

Physical Activity and Cardiovascular Risk: No Such Thing As 'Too Little, Too Late'

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Atherosclerotic cardiovascular disease (CVD) remains the leading cause of premature morbidity and mortality in the world today, and is on course to cost the global economy > US\$1 trillion by 2030¹. Although the clinical manifestations of CVD are seldom seen prior to middle-age, current evidence points to a decades-long subclinical period of the disease prior to the appearance of overt complications. While the exact physiological processes underlying this evolution are still poorly understood, it has been estimated that virtually all of the population attributable risk for CVD can be attributed to just nine lifestyle-related (and therefore modifiable) risk factors: namely abnormal lipids; smoking; hypertension; diabetes; abdominal obesity; psychosocial factors; low consumption of fruits and vegetables; and lack of regular physical activity². Timely prevention strategies to alter lifestyle behaviours and reduce these risk factors are therefore likely to offer the greatest benefits to cardiovascular health and longevity at a population level.

Less than 1/3 of adults and 1/5 of adolescents are now estimated to meet recommended daily exercise guidelines, resulting in a physical inactivity pandemic responsible for > 3 million deaths and the loss of almost 70 million disability-adjusted life-years (DALYs) per year^{3,4}. While the ability of regular physical activity to reduce CVD risk is virtually indisputable⁵, less well understood is the age at which this is most effective, or the effect that other co-morbidities/risk factors have on this relationship. Accumulating evidence suggests that it is never too early to start prevention strategies for CVD, and that early interventions to reduce long-term exposure to risk factors are essential if CVD risk is to be minimised across the lifespan⁶. But what of individuals in later life for whom these strategies are already too late? Can following an active lifestyle in middle age attenuate the risk of a premature death – even in individuals who are already exposed to a significant cumulative burden of CVD risk factors?

In the paper published today in the *European Journal of Preventive Cardiology*, Ekblom-Bak et al address this question by utilising data from a population cohort of > 3500 individuals in order to investigate the association between physical activity levels at age 60 and CVD incidence and mortality over two decades of follow-up⁷. Using a combination of detailed laboratory and questionnaire data collected at baseline and access to long-term linkage to national patient registers over the next 20 years, the authors were able to investigate the risk reduction afforded by different levels of physical activity in middle-aged individuals both with and without the metabolic syndrome – a clustering of CVD risk factors known to significantly increase the risk of premature morbidity and mortality. The study has a number of important findings which not only add to the existing weight of evidence favouring physical activity for CVD risk reduction, but also add new insights to potential contributing mechanisms. Firstly, in line with previous studies, the authors found that sedentary behaviour and the presence of metabolic syndrome were both independently associated with an increased risk of CVD incidence and mortality – with the most pronounced risk occurring in individuals who fulfilled both

criteria. Interestingly, however, being sedentary was found to relate to an equivalent risk of all-cause mortality regardless of metabolic syndrome status, suggesting a detrimental effect of sedentariness on longevity beyond that caused by cardiometabolic abnormalities and CVD. Secondly, mediation analysis was carried out to investigate potential indirect effects of physical activity on outcomes and identified fibrinogen as a potential mechanistic pathway in participants with and without metabolic syndrome – highlighting the additional role of inflammatory/prothrombotic pathways in CVD development. Lastly, they demonstrated that physical activity was able to reduce the risk of CVD incidence and all mortality even at this relatively advanced age. Perhaps most importantly, however, they showed that these gains could be achieved even in individuals with established CVD risk factor burden who were doing only the lightest levels of activity – suggesting that any attempt to reduce sedentary behaviour is likely to be beneficial even in later life.

This paper has a number of notable strengths. The large sample size and high response-rate during recruitment result in a cohort that is likely representative of the general population, ensuring that findings reported here can be translated to the population at large. In addition, the strict age criteria at recruitment ensures that findings are less likely to be confounded by differences in age, which usually require statistical adjustment in the majority of cohort studies. Perhaps the most noticeable strength is the separation of the cohort into those with metabolic syndrome vs those without, allowing the impact of physical activity in middle-age individuals with high risk factor burden to be assessed independently of their healthier peers. It must also be pointed out that there are also a number of weaknesses inherent to cohort studies of this nature. Firstly, the authors use of subjective measures of physical activity as their main exposure raises the possibility of recall bias when compared to more objective measures – as they themselves have acknowledged in their limitations. The comparison of questionnaire responses to accelerometer data in a small subset of participants, however, does add confidence to their findings. Secondly, and perhaps more importantly, a lack of information on physical activity levels and other health activities prior to baseline in this cohort means that it is not possible to decipher whether the observed reductions in CVD risk are the result of their physical activity levels at age 60 *per se*, or whether these individuals are protected through reduced exposure to other risk factors prior to this point. This latter point is crucial from a public health perspective, as it determines the extent to which positive lifestyle changes in later life may independently influence future CVD risk.

Current medical guidelines recommend that adults – including older adults – should aim to achieve at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity exercise per week⁸. While these guidelines are evidence-based and designed to maximise risk reduction at a population level, the targets set can often be seen as daunting – and in many cases unachievable – for older individuals who may be limited by a multitude of other physical and mental comorbidities. With results from this study once again demonstrating that considerable benefits to health can be achieved by any reduction in sedentary behaviour, there are a number of important public health messages which must continue to be conveyed. Firstly, it is vital that public health initiatives continue to recommend that any form of physical activity is likely to be beneficial and should be prioritized in all individuals – even if the levels of activity achieved are limited by other medical conditions⁹. Secondly, it must be stressed that this advice is also relevant to middle-aged or elderly individuals with underlying health conditions or a history of poor health behaviours until this point^{10,11}, who may mistakenly believe that attempts at lifestyle change at this stage are ‘too little too late’. This is almost certainly not the case, however, as demonstrated both by the current study, and by recent research from the EPIC-Norfolk cohort in which a 1kJ/kg/day increase in physical activity energy expenditure over 5 years (the equivalent of moving from sedentary behaviour to meeting WHO physical activity guidelines over this timeframe) resulted in 29% reduction in CVD mortality over 12.5 years in middle-aged and older adults¹². Finally,

it should also be remembered that CVD and mortality rates do not paint the full picture of the myriad benefits associated with physical activity, which is unique in its ability to – amongst other things – improve mental health, reduce falls, and prevent disability. The promotion of regular physical activity at any age will therefore result in people not only living longer, but also living healthier.

In summary, findings from this long-term population study suggest that even light levels of physical activity in middle-age can reduce the risk of CVD and mortality compared to sedentary behaviour, and that this risk reduction is apparent even in individuals with established cardiometabolic abnormalities such as the metabolic syndrome. While public health initiatives should continue to advocate that early prevention strategies are essential for lifetime gain, it must also be made clear that – when it comes to physical activity – some is better than none, and its better late than never.

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