Effects of adding exercise to usual care in patients with either hypertension, type 2 diabetes or cardiovascular disease: a systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Objective To assess the beneficial and harmful effects of adding exercise to usual care for people with hypertension, type 2 diabetes mellitus and/or cardiovascular disease.

Design Systematic review with meta-analysis and trial sequential analysis of randomised clinical trials.

Data sources The CENTRAL, MEDLINE, EMBASE, Science Citation Index Expanded on Web of Science and BIOSIS searched from inception to July 2020.

Eligibility criteria for selecting studies We included all randomised clinical trials adding any form of trialist defined exercise to usual care versus usual care in participants with either hypertension, type 2 diabetes or cardiovascular disease irrespective of setting, publication status, year and language.

Outcome and measures The primary outcomes were all-cause mortality, serious adverse events and quality of life.

Data extraction and synthesis Five independent reviewers extracted data and assessed risk of bias in pairs. Our methodology was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Grading of Recommendations Assessment, Development and Evaluation and Cochrane Risk of Bias-version 1.

Results We included 950 trials, of which 248 trials randomising 21 633 participants reported on our predefined outcomes. All included trials were at high risk of bias. The major types of exercise reported were dynamic aerobic exercise (126/248 trials), dynamic resistance exercise (25/248 trials), and combined aerobic and resistance exercise (58/248 trials). The study participants were included due to cardiovascular diseases (189/248 trials), type 2 diabetes (41/248 trials) or hypertension (16/248 trials). The median intervention period was 3 months (IQR: 2–4 months) and the median follow-up period was 6 months (IQR: 3–8 months) after randomisation. Meta-analyses and trial sequential analyses showed evidence of a beneficial effect of adding exercise to usual care when assessing all-cause mortality (risk ratio (RR) 0.82; 95% CI 0.73 to 0.93; I^2=0%, moderate certainty of evidence) and serious adverse events (RR 0.79; 95% CI 0.71 to 0.88; I^2=0%, moderate certainty of evidence). We did not find evidence of a difference between trials from different economic regions, type of participants, type of exercise or duration of follow-up. Quality of life was assessed using several different tools, but the results generally showed that exercise improved quality of life, but the effect sizes were below our predefined minimal important difference.

Conclusions A short duration of any type of exercise seems to reduce the risk of all-cause mortality and serious adverse events in patients with either hypertension, type 2 diabetes or cardiovascular diseases. Exercise seems to have statistically significant effects on quality of life, but the effect sizes seem minimal.

PROSPERO registration number CRD42019142313.

WHAT IS ALREADY KNOWN?

⇒ Previous individual trials have been underpowered to investigate the effects of adding exercise intervention to usual care on major clinical outcomes

⇒ Previous reviews have focused on selected types of exercise and narrow patient groups leading to loss of power and conflicting results.

WHAT ARE THE NEW FINDINGS?

⇒ A short duration of any type of exercise seems to reduce the risk of all-cause mortality and serious adverse events in patients with either hypertension, type 2 diabetes or cardiovascular diseases.

⇒ Exercise has significant effect on quality of life but seems clinically minimal.

⇒ Our results show that adding exercise to usual care seems to be beneficial and could be prescribed globally as a supplemental to non-pharmacological intervention to all patients with either hypertension, type 2 diabetes or cardiovascular disease.

INTRODUCTION

In 2019, nearly 18.6 million deaths were due to cardiovascular disease worldwide.[1] The two leading comorbidities and risk factors of cardiovascular disease are hypertension and type 2 diabetes. The complications of hypertension and type 2 diabetes are linked with developing macrovascular and microvascular diseases, leading to cardiovascular adverse events and related deaths.[2–4] Currently, an estimated 1.4 billion adults are living with hypertension. Likewise, type 2 diabetes is

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the seventh-leading cause of disability-adjusted life-years worldwide,[5] accounting for 1.5 million deaths in 2019.[6] The substantial burden of these diseases is disproportionately high in low-income and middle-income countries.[5 7 8]

Despite well-documented evidence-based treatment and management strategies, the control of hypertension, type 2 diabetes and cardiovascular disease is suboptimal.[5 9] The intricate linkage of physical inactivity and sedentary lifestyle plays a substantial role in propagating the burden of these non-communicable diseases.[4 9 10] Consequently, exercise is among the most recommended lifestyle interventions for secondary and tertiary prevention and management of hypertension, type 2 diabetes and cardiovascular diseases.[11–13] Exercise exists in different forms.[14] Based on involvement of muscle activity, intensity and frequency, it can be either dynamic or static. Dynamic aerobic exercise, dynamic resistance exercise and combined aerobic and resistance exercise are some of the common forms of exercise recommended for manangement of various non-communicable disease.[15] Apart from this isometric (static) resistance exercise, yoga and other balance and flexibility enhancing exercises are being practised throughout the globe.

The European Society of Cardiology,[16] the American Diabetes Association,[17] the American Heart Association[15] have recommended moderate to vigorous physical activity, primarily aerobic and resistance exercises, 3–5 times per week for patients with hypertension, type 2 diabetes or cardiovascular diseases. However, the evidence behind these recommendations and the choice of type of exercise, including the duration and intensity of the exercise, is not well documented. Various systematic reviews and meta-analyses of randomised trials have shown beneficial effects of exercises in (1) reducing cardiovascular risk factors such as elevated blood pressure, glucose intolerance and hyperlipidaemia,[18–22] (2) improving motor and cardiorespiratory functions[23 24] and (3) improving morphological composition.[13 14] Only non-randomised studies have documented that exercise reduces the risk of death.[25–27] Randomised clinical trials on the effects of exercise in the prevention of mortality, serious adverse events (SAEs) and other clinical outcomes remain inconclusive.[28–30] Previous reviews on the beneficial effects of exercise on improving quality of life also remain uncertain, primarily due to smaller trials with potential biases.[24 31–33]

No prior systematic reviews have pooled trials assessing any form of exercise as secondary or tertiary prevention in participants with either hypertension, type 2 diabetes or cardiovascular disease,taking into account both random and systematic errors.[14]

In this systematic review with meta-analysis and trial sequential analysis, we aim to assess the beneficial and harmful effect of adding exercise to usual care in patients with hypertension, type 2 diabetes and cardiovascular diseases.

METHODS

Our review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews evaluating interventions in healthcare.[34] The methodology has been described in detail in our prepublished protocol registered prior to the systematic literature search.[14]

Search strategy and selection criteria

In brief, we included all randomised clinical trials assessing the effects of adding exercise (as defined by trialists) to usual care (as defined by trialists-any routine care received by the patients) versus usual care (same usual care as in the intervention group) in patients with either hypertension, type 2 diabetes or cardiovascular disease. Trials were included irrespective of setting, trial duration, publication status, publication year and language. We searched from their inception to July 2020 in the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Science Citation Index Expanded on Web of Science, BIOSIS, Google Scholar and ClinicalTrials.gov. The detailed search strategy can be found in online supplemental S1 text. In addition, we manually searched reference lists of previously published reviews.

Data collection and risk of bias

Five authors (AR, TBA, SD, MM and RP) independently extracted data using a standardised data extraction sheet and assessed risk of bias using the Cochrane Risk of Bias-version 1 (RoB1)[35] in pairs. The following bias domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, for profit bias and other risks of bias. Any disagreements were resolved through discussion with a third author (JCJ or EEN). We contacted authors of all trials via email to retrieve missing information and individual patient data and to access full text wherever necessary. The email was sent to corresponding author only once and for authors whose email was outdated or not available we searched for research gate profile accessed through their name and wrote an individual private message regarding the same.

Outcomes and subgroup analyses

Our primary outcomes were all-cause mortality, SAEs and quality of life. SAEs are defined as proportion of participants with an SAE defined as any untoward medical occurrence that resulted in death; was life threatening; was persistent; or led to significant disability, nephrotoxicity, superinfection, need for respiratory support, need for circulatory support or prolonged hospitalisation or as defined by International Council for Harmonisation guideline for Good Clinical Practice guidelines or as referred by trialists.[14 36] The secondary outcomes were cardiovascular mortality, myocardial infarction and stroke.[14] For all outcomes, we used trial results reported to the longest follow-up.

The secondary outcomes blood pressure (systolic and diastolic both) and microvascular complications as mentioned in protocol are not reported in this article. We plan to discuss effect of exercise on blood pressure separately in another article due to share volume of data which if included would have been difficult to present and summarise in this paper. For microvascular complications, we did not find any data to report.

We planned several subgroup analyses (see the Results section): (1) different types of exercise (as defined by trialists), (2) different disease group—hypertension, type 2 diabetes and cardiovascular disease (as defined by trialists); cardiovascular disease as defined by WHO includes cerebrovascular disease, rheumatic heart disease, deep vein thrombosis, pulmonary thrombosis, coronary artery disease such as myocardial infarction and heart failure,[37] (3) high-income countries versus low-income and middle-income countries (as defined by The World Bank country classification),[38] (4) trials at high risk of bias compared with trials at low risk of bias.[14] In addition, we added two post hoc subgroup analyses: (1) trials including biological male compared with biological female compared with trials including both biological

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genders and (2) short-term follow-up (≤median follow-up) compared with long-term follow-up (>median follow-up).

Data analysis

We used and STATA V.17 (StataCorp) for all statistical analyses.[39] We assessed three primary outcomes, and therefore, we considered a p value of 0.025 as the threshold for statistical significance for primary outcomes and 0.05 for secondary outcomes.[14] We conducted both fixed-effect and random-effect meta-analysis and primarily reported the most conservative result and considered the less conservative results as a sensitivity analysis.[14 40] We analysed different quality of life scales separately to avoid the methodological problems with using standardised mean difference.[41] The predetermined minimal important difference for quality of life scales was used, calculated as the mean difference of the observed SD divided by two in the control group.[42] We investigated possible heterogeneity by visual inspection of forest plots, by calculating inconsistency (I^2 and by performing subgroup analysis (test of interaction). We assessed small study bias through funnel plots. We performed trial sequential analysis to control for the risks of type I errors and type II errors.[43] We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of evidence.[44 45] Further, we also conducted a separate GRADE rating for type of participants and type of exercise.

RESULTS

Study characteristics

Based on our literature search on 6 July 2020, we identified 32 739 references through databases search and 531 references via Google Scholar, ClinicalTrials.gov and previous meta-analysis. We excluded 10 484 reference duplicates. Thus, we screened 22 786 records and excluded 20 525 based on titles and abstract. We assessed 2261 full text for eligibility. Of these, we could not find the full text for 62 studies. We excluded 990 studies based on our inclusion and exclusion criteria. This resulted in 1272 publications reporting the results of 950 trials. A total of 248 trials randomising 21 633 participants reported on all-cause mortality, SAEs, quality of life and/or other clinical events (figure 1).

The characteristics of the included trials are summarised in online supplemental S1 table. Most trials (219/248; 88%)

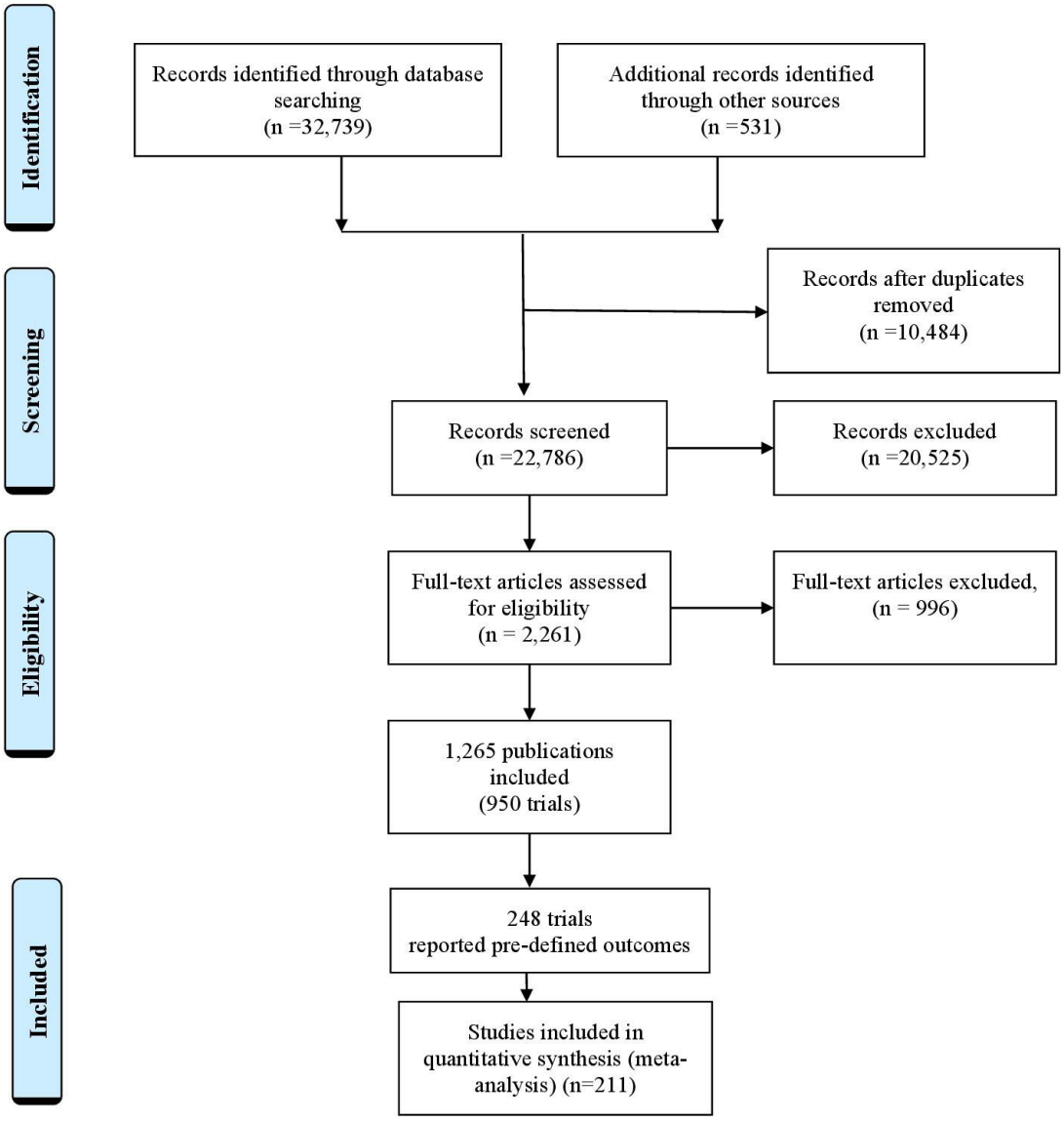

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

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Table 1 Summary of characteristics of included studies

Study characteristics	n (%)
Gender (n=248)	
Trials with male participants only	23 (9.3)
Trials with female participants only	6 (2.4)
Trials with both male and female participants	219 (88.3)
Type of participants (n=248)	
Cardiovascular disease	189 (76.2)
Type 2 diabetes	41 (16.5)
Hypertension	16 (6.5)
Cardiovascular disease+type 2 diabetes	2 (0.8)
Trials from economic region (n=248)	
High income countries	205 (82.6)
Low-income and middle-income countries	43 (17.3)
Type of exercise intervention (n=248)	
Dynamic aerobic exercise	126 (50.8)
Dynamic resistance exercise	25 (10.1)
Combined exercise	58 (23.4)
Body mind therapies	25 (10.1)
Inspiratory muscle training	4 (1.6)
Isometric resistance exercise	2 (0.8)
Stroke functional exercise	8 (3.2)
Median exercise intervention period (n=248)	3 months (IQR: 2–4 months)
Median follow-up period (n=248)	6 months (IQR: 3–8 months)
Median volume of exercise (n=162)	135 min/week (IQR: 90–180 min/week)

IQR, Inter-Quartile Range.

included both male and female participants. The number of participants in each trial ranged from 14[46 47] to 2331.[48] The median intervention period was 3 months (IQR: 2 –4 months) and the median follow-up period was 6 months (IQR: 3–8 months). Most trials (189/248; 76%) included participants with cardiovascular diseases, followed by trials including participants with type 2 diabetes (41/248; 17%) and hypertension (16/248; 7%). The experimental interventions were dynamic aerobic exercise in (126/248; 51%) trials, combined aerobic and resistance exercise in 58/248 (23%) trials, dynamic resistance exercise in (25/248; 10%) trials and body-mind therapies in 25/248 (10%). The median duration of the exercise interventions was 135 min/week (IQR: 90–180 min/week) (table 1). The majority of the included trials (205/248; 83%) were conducted in high-income countries, and only (43/248; 17%) trials were conducted in low-income and middle-income countries.

Table 2 summarises the baseline characteristics of the included participants.

Primary outcomes

All-cause mortality

Ninety-eight trials randomising 12 976 participants reported on all-cause mortality. A total of 434 of 6649 (6.5%) participants randomised to exercise died compared with 525 of 6327 (8.3%) control participants. The median assessment time point was at 6 months (IQR: 3–12 months) after randomisation. Meta-analysis showed evidence of a beneficial effect of adding exercise to the usual care (risk ratio, RR 0.82; 95% CI 0.73 to 0.93; p=0.0014).Visual inspection of forest plot (figure 2) and I^2 statistics indicated no statistical heterogeneity (I^2=0%). Trial sequential analysis showed that there was enough information to confirm that exercise compared with control reduced the risk of death by 18% (figure 3). We assessed this outcome results as high risk of bias (online supplemental S1 figure) and the certainty of the evidence as moderate (table 3). Funnel plot indicated no small study bias (online supplemental S2 figure). None of our preplanned subgroup analyses showed evidence of a difference (figure 4).

Serious adverse events

One hundred and fifty trials randomising 16 241 participants reported on SAEs. A total of 578 of 8473 (6.8%) participants

Table 2 Baseline characteristics of included studies

	Trials providing information	Intervention	No analysed (intervention)	Usual care	No analysed (usual care)
Age—years (SD)	228	60.79 (6.3)	8468	59.43 (8.5)	7386
Male sex—n (%)	221	6468 (65.2)	9926	5869 (67.2)	8737
Female sex—n (%)	221	3458 (34.8)	9926	2868 (32.8)	8737
BMI	82	29.45 (4.5)	2656	31.07 (4.3)	2269
Baseline medications n (%)					
Anti hypertensive drugs(not classified)	25	919 (65.1)	1412	570 (51.1)	1115
Beta-blockers	97	3324 (66.0)	3165	3201 (67.3)	4705
Diuretics	76	2763 (70.4)	3923	2352 (64.6)	3639
ACEI	91	3304 (75.6)	4368	3088 (76.5)	4039
Calcium channel blockers	31	332 (24.1)	1377	300 (24.2)	1242
Nitrates	32	579 (44.2)	1310	517 (42.5)	1216
ARB	12	145 (39.3)	369	121 (34.8)	348
Digitalis	12	116 (23.0)	505	119 (25.1)	475
Diagoxin	30	887 (42.7)	2076	891 (43.7)	2041
Aspirin (anticoagulant)	20	569 (69.1)	823	576 (73.4)	785
Acetylsalycylic acid	4	109 (90.1)	121	108 (93.9)	115
Lipid lowering drugs (statin, fibrate, omega)	41	994 (52.4)	1898	740 (46.5)	1590
Glycaemic control					
Metformin	4	300 (70.1)	428	292 (76.2)	383
Insulin	15	112 (14.3)	781	91 (15.7)	579
Oral hypoglycaemic agents (OHA)	15	600 (69)	869	429 (68.5)	626
Insulin+OHA	8	196 (28.8)	681	127 (23.3)	545

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index.

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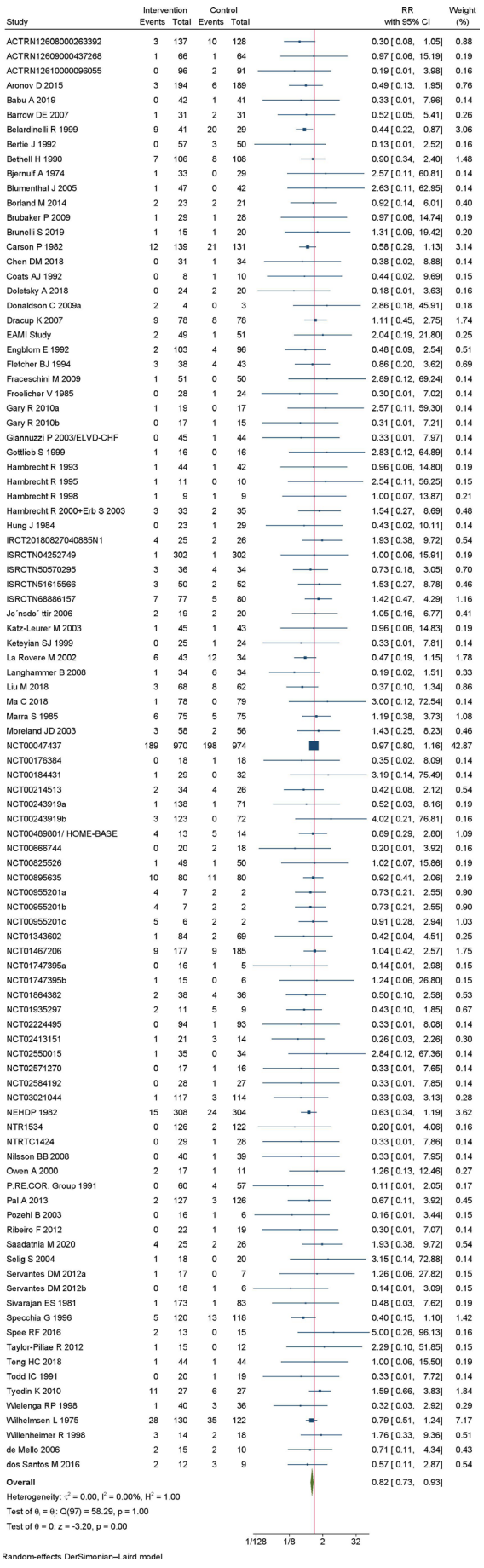

Figure 2 Forest plot on all-cause mortality. RR, risk ratio.

randomised to exercise had an SAE compared with 716 of 7768 (9.2%) control participants. The median assessment time point was at 6 months (IQR: 3–12 months). Meta-analysis showed evidence of a beneficial effect of adding exercise to the usual care (RR 0.79; 95% CI 0.71 to 0.88; p=0.0000). Visual inspection of forest plot (figure 5) and I^2 statistics indicated no statistical heterogeneity (I^2=0%). Trials sequential analysis showed that there was enough information to confirm that exercise compared with control reduced the risk of SAEs by 21% (figure 6). We assessed this outcome results as high risk of bias (online supplemental S3 figure) and the certainty of the evidence as moderate (table 3). Funnel plot indicated no small study bias (online supplemental S4 figure). None of our preplanned subgroup analyses showed evidence of a difference (figure 7).

Quality of life

Ninety-six trials randomising 7676 participants reporting on health-related quality of life. The identified trials assessed seven different scales, that is, 36-Item Short Form Health Survey (SF36) Physical component, SF36 Mental component, Minnesota Living with Heart Failure Questionnaire (MLHFQ), SF12 Physical component, SF12 Mental component, Barthel Index of Activity of Daily Living and Kansas City Cardiomyopathy Questionnaire (KCCQ). Each scale was analysed separately and meta-analyses showed that adding exercise to usual care improved quality of life when assessing four of these seven scales (SF36 Mental component (MD 2.9; 95% CI 1.04 to 4.77; p=0.0000), SF36 Physical Component (MD 3.34; 95% CI 2.01 to 4.59; p=0.0000), MLHFQ (MD −1.31; 95% CI −1.88 to −0.74; p=0.0000), Barthel Index of Activity of Daily Living (MD 14.33; 95% CI 3 to 25.66; p=0.0000). However, except for the trial assessing quality of life using Barthel Index (8), the shown effect sizes were all below our predetermined minimal important differences.

Meta-analyses of the three remaining scales SF12 Physical component (MD 0.58; 95% CI −1.09 to 2.26; p=0.58), SF12 Mental Component (MD=3.69; 95% CI 0.31 to 7.06; p=0.032), and KCCQ (MD 3.67; 95% CI −1.05 to 8.38: p=0.13) did not show evidence of a difference. All meta-analyses and trial sequential analyses of quality of life data are included in online supplemental S4 text and the corresponding figures are included in online supplemental S20-S44 figure.

Secondary outcomes

Cardiovascular mortality

Twenty-three trials randomising 6068 participants reported on cardiovascular mortality. A total of 218 of 3033 (7.2%) participants randomised to exercise died due to a cardiovascular cause compared with 295 of 3035 (9.7%) control participants. The median assessment time point was 12 months (IQR: 4–36 months). Meta-analysis showed evidence of a beneficial effect of adding exercise to usual care (RR 0.75; 95% CI 0.64 to 0.89; p=0.0000). Visual inspection of forest plots and I^2 statistics indicated no statistical heterogeneity (I^2=0%) (online supplemental S5 figure). Trials sequential analysis showed that there was enough information to confirm that exercise compared with control reduced the risk of cardiovascular mortality (online supplemental S6 figure). We assessed this outcome results as high risk of bias (online supplemental S7 figure) and the certainty of the evidence moderate (table 3). Funnel plot indicated no small study bias (online supplemental S8 figure). None of our preplanned subgroup analyses showed evidence of a difference (online supplemental S9 figure).

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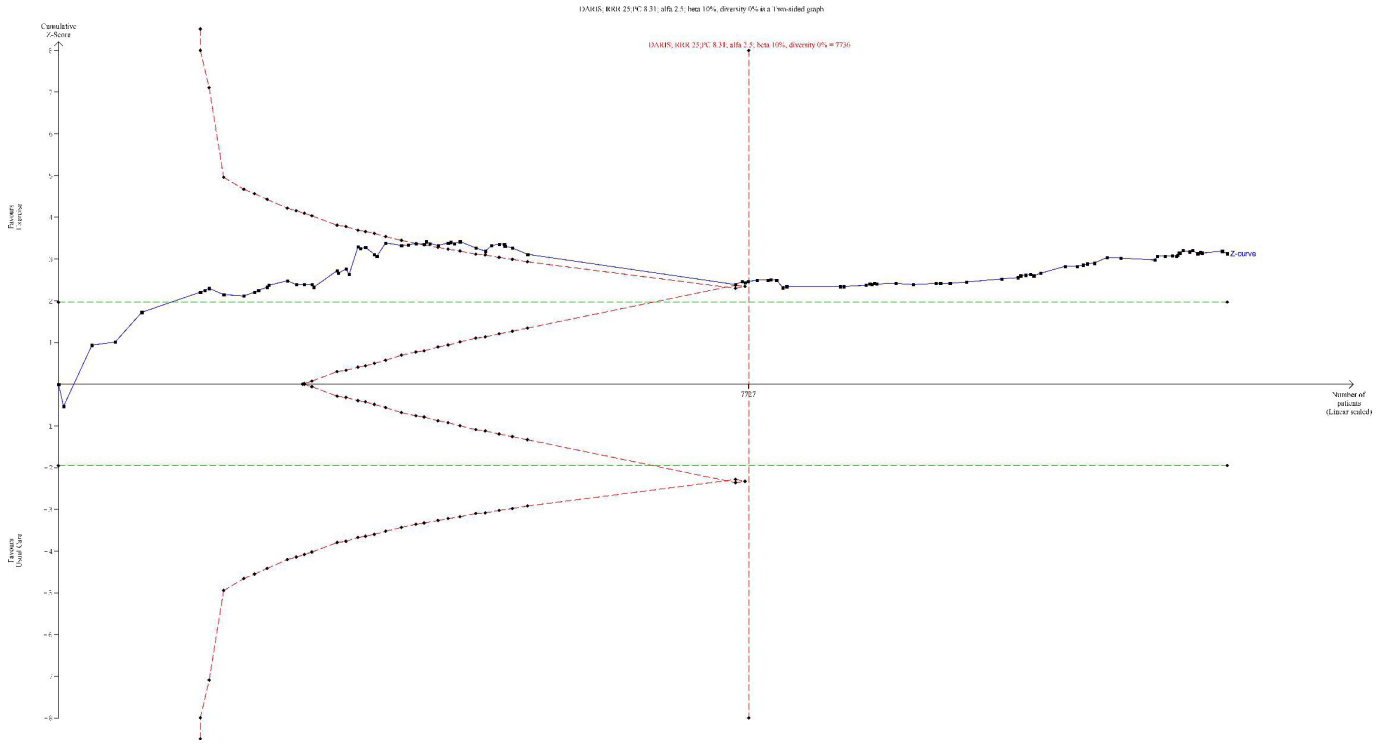

Figure 3 Trial sequential analysis of participants on all-cause mortality.

Myocardial infarction

Thirty-three trials randomising 6397 participants reported on myocardial infarction. A total of 113 of 3220 (3.5%) participants randomised to exercise had a myocardial infarction compared with 142 of 3177 (4.5%) control participants. The median assessment time point was at 12 months (IQR: 6–21 months). Meta-analysis showed no evidence of a difference of adding exercise to usual care (RR 0.83; 95% CI 0.65 to 1.06; p=0.86). Visual inspection of forest plots and I^2 statistics indicated no statistical heterogeneity (I^2=0%) (online supplemental S10 figure). Trials sequential analysis showed that there was not enough information to confirm or reject that exercise compared with control reduced the risk of myocardial infarction by 25% (online supplemental S11 figure). We assessed this outcome results as high risk of bias (online supplemental S12 figure) and the certainty of the evidence as low (table 3). Funnel plot indicated no small study bias (online supplemental S13 figure). None of our preplanned subgroup analyses showed evidence of a difference (online supplemental S14 figure).

Table 3 Summary of findings

Adding exercise to usual care for patient with hypertension, type 2 diabetes and cardiovascular diseases					
Patient or population: hypertension, type 2 diabetes and cardiovascular disease **Intervention: exercise** **Comparison: usual care**					
Outcomes	**No of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects***	
				Risk with usual care	**Risk difference with exercise**
All-cause mortality follow-up: median 6 months	12 976 (99 RCTs)	⨁⨁⨁◯ MODERATE†	**RR 0.82** (0.73 to 0.93)	83 per 1.000	**15 fewer per 1.000** (22 fewer to 6 fewer)
Serious adverse event follow-up: median 6 months	16 241 (151 RCTs)	⨁⨁⨁◯ MODERATE†	**RR 0.79** (0.71 to 0.88)	92 per 1.000	**19 fewer per 1.000** (27 fewer to 11 fewer)
Cardiovascular mortality follow-up: median 12 months	6068 (23 RCTs)	⨁⨁⨁◯ MODERATE†	**RR 0.75** (0.64 to 0.89)	97 per 1.000	**24 fewer per 1.000** (35 fewer to 11 fewer)
Myocardial Infarction follow-up: median 12 months	6397 (33 RCTs)	⨁⨁◯◯ LOW†‡	**RR 0.83** (0.65 to 1.06)	45 per 1.000	**8 fewer per 1.000** (16 fewer to 3 more)
Stroke follow-up: median 3.6 months	3934 (22 RCTs)	⨁⨁◯◯ LOW†‡	**RR 0.93** (0.64 to 1.34)	28 per 1.000	**2 fewer per 1.000** (10 fewer to 9 more)

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
†Downgraded one for risk of bias, as most of the domains were unclear in risk of bias assessment.
‡Downgraded one for imprecision due to trial sequential analysis showing that there was not enough information to confirm or reject a RR 25%. Moreover, the meta-analysis showed wide CI.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomised clinical trial; RR, risk ratio.

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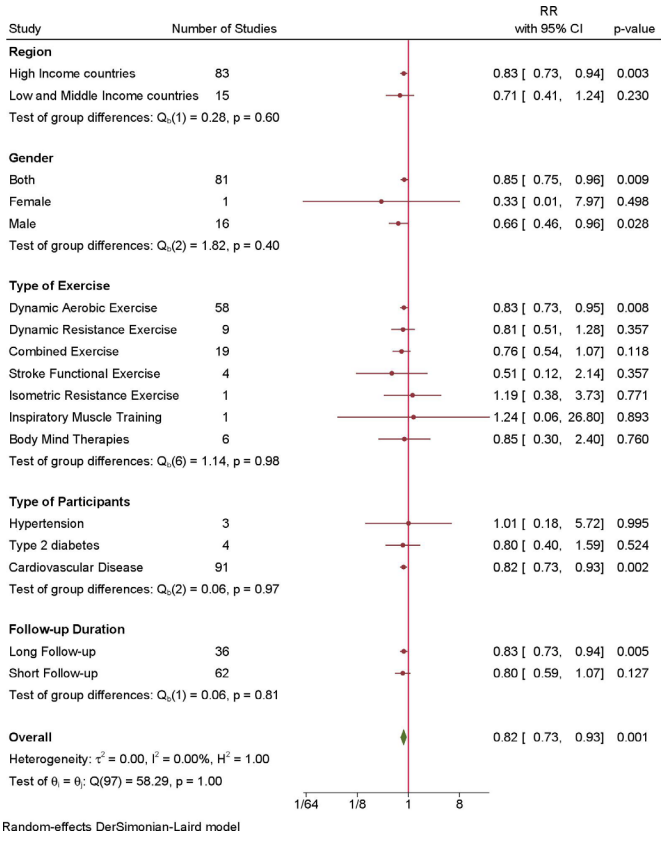

Figure 4 Forest plot of subgroup analysis on all-cause mortality. RR, risk ratio.

Stroke

Twenty-two trials randomising 3930 participants reported on stroke. A total of 52 of 1986 (2.6%) participants randomised to exercise had a stroke, compared with 54 of 1948 (2.8%) control participants. The median assessment time point was at 3.6 months (IQR: 3–6.5 months). Meta-analysis showed no evidence of a difference of adding exercise to usual care (RR 0.93; 95% CI 0.64 to 1.34; p=0.69). Visual inspection of forest plots and I^2 statistics indicated no statistical heterogeneity (I^2=0%) (online supplemental S15 figure). Trials sequential analysis showed that there was not enough information to confirm or reject that exercise compared with control reduced the risk of stroke by 25% (online supplemental S16 figure). We assessed this outcome results as high risk of bias (online supplemental S17 figure) and the certainty of the evidence as low (table 3). Funnel plot indicated no small study bias (online supplemental S18 figure). None of our preplanned subgroup analyses showed evidence of a difference (online supplemental S19 figure).

DISCUSSION

Our systematic review with meta-analysis and trial sequential analysis showed with moderate certainty that adding exercise to usual care reduced the risk of all-cause mortality by 18%, SAEs by 21% and cardiovascular mortality by 25% in patients with either hypertension, type 2 diabetes or cardiovascular disease. It should be noted that the intervention length (median: 3 months) was short, the intervention volume was low (median 135 mins/week), and the follow-up period was short (median 6 months). The shown beneficial effect sizes of exercise correspond to the effect sizes of, for example, a pharmacological reduction in systolic blood pressure of 10 mm Hg.[49] Our results show that a

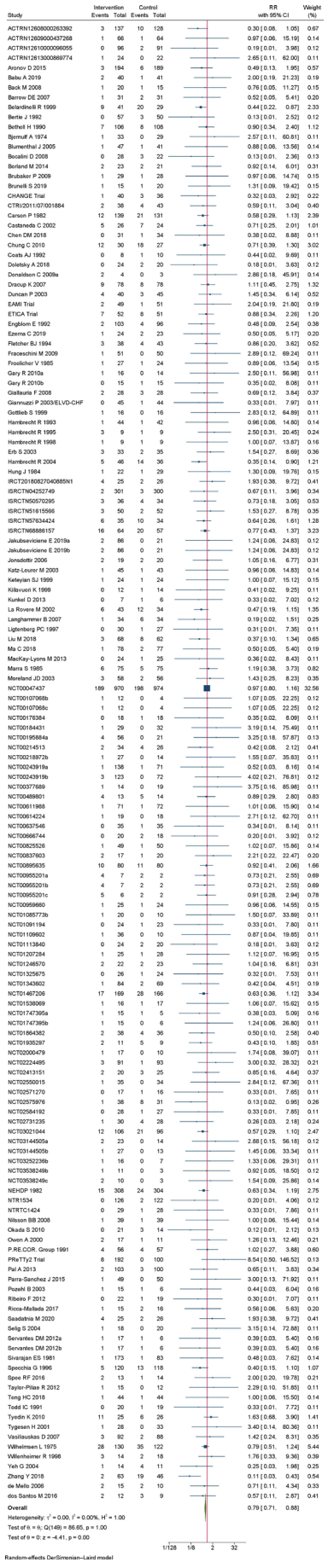

Figure 5 Forest plot on serious adverse events. RR, risk ratio.

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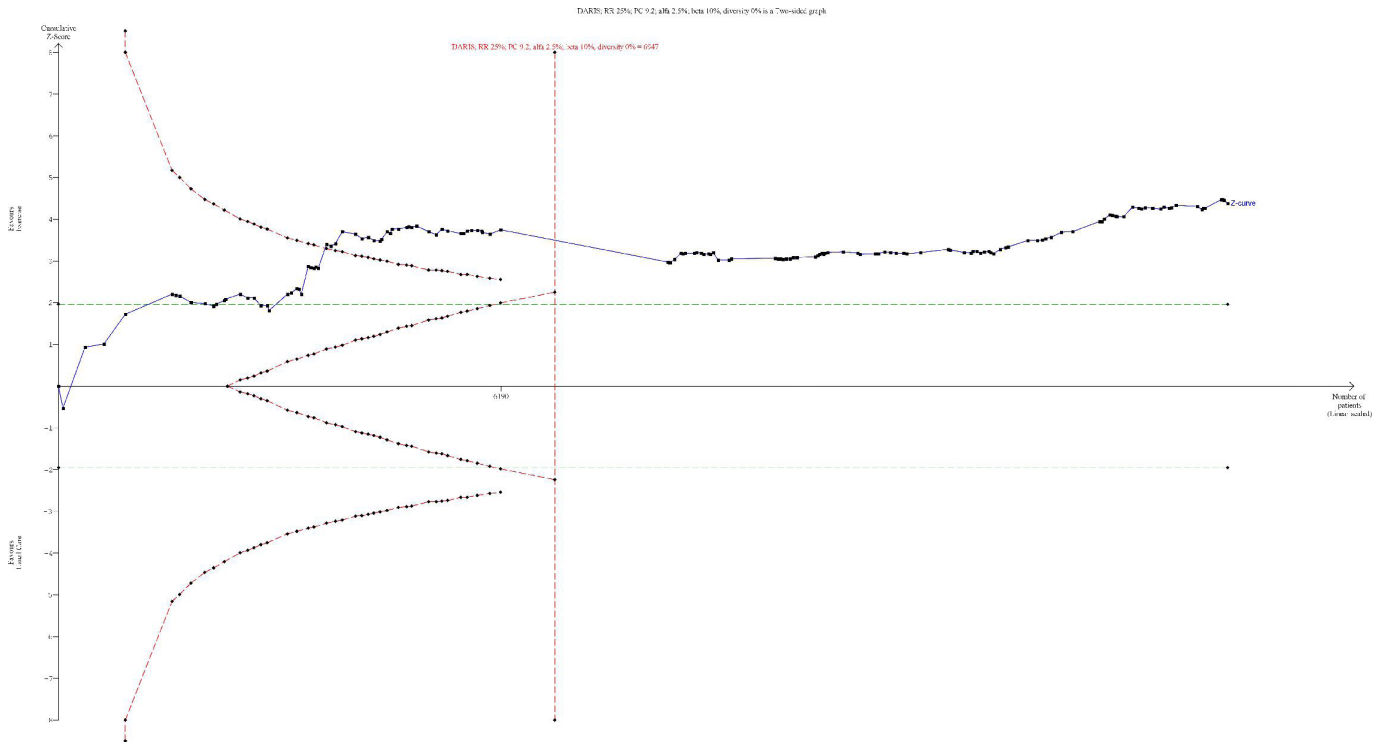

Figure 6 Trial sequential analysis of participants on serious adverse events.

relatively limited amount of exercise is safe and seems to result in a reduced risk of death and SAEs within a short time period, but the long-term effects of exercise are unclear based on our results. Our reported beneficial effects of exercise were independent of the duration of follow-up, type of exercise and presence of hypertension, diabetes or cardiovascular disease. However, we must acknowledge that most trials were small, and all outcome results were at high risk of bias, and the certainty of this evidence was moderate, so our results need to be interpreted with some caution. Nevertheless, our results highlight the potential role of exercise as a safe intervention in preventing risk of premature deaths and SAEs in addition to the well-documented physical and physiological changes.[15–17 22 50]

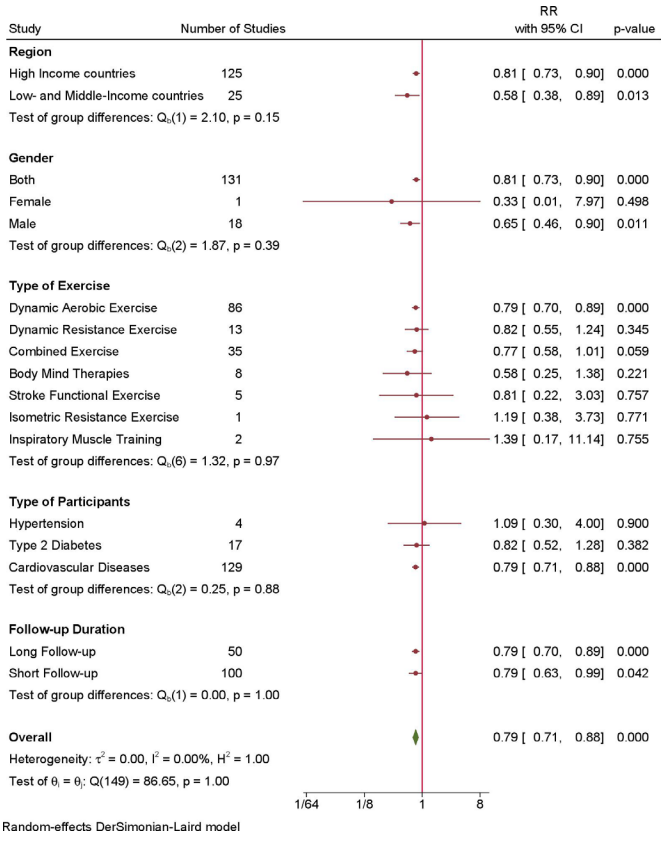

Figure 7 Forest plot of subgroup analysis on serious adverse events. RR, risk ratio.

In contrast to our review, previous Cochrane reviews on exercise-based rehabilitation compared with no exercise reported beneficial effects for specific cardiovascular diseases (such as coronary heart disease, heart failure, stroke and stable angina) and in one review for cardiovascular mortality,[28] but none of these reviews showed beneficial effects on all-cause mortality.[24 28 32 33 51] These reviews like ours have highlighted that the trials on exercise intervention are small, usually with short follow-up, and lack reporting on clinical events and on results of high risks of bias. However, all of these reviews involved only specific types of cardiovascular disease and the inclusion was restricted to certain types of exercise intervention only. Similar to our results, the survival benefits of engaging in muscle strengthening exercise or aerobic exercise, and/or combined exercise has also been reported in US population-based cohort studies with long follow-ups of 8.75 years.[52] The risk reduction in mortality and SAE even for short period of follow-up as presented in this review needs to be cautiously interpreted and warrants further investigation.

We also found that adding exercise to usual care was associated with small but statistically significant improvements in quality of life across SF36 Physical and Mental Domain, MLHFQ, and Barthel Index of Activity of Daily Living. However, except for Barthel Index, the improvements were below the predefined minimal important differences, which

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indicate that exercise may have minimal clinically important effects on quality of life. The minimal important clinical difference in this review is based on Cohen's d definition, that is, the observed SD divided by '2' which is rather conventional.[42] Quantification of minimal important differences, especially when analysing continuous outcomes, has challenges. However, to avoid emphasising statistically significant results without importance to patients and to avoid generalising and data-driven conclusions, it is of utmost importance to predefine thresholds for clinical significance as we have done in our predefined protocol. We adopted sample dependent distributional approach as compared with sample independent—anchor-based method, which yields clinical difference, but it is not clear if they are minimal.[53] For instance, in our review, the minimal clinical important difference for heart failure patient assessed through KCCQ was 8.5, however, much lower minimal clinical difference score +4.3[54] and +5.7[55] has been reported. This small yet significant improvement in quality of life reported in this review is still of vital importance as health-related quality of life has been found to be a strong and independent predictor of mortality and hospitalisation across all geographic regions among heart failure patients[56] and may likely be with other cardiovascular disease too. Previous systematic reviews have shown some positive influence of adding exercise to usual care but in most cases, it is inconclusive mainly due to lack of studies.[32 33 51] The results for quality of life scores need to be cautiously interpreted because of high statistical heterogeneity but it is a common phenomenon for continuous outcome with a high number of studies.[57]

Test for subgroup differences indicated no significant difference between trials from high-income versus low-and-middle-income countries, however, it was noteworthy that only 43/248 trials (17%) were from low-income and middle-income countries. It reiterates a critical gap in evidence being generated from low-income and middle-income countries, where almost three-quarters of hypertension, type 2 diabetes and cardiovascular disease-related deaths occur.[58]

Our review has several strengths. We followed our peer-reviewed protocol, which was registered and published before the literature search began. We included data from both published and unpublished trials, irrespective of the trial duration. We had comprehensive search irrespective of year of publication and language. Data were extracted by five authors in pairs in order to minimise inaccuracy in data extraction. The risk of bias was assessed using Cochrane RoB1 tool, the certainty of evidence using GRADE, trial sequential analysis to control the risks of random errors and an eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed.[40] The statistical and visual representation showed very low statistical heterogeneity for all-cause mortality, SAEs, and other clinical events, hence justifying pooling of all types of exercise and different types of participants in one meta-analysis. We also did not identify signs of small study bias in our review.

Our review also has limitations. All trials were classified as overall high risk of bias. For example, most of the included trials failed to define the process of randomisation, allocation concealment and lost to follow-up adequately. Blinding of participants was impossible to maintain in many exercise interventions, which may have led to different psychological and physical responses if participants believed they had been assigned to usual standard care rather than a new exercise intervention.[48] Likewise, lack of adequate blinding of outcome assessors in most trials may have overspilled trialists'' preconceived notions of intervention to the participants.[59] Due to the high risks of bias, our results may overestimate the beneficial effects of exercise. However, all-cause mortality may be robust against lack of adequate blinding. The median follow-up length of the trials included in the review was short (6 months) and long-term follow-up data were not available. Further studies with long-term follow-up data may further add to the current evidence.

We also need to acknowledge that we have pooled different types of cardiovascular disease, hypertension and diabetes together, as well as different types of exercise which may lead to clinical heterogeneity. We did not identify any signs of statistical heterogeneity in the subgroup analysis, but this may partly be due to lack of power. The trials reporting all-cause mortality and SAEs were predominantly trials with cardiovascular disease and showed a statistically significant beneficial effect of adding exercise to usual care. The lack of sufficient trials for hypertension and type 2 diabetes might have skewed the overall result towards the result for cardiovascular disease. Similarly, trials reporting these clinical outcomes were majorly involved in dynamic aerobic exercise. The considerable lack of trials involving other forms of exercise also needs to be accounted, as evidence has suggested that the risk of mortality may differ according to type of exercise involved.[60] Although we did not observe any significant subgroup difference in any of our analyses, it is theoretically possible that the effects of exercise differ per different types of exercise and different types of diseases. In addition, GRADE rating of the evidence for each of the types of participants and types of exercise have further highlighted that the certainty of evidence for primary outcomes ranged from low to moderate (see online supplemental S2 table). The pooling of different types of participants and different types of interventions need to be considered when interpreting our results.

The definitions of usual care differ between the included trials. Even though we did not observe any heterogeneity in our analyses, it is theoretically possible that the effects of exercise depend on the intensity of usual care. The shown effect of adding exercise to usual care may interact with how comprehensive and intensive the usual care is. Intensive usual care may have produced lower beneficial effect of exercise and vice versa.[61] In case of hypertension, type 2 diabetes and cardiovascular disease, usual care often includes advice for exercise from healthcare provider; however, recent study showed that advice alone does not have substantial effect on the outcomes as compared with healthcare worker-led physical intervention.[62] In addition, individuals with hypertension, type 2 diabetes and cardiovascular disease live with many comorbidities. Though not studied discretely in this review they may have altered the effect size. Likewise, individual physiological characteristics, mental status and attitude may have affected the uptake of exercise when added to their usual care and may have affected the outcomes of the studies. However, assessing such effects is out of the scope of this review.

We were not able to find 62 full text articles, mostly of Chinese language (online supplemental references). As per protocol, we contacted authors through email and followed up on ResearchGate wherever possible, however, no further information was available. These studies mostly include body mind therapies and are less likely to report on mortality and SAEs, and we believe it will not alter the final conclusion of this review. Furthermore, the lack of information on baseline

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characteristics, disease severity, concurrent medication use, exercise volume and intensities in majority of trials limits the discussion of findings of this review.

CONCLUSIONS

This review demonstrates that adding a short and low-moderate volume exercise intervention to usual care is safe and seems to lower the risk of all-cause mortality, SAEs and cardiovascular mortality in patients with either hypertension, type 2 diabetes or cardiovascular disease. The effects of exercise on quality of life seems to be significant but the effect sizes seem minimal.

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