Physical Activity: Can There Be Too Much of a Good Thing?

Running title: Huxley; Physical activity and cardiovascular risk

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It is widely-acknowledged that physical activity in some way, shape or form is beneficial to a person’s health, a concept that has been around for more than two millennia having been first espoused by Hippocrates: “Eating alone will not keep a man well; he must also take exercise”\textsuperscript{1}. Therefore it should come as no surprise that in this issue of \textit{Circulation} Armstrong and colleagues’ present findings from the Million Women’s Study, which highlight the beneficial effects on the risk of coronary heart disease, cerebrovascular disease and venous thromboembolism, which regular moderate physical activity confers among active healthy, middle-aged women in the United Kingdom\textsuperscript{2}. Findings from the current have brought some clarity with respect to the questions of how much, how often, and how hard, middle-aged women need to do physical activity to accrue the greatest vascular benefits.

The key findings from this paper relate to the frequency, intensity and total amount of physical activity that were associated with optimal vascular benefits among middle-aged women. Interestingly, the relationship between frequency of activity (either strenuous or any) and vascular risk was not linear but rather U-shaped; in women who engaged in strenuous activity (defined as “enough to cause sweating or a fast heart rate”) the optimal frequency of activity in terms of vascular risk reduction was 2-3 times per week which was associated with significant relative risk reductions of 17-19\% compared with the rarely/never group. Any further increase in frequency of strenuous exercise beyond that point was associated with an increased vascular risk. For any activity –that mainly included walking, gardening and housework – the optimal frequency was 4-6 times per week (compared with rarely/never) which was associated with a slightly greater 17-25\% reduction in the risk of vascular outcomes in this population. And as with frequency of activity, there was also no evidence of a linear association between total amount of physical activity and reductions in vascular risk with the greatest difference in
vascular risk occurred between the least active women (less than 40 excess Metabolic Equivalents [MET] hours per week) versus all other groups.

Ascertaining a valid and reliable measure of physical activity and its relationship with health outcomes requires numerous hurdles to be overcome. Physical activity must be measured (preferably at more than one-time point) in a large enough sample of people for a long enough period of time in order to accrue a sufficient number of events for estimates of the association between physical activity and vascular disease to be derived. Reliably estimating the volume of physical activity is notoriously challenging. This has, in part, been due to the inherent difficulties in accurately measuring not only the frequency of physical activity but also its type, intensity and duration as well as variations in activity level over time. Comparability between studies has also been impeded by a general lack of consistency as to which activities constitute physical activity. For example, The Million Women Study is one of the few large cohort studies to measure housework and to include it as a form of moderate physical activity.

In many ways the current study has been able to overcome these methodological challenges by sheer virtue of its size and length of follow up. Between 1996-2001, more than 1.1 million healthy British women with a mean age of 56 years were recruited into the study. At baseline, the women were asked how often they did ‘any exercise’ and how often they did ‘strenuous exercise’. At a resurvey three years later 44% of participants reported how many hours they spent each week on a range of physical activities including housework, gardening, walking or exercise that caused ‘sweating or a fast heart-rate’. When relying on self-report data of this type, it’s crucial to understand how valid the methods for assessing the exposure are. In a previous publication from the same group, the authors examined the level of agreement between activity measured at the two time-points. For strenuous activity, absolute agreement for
questionnaires two years apart was 52% ($\kappa$ weighted = 0.51) and for any physical activity 47% ($\kappa$ weighted = 0.58) suggesting that there was moderate agreement between the studies or in other words, the level of physical activity that women reported doing was in reasonable agreement with what was actually done.

Over the course of nine years of follow-up and after excluding women who may have been asymptomatic for serious disease at the commencement of the study, there were more than 49,000 cases of incident coronary heart disease, over 17,000 strokes and 14,500 venous thromboembolism events. Compared to being ‘inactive’ doing any form of exercise at least once a week was associated with the greatest reductions in the risk of incurring any of these vascular events. Increments in the amount of physical activity beyond once a week were associated with smaller benefits up to a certain point beyond which there were no gains in terms of reduced risk of vascular outcomes. The point of inflection depended on the type of vascular event as well as the intensity of activity. But in general, undertaking moderate exercise on 4-6 days of the week was associated with the greatest reductions in relative risk estimates compared with women who were inactive. For strenuous exercise, compared with never, restricting the activity to 2-3 days of the week was optimal. Notably, increases in the frequency of strenuous exercise above 3 times per week were associated with significantly increased vascular risk (compared with strenuous exercise 2-3 times per week).

The possibility of confounding is always a concern with observational data. In the current study, the women who reported doing strenuous exercise daily comprised only 3.2% of the population compared with 47% of women in the reference group who reported no strenuous exercise. And, rather counterintuitively, the prevalence of current smokers was similar in both groups at 25%– considerably higher than the prevalence estimates for women who did strenuous
exercise between 1-6 times per week. Even though the results were adjusted for smoking (and other risk factors) the authors acknowledge that residual confounding may have persisted and thus, may have explained some of the association between physical activity and vascular risk in the most active women.

Although the current findings are consistent with the literature they are not directly comparable with those from other cohorts as the metric used to quantify the absolute volume of activity in the Million Women Study was the excess MET as opposed to the more commonly used MET. A MET is the ratio of the metabolic rate of an activity to the rate of energy expended while sitting quietly: 1 MET is the rate of energy expenditure while at rest and so a 3 MET activity (such as housework) expends three times the energy used by the body at rest. Therefore, a 3 MET activity undertaken for 60 minutes is equivalent to 180 MET-minutes (or 3 MET-hrs) of physical activity. Moderate intensity exercise – such as walking, gardening, and housework -typically equates to 3-6 METs, whereas vigorous activity (such as cycling) is estimated to be 6 or more METs. In contrast, an excess MET is defined as the excess energy expenditure associated with any given activity above that of the basal metabolic rate obtained by subtracting one MET from each multiplier prior to calculations i.e. the excess MET associated with walking for 60 mins is 120 MET-minutes (or 2 excess MET-hrs as opposed to 3 MET-hrs). Calculating excess-MET hrs takes into account differences in the proportion of energy expenditure attributable to resting metabolic rate during low versus high activities and thus is a better indicator for assessing the actual amount of energy expended as a result of physical activity. For example, in low-intensity activities such as housework (which accounts for more than half of all activity in the current study) the proportion of energy expenditure attributable to resting metabolic rate is higher than of high intensity activities.
The use of excess MET-hours versus MET-hours to estimate physical activity levels between studies is likely to explain some of the observed variation in reported activity levels between comparable populations. For example, in the current study, the amount of physical activity in women reporting any exercise varied from 58 excess MET-hrs in the ‘rarely/never active’ group to 79 excess MET-hrs per week in the ‘daily’ category. In comparison, among women (average age of 50 yrs) in the European Prospective Investigation into Cancer and Nutrition (EPIC) mean MET-hrs per week were 50 in the inactive group and 145 MET-hrs in the most active group 9. Finally, data from the Nurses’ Health Study (mean age 64 yrs) show considerably lower levels of total physical activity with an average of 1.3 MET hours per week in the least active group to 37.6 MET-hours in the most active group; these low activity levels in the latter study are likely to reflect in part the non-inclusion of household activity 10. But irrespective of how physical activity was calculated, women in the Million Women Study were all at the more active end of the spectrum, and thus the generalizability of the findings to women who are largely inactive remains unclear.

Current recommendations suggest that for cardiovascular health adults should be doing at least 30 minutes of moderate-intensity aerobic activity at least 5 days per week in bouts of 10 minutes of more or 25 minutes of vigorous aerobic activity at least 3 days per week, or a combination thereof 11. In total, this amount of activity would equate to approximately 8-12 MET-hrs per week. In the current study, even women who reported doing no physical activity at study baseline still accrued over 15 excess MET-hrs per week (after excluding housework) predominantly through walking and gardening 3. In comparison, in England, nationally representative data indicate that only 28% of women aged 55-64 yrs 12 (and a similar percentage in the United States 13) meet the recommended guidelines for physical activity. Part of the
disparity in prevalence estimates between the current study and national figures is likely to be a consequence of the healthy-volunteer effect. However, as women in the study had similar levels of other vascular risk factors (such as smoking and body mass index) comparable to that of the general population, it is unlikely that they differed that dramatically from the rest of the population in terms of physical activity levels. Rather, aforementioned differences in how physical activity is defined and measured between studies are likely to explain some of the variation.

In conclusion, in healthy, active middle-aged women, moderate and frequent physical activity was optimal for vascular risk reduction. These findings may offer some hope – and perhaps even a dash of inspiration - to the estimated 30% of adults worldwide who struggle to achieve the recommended levels of physical activity \(^1\). To paraphrase Hippocrates, walking may well be woman’s best medicine.

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**References:**


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