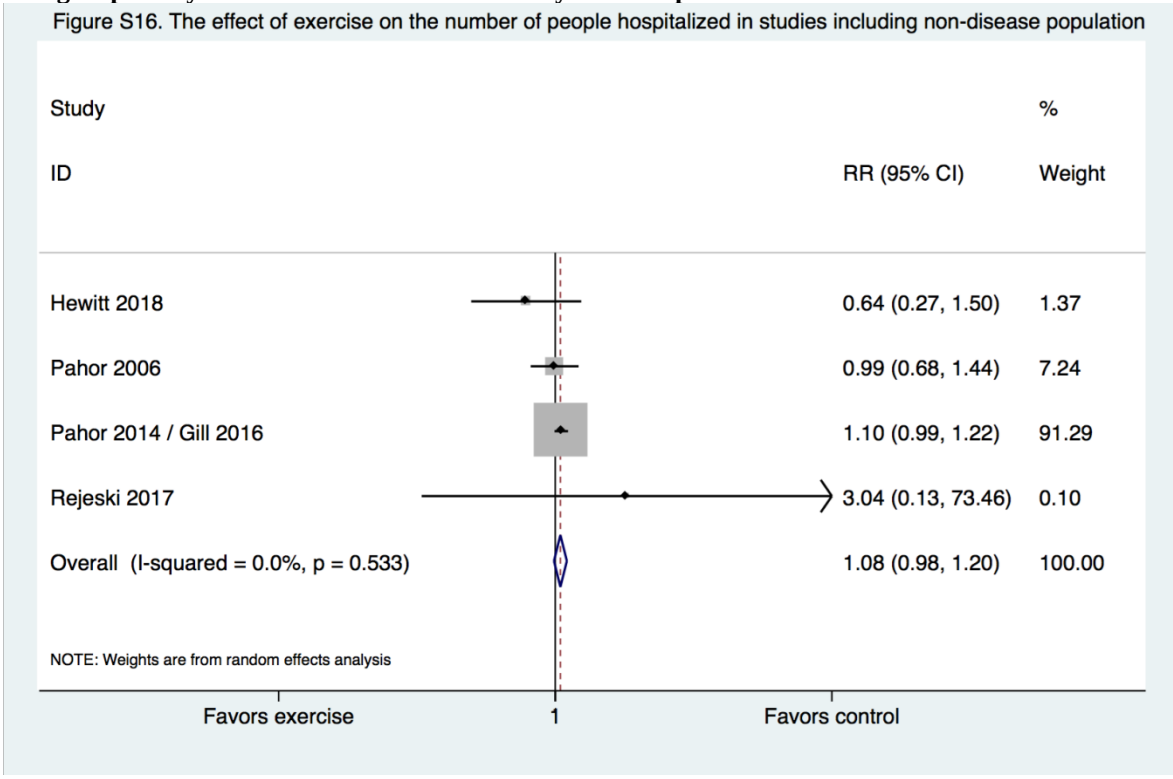
RR (95% CI): 0.997 (0.89-1.11), p=0.955
I^2=37.2%

Sensitivity Analysis 6. Restricted to studies with a low risk of attrition bias



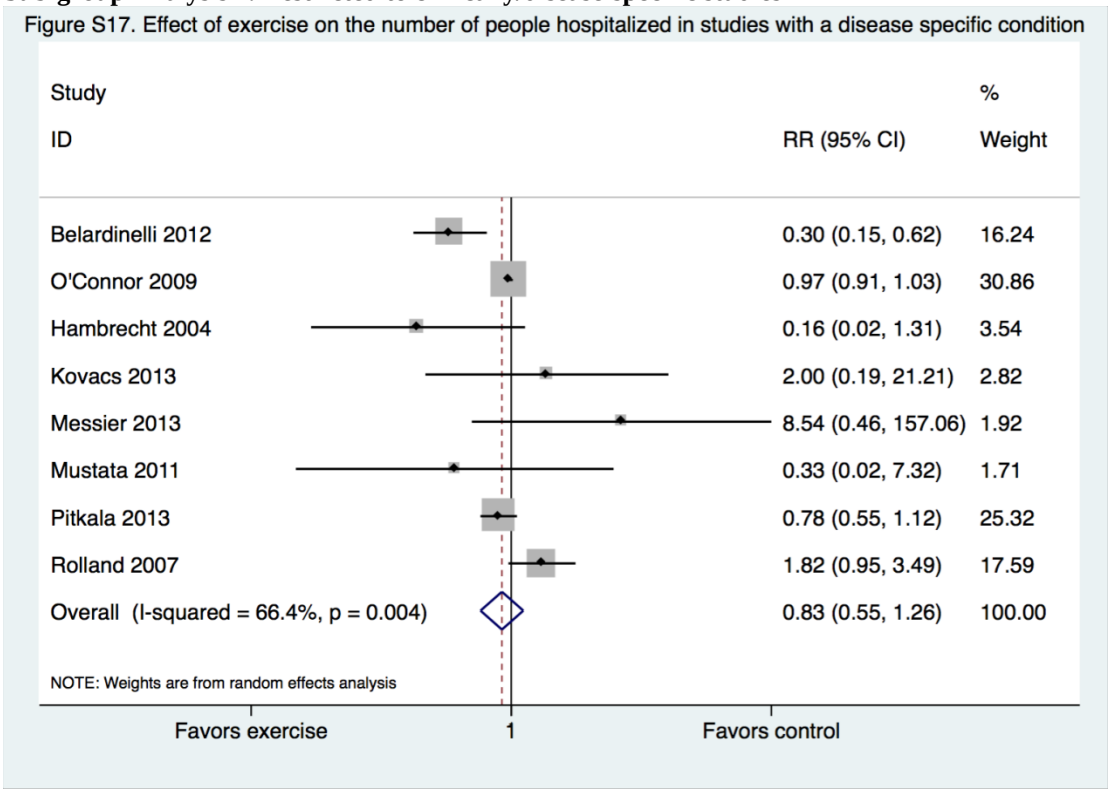
RR (95% CI): 0.941 (0.79-1.12), p=0.496
I^2=65.6%

Sub-group Analysis 1. Restricted to non-clinically/disease-specific studies



RR (95% CI): 1.08 (0.98-1.20), p=0.12
I^2=0.0%

Sub-group Analysis 2. Restricted to clinically/disease-specific studies



RR (95% CI): 0.83 (0.55-1.27), p=0.393
I^2=66.4%

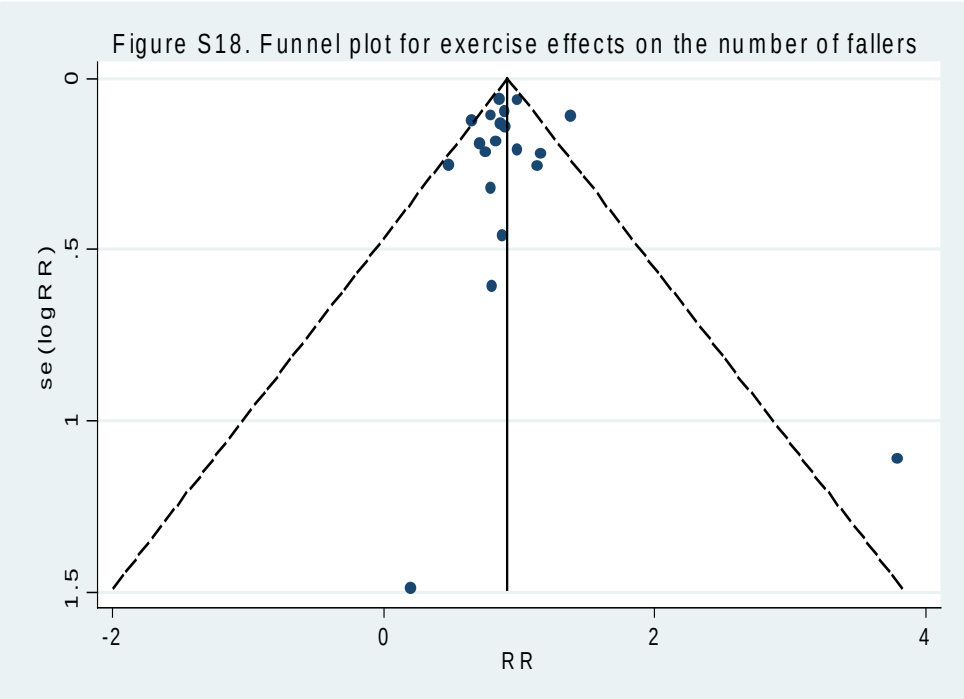
Table S2. Meta-regression on the association between the number of people hospitalized and exercise-related variables

Meta-regression	Categories	Exp (b) (SE)	*p*-value
Exercise frequency (n=12)	<2x/week (ref) 3x/week >3x/week	 0.46 (0.24) 1.10 (0.26)	 0.17 0.67
Effective frequency (n=9)	<2x/week (ref) Between 2-3x/week >3x/week	 0.30 (0.18) 1.01 (0.36)	 0.094 0.98
Exercise volume (n=11)	<120/min/week (ref) Between 120-179 min/week ≥180 min/week	 1.47 (1.21) 1.37 (1.07)	 0.66 0.69
Effective volume (n=9)	≤60 min/week (ref) Between 61-120 min/week >120 min/week	 0.68 (0.57) 0.71 (0.50)	 0.66 0.64
Exercise intensity (n=11)	Moderate (ref) Vigorous intensity	 3.40 (6.7)	 0.55
Exercise type (multicomponent only as reference) (n=12)	Multicomponent (ref) Aerobic Strength Others (tai-chi and dance)	 0.96 (0.76) 0.34 (0.39) 1.03 (0.62)	 0.76 0.36 0.96
Exercise type (others vs. multicomponent + balance) (n=12)	Others (ref) Multicomponent + balance	 0.92 (0.14)	 0.58

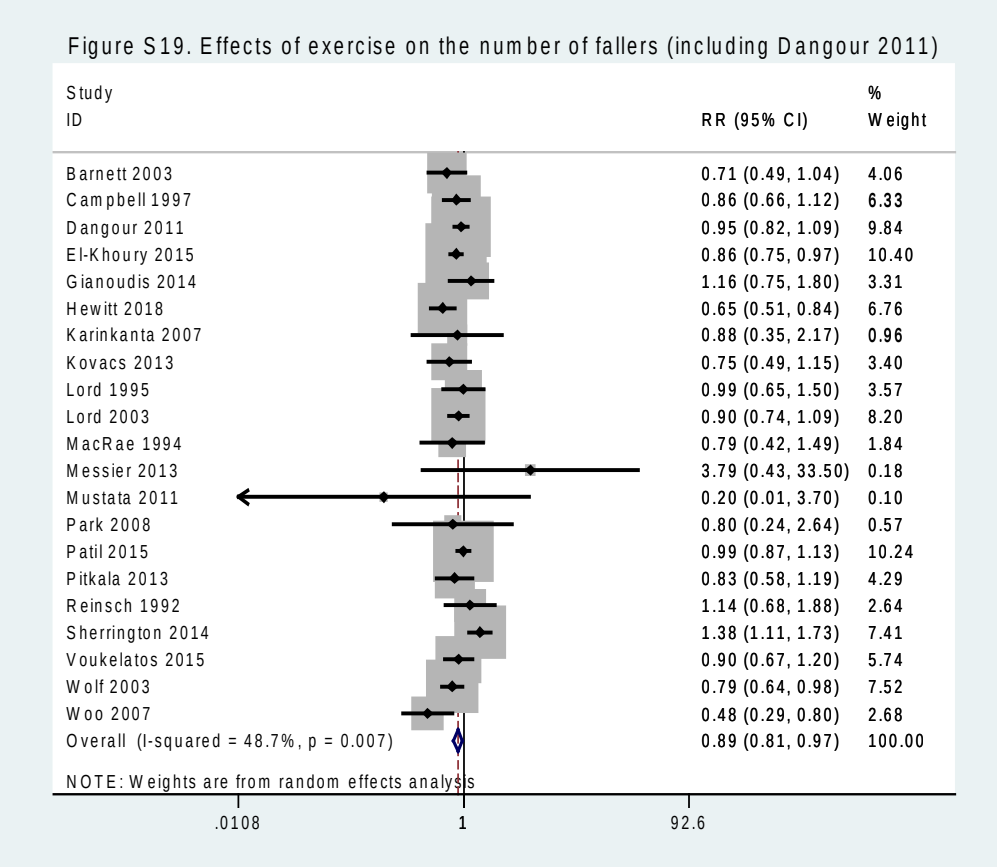
Legend: Exp: exponential, SE: standard error

Appendix 8. Meta-analyses and meta-regressions for the outcome “Fallers”

Funnel Plot

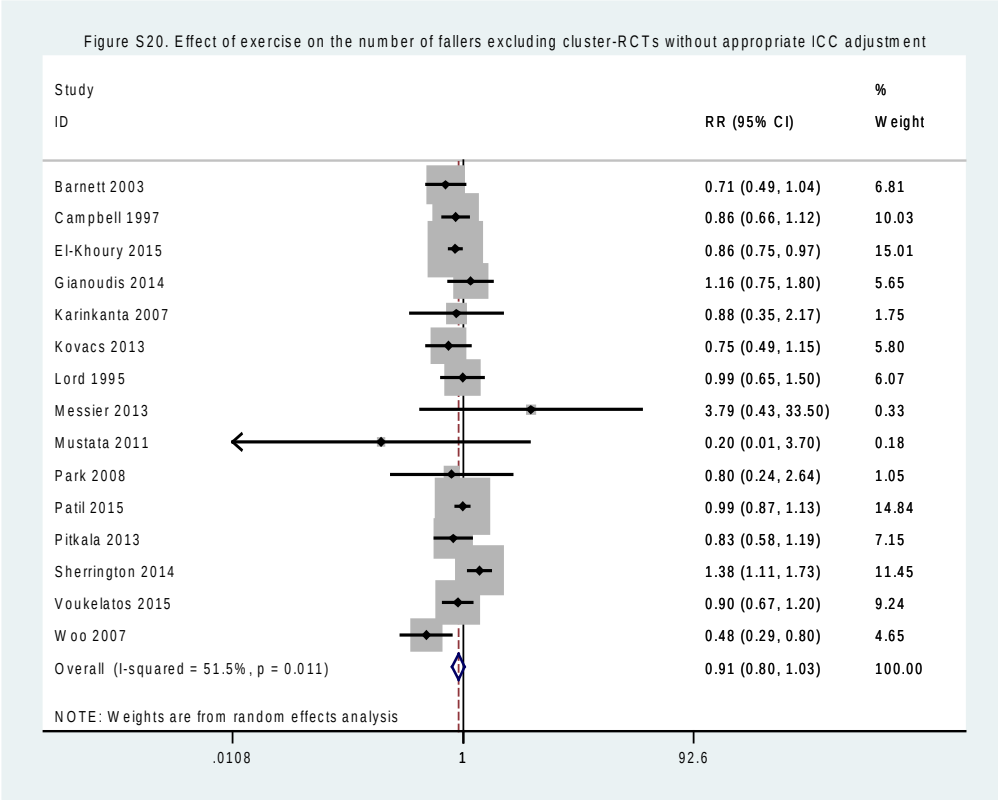


Sensitivity Analysis 1. Including studies with very low exercise compliance



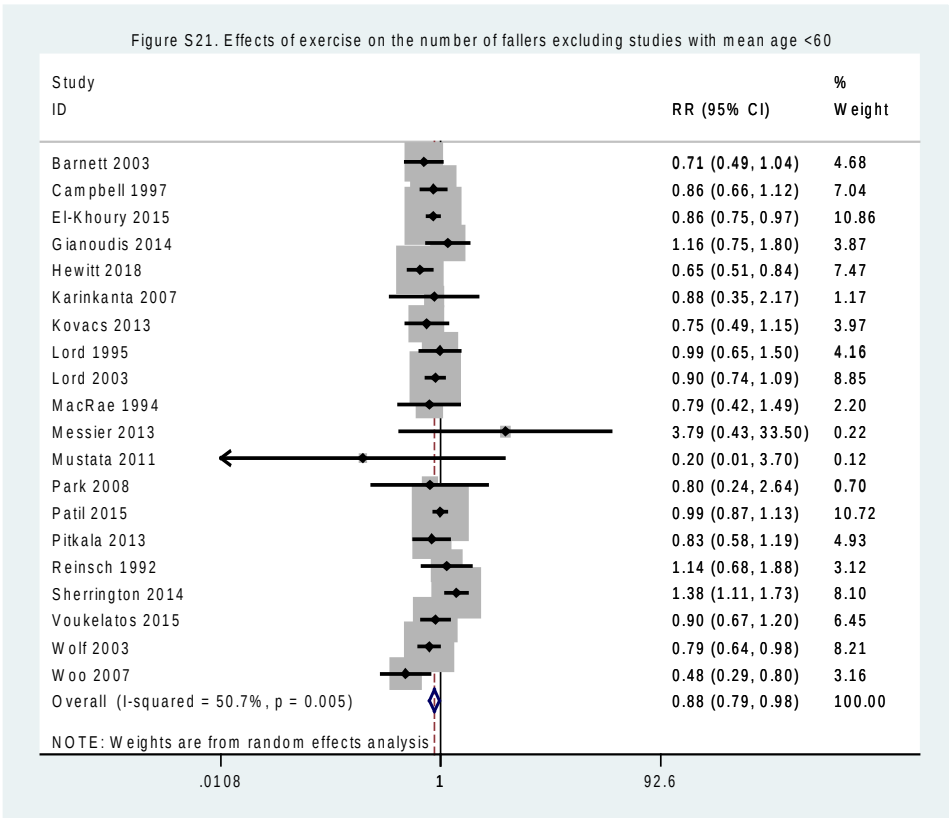
RR (95% CI): 0.89 (0.81-0.97), p=0.011
I^2=48.7%

Sensitivity Analysis 3. Excluding cluster-RCTs with no adjustments for the design effect



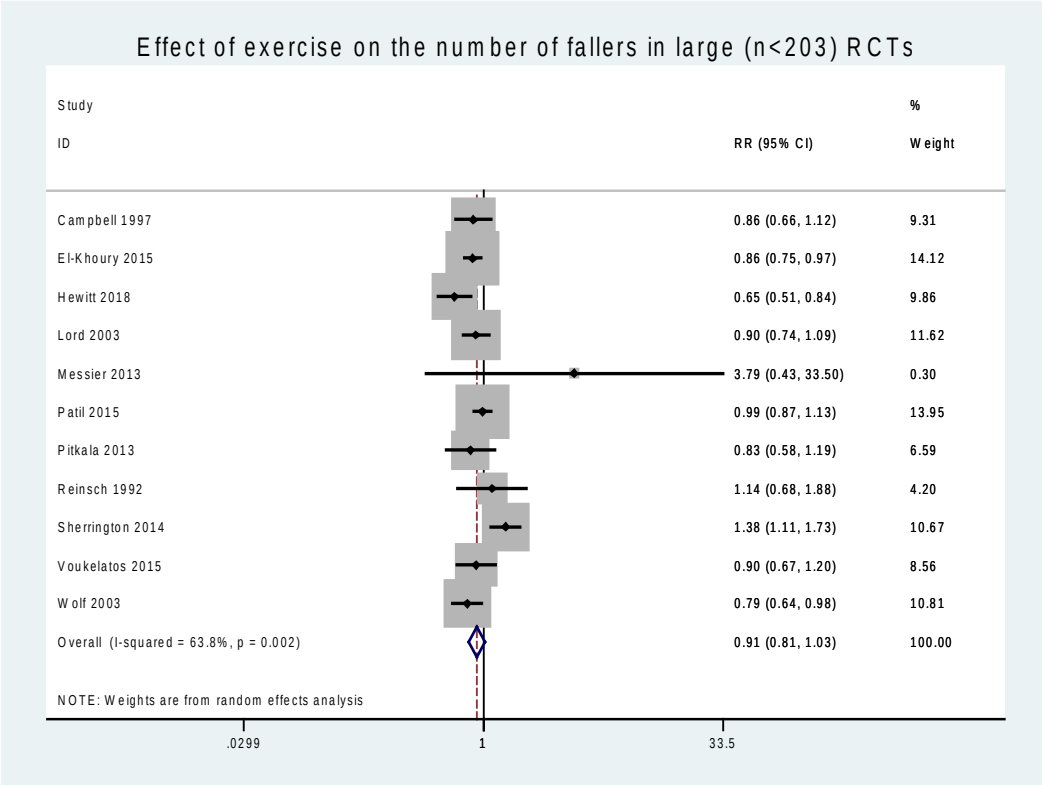
RR (95% CI): 0.91 (0.80-1.03), p=0.14
I^2=51.5%

Sensitivity Analysis 4. Excluding studies in which the population had a mean age < 60 years



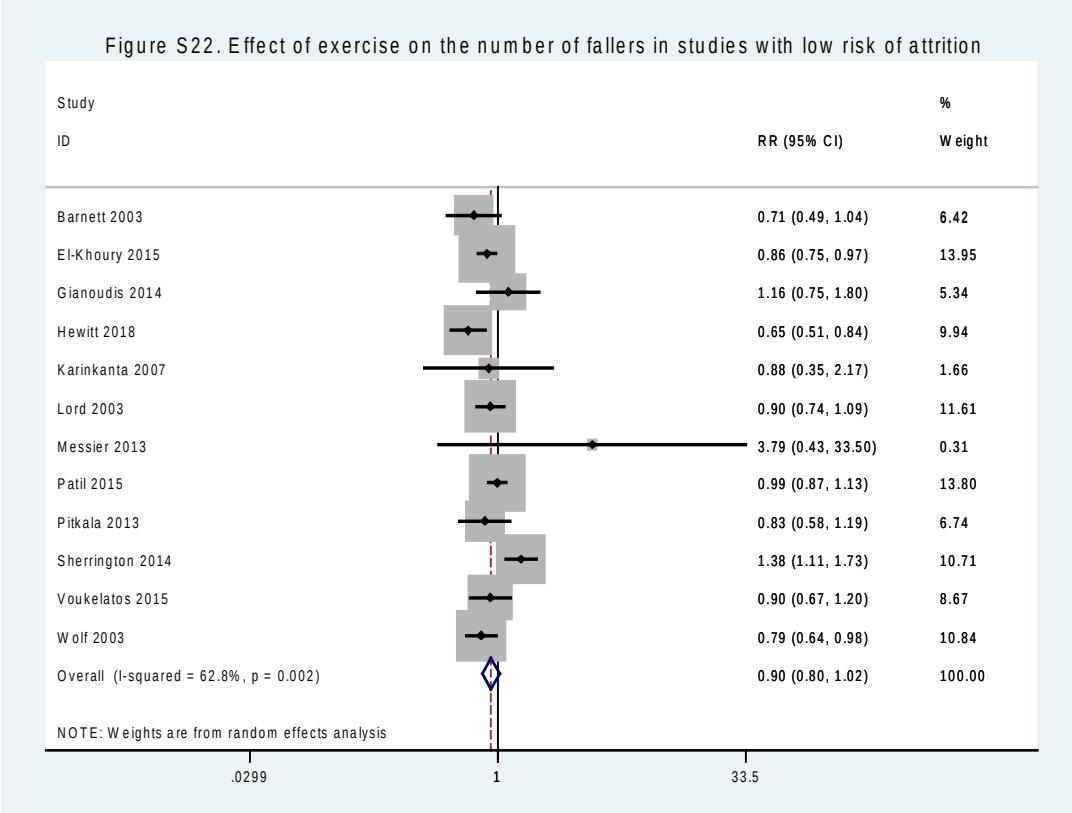
RR (95% CI): 0.88 (0.80-0.98), p=0.015
I^2=50.7%

Sensitivity Analysis 5. Restricted to studies larger than the median (>203 participants)



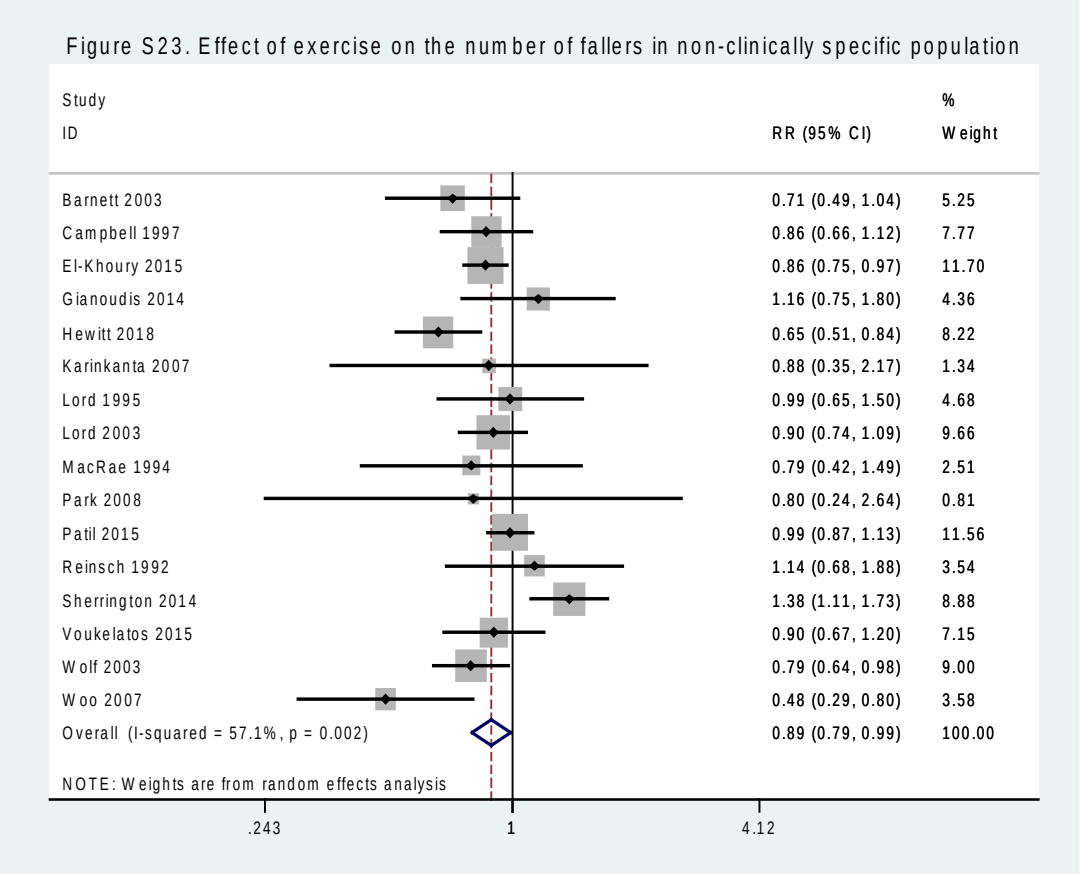
RR (95% CI): 0.91 (0.81-1.02), p=0.12
I^2=63.8%

Sensitivity Analysis 6. Restricted to studies with a low risk of attrition bias



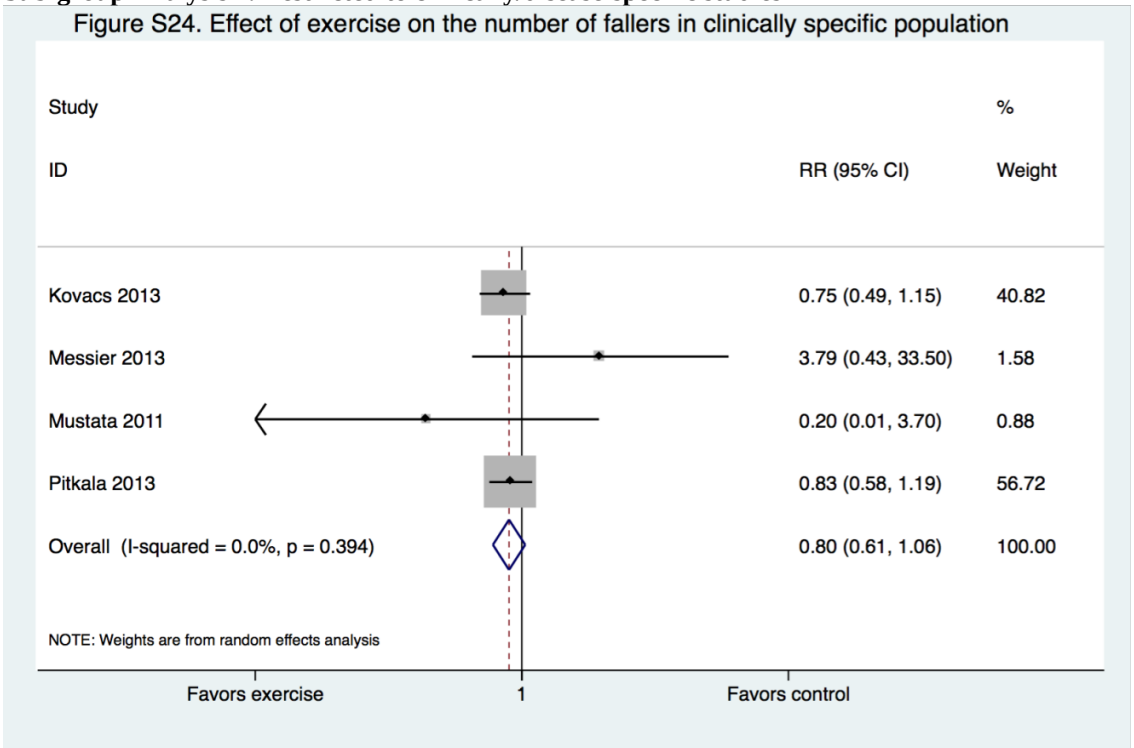
RR (95% CI): 0.90 (0.80-1.02), p=0.10
I^2=62.8%

Sub-group Analysis 1. Restricted to non-clinically/disease-specific studies



RR (95% CI): 0.89 (0.79-0.99), p=0.034
I^2=57.1%

Sub-group Analysis 2. Restricted to clinically/disease-specific studies



RR (95% CI): 0.81 (0.61-1.06), p=0.12
I^2=0.0%

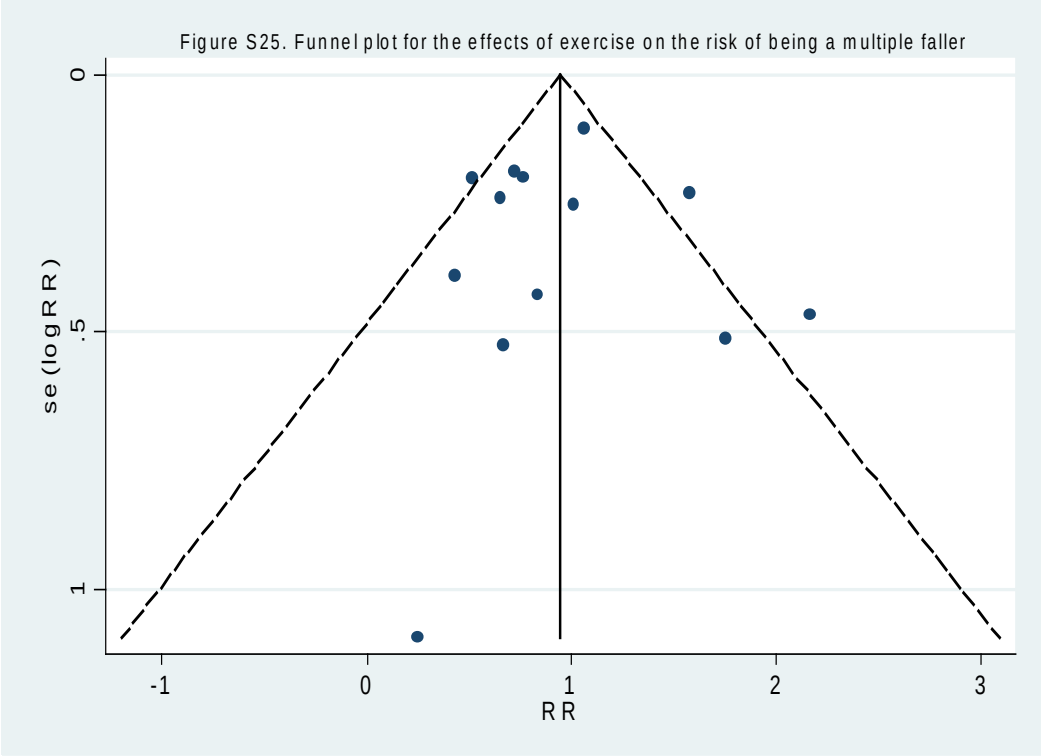
Table S3. Meta-regression on the association between the risk of becoming a faller and exercise-related variables

Meta-regression	Categories	Exp (b) (SE)	*p*-value
Exercise frequency (n=20)	<2x/week (ref) 3x/week >3x/week	 1.01 (0.12) 1.35 (0.19)	 0.92 0.050
Effective frequency (n=13)	<2x/week (ref) Between 2-3x/week >3x/week	 0.65 (0.16) 1.60 (0.25)	 0.12 0.014
Exercise volume (n=16)	<120/min/week (ref) Between 120-179 min/week ≥180 min/week	 1.22 (0.16) 1.27 (0.30)	 0.15 0.32
Effective volume (n=10)	≤60 min/week (ref) Between 61-120 min/week >120 min/week	 1.25 (0.19) No studies	 0.18
Exercise intensity (n=17)	Moderate (ref) Vigorous intensity	 1.30 (0.28)	 0.24
Exercise type (multicomponent only as reference) (n=20)	Multicomponent (ref) Aerobic Strength Others (tai-chi and dance)	 0.95 (0.22) 0.96 (0.48) 0.75 (0.13)	 0.84 0.94 0.12
Exercise type (others vs. multicomponent + balance) (n=20)	Others (ref) Multicomponent + balance	 1.18 (0.16)	 0.25

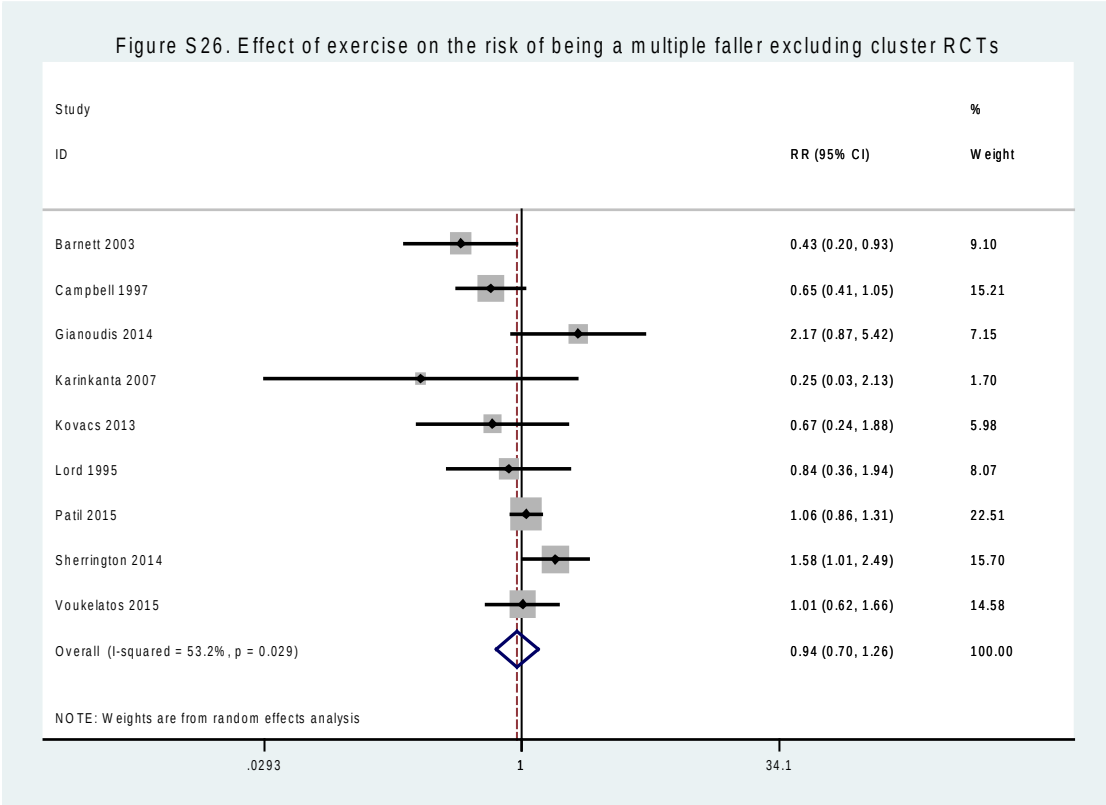
Legend: Exp: exponential, SE: standard error

Appendix 9. Meta-analyses and meta-regressions for the outcome “Fallers with multiple falls”

Funnel Plot



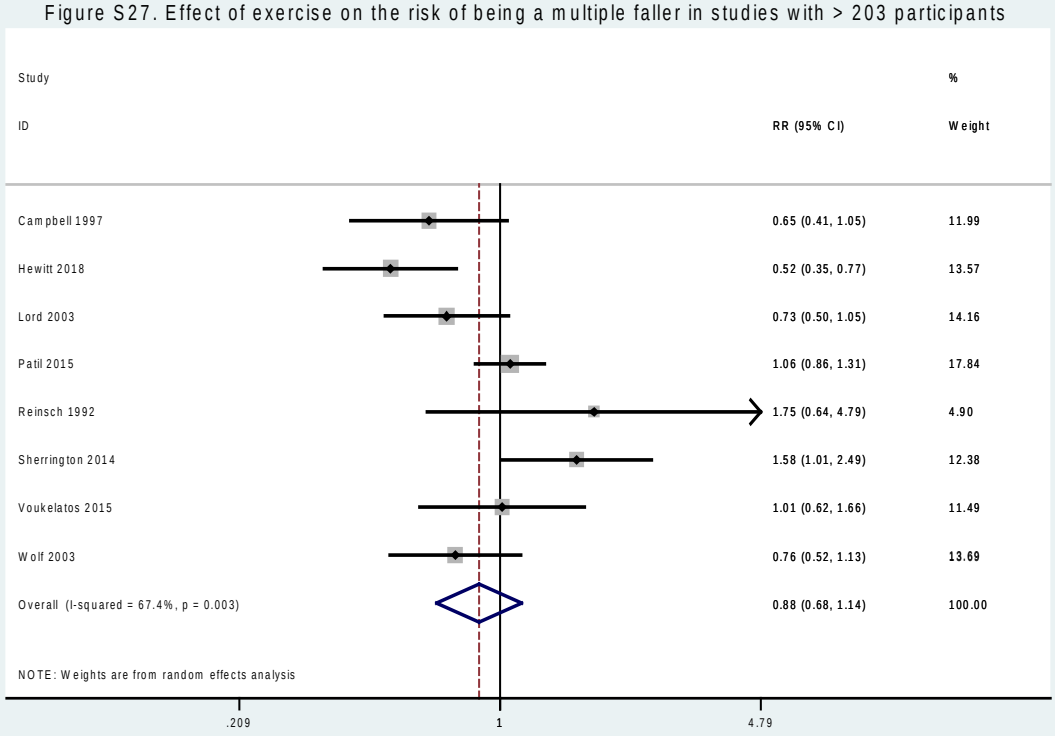
Sensitivity Analysis 3. Excluding cluster-RCTs with no adjustments for the design effect



RR (95% CI): 0.94 (0.70-1.26), p=0.68
I^2=53.2%

Analysis 5. Restricted to studies larger than the median (>203 participants)

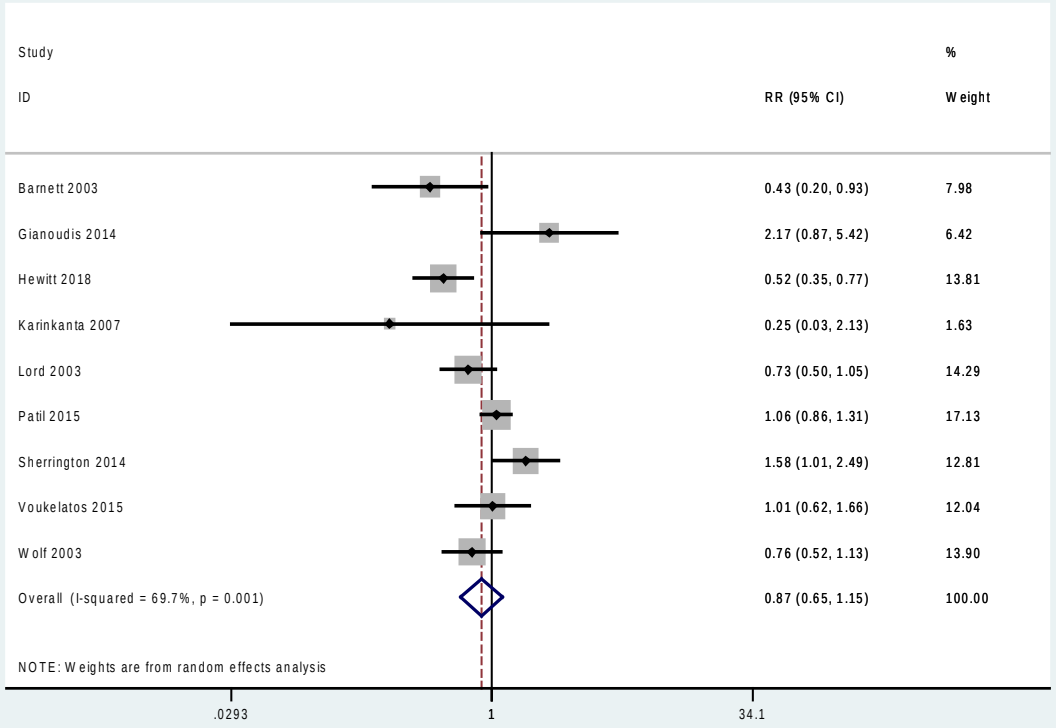
Figure S27. Effect of exercise on the risk of being a multiple faller in studies with > 203 participants



RR (95% CI): 0.88 (0.68-1.14), p=0.33
I^2=67.4%

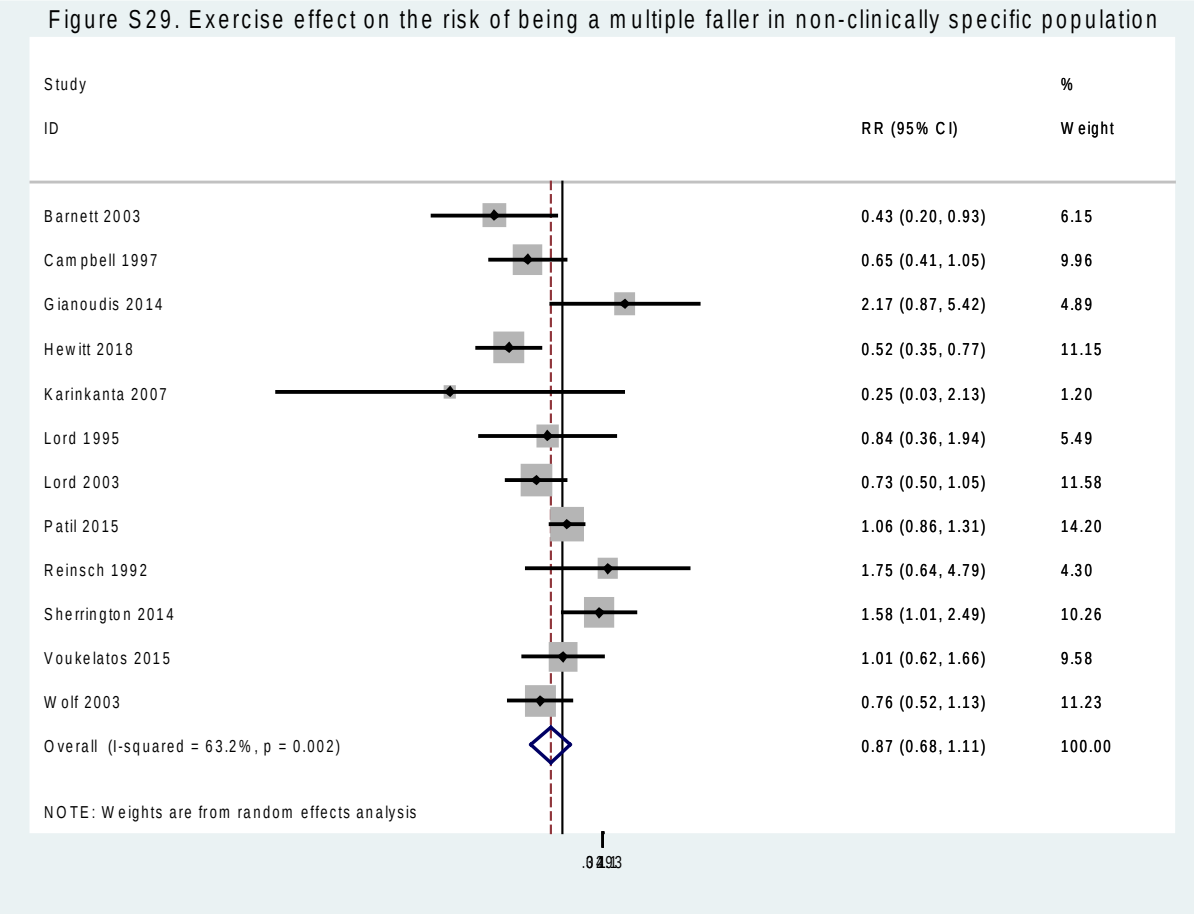
Sensitivity Analysis 6. Restricted to studies with a low risk of attrition bias

Figure S28. Exercise effect on the risk of being a multiple faller in studies with low risk of attrition bias



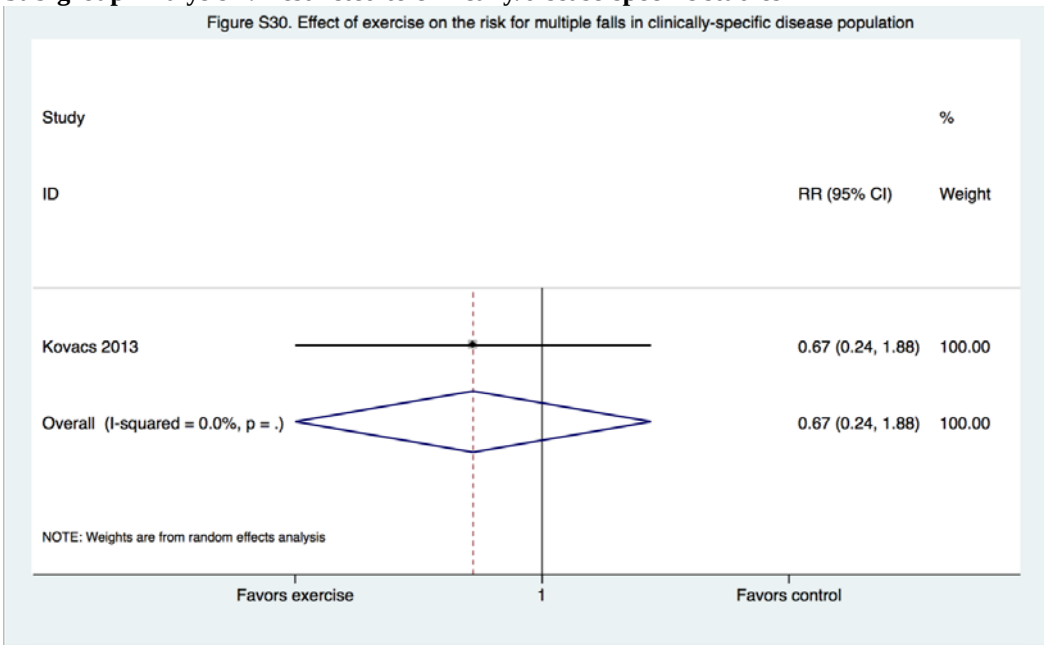
RR (95% CI): 0.87 (0.65-1.15), p=0.32
I^2=69.7%

Sub-group Analysis 1. Restricted to non-clinically/disease-specific studies



RR (95% CI): 0.87 (0.68-1.11), p=0.25
I^2=63.2%

Sub-group Analysis 2. Restricted to clinically/disease-specific studies



RR (95% CI): 0.67 (0.24-1.88), p=0.45
I^2=

Table S3. Meta-regression on the association between the risk of being a multiple faller and exercise-related variables

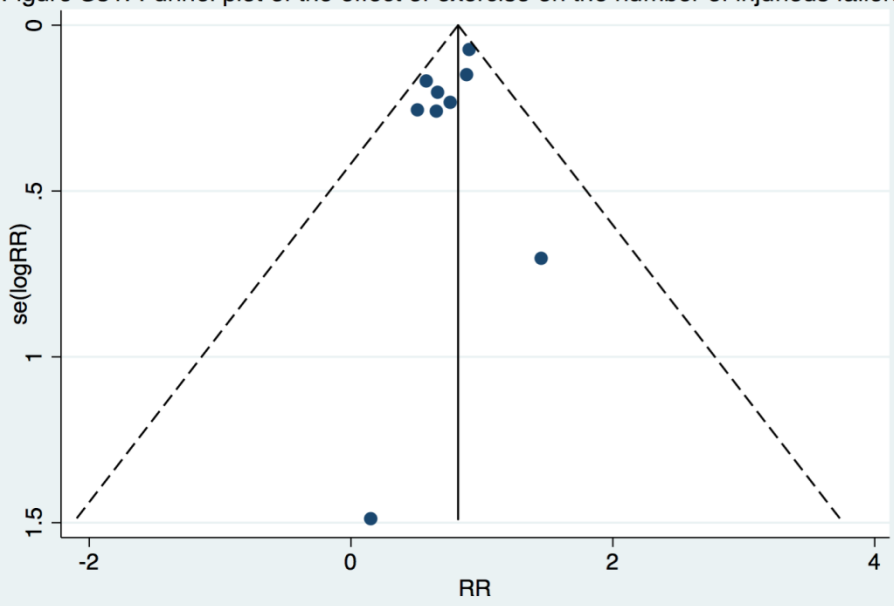
Meta-regression	Categories	Exp (b) (SE)	*p*-value
Exercise frequency (n=13)	<2x/week (ref) 3x/week >3x/week	 1.29 (0.38) 1.75 (0.55)	 0.40 0.10
Effective frequency (n=9)	<2x/week (ref) Between 2-3x/week >3x/week	 0.32 (0.40) 2.01 (0.89)	 0.40 0.16
Exercise volume (n=10)	<120/min/week (ref) Between 120-179 min/week ≥180 min/week	 1.36 (0.37) 2.76 (1.73)	 0.29 0.15
Effective volume (n=7)	≤60 min/week (ref) Between 61-120 min/week >120 min/week	 1.29 (0.49) No studies	 0.54
Exercise intensity (n=11)	Moderate (ref) Vigorous intensity	 1.90 (1.02)	 0.26
Exercise type (multicomponent only as reference) (n=13)	Multicomponent (ref) Aerobic Strength Others (tai-chi and dance)	 1.15 (0.57) 0.28 (0.34) 0.87 (0.41)	 0.78 0.32 0.78
Exercise type (others vs. multicomponent + balance) (n=13)	Others (ref) Multicomponent + balance	 1.08 (0.36)	 0.81

Legend: Exp: exponential, SE: standard error

Appendix 10. Meta-analyses for the outcome “Injurious fallers”

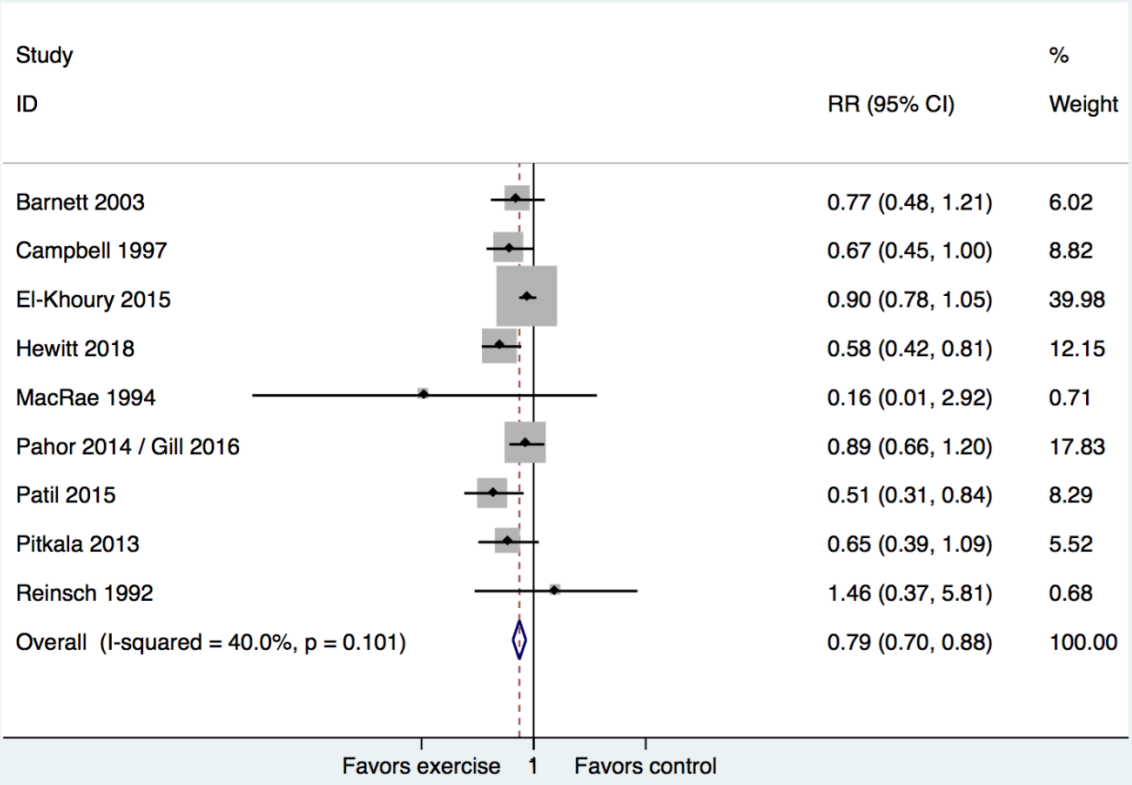
Funnel Plot

Figure S31. Funnel plot of the effect of exercise on the number of injurious fallers



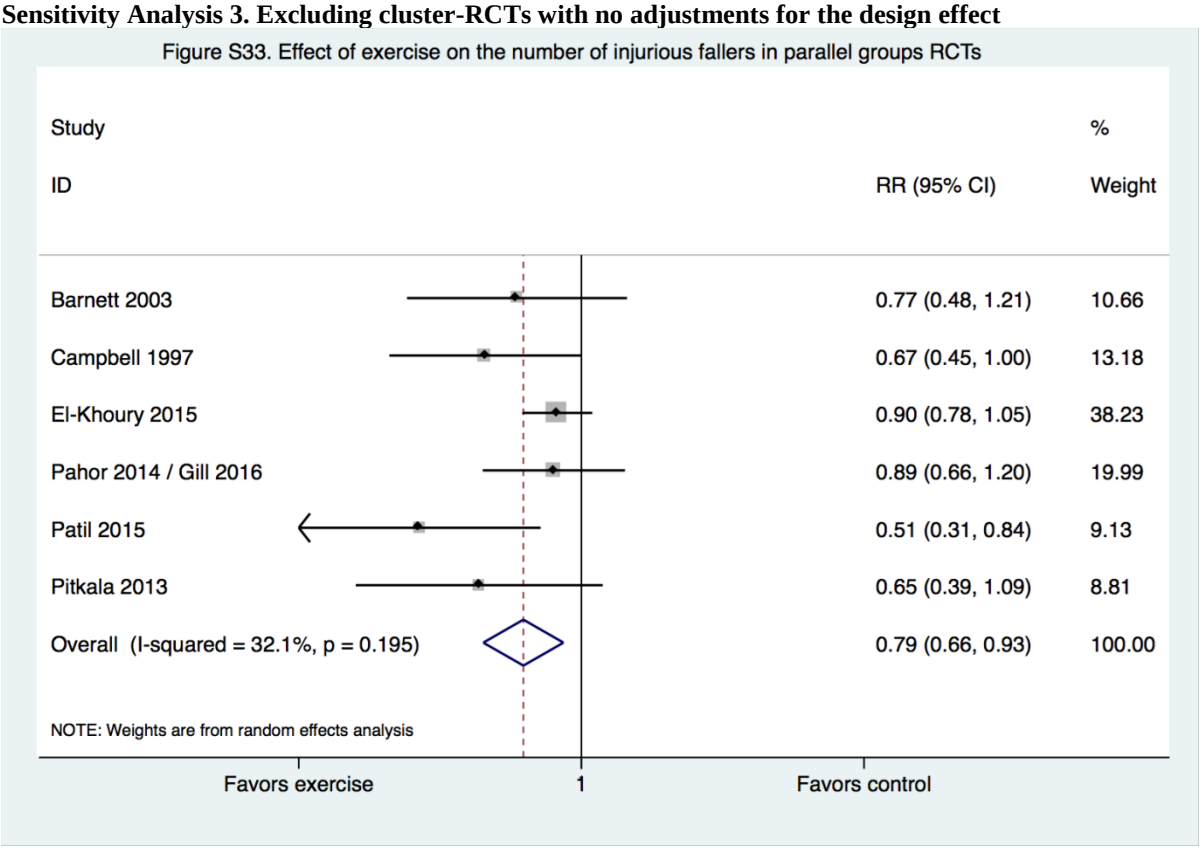
Sensitivity Analysis 1. Fixed-effect model

Figure S32. Effect of exercise on the number of injurious fallers, fixed-effect model



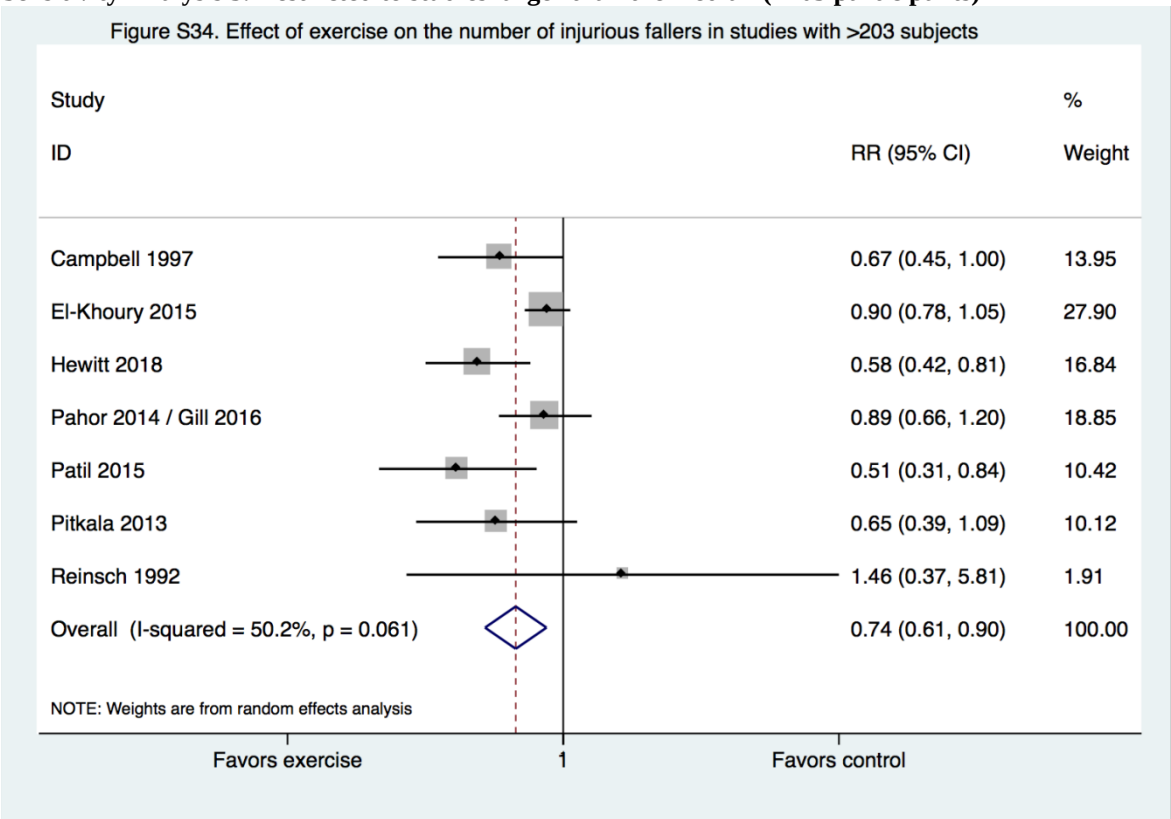
RR (95% CI): 0.79 (0.70-0.88), p<0.001
I^2= 40.0%

Sensitivity Analysis 3. Excluding cluster-RCTs with no adjustments for the design effect



RR (95% CI): 0.79 (0.67-0.93), p=0.005
I^2= 32.1%

Sensitivity Analysis 5. Restricted to studies larger than the median (>203 participants)

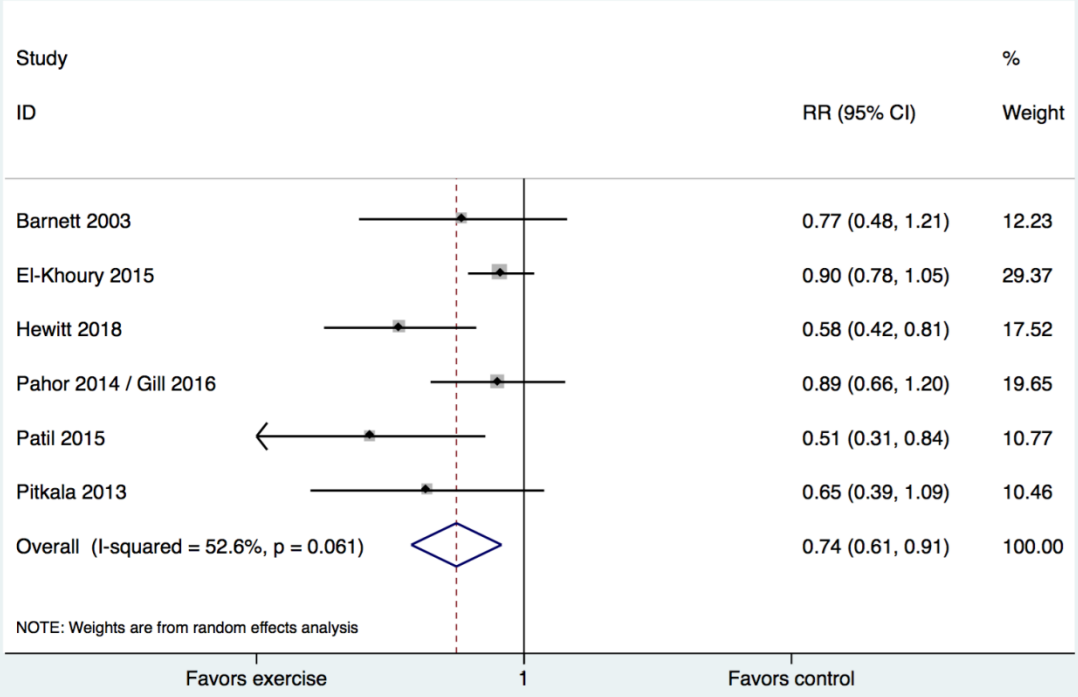


RR (95% CI): 0.74 (0.61-0.90), p=0.003

I^2= 50.2%

Sensitivity Analysis 6. Restricted to studies with a low risk of attrition bias

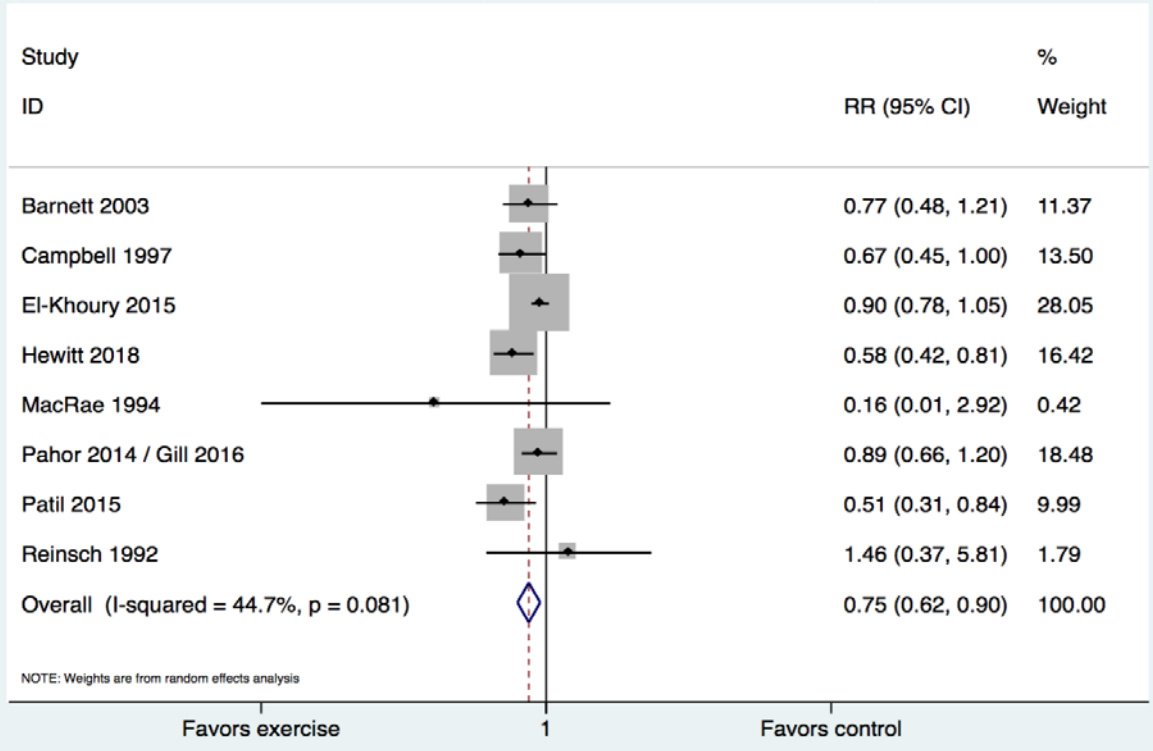
Figure S35. Effect of exercise on the number of injurious fallers in studies with low risk of attrition



RR (95% CI): 0.74 (0.61-0.91), p=0.003
I^2= 52.6%

Sub-group Analysis 1. Restricted to non-clinically/disease-specific studies

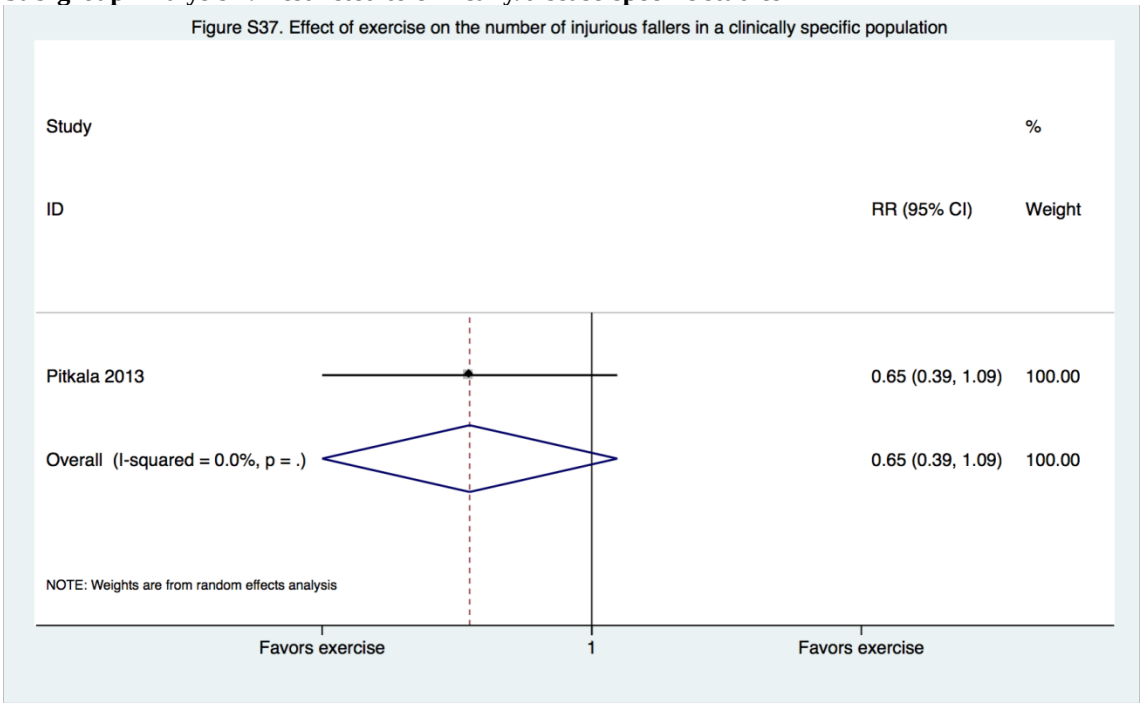
Figure S36. Effect of exercise on the number of injurious fallers in studies with no clinically-specific population



RR (95% CI): 0.75 (0.62-0.90), p=0.003

I^2= 44.7%

Sub-group Analysis 2. Restricted to clinically/disease-specific studies



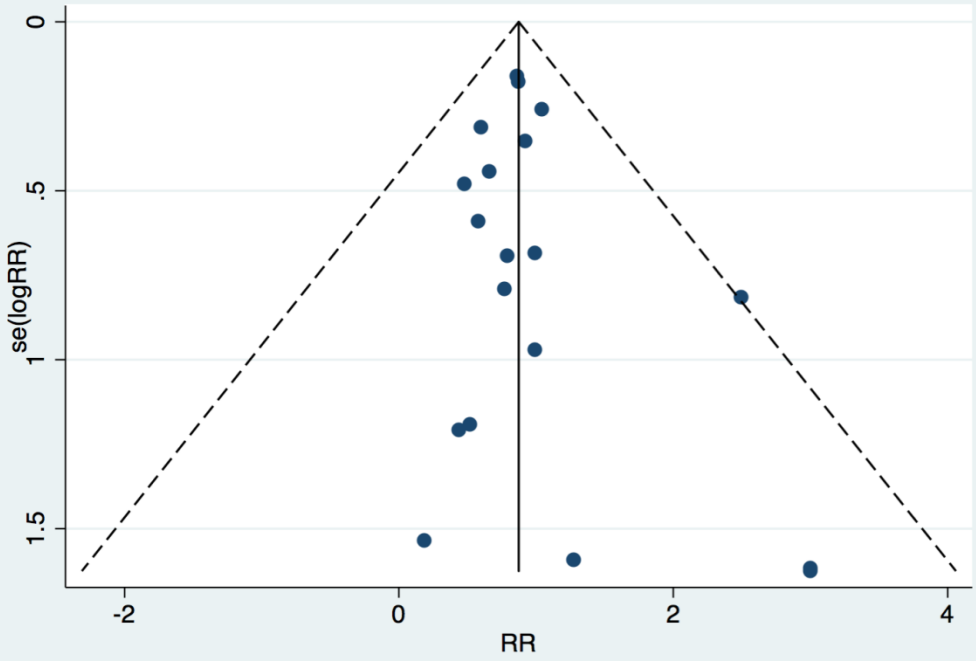
RR (95% CI): 0.65 (0.39-1.09), p=0.10

I^2= none

Appendix 11. Meta-analyses and meta-regressions for the outcome “People with fractures”

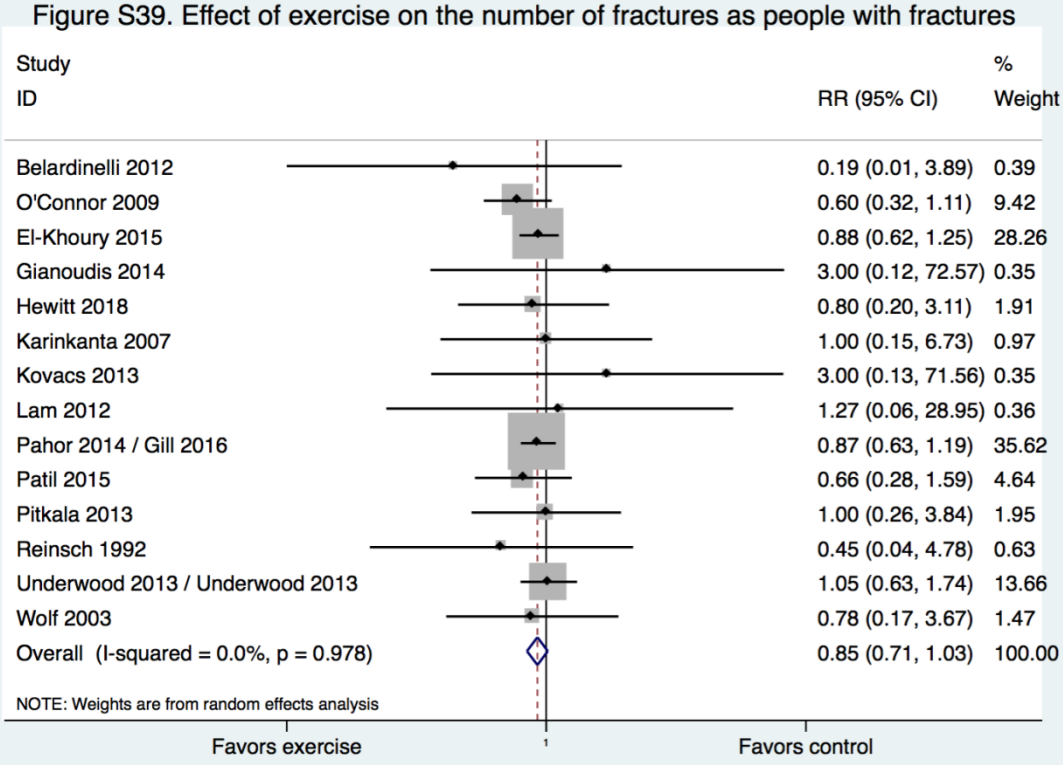
Funnel Plot

Figure S38. Funnel plot of the effect of exercise on the number of people with fractures



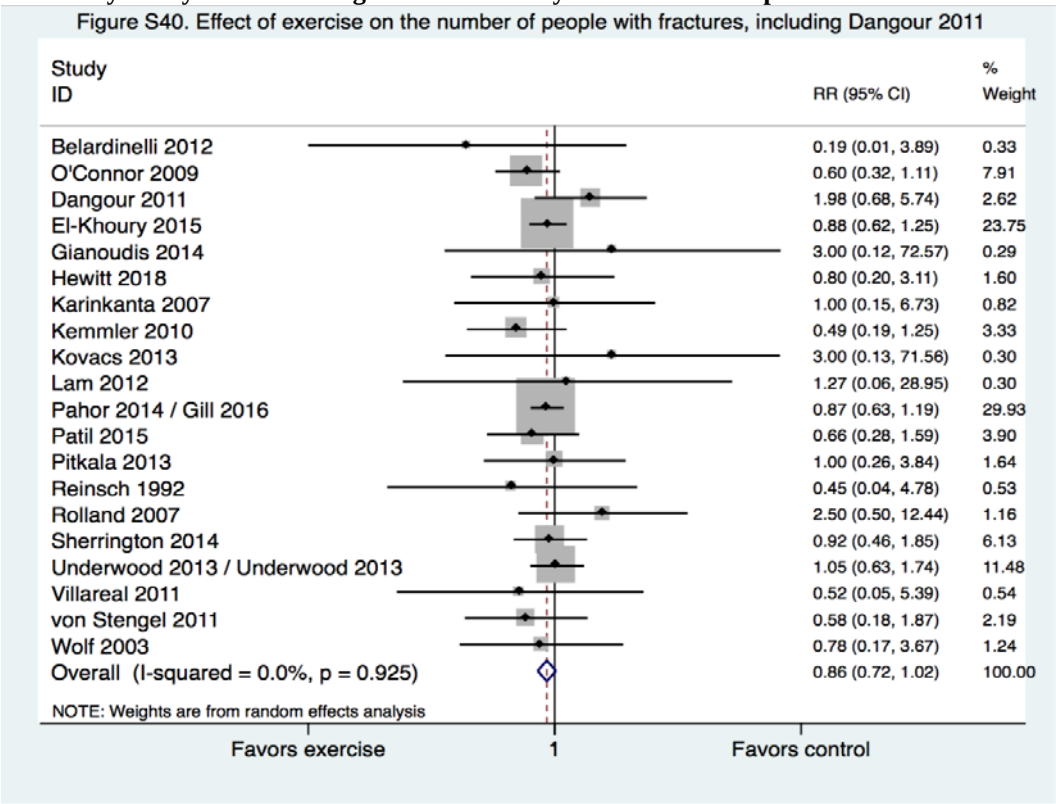
Sensitivity Analysis. Excluding studies (n=5) without data on the number of people sustaining a fracture

Figure S39. Effect of exercise on the number of fractures as people with fractures



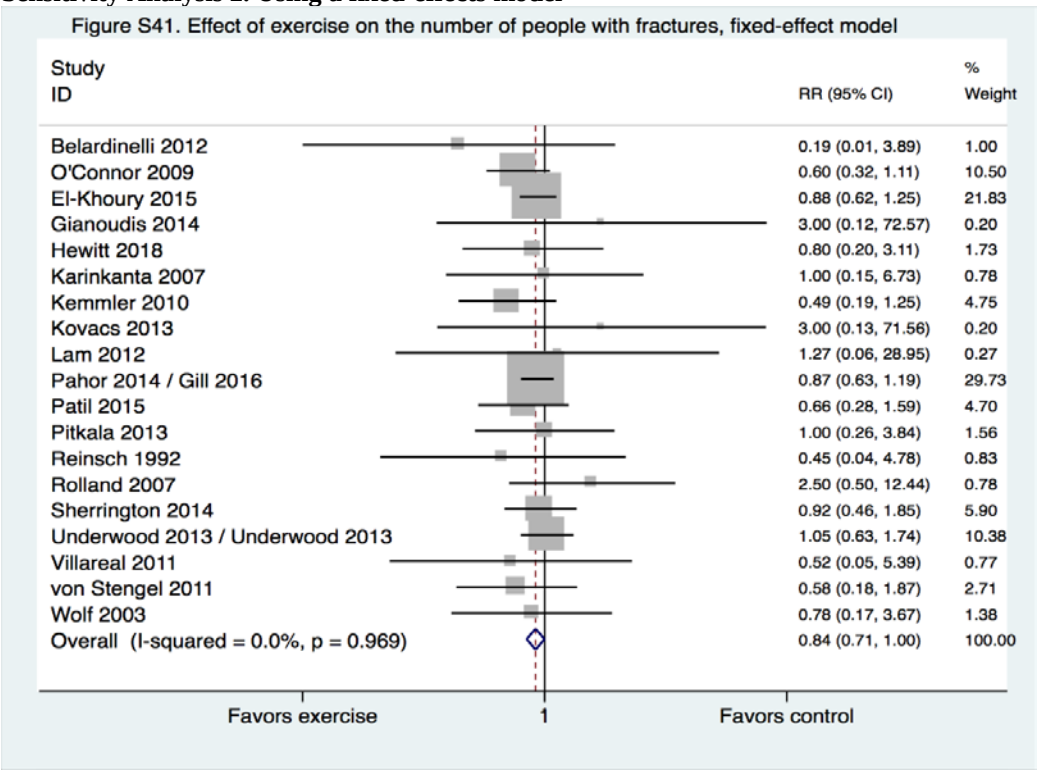
RR (95% CI): 0.85 (0.71-1.03), p=0.098
I^2= 0.0%

Sensitivity Analysis 1. Including studies with very low exercise compliance



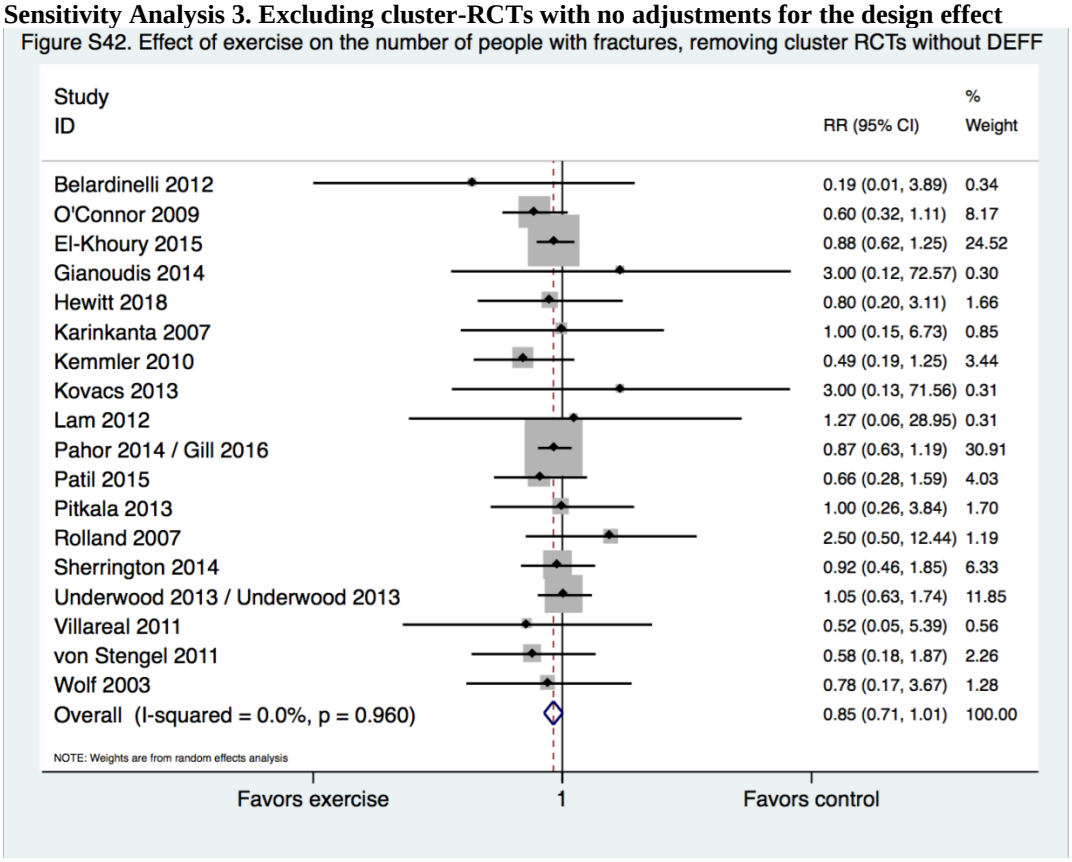
RR (95% CI): 0.86 (0.73-1.02), p=0.090
I^2= 0.0%

Sensitivity Analysis 2. Using a fixed-effects model



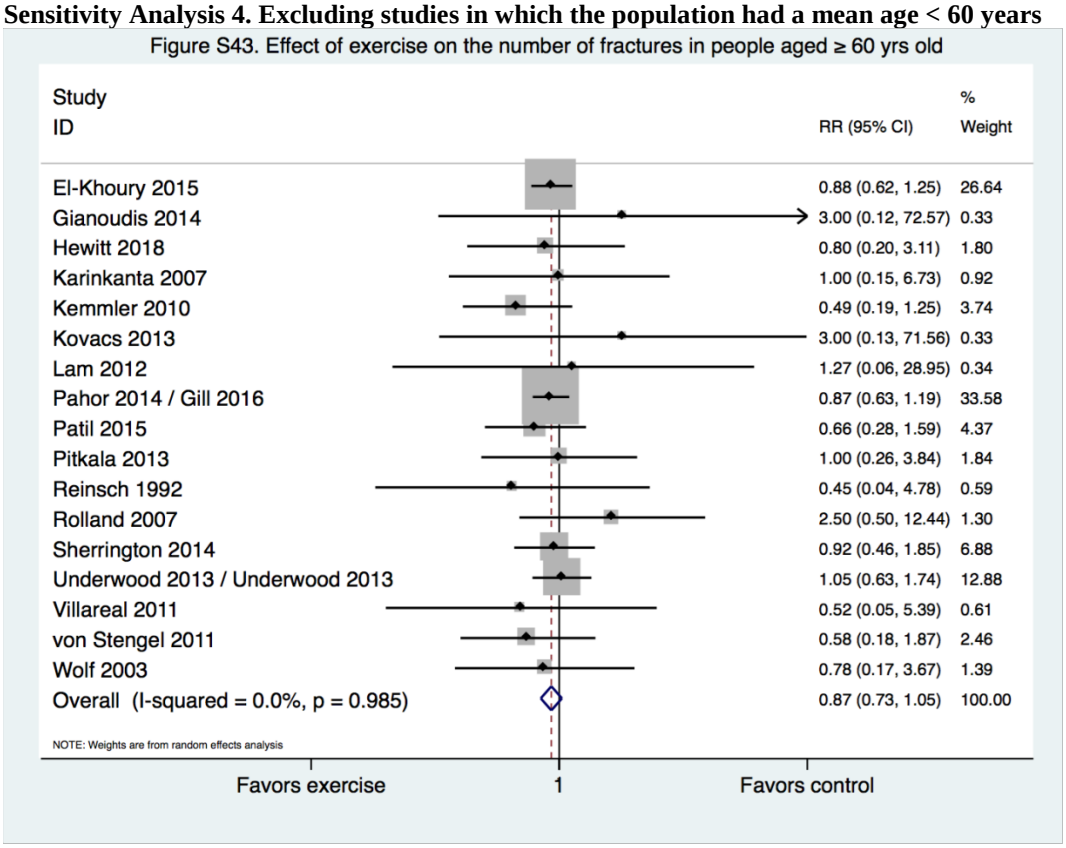
RR (95% CI): 0.84 (0.71-0.99), p=0.047
I^2= 0.0%

Sensitivity Analysis 3. Excluding cluster-RCTs with no adjustments for the design effect



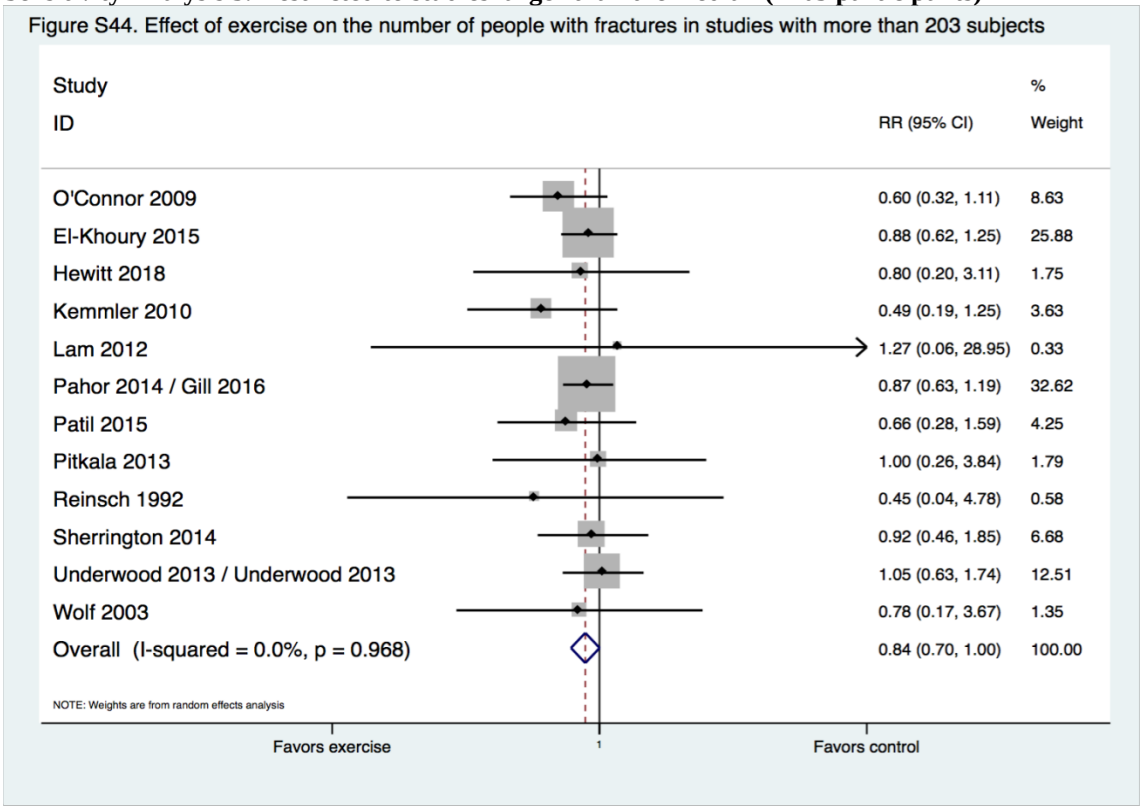
RR (95% CI): 0.85 (0.71-1.01), p=0.060
I^2= 0.0%

Sensitivity Analysis 4. Excluding studies in which the population had a mean age < 60 years



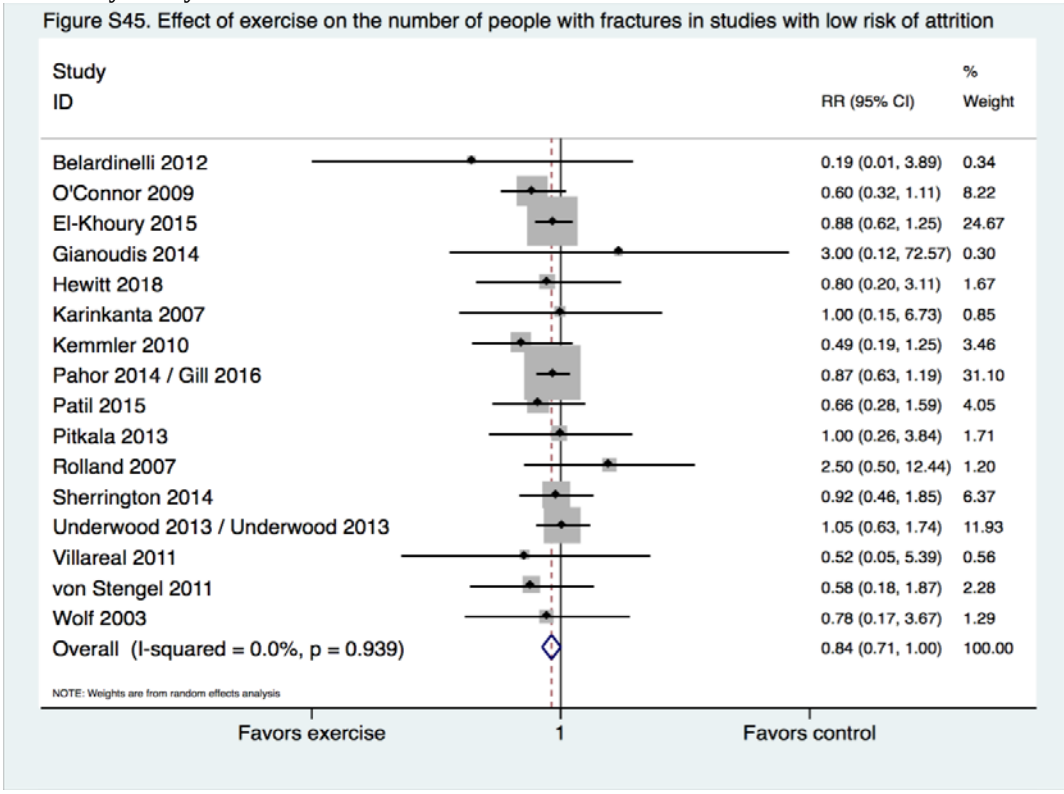
RR (95% CI): 0.87 (0.73-1.05), p=0.14
I^2= 0.0%

Sensitivity Analysis 5. Restricted to studies larger than the median (>203 participants)



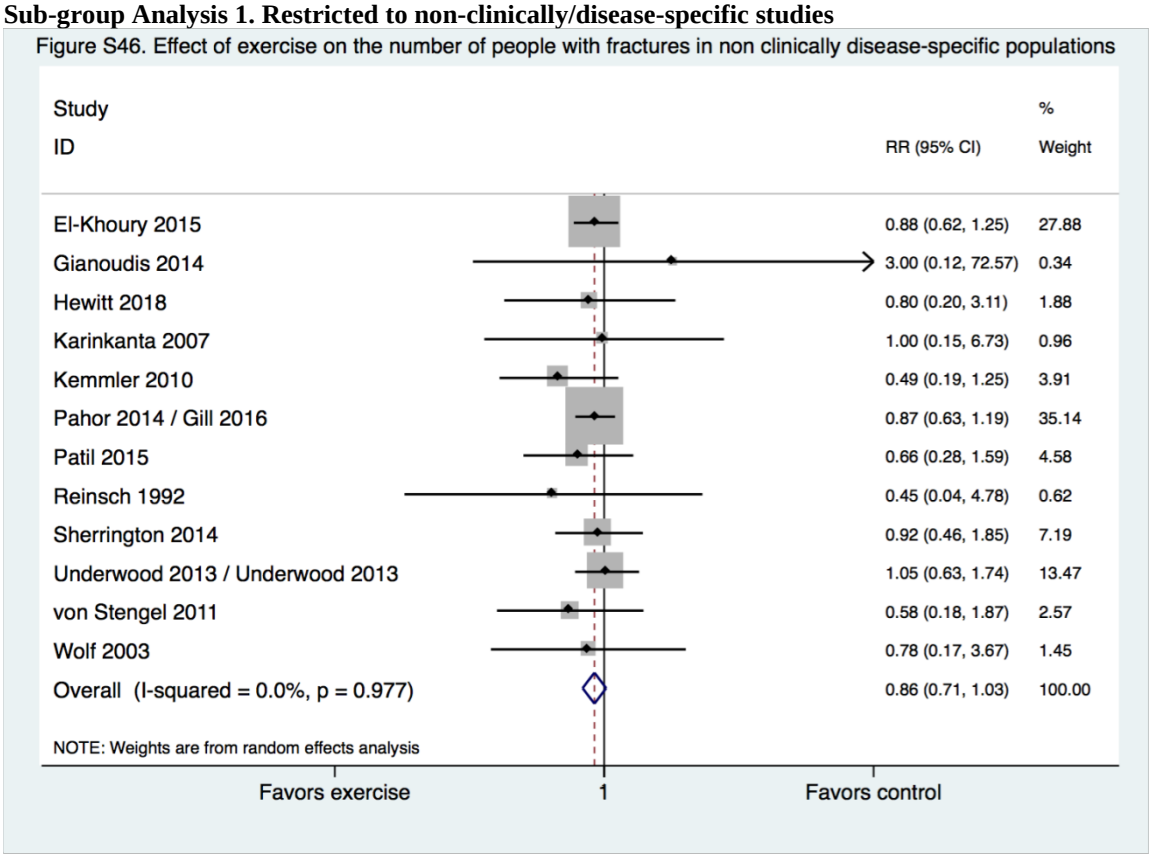
RR (95% CI): 0.84 (0.70-1.00), p=0.053
I^2= 0.0%

Sensitivity Analysis 6. Restricted to studies with a low risk of attrition bias



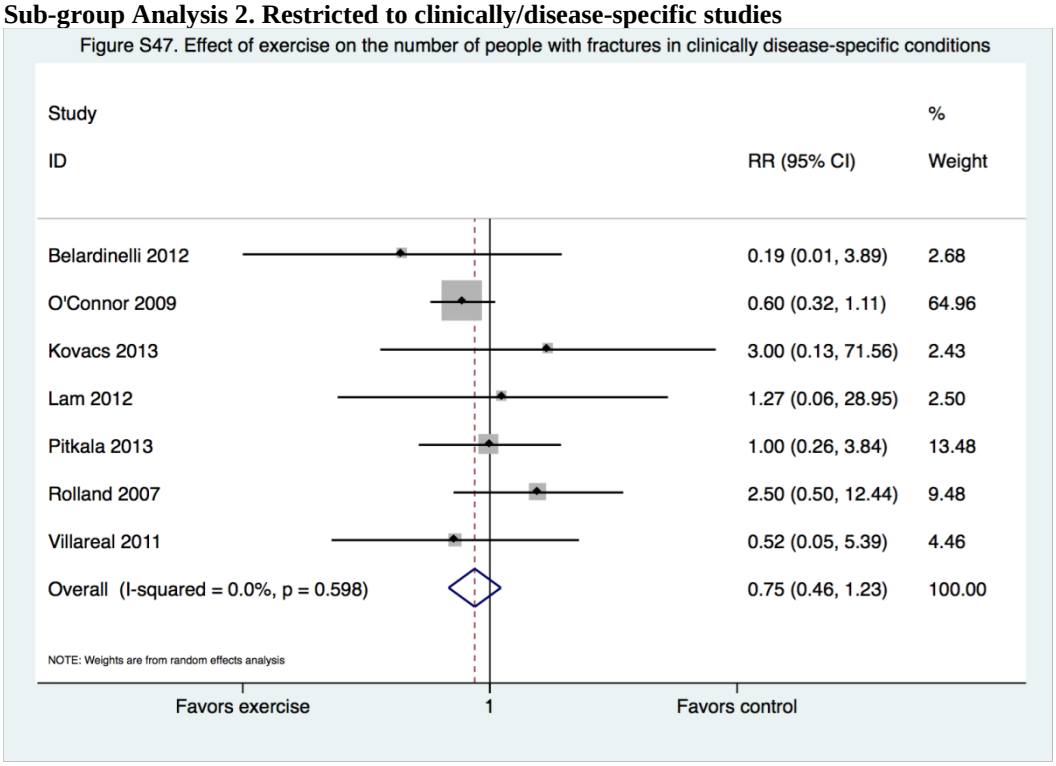
RR (95% CI): 0.84 (0.71-1.00), p=0.053
I^2= 0.0%

Sub-group Analysis 1. Restricted to non-clinically/disease-specific studies



RR (95% CI): 0.86 (0.71-1.03), p=0.10
I^2= 0.0

Sub-group Analysis 2. Restricted to clinically/disease-specific studies



RR (95% CI): 0.75 (0.46-1.23), p=0.25
I^2= 0.0%

Table S4. Meta-regression on the association between the risk of having sustained a fracture and exercise-related variables

Meta-regression	Categories	Exp (b) (SE)	*p*-value
Exercise frequency (n=19)	<2x/week (ref) 3x/week >3x/week	 0.89 (0.46) 0.85 (0.15)	 0.83 0.37
Effective frequency (n=15)	<2x/week (ref) Between 2-3x/week >3x/week	 0.58 (0.20) 0.95 (0.19)	 0.15 0.78
Exercise volume (n=16)	<120/min/week (ref) Between 120-179 min/week ≥180 min/week	 0.86 (0.23) 0.79 (0.21)	 0.58 0.39
Effective volume (n=13)	≤60 min/week (ref) Between 61-120 min/week >120 min/week	 0.79 (0.22) 0.89 (0.19)	 0.41 0.60
Exercise intensity (n=18)	Moderate (ref) Vigorous intensity	 0.71 (0.25)	 0.35
Exercise type (multicomponent only as reference) (n=19)	Multicomponent (ref) Aerobic Strength Others (tai-chi and dance)	 0.66 (0.21) 1.15 (1.12) 0.98 (0.70)	 0.21 0.89 0.98
Exercise type (others vs. multicomponent + balance) (n=19)	Others (ref) Multicomponent + balance	 1.03 (0.22)	 0.89

Legend: Exp: exponential, SE: standard error

Appendix 12. Number of participants and events included in the main analysis per study and per outcome.

Studies	Mortality		Hospitalization		Fallers (≥ 1 fall)		Multiple fallers (≥ 2 falls)		Number of people sustaining a fracture		Number of injurious fallers	
	Exercise cases/n	Control cases/n	Exercise cases/n	Control cases/n	Exercise cases/n	Control cases/n	Exercise cases/n	Control cases/n	Exercise cases/n	Control cases/n	Exercise cases/n	Control cases/n
Belardinelli et al 2012	4/63	10/60	8/63	25/60	N/A	N/A	N/A	N/A	0/63	2/60	N/A	N/A
Barnett 2003	0/83	3/80	N/A	N/A	27/76	37/74	8/76	18/74	N/A	N/A	22/76	28/74
Campbell 1997	2/116	4/117	N/A	N/A	53/116	62/117	22/116	34/117	N/A	N/A	27/103	43/110
Dangour 2011[a]	9/450	6/504	N/A	N/A	189/402	198/398	N/A	N/A	10/402	5/398	N/A	N/A
El-Khoury 2015	5/352	6/354	N/A	N/A	189/352	222/354	N/A	N/A	49/352	56/354	170/352	189/354
Galvao 2014	1/50	0/50	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gianoudis 2014	1/81	1/81	N/A	N/A	29/81	25/81	13/81	6/81	1/81	0/81	N/A	N/A
Hambrecht 2004	N/A	N/A	1/51	6/50	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hewitt 2018	15/113[b]	14/108[b]	8/113	12/108	50/113	73/108	26/113	48/108	5/113[b]	6/108[b]	34/113	56/108
Karinkanta 2007	0/37	1/37	N/A	N/A	7/37	8/37	1/37	4/37	2/37	2/37	N/A	N/A
Kemmler 2010	0/123	1/123	N/A	N/A	N/A	N/A	N/A	N/A	6/115	12/112	N/A	N/A
King 2002	0/51	1/49	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kovacs 2003	4/41	10/41	2/41	1/41	16/32	20/30	5/32	7/30	1/41	0/41	N/A	N/A
Lam 2012	1/171[b]	2/218[b]	N/A	N/A	N/A	N/A	N/A	N/A	1/171[b]	1/218[b]	N/A	N/A
Lam 2015	1/147	3/131	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lord 1995	N/A	N/A	N/A	N/A	26/75	33/94	8/75	12/94	N/A	N/A	N/A	N/A
Lord 2003	5/280[b]	1/271[b]	N/A	N/A	109/259	117/249	40/259	53/249	N/A	N/A	N/A	N/A

MacRae 1994	N/A	N/A	N/A	N/A	10/28	14/31	N/A	N/A	N/A	N/A	0/28	3/31
Merom 2016	3/277 [b]	2/251 [b]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Messier 2013	N/A	N/A	4/136	0/129	4/136	1/129	N/A	N/A	N/A	N/A	N/A	N/A
Munro 2004[a]	283/2283	505/4137	853/2283	1473/4137	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mustata 2011	N/A	N/A	0/10	1/10	0/10	2/10	N/A	N/A	N/A	N/A	N/A	N/A
O'Connor 2009	189/1159	198/1171	729/1159	760/1172	N/A	N/A	N/A	N/A	16/1159	27/1172	N/A	N/A
Pahor 2006	2/213	2/211	44/213	44/211	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pahor 2014	48/818	42/817	396/818	360/817	N/A	N/A	N/A	N/A	66/818	76/817	75/818	84/817
Park 2008	N/A	N/A	N/A	N/A	4/25	5/25	N/A	N/A	N/A	N/A	N/A	N/A
Patil 2015	0/205	4/204	N/A	N/A	140/205	141/204	98/205	92/204	8/205	12/204	20/205	39/204
Pitkala 2013	2/70	8/70	29/70	37/70	29/70	35/70	N/A	N/A	4/70	4/70	17/70	26/70
Prescott 2008	2/36	4/30	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Reinsch 1992	N/A	N/A	N/A	N/A	22/57	17/50	10/57	5/50	1/56	2/50	5/57	3/50
Rejeski 2017	0/81	1/82	1/81	0/82	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rolland 2007	7/67	8/67	20/67	11/67	N/A	N/A	N/A	N/A	5/67	2/67	N/A	N/A
Sherrington 2014	10/171	9/169	N/A	N/A	98/171	70/169	40/171	25/169	14/171	15/169	N/A	N/A
Underwood 2013	98/398 [b]	114/493 [b]	N/A	N/A	N/A	N/A	N/A	N/A	33/398[b]	39/493[b]	N/A	N/A
Van Uffelen 2008	0/86	1/93	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Villareal 2011	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1/26	2/27	N/A	N/A
Von Stengel 2011	0/50	1/51	N/A	N/A	N/A	N/A	N/A	N/A	4/50	7/51	N/A	N/A
Voukelatos 2015	4/192	0/194	N/A	N/A	54/159	68/180	25/159	28/180	N/A	N/A	N/A	N/A
Winters-Stone 2011	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Wolf 2003	2/146 [b]	2/141 [b]	N/A	N/A	69/145	85/141	33/145	42/141	4/145[b]	5/141[b]	N/A	N/A
Woo 2007	N/A	N/A	N/A	N/A	15/60	31/60	N/A	N/A	N/A	N/A	N/A	N/A

Note. N/A, not applicable – N/A was used when either no usable data was available or no event occurred in both exercisers and controls
[a]These studies did not enter into the primary analysis for any of the outcomes due to low compliance to the intervention
[b]For these cluster RCTs, intra-cluster correlation (ICC) values were used to estimate the effective sample size using the design effect