Exercise is Medicine: at any Dose?

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Physical inactivity has been labelled a pandemic due to its increasing global prevalence and its health, economic, environmental and social consequences. More than half of United States adults fail to meet the 2008 physical activity (PA) recommendations of 30 min daily of moderate-intensity exercise (e.g. brisk walking, dancing, gardening) or 75 min weekly of vigorous-intensity exercise (e.g. running, fast cycling, competitive sports). Hence, increasing PA is essential for public health because it improves primary and secondary disease prevention across the population.

The benefits of exercise are indisputable and the current perception is that a curvilinear relationship exists between the amount of PA and the related health benefits. Many studies have demonstrated that PA is associated with reduced risk of cardiovascular diseases, diabetes, cancer, and dementia in a dose-dependent fashion. However, recent studies suggest that high doses of exercise can be harmful and are associated with increased risk of cardiovascular mortality.[1-4] These findings were interpreted to mean that exercise may harm the heart at a certain dose. The 'too much exercise hypothesis' may cause confusion about the benefits of exercise and the optimal dose of PA to prescribe in clinical practice. What dose of exercise is needed to promote health? Do larger doses elicit larger health benefits? What is the cut-off between the beneficial and possibly detrimental effects of exercise?

Lowest effective dose

Several studies assessed the minimum amount of PA needed to provide cardiovascular benefits. A large Taiwanese study demonstrated that individuals exercising 15 min/day at a moderate intensity had a reduced risk of all-cause mortality (Table 1) and a 3 year longer estimated life expectancy compared to their inactive peers.[5] These data were reinforced by

a pooled analysis of 6 American and European cohorts.[6] Individuals performing PA in doses below the PA recommendations had a reduced risk for mortality over 14.2 years compared to physically inactive peers. Runners participating in the Aerobics Center Longitudinal Study running only 5 to 10 min/day had a reduction in cardiovascular mortality and all-cause mortality over 15 years of follow-up.[7] These studies suggest that even short bouts of PA can have substantial health benefits. While lack of time is a critical barrier to PA, these results[5,7] suggest that even the busiest individuals should have time for this lowest effective dose of PA.

Moderate to highest tolerable dosage

Increasing from the minimum effective levels of moderate (15 min/day)[5] or vigorous intensity (8 min/day)[6,7] PA to the national PA guidelines of 30 min/day of moderate-intensity or 75 min/week of vigorous-intensity exercise appears to be associated with increased health benefits. Every additional 15 min of moderate intensity PA was associated with a 4% further reduction of all-cause mortality over 13 years in the Taiwanese population.[5] These benefits were independent of age, sex and cardiovascular history. The greatest benefit was obtained by the most active individuals (63-88 min/day), with higher mortality reductions for vigorous *versus* moderate intensity exercise.[5] Similar findings were observed in US and European cohorts. Individuals performing PA at a dose of 3x to 5x the current recommendations reported the lowest mortality rates over 14.2 years.[6] Higher PA doses, up to 10x the recommended PA levels, were associated with mortality rates comparable to the 3-5x group. In the National Runners and Walkers Studies, cardiovascular mortality over 10.4 years was reduced in survivors of MI who exercised 8 to 24 min/day compared to patients who exercised at lower doses.[2] The largest reduction in

cardiovascular mortality was observed in patients who exercised 38 to 96 min/day. The Cooper Institute data confirmed that 7 min/day of high intensity PA was associated with reduced cardiovascular mortality over 15 years, but revealed that running 51 to ≥176min/week was not associated with additional benefits.[7] Similarly, the Copenhagen City Heart Study demonstrated that all-cause mortality was lower over 12 years among joggers exercising <60 min/week than in non-joggers.[1] More jogging (up to >240 min/week) was not associated with additional mortality benefits. These data suggest that higher doses of moderate intensity PA are related to larger health benefits, whereas PA beyond the lowest effective dose for high intensity exercise is not associated with further reduced mortality rates.

Potential harmful doses of PA

The curvilinear relationship between PA and health does not include an upper limit, but suggests that the reduction in risk for each increase in activity is smaller at higher doses. Recent studies suggest that a U- or J-shaped curve better reflects the association between PA dose and health.[1-4] In the Copenhagen study, all-cause mortality over 12 years was lower among light joggers (6.8%-vs-31.0%; HR=0.22, CI=0.10-0.47) and also was lower among moderate joggers (20.5%-vs-31.0%; HR=0.66, CI=0.32-1.38) compared to non-joggers, but no significant differences in mortality rates were observed between strenuous joggers (61.1%-vs-31.0%; HR=1.97, CI=0.48-8.14) and non-joggers.[1] However, there were few strenuous joggers (n=36) and strenuous joggers' deaths (n=2) in this study, and non-jogging controls were allowed to walk or bike <2 hours/week. These limitations may importantly influence study outcomes.

Similarly, participants of the Million Women Study performing daily strenuous PA had an incidence of cerebrovascular disease and venous thromboembolism over 9 years comparable to their inactive peers, while participants performing 2-3 sessions/week had a lower incidence of cerebrovascular disease and venous thromboembolism.[4] However, daily exercisers more frequently smoked (25.6%) compared to non-exercisers (24.8%), and 20.1% of daily exercisers reported a low socioeconomic status compared to 13.1% of individuals exercising 2-3 sessions/week.

Also, the National Runners and Walkers Studies demonstrated that the benefits of exercise were attenuated in cardiac patients who ran >7.1 km/day or walked >10.7 km/day. Patients exceeding these PA thresholds reported a mortality risk over 10.4 years that was similar to inactive survivors following MI.[2] Similarly, the German KAROLA-study found that cardiac patients who performed daily strenuous PA had a higher all-cause mortality rate over 8.1 years than patients exercising 2–4 sessions/week. The risk for cardiovascular mortality did not differ between patients exercising daily and 2-4 sessions/week.[3] In contrast, the patients with coronary heart disease who rarely exercised had a much higher all-cause and cardiovascular mortality risk compared to patients exercising 2-4 sessions/week.

These observations have important implications. First, high doses of strenuous or vigorous PA are not associated with increased mortality in healthy individuals, but may attenuate the health benefits associated with PA. Second, high doses of daily PA well above the PA recommendations are slightly but significantly associated with increased mortality risk in patients with cardiovascular disease.[3] Patients with cardiovascular disease are recommended to follow the ACC/AHA guidelines which prescribe 30 to 60 minutes of

moderate-intensity exercise, at 5 to 7 days/week, supplemented by an increase in daily lifestyle activities (e.g., walking at work, gardening, household work).[8] These PA doses are proven to be a powerful intervention for the prevention of future morbidity and mortality in cardiovascular patients.

Conclusions

There is no known upper limit for moderate intensity PA in healthy individuals, but doses >100 min/day do not appear to be associated with additional reductions in mortality rates.[5] For vigorous PA, low doses are related to large benefits, whereas doses up to 10x the recommended PA levels are not associated with further reductions in mortality rates[5-7] . Some studies suggest an attenuation of health benefits at higher PA doses, but methodological flaws may limit the validity of these observations[1,4]. No dose of vigorous PA causes higher mortality rates than physical inactivity. PA is one of the best modifiable factors for the prevention of non-communicable diseases and mortality, so it is important for clinicians to keep emphasizing that 'Exercise is Medicine'.

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Table 1: Overview of studies investigating the association between exercise dose and risk for morbidity or mortality

Study	Cohort characteristics	Follow-up time	Exercise dose	Exercise intensity	Absolute risks* *Exercise dose vs Inactive reference group*		Risk ratios
Copenhagen City Heart Study [1]	Danish joggers (N=1,098) and non-joggers (N=3,950)	12 years	<1 hour/week	Vigorous	All-cause mortality:	9.9% vs 31.0%	HR=0.32, CI 0.20-0.51
			>4 hours/week	Vigorous	All-cause mortality:	10.8% vs 31.0%	HR=0.35, CI 0.05-2.54
National Runners and Walkers Studies [2]	N=2,377 American heart attack survivors	10.4 years	8 to 13 min/day	Vigorous	Cardiovascular mortality:	19.0% vs 24.1%	HR 0.79, CI 0.58-1.05
			14 to 24 min/day	Moderate			
			38 to 51 min/day	Vigorous	Cardiovascular mortality:	8.9% vs 24.1%	HR 0.37, CI 0.19-0.66
			72 to 96 min/day	Moderate			
			>7.1 km/day	Vigorous	Cardiovascular mortality:	21.2% vs 24.1%	HR 0.88, CI 0.45-1.58
			>10.7 km/day	Moderate			
KAROLA-study [3]	N=1,038 German patients with coronary heart disease aged 30 – 70 years	8.1 years	0-1 session/week	N/A	All-cause mortality:	40% vs 7.5%#	HR=5.36, CI 3.26-8.81#
					Cardiovascular mortality:	28.3% vs 4.4%#	HR=6.40, CI 3.43-11.96#
			7 sessions/week	N/A	All-cause mortality:	13.3% vs 7.5%#	HR 1.78, CI 1.04-3.04#
					Cardiovascular mortality:	7.9% vs 4.4%#	HR 1.79, CI 0.89-3.60#
Million Women Study [4]	N=1,119,239 English and Scottish women aged 50 to 64 years	9 years	2-3 sessions/week	Vigorous	Coronary heart disease: Cerebrovascular disease: Venous thromboembolism:	4.4% vs 5.4% 1.6% vs 1.9% 1.3% vs 1.5%	HR 0.81, CI 0.79-0.83 HR 0.81, CI 0.78-0.84 HR 0.83, CI 0.79-0.87
			7 sessions/week	Vigorous	Coronary heart disease: Cerebrovascular disease: Venous thromboembolism:	4.8% vs 5.4% 1.9%-vs-1.9% 1.6%-vs-1.5%	HR 0.89, CI 0.84-0.93 HR 0.96, CI 0.89-1.04 HR 1.08, CI 0.99-1.17
MJ Health Management Institution study [5]	N=416,175 Taiwanese adults from the general population (≥ 20 years)	13 years	15 min/day	Moderate	All-cause mortality:	2.2% vs 2.5%	HR 0.86, CI 0.81-0.91
			63 min/day	Vigorous	All-cause mortality:	1.5% vs 2.5%	HR 0.60, CI 0.53-0.68
			88 min/day	Moderate	All-cause mortality:	1.7% vs 2.5%	HR 0.68, CI 0.62-0.75
National Cancer Institute Cohort Consortium study [6]	N=661,137 Pooled analyses of 6 population-based American and European prospective cohorts	14.2 years	<1x current PA recommendations	Moderate or vigorous	All-cause mortality:	17.4% vs 21.8%	HR 0.80, CI 0.78-0.82
			3-5x current PA recommendations	Moderate or vigorous	All-cause mortality:	13.3% vs 21.8%	HR 0.61, CI 0.59-0.62
			≥10x current PA recommendations	Moderate or vigorous	All-cause mortality:	15.0% vs 21.8%	HR 0.69 CI 0.59-0.78
Aerobics Center Longitudinal Study [7]	N=55,137 American adults from the general population (≥ 18 years)	15 years	5 to 10 min/day	Vigorous	All-cause mortality: Cardiovascular mortality:	4.7% vs 6.8% 1.2% vs 2.6%	HR 0.70, CI 0.58-0.85 HR 0.45, CI 0.31-0.66
			≥25 min/day	Vigorous	All-cause mortality: Cardiovascular mortality:	5.2% vs 6.8% 1.8% vs 2.6%	HR 0.77, CI 0.63-0.92 HR 0.67, CI 0.48-0.93

** This column demonstrates a comparison of the absolute risk for mortality or morbidity between a specific exercise dose group and the inactive control group of the referenced study.*
Absolute risks were estimated based on the group size, absolute number of deaths and provided hazard ratios.
#The KAROLA-study assigned an exercise dose of 2–4 sessions/week as the reference group for their statistical analyses.
N/A data not available