Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study

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ABSTRACT

Objective To determine the comparative effectiveness of exercise versus drug interventions on mortality outcomes.

Design Metaepidemiological study.

Eligibility criteria Meta-analyses of randomised controlled trials with mortality outcomes comparing the effectiveness of exercise and drug interventions with each other or with control (placebo or usual care).

Data sources Medline and Cochrane Database of Systematic Reviews, May 2013.

Main outcome measure Mortality.

Data synthesis We combined study level death outcomes from exercise and drug trials using random effects network meta-analysis.

Results We included 16 (four exercise and 12 drug) meta-analyses. Incorporating an additional three recent exercise trials, our review collectively included 305 randomised controlled trials with 339 274 participants. Across all four conditions with evidence on the effectiveness of exercise on mortality outcomes (secondary prevention of coronary heart disease, rehabilitation of stroke, treatment of heart failure, prevention of diabetes), 14 716 participants were randomised to physical activity interventions in 57 trials. No statistically detectable differences were evident between exercise and drug interventions in the secondary prevention of coronary heart disease and prediabetes. Physical activity interventions were more effective than drug treatment among patients with stroke (odds ratios, exercise *v* anticoagulants 0.09, 95% credible intervals 0.01 to 0.70 and exercise *v* antiplatelets 0.10, 0.01 to 0.62). Diuretics were more effective than exercise in heart failure (exercise *v* diuretics 4.11, 1.17 to 24.76). Inconsistency between direct and indirect comparisons was not significant.

Conclusions Although limited in quantity, existing randomised trial evidence on exercise interventions suggests that exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes.

INTRODUCTION

Physical activity has well documented health benefits.[1] Population level cohort studies have shown that people who exercise enjoy a higher quality of life and improved health status compared with those with sedentary behaviours, with subsequent reductions in their risk of adverse outcomes such as admissions to hospital. Randomised controlled trials have shown similarly favourable findings in arthritis,[2] cancer,[3][4] diabetes,[5] heart disease,[6] and respiratory illnesses,[7] among other chronic conditions.[8][9] Large scale observational studies have also established a clear association between exercise and all cause mortality.[10–12] Given the overwhelming evidence in support of the health benefits of exercise,[13] the Global Burden of Disease study has recently ranked physical inactivity as the fifth leading cause of disease burden in western Europe, and as one of the top modifiable risk factors along with smoking.[14]

Despite recent calls to encourage physical activity as a strategy to ward off the emerging burden of chronic conditions, including heart disease and diabetes,[15] population level physical activity measures are discouraging. In the United Kingdom, only 14% of adults exercise regularly, with roughly one third of adults in England meeting recommended levels of physical activity.[16] In contrast, utilisation rates of prescription drugs continue to rise sharply, increasing to an average of 17.7 prescriptions for every person in England in 2010, compared with 11.2 in 2000.[17]

Abundant evidence from randomised controlled trials shows the mortality benefits of certain drugs such as simvastatin in the secondary prevention of cardiovascular disease,[18] which is the most widely prescribed drug in the United Kingdom. Research on the mortality benefits of exercise, however, remains primarily observational with a limited number of randomised trials in select treatment areas.[19] More importantly, evidence on how physical activity interventions fare compared with drug interventions in reducing the risk of all cause mortality is lacking.

We performed a comprehensive review of published meta-analyses on topics with randomised trial evidence on both exercise and drug interventions. For each condition, we combined the data from multiple pairwise meta-analyses in network meta-analyses to assess the geometry of the existing evidence and to determine the comparative effectiveness of drug and exercise interventions in reducing the risk of mortality.

METHODS

Identification of relevant evidence

We used three steps to identify the relevant body of evidence. Firstly, we searched Medline for meta-analyses of randomised controlled trials evaluating the effectiveness of exercise based interventions on mortality outcomes. Our search strategy included terms for exercise interventions (exercise OR physical activity), mortality outcomes (mortality

OR death OR survival), and meta-analysis of randomised controlled trials (randomized OR meta-analysis) in the title, abstract, or keywords (latest search 11 December 2012).

Secondly, for all conditions with evidence on the effectiveness of exercise interventions on mortality outcomes, we identified meta-analyses that evaluated the impact of specific drug interventions on mortality outcomes. We identified the list of relevant drug interventions using clinical practice guidelines, developed by respective European and US clinical specialty organisations (for example, American Heart Association, European Society of Cardiology). In cases where clinical practice guidelines did not give clear guidance around indicated drug treatments, we consulted the US National Library of Medicine's Medline Plus website (www.nlm.nih.gov/medlineplus/). For each drug of interest we searched the Cochrane Database of Systematic Reviews to identify the most up to date meta-analysis. In cases where Cochrane reviews did not exist, we searched Medline using terms for drug names, mortality outcomes (mortality OR death OR survival), and meta-analysis of randomised controlled trials (randomized OR meta-analysis).

Finally, we developed a separate search strategy in Medline to identify randomised head to head comparisons of exercise versus drug interventions (and their meta-analyses) for all conditions with evidence on the effectiveness of exercise interventions on mortality outcomes. The objective of this search was to capture additional recent trials of exercise versus control intervention that were not included in the meta-analyses evaluating the effectiveness of exercise based interventions on mortality outcomes. This search included terms for exercise interventions (exercise OR physical activity), mortality outcomes (mortality OR death OR survival), and Cochrane Collaboration's sensitivity and precision maximising terms for randomised controlled trials (latest search 27 May 2013).[20]

In all three steps we selected the most recent review if more than one eligible meta-analysis was published for a given condition or disease and for each particular intervention. We considered studies embedded within meta-analyses (or single studies identified in the third step) to be eligible for inclusion if they were randomised controlled trials comparing the effectiveness of exercise and drug interventions with another or with control (placebo or usual care) on mortality outcomes.

Data extraction
From each eligible trial we extracted the publication year, condition, number of participants, and number of deaths in each trial arm. In cases where mortality outcomes were reported at multiple time points, we selected the longest follow-up duration. One investigator (HN) extracted data and another (Anthony J Damico) checked for accuracy.

Evaluation of the geometry of evidence
We developed network diagrams to visualise the geometry of the available evidence;[21] [22] that is, the frequency of comparisons between exercise and drug interventions to show the distribution of trial participants across different treatment modalities (and control). In each network diagram, the size of the nodes was proportional to the number of participants receiving a given intervention (or control), and the thickness of the lines connecting the nodes was proportional to the number of randomised participants in the trials between interventions. We developed two sets of network diagrams. In the first we compared exercise to all identified classes of drugs. In the second we pooled all drug interventions into one group to show the relative size of the patient population included in the trials of exercise versus drug interventions.

Statistical analysis
We first qualitatively summarised included trials, describing the types of direct and indirect comparisons. For each direct comparison between two treatments we conducted pairwise meta-analyses using the DerSimonian-Laird (random effects) method,[23] and statistically inspected heterogeneity using the I^2 measure. We used rough I^2 thresholds of 25%, 50%, and 75% to define low (<25%), moderate (25–49%), high (50-75%), and very high (>75%) heterogeneity. To determine the comparative effectiveness of exercise and drug interventions, we then conducted network meta-analysis, which is a generalisation of indirect comparisons across pairwise meta-analyses.[24] This type of analysis allows for comparing interventions in the absence of head to head trials comparing all the interventions of interest.[25] In cases where both direct (from trials that include a specific pairwise comparison) and indirect (from a network of trials that do not include that comparison) sources of evidence exist, network meta-analysis is capable of simultaneously combining both types of evidence. This analysis preserves the within trial randomised treatment comparison of each trial while combining all available comparisons between treatments.

We combined study level relative treatment effects using bayesian Markov chain Monte Carlo methods in WinBUGS version 1.4.3. We used the model developed by Dias and colleagues for the UK National Institute for Health and Care Excellence Decision Support Unit.[26] [27] Our models adopted random effects, taking into account potential heterogeneity by assuming that each treatment was drawn from the same distribution, the mean and variance of which were estimated from the data.[28] We also performed fixed effect analyses under the assumption that no between study heterogeneity existed.[29] Our model selection was based on two criteria. Firstly, we evaluated the deviance information criterion between the two sets of analyses, which favoured random effects models. Secondly, we qualitatively judged the fixed effect model assumption to be too strong given the potential differences in patient populations across drug and exercise trials.[25]

We statistically evaluated the consistency of direct and indirect evidence in network meta-analyses using the Bucher method.[30] This method, commonly used to investigate potential inconsistency in evidence networks,[31] [32] was based on conducting random effects pairwise meta-analyses on all comparisons and calculating the difference in log odds ratios between direct and indirect estimates for each closed loop of the network (that is, in all instances where both direct and indirect comparisons could be generated for each contrast in the network).

We reported our findings in terms of odds ratios. The difference between treatments was assessed on the basis of 95% credible intervals. Such intervals can be interpreted as indicating a 95% probability that the true odds ratio falls within the reported range. If a 95% credible interval does not include the null value 1.00, this can be interpreted as indicating <5% probability that there is no difference between the two comparators. Given the bayesian nature of the statistical analyses, we neither estimated nor reported P values for the network meta-analyses.

Primary analyses were at the intervention level, comparing exercise with all relevant drug interventions for a given condition. In a separate analysis we also pooled the drugs and estimated the comparative effectiveness of exercise versus all drug interventions. The analyses were based on the total number of participants per trial arm, as reported in the identified meta-analyses.

RESULTS

Eligible meta-analyses

Our electronic search of exercise meta-analyses retrieved 225 titles and abstracts (figure 1). After exclusions, we included four meta-analyses of exercise interventions reporting mortality outcomes (see supplementary table). One meta-analysis evaluated the effectiveness of exercise interventions for the secondary prevention of coronary heart disease,[33] one for stroke,[34] one for heart failure,[35] and one for prediabetes.[36] In addition we separately identified 12 meta-analyses of drug interventions (out of 534 titles and abstracts in Medline), which were considered to be relevant drug options for each of the four conditions that had evidence on exercise interventions: statins,[18] β blockers,[37] angiotensin converting enzyme inhibitors,[38] and antiplatelets for the secondary prevention of coronary heart disease;[39] anticoagulants[40] and antiplatelets[41] for stroke;[42] angiotensin converting enzyme inhibitors,[43] diuretics,[44] β blockers,[45] and angiotensin receptor blockers for heart failure;[46] α glucosidase inhibitors, thiazolidinediones, biguanides, angiotensin converting enzyme inhibitors, and glinides for prediabetes.[36] Publication dates for meta-analyses of drug interventions ranged from 1999 to 2013 (see supplementary table).

Most of the meta-analyses of drug interventions were placebo controlled. However, one meta-analysis included direct head to head trials comparing anticoagulants with antiplatelets for the treatment of stroke,[47] and one meta-analysis included a direct comparison between angiotensin receptor blockers and angiotensin converting enzyme inhibitors for the treatment of heart failure.[46] Similarly, the meta-analysis on prediabetes included not only the placebo controlled trials of drug and exercise interventions but also their direct head to head comparisons.[36]

In total, our original search identified 16 (four exercise and 12 drug) meta-analyses, including 54 exercise trials and 248 drug trials. Our separate electronic search in Medline, which yielded 2964 abstracts and titles, did not identify any additional direct head to head trials of exercise and drug interventions evaluating mortality outcomes for coronary heart disease, stroke, heart failure, and prediabetes. This search captured 31 of the 54 exercise trials that were already included in the four exercise meta-analyses. It also captured another three recent trials of exercise versus control intervention published between 2008 and 2012 (total sample size 2041) that had not been included in the four meta-analyses. Including these three exercise trials in the analysis, our meta-epidemiological review collectively included 305 randomised controlled trials with 339 274 participants. Of those, 57 trials concerned exercise interventions, including 14 716 participants.
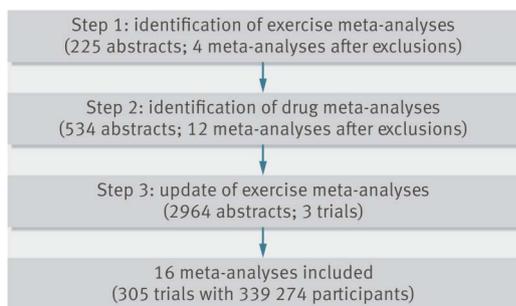
Figure 1 Steps involved in study identification and selection.

Characteristics of exercise interventions

The characteristics of the exercise interventions varied across treatment areas. Differences included the mode of physical activity and its frequency, intensity, and duration. Exercise based cardiac rehabilitation was typically a component of comprehensive cardiac care of patients with coronary heart disease.[33] Rehabilitation in this population included inpatient, outpatient, community based, or home based exercise interventions. Patients with stroke received a mix of cardiorespiratory and muscle strengthening exercises.[34] Similarly, exercise interventions targeting patients with chronic heart failure included aerobic and resistance training.[35] Physical activity was often a component of multifactorial lifestyle modification interventions to prevent diabetes among people with impaired glucose tolerance and impaired fasting glucose—that is, prediabetes.[36]

Comparability of trial and patient population characteristics

Conceptual heterogeneity between drug and exercise trials was minimal among patients with coronary heart disease (about 60–100% of patients had myocardial infarctions), heart failure (patients were predominantly New York Heart Association class II-IV), and prediabetes (patients had impaired glucose tolerance and impaired fasting glucose with a balanced profile of obesity and cardiovascular disease risk factors across exercise and drug trials). However, the baseline disease severity of patient populations was considerably different in stroke trials. While survivors participating in drug trials were within two weeks of onset of stroke, patients included in exercise trials were predominantly ambulatory and could be up to 150 days after stroke.

In all four conditions, trial characteristics varied for eligibility criteria, follow-up duration, and blinding of participants, investigators, and assessors (see supplementary table). In general, variability within pairwise meta-analyses was greater than between exercise and drug interventions. Statistical variability in effect sizes was low in the majority of pairwise meta-analyses, with moderate between study heterogeneity present in the trials of angiotensin converting enzyme inhibitors in the secondary prevention of coronary heart disease ($I^2 = 40\%$), trials of β blockers in heart failure ($I^2 = 34\%$), and trials comparing angiotensin receptor blockers with angiotensin converting enzyme inhibitors in heart failure ($I^2 = 39\%$).

Geometry of available evidence

In all four conditions, relatively few participants were randomised to exercise interventions compared with the available evidence on drugs. Thirty four trials concerned exercise interventions in the secondary prevention of coronary heart disease (n=10 984 participants) compared with 43 trials of statins (n=55 151), 80 of β blockers (n=53 456), 15 of angiotensin converting enzyme inhibitors (n=15 104), and 27 of antiplatelets (n=38 076). No direct head to head trials compared any of the drug or exercise interventions in the identified meta-analyses, resulting in a star shaped evidence network for the secondary prevention of coronary heart disease (figure 2).

Three trials concerned exercise interventions among patients with stroke (n=227) compared with 10 trials of anticoagulants (n=22 786), 14 of antiplatelets (n=43 041), and three directly comparing anticoagulants with antiplatelets (n=11 567, figure 2).

In the case of heart failure, 18 trials concerned exercise interventions (n=3669) compared with five trials of angiotensin converting enzyme inhibitors (n=12 763), three of diuretics (n=202), 21 of β blockers (n=23 122), 11 of angiotensin

Figure 2 Network of available comparisons between exercise and individual drug interventions in coronary heart disease, stroke, heart failure, and prediabetes. Size of node is proportional to number of trial participants, and thickness of line connecting nodes is proportional to number of participants randomised in trials directly comparing the two treatments. ACE=angiotensin converting enzyme.
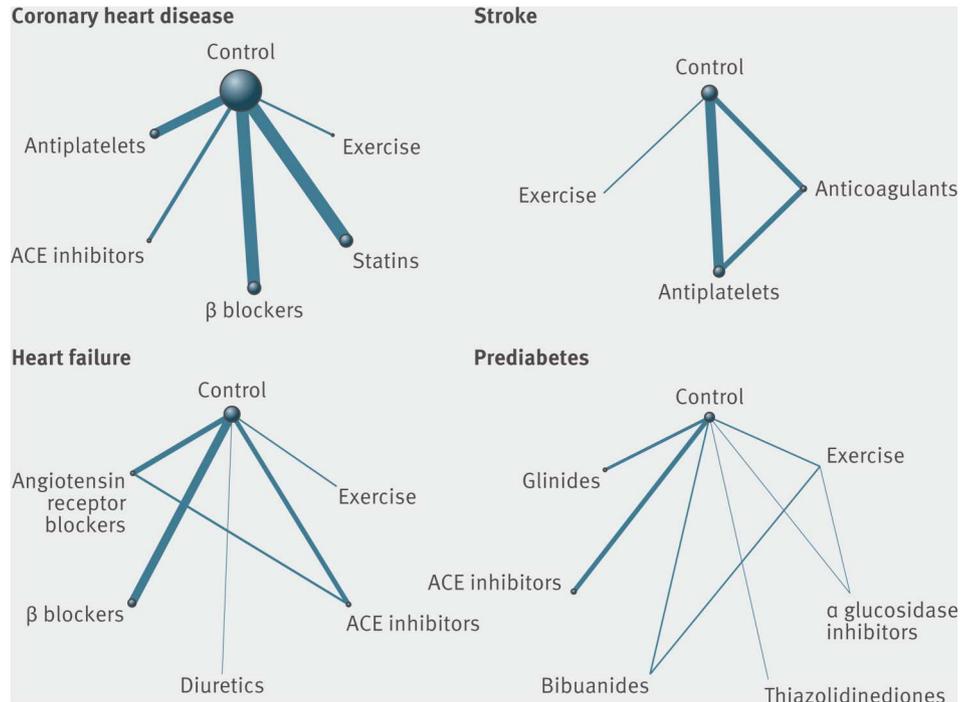
receptor blockers (n=11 795), and eight directly comparing angiotensin receptor blockers with angiotensin converting enzyme inhibitors (figure 2).

Two trials were of exercise interventions among participants with prediabetes (n=1081 participants). In comparison, one trial was of α glucosidase inhibitors (n=1368), one of thiazolidinediones (n=407), two of angiotensin converting enzyme inhibitors (n=14 575), and one of glinides (n=9306). One trial directly compared exercise with α glucosidase inhibitors (n=1778), and two multiarm trials including 3615 participants compared exercise, biguanides, and control (figure 2). When the drug trials were pooled, 5685 participants with coronary heart disease were randomised to exercise compared with 85 421 randomised to control and 81 655 to drug interventions (figure 3). In a similar fashion, considerably fewer participants were

randomised to physical activity interventions in stroke trials (n=117), heart failure trials (n=1830), and prediabetes trials (n=2491). Respective numbers of participants randomised to drug interventions were 44 731, 30 024, and 14 867.
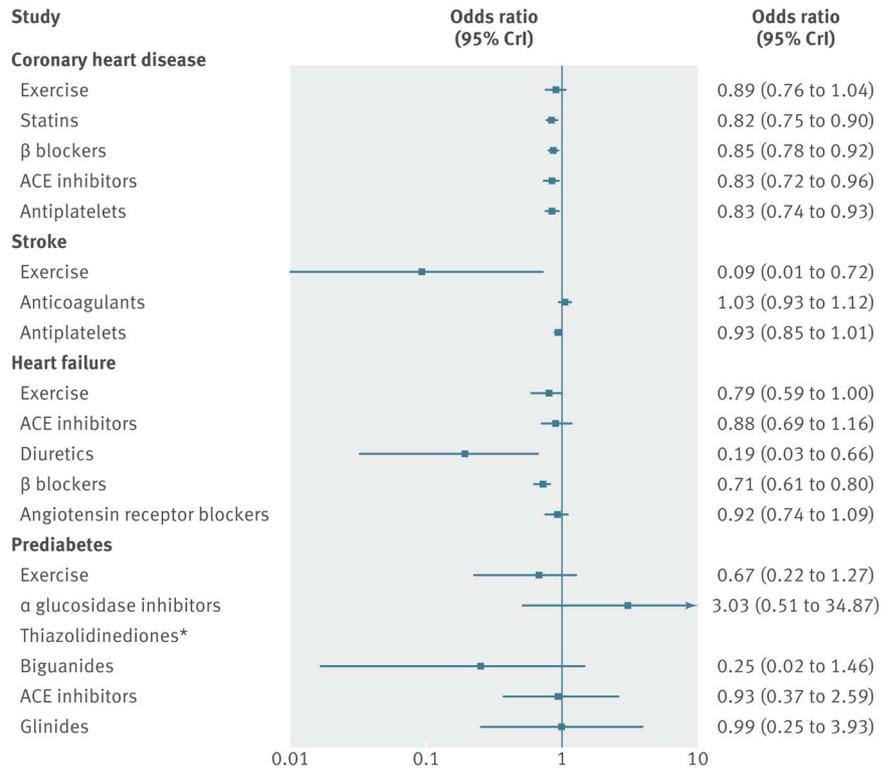
Comparative effectiveness of exercise and drugs

In coronary heart disease the odds of mortality was reduced with use of statins (odds ratio 0.82, 95% credible interval 0.75 to 0.90), β blockers (0.85,0.78 to 0.92), angiotensin converting enzyme inhibitors (0.83, 0.72 to 0.96), and antiplatelets (0.83, 0.74 to 0.93) compared with control, whereas exercise interventions had a similar point estimate but wider credible intervals that extended on both sides of 1.00 (odds ratio 0.89, 95% credible interval 0.76 to 1.04, figure 4). When compared head to head in network meta-analyses, all interventions were not

Figure 3 Network of available comparisons between exercise and all drug interventions in coronary heart disease, stroke, heart failure, and prediabetes. Size of node is proportional to number of trial participants, and thickness of line connecting nodes is proportional to number of participants randomised in trials directly comparing the two treatments.
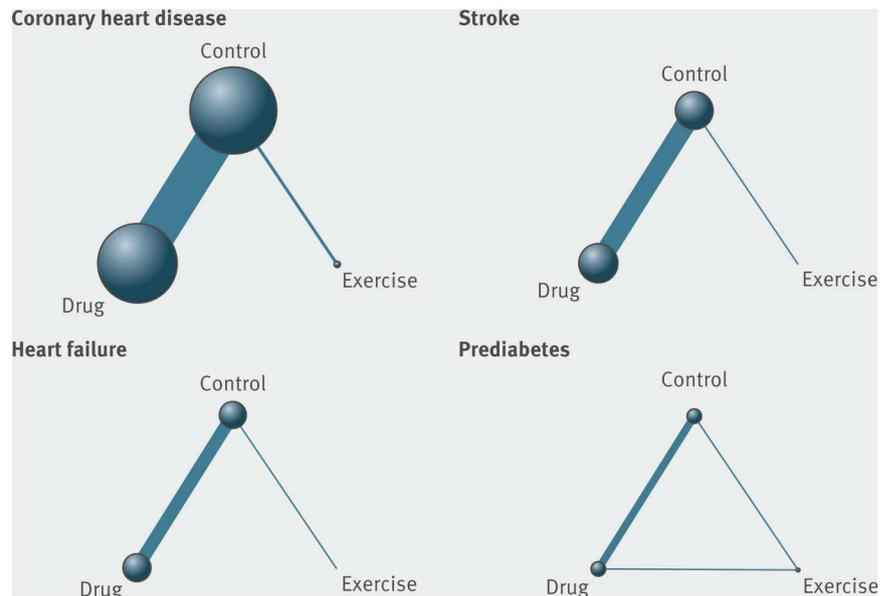
Figure 4 Findings of network meta-analysis: effects of exercise and drug interventions compared with control on mortality outcomes in coronary heart disease, stroke, heart failure, and prediabetes. Results shown are odds ratios and 95% credible intervals. Odds ratios lower than 1.00 favour intervention compared with control. ACE=angiotensin converting enzyme. *Number of data points for thiazolidinediones was insufficient to obtain an estimate of odds ratio compared with control.

Study	Odds ratio (95% CrI)
Coronary heart disease	
Exercise	0.89 (0.76 to 1.04)
Statins	0.82 (0.75 to 0.90)
β blockers	0.85 (0.78 to 0.92)
ACE inhibitors	0.83 (0.72 to 0.96)
Antiplatelets	0.83 (0.74 to 0.93)
Stroke	
Exercise	0.09 (0.01 to 0.72)
Anticoagulants	1.03 (0.93 to 1.12)
Antiplatelets	0.93 (0.85 to 1.01)
Heart failure	
Exercise	0.79 (0.59 to 1.00)
ACE inhibitors	0.88 (0.69 to 1.16)
Diuretics	0.19 (0.03 to 0.66)
β blockers	0.71 (0.61 to 0.80)
Angiotensin receptor blockers	0.92 (0.74 to 1.09)
Prediabetes	
Exercise	0.67 (0.22 to 1.27)
α glucosidase inhibitors	3.03 (0.51 to 34.87)
Thiazolidinediones*	
Biguanides	0.25 (0.02 to 1.46)
ACE inhibitors	0.93 (0.37 to 2.59)
Glinides	0.99 (0.25 to 3.93)

different beyond chance: there were no statistically detectable differences among any of the exercise and drug interventions in terms of their effects on mortality outcomes (table 1).

Unlike any of the drug interventions, exercise was significantly more effective than control in reducing the odds of mortality (0.09, 0.01 to 0.72) among patients with stroke (figure 4). When compared head to head in network meta-analyses, exercise interventions were more effective than anticoagulants (0.09, 0.01 to 0.70) and antiplatelets (0.10, 0.01 to 0.62), albeit with considerable uncertainty owing to the small number of events in exercise trials (table 2). Anticoagulants were also marginally worse than antiplatelets (1.11, 1.00 to 1.21).

In heart failure, fewer deaths occurred with diuretics (0.19, 0.03 to 0.66) and β blockers (0.71, 0.61 to 0.80) compared with control (figure 3). Diuretics were more effective than exercise (0.24, 0.04 to 0.85), angiotensin converting enzyme inhibitors (0.21, 0.03, 0.76), β blockers (0.27, 0.04 to 0.93), and angiotensin receptor blockers (0.21, 0.03 to 0.73, table 3). Angiotensin receptor blockers were associated with more deaths compared with β blockers (1.30, 1.02 to 1.61).

Neither exercise nor drug interventions were clearly effective in reducing the odds of mortality in prediabetes (figure 4).

There were also no major detectable differences between any comparator interventions (table 4).

In secondary analyses comparing exercise with the drug interventions pooled together, there was no definitive differences between drug and exercise interventions in coronary heart disease, heart failure, and prediabetes, but effect sizes had modestly substantial uncertainty for heart failure and prediabetes (table 5). Although exercise interventions were more effective than drugs in reducing the odds of mortality among patients with stroke, this finding was associated with large uncertainty in the exact estimate of the treatment effect owing to the small number of events.

In all network meta-analyses with closed loops, there was no statistically detectable inconsistency between direct and indirect evidence (see supplementary table).

DISCUSSION

This metaepidemiological study of 16 meta-analyses including 305 randomised controlled trials with 339 274 participants highlights the near absence of evidence on the comparative effectiveness of exercise and drug interventions on mortality outcomes. Existing evidence on the mortality benefits of physical

Table 1 Findings of network meta-analyses: comparative effects of exercise and drug interventions on mortality outcomes in coronary heart disease. Values are odds ratios (95% credible intervals)

Intervention	Comparator drugs			
	Statins	β blockers	ACE inhibitors	Antiplatelets
Exercise	1.08 (0.90 to 1.30)	1.05 (0.87 to 1.25)	1.08 (0.87 to 1.33)	1.07 (0.88 to1.30)
Statins	–	0.97 (0.85 to 1.10)	0.99 (0.84 to 1.18)	0.99 (0.85 to1.15)
β blockers	–	–	1.03 (0.87 to 1.21)	1.02 (0.89 to1.17)
ACE inhibitors	–	–	–	0.99 (0.83 to1.19)

ACE=angiotensin converting enzyme.
Estimates lower than 1.00 favour row defining intervention.

Table 2 Findings of network meta-analyses: comparative effects of exercise and drug interventions on mortality outcomes in stroke. Values are odds ratios (95% credible intervals)

Intervention	Comparator drugs	
	Anticoagulants	Antiplatelets
Exercise	0.09 (0.01 to 0.70)	0.10 (0.01 to 0.62)
Anticoagulants	–	1.11 (1.00 to 1.21)

Estimates lower than 1.00 favour row defining intervention.

activity is limited to the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes. Perhaps unsurprisingly, the amount of evidence on the mortality benefits of exercise is considerably smaller than that on drug interventions. There is also a clear lack of exercise and drug comparisons: trials evaluating the effectiveness of pharmacotherapy rarely included physical activity as a comparator. Albeit this considerable asymmetry in the evidence base, our analysis suggests that exercise potentially had similar effectiveness to drug interventions with two exceptions. In the case of stroke rehabilitation, exercise seemed to be more effective than drug interventions. In heart failure, diuretics outperformed all comparators, including exercise. When the drug interventions were considered together in sensitivity analyses, exercise and drug interventions did not differ in terms of their mortality benefits in all conditions except for stroke rehabilitation, where exercise interventions were associated with a reduction in the odds of mortality more than drug interventions.

Geometry of existing evidence

Evidence from randomised controlled trials on the mortality benefits of exercise is scarce. Even in treatment areas where such evidence exists, exercise trials evaluating mortality outcomes were at a disadvantage in two ways: considerably fewer trials evaluated exercise than drugs (57 out of 305 trials), and fewer people participated in exercise trials (14 716 out of 339 274 participants).

Our findings reflect the bias against testing exercise interventions and highlight the changing landscape of medical research, which seems to increasingly favour drug interventions over strategies to modify lifestyle. The current body of medical literature largely constricts clinicians to drug options.[48] This blind spot in available scientific evidence prevents prescribers and their patients from understanding the clinical circumstances where drugs might provide only modest improvement but exercise could yield more profound or sustainable gains in health. The lopsided nature of modern medical research may fail to detect

the most effective treatment for a given condition if that treatment is not a prescription drug.

As the disparity between exercise based and drug based treatment evidence has increased, clinical practice guidelines have followed suit.[49 50] For example, although earlier versions of the United States' national cholesterol education programme guidelines advised the use of statins only after exhausting interventions for intensive lifestyle modification for the prevention of coronary heart disease in people with high cholesterol levels,[51] subsequent versions progressively lowered the threshold for drug treatment and considerably expanded both the scope and the intensity of drug treatment.[52]

Clinical practice implications of this study

The findings of our review suggest that exercise and many drug interventions are often potentially similar in terms of their mortality benefits; exercise interventions should therefore be considered as a viable alternative to, or alongside, drug therapy. Indeed, an increasing number of experts recommend prescribing an "exercise pill" as a preventive strategy to reduce morbidity and mortality.[53 54] According to the US Centers for Disease Control and Prevention, roughly one third of clinicians prescribe exercise in primary care.[55] However, as previous systematic reviews have shown, there is considerable uncertainty as to the effectiveness of primary care interventions for increasing physical activity.[56 57] As previously recommended, primary care doctors should give brief advice to most patients about the benefits of exercise and refer patients with chronic disease to a rehabilitation programme that includes an exercise intervention.[58] Previous research has shown that patients with a variety of chronic conditions can expect to improve their functional capacity as well as muscle strength by a range of exercise interventions.[8 9] Although we considered exercise interventions as a group, a more nuanced consideration of the effectiveness of different types of physical activity is warranted. Among the four therapeutic conditions considered in our review, exercise interventions varied in terms of their type, intensity, and duration, highlighting the need to tailor exercise regimens for individual patient circumstances, such as baseline disease severity and mobility. The relative dearth of evidence leaves substantial uncertainty on which patients would benefit more from what type of exercise, and which forms of exercise may not be effective in different settings.

Complicating matters further, the evidence on the potentially harmful side effects of exercise interventions is limited. Individual trials included in the meta-analyses did not report adverse events associated with exercise interventions in a systematic manner. Nevertheless, some existing information is encouraging: according to a 10 year follow-up study of exercise based

Table 3 Findings of network meta-analyses: comparative effects of exercise and drug interventions on mortality outcomes in heart failure. Values are odds ratios (95% credible intervals)

Intervention	Comparator drugs			
	ACE inhibitors	Diuretics	β blockers	ARBs
Exercise	0.89 (0.59 to 1.23)	4.11 (1.17 to 24.76)	1.11 (0.82 to 1.46)	0.86 (0.62 to 1.16)
ACE inhibitors	–	4.66 (1.32 to 28.21)	1.24 (0.96 to 1.71)	0.96 (0.78 to 1.27)
Diuretics	–	–	0.27 (0.04 to 0.93)	0.21 (0.03 to 0.73)
β blockers	–	–	–	0.77 (0.62 to 0.98)

ACE=angiotensin converting enzyme; ARBs=angiotensin receptor blockers.
Estimates lower than 1.00 favour row defining intervention.

Table 4 Findings of network meta-analyses: comparative effects of exercise and drug interventions on mortality outcomes in prediabetes. Values are odds ratios (95% credible intervals)

| Intervention | Comparator drugs | | | |
	AGIs	Biguanides	ACE inhibitors	Glinides
Exercise	0.22 (0.02 to 1.18)	2.67 (0.41 to 36.39)	0.73 (0.14 to 1.96)	0.69 (0.10 to 2.52)
AGIs	–	13.39 (0.99 to 519.75)	3.26 (0.42 to 43.94)	3.06 (0.33 to 48.01)
Biguanides	–	–	0.26 (0.01 to 1.85)	0.25 (0.01 to 2.08)
ACE inhibitors	–	–	–	0.93 (0.18 to 5.49)

AGIs=o glucosidase inhibitors; ACE=angiotensin converting enzyme.
Estimates lower than 1.00 favour row defining intervention.

rehabilitation of patients with heart failure, there were no important adverse events requiring the interruption of any training sessions.[59] Indeed, authors of the Cochrane review on exercise rehabilitation for heart failure found no evidence to suggest that such programmes cause harm.[35] Similarly, authors of the Cochrane review on exercise training for stroke survivors concluded that participation in exercise training programmes seems to be safe.[34] For the secondary prevention of coronary heart disease, rates of adverse events in exercise rehabilitation settings are low.[60]

Limitations of this study

Our findings should be interpreted in light of their limitations. Firstly, although exercise seemed to be more effective than drug interventions in stroke rehabilitation, and diuretics seemed to be more effective than exercise interventions in heart failure treatment, these findings should be interpreted with caution given the scarceness of data and the different settings involved. Although between study heterogeneity was generally low, with no statistical evidence of inconsistency between direct and indirect comparisons, it remains a possibility that potential imbalances in the distribution of unobserved or unmeasured effect modifiers across the contrasts affected the findings,[61] potentially confounding the comparative estimates between drugs and exercise. Accordingly, we caution that the comparison of exercise and drug interventions should be tempered by the additional differences in patient populations across different trials.

Secondly, the definition of exercise interventions varied across the list of included trials, limiting the generalisability of our findings to different types of physical activity. Thirdly, several meta-analyses of drug interventions were outdated and it was logistically difficult to try to update so many drug meta-analyses. As a result, our review may have underestimated the magnitude of data available on drug interventions. Conversely, it is unlikely that we missed substantial randomised trial data on exercise, thus the relative dearth of evidence on exercise versus evidence on drugs may be even more prominent. Our Medline search identified only three new exercise trials,[59 62 63] although it captured 31 of the 54 older ones that had been included in previous meta-analyses. Based on the capture-recapture principle, we may have missed another two exercise trials only—that is, 3x (54−31)/31. Overall, the evidence on the effects of exercise is clearly outnumbered by the evidence on drugs. Moreover, if anything, there is evidence that updated meta-analyses tend to show smaller treatment effects,[64] so the benefits of some drug interventions may be overrated.

Fourthly, exercise trials often included some drug interventions (although the details of drug treatments were limited), which were given similarly to both the physical therapy and the usual care arms, suggesting that the observed effect of exercise possibly represented the added benefit of exercise over and above the benefit conferred by drug interventions. This might have underestimated the effectiveness of exercise on mortality, according to the findings of recent research showing that statin treatment may decrease the fitness benefits of exercise.[65]

As an overview of published meta-analyses, our review also shares the limitations of the existing evidence. Previous reviews (and the randomised controlled trials on which they are based) did not always make clear the settings in which physical interventions were undertaken, how they were carried out, and potential factors responsible for the success or failure of the intervention. It is particularly important to characterise these so-called "support factors" of exercise interventions in randomised controlled trials (for example, extent of supervision, individual level versus group level activity), which would allow future researchers and practitioners to replicate successful interventions and avoid unsuccessful ones.[66]

Future directions

Despite its limitations, this meta-epidemiological review is the first to compare the mortality benefits of exercise and drug interventions. This comprehensive look at the existing body of evidence highlights the need to perform randomised trials on the comparative effectiveness of exercise and drug interventions.

Given the scarcity of financial resources to fund future trials of exercise interventions, one option would be to require such evidence from pharmaceutical companies that are under increasing pressure to perform active-comparator trials for market entry.[67 68] For example, regulators should consider requiring pharmaceutical sponsors of new drugs to include exercise interventions as an active comparator arm in drug trials. In cases where drug options provide only modest benefit, patients deserve to understand the relative impact that physical activity might have on their condition.

Table 5 Findings of network meta-analyses: comparative effects of exercise and all drug interventions on mortality outcomes in coronary heart disease, stroke, heart failure, and prediabetes

Treatment area	Odds ratio (95% CrI) drugs v exercise
Coronary heart disease	0.94 (0.80 to 1.11)
Stroke	8.66 (1.28 to 245.10)*
Heart failure	0.99 (0.73 to 1.36)
Prediabetes	1.43 (0.81 to 3.11)

Estimates lower than 1.00 favour drug interventions, estimates higher than 1.00 favour exercise.
*Odds ratio was associated with considerable uncertainty owing to extremely small numbers of events in exercise trials.

What is already known on this topic

Population level cohort studies suggest that physical activity is associated with a decreased risk of mortality A large number of randomised controlled trials show the mortality benefits of certain drug interventions

What this study adds

► Evidence on the mortality benefits of drug and exercise interventions for common diseases varies widely, highlighting the paucity of data on the effectiveness of exercise interventions in randomised trials

► Based on available data on the secondary prevention of coronary heart disease, stroke, heart failure, and prediabetes, physical activity is potentially as effective as many drug interventions

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