VIEWPOINT

Exercise Is Medicine At Any Dose?

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Supplemental content at jama.com

Physical inactivity has been labeled a pandemic due to its increasing global prevalence and its health, economic, environmental, and social consequences. More than half of US adults fail to meet the 2008 physical activity recommendations of 30 minutes of moderate-intensity exercise daily (eg, brisk walking, dancing, and gardening) or 75 minutes of vigorous-intensity exercise weekly (eg, running, fast cycling, and competitive sports). Hence, increasing physical activity 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 physical activity and the related health benefits. Many studies have demonstrated that physical activity 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 physical activity to prescribe in clinical practice. What dose of exercise is needed to promote health? Do larger doses elicit larger health benefits? What is the cutoff between the beneficial and possibly detrimental effects of exercise?

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Lowest Effective Dose

Several studies have assessed the minimum amount of physical activity needed to provide cardiovascular benefits. A large Taiwanese study demonstrated that individuals exercising 15 minutes a day at a moderate intensity had a reduced risk of all-cause mortality (eTable in the Supplement) and a 3-year longer estimated life expectancy compared with their inactive peers.[5] These data were reinforced by a pooled analysis of 6 US and European cohorts.[6] Individuals performing physical activity in doses below the physical activity recommendations had a reduced risk for mortality over 14.2 years compared with physically inactive peers. Runners participating in the Aerobics Center Longitudinal Study running only 5- to 10-minutes a 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 physical activity can have substantial health benefits. Although lack of time is a critical barrier to engaging in physical activity, these results[5,7] suggest that even the busiest individuals should have time for this lowest effective dose of physical activity.

Moderate to Highest Tolerable Dosage

Increasing from the minimum effective levels of moderate (15 minutes a day)[5] or vigorous intensity (8 minutes a day)[6,7] physical activity to the national physical activity guidelines of 30 minutes a day of moderate-intensity exercise or 75 minutes a week of vigorous-intensity exercise appears to be associated with increased health benefits. Every additional 15 minutes of moderate-intensity physical activity 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 minutes a day), with higher mortality reductions for vigorous-intensity vs moderate-intensity exercise.[5]

Similar findings were observed in US and European cohorts. Individuals performing physical activity at a dose of 3 to 5 times the current recommendations reported the lowest mortality rates over 14.2 years.[6] Higher physical activity doses, up to 10 times the recommended physical activity levels, were associated with mortality rates comparable with the 3 to 5 times group. In the National Walkers' and Runners' Health studies, cardiovascular mortality over 10.4 years was reduced among survivors of myocardial infarction who exercised 8 to 24 minutes a day compared with patients who exercised at lower doses.[2] The largest reduction in cardiovascular mortality was observed among patients who exercised 38 to 96 minutes a day. Data from the Cooper Institute confirmed that 7 minutes a day of high-intensity physical activity was associated with reduced cardiovascular mortality over 15 years, but revealed that running 51 to 176 minutes or more a 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 less than 60 minutes a week than in nonjoggers.[1] More jogging (up to >240 minutes/week) was not associated with additional mortality benefits. These data suggest that higher doses of moderate-intensity physical activity are related to larger health benefits, whereas physical activity beyond the

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lowest effective dose for high-intensity exercise is not associated with further reduced mortality rates.

Potential Harmful Doses of Physical Activity

The curvilinear relationship between physical activity 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 physical activity dose and health.[1-4] In the Copenhagen study, all-cause mortality over 12 years was lower among light joggers (6.8% for light joggers vs 31.0% for nonjoggers; HR, 0.22 [95% CI, 0.10-0.47]) and also was lower among moderate joggers (20.5% for moderate joggers vs 31.0% for nonjoggers; HR, 0.66 [95% CI, 0.32-1.38]) compared with nonjoggers, but no significant differences in mortality rates were observed between high-intensity joggers (defined as those exercising >3 times weekly for >4 hours at a fast pace) and nonjoggers (61.1% for high-intensity joggers vs 31.0% for nonjoggers; HR, 1.97 [95% CI, 0.48-8.14]).[1] However, there were few high-intensity joggers (n = 36) and high-intensity joggers' deaths (n = 2) in this study, and nonjogging controls were allowed to walk or bike less than 2 hours a week. These limitations likely influenced study outcomes.

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

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

These observations have important implications. First, high doses of strenuous or vigorous physical activity are not associated with increased mortality in healthy individuals, but may attenuate the health benefits associated with physical activity. Second, high doses of daily physical activity well above the physical activity 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 American College of Cardiology and American Heart Association guidelines, which prescribe 30 to 60 minutes of moderate-intensity exercise 5 to 7 days a week, supplemented by an increase in daily lifestyle activities (eg, walking at work, gardening, and household work).[8] These physical activity doses are proven to be an effective intervention for the prevention of future morbidity and mortality in patients with cardiovascular disease.

Conclusions

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

ARTICLE INFORMATION

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Thompson reports receiving research grants from the National Institutes of Health, Genomas, Aventis, Regeneron, and Sanofi; serving as a consultant for AstraZeneca, Regeneron, Merck, Genomas, Abbott, Sanofi, and Pfizer; receiving speaker honoraria from Merck and AstraZeneca: owning stock in General Electric, JA Wiley Publishing, Johnson & Johnson, Abbvie, and Abbott. No other disclosures were reported.

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Supplementary Online Content

Eijsvogels TMH, Thompson PD. Exercise is medicine: at any dose? *JAMA*.
doi:10.1001/jama.2015.10858.

eTable. Overview of Studies Investigating the Association Between Exercise Dose and Risk of Morbidity or Mortality

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

Study	Cohort characteristics	Follow-up time	Exercise dose	Exercise intensity#	Absolute risks for Exercise Dose vs Inactive reference group*	Risk ratios
Copenhagen City Heart Study [1]	Danish joggers (N=1098) and nonjoggers (N=3950)	12 y	<1 hour/wk	Vigorous	All-cause mortality: 9.9% vs 31.0%	HR=0.32, CI 0.20-0.51
			>4 hours/wk	Vigorous	All-cause mortality: 10.8% vs 31.0%	HR=0.35, CI 0.05-2.54
National Runners and Walkers Studies [2]	N=2377 US survivors of myocardial infarction	10.4 y	8 to 13 min/d	Vigorous	Cardiovascular mortality: 19.0% vs 24.1%	HR 0.79, CI 0.58-1.05
			14 to 24 min/d	Moderate		
			38 to 51 min/d	Vigorous	Cardiovascular mortality: 8.9% vs 24.1%	HR 0.37, CI 0.19-0.66
			72 to 96 min/d	Moderate		
			>7.1 km/d	Vigorous	Cardiovascular mortality: 21.2% vs 24.1%	HR 0.88, CI 0.45-1.58
			>10.7 km/d	Moderate		
KAROLA-study [3]	N=1038 German patients with coronary heart disease aged 30 – 70 y	8.1 y	0-1 session/wk	N/A	All-cause mortality: 40% vs 7.5%# Cardiovascular mortality: 28.3% vs 4.4%#	HR=5.36, CI 3.26-8.81# HR=6.40, CI 3.43-11.96#
			7 sessions/wk	N/A	All-cause mortality: 13.3% vs 7.5%# Cardiovascular mortality: 7.9% vs 4.4%#	HR 1.78, CI 1.04-3.04# HR 1.79, CI 0.89-3.60#
Million Women Study [4]	N=1 119 239 English and Scottish women aged 50 – 64 y	9 y	2-3 sessions/wk	Vigorous	Coronary heart disease: 4.4% vs 5.4% Cerebrovascular disease: 1.6% vs 1.9% Venous thromboembolism: 1.3% vs 1.5%	RR 0.81, CI 0.79-0.83 RR 0.81, CI 0.78-0.84 RR 0.83, CI 0.79-0.87
			7 sessions/wk	Vigorous	Coronary heart disease: 4.8% vs 5.4% Cerebrovascular disease: 1.9%-vs-1.9% Venous thromboembolism: 1.6%-vs-1.5%	RR 0.89, CI 0.84-0.93 RR 0.96, CI 0.89-1.04 RR 1.08, CI 0.99-1.17
MJ Health Management Institution study [5]	N=416 175 Taiwanese adults from the general population (≥ 20 y)	13 y	15 min/d	Moderate	All-cause mortality: 2.2% vs 2.5%	HR 0.86, CI 0.81-0.91
			63 min/d	Vigorous	All-cause mortality: 1.5% vs	HR 0.60, CI 0.53-0.68

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						2.5%	
			88 min/d	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 y	<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 y	5 to 10 min/d	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/d	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

Abbreviation: N/A, data not available, PA, physical activity
 # Moderate intensity exercise includes activities with a Metabolic Equivalent of Task (MET) score between 3.0 and 5.9. Examples of moderate intensity activities include brisk walking (>3 miles/h), bicycling (<10 miles/h), doubles tennis or ballroom dancing. Vigorous intensity exercise includes activities with a MET score larger than 6.0. Examples of vigorous intensity activities include uphill walking or race walking, bicycling (>10 miles/h), running, jogging, singles tennis and aerobic dancing.
** 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

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