Exercise trials for blood pressure control: keeping it REAL

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A pill that mimicked the effects of physical activity and exercise on the cardiovascular system would be the biggest blockbuster ever. It would be a poly-pill in its range of action with few serious adverse effects. On its patent expiry, the drug would be put in the water supply. Regrettably, there is no such pharmacological miracle in sight. Moreover, the current landscape is such that the dialogue around the expected benefits of exercise is omnipresent but doctors rarely ‘prescribe’ it and relatively few people initiate or adhere to it in the long term.

Naci and colleagues1 recently reported the outcomes of an elegant network meta-analysis, comparing exercise and drug interventions in lowering systolic blood pressure (SBP). They catalogued 391 randomised controlled trials (RCTs) involving nearly 40 000 subjects. After this mammoth effort, they conclude that there are modest but consistent reductions in SBP in exercise interventions across all populations and the SBP-lowering effects of exercise were similar to antihypertensives, particularly in hypertensive people.

In 2018, a BJSM editorial introduced the REAL framework;2 incorporating simple principles to increase the usefulness of exercise research. REAL tapped into the global debate about how relevant clinical research really is.3 Here, we appraise the exercise trial literature reviewed by Naci and colleagues by retrofitting the four most relevant aspects of the taxonomy developed by John Ioannidis (Supplemental Table 1); REAL is a simplified version of this.4

DOES THE RESEARCH REFLECT REAL LIFE? DOES IT MATTER?

Clinical decision-making is not generally based on dichotomised choices; yet, the most robust RCT evidence is developed as if this were the case. Moreover, RCTs are limited in their capacity to reflect routine care, and this is evident in the exercise literature with small patient numbers, limited adverse effect assessment, difficulty of including a placebo comparator and under-representation of typical patients taking multiple medications.5 While it is not possible to ascertain if the RCT outcomes in the Naci meta-analysis have been realised in the real world, it is fair to say that the characteristics of the patients seen in routine clinical care are likely to vary from the 39 742 participants in the RCTs. But does this matter? It likely does. The Naci et al’s study highlighted that further work needs to be undertaken to determine the generalisability of the review’s findings. For example, the exercise RCTs in their review largely included healthy adults with optimal or mildly elevated blood pressure. And in the studies recruiting participants with elevated SBP, the exercise intervention was often used to augment antihypertensive drug treatment. Mean age across the exercise and drug treatments ranged from 49 to 55 years and elderly people, who account for a very large proportion of hypertensive patients, are likely to be severely under-represented; the benefits and risks of both drugs and exercise might be quite different in older populations and those with multiple comorbidities.

ARE METHODS VERIFIABLE AND UNBIASED?

Using the Cochrane risk of bias tool, the authors demonstrate that 18 of the 20 randomly selected exercise trials had a high ‘risk of bias’ on at least one of the four criteria assessed. While the drug trials did perform marginally better in this domain, it is clear that interventional researchers need to ‘lift their game’ in terms of trial design and reporting quality. Predictably, for nearly all exercise trials, the intervention was unblinded. The risk of bias due to lack of blinding was increased by the general failure to use demonstrably objective measures for blood pressure assessment (eg, ambulatory blood pressure monitors). Further, 14 trials had ‘high’ or ‘unclear’ risk of biases in relation to reported outcomes (attrition bias and selective reporting).

Registering clinical trials is a key strategy to transparency and selective outcome reporting.5 We reviewed all 40 randomly selected trials assessed for risk of bias and found only three exercise trials mentioned registration in the published manuscripts (14 were published in the last decade); this clearly needs to be remedied in the future. We also note that only one of the 20 drug trial publications mentioned registration; the remainder would have commenced or were published prior to the 2004 statement by the International Committee of Medical Journal editors regarding public registration as a condition for publication.5 Also worth keeping in mind that the biases assessed in the Cochrane tool are only the tip of the iceberg in terms of the long list of potential biases that could impact on study outcomes.

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DOES THE RESEARCH REFLECT TOP PATIENT PRIORITIES?

The review’s research question is framed as a direct comparison—‘how does the SBP-lowering effect of drugs compared with that of exercise?’ At a simplistic level, this is not really the evidence that informs a direct choice for clinicians or patients. The two treatments should, and often do, coexist. Patients with borderline high blood pressure should be advised to exercise before resorting to prescribed drugs; exercise is a potential add-on for patients with clearer indications for drug treatment. Although Naci suggest that head to head trials are needed, the fact that there are none whatsoever (!) may imply that this is actually not a choice made frequently in real-world clinical practice. While the Naci meta-analysis provides the best current evidence for the comparative effect of exercise versus drugs on SBP, the practical implications for clinical practice are largely unrelated to that direct comparison. It is likely that the benefits from exercise are what is relevant to patients and should guide when it is recommended. A choice is not required—people can do both, either or neither. Further, we do not have drugs that can provide the full range of exercise benefits, even if on a SBP measure they might be comparable.
IS THE RESEARCH WORTH THE MONEY?

While brief exercise interventions appear to be excellent value for money and the rationale for undertaking further exercise and blood pressure research is compelling, one may question their value unless researchers can dramatically improve the design issues we mention above. The key clinical questions for any further research are not about comparative efficacy alone, but around the types and volume of exercise that will provide the best return in terms of long-term adherence and effectiveness. Such studies will need to be large, prospectively registered, pragmatic, multi-centre, involving head-to-head comparisons of different exercise regimens and consider the multiple potential beneficial effects of exercise, beyond narrow primary outcomes.

A necessary ingredient for success will be funders’ willingness to invest in such ambitious research enterprises.

John Ioannidis, senior author of the network meta-analysis, is a realist, and most importantly an optimist. In line with this philosophy, this editorial was written as an opportunity to pause and reflect on how research (including that undertaken by us) can keep it REAL by better tailoring our science to the needs of the health system, patients and clinicians.

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