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Can we proceed with physical activity recommendations if (almost) no clinical trial data exist on mortality?

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Observational studies consistently show reduced mortality rates among participants with higher physical activity levels compared with participants with less activity.[12] However, as Kujala eloquently points out,[3] there are sparse data from randomised trials leading some argue that a causal relationship of physical activity with mortality cannot be confirmed. As current physical activity guidelines were developed primarily based on observational studies of physical activity and clinical outcomes,[4] one might question how despite the lack of trial data—the gold standard for causality inference—policy and medical advice for physical activity can be made. This opinion piece aims to highlight some of the challenges and implications of examining physical activity and mortality solely through a lens which sees causality only when randomised trial data are available.

WHERE IS THE PHYSICAL ACTIVITY AND MORTALITY TRIAL?

To our knowledge, there are currently no completed randomised trials of physical activity where mortality is a prespecified primary outcome, and where analyses are adequately powered to examine the effects of physical activity on mortality. While several large trials, such as LIFE[5] and Look AHEAD,[6] were able to provide a secondary look at mortality, they were not designed with mortality as a primary outcome. (And, further, Look AHEAD was not designed to exclusively target physical activity, but rather both diet and physical activity in order to achieve and maintain weight loss.) Thus, null findings for mortality or other clinical outcomes should be interpreted cautiously due to a lack of statistical power. For example, the LIFE study comprised 1635 adults between the ages of 70 and 89 years who were followed for an average duration of 2.6 years.[5] Using the average probability of death, and the estimated reduction in mortality from a large observational study[2] comparing those who participated in at least 150 min of moderate-to-vigorous activity with those who did no activity (HR=0.80), the post hoc estimated power to detect this mortality difference between

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the groups in the LIFE study was approximately 20%. Even if we assumed a more extreme HR of 0.60, based on observational studies where accelerometers were used to measure physical activity more precisely, the estimated power would still be 70%.

While the randomised trial design is considered the gold standard for causal inference, valid results will only be obtained if such trials are well designed and conducted. A key feature for a well-conducted trial is that compliance must be high. Additionally, if mortality is the specified outcome of interest and the trial is conducted among healthy populations—even older, healthy adults—the trial has to run over a period of many years. The effort and cost to achieve and maintain high compliance over the long duration is daunting, if not insurmountable. It may be tempting to simply use a study population at higher risk of mortality, but medical management of higher risk populations may present a different challenge. Additionally, such results may not be generalisable to the larger population at usual risk. In the Look AHEAD study, which found no significant reductions in cardiovascular disease between the intervention and control groups, the study population was overweight and obese type 2 diabetics. These patients were medically managed for several known cardiovascular risk factors, including use of diabetes medication and cholesterol-reducing drugs such as statins. The authors noted that this medical management may have reduced the observed effect of the intervention, since physical activity has overlapping effects.[6] With long intervention durations, volunteer bias, compliance issues and selection bias for drop-outs, all may further lead to trial results being no more valid—and, possibly less valid—than results from observational studies.

Additionally, physical activity is a multidimensional concept, made up of dose (total volume), frequency, duration, intensity and activity type. While physical activity guidelines specify a minimum volume of at least 150 min/week of moderate-to-vigorous physical activity, there is little consensus on the optimum frequency, duration or type.[7]

In an attempt to answer some of the gaps in knowledge, Generation 100 is an ongoing randomised controlled trial, launched in 2012, of 1567 older adults, aged ≥70 years, evaluating the effects of 5 years of physical activity training on mortality.[8] This effort is laudable and will provide crucial data. But, it cannot answer all questions—for example, will the findings apply to younger individuals? What about other regimes (doses) of training? Because it is unlikely that many such trials will be carried out with high compliance over the long term, we will have to rely on other avenues of evidence for deducing a causal relation between physical activity and mortality.

IMPROVING OBSERVATIONAL STUDY DATA

Observational evidence from prospective cohort studies has consistently shown a strong, inverse dose response of physical activity and mortality rate across different studies, countries and populations. Since the 2009 meta-analysis by Löllgen *et al*, which consisted of 271 000 subjects across 38 prospective studies,[9] there have also been two additional large studies: Arem *et al* pooled data from 661 137 adults with a median follow-up time of 14.2 years[1], and Lear *et al*, as part of the PURE study, examined 130 843 from 17 different countries with diverse socioeconomic status.[2]

While observational studies have inherent limitations, such as misclassification and residual confounding, careful design and analyses can mitigate their potential impact. Physical activity assessment has, in the past, focused on leisure-time activity assessed through questionnaires. With the increased usage of objective tools, such as accelerometers, greater precision of measurement of total and domain-specific activity volume can be achieved, including transportation, occupational and household or child care activities with minimal additional participant burden. In addition, accelerometers can assess lower intensity activities and sedentary behaviours, which are often neglected in physical activity questionnaires, as well as patterns of physical activity. (The trade-off is that devices currently do not capture well the context in which the activity occurs— eg, housework vs leisure.)

It has been noted that the frequent comparison group in observational studies, the 'inactive' group, may comprise not only those who are able to be active and choose not to, but also of those who are not active because of an inability to become active. This is a valid concern. Current observational studies with functional measures have the ability to investigate this heterogeneity within the 'inactive' reference group. Studies of younger populations, and particularly select cohorts, are less likely to be subject to the bias where inactive persons also are physically unable to be active. For example, in the Women's Health Study, where an inverse association was observed between reported physical activity and clinical outcomes,[10] the baseline population was selectively chosen to be part of the trial testing aspirin and vitamin E for the prevention of cancer and cardiovascular disease.[11] Thus, all participants had to be free from cancer and cardiovascular disease, in addition to other health conditions that would preclude their participation in a trial for at least 5 years (at trial end, the average follow-up was 10 years). This likely led to a selectively healthier population in that study. However, we agree that in studies of older persons, the physical function and ability of the least active group is likely to be an issue.

To further complicate reaching a consensus from physical activity observational analyses, variables such as body mass index, hypertension, high cholesterol, diabetes, physical fitness and physical function are often treated as potential confounders and included in the statistical model. Studies, including randomised trials, have shown that physical activity reduces body mass index, rates of hypertension, high cholesterol and diabetes, while increasing physical fitness and maintaining physical function.[5,6,12,13] As many of these are also known to be associated with mortality, controlling for them as confounders, while they are potentially intermediates and on the causal pathway, may reduce the strength of the observed association. One could argue that they should not be adjusted for, since they represent mediators in the causal pathway and not true confounders.

To summarise, in the absence of a randomised trial, physical activity and mortality studies have satisfied many of the Hill criteria for causality (which although conventionally used are not *sine qua non* criteria for this purpose),[14] thus arguing that the relation is more likely causal than not. The studies show a strong, inverse dose response across many studies and populations after adjusting for known confounders. Physical activity has also been shown, including in randomised trials, to be associated with mortality risk factors,[12] providing potential biological mechanisms for the effect of increased activity on mortality rate. While

randomisation would satisfy many concerns over residual confounding, intervention studies also have inherent limitations such as volunteer bias, compliance issues, selection bias due to drop-outs, generalisability and limited ability to test specific doses of physical activity since a free-living population has too many patterns to feasibly test. Simply ignoring all available evidence save those from intervention studies does a disservice to the rich totality of evidence available, much of it while subject to limitations is not without value.

PHYSICAL ACTIVITY RECOMMENDATIONS AND PRESCRIPTION

While the causality of physical activity and mortality cannot be currently satisfied on the basis of randomised trial data alone, few would disagree that physical activity has been shown, including in trials, to be associated with many health benefits, in some cases, similarly in magnitude to pharmaceuticals.[12] It is also important to acknowledge that mortality alone—or even including other clinical outcomes ('hard endpoints')—cannot be the only outcomes that are meaningful to people. Physical activity has also been shown to improve quality of life, including decreasing the rate of major mobility disability[5] and cognition.[15] We also have, for example, randomised trial data from cardiac rehabilitation studies showing that exercise intervention improves quality of life, in addition to the hard outcomes of cardiovascular mortality and reduced hospitalisations.[16]

In conclusion, we believe that even with the lack of randomised trial data on physical activity and mortality, it is important to continue prescribing physical activity because of the large body of evidence currently available from both observational studies (including ones with mortality outcomes) and randomised controlled trials addressing a large range of health outcomes and quality of life.

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