Linking volume and intensity of physical activity to mortality

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In a study of 96,476 participants from the UK Biobank cohort who had their physical activity objectively measured by accelerometer, both volume and intensity of physical activity were associated with risk of mortality.

While there is a wealth of epidemiological evidence that higher levels of physical activity are associated with lower risk of mortality and other adverse health outcomes[1], the interrelationship between volume and intensity of physical activity and mortality risk has been unclear. In this issue of *Nature Medicine*, Strain and colleagues demonstrate, in 96,476 participants from UK Biobank, that the overall physical activity energy expenditure (PAEE) and the proportion of this expenditure undertaken in moderate-to-vigorous physical activity (MVPA), were both associated with risk of mortality[2].

Physical activity guidelines worldwide typically recommend undertaking at least 150 minutes of moderate intensity physical activity or at least 75 minutes of vigorous physical activity per week[3-5]. Within these guidelines, physical activity intensity is often described in METs – or metabolic equivalents – with 1 MET being equivalent to resting metabolic rate[6]. Moderate intensity activity is typically defined as 3.0-5.9 METs, with the lower end of the range equivalent to walking at 4 $km.h^{-1}$ (2.5 mph) on level ground; intensities higher than 6.0 METs are vigorous; and all activities of at least 3 METs are often grouped as MVPA. An important consideration is that the evidence underpinning these guidelines is largely based on epidemiological data in which physical activity was assessed using self-report questionnaires. This can limit the ability to generate robust estimates of the quantitative relationships between physical activity level and risk of adverse health outcomes. When asked, people tend to over-report the amount of physical activity they undertake substantially and by an inconsistent amount, which has the dual effect of inflating the apparent amount of physical activity required to obtain health benefits, and attenuating the apparent strength of the relationship between physical activity and health outcomes[7]. A second, related, issue is that it is difficult to obtain a robust measure of light intensity physical activity (1.5-2.9 METs) from self-report questionnaires, which means that its association with health outcomes has been unclear. This is of practical importance as the majority of our PAEE is in the light intensity range.

Strain and colleagues address this by using physical activity data gathered objectively using wrist-worn accelerometers from a subset of 96,476 participants in UK Biobank – a population-based cohort of over 500,000 men and women who had extensive data collected on lifestyle, medical history and environment, as well as physical assessments and biological samples collected, during a baseline assessment between 2006-2010, and are continuing to have health-related outcomes followed up via data linkage to health records [8]. Accelerometer measures of physical activity were made in a subset of UK Biobank participants between 2013-2015 who, in Strain *et al*'s analysis, were followed up for a median of 3.1 years, during which time 732 died. Their data show that, compared to a reference group with a PAEE of ~15 $kJ.kg^{-1}.day^{-1}$ (~1,000 kJ or 250 kcal/day for a 70 kg person) and 10% of this expenditure in MVPA (equivalent to ~7 min/day of MVPA at 3 METs), keeping PAEE constant but increasing the proportion of MVPA to 20% (~16 min/day MVPA) resulted 30% lower risk of mortality, in analyses adjusted for a range of covariates. In contrast, when the proportion of PAEE in MVPA was fixed at 10%, increasing PAEE from ~15 $kJ.kg^{-1}.day^{-1}$ to ~20 and ~30 $kJ.kg^{-1}.day^{-1}$ PAEE (~335 and ~500 kcal/day for a 70 kg person, ~13 and ~20 mins/day MVPA) was associated with 21% and 54% lower risks of mortality, respectively. Interestingly, mortality risk was minimised (at 76-78% lower risk than the reference group) with a PAEE of ~40 $kJ.kg^{-1}.day^{-1}$ – the median PAEE for the cohort – irrespective of the proportion of PAEE in MVPA, with higher expenditures leading to no further lowering of risk[2] (Figure 1). The practical implication is, assuming these relationships are causal, that those undertaking less than the population median level of PAEE (about 670 kcal/day for a 70kg person), would benefit from undertaking a larger proportion of their PAEE in MVPA and/or increasing PAEE at any intensity, whereas those who are already achieving this level of PAEE would achieve no further gains in terms of mortality risk from doing more. This leads to the key observation that the greatest potential for mortality risk reduction occurs in those with the lowest levels of PAEE, supporting the general public health message that "any activity is better than none, and more is better still" [3].

Of particular note, the dose-response relationship in Strain and colleagues' analysis differs substantially from analyses using self-reported physical activity as the exposure variable. For example, in a pooled cohort analysis of 654,827 individuals who had physical activity assessed by self-report, undertaking 150-300 $min.week^{-1}$ of moderate intensity physical activity (i.e. achieving physical activity guidelines) was associated with a 32% lower risk of mortality compared to a reference group undertaking no leisure-time MVPA[9]. A similar risk reduction achieved with just ~110 $min.week^{-1}$ of accelerometer-measured MVPA in the Strain *et al* analysis[2]. As the reference group in the analysis by Strain et al. undertook ~50 min of MVPA per week, rather than none2, this suggests that the benefit in terms of lowering mortality risk for an additional minute of accelerometer-measured MVPA is about two and a half times as great as that associated with an additional minute of self-reported MVPA. Furthermore, the maximal mortality risk reduction observed with high levels of activity was about twice as great (~76-78% vs 41%), and occurred at a lower level of MVPA (~320 vs >450 min/week), when physical activity was objectively measured rather than self-reported [2,9]. It should be noted that the observational nature of the data limit the ability to make firm conclusions about the causality of the relationship between physical activity and mortality. It is, however, important to acknowledge the difficulties of performing gold-standard randomised controlled trials on the effect of physical activity on mortality in the general population as the low mortality rate (risk of death within the next 10 years for a healthy, normal weight, non-smoking, but inactive woman in the UK aged 50-59 years, is less than 3%[10]) means that a trial would need to be unfeasibly large and long to have sufficient power to detect an effect. Furthermore, the authors' follow-up period at 3.1 years is short and this increases potential for reverse causality (that is, a disease, often undiagnosed, at baseline leading to lower levels of physical activity), even when those with prevalent disease at baseline are excluded[11]. Finally, covariates used for adjustment in statistical models were measured ~5.7 years on average before measurement of physical activity. If these deteriorated more in the period between their measurement and measurement of physical activity in those who died compared to those who survived, the mortality risk reductions associated with physical activity may have been overestimated. The influence of the latter two aspects on the findings will both be reduced with longer-term follow-up.

With the increasing use and decreasing cost of wearable consumer devices to track physical activity, Strain and colleagues' findings, if they persists with longer term follow-up, and are corroborated with data from other studies, may result in a future shift in physical activity guidelines to revise the amount of *accelerometer-measured* physical activity required for health benefits downwards from current recommendations. Such a shift may make engaging in physical activity seem more achievable for those who are currently inactive. Of note, a recent meta-analysis of 36,383 participants across eight studies, similarly reported a steeper dose-response relationship between accelerometer-measured physical activity and mortality risk than that observed in studies using self-reported physical activity as the exposure[12], so a critical mass of evidence in this area is starting to accumulate.

Overall Strain and colleagues study[2] is an important one; its large size and objective measurement of physical activity provides more robust quantification of the dose-response relationship between physical activity and mortality than has previously been possible. The benefits of physical activity may be greater, and the levels of activity at which they occur may be lower, than we previously considered. This could have implications for population-level physical activity recommendations in the future.

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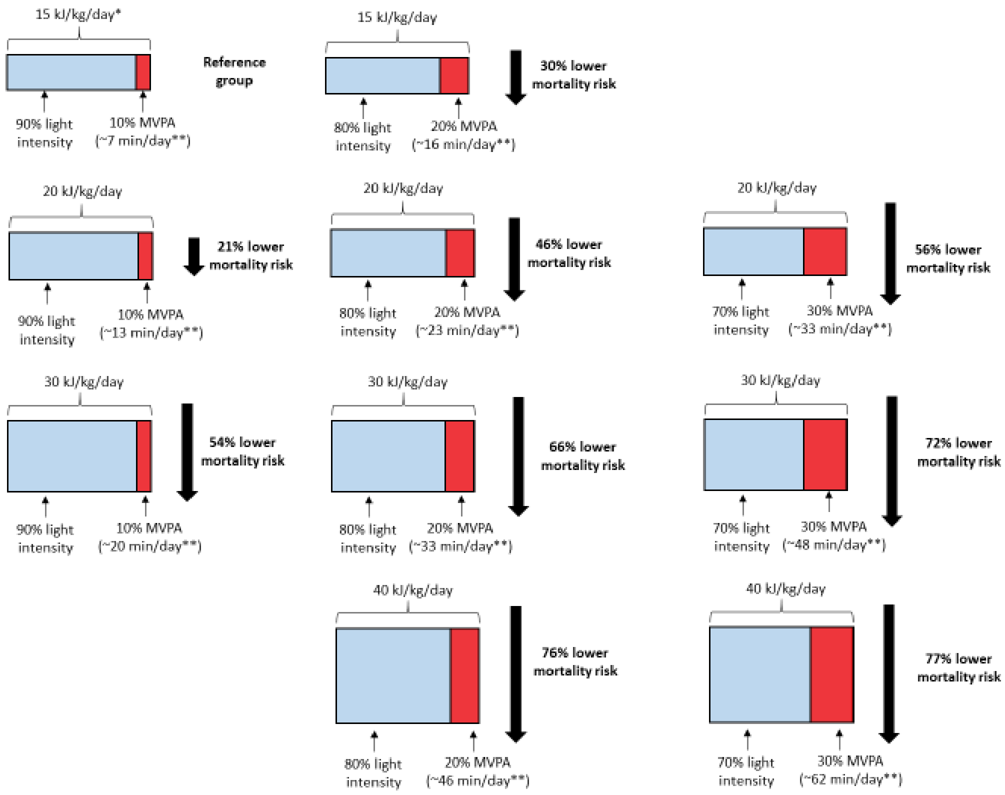

*for a 70 kg person, 15 kJ/kg/day is ~250 kcal/day; 20 kJ/kg/day is ~ 335 kcal/day; 30 kJ/kg/day is ~ 500 kcal/day; and 40 kJ/kg/day is ~670 kcal/day
**for physical activity at an intensity of 3 METs, equivalent to walking at ~4 km/h (2.5 mph)

Figure 1 Legend

Higher levels of physical activity are associated with a lower risk of mortality. Strain et al. used data from accelerometers to study the association between physical activity and risk of mortality in 96,476 participants from the UK Biobank. For a 70-kg person, 15 kJ kg^{-1} per day ('15 kJ/kg/day'; top row) is ~250 kcal per day; 20 kJ kg^{-1} per day is ~335 kcal per day; 30 kJ kg^{-1} per day is ~500 kcal per day; and 40 kJ kg^{-1} per day is ~670 kcal per day. All MVPA information in parentheses (min/day) is for physical activity above an intensity of 3 METs, equivalent to walking at 4 km per hour (2.5 mph).