

"IDEAL AMOUNT OF EXERCISE FOR A HEALTHY LIFE: HAVE WE SOLVED THE GOLDBLOCKS PROBLEM?" – REVIEW OF THE LITERATURE

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ABSTRACT

There is an increasing interest in the place of physical activity to counter the increasing risk of non-communicable diseases and its complications in the community. Debate remains just how much exercise is too little, too much or just right to improve health and longevity. This article reviews the present evidence of physical activity on mortality and the possible ideal recommendations on physical activity.

Key words: Ideal, recommendation, exercise, physical activity, healthy lifestyle

INTRODUCTION

In recent times, there has been an increasing interest in the place of physical activity to counter the ever increasing risk of non-communicable diseases and its complications in the community. However, the debate remains just how much exercise is too little, too much or just right to improve health and longevity. There is no doubt that any amount of exercise is better than none. Exercise is known to reduce risks of many chronic diseases, cancer and premature death (Table 1). The clear majority of these studies show a dose-response association of physical activity in reducing mortality, without any upper limit of safe activity (1-6, 8-13, 15-18, 20-26, 28-30, 32-33, 38-39). Minority of studies show increased risk at the higher end of the activity range, raising concerns whether frequent, strenuous exercise, exceeding current recommendations, can be potentially dangerous and harmful to health and wellbeing contributing to early mortality (7, 14) and few studies showed no dose-response association (19, 27, 31, 34, 35, 36, 37).

Despite having a reasonable amount of evidence, the recommendation for exercise does not come with clear dosing instructions. The current guidelines call for a minimum of 75 vigorous-intensity or 150 moderate-intensity minutes per week (7.5 metabolic equivalent hours per week) of aerobic activity to build and maintain health and fitness (40). Moderate-intensity physical activity requires a moderate amount of effort that noticeably accelerates the breathing and heart rate. Examples of the moderate-intensity physical activity include brisk walking, dancing, bicycling with – light effort (10-12 mph), gardening, housework and domestic chores, active involvement in sport and games with children, walking domestic animals and carrying or moving moderate loads (<20kg). Vigorous-intensity physical activity requires a large amount of effort that leads to rapid breathing and a substantial increase in heart rate. Examples of the vigorous-intensity physical activity include running, brisk walking up a hill, bicycling fast (14-16 mph), fast swimming, aerobics, competitive sports and games and carrying or moving heavy loads of >20kg (40). However,

the guidelines have not been very clear whether the recommended amount of exercise represents the minimum or the ideal and also regarding the upper limit of exercise for longevity benefit.

PHYSICAL INACTIVITY KILLS

According to the World Health Organization, physical inactivity has been identified as the fourth-leading risk factor for death for people all around the world (41). The studies have shown that sedentary behaviour can lead to death from cardiovascular events and cancer as well as cause chronic conditions such as Type 2 diabetes. Prolonged sitting, for eight to 12 hours or more a day, increased the risk of developing type 2 diabetes by 90% and sedentary behaviour increases our risk disease or premature death, even if we exercise (42). Researchers from Toronto who analyzed 47 studies demonstrated that sedentary behavior (remaining seated still) outweighs the benefit we get from exercise, can lead to death from cardiovascular events and cancer as well as can cause chronic conditions

Table 1: Summary of studies on physical activity and mortality †

Study	Design	Activity studied	Association studied	Population	Conclusions
Li T [1] (2015)	Meta-analysis	Physical activity	Cancer mortality	General population and cancer survivors (71 studies)	Inverse non-linear dose-response between the effects of physical activity and cancer mortality
Li Y [2] (2015)	Meta-analysis	Physical activity	Cancer mortality	General population (59,362)	Inverse dose-response between the effects of pre-diagnosis physical activity and cancer mortality
Loprinzi PD [3] (2015)	Prospective cohort	Physical activity	All-cause mortality	1999-2006 NHANES	Moderate-to-vigorous physical activity even below the minimum recommendation (7.5 MET hours per week) associated with survival benefit Greatest survival benefit occurred at approximately 5 times the minimum recommendation Very high levels (e.g. 10 times the minimum recommendation) did not appear to have harmful effects
Hupin D [4] (2015)	Meta-analysis	Physical activity	All-cause mortality	>60 years (122,417)	Inverse linear dose-response between the effects of physical activity and all-cause mortality
Gebel K [5] (2015)	Prospective cohort	Physical activity	All-cause mortality	Adults 45-75 years (204,542)	Inverse dose-response between the effects of physical activity and all-cause mortality. Proportion of vigorous activity out of the total physical activity revealed an inverse dose-response relationship with all-cause mortality
Arem H [6] (2015)	Prospective cohort	Physical activity	All-cause mortality, cardiovascular mortality, cancer mortality	6 studies (661,137)	Benefit was observed even among those performing less than the recommended minimum physical activity of 7.5 metabolic equivalent hours per week Upper threshold for mortality benefit occurred at 3 to 5 times the physical activity recommendation; however, compared with the recommended minimum, the additional benefit was modest There was no evidence of harm at 10 or more times the recommended minimum
Schnohr P [7] (2015) **	Prospective cohort	Jogging	All-cause mortality	Healthy joggers (1,098; study population) and non-joggers (3,950; control population)	U-shaped association between all-cause mortality and dose of jogging. Light and moderate joggers have lower mortality than non-joggers, whereas strenuous joggers have a mortality rate not statistically different from that of the sedentary group. Optimal dose of jogging was 1 - 2.4 h per week, optimal frequency 2-3 times per week or ≤1 time per week and optimal pace slow or average
Matthews CE [8] (2015)	Prospective cohort	Sitting time	All-cause and cardiovascular mortality	Adults 59-82 y (154,614)	Greater sitting time (≥12 vs < 5 h/d) was associated with increased risk. In less active adults (<2 h/d total activity), replacing 1 h/d of sitting with an equal amount of activity was associated with a

					benefit for both exercise and non-exercise activities. Among more active participants (>2 h/d total activity), replacement of sitting time with purposeful exercise was associated with lower mortality but not with non-exercise activity
Wu CY [9] (2015)	Prospective cohort	Physical activity	All-cause, cardiovascular, and cancer mortality	Adults ≥ 65 years (77,541)	Compared to subjects with no physical activity, those who had physical activity for ≥30 min 1-2 times per week had a decreased risk of mortality. Subjects with physical activity for ≥30 min 3-5 times per week had a further decreased risk
van der Ploeg HP [10] (2014)	Prospective cohort	Standing time	All-cause mortality	Adults ≥ 45 years (221,240)	Dose-response association between standing time and all-cause mortality
Lee DC [12] (2014)	Prospective cohort	Running	All-cause and cardiovascular mortality	Adults 18-100 years (55,137)	Mortality benefit in runners was similar across quintiles of running time, distance, frequency, amount, and speed. Weekly running of even <51 min, <6 miles, 1 to 2 times, <506 metabolic equivalent minutes, or <6 miles/h was sufficient to reduce the mortality
Kelly P [11] (2014)	Meta-analysis	Walking and cycling	All-cause mortality	18 studies	The inverse association between both walking and cycling and risk of all-cause mortality. Largest benefit is in the categories of 1–120 minutes per week of walking and 1–101 minutes per week of cycling, with decreasing rates of beneficial effects as the exposure to walking or cycling increased
Hamer M [13] (2014)	Prospective cohort	Physical activity	All-cause mortality, cardiovascular mortality and death by other causes	Adults ≥50 years (10,426)	Inverse dose-response association between physical activity and mortality
Mons U [14] (2014) **	Prospective cohort	Physical activity	All-cause and cardiovascular mortality, major cardiovascular events	Subjects with stable coronary heart disease (1038)	Reverse J-shaped associations of physical activity level with cardiovascular mortality
Sadarangani KP [15] (2014)	Prospective cohort	Physical activity	All-cause and cardiovascular mortality	Adults ≥50 years with diabetes (3,038)	Inverse dose-response association with overall physical activity
Williams PT [16] (2013)	Prospective cohort	Physical activity	All-cause, cardiovascular disease, ischemic heart disease and diabetes mortality	8,436 males and 33,586 females	Inverse dose-response association. Benefits extend to levels of activity exceeding the current exercise guidelines
Chau JY [17] (2013)	Meta-analysis	Sitting time	All-cause mortality	Six studies (595,086; mainly female, middle-aged or older adults from high-income countries)	Non-linear dose-response association between daily total sitting time and all-cause mortality

Williams PT [18] (2013)	Prospective cohort	Running and walking	All-cause, cardiovascular disease, cerebrovascular disease, dysrhythmia and heart failure mortality	Adults using anti-hypertensive medications (10880)	Nonlinear inverse dose-response association with level of activity for all end points except diabetes mellitus, and cerebrovascular Merely meeting guideline levels (1.07-1.8 METh/d) did not significantly reduce mortality Results did not differ between running and walking
Johnsen NF [19] (2013) *	Prospective cohort	Leisure time physical activities (sports, cycling, gardening, do-it-yourself activity)	All-cause mortality	Adults 50-64 years (55,705)	Mortality was lower with participation in leisure time physical activities, but there was no incremental benefit in increasing the dose
Kodama S [20] (2013)	Meta-analysis	Physical activity	All causes mortality and cardiovascular disease	Diabetics (17 studies)	Inverse dose-response association of physical activity with all-cause mortality and cardiovascular disease risk
Brown WJ [21] (2012)	Prospective cohort	Physical activity	All causes mortality	Women aged 70-75 years (7,080) and men aged 65-83 years (11,668)	Inverse dose - response relationship between physical activity and all-cause mortality Risk reductions were 30-50% greater in women than in men in every physical activity category
Matthews CE [22] (2012)	Prospective cohort	Sedentary behaviors	All-cause, cardiovascular and cancer mortality	Adults 50-71 y (240,819)	Sedentary behaviors were positively associated with mortality. Even among adults reporting high levels of moderate-vigorous physical activity (>7 h/wk), high amounts of television viewing (≥7 h/d) remained associated with increased risk
Samitz G [23] (2011)	Meta-analysis	Physical activity	All causes mortality	80 studies (1,338,143)	Inverse dose - response relationship between total and domain-specific physical activity and all-cause mortality Risk reduction per unit of time increase was largest for vigorous exercise
Wen CP [24] (2011)	Prospective cohort	Physical activity	All-cause and cancer mortality	416,175	Every additional 15 min of daily exercise beyond the minimum amount of 15 min a day further reduced all-cause mortality by 4% and cancer mortality by 1%
Woodcock J [25] (2011)	Meta-analysis	Physical activity	All causes mortality	22 studies (977,925)	Inverse dose - response relationship between total and domain-specific physical activity and all-cause mortality
Warren TY [26] (2010)	Meta-analysis	Sedentary behavior	Cardiovascular disease mortality	Men 20-89 yr (7744)	Men who reported >10 h/wk riding in a car or >23 h/wk of combined sedentary behavior (riding in a car and watching TV) had 82% and 64% greater risk of dying from CVD than those who reported <4 or <11 h/wk respectively
Stessman J [27] (2009) *	Prospective cohort	Physical activity	All-cause mortality	Adults 70-88 y (1861)	Participation in higher levels of PA did not show a dose-dependent association with mortality

Katzmarzyk PT [28] (2009)	Prospective cohort	Physical activity, sitting time	All-cause and Cardiovascular disease mortality	Adults 18-90 yr (17,013)	Dose-response association between sitting time and mortality independent of leisure time physical activity
Moholdt T [29] (2008)	Prospective cohort	Physical activity	All-cause mortality and cardiovascular mortality	Adults with coronary heart disease (3,504)	Inverse dose - response relationship between physical activity (frequency and strength of exercise) and all-cause mortality This inverse association became stronger with increasing frequency of activity
Hamer M [30] (2008)	Meta-analysis	Walking	All-cause and cardiovascular disease mortality	18 studies (459,833)	Inverse dose-response relationship across the highest, intermediate, and lowest walking categories with regard to all-cause and cardiovascular mortality Walking pace was a stronger independent predictor of overall risk compared with walking volume
Wisløff U [31] (2006) *	Prospective cohort	Physical activity	Cardiovascular mortality	56,072	There was no additional benefit from increasing the duration or the number of exercise sessions per week beyond a single weekly bout of exercise
Khaw KT [32] (2006)	Prospective cohort	Physical activity (work and leisure time)	All-cause and cardiovascular disease mortality	Adults 45-79 y (22,191)	Relative risks for all-cause mortality in those who were moderately inactive (sedentary job with <0.5 h recreational activity per day or standing job with no recreational activity), moderately active (sedentary job with 0.5–1 h recreational activity per day, or standing job with <0.5 h recreational activity per day, or physical job with no recreational activity) and active (sedentary job with >1 h recreational activity per day, or standing job with >1 h recreational activity per day, or physical job with at least some recreational activity, or heavy manual job), compared with those who were inactive (sedentary job and no recreational activity) were 0.83, 0.68, and 0.68, respectively
Lan TY [33] (2006)	Prospective cohort	Physical activity	Total mortality	Adults ≥ 65 y (2113)	Inverse dose - response relationship between physical activity and all-cause mortality Protection of exercise against death also increases with the number of types of activities Among the three components of energy expenditure (intensity, frequency, and duration), only intensity was significantly associated with mortality reduction

Janssen I [34] (2006) *	Prospective cohort	Physical activity	All-cause mortality	Elderly with coronary artery disease (1045)	Curvilinear inverse dose - response relationship between physical activity and all-cause mortality, such that greater benefits were seen at the lower end of the energy expenditure scale, with a plateau occurring at approximately 4000 kcal/wk
Bucksch J [35] (2005) *	Prospective cohort	Physical activity	All-cause mortality	Adults 30-69 y (7187)	Inverse dose - response relationship between physical activity of moderate intensity and all-cause mortality in women but not in men
Lam TH [36] (2004) *	Case-control study	Physical activity	All-cause and cause-specific mortality	24,079 dead cases and 13,054 live controls	No dose-response gradient was observed between physical activity and mortality beyond the level of <1 episode per month
Yu S [37] (2003)*	Case-control study	Physical activity	All-cause, cardiovascular and coronary heart disease mortality	Men 49-64 y (1975)	Inverse dose-response relation was found for heavy intensity leisure time physical activity but not for light and moderate intensity activity
Leon AS [38] (1997)	Prospective cohort	Physical activity	All-cause and coronary heart disease mortality	Middle-aged men at high risk for coronary heart disease (12,138)	No dose-response gradient was observed between physical activity and mortality beyond the group with an average leisure time physical activity of 22.7 min/d (range 10-36 min/d)
Paffenbarger RS Jr [39] (1986)	Prospective cohort	Physical activity	All causes mortality	Harvard alumni aged 35-74 y (16,936)	Inverse dose-response gradient was observed between physical activity and mortality from less than 500 to 3500 kcal per week, beyond which benefit was only slight

† 39 studies related to association of mortality with dose of exercise found during PubMed search “exercise[Title/Abstract] OR physical activity[Title/Abstract]] AND ((dose[Title/Abstract] OR amount[Title/Abstract])) AND mortality[Title/Abstract]”

* Studies which did not show a dose-response association

** Studies showing increased risk at the higher end of the activity range

such as Type 2 diabetes. Prolonged sitting, for eight to 12 hours or more a day, increased the risk of developing type 2 diabetes by 90% and sedentary behaviour increases our risk disease or premature death, even if we exercise (42). Researchers from Toronto who analyzed 47 studies demonstrated that sedentary behavior (remaining seated still) outweighs the benefit we get from exercise, can lead to death from cardiovascular events and cancer as well as can cause chronic conditions such as Type 2 diabetes. Prolonged sitting, for eight to 12 hours or more a day has shown to increase the risk of developing type 2 diabetes by

90%. However, regular exercise can lower the negative health impact of sedentary behaviour.

HOW MUCH EXERCISE IS IDEAL?

Three new large-scale studies provide some clarity to the above debate, suggesting that the ideal dosage of exercise for a longer life is a slightly higher than what is currently recommended, but less than many of us might expect. The studies also found that prolonged or intense exercise is unlikely to be harmful and could add years to people's lives (5, 6).

In the first of the three studies done to study this area, researchers utilized pooled data about people's exercise habits from six large, ongoing health surveys in the National Cancer Institute Cohort Consortium, with information on more than 660,000, mostly middle-aged adults in order to study the mortality benefit with the duration of exercise (6). This study included more than 116,000 deaths, with a median follow-up of 14 years. Using this data, the researchers stratified the adults by their weekly exercise time, from those who did not exercise at all to those who worked out for 10 times the current recommendations or more, and

mortality data for the groups. As expected, the people who did not exercise at all were at the highest risk of premature death. Those who exercised a little, but not meeting the present recommendations, still lowered their risk of premature death by 20%. Those who met guidelines precisely, completing 150 minutes per week of moderate exercise, had 31% less risk of dying during the 14-year period compared with those who never exercised. The ideal for exercise benefits, however, came among those who reached 3 to 5 times the physical activity recommendation, working out moderately, mostly by walking, for 450 minutes per week, or a little more than an hour per day. They were 39% less likely to die prematurely compared to than people who never exercised. Beyond that point, the benefits plateaued, but never significantly declined. Those few individuals engaging in 10 times or more than the recommended exercise dosage, gained almost the same reduction in mortality risk (39% vs. 31%) as people who simply met the guidelines without any increased their risk of dying prematurely. A similar dose-response relationship was also observed for mortality due to cardiovascular disease and to cancer.

The second new study done by the Australian researchers reached a similar conclusion regarding the mortality benefit and the intensity of exercise and mortality (5). For this study, Australian researchers closely examined health survey data for more than 200,000 Australian adults of aged 45 and above to determine how much time each person spent exercising and how much of that exercise qualified as vigorous; running or jogging instead of walking, or playing competitive singles tennis versus a sociable doubles game. During 1.4 million person-years of follow-up, 7435 deaths were registered. They also found that meeting the exercise guidelines substantially reduced the risk of early death, even if someone's exercise was moderate, such as walking. Those who spent up to 30% of their weekly exercise time in

vigorous activities were 9% less likely to die prematurely than people who exercised for the same amount of time but always moderately, while those who spent more than 30% of their exercise time in strenuous activities gained an extra 13% reduction in early mortality when compared with people who never exercised. The researchers did not see any increase in mortality, even among those few people completing the largest amounts of intense exercise.

The third study looked at data from the NHANES (National Health and Nutritional Examination Survey) from 1999-2006 in the United States where they followed up the study cohort till 2011 (3). 48 different individual physical activities (e.g., swimming, running, bicycling) were assessed. The total moderate-to-vigorous physical activity (MVPA) MET-min-month was calculated based on these 48 individual physical activities. Engaging in MVPA even below the minimum recommendation was associated with survival benefits, and the greatest survival effects occurred at a dose of approximately 5 times the minimum recommendation (45% reduction of the risk of all-cause mortality). Although very high levels (e.g., 10 times the minimum recommendation) of self-reported MVPA did not demonstrate the greatest survival effects, high levels of physical activity did not appear to have harmful effects. These results were comparable with the above two studies.

These were not randomized trials and the reliance on people's recall of exercise habits was a major limitation. Therefore, the only conclusion that the researchers could demonstrate was the association of reduced mortality rate with exercise. Still, this association was strong and consistent and the takeaway message seemed straightforward. These studies reinforced a universal conclusion: a modest amount of weekly exercise can produce huge benefits. It has also

shown that high levels of exercise appear to carry no excess risks. They also provide important evidence to 'inactive' individuals by showing that modest amounts of activity provide substantial benefits, while reassuring 'very active' individuals of no exercise-associated increase in mortality.

RECOMMENDATIONS

So how could one reduce the time you spend in inactivity that is harmful and optimize physical activity for a healthy life?

Be aware of how much time is spent sedentary and make a goal of reducing that number a little bit each week. Also, make it a goal to stand up or walk around for a minute or three once every half an hour spent sedentary. Anyone who is physically capable of activity should try to reach at least 150 minutes, and a peak of about 450 minutes (3 to 5 times the recommended) of leisure time physical activity per week. Larger doses (10 or more times the minimum) do not seem to be unsafe but with no additional benefit over the above recommendations.

In conclusion, health care professionals should encourage inactive adults to perform leisure time physical activity and do not need to discourage adults who already participate in high-activity levels. Physical activity should be endorsed in clinical and public health activity guidelines to maximize the population benefits of exercise.

REFERENCES

1. Li T, Wei S, Shi Y, Pang S, Qin Q, Yin J et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *British Journal of Sports Medicine*. 2015; **18**: doi:pic:bjssports-2015-094927. 10.1136/bjssports-2015-094927. [Epub ahead of print]

2. Li Y, Gu M, Jing F, Cai S, Bao C, Wang J et al. Association between physical activity and all cancer mortality: Dose-response meta-analysis of cohort studies. *International Journal of Cancer*. 2015; 28: doi: 10.1002/ijc.29828. [Epub ahead of print]
3. Loprinzi PD. Dose-response association of moderate-to-vigorous physical activity with cardiovascular biomarkers and all-cause mortality: Considerations by individual sports, exercise and recreational physical activities. *Preventive Medicine*. 2015; 22(81): 73-77.
4. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, Gaspoz JM et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥ 60 years: a systematic review and meta-analysis. *British Journal of Sports Medicine*. 2015; 49(19): 1262-1267.
5. Gebel K, Ding D, Chey T, Brown WJ, Bauman AE et al. Effect of Moderate to Vigorous Physical Activity on All-Cause Mortality in Middle-aged and Older Australians. *Journal of the American Medical Association International Medicine*. 2015; 6:doi:0.1001/jamainternmed.2015.0541. [Epub ahead of print]
6. Arem H, Moore SC, Patel A, Hartge P, Campbell PT, Adami HO et al. Leisure Time Physical Activity and Mortality: A Detailed Pooled Analysis of the Dose-Response Relationship. *Journal of the American Medical Association International Medicine*. 2015; 6:doi:10.1001/jamainternmed.2015.0533. [Epub ahead of print]
7. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of Jogging and Long-Term Mortality: The Copenhagen City Heart Study. *Journal of American College of Cardiology*. 2015; 65(5): 411-419.
8. Matthews CE, Moore SC, Sampson J, Blair A, Xiao Q, Keadle SK et al. Mortality Benefits for Replacing Sitting Time with Different Physical Activities. *Medicine and Science in Sports and Exercise*. 2015 Sep; 47(9): 1833-1840.
9. Wu CY, Hu HY, Chou YC, Huang N, Chou YJ, Li CP. The association of physical activity with all-cause, cardiovascular, and cancer mortalities among older adults. *Preventive Medicine*. 2015; 72: 23-29.
10. van der Ploeg HP, Chey T, Ding D, Chau JY, Stamatakis E, Bauman AE. Standing time and all-cause mortality in a large cohort of Australian adults. *Preventive Medicine*. 2014; 69: 187-191.
11. Kelly P, Kahlmeier S, Götschi T, Orsini N, Richards J, Roberts N et al. Systematic review and meta-analysis of reduction in all-cause mortality from walking and cycling and shape of the dose-response relationship. *International Journal of Behavioral Nutrition and Physical Activity*. 2014; 24: 11: 132.
12. 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 Aug 5; 64(5): 472-81.
13. Mons U, Hahmann H, Brenner H. A reverse J-shaped association of leisure time physical activity with prognosis in patients with stable coronary heart disease: evidence from a large cohort with repeated measurements. *Heart*. 2014; 100(13): 1043-1049.
14. Sadarangani KP, Hamer M, Mindell JS, Coombs NA, Stamatakis E. Physical activity and risk of all cause and cardiovascular disease mortality in diabetic adults from Great Britain: pooled analysis of 10 population-based cohorts. *Diabetes Care*. 2014; 37(4): 1016-1023.
15. Williams PT. Dose-response relationship of physical activity to premature and total all-cause and cardio-vascular disease mortality in walkers. *Public Library of Science One*. 2013; 8(11): e78777.doi: 10.1371/journal.pone.0078777
16. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE et al. Daily sitting time and all-cause mortality: a meta-analysis. *Public Library of Science One*. 2013; 8(11): e80000.doi: 10.1371/journal.pone.0080000.
17. Williams PT. Walking and running produce similar reductions in cause-specific disease mortality in hypertensives. *Hypertension*. 2013; 62(3): 485-491.
18. Johnsen NF, Ekblond A, Thomsen BL, Overvad K, Tjønneland A. Leisure time physical activity and mortality. *Epidemiology*. 2013; 24(5): 717-725.
19. Hamer M, de Oliveira C, Demakakos P. Non-exercise physical activity and survival: English longitudinal study of aging. *American Journal of Preventive Medicine*. 2014; 47(4): 452-460.
20. Kodama S, Tanaka S, Heianza Y, Fujihara K, Horikawa C, Shimano H et al. Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes: a meta-analysis. *Diabetes Care*. 2013; 36(2): 471-479.
21. Brown WJ, McLaughlin D, Leung J, McCaul KA, Flicker L, Almeida OP et al. Physical activity and all-cause mortality in older women and men. *British Journal of Sports Medicine*. 2012; 46(9): 664-668.
22. Matthews CE, George SM, Moore SC, Bowles HR, Blair A, Park Y et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. *American Journal of Clinical Nutrition*. 2012; 95(2): 437-445.
23. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *International Journal of Epidemiology*. 2011; 40(5): 1382-1400.
24. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC et al. The minimum

- amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011; 378(9798): 1244-1253.
25. Woodcock J, Franco OH, Orsini N, Roberts I. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. *International Journal of Epidemiology*. 2011; 40(1): 121-138.
 26. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase the risk of cardiovascular disease mortality in men. *Medicine and Science in Sports and Exercise*. 2010; 42(5): 879-885.
 27. Stessman J, Hammerman-Rozenberg R, Cohen A, Ein-Mor E, Jacobs JM. Physical activity, function, and longevity among the very old. *Archives of International Medicine*. 2009; 169(16): 1476-1483.
 28. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Medicine and Science in Sports and Exercise*. 2009; 41(5): 998-1005.
 29. Moholdt T, Wisløff U, Nilsen TI, Slørdahl SA. Physical activity and mortality in men and women with coronary heart disease: a prospective population-based cohort study in Norway (the HUNT study). *European Journal of Cardiovascular Prevention and Rehabilitation*. 2008; 15(6): 639-645.
 30. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. *British Journal of Sports Medicine*. 2008; 42(4): 238-243.
 31. Wisløff U, Nilsen TI, Droyvold WB, Mørkved S, Slørdahl SA, Vatten LJ. A single weekly bout of exercise may reduce cardiovascular mortality: how little pain for cardiac gain? 'The HUNT study, Norway'. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2006; 13(5): 798-804.
 32. Khaw KT, Jakes R, Bingham S, Welch A, Luben R, Day N et al. Work and leisure time physical activity assessed using a simple, pragmatic, validated questionnaire and incident cardiovascular disease and all-cause mortality in men and women: The European Prospective Investigation into Cancer in Norfolk prospective population study. *International Journal of Epidemiology*. 2006; 35(4): 1034-1043. Epub 2006 May 18.
 33. Lan TY, Chang HY, Tai TY. The relationship between components of leisure physical activity and mortality in Taiwanese older adults. *Preventive Medicine*. 2006; 43(1): 36-41.
 34. Janssen I, Jolliffe CJ. Influence of physical activity on mortality in elderly with coronary artery disease. *Medicine and Science in Sports and Exercise*. 2006; 38(3): 418-427.
 35. Bucksch J. Physical activity of moderate intensity in leisure time and the risk of all-cause mortality. *British Journal of Sports Medicine*. 2005; 39(9): 632-638.
 36. Lam TH, Ho SY, Hedley AJ, Mak KH, Leung GM. Leisure time physical activity and mortality in Hong Kong: a case-control study of all adult deaths in 1998. *Annals of Epidemiology*. 2004; 14(6): 391-398.
 37. Yu S, Yarnell JW, Sweetnam PM, Murray L; Caerphilly study. What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart*. 2003; 89(5): 502-506.
 38. Leon AS, Myers MJ, Connett J. Leisure time physical activity and the 16-year risks of mortality from coronary heart disease and all-causes in the Multiple Risk Factor Intervention Trial (MRFIT). *International Journal of Sports Medicine*. 1997; 18 Suppl 3: S208-215.
 39. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *New England Journal of Medicine*. 1986; 314(10): 605-613.
 40. Eckel RH, Jakicic JM, Ard JD et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Force on Practice Guidelines. *Journal of American College of Cardiology*. 2014; 63: 2960-2984.
 41. Global recommendations on physical activity for health. World Health Organization. 2010. ISBN: 9789241599979.
 42. Biswas A, Faulkner GE, Bajaj RR et al. Sedentary Time and Its Association with Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis: Sedentary Time and Disease Incidence, Mortality, and Hospitalization. *Annals of Internal Medicine*. 2015; 162(2): 123-132 Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task.