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REVIEW

Prevention and epidemiology

Personalized exercise dose prescription

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Physical activity (PA) is associated with increased longevity and decreased risk of cardiovascular disease, however, the majority of the general population is still sedentary. In order to maximize the health benefits of PA, health care practitioners should be familiarized with the appropriate dose of exercise for each healthy individual, depending on their habitual PA and relative fitness. The aim of this review is to quantitatively describe the lowest and the highest level of exercise that has health benefits, and what should hypothetically be considered 'the sweet spot'. Analysis of the current literature allows us to develop personalized 'exercise prescription' for healthy individuals.

Keywords Physical activity • Exercise prescription • Cardiovascular disease

> If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.
>
> -Hippocrates (400 B.C.)

Introduction

Physical inactivity is an important independent risk factor for cardiovascular (CV) disease (CVD), and correcting sedentary lifestyles is a convenient therapy physicians can prescribe to their patients.[1]

European Guidelines on Cardiovascular Disease Prevention in clinical practice 2016 as well as guidelines released by the US government in 2008 and by the World Health Organization (WHO) in 2010 recommend 150 min of moderate physical activity (PA) per week or 75 min of vigorous-intensity aerobic exercise, or equivalent combination of both[2,3] in order to achieve longevity benefits.[4] Despite the accessibility of information and awareness of the health benefits of exercise, 60% of the US population fails to engage in PA on a regular basis.[5] With the ease of accessibility of information in the modern world, it is unlikely that the epidemic of sedentary lifestyle would result from unawareness of PA-related health benefits. More likely, current recommendations for PA are set too high for most of the general population.[6] Simplification of current PA recommendations is necessary to motivate the general population to engage in PA.

Despite the fact that different studies have focused on different health outcomes, they have demonstrated similar trends in achieving various health benefits with lower amounts of PA than currently recommended.[7,8] Decreased risk of premature all-cause mortality as well as decreased risk of CVD mortality and lower incidence of CVD are only some of major health benefits demonstrated with lower levels of PA than currently recommended. Setting lower standards for PA intensity may motivate sedentary individuals to start exercising.

On the other end of the exercise–health benefits relationship, the point at which PA may exert a detrimental effect on overall health, has not been established by guidelines. The debate over whether more exercise necessarily leads to greater health benefits and the upper limit of these health benefits is ongoing. Nevertheless, when adjusted for total amount of PA, it is becoming apparent that within limits, vigorous exercise offers a more beneficial profile for cardioprotection than moderate-intensity exercise.[9]

The focus of this review is to evaluate studies that examine the quantity of exercise and its longevity benefits to answer several questions: what is the lowest level of exercise that has health benefits, what is the highest level of exercise that still improves health and what would be 'the sweet spot' for exercise in order to achieve maximal health benefits. Furthermore, evaluation of the current literature will provide hypothetical 'exercise prescription' for healthy individuals depending on their relative fitness levels.

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Methods

For the purpose of this review, PubMed database was electronically searched using the following terms individually and with MESH conjunctions 'AND' and 'OR': 'physical activity', 'exercise', 'exercise prescription', 'cardiovascular disease' and 'cardiovascular fitness'. The reference lists of the included studies were also searched for the relevant studies not found during the initial search. Inclusion criteria for subjects were: human subjects, age between 18 and 100 years, healthy subjects (not diagnosed with medical disease, such as coronary disease, cancer or other chronic medical condition) and publication date after the Global recommendations on PA from WHO were published in 2007. Additionally, few relevant studies published before 2007 were included in the analysis. Animal studies as well as studies written in languages other than English were excluded from the analysis. *Table 1* lists all studies that met search criteria and that were included in the proposed, hypothetical personalized exercise prescription summarized in *Table 2*. Studies included were epidemiological, and subjects reported their level of PA through standardized questionnaires. Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure more than at rest and can be quantified as absolute or relative. Absolute PA is defined by the amount of energy expended per minute of activity and is expressed in metabolic equivalent (MET) or oxygen uptake per time unit (mL/min)—peak oxygen uptake (VO_2peak). The MET is an estimate of energy expenditure while sitting at rest and corresponds to 3.5 mL O_2/kg/min.[4] Measurement of VO_2peak is the strongest determinant of cardiorespiratory fitness (CRF), which is defined as the maximal amount of oxygen (O_2) that can be taken in, transported to and utilized by the working tissue during dynamically strenuous exercise involving large muscle mass.[20] Relative CRF level is based on a person's own perception of his or her exertion. This should be assessed during each clinical encounter and is related to the level of effort required to perform an activity which can be expressed as an index of individual rate of effort called the rating of perceived exertion (RPE) or frequency of breathing (Talk test).[4] For the purpose of our review article, we grouped relative CRF levels in four main categories: 1st CRF category is the sedentary population, not engaged in any PA, 2nd CRF category is the population that reports being somewhat active [walking to/from work/occasionally engaged in exercise or leisure time PA (LTPA)], 3rd CRF group is engaged in guidelines-recommended level of PA, and 4th CRF group are athletes and professional sport's players. Leisure time PA includes sports, conditioning exercises, and household tasks (gardening, cleaning, and home repair). Exercise PA is a planned, structured, and repetitive type of PA, with the goal to improve or maintain VO_2peak (CRF). It is typically assessed by frequency, intensity, time, and type of exercise (FITT proposition): Frequency stands for the number of times the PA is performed; Intensity is defined as magnitude of the effort required to perform an activity; Time is duration of the PA and Type of PA is generally divided into aerobic (or cardio) PA and resistance PA (strength training).[21] The total volume of PA is the overall amount of energy expended during exercise, over a period of time, usually expressed as kilocalories (kcal)/week or MET-h/week.

Results

How much is enough? Lowest beneficial level of exercise. Total volume or *energy expenditure*

From the health care provider perspective, it is important to address the type of PA that patients enjoy and provide patients with examples of PA in their daily routine (such as housework, walking to and from work, climbing the stairs instead of using an elevator). For practical application of preventive medicine in terms of patient motivation for exercise, we need to know how much exercise we should prescribe to each healthy individual.[6,22]

The current guidelines recommend 150 min/week of moderate intensity PA (3–6 METs) or 75 min of vigorous intensity PA (>6 METs) which is equivalent to ~1000 kcal/week or ~10–11 MET-h/week. This level of energy expenditure has been shown to decrease premature mortality overall by 20–32%.[7,23] Interestingly, recent studies have shown that a lesser amount of PA than is currently recommended can still have significant health benefits.[7,14,15] For example, even moderate PA for a total of 200–600 kcal/week (half of the currently recommended 1000 kcal/week or 10 MET-h/week) is associated with a decrease in CVD events by 27%.[16] Expenditure of 500–999 kcal/week, (10 MET-h/week)[5] was shown to be related to decreased risk of coronary heart disease (CHD). Recently, Lee *et al.*[8] have shown that even ≤8.4 MET-h/week of PA decreases CVD mortality by 52%. Physical activity of only 0.1 to ≤7.5 MET-h/week was shown to be related to 20% lower mortality risk.

How long and how frequently should one exercise?

Most exercise-dose studies are observational studies that use questionnaires to assess an individual's level of PA; self-reported PA is subjective and can lead to measurement errors and, often, overestimation of PA. Therefore, the benefits of exercise may be underestimated by this method, leading to potentially significant health benefits of lower than reported levels of exercise.[24]

Less than half the currently recommended PA (75 min of brisk walking per week) is associated with a 1.8 year gain in life expectancy after age 40 compared to a sedentary lifestyle (relative CRF group 1, *Table 2*).[11] Two large studies, Women's Health Study and Nurse's Health Study II have associated LTPA (≥3 MET), such as brisk walking for only 1 h per week (10 min/day on most days of the week), with a 20–50% reduction in CHD risk.[17,25] These studies have shown a positive correlation between duration of walking and degree of reduction in CHD and all-cause mortality risk. However, this relationship is not linear, but instead curves up to 100 min a day, after which additional minutes of exercise afford no extra health benefits.

The Nord-Trøndelag Health Study (HUNT), reported, that only a single bout of high-intensity exercise per week reduced the risk of CVD death by 39% in men and 51% in women.[26] Running only 5–10 min per day or less than 60 min per week was shown to decrease CVD mortality by 38% and all-cause mortality by 28%.[8] While this study showed no significant trend for linearity of the dose–response relationship between exercise and longevity, another study[7] revealed a curvilinear relationship and maximal health benefits with 85 min of moderate or 55 min of vigorous exercise per week; both have shown significant health benefits for half the time of PA than currently recommended.

Regarding the frequency of exercise, several studies suggest shorter bouts of exercise fewer times per week,[7,14] while other studies have found no difference between short bouts of exercise and longer sessions in lowering CHD risk.[27]

Sedentary population (Relative CRF Category 1 in *Table 2*) should be guided, to begin with 15 min of daily walking or 30 min 3 times per

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Table 1 Summary of the studies cited and included in the review

Study	Study type	Number of subjects	Age/gender	Follow up	Intensity of PA	Results/outcomes
Lee *et al.*[25]	Cohort	39 372, from Women's Health Study	Age >45 year/ female	Average 5 years	All intensity, from walking to vigorous exercise	Duration of PA: 1 h/week walking 14% lower risk of CHD, 1–1.5 h 50% lower risk of CHD, >2 h/week 52% lower risk of CHD, Intensity: <2 mph (3.2 km/h) 44% lower risk of CHD, 2.0–2.9 mph (3.2–4.7 km/h) 29% lower risk of CHD and 3 mph (4.8 km/h) 48% lower risk of CHD
Manson *et al.*[18]	Cohort	72 488 women	40–65 year old/ female	8 years	Four quintile group for total PA score expressed as MET-hours per week	Duration: 1–2.9 h/week of walking at > 3 mph associated with 30% decrease in coronary events, 3 or more h/week of walking at the same (brisk) pace associated with 35% decrease in coronary events. Intensity: walking 2–2.9 mph decreases risk of coronary events by 25% and brisk walk >3 mph decreases risk of coronary events by 36%
Arem *et al.*[15]	Cohort	661 137 men and women	Age 21–98 year/ 56% women		Leisure time moderate-to-vigorous exercise	20% lower mortality risk with aerobic PA less then recommended, (0–7.5 MET h/week), 31% lower mortality risk at 1–2 x the recommended minimum of aerobic PA (7.5–15 MET h/week), 37% lower mortality risk at 2–3 × the recommended minimum of aerobic PA (15–22 MET h/ week) and the gold spot of 39% lower mortality risk at 3–5 × the recommended minimum aerobic PA (22.5–40 MET h/week). No higher mortality risk with PA levels as high as 10 times the recommended minimum
Moore *et al.*[11]	Cohort	654 827, National Cancer Institute Cohort Consortium	21–90 year/56% women	10 years	All intensities	PA level of 0.1–3.74 MET-h/ week (equivalent of brisk walking up to 75 min/week) was associated with a gain of 1.8 year in life expectancy relative to no PA. WHO recommended minimum of PA of 7.5–14.9 MET-h/week (equivalent to 150–299 min of brisk walking per week)- the gain in life expectancy was 3.4 year. Two times the minimum recommended level 15–22.4

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Table 1 Continued

Study	Study type	Number of subjects	Age/gender	Follow up	Intensity of PA	Results/outcomes
						MET-h/week (equivalent of brisk walking for 300–449 min/week) the gain in life expectancy was 4.2 year. Highest level of 22.5+ MET-h/week was associated with a gain of 4.5 year in life expectancy
Armstrong *et al.*[12]	Cohort	The Million Women Study	1.3 million women ages 50–64 year	9 years	Frequency of moderate and vigorous exercise (walking, gardening, cycling, housework and strenuous exercise)	Strenuous PA 2–3 times per week was associated with 19% lower risk of CHD, while strenuous PA 4–6 times per week was associated with 20% lower risk of CHD. Risk of CHD was significantly increased in women reporting daily strenuous PA in comparison to those reporting 2–3 times per week
Schnohr *et al.*[14]	Cohort	Copenhagen City Heart Study	Age 20–93 year (1098 healthy joggers and 3950 healthy non-joggers)/ 5048 men and women	12 years	Light vs. moderate vs. strenuous exercise compared to sedentary group	Duration of PA: jogging 1–2.4 h per week was associated with 69% lower risk all-cause mortality compared to sedentary subjects, frequency: 2–3 times per week of jogging was associated with 68% lower risk of mortality compared to sedentary group. Light joggers had 78% lower mortality and moderate joggers had 34% lower mortality compared to sedentary group while strenuous joggers had no difference in a mortality rate from that of the sedentary group
Rahman *et al.*[38]	Cohort	Cohort of Swedish Men (COSM)	33 012 men, average age 60	13 years	Level of activity at work, housework, walking/bicycling, and exercise	Walking/bicycling >20 min/day was associated with 21% risk reduction of incidence HF compared to sedentary group. U-shape association between TPA and HF risk was detected with both extremely high and extremely low levels of TPA associated with an increased risk of HF
Sesso *et al.*[5]	Cohort	Harvard Alumni Study, 17 835 men	Average age 57.7 (range 39–88 years)	166 410 person-years	The type and intensity of PA, Light (MET <4), moderate (4–6 METs), and vigorous (>6 METs)	L-shaped association between increasing levels of PA and the risk of CHD in the age-adjusted model. PA level of energy expenditure of 4200 kJ/week was associated with 20% reduction in CHD

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Table 1 *Continued*

Study	Study type	Number of subjects	Age/gender	Follow up	Intensity of PA	Results/outcomes
						risk. Those expending 2100–4200 kJ/week in total PA (lower than recommendations) had possible (nonsignificant) 10% reduction in risk of CHF
Lee *et al.*[8]	Cohort	55 137 subjects	Average age 44 (18–100 years)	15 years	Running	Runners who run less than is currently recommended, (<51 min/week, or 5–10 min/day, slow speed <6 mph) had lower risk of CV (55%) and all-cause mortality (31%) compared to non-runners. Mortality benefits were similar between lower and higher doses of weekly running time
Wen *et al.*[7]	Cohort	416 175 individuals	199 265 men and 216 910 women	Average 8 years	Four intensity categories: light (walking), moderate (brisk walking), medium-vigorous (jogging) high-vigorous (running)	90 min/week of PA of 4 MET intensity (4.6 MET-h/week) has 14% risk reduction of all-cause mortality and 3 years longer life expectancy, 200 min/week of PA of 3.7 MET intensity (12 MET-h/week) has 20% risk reduction of all-cause mortality, 361 min/week of PA of 4.1 MET intensity (22MET-h/week) has 29% risk reduction of all-cause mortality, 523 min/week of PA of 5 MET intensity (40.7 MET-h/week) has 35% risk reduction of all-cause mortality
Gebel *et al.*[9]	Cohort	204 542 adults	Age 45–75, 55.2% were women	1 444 927 person-years	Different proportions of total MVPA as vigorous activity. PA was measured with the Active Australia Survey	10–140 min/week of MVPA was associated with 34% risk reduction for all-cause mortality, 150–299 min/week of MVPA was associated with 47% risk reduction for all-cause mortality while 300 min/week was associated with 54% risk reduction for all-cause mortality compared with no MVPA

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Table 2 **Individualized exercise prescription**

Relative CRF category (self-reported)			1—Sedentary		2—Somewhat active		3—Active/fit		4—Engaged in Sports
Goals of total PA (MET-h/week)			0–7.4		7.5–15		16–40		Above 40
Absolute PA intensity	**Light, less than 3 METs (walking)**	Speed (mph)	2–2.9[10]		N/A		N/A		N/A
		Duration (min/week)	75–90		N/A		N/A		N/A
		Frequency (times per week)	3		N/A		N/A		N/A
	Moderate, 3–5.9 METs (brisk walking)	Speed (mph)	3–4[8]	→ After 6–8 weeks →	3–4	→ After 6–8 weeks →	3–4	→ NO add. benefits →	N/A
		Duration (min/week)	75–90[11]		150–299		300–750		N/A
		Frequency (times per week)	3 or daily[10]		3–5		5–7		N/A
	Transition		**↓ AFTER 6–8 weeks ↓**		**↓ After 6–8 weeks ↓**		**↓ After 6–8 weeks ↓**		**↓ No add. benefits ↓**
	Vigorous, 6–12 METs (running)	Speed (mph)	5–6[8]		7.–7.5[12]		8[12]		8[7]
		Duration (min/week)	35–70[7]		75		150–375[9,12]		↑700
		Frequency (times per week)	1–2[8,13]		2–3[13,14]		4–6[9,13]		Daily
Potential health benefits			14–28% lower premature all-mortality risk[7,8,15], 15–27% lower risk of CAD[5,7,16–18], 1.8–2.5 year gain in life expectancy[7,11]		20–32% lower premature all-mortality risk[7,8,15,19], 21–32% lower risk of CAD[5,7,13,16–18], 3.4–4.2 year gain in life expectancy[7,11]		29–47% lower premature all-mortality risk[7,9,14,15], 27–44% lower risk of CAD[5,7,13,16–18], 4.2–4.5 year gain in life expectancy[12,18]		No additional health benefits after 40 MET-h/week[5,7,15,13]

Relative CRF Category 1, Sedentary:	Not engaged in any PA
Relative CRF Category 2, Somewhat active:	Walking to/from work and occasionally engaged in exercise or LTPA
Relative CRF Category 3, Active fit:	Engaged in guidelines-recommended level of PA
Relative CRF Category 4, Engaged in Sports:	Athletes and professional sport's players

CAD, coronary artery disease; CRF, cardiorespiratory fitness; LTPA, leisure time physical activity; MET, metabolic equivalents; N/A, not applicable; PA, physical activity.

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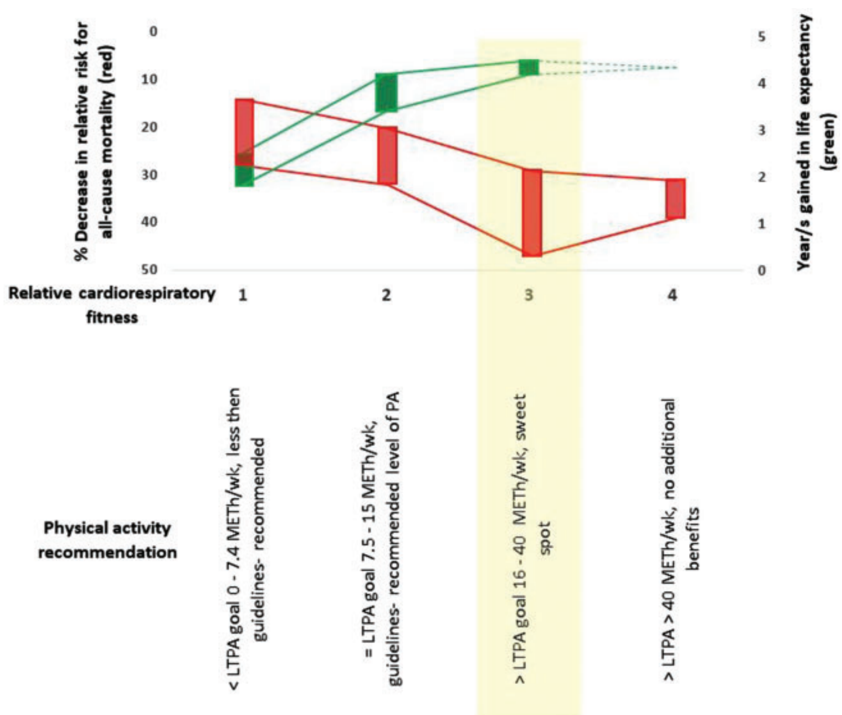

Take-home figure Relationship between different levels of physical activity suggested for each relative cardiorespiratory fitness category (1–4) on X axis, and percentage decrease in relative risk for all-cause mortality (red) on Y1 axis and year/(s) of gain in life expectancy (green) on Y2 axis. The bars represent the range in reduction of all-cause mortality relative risk (red bars) and the range in year(s) of gain in life expectancy (green bars) of the cited studies. Doted green lines between relative cardiorespiratory fitness Categories 3 and 4 represent supposedly unchanged life expectancy with additional exercise (>40 MET-h/week) above already achieved benefits with exercise level of 16–40 MET-h/week. LTPA, leisure time physical activity; relative cardiorespiratory fitness Category 1; not engaged in any physical activity; relative cardiorespiratory fitness Category 2, walking to/from work and occasionally engaged in exercise or leisure time physical activity; relative cardiorespiratory fitness Category 3, engaged in guidelines-recommended level of physical activity; relative cardiorespiratory fitness Category 4, athletes and professional sport's players. MET, metabolic equivalent.

week. After 6–8 weeks[10] of this exercise prescription (or longer depending on the individual's fitness and overall health), a more vigorous exercise regimen can be introduced such as 35–70 min of jogging per week divided into 2–3 sessions per week or 5–10 min of jogging per day. Applying this gradual approach,[10] the goal should be to motivate beginners to start with habitual exercise and then to progress toward either more effective-higher intensity exercise or towards the next level (toward relative CRF Category 2) to meet current recommendations (*Table 2*). If the sedentary population is instructed to start with half of the exercise currently recommended, it is more likely that they will not be discouraged from incorporating exercise into their weekly routine.[6] Moreover, positive changes in exercise habits in middle adulthood or later has been shown to reduce the risk of coronary events when compared to individuals who remain sedentary.[18]

At what pace should one walk/run?

When it comes to minimum intensity of exercise required to gain health benefits, it is important to distinguish between various types of aerobic exercise (e.g. walking, running, cycling) in order to create a personalized exercise prescription. Lee *et al.*[28] reported an inverse relationship between self-reported relative intensity of PA and risk of CHD in older individuals (mean age 66 years) that have not fulfilled the current recommended activity level of 1000 kcal/week. This indicates that health benefits in the older population can be achieved with less than the currently recommended amount of PA. According to current guidelines, a combination of moderate-intensity (3–6 METs) and vigorous-intensity (>6 METs) exercise should be used in order to achieve health benefits where 2 min of moderate-intensity exercise equals 1 min of vigorous-intensity exercise.[2] However, this substitution has been called into question as vigorous activity appears to be more beneficial than moderate-intensity level of exercise at the same total energy expenditure.[9] The Aerobic Center Longitudinal Study (ACLS) used the maximal treadmill exercise test to measure CRF (VO_2peak, and found an inverse relationship between CRF and all-cause mortality.[29] Higher level of CRF (measured by VO_2peak) has shown to be protective against CV and all-cause mortality.[30] The HUNT study showed that vigorous-intensity exercise (80–90% of VO_2peak) is associated with higher VO_2peak than moderate-intensity exercise, and a similar observation came from recent meta-analysis showing that higher exercise intensity caused greater improvement in VO_2peak.[31] Vigorous-intensity training can be

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prescribed to individuals who are in relative CRF Category 1 (*Table 2*) only if they have already engaged in moderate-intensity exercise for at least 6–8 weeks.[10] Individuals at CRF Level 2 who are somewhat active (e.g. transportational walking, cycling), but still not meeting current recommendations,[2] should be encouraged to engage in LTPA to meet recommendations in order to enhance their health benefits from PA. The majority of sedentary people are resistant to engage in exercise due to fear of injury or false perceptions that vigorous exercise is the only efficient method of achieving health benefits. Among this group of people, (CRF Category 1, *Table 2*) implementation of light-to-moderate activity will decrease their relative risk (RR) of coronary disease by 15%,[18] and more importantly, through graded exercise transition toward higher fitness levels, help them obtain even more health benefits.

Brisk walking is a moderate-intensity exercise that has been shown to have significant health benefits and is the most frequently reported type of PA in the general population.[18,19,32]

When counselling patients about PA, benefits of LTPA should be emphasized. Various daily activities such as housework, gardening, yard work, dancing, and even occupational work can account for a significant amount of the current PA recommendations for CV health benefits. Jogging at 5 mph (6 METs) for 1–2.4 h/week[14] meets current recommendations and should be advised for individuals in relative CRF Category 2 (*Table 2*).

Is there an upper limit for exercise with health benefits?

Can 'The dose makes the poison' be applied to level of PA prescribed by clinicians? If we view the recommendation of a lifestyle change as a free-of-charge prescription, it is imperative that the dose-response question be addressed.

Multiple health benefits, lower rates of disability, and higher life expectancy[33–35] are related to a moderate level of exercise. Extreme endurance and competitive sports involve a much higher level of exercise than current guidelines recommend with questionable additional health benefits.[36] Professional athletes often expend 200–300 MET-h/week while training for and competing in these extreme sporting events. This level of energy expenditure is 10-fold greater than the current recommended dose of exercise.[34] Whether the dose-response relationship between exercise level and health benefits is curvilinear,[7,16] U-shaped, or reversed J shape[14,37,38] is still up for debate according to the literature. One group of published data poses numerical suggestions for the upper limit of exercise-related health benefits, after which health benefits plateau or even decline health effects could be attributed to exercise.[5,7,37] In COSM study total PA of more than 46 MET-h/day was associated with increased incidence of heart failure.[38] Earlier data[16,25] showed an inverse linear relationship between the amount of exercise and the risk of CVD. Compared to a sedentary group (<200 kcal/week), Mora *et al.*[16] found a RR reduction associated with 200–599, 600–1499, and ≥1500 kcal/week (27%, 32%, and 41%, respectively) suggesting more energy expenditure than currently recommended (1000 kcal/week) has an even better CV impact and this level would fit in our 'sweet spot' (*Take-home figure*). Arem *et al.*[15] showed performing 10 or more times the recommended minimum of ≥75 MET-h/week had no elevated mortality risk, but had a lower risk reduction in all-cause mortality when compared to individuals engaged in a moderate amount of PA. The longevity benefit threshold was approximately three to five times the recommended PA minimum (22.5 to ≤40 MET-h/week), beyond which there was no additional benefit. Studies with a maximum of 21.7[18] and 25[7] MET-h/week observed an inverse linear relationship between exercise and mortality, with the highest reported level of exercise being within our proposed 'sweet spot' (22.5 to ≤40 MET-h/week). These studies fell at the bottom of the J/U-shaped curve when a wider range of exercise levels was analyzed.[15]

In terms of frequency of exercise, 6 days a week of 1-h sessions of vigorous exercise would probably be an upper limit for exercise-related health benefits.[13]

What is the sweet spot?

Walking, running, cycling

Brisk walking is the best option for the sedentary population who are at risk of falls and joint injuries but are motivated to engage in exercise and need graded approach toward more vigorous PA. For fitness levels 1 and 2, the optimal duration of walking is at least 3–5 h per week[18] at ≥3 mph. To maximize their health benefits, individuals at relative CRF Level 3 should engage in longer bouts of brisk walking such as 7–12 h/week, (basically 1–2 h daily). Due to the time-consuming nature of walking, individuals in relative CRF Category 3 of PA (*Table 2*) should consider alternatives such as running to achieve the goal of 16–40 MET-h/week.

Twenty minutes of cycling (~3.6 METs) per day,[38] at 10–12 mph[1] has been proven to be beneficial for CV, and overall health 230 min/week of cycling was shown to decrease premature mortality risk by 21%.[19]

Vigorous PA is more effective at lowering blood pressure and improving lipid and anti-inflammatory profiles in diabetes mellitus.[39,40] It is less time consuming and more efficient in achieving longevity than moderate exercise is a perfect solution for those having time constraints.

In the exercise prescription, individuals who already meet current recommendations of PA (relative CRF Category 3, *Table 2*) should increase their exercise and aim for 'the sweet spot'. Running 2.5–5 h at a speed of 7–8 mph, four to six times per week[12] sounds demanding but will decrease CVD and premature all-cause mortality risk by 30–40% and add 4.5 years of life.

Although resistance training regimens and health benefits are not the main focus of this review, we found it important to mention its role in preventive medicine. Reduction of resting blood pressure and low-density lipoprotein cholesterol and increase in high-density cholesterol are some of its benefits.[41] It is known that resistance training reduces bone loss, enhances muscle mass, and is recommended as a part of exercise program for osteoporosis prevention and treatment.[4]

Conclusion

Taken together, there is no universal exercise prescription although hypothetically, general guidelines can be developed for all levels of CRF. An individualized approach in terms of a patient's CRF and health/disease status, on one side, and exercise type and dosage, on the other side, needs to be considered. Sedentary individuals will

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benefit from moderate PA in less than currently recommended dosages if they exercise daily. Advising sedentary, healthy individuals to participate in less than the currently recommended level of PA, and highlighting longevity benefits of only 15–30 min of brisk walking three times per week, can motivate more people to engage in PA. On the other hand, for active and fit healthy individuals, jogging and running will improve their longevity to a greater extent than moderate-intensity PA. These individuals should be encouraged to participate in more than currently recommended level of exercise to achieve the 'sweet spot' of the U-shaped curve.[9] Overall 16 to <40 MET-h/week of total PA appears to be the most efficient prescription for this population.

Limitations

This review is based on epidemiological studies that evaluated the effects of a broad spectrum of exercise levels on the health outcomes in healthy populations. In most of the studies, subjects reported their exercise levels using questionnaires and investigators quantified their PA as 'moderate' or 'vigorous' and assigned them appropriate METs. Multiple factors can affect the absolute intensity of someone's PA (CRF level and motivation).[42] Therefore, epidemiological studies provide general information of the PA effects on health outcomes. Another limitation of epidemiological studies is selection bias, meaning that individuals who participate in exercise studies tend to have healthier lifestyle compared to individuals who do not participate. Randomized Clinical Trials of exercise intensity, duration, and frequency on premature all-cause mortality and CVD mortality are needed to address the relationship between exact levels of PA and potential morbidity-prevention benefits. Finally, this manuscript mainly focuses on aerobic exercise and not resistance exercise regimen. However, realizing that muscular strength is also strongly related to CVD risk factors and prognosis and may be important in elderly patients, some resistance exercise is certainly ideally combined with aerobic exercise training.[43]

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