

7-2017

Running as a Key Lifestyle Medicine for Longevity

Duck-Chul Lee

Iowa State University, dcllee@iastate.edu

Angelique G. Brellenthin

Iowa State University, abrellen@iastate.edu

Paul D. Thompson

Hartford Hospital

Xuemei Sui

University of South Carolina - Columbia

I-Min Lee

Harvard Medical School

See next page for additional authors

Follow this and additional works at: https://lib.dr.iastate.edu/kin_pubs



Part of the [Cardiovascular Diseases Commons](#), [Exercise Science Commons](#), and the [Expeditionary Education Commons](#)

The complete bibliographic information for this item can be found at https://lib.dr.iastate.edu/kin_pubs/82. For information on how to cite this item, please visit <http://lib.dr.iastate.edu/howtocite.html>.

This Article is brought to you for free and open access by the Kinesiology at Iowa State University Digital Repository. It has been accepted for inclusion in Kinesiology Publications by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

Running as a Key Lifestyle Medicine for Longevity

Abstract

Running is a popular and convenient leisure-time physical activity (PA) with a significant impact on longevity. In general, runners have a 25%–40% reduced risk of premature mortality and live approximately 3 years longer than non-runners. Recently, specific questions have emerged regarding the extent of the health benefits of running versus other types of PA, and perhaps more critically, whether there are diminishing returns on health and mortality outcomes with higher amounts of running. This review details the findings surrounding the impact of running on various health outcomes and premature mortality, highlights plausible underlying mechanisms linking running with chronic disease prevention and longevity, identifies the estimated additional life expectancy among runners and other active individuals, and discusses whether there is adequate evidence to suggest that longevity benefits are attenuated with higher doses of running.

Keywords

Running, Physical activity, Exercise, Mortality, Cardiovascular disease

Disciplines

Cardiovascular Diseases | Exercise Science | Expeditionary Education | Kinesiology

Comments

This accepted article is published as 82. Lee DC, Brellenthin AG, Thompson PD, Sui X, Lee IM, Lavie CJ. Running as a key lifestyle medicine for longevity. *Prog Cardiovasc Dis*. 2017;60(1):45-55. DOI: [10.1016/j.pcad.2017.03.005](https://doi.org/10.1016/j.pcad.2017.03.005). Posted with permission.

Authors

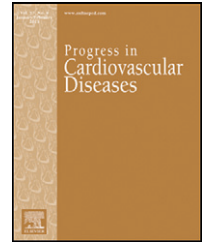
Duck-Chul Lee, Angelique G. Brellenthin, Paul D. Thompson, Xuemei Sui, I-Min Lee, and Carl J. Lavie



Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com



Running as a Key Lifestyle Medicine for Longevity



Duck-chul Lee^{a,*}, Angelique G. Brellenthin^a, Paul D. Thompson^b, Xuemei Sui^c, I-Min Lee^d, Carl J. Lavie^e

^aDepartment of Kinesiology, College of Human Sciences, Iowa State University, Ames, IA

^bDepartment of Cardiology, Hartford Hospital, Hartford, CT

^cDepartment of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC

^dBrigham and Women's Hospital, Harvard Medical School, Boston, MA

^eDepartment of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, LA

ARTICLE INFO

Keywords:

Running
Physical activity
Exercise
Mortality
Cardiovascular disease

ABSTRACT

Running is a popular and convenient leisure-time physical activity (PA) with a significant impact on longevity. In general, runners have a 25%–40% reduced risk of premature mortality and live approximately 3 years longer than non-runners. Recently, specific questions have emerged regarding the extent of the health benefits of running versus other types of PA, and perhaps more critically, whether there are diminishing returns on health and mortality outcomes with higher amounts of running. This review details the findings surrounding the impact of running on various health outcomes and premature mortality, highlights plausible underlying mechanisms linking running with chronic disease prevention and longevity, identifies the estimated additional life expectancy among runners and other active individuals, and discusses whether there is adequate evidence to suggest that longevity benefits are attenuated with higher doses of running.

© 2017 Elsevier Inc. All rights reserved.

Contents

Longevity benefits of running	46
Is running more important for longevity than other lifestyle and health risk factors?	46
Potential mechanisms linking running to health outcomes	48
Is running better than other types of PA for longevity?	49
How much longer can runners live?	50
Is there too much running for longevity?	51
Potential upper threshold for longevity benefits of running	53
Conclusion	53
Statement of conflict of interest	53
References	53

Statement of Conflict of Interest: see page 53.

* Address reprint requests to Duck-chul Lee, PhD, Assistant Professor, Department of Kinesiology, College of Human Sciences, Iowa State University, 251 Forker Building, 534 Wallace Road, Ames, IA 50011.

E-mail address: dclee@iastate.edu (D. Lee).

<http://dx.doi.org/10.1016/j.pcad.2017.03.005>

0033-0620/© 2017 Elsevier Inc. All rights reserved.

Abbreviations and Acronyms

ACLS = Aerobics Center Longitudinal Study
BMI = body mass index
BP = blood pressure
CCHS = Copenhagen City Heart Study
CHD = coronary heart disease
CI = confidence interval
CRF = cardiorespiratory fitness
CVD = cardiovascular disease
DM = diabetes mellitus
ECG = electrocardiogram
EEE = extreme endurance exercise
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
HTN = hypertension
MET = metabolic equivalent
PAF = population attributable fraction
PA = physical activity
RCT = randomized controlled trial
US = United States
WHO = World Health Organization

Regular physical activity (PA) prevents chronic diseases and reduces the risk of premature cardiovascular disease (CVD) and all-cause mortality.^{1,2} There is also some evidence indicating that vigorous-intensity aerobic PA (defined as any activity requiring an energy expenditure of ≥ 6 metabolic equivalents [METs]) could be superior to moderate-intensity aerobic PA (3–6 METs) in reducing the risk of premature mortality.^{3–5} The United States (US) and World Health Organization (WHO) PA guidelines recommend 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic PA (equal to ≥ 500 MET-min/wk).^{6,7} However, self-report data from the 2015 National Health Interview Survey indicate that only approximately 50% of Americans obtain this minimum recommended amount of PA.⁸ This estimate drops dramatically, to

5%–10%, using PA data collected via objective measures.^{9,10}

Running is among the most popular types of exercise and PA in individuals who do engage in vigorous-intensity PA.^{11,12} Running participation has grown throughout the past decade, and it peaked in 2013 when approximately 19 million individuals finished a road race of any distance.¹³ More recent reports from the 2015 race season indicated that there were 17.1 million running participants, and the total number of road races increased by 2300 between 2014 and 2015, suggesting that running remains a popular leisure-time activity.¹³ Running is an attractive mode of exercise for many reasons. Compared with other types of vigorous-intensity sports and exercises, running mitigates many barriers to being physically active. Running is easily accessible and convenient since it does not require a gym membership or specialized equipment or training. Furthermore, even slow jogging is consistently considered a vigorous-intensity PA, so it reduces the time commitment of exercise to reach the recommended levels of PA, which is often cited as the primary barrier preventing people from exercising.^{14,15} Moreover, mounting evidence suggests that running durations below the

recommended guidelines of ≥ 75 min/wk of vigorous-intensity PA offer substantial, and possibly maximal, protections against mortality.^{16,17} Running may confer superior benefits over other types of vigorous-intensity PA, since it is more strongly associated with lower body weights and smaller waist circumferences.¹⁸ Therefore, running may be an ideal exercise modality from both an individual and a public health standpoint.

Longevity benefits of running

There are several large population-based cohort studies, which have examined all-cause mortality and other health outcomes among runners compared with non-runners.^{17,19–22} Overall, these studies found that after adjusting for age and sex, runners have 30%–45% lower risk of all-cause mortality. After further controlling for smoking status, alcohol consumption, socioeconomic variables, body mass index (BMI), and other types of PA, the impact of running on reducing all-cause mortality remains substantial, reducing the risk of premature death by 25%–40%.

Running is protective against both CVD and cancer, the two leading causes of death in most developed countries including the US.²³ The risk of CVD-related mortality is reduced 45%–70% in runners compared with non-runners after adjusting for potential confounders.^{17,19,20,22} Runners also have 30%–50% reduced risk of cancer-related mortality compared with non-runners after adjusting for confounders.^{20–22} Beyond CVD and cancer, there is additional evidence that running may be protective against mortality resulting from neurological conditions, such as Alzheimer's and Parkinson's disease, and respiratory infections.²⁰

Runners also tend to engage in other healthy behaviors that contribute to their increased longevity such as maintaining a normal body weight, not smoking, and consuming light-to-moderate amounts of alcohol.²⁴ Most studies have adjusted their models to account for these confounders.^{17,19–22} However, there is evidence suggesting that it might be important to tease apart the effects of running on mortality relative to each of these covariates rather than simply controlling for them. We found that there was a greater mortality benefit in runners in both patient and healthy populations, smokers and non-smokers, and lean and overweight individuals in stratified subsample analyses of data from over 55,000 men and women aged 18–100 years (Fig 1).¹⁷ The mortality benefits of running were consistent regardless of age, sex, and alcohol consumption. In this large cohort, runners overall had 30% and 45% lower risks of all-cause and CVD mortality, respectively, compared with non-runners, after adjusting for a comprehensive set of potential confounders.

Is running more important for longevity than other lifestyle and health risk factors?

The WHO has reported that 6% of premature mortality is related to physical inactivity.²⁵ Another recent review indicated that physical inactivity causes 9% of all-cause mortality worldwide.¹ Physical inactivity has been cited as the 4th

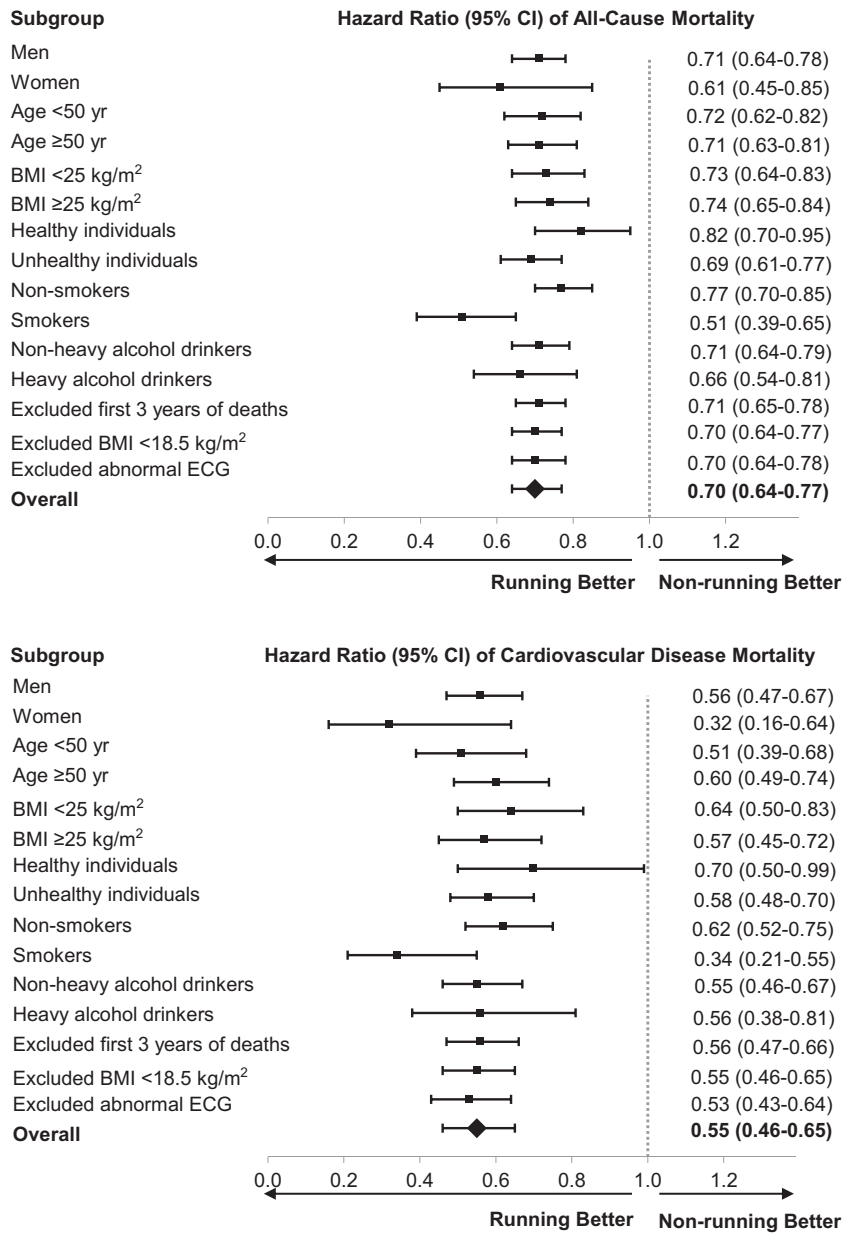


Fig 1 – Hazard ratios of all-cause and cardiovascular disease mortality by subgroup. The reference group for all analyses is non-runners. Hazard ratios were adjusted for baseline age, sex (not in sex-stratified analyses), examination year, smoking status (never, former, or current. Not in smoking-stratified analyses), alcohol consumption (heavy drinker or not. Not in alcohol drinking-stratified analyses), other physical activities except running (0, 1–499, or ≥500 MET-min/wk), and parental cardiovascular disease (yes or no). Unhealthy was defined as the presence of one or more of the following: abnormal electrocardiogram (ECG), hypertension, diabetes, or hypercholesterolemia. Heavy alcohol drinking was defined as >14 and >7 drinks/wk for men and women, respectively (adapted from Lee et al.¹⁷).

leading global risk factor for death, especially in middle-to-high income countries, after high blood pressure (BP) (1st), cigarette smoking (2nd), and high blood glucose (3rd).²⁵ Overweight/obesity and high cholesterol were found to be the 5th and 6th leading risk factors for death. All of these factors contribute to developing chronic diseases, such as CVD and cancer, leading to increased risk of premature mortality. Identifying and ranking risk factors provides public health policymakers with a quantitative estimate of the

potential relative impact (i.e., proportional reduction in mortality that would be expected by interventions to reduce the risk factor of interest). Since running is one of the most popular and convenient leisure-time PA, it is informative to compare the relative contribution of running versus other risk factors on disease prevention and health promotion from a public health perspective.

We have estimated the population attributable fraction (PAF) for running and other health risk factors to quantify

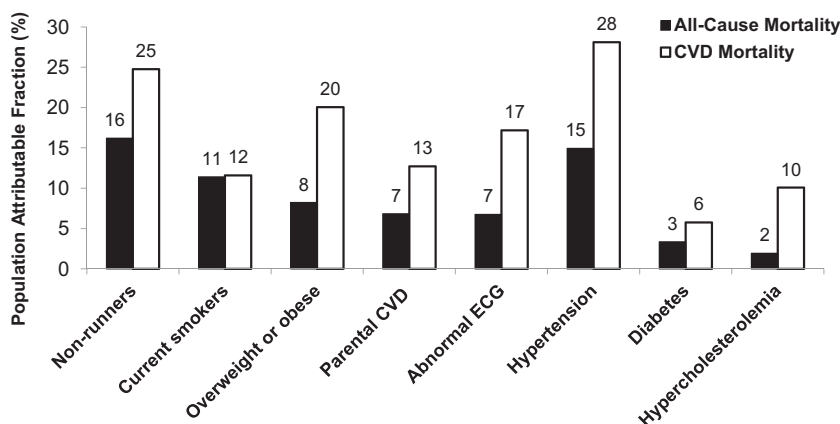


Fig 2 – Population attributable fraction (PAF) by running and other lifestyle and health risk factors. PAF was adjusted for baseline age, sex, examination year, and all other risk factors in the figure. PAF was computed as $P_c (1 - 1/HR_{adj})$, where P_c is the prevalence of the mortality predictor among mortality cases, and HR_{adj} is the multivariable hazard ratio for mortality associated with the specified mortality predictor (adapted from Lee et al.¹⁷).

their relative influence on mortality.¹⁷ Running was as important as hypertension (HTN) in the multivariable analyses, and more important than overweight/obesity or smoking as an attributable factor to prevent premature mortality in our sample. Running accounted for 16% and 25% of all-cause and CVD mortality, respectively (Fig 2). If all non-runners became runners in this population, 16% of all-cause and 25% of CVD mortality deaths would be prevented in the context of population-mortality burden.

A possible limitation in this comparison is that running was measured by self-report, whereas other clinical risk factors such as BP and fasting glucose were measured objectively. Thus, there may be a measurement error in the running estimate due to recall bias and social desirability. To reduce this potential error, we also examined cardiorespiratory fitness (CRF), a more objective marker for recent PA, that was obtained from a laboratory maximal treadmill test.²⁶ The results were similar to our findings on reported running, and indicated that low CRF accounted for 16% of all deaths as the leading mortality predictor, followed by HTN, smoking, obesity, hypercholesterolemia, and diabetes mellitus (DM).

The consistent findings of the significant contributions of running and CRF on mortality outcomes underscore the importance of including PA and CRF assessments in routine medical examinations along with other clinical tests (e.g., BP and lipid profile). Running, as a key lifestyle medicine, could make a substantial public health impact on disease prevention and longevity.

Potential mechanisms linking running to health outcomes

There are many purported mechanisms through which running may reduce premature mortality (Fig 3). Numerous epidemiological studies have reported associations between running/vigorous exercise and improvements in various chronic disease risk factors, including HTN, dyslipidemia,

body composition, insulin sensitivity, blood glucose regulation, disability, bone mineral density, and CRF.^{27–30} Running/vigorous exercise may reduce some types of cancer-related mortality (e.g., breast and colon cancer) through its effects on body composition and female hormones (estrogen and progesterone in breast cancer).²⁹ Dose-dependent associations have also been found between PA and improved cognitive function and reduced depressive symptoms,^{31–33} potentially reducing mortality related to some neurological or psychiatric conditions.

Notably, running may particularly benefit CVD mortality through its robust effects on CRF,^{34,35} which is generally better enhanced with vigorous-intensity PA.^{7,36} We found that every 30 min of additional weekly running time was associated with 0.5 MET higher CRF after adjusting for age and sex.¹⁷ In fact, after further adjustment for CRF, mortality benefits of running were no longer significant.³⁷ This implies that CRF mediates the relationship between running and reduced mortality. This potentially causal pathway is supported by previous findings indicating that CRF could be the strongest predictor of mortality.²⁶ CRF has also been associated with increased gray matter volume in the hippocampus and prefrontal cortex, which could have important implications for neurological disease-related mortality.³⁸

A meta-analysis of 49 randomized, controlled trials (RCTs), conducted in 2024 adults, found that running interventions, compared with inactive control groups, produced improvements in body composition, CRF, and high-density lipoprotein cholesterol (HDL-C), particularly with training durations greater than 1 year.³⁹ Also, vigorous-intensity PA confers equal, if not greater, benefits than low- or moderate-intensity PA on BP (particularly diastolic BP), HDL-C, blood glucose control, insulin sensitivity, and CRF.²⁸ Running may further improve certain CVD risk factors, such as adiposity and CRF, even after it is matched on energy expenditure with other types of vigorous-intensity PA.¹⁸ This may indicate that there is something inherent to running that is uniquely advantageous with regard to various health indicators.

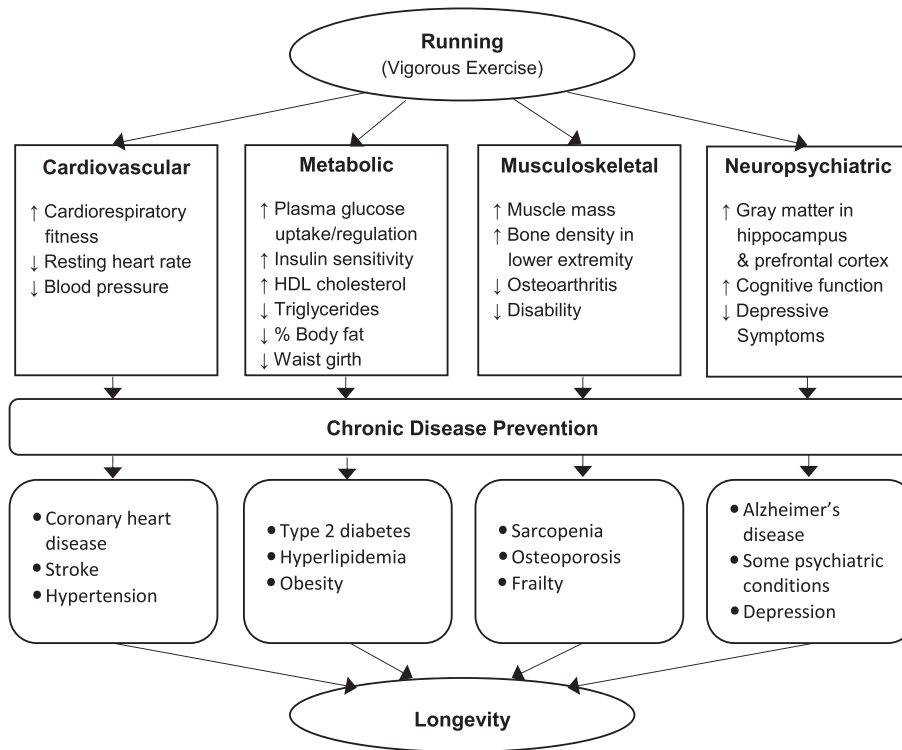


Fig 3 – Potential mechanistic pathway between running/vigorous exercise and increased longevity. An up arrow (↑) indicates an increase and a down arrow (↓) indicates a decrease.

There has also been growing interest in examining the effects of intermittent, high-intensity interval exercise versus traditional, continuous exercise prescriptions.⁴⁰ RCTs conducted in various populations, including CVD patients and obese individuals, have found that short duration, high-intensity interval training (typically cycling) produces similar improvements in body composition, blood lipids, insulin sensitivity, and CRF as continuous moderate-intensity exercise, but with significantly shorter exercise durations.^{40–42} There is also research in healthy individuals suggesting that interval running is just as effective as continuous running for some CVD risk factors, but with less than a third of the time commitment.⁴³ Further research into the effects of interval running in deconditioned and/or patient populations is warranted, especially given that novice exercisers are often told to begin a walking–jogging program consisting of short bouts of jogging interspersed with walking.

Is running better than other types of PA for longevity?

One of the most commonly asked questions regarding PA and health is simply, “What type of exercise or PA is the best for health?” Likewise, because running is so popular and convenient, people are often curious about whether or not running is better than other types of exercise or PA. We conducted a simple joint stratification analysis to address this question using the Aerobics Center Longitudinal Study (ACLS) data. We dichotomized both leisure-time running and other PA except running into two categories to simplify the complicated joint

associations on mortality as well as to preserve adequate statistical power (Fig 4). Individuals who were not runners and did not meet recommended guidelines (≥ 500 MET-min/wk) through other PA (“Non-Runners” and “Inactive”) were the reference group. Runners who did not meet recommended guidelines of other non-running PA (“Runners” and “Inactive”) had 30% lower risk of all-cause mortality (sole benefits of running). Non-runners who accumulated ≥ 500 MET-min/wk of other PA except running (“Non-Runners” and “Active”) had only a 12% lower risk of death (sole benefits of other PA except running). When we directly compared these two groups (running vs. other PA), we found that runners who were inactive in other PA had a 27% lower risk of death (HR = 0.73; 95% CI = 0.65–0.84) versus non-runners who were active in other PA. These results suggest that running may possibly provide a larger mortality benefit than other types of PA in this relatively healthy and mostly non-Hispanic white population although further investigation using objective measures of running and PA is needed.

However, as expected, the greatest mortality benefit, a 43% lower risk of death, was observed in runners who were also active in other PA (“runners” and “active”). Therefore, to get the maximal mortality benefits, participating in both running and other various PA is the best choice. For most inactive individuals, however, starting with light or moderate-intensity PA, such as brisk walking and adding vigorous-intensity PA such as running or other individually preferable PA later would be safe, attainable, and still beneficial for health and fitness, as recommended by the US and WHO PA guidelines.^{6,7}

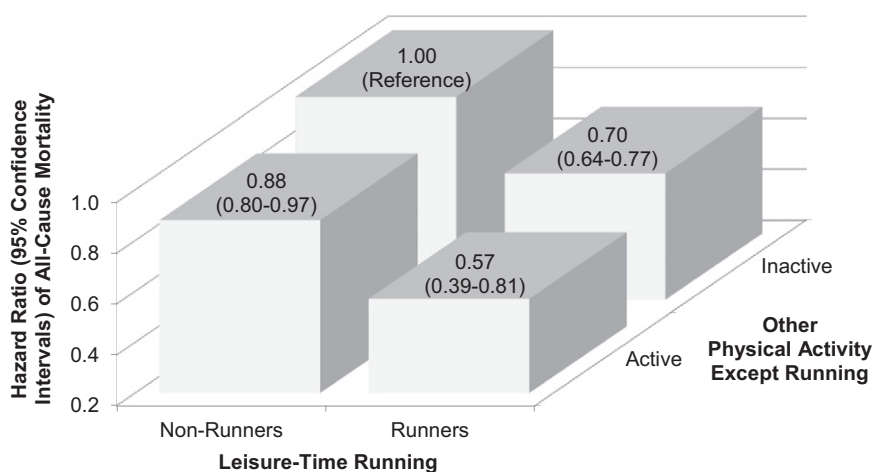


Fig 4 – Hazard ratios of all-cause mortality by combinations of participating in running and/or other PA except running. The analysis was adjusted for baseline age, sex, examination year, smoking status, alcohol consumption, and parental history of cardiovascular disease. The number of participants (number of deaths) was 24,876 (2248) in inactive non-runners; 17,245 (609) in active non-runners; 9023 (525) in inactive runners; and 3993 (31) in active runners. “Active” was defined as meeting the 2008 US PA guidelines (≥ 500 MET-min/wk) by participating in other aerobic PA except running (such as cycling, swimming, walking, basketball, racquet sports, aerobic dance, and other sports-related activities) whereas being labeled a “runner” was defined as participating in any amount of running, whether above or below recommended PA guidelines. These results are from 55,137 men and women, aged 18–100 years (mean age 44).

Another cohort study examined different types of exercise separately while adjusting for all other activities and potential confounders using the data of 44,551 men aged 40–75 years at baseline from the Health Professionals Follow-up Study.⁴⁴ Among various vigorous-intensity exercises and sports including running, cycling, swimming, tennis, rowing, racquetball, and moderate-intensity brisk walking, the authors found that only running, tennis, and brisk walking were inversely associated with CVD risk. In particular, men in the highest PA category (≥ 5 h/wk) of each running, tennis, and brisk walking had a 46%, 28%, and 23% lower CVD risk, respectively, compared with men not participating in each PA, implying running’s superiority for CVD prevention. Conversely, another study from over 80,000 British men and women (mean age 52 years) reported a significant risk reduction in CVD and all-cause mortality only for swimming, racquet sports, and aerobics, but not for running, cycling, and football.¹⁹ One possible explanation for the non-significant results associated with running (HR = 0.87, 95% CI = 0.68–1.11 for all-cause mortality and HR = 0.81, 95% CI = 0.47–1.39 for CVD mortality) was the low statistical power from the relatively low number of mortality events (68 deaths from any cause and 13 deaths from CVD). These mixed results, however, make it difficult to conclude the relative importance between running and other PA, thus more research is required.

Another comparison is often drawn between running and walking on health. In a recent large cohort of over 400,000 Taiwanese individuals, researchers found that 5-min and 25-min runs generated the same mortality benefits as 15-min and 105-min walks, respectively, with a ratio of 1:3 to 1:4.⁴⁵ This notable finding confirms that running is more time efficient and could therefore be a better choice for busy, yet healthy individuals. However, because walking is usually

safer and easier to start and sustain, the choice between running and walking should be made not only based on time efficiency, but also individual lifestyle, CRF level, health conditions, and personal preferences.

How much longer can runners live?

Most cohort studies automatically adjust for age in their analyses, but data from age-group separated analyses indicate that mortality outcomes are not only similar among young (<50 years) and old (≥ 50 years) runners, but that longevity benefits are clearly the greatest among those who continue to run throughout their lives.^{17,19} Unfortunately, running participation declines with age. Twenty to 30% of 18–29 year olds indicate that they run or jog in their free time. Running participation continues to decline 5%–10% each decade, and less than 2% of people continue to run past 65 years of age.¹²

Calculating life expectancy from self-reported running is complex and often follows various statistical approaches. Nevertheless, life expectancy is a metric that is easy to understand and could convey a powerful public health message. We found that runners had a 3.2 years longer life expectancy, compared with non-runners, based on a survival analysis from the ACLS cohort.¹⁷ We used a conservative approach in this life expectancy estimation by adjusting for a comprehensive set of confounders, including baseline age, sex, examination year, parental history of CVD, lifestyle factors (current smoking, overweight/obesity), and medical conditions (abnormal electrocardiogram (ECG), HTN, diabetes, and hypercholesterolemia). Research from the Copenhagen City Heart Study (CCHS) also found 2.6 and 3.1 years of

increased survival in male and female joggers, respectively, compared with non-joggers, based on a survival analysis after adjusting for a similar set of confounders and mediators (i.e., medical conditions).²²

The increased longevity among runners is similar to that observed in other, more broadly categorized types of PA. In an Asian sample of over 400,000 individuals, life expectancy at age 30 was 4.2 years longer for men and 3.7 years longer for women in those who performed ≥ 150 min/wk of moderate-intensity PA compared with inactive individuals without statistical adjustment for confounders.⁴⁶ At age 60, the extended life expectancy among active adults was 3.5 years in men and 3.6 years in women. Thus, the longevity benefits decreased slightly with age, but remained similar, possibly indicating that even fewer years of exercise, perhaps from a late start in life, provided comparable longevity benefits. Another investigation conducted a pooled analysis of six cohort studies with over 650,000 participants from Western populations. The average gain in life expectancy after age 40 was 3.4 years among individuals who met the minimum recommended PA (equivalent to 150–299 min/wk of brisk walking) relative to those with no leisure-time PA after controlling for potential confounders.⁴⁷ Moreover, the gain in life expectancy was 4.2 years among those who performed two times the minimum recommended PA (equivalent to 300–449 min/wk of brisk walking). The association between PA and life expectancy was similar between men and women and was evident at every BMI level, educational status, race/ethnicity, smoking status, and comorbid conditions. Performing even half of the PA, 75 min/wk of PA, was associated with a gain of 1.8 years in life expectancy, compared with no activity. The statistical methods used to estimate life expectancy are different between studies, but the consensus is that runners have an approximately 3 years longer life expectancy, compared with non-runners, irrespective of sex, race/ethnicity, and body weight. This increase in life expectancy of 3 years is consistent with other PA studies.

One could argue that runners, or active people in general, live longer by the same amount of time they have run or exercised throughout their lives, and that running and exercise may not actually be worthwhile because the longevity bonus is negated by the equivalent amount of time spent exercising. This argument collapses by simply estimating the numbers. Using 150 min/wk (2.5 h/wk) of exercise based on the current PA guidelines, the total years of exercise time from the age of 30 to 80 years is only 0.74 years (2.5 h/wk \times 52 weeks \times 50 years = 6500 h, divided by 8760 h/year). In our running study, the average reported running time was approximately 120 min/wk among runners, aged 44 years at baseline. In this case, the total running time from the age of 44 to 80 years was 0.43 years, based on the same calculation. Running still provides 2.8 years of additional life even after subtracting the total running time of 0.43 years from the 3.2 years of extended life among runners found from the ACLS cohort. Therefore, a net “running” to “longevity benefit” ratio is roughly 1:7 (0.43:2.8), suggesting 1 hour of running provides an additional 7 h of extended life. It is controversial whether progressively more running provides further mortality benefits, but running certainly provides cost-effective longevity

benefits. It is also noteworthy that there are several other benefits of regular PA such as enhanced quality of life and improved physical and cognitive function in later life.^{31,48}

Is there too much running for longevity?

Some recent studies suggest that excessive endurance exercise (EEE), such as habitual running, may cause adverse effects on cardiac structure and function.^{27,49–53} Some postulated mechanisms linking EEE to potential adverse cardiac effects include increased vascular oxidative stress and inflammation, myocardial fibrosis, and structural changes in the heart and its autonomic control.^{50,54–56} A study on 52,755 participants in the Vasaloppet 90 km cross-country ski marathon found that those who had completed more races than infrequent participants had a higher risk of developing atrial fibrillation over 10-years of follow-up although more dangerous arrhythmias such as ventricular tachycardia/ventricular fibrillation/cardiac arrest were not associated.⁵⁷ Similar results on adverse cardiac effects of EEE were also reported in other studies.^{58–60} We observed a slightly higher prevalence of abnormal ECG in the highest running group compared with low-to-moderate running groups (Fig 5), although not statistically different. We also observed that runners with higher weekly running times of ≥ 81 min/wk had a significantly higher prevalence of parental history of CVD, compared with runners running 1–80 min/wk ($p < 0.05$).

However, these two factors, an abnormal ECG and a family history of CVD, could also serve as motivators for some people to engage in greater amounts of running to prevent CVD events. Therefore, it is difficult to determine whether strenuous running may cause abnormal ECG or whether strenuous runners do not get further mortality benefits because they have a family history of CVD from this cross-sectional observation.

We found in another examination that only coronary heart disease (CHD) deaths, unlike other causes of death, were relatively greater with higher doses of running (a reverse J-shaped association; Fig 6). This association between running and CHD may mostly explain the reverse J-shaped curve between running and all-cause mortality.^{51,61} This finding is consistent with the previous suggestion of the potential adverse effect of EEE, specifically on CVD outcomes. However, the associations of running with other causes of death are not reverse J-shaped, but are more L-shaped, suggesting no increased likelihood of adverse effects, but rather consistent mortality benefits from increased running on various health outcomes such as cancer and stroke.

We compared three well-known running studies to answer the question of whether more running is better or worse for longevity.⁶² All studies indicated significant mortality benefits with light-to-moderate running compared with no running. These benefits were lost at the highest dose of running suggesting that more running may not be better for longevity and raises the possibility that “more could be worse” for CVD and all-cause mortality. Nevertheless, all three studies indicated no significantly increased risk of mortality, even at the highest dose of running compared with no running. Therefore, more running is not necessarily worse, although

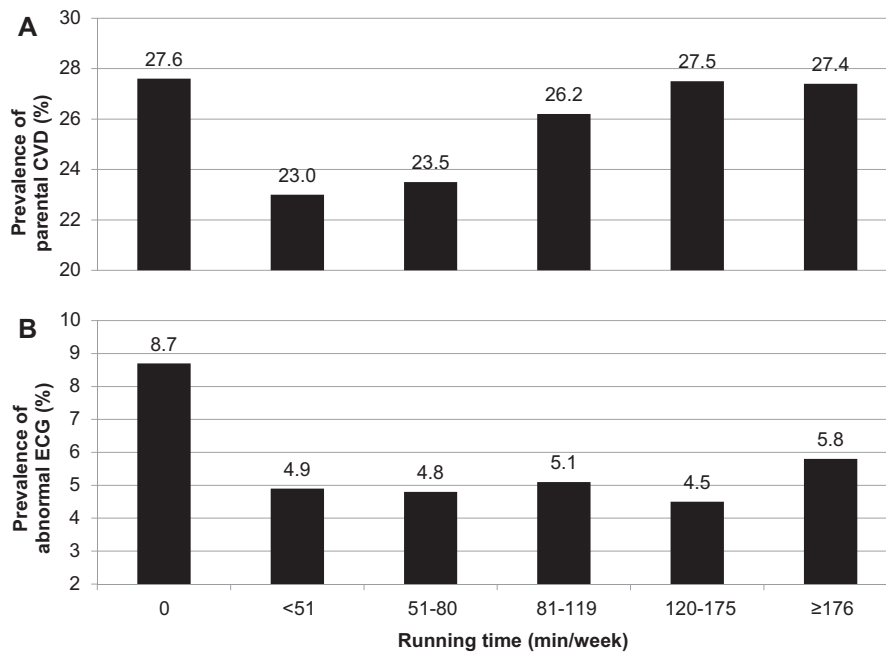


Fig 5 – Prevalence of parental history of cardiovascular diseases (CVD) (A) and abnormal electrocardiogram (ECG) (B) by weekly running time (adapted from Lee et al.¹⁷).

there may be no further mortality benefits in excessive running.

Comparing the highest running dose to the lower running dose, two relatively small studies revealed that the highest running dose was associated with a significantly increased risk of mortality. Our study, however, with the largest sample size with over 55,000 adults demonstrated no increased risk of all-cause and CVD mortality even in the highest running group (e.g., ≥ 4.5 h/wk) compared with the light running group (e.g., < 51 min/wk). This was consistent in men and women,

the young and old individuals, and slow and fast runners. There are other observational studies showing greater CVD benefits at higher doses of running with a linear trend in different populations.^{44,63} Therefore, well-controlled, intervention studies are certainly needed to address the controversial issue as to whether or not large doses of running further reduce or actually increase the risk of developing CVD, particularly CHD, risk factors and biomarkers.

Concern about the possibility of increased CHD events with high doses of running applies only to a small number of

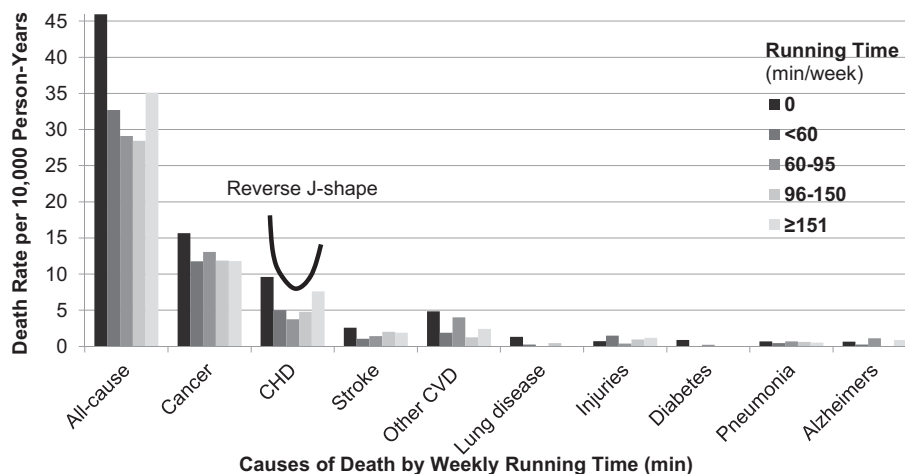


Fig 6 – Death rate for major causes of death by weekly running time. Participants are classified into non-runners and four quartiles of weekly running time. Death rates are adjusted for baseline age, sex, and examination year. Causes of death are divided into all-cause, cancer, CHD, stroke, other CVD except CHD and stroke, chronic respiratory (lung) disease, unintentional injuries, diabetes, pneumonia and influenza, and Alzheimer disease. Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease (adapted from Lee et al.⁵²).

Table 1 – Recommended upper limit of running doses for longevity benefits.^a

Running Characteristics	Recommended Upper Limit of Running
Time	≤4.5 h/wk
Distance	≤30 miles/wk
Frequency	≤6 times/wk
Total amount	≤50 MET-h/wk

^a Results from 55,137 men and women from the Aerobics Center Longitudinal Study (adapted from Lee et al.⁶²).

individuals and should not obviate the observation that running and other PA even below the current minimum PA guidelines can significantly reduce premature mortality.^{16,17,46,47,64}

Potential upper threshold for longevity benefits of running

It is too early to conclude that large amounts of running have adverse health effects. There is, however, benefit in providing a cut point for an effective and safe amount of running as a guide. We used the ACLS data⁶² to identify potential upper limits of running beyond which additional running provided no further mortality benefits, although there was also no excess risk of harm (Table 1).

These potential benefit thresholds are similar to findings from other large cohort studies on the dose–response relationships between PA and mortality. Findings from the US National Cancer Institute Cohort Consortium of over 660,000 men and women indicated a benefit threshold at approximately 40 MET-h/wk of moderate-to-vigorous intensity aerobic PA beyond which no additional mortality benefits were found.⁶⁵ This study also found no significant harm or risk beyond this threshold compared with inactivity. Another study of 1.1 million British women observed that those reporting strenuous PA such as running up to 6 times/wk had progressive CHD risk reduction compared with inactive women.⁶⁶ There was, however, no further decrease in risk with daily strenuous PA beyond this level, suggesting ≤6 times/wk as the upper benefit threshold. This aligns with our upper threshold for running frequency. Another study also observed a reverse J-shaped association between running or walking and all-cause and CVD mortality in 2377 heart attack survivors.⁵¹ Running or walking progressively decreased CVD mortality risk at most exercise levels, but this benefit was attenuated at the highest exercise levels of >50 MET-h/wk, the equivalent to running >30 miles/wk or walking briskly >47 miles/wk. This again is similar to the upper limit of benefit from running found in our study. The CCHS of 5048 relatively healthy adults observed a similar reverse J-shaped association between jogging and all-cause mortality, suggesting the loss of mortality benefits even in moderate joggers (e.g., ≥4 times/wk or ≥2.5 h/wk) compared with sedentary non-joggers.¹⁶ The relatively lower longevity threshold in this study (<4 times/wk or <2.5 h/wk) compared with ours (<6 times/wk or <4.5 h/wk) is partly due to the small numbers of deaths ($n = 8$) among moderate joggers. Another review study found that most studies have reported significant all-cause or CVD mortality benefits of vigorous-intensity exercise up to 50 MET-h/wk,

although maximum benefits were already achieved at lower exercise doses.⁶⁴ All of these data support the possible benefit threshold that we identified wherein further running may not provide additional longevity benefits, although most studies indicate no harm or excess risk of mortality even at the extreme amount of running or aerobic exercise. These findings, however, question the current, overarching PA paradigm of “the more, the better” and may help shift the focus toward promoting the benefits of even small amounts of PA to reduce sedentary (sitting) time, which is an emerging health hazard in most developed countries.

Whether or not there is an upper threshold for the benefits of running and PA will remain controversial, and any conclusions on a longevity benefit threshold should be interpreted with caution, since most results are generated from self-reported behaviors in largely Western populations. More objective measures of running such as accelerometry will be helpful to determine accurately the ideal amount of running for health. The above recommended upper limits of running are much higher than achievable by most people. It is also important to mention the increased risk of musculoskeletal injury with increasing weekly running time and distance.^{67,68} Nearly 70% of serious runners become injured during a one year period,⁶⁹ and high rates of injury in the highest running categories could potentially impact mortality outcomes, although no data are currently available.

Conclusion

There is compelling evidence that running provides significant health benefits for the prevention of chronic diseases and premature mortality regardless of sex, age, body weight, and health conditions. There are strong plausible physiological mechanisms underlying how running can improve health and increase longevity. Running may be the most cost-effective lifestyle medicine from public health perspective, more important than other lifestyle and health risk factors such as smoking, obesity, HTN, and DM. It is not clear, however, how much running is safe and efficacious and whether it is possible to perform an excessive amount of exercise. Also, running may have the most public health benefits, but is not the best exercise for everyone since orthopedic or other medical conditions can restrict its use by many individuals.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

REFERENCES

1. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380:219–229.

2. Sallis R, Franklin B, Joy L, Ross R, Sabgir D, Stone J. Strategies for promoting physical activity in clinical practice. *Prog Cardiovasc Dis.* 2015;57:375-386.
3. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol.* 2011;40:1382-1400.
4. Lee IM, Paffenbarger RS. Associations of light, moderate, and vigorous intensity physical activity with longevity. The Harvard Alumni Health Study. *Am J Epidemiol.* 2000;151:293-299.
5. Shiroma EJ, Sesso HD, Moorthy MV, Buring JE, Lee IM. Do moderate-intensity and vigorous-intensity physical activities reduce mortality rates to the same extent? *J Am Heart Assoc.* 2014;3:e000802.
6. World Health Organization. Global recommendations on physical activity for health. <http://www.who.int/dietphysicalactivity/publications/9789241599979/en/> 2015.
7. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee. Report, 2008. Washington, DC: U.S. Department of Health and Human Services; 2008.
8. Centers for Disease Control. Facts about physical activity. <https://www.cdc.gov/physicalactivity/data/facts.htm> 2014.
9. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the united states measured by accelerometer. *Med Sci Sport Exerc.* 2008;40:181-188.
10. Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S.: adults compliance with the Physical Activity Guidelines for Americans. *Am J Prev Med.* 2011;40:454-461.
11. Tudor-Locke C, Johnson WD, Katzmarzyk PT. Frequently reported activities by intensity for U.S. adults. *Am J Prev Med.* 2010;39:e13-e20.
12. Dai S, Carroll DD, Watson KB, Paul P, Carlson SA, Fulton JE. Participation in types of physical activities among US adults—National Health and Nutrition Examination Survey 1999–2006. *J Phys Act Health.* 2015;12:S128-S140.
13. Running USA. 2016 State of the sport—U.S. road race trends. <http://www.runningusa.org/state-of-sport-us-trends-2015?returnTo=main> 2016.
14. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical activities. *Med Sci Sport Exerc.* 2011;43:1575-1581.
15. Centers for Disease Control. Overcoming barriers to physical activity. <https://www.cdc.gov/physicalactivity/basics/adding-pa/barriers.html> 2011.
16. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality. *J Am Coll Cardiol.* 2015;65:411-419.
17. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol.* 2014;64:472-481.
18. Williams PT. Non-exchangeability of running vs. other exercise in their association with adiposity, and its implications for public health recommendations. *PLoS One.* 2012;7:e36360.
19. Oja P, Kelly P, Pedisic Z, et al. Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults. *Br J Sports Med.* 2016, <http://dx.doi.org/10.1136/bjsports-2016-096822>.
20. Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and mortality among aging runners. *Arch Intern Med.* 2008;168:1638-1646.
21. Wang N, Zhang X, Xiang Y-B, et al. Associations of Tai Chi, walking, and jogging with mortality in Chinese men. *Am J Epidemiol.* 2013;178:791-796.
22. Schnohr P, Marott JL, Lange P, Jensen GB. Longevity in male and female joggers: the Copenhagen City Heart Study. *Am J Epidemiol.* 2013;177:683-689.
23. Centers for Disease Control. FastStats—leading causes of death. <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm> 2014.
24. O'Keefe JH, Bhatti SK, Bajwa A, DiNicolantonio JJ, Lavie CJ. Alcohol and cardiovascular health: the dose makes the poison...or the remedy. *Mayo Clin Proc.* 2014;89:382-393.
25. World Health Organization. *Global heart risks: mortality and burden of disease attributable to selected major risks.* 2009. [Geneva, Switzerland].
26. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med.* 2009;43:1-2.
27. Lavie CJ, Lee DC, Sui X, et al. Effects of running on chronic diseases and cardiovascular and all-cause mortality. *Mayo Clin Proc.* 2015;90:1541-1552.
28. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol.* 2006;97:141-147.
29. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. *Compr Physiol.* 2012;2:2775-2809.
30. Johansson J, Nordström A, Nordström P. Objectively measured physical activity is associated with parameters of bone in 70-year-old men and women. *Bone.* 2015;81:72-79.
31. de Souto Barreto P, Delrieu J, Andrieu S, Vellas B, Rolland Y. Physical activity and cognitive function in middle-aged and older adults. *Mayo Clin Proc.* 2016;91(11):1515-1524.
32. Galper DI, Trivedi MH, Barlow CE, Dunn AL, Kampert JB. Inverse association between physical inactivity and mental health in men and women. *Med Sci Sports Exerc.* 2006;38:173-178.
33. Lavie CJ, Menezes AR, De Schutter A, Milani RV, Blumenthal JA. Impact of cardiac rehabilitation and exercise training on psychological risk factors and subsequent prognosis in patients with cardiovascular disease. *Can J Cardiol.* 2016;32:S365-S373.
34. Myers J, McAuley P, Lavie C, Despres J, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis.* 2015;57(4):306-314.
35. DeFina LF, Haskell WL, Willis BL, et al. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? *Prog Cardiovasc Dis.* 2015;57:324-329.
36. Williams PT. Usefulness of cardiorespiratory fitness to predict coronary heart disease risk independent of physical activity. *Am J Cardiol.* 2010;106:210-215.
37. Lee DC, Sui X, Ortega FB, et al. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med.* 2011;45:504-510.
38. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiol Aging.* 2014;35:S20-S28.
39. Hesperhol Junior LC, Pillay JD, van Mechelen W, Verhagen E. Meta-analyses of the effects of habitual running on indices of health in physically inactive adults. *Sports Med.* 2015;45:1455-1468.
40. Benda NM, Seeger JP, Stevens GG, et al. Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients. *PLoS One.* 2015;10:e0141256.
41. Fisher G, Brown AW, Bohan Brown MM, et al. High intensity interval- vs moderate intensity- training for improving cardiometabolic health in overweight or obese males: a randomized controlled trial. *PLoS One.* 2015;10:e0138853.
42. Jelleymann C, Yates T, O'Donovan G, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obes Rev.* 2015;16:942-961.

43. Nybo L, Sundstrup E, Jakobsen MD, et al. High-intensity training versus traditional exercise interventions for promoting health. *Med Sci Sport Exerc.* 2010;42:1951-1958.
44. Chomistek AK, Cook NR, Flint AJ, Rimm EB. Vigorous-intensity leisure-time physical activity and risk of major chronic disease in men. *Med Sci Sport Exerc.* 2012;44:1898-1905.
45. Wen CP, Wai JPM, Tsai MK, Chen CH. Minimal amount of exercise to prolong life: to walk, to run, or just mix it up? *J Am Coll Cardiol.* 2014;64:482-484.
46. Wen CP, Wai JPM, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet.* 2011;378:1244-1253.
47. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med.* 2012;9:e1001335.
48. Bouaziz W, Vogel T, Schmitt E, Kaltenbach G, Geny B, Lang PO. Health benefits of aerobic training programs in adults aged 70 and over: a systematic review. *Arch Gerontol Geriatr.* 2017;69:110-127.
49. Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J.* 2008;29:1903-1910.
50. Wilson M, O'Hanlon R, Prasad S, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol.* 2011;110:1622-1626.
51. Williams PT, Thompson PD. Increased cardiovascular disease mortality associated with excessive exercise in heart attack survivors. *Mayo Clin Proc.* 2014;89:1187-1194.
52. Lee DC, Lavie CJ, Vedanthan R. Optimal dose of running for longevity. *J Am Coll Cardiol.* 2015;65:420-422.
53. Lavie CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system. *Circ Res.* 2015;117:207-219.
54. Shave R, Baggish A, George K, et al. Exercise-induced cardiac troponin elevation. *J Am Coll Cardiol.* 2010;56:169-176.
55. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J.* 2012;33:998-1006.
56. Knez WL, Coombes JS, Jenkins DG. Ultra-endurance exercise and oxidative damage: implications for cardiovascular health. *Sports Med.* 2006;36:429-441.
57. Andersen K, Farahmand B, Ahlbom A, et al. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J.* 2013;34:3624-3631.
58. Baldesberger S, Bauersfeld U, Candinas R, et al. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. *Eur Heart J.* 2008;29:71-78.
59. Claessen G, Colyn E, La Gerche A, et al. Long-term endurance sport is a risk factor for development of lone atrial flutter. *Heart.* 2011;97:918-922.
60. Pelliccia A, Maron BJ, Culasso F, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation.* 2000;102:278-284.
61. O'Keefe JH, Franklin B, Lavie CJ. Exercising for health and longevity vs peak performance: different regimens for different goals. *Mayo Clin Proc.* 2014;89:1171-1175.
62. Lee DC, Lavie CJ, Sui X, Blair SN. Running and mortality: is more actually worse? *Mayo Clin Proc.* 2016;91:534-536.
63. Williams PT. Reductions in incident coronary heart disease risk above guideline physical activity levels in men. *Atherosclerosis.* 2010;209:524-527.
64. Eijsvogels TMH, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the extremes. *J Am Coll Cardiol.* 2016;67:316-329.
65. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175:959-967.
66. Armstrong MEG, Green J, Reeves GK, Beral V, Cairns BJ. Million Women Study Collaborators. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation.* 2015;131:721-729.
67. Hootman JM, Macera CA, Ainsworth BE, Martin M, Addy CL, Blair SN. Association among physical activity level, cardiorespiratory fitness, and risk of musculoskeletal injury. *Am J Epidemiol.* 2001;154:251-258.
68. Van Gent RN, Siem D, van Middelkoop M, et al. Incidence and determinants of lower extremity running injuries in long distance runners: a systematic review. *Br J Sports Med.* 2007;41:469-480.
69. Hreljac A. Impact and overuse injuries in runners. *Med Sci Sports Exerc.* 2004;36:845-849.