PART F. CHAPTER 6. ALL-CAUSE MORTALITY, CARDIOVASCULAR MORTALITY, AND INCIDENT CARDIOVASCULAR DISEASE

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INTRODUCTION

The *Physical Activity Guidelines Advisory Committee Report, 2008*[1] concluded that the amount of moderate-to-vigorous physical activity is inversely associated with all-cause mortality, cardiovascular disease (CVD) mortality, and incident CVD. All of the dose-response data used to develop the physical activity targets for the *2008 Physical Activity Guidelines*[2] were developed using epidemiologic data from longitudinal cohort studies with moderate-to-vigorous physical activity as the lone physical activity exposure.

In 2008, the Advisory Committee[1] relied mostly on the primary literature to perform its work on all-cause mortality, CVD mortality, and CVD. Since then, studies on the relationship of moderate-to-vigorous physical activity to these outcomes have continued to be published. In 2008, the assessment of CVD as an outcome was principally limited to coronary artery disease.[1] Since then, studies have been published on incident cerebrovascular disease—primarily ischemic stroke—and incident heart failure. In addition, due to the volume of conducted studies, reviews, pooled analyses, and meta-analyses with many component studies and large sample sizes now are available on the relationship of moderate-to-vigorous physical activity to all-cause mortality, CVD mortality, and CVD. The abundance of reviews permitted the Subcommittee to rely on systematic reviews, meta-analyses, and pooled analyses to perform our review.

In 2008, the Advisory Committee[1] began to define a dose-response relationship among moderate-to-vigorous physical activity and both all-cause and CVD mortality as a curvilinear one, with an early decrease in risk with greater amounts of moderate-to-vigorous physical activity, and with continuing benefit with still greater physical activity amounts. While undertaking the current review, the Subcommittee believed it important to confirm whether this relationship still holds with new data, and to examine whether it extends to the various CVD outcomes of incident CVD, cerebrovascular disease (ischemic stroke), and incident heart failure.

REVIEW OF THE SCIENCE

Overview of Questions Addressed

This chapter addresses three major questions and related subquestions:

1. What is the relationship between physical activity and all-cause mortality?
   a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
   b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?
2. What is the relationship between physical activity and cardiovascular disease mortality?
   a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
   b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?
3. What is the relationship between physical activity and cardiovascular disease incidence?
   a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
   b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?

Data Sources and Process Used to Answer Questions

The Exposure Subcommittee determined that systematic reviews, meta-analyses, and pooled analyses provided sufficient literature to answer all three research questions. One search and triage process was conducted for Questions 1 through 3, which covered all-cause mortality, cardiovascular disease mortality, and cardiovascular disease incidence. For complete details on the systematic literature review process, see *Part E. Scientific Literature Search Methodology*.

Question 1. What is the relationship between physical activity and all-cause mortality?

a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
b) Does the relationship vary by age, sex, race/ethnicity, or socioeconomic status, and weight status?

Source of Evidence: Systematic reviews, meta-analyses, pooled analyses

Conclusion Statements

Strong evidence demonstrates a clear inverse dose-response relationship between the amount of moderate-to-vigorous physical activity and all-cause mortality. The strength of the evidence is very unlikely to be modified by more studies of these outcomes. **PAGAC Grade: Strong.**

Strong evidence demonstrates a dose-response relationship between physical activity and all-cause mortality. The shape of the curve is nonlinear, with the greatest benefit seen early in the dose-response relationship. The relationship of moderate-to-vigorous physical activity and risk reduction has no lower limit. Risk appears to continue to decrease with increased exposure up to at least three to five times the amounts of the lower bound of moderate-to-vigorous physical activity recommended in the 2008 Guidelines (i.e., 150 minutes per week). The new data are consistent with those used to develop the 2008 Guidelines. **PAGAC Grade: Strong.**

Strong evidence demonstrates that the dose-response relationships between moderate-to-vigorous physical activity and all-cause mortality do not vary by age, sex, race, or weight status. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether these relationships vary by ethnicity or socioeconomic status. **PAGAC Grade: Not assignable.**

Review of the Evidence

An initial search for systematic reviews, meta-analyses, pooled analyses, and reports identified sufficient literature to answer the research question as determined by the Subcommittee. Additional searches for original research were not needed.

In data collected from 2006 to 2017, the outcomes of all-cause mortality, CVD mortality, and incident CVD were often considered in the same systematic reviews and meta-analyses. Therefore, the systematic reviews and meta-analyses contributing to the understanding of the relation of physical activity to these three outcomes had significant overlap. Similarly, many of the same studies appeared in the systematic reviews and meta-analyses identified in our searches. In this section, we deal only with all-cause mortality.

A total of 12 existing reviews were included in the analysis of the relation of physical activity to all-cause mortality: 2 systematic reviews,[3, 4] 7 meta-analyses,[5-11] and 3 pooled analyses.[12-14] Of these 12 reviews, 5 also addressed CVD mortality and are reported later in the chapter. Follow-up for these studies ranged from 3.8 to longer than 20 years, and up to 3.4 million participants in total were studied across these reviews and meta-analyses.

The two systematic reviews included a large number of contributing studies: 121[3] and 254.[4] However, in Milton et al,[3] only seven addressed all-cause mortality, nine addressed CVD, and three addressed stroke. For Warburton et al,[4] 70 component studies addressed all-cause mortality, 49 addressed CVD, and 25 addressed stroke. The total numbers for each outcome were not reported. The studies covered extensive timeframes: from 1990 to 2013 and from 1950 to 2008, respectively.

The meta-analyses ranged from 9 to 80 studies. Most meta-analyses covered an extensive timeframe: from inception of the database to 1 year before publication,[5, 7, 10, 11] from 1945 to 2013,[8] and from 1970s and 1990s to 2007 and 2006.[6, 9] The pooled analyses include data from six prospective cohort studies Arem et al[12] and Moore et al,[13] (used the same six cohorts) and from 11 cohorts O'Donovan et al.[14]

The majority of the included reviews examined self-reported leisure time moderate-to-vigorous physical activity. Most reviews also established specific physical activity dose categories in metabolic equivalents of task (MET) for minutes or hours per week using quartiles or a variety of categories such as inactive and low, medium, and high levels of physical activity, or high versus low levels of physical activity.

Three reviews addressed specific types of physical activity. Kelly et al[8] studied cycling and walking. Samitz et al[10] studied domain-specific physical activity defined into leisure-time physical activity, activities of daily living, and occupational physical activity. Hamer and Chida[6] studied habitual walking only.

One pooled analysis[14] separately examined individuals who meet the physical activity guidelines in one or two sessions in addition to the usual physical activity categories (inactive, insufficiently active, and regularly active). Merom et al[15] examined dancing versus walking.

Evidence on the Overall Relationship

All the included reviews addressed all-cause mortality as an outcome and five of them also examined CVD mortality.

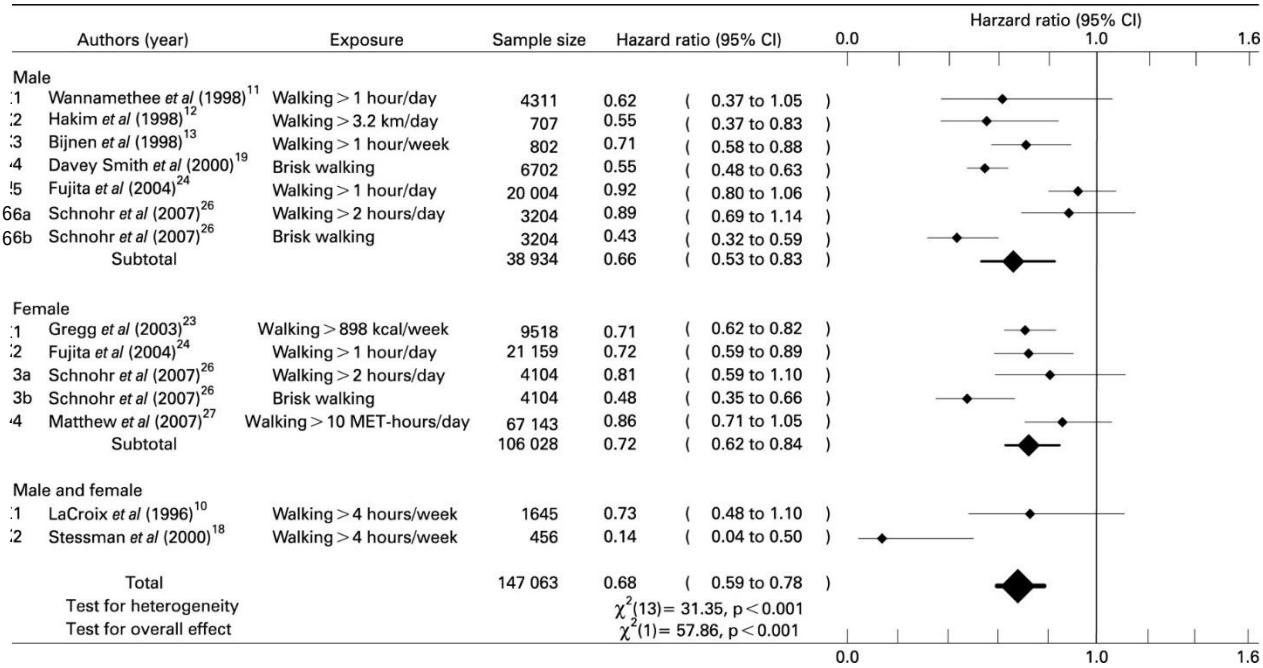
All studies reported an inverse relationship between moderate-to-vigorous physical activity and all-cause mortality in a dose-response fashion as described below. There were no null studies. The pooled analysis, in which individuals meeting guidelines in one or two sessions per week and individuals meeting guidelines with three or more sessions per week were compared to an inactive group, showed no differences in the effect sizes for all-cause mortality between individuals meeting guidelines in 1 to 2 sessions per week (hazard ratio (HR)= 0.60; confidence interval (CI): 0.45-0.82) and individuals meeting guidelines in 3 or more sessions per week (HR=0.59; CI: 0.48-0.73), compared to the inactive group.[14]

In the analysis by Kelly et al,[8] the effect sizes for cycling and walking were similar. For exercise of 11.25 MET-hours per week (675 MET-minutes per week), the reduction in risk for all-cause mortality was 11 percent (95% CI: 4%-17%) for walking and 10 percent (95% CI: 6%-13%) for cycling. The shape of the dose-response relationship was modeled through meta-analysis of pooled relative risks within three exposure intervals. Consistent with other studies, the dose-response analysis showed that for walking or cycling, the greatest reduction in risk for all-cause mortality occurred within the lowest exposure categories of physical activity.

Hamer and Chida[6] studied the effect of walking only on both all-cause mortality and CVD mortality. The analysis included 18 prospective studies with 459,833 total participants. The Forest plots, displayed in Figure F6-1, show a dose-response for amount (volume of walking) and walking pace. Hamer and Chida[6] found walking pace to be a stronger independent predictor of all-cause mortality than volume: 48 percent versus 26 percent risk reductions, respectively. However, within the exposure categories the

studies had considerable heterogeneity. The greatest walking exposure groups averaged more than 5.2 hours per week or more than 10.7 miles per week, and the groups ranged from more than 1 hour per week to more than 2 hours per day and more than 6.0 miles per week to more than 12.4 miles per week. Walking pace was generally assessed as a relative rather than an absolute measure, although several studies defined ''brisk'' as more than 3.0 miles per hour and ''moderate'' as 2.0 to 2.9 miles per hour. Minimal walking categories averaged approximately 3 hours per week (ranging from approximately 30 minutes per week to approximately 5 hours per week) or 6.1 miles per week (ranging from approximately 3.1 miles per week to approximately 9.3 miles per week), which equated to a casual or moderate walking pace of approximately 2 miles per hour.

Figure F6-1. The Association Between Walking and All-Cause Mortality in Men and Women



Note: Walking is favored, with a shift of the estimate to the left. These estimates are similar to the effects on cardiovascular disease mortality in Question 2, Figure F6-4.
Source: Reproduced from [Walking and primary prevention: A meta-analysis of prospective cohort studies, Hamer and Chida[6], 42, 2008] with permission from BMJ Publishing Group Ltd.

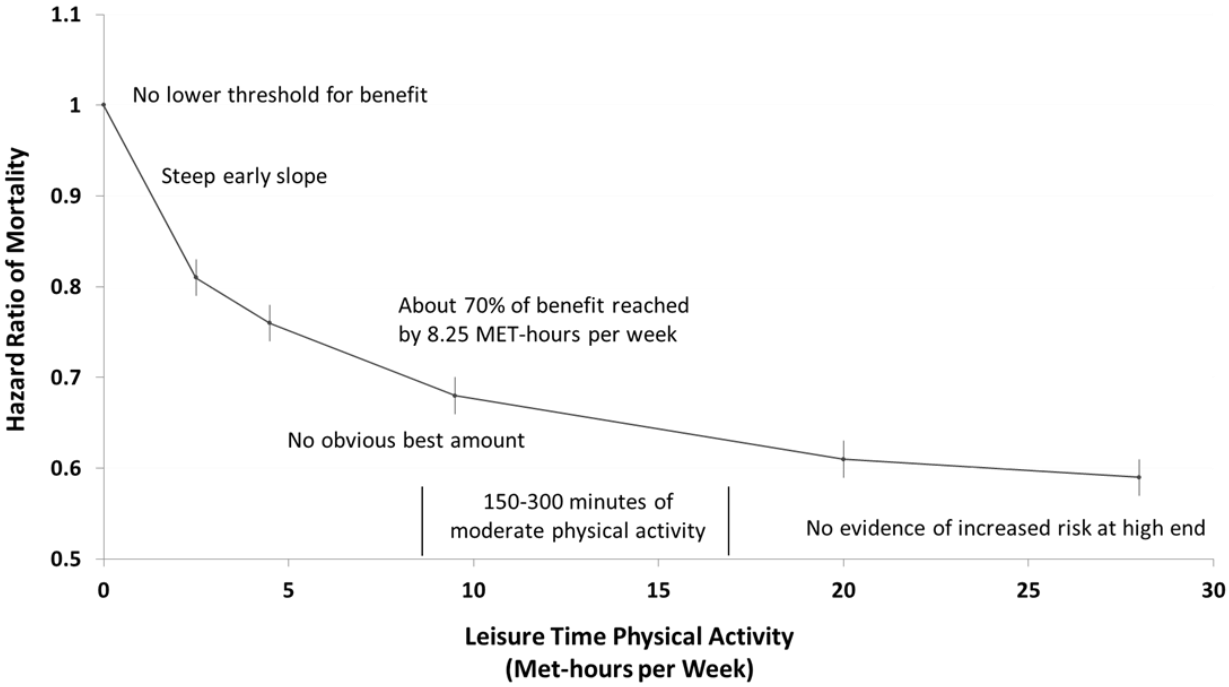
Dose-response: Every one of the 12 studies within our analysis demonstrated a significant inverse dose-response relationship with all-cause mortality across physical activity exposure groups. The uniformity and strength of these relationships led to the strength of association finding for this subquestion. The uniformity of findings prompted us to highlight the two pooled analyses of Arem et al[12] and Moore et al.[13] In these pooled analyses of six studies, combining data at the individual level allowed an

examination of the strength of effects and confidence boundaries across large populations with great precision.

Moore et al[13] reported a pooled analysis of the association of leisure-time physical activity with mortality during follow-up in pooled data from six prospective cohort studies in the National Cancer Institute Cohort Consortium. The combined pooled cohort included 654,827 individuals, ages 21 to 90 years. Moderate-to-vigorous physical activity in MET-hours per week was used to generate adjusted survival curves (for participants ages 40 years and older), with 95% confidence intervals derived by bootstrap. The study included a median 10 years of follow-up and 82,465 deaths. Figure F6-2 shows the survival curves against several characteristics of the relationship common among the studies reporting on dose-response on all-cause mortality. The survival curve from this analysis demonstrates several important points:

1. The beneficial effect has no lowest threshold.
2. The slope is steepest at the lowest amounts of moderate-to-vigorous physical activity.
3. At least 70 percent of the potential benefit on all-cause mortality is reached by achieving 8.25 MET-hours (150 minutes) per week of moderate-to-vigorous physical activity.
4. There is no obvious best amount.
5. There is no apparent upper threshold.
6. Benefits continue to accrue as more physical activity is accrued.
7. Activity volumes (amounts) up to four times the 2008 Guidelines[2] (150-300 minutes moderate-intensity physical activity) show no evidence of increased mortality risk.

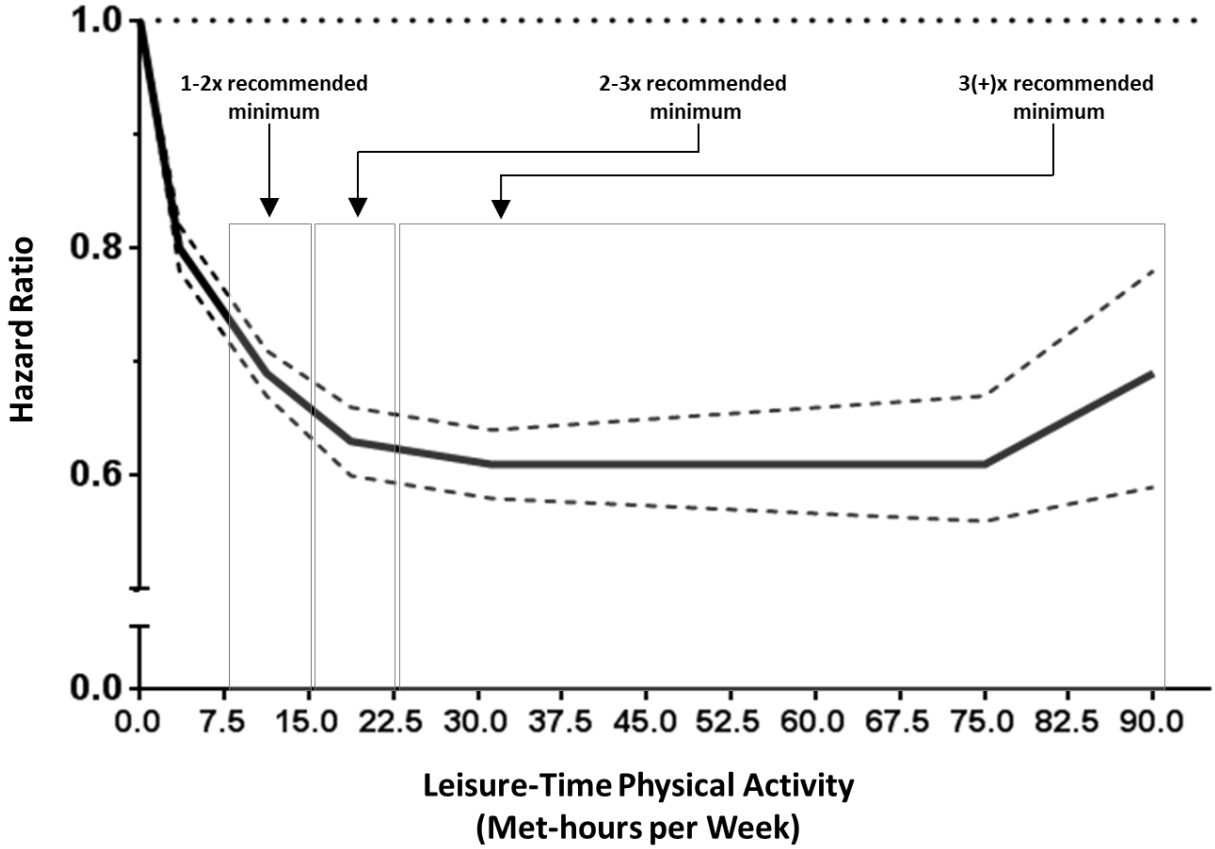
Figure F6-2. Relationships of Moderate-to-Vigorous Physical Activity to All-Cause Mortality, with Highlighted Characteristics Common to Studies of This Type



Source: Adapted from data found in Moore et al., 2012.[13]

Similarly, Arem et al[12] reported a pooled analysis of six studies in the National Cancer Institute Cohort Consortium (baseline collection in 1992-2003; the same studies reported in Moore et al.[13] These were population-based prospective cohorts in the United States and Europe, with self-reported physical activity analyzed in 2014. A total of 661,137 men and women (median age, 62 years; range 21 to 98 years) and 116,686 deaths were included. Cox proportional hazards regression with cohort stratification was used to generate multivariable-adjusted hazard ratios and 95% confidence intervals. Median follow-up time was 14.2 years. The dose response-relationship from this report is shown in Figure F6-3. Several characteristics of this dose-response relationship are reminiscent of that of Moore et al[13] (Figure F6-2). However, several differences in results are described below.

Figure F6-3. Relationships of Moderate-to-Vigorous Physical Activity to All-Cause Mortality, with Highlighted Characteristics Common to Studies of this Type



Source: Adapted from data found in Arem et al., 2015.[12]

Here the relationship is carried out to a category (greater than 75 MET-hours per week) representing approximately ten times the exposure of the lower end of the 2008 Guidelines[2] (i.e., 150 minutes per week). At this greater exposure, an apparent uptick in mortality risk occurs. This possible uptick is not apparent in the Moore et al[13] study that went only to about four times the Guidelines exposure. In the Arem et al[12] pooled study of 661,137 individuals only 18,831 participants (2.8% of the total) were included in the 40 to 75 MET-hours per week category, and only 4,077 (0.62%) in the more than 75 MET-hours per week category.[12] These accounted for only 1,390 (1.2%) and 212 (0.18%) of 116,686 deaths in the combined analysis, respectively, and the error bars are large. Figure F6-3 indicates that the point estimate of risk for the greatest exposure group is the same as the estimate for those meeting the 2008 Guidelines (7.5 to 15 MET-hours per week, or 150 to 300 minutes per week). This apparent uptick in risk at extreme volumes of exercise has been observed before. Paffenbarger et al[16, 17] reported it in the Harvard Alumni Heart study for CVD (heart attack) risk, in 1978 and 1993. However, as in these previous

reports, the apparent rise in risk at very high amounts of moderate-to-vigorous physical activity did not reach the level of statistical significance.[12]

In a seminal paper in 2016, Ekelund et al[5] examined the associations of sedentary behavior (sitting and television watching) and physical activity (moderate-to-vigorous physical activity) with all-cause mortality. See *Part D. Integrating the Evidence* and *Part F. Chapter 2. Sedentary Behavior* for more details on these interactions. Using 16 contributing studies, combining data across all studies to analyse the association of daily sitting time and physical activity with all-cause mortality, estimating summary hazard ratios using Cox regression, and expressing physical activity in terms of MET-hours per week of moderate-to-vigorous physical activity, Ekelund et al[5] found the same curvilinear relationships among physical activity and all-cause mortality as observed Arem et al[12] and Moore et al.[13]

Evidence on Specific Factors

Demographic factors and weight status: Most studies reported overall distributions of demographic factors (race, sex, weight status) across exposure groups within individual studies in their reviews and meta-analyses. Given the nature of meta-analyses—conducted at the study level versus the individual level—it is difficult to detect differential effects by demographic factors and weight status unless the specific component studies performed them within their analysis. Some studies examined subgroup effects directly in their review or meta-analysis; one focused on adults older than 60 years.[7] In such studies, no subgroup effects were detected. The O'Donovan et al[14] analysis of "weekend warrior" physical activity behavior on all-cause mortality, showed no differential responses by sex.

However, the pooled analyses[12, 13] permit a direct examination of the relative effects across demographic categories. In these studies, effects are reported for strata across sex, race, and body mass index (BMI) and the aggregate event data reported according to strata. Although not directly tested in these reports, no differential effects across sex, race, or BMI strata are readily apparent. Strata for socioeconomic status and ethnicity were not reported.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Comparing 2018 Findings with the 2008 Scientific Report

Compared with the 2008 Advisory Committee, this Subcommittee's review of systematic reviews, meta-analyses, and pooled studies exploited the analysis of larger cohorts and provided more precision

around the effect size estimates. Our review identified the same dose-effect estimates relating moderate-to-vigorous physical activity with all-cause mortality as was described in 2008. Given the large population sizes and heterogeneity studied, we have more confidence in the precision of these numbers as well as their generalizability to U.S. adult men and women, and populations of all races, ages, and body sizes.

Question 2. What is the relationship between physical activity and cardiovascular disease mortality?

a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
b) Does the relationship vary by age, sex, race/ethnicity, or socioeconomic status, and weight status?

Source of Evidence: Systematic reviews, meta-analyses, pooled analyses

Conclusion Statements

Strong evidence demonstrates that a strong inverse dose-response relation exists between amount of moderate-to-vigorous physical activity and cardiovascular disease mortality. The strength of the evidence is very unlikely to be modified by more studies of this outcome. **PAGAC Grade: Strong.**

Strong evidence demonstrates that the shape of the curve is nonlinear, with the greatest benefit seen early in the dose-response relationship. The relationship of moderate-to-vigorous physical activity and risk reduction has no lower limit. Risk appears to continue to decrease with increased exposure up to at least three to five times the amounts of moderate-to-vigorous physical activity recommended in the 2008 Guidelines (i.e., 150 minutes per week). The new data are consistent with those used to develop the 2008 Guidelines. **PAGAC Grade: Strong.**

Strong evidence demonstrates that these relationships do not vary by age, sex, race, or weight status. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether these relationships vary by ethnicity or socioeconomic status. **PAGAC Grade: Not assignable.**

Review of the Evidence

An initial search for systematic reviews, meta-analyses, pooled analyses, and reports identified sufficient literature to answer the research question as determined by the Subcommittee. Additional searches for original research were not needed.

In data collected from 2006 to 2017, the outcomes of all-cause mortality, CVD mortality, and incident CVD were often considered in the same systematic reviews and meta-analyses. Therefore, the systematic reviews and meta-analyses contributing to the understanding of the relation of physical activity to these three outcomes had significant overlap. Similarly, many of the same studies appeared in the systematic reviews and meta-analyses identified in our searches. In this section, we address only CVD mortality; however, the format and conclusions differ little from those made for all-cause mortality.

A note on nomenclature is necessary here. For this discussion, CVD mortality refers to mortality attributable to CVD in its broadest sense. CVD refers to diseases beyond coronary artery disease, but does not include:

- non-atheromatous or infectious valvular disease and others, such as diseases due to coronary heart disease secondary to coronary artery disease,
- cerebrovascular disease secondary to a cerebrovascular accident or stroke,
- heart failure of ischemic (coronary) or non-ischemic etiology.

A total of six existing reviews were included: one systematic review,[3] three meta-analyses,[5, 6, 18] and two pooled analyses.[14, 15] The reviews were published from 2008 to 2017. The systematic review[3] included 121 studies and a timeframe from 1983 to 2013. The meta-analyses included a range of 16 to 36 studies and covered an extensive timeframe: Ekelund et al,[5] from inception of the database to 2015; Hamer and Chida,[6] and Wahid et al,[18] from 1970s and 1980s to 2007 and 2014 respectively. The pooled analyses included data from 11 cohorts, each from different population surveys.[14, 15]

The majority of the included reviews examined self-reported leisure time moderate-to-vigorous physical activity. Most reviews also established specific physical activity dose categories in MET-minutes or MET-hours per week using quartiles or a variety of categories such as inactive and low, medium, and high levels of physical activity, or high versus low levels of physical activity.

One pooled analysis[14] examined a “weekend warrior” category (meeting the physical activity guidelines in one or two sessions per seek) in addition to the usual physical activity categories (insufficiently active and regularly active) compared to an inactive group. Two reviews addressed specific types of physical activity: dancing[15] and habitual walking.[6]

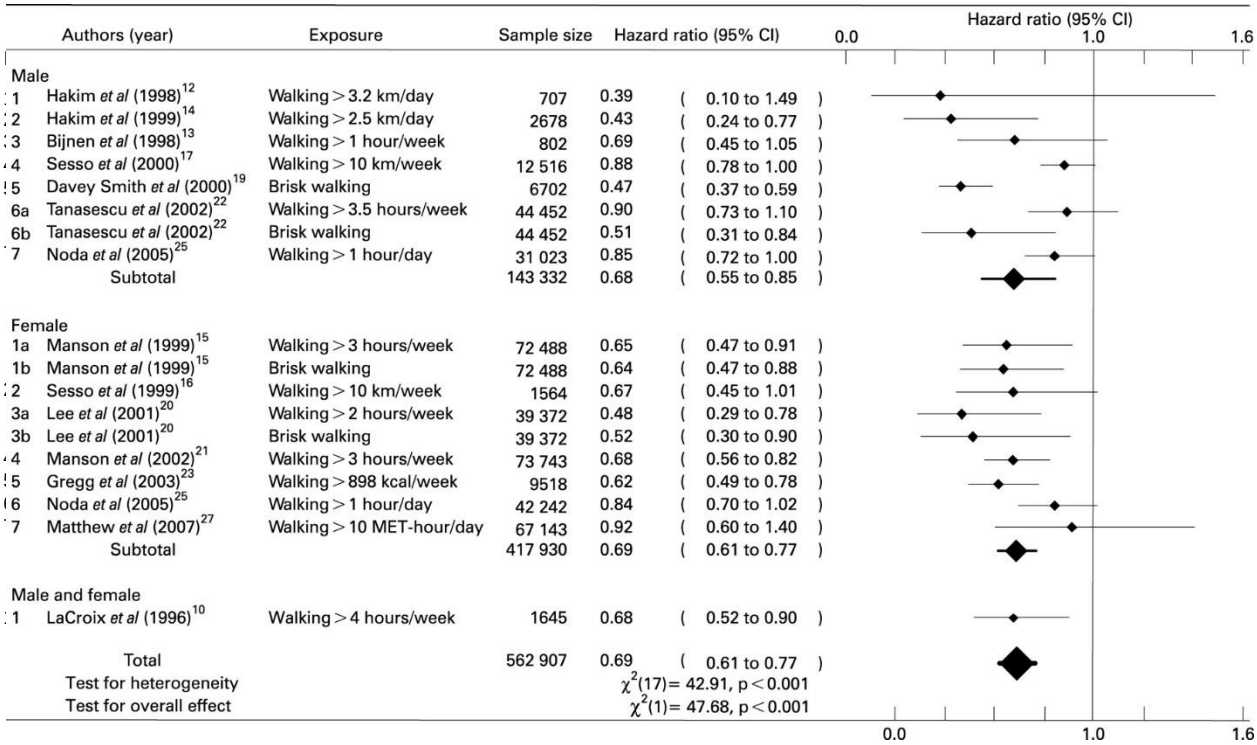
Evidence on the Overall Relationship

All of the included reviews addressed CVD mortality and four of them also assessed all-cause mortality in addition to other outcomes.

As it was for all-cause mortality, all reviews reported an inverse relationship between moderate-to-vigorous physical activity and all-cause mortality in a dose-response fashion, as described below. The reviews included no null studies. The pooled analysis in which individuals meeting guidelines in one or two sessions per week and individuals meeting guidelines with three or more sessions per week were compared to an inactive group, showed no differences (overlapping hazard ratios) in the effect sizes for CVD mortality (HR=0.59 to 0.60).

As noted above, Hamer and Chida[6] studied walking only on both all-cause mortality and CVD mortality. The analysis included 18 prospective studies with 459,833 total participants. The Forest plots for CVD mortality are shown in in Figure F6-4. The effect sizes and confidence intervals for all categories of walking pace and amount are reminiscent of those determined for all-cause mortality (Figure F6-1). This is an example of how closely aligned the moderate-to-vigorous physical activity relationship is for both CVD mortality and all-cause mortality within and across studies.

Figure F6-4. The Association Between Walking and Cardiovascular Mortality Risk in Men and Women



Note: Walking is favored, with a shift of the estimate to the left. Notice the similarity of these estimates to the effects on all-cause mortality in Question 1, Figure F6-1.
Source: Reproduced from [Walking and primary prevention: A meta-analysis of prospective cohort studies, Hamer and Chida[6], 42, 2008] with permission from BMJ Publishing Group Ltd.

Dose-response: Here also, the findings for the dose-response relationships between moderate-to-vigorous physical activity and CVD mortality are basically identical to those found for the relationships between moderate-to-vigorous physical activity and all-cause mortality.

Every one of the 12 studies within our analysis demonstrated a significant inverse dose-response relationship with CVD mortality across physical activity exposure groups. The uniformity and strength of these relationships led to the strength of association finding for this subquestion.

Wahid et al[18] used 36 studies, 33 pertaining to CVD and 3 pertaining to type 2 diabetes mellitus to model the effects of three physical activity categories (low physical activity, 0.1-11.5 MET-hours per week; medium physical activity, 11.5-29.5 MET-hours per week; and high physical activity; ≥29.5 MET-hours per week) in a dose-response fashion on CVD incidence and mortality, coronary heart disease incidence and mortality, myocardial infarction incidence, heart failure incidence, and stroke incidence. For those conditions for which all three categories had entries (CVD incidence, CVD mortality, stroke incidence and

CHD incidence), all but CVD mortality demonstrated a strong curvilinear dose-response relationship across categories.

Evidence on Specific Factors

Demographic factors and weight status*:* Similar to all-cause mortality, the studies providing the strongest evidence regarding subgroup moderation effects on CVD mortality were the pooled analyses of Merom et al[15] and O'Donovan et al.[14] Again, as for all-cause mortality, no differential effects across sex, race, or BMI strata were readily apparent. Strata for socioeconomic status and ethnicity were not reported.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Question 3. What is the relationship between physical activity and cardiovascular disease incidence?

a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?

Source of evidence: Systematic reviews and meta-analyses

Conclusion Statements

Strong evidence demonstrates a significant relationship between greater amounts of physical activity and decreased incidence of cardiovascular disease, stroke, and heart failure. The strength of the evidence is unlikely to be modified by more studies of these outcomes. **PAGAC Grade: Strong.**

Strong evidence demonstrates a significant dose-response relationship between physical activity and cardiovascular disease, stroke, and heart failure. When exposures are expressed as energy expenditure (MET-hours per week), the shape of the curve for incident CVD appears to be nonlinear, with the greatest benefit seen early in the dose-response relationship. It is unclear whether the shapes of the relations for incident stroke and heart failure are linear or nonlinear. There is no lower limit for the relation of MPVA and risk reduction. Risk appears to continue to decrease with increased exposure up to at least five times the current recommended levels of moderate-to-vigorous physical activity. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether these relationships vary by age, sex, race, ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Review of the Evidence

An initial search for systematic reviews, meta-analyses, pooled analyses, and reports identified sufficient literature to answer the research question as determined by the Subcommittee. Additional searches for original research were not needed.

A total of 10 existing reviews were included: 1 systematic review[4] and 9 meta-analyses.[18-26] The reviews were published from 2008 to 2016. The systematic review[4] included 254 studies published between 1950 and 2008.

The meta-analyses included a range of 12 to 43 studies. Most meta-analyses covered an extensive timeframe: from database inception to 2013,[25] from 1954 and 1966 to 2007,[24, 26] and from the 1980s and 1990s to 2005–2016.[18-23]

The majority of included reviews examined self-reported physical activity. Different domains of physical activity were also assessed, including total[21]; occupational and leisure[20]; occupational, leisure, and transport[23]; and leisure physical activity only.[24] Some reviews also established specific dose categories in MET-minutes or MET-hours per week.[18, 21, 22, 26] Other reviews used minimal or low versus moderate or high physical activity levels as reported in individual studies.[4, 19, 24] Two meta-analyses specifically examined tai chi[25] and walking.[26]

Included reviews addressed the incidence of CVD in a variety of ways. Several addressed incident coronary heart disease,[21, 23, 24, 26] incident stroke,[19, 21, 25] and incident heart failure.[20, 22] Warburton et al[4] reviewed incident stroke and coronary (ischemic) heart disease. Wahid et al[18] used 33 studies to address CVD incidence and mortality, coronary heart disease incidence and mortality, myocardial infarction incidence, heart failure incidence, and stroke incidence. Thus, in all, six studies addressed incident coronary heart disease; five studies addressed incident stroke; and three studies addressed incident heart failure.

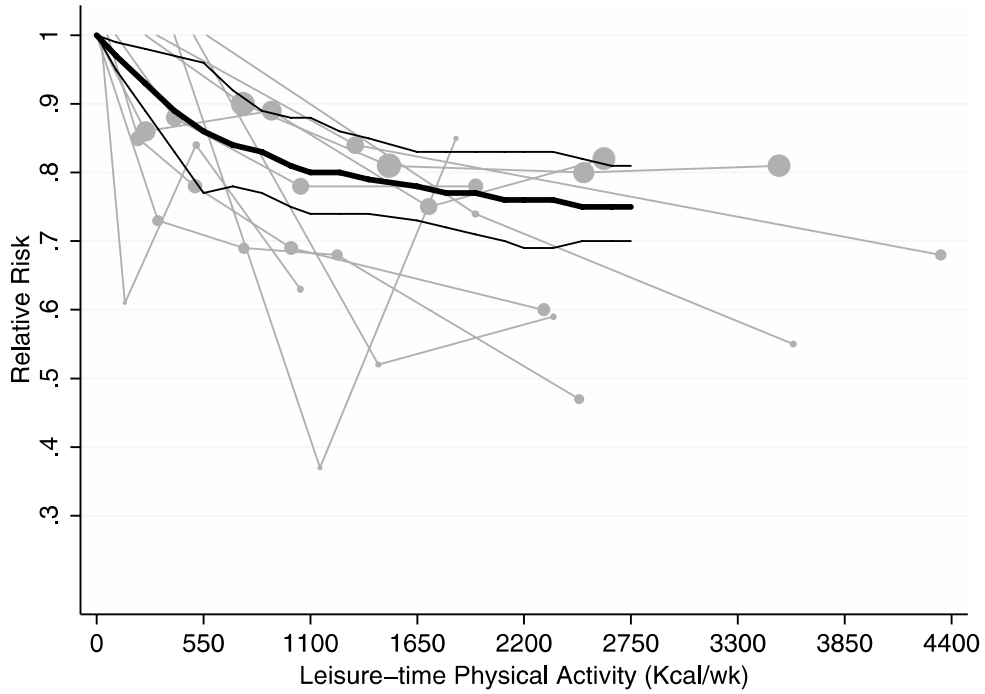
Evidence on the Overall Relationship

All six studies addressing incident coronary heart disease, the five studies addressing incident stroke, and the three studies addressing incident heart failure demonstrated significant dose-response inverse relationships with increased amounts of physical activity. There were no null studies. The shapes of the relationships are discussed below.

Coronary Heart Disease

Sattelmair et al[23] performed a pooled sample meta-analysis of epidemiologic studies to investigate the relationship of MPVA to incident coronary heart disease. Pooled dose-response estimates were derived from qualitative estimates describing low, moderate, and high physical activity. Of the 33 studies initially selected for analysis, 9 permitted quantitative estimates of kilocalories per week of moderate-to-vigorous physical activity. Those participating in leisure-time physical activity at the lower limit of the 2008 Guidelines[2] had a 14 percent reduced risk of developing coronary heart disease (Relative Risk (RR)=0.86 +/-0.09) compared with those reporting no leisure-time physical activity. They reported an inverse dose-response relationship similar to the curves for all-cause mortality and CVD mortality. These curves are characterized by an early decrease in risk, continued benefit with greater exposure, no lower threshold, and no upper limit (Figure F6-5). One MET-hour per week is approximately equal to 1.05 kilocalories per kilogram (kg) per week. Therefore, for a 70 kg individual, the lower boundary of the 2008 Guidelines[2] for moderate-to-vigorous physical activity is achieved at 600 kilocalories per week.

Figure F6-5. Plot with Spline and 95% Confidence Intervals of Relative Risk of Coronary Heart Disease by Kilocalories per Week of Leisure-time Physical Activity



Note: Individual study results are plotted with grey lines; the thick black line shows the trend line for both sexes combined from a random spline-fit model and the thinner black lines show the 95% CI for the trend.
Source: Sattelmair et al., 2011,[23] Dose response between physical Activity and Risk of Coronary Heart Disease, a Meta-Analysis, Circulation, 124: 789-795. https://doi.org/10.1161/CIRCULATIONAHA.110.010710

This analysis points to an important aspect of understanding how the interpretation of dose-response relationships may depend on the modeling parameters. When the dose-response relationships of the pooled studies are modeled using the qualitative exposures of low, moderate, and high physical activity, the dose-response relationship appears linear. When, however, the physical activity exposures are modeled according to MET-hours per week (Figure F6-5), the curvilinear relationship is revealed.

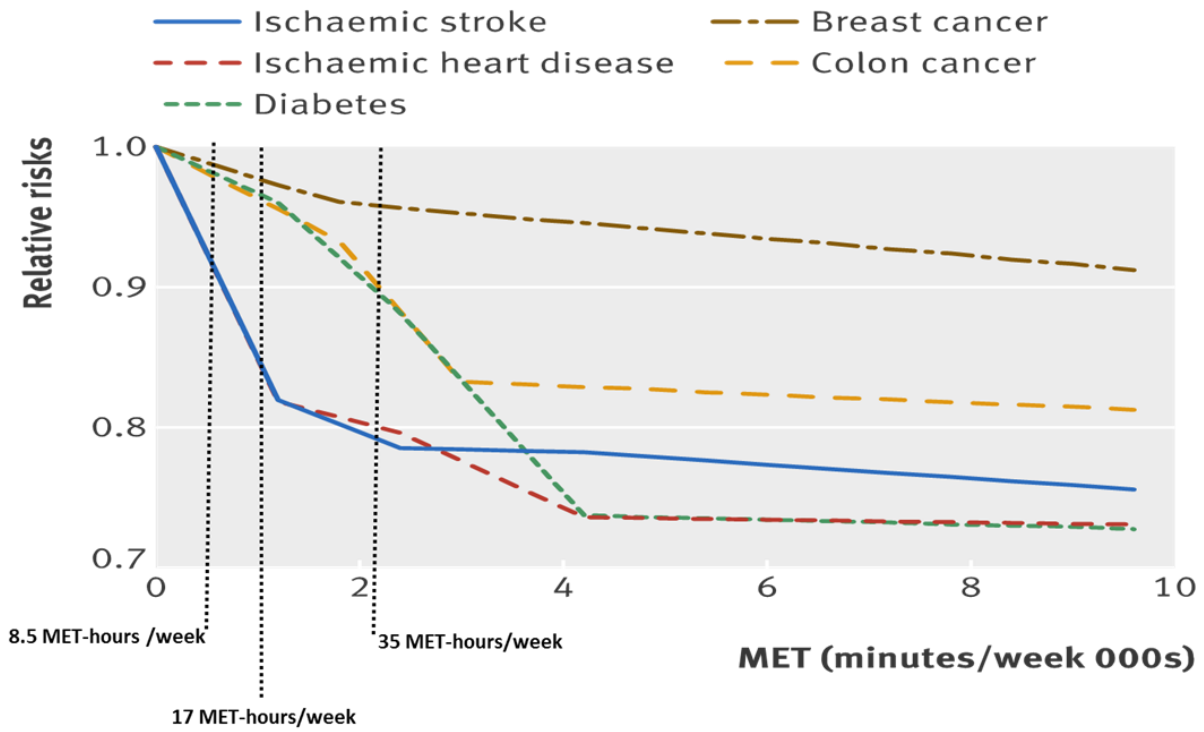
Evidence on Specific Factors

Demographic factors and weight status*:* As it was for previously studied outcomes in this chapter, the studies providing the strongest evidence regarding subgroup moderation effects on cardiovascular mortality were the pooled analyses; particularly that of Sattelmair et al.[23] Of the six studies dealing with incident CHD in our analysis, to the best of our knowledge, only Sattelmair et al[23] explicitly tested for disease modification by specific factors. Although no interactions were reported for effect modification by race or BMI strata, they observed a significant interaction by sex (*P*=0.03); the association was stronger among women than men.

Stroke and Coronary Heart Disease

Kyu et al[21] studied the dose-response associations between total physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events using 174 studies: 43 for ischemic heart disease, and 26 for ischemic stroke. Total physical activity in MET-minutes per week was estimated from all included studies. Continuous and categorical dose-responses between physical activity and outcomes were assessed. Categorical dose-response compared insufficiently active (less than10 MET hours per week), low active (10 to 66 MET-hours) moderately active (67 to 133 MET-hours) and highly active (greater than or equal to 134 MET-hours). Compared with insufficiently active individuals, the risk reduction for those in the highly active category was 25 percent (RR=0.754; 95% CI: 0.704-0.809) for ischemic heart disease and 26 percent (RR=0.736; 95% CI: 0.659-0.811) for ischemic stroke. Again, for ischemic stroke and ischemic heart disease (equivalent to coronary heart disease), the same typical curvilinear dose-response relationship is seen as for all-cause mortality and CVD mortality. However, the initial and maximal effect sizes are attenuated, so that achieving the lower bound of the 2008 Guidelines[2] achieves only 36 percent reduction in initial risk for incident ischemic stroke and heart failure (Figure F6-6).

Figure F6-6. Dose-Response Relationships Between Total Physical Activity and Risk of Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke Events Using 174 Studies (43 For Ischemic Heart Disease, and 26 For Ischemic Stroke)



Note: For reference, shown are the lower end (8.5 MET-hours/week) and upper bounds (17 MET-hours/week) of the 2008 Guidelines for moderate-to-vigorous physical activity. Also indicated is the moderate-to-vigorous physical activity amount associated with normalization of the risk from greater than 8 hours per day of sedentary activity from Ekelund, 2016 (35 MET-hours/week).
Source: Reproduced from [Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013, Kyu et al[21], 354, 2016] with permission from BMJ Publishing Group Ltd. and Ekelund et al., 2016.[5]

Evidence on Specific Factors

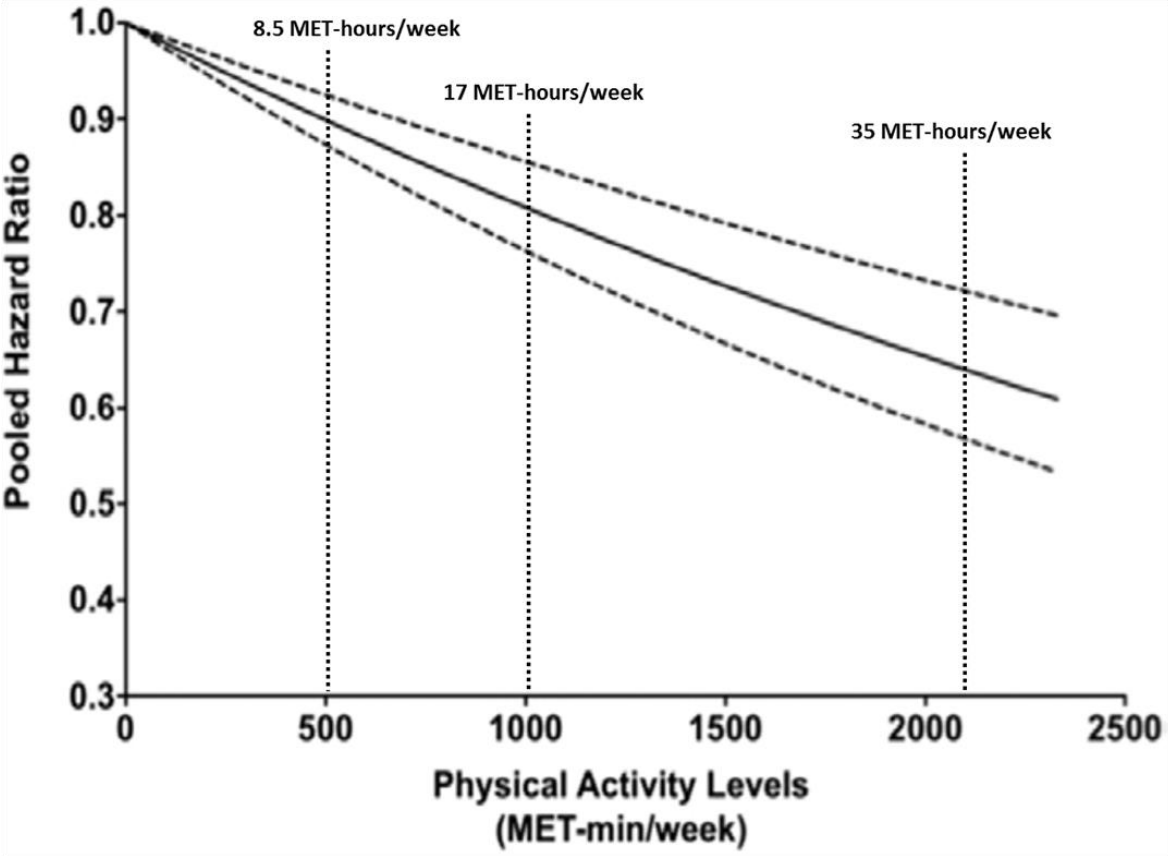
Demographic factors and weight status*:* No effect modifications by age, sex, or weight status were reported for the five reviews that studied incident ischemic stroke. Socioeconomic status and race/ethnicity were not reported in these studies.

Heart Failure

Pandey et al[22] studied the categorical dose-response relationships between physical activity and heart failure risk. As in the previously discussed analysis by Kyu et al,[21] these authors used generalized least-squares regression modeling to assess the quantitative relationship between physical activity (MET-minutes per week) and heart failure risk across studies reporting quantitative physical activity estimates.

Twelve prospective cohort studies with 20,203 heart failure events among 370,460 participants (53.5% women; median follow-up, 13 years) were included. As seen in Figure F6-7, the greatest levels of physical activity were associated with significantly reduced risk of heart failure (pooled HR for highest versus lowest physical activity=0.70; 95% CI: 0.67-0.73). Compared with participants reporting no leisure-time physical activity, those who engaged in 2008 Guidelines -recommended minimum levels of physical activity (500 MET-minutes per week[2] had modest reductions in heart failure risk (pooled HR=0.90; 95% CI: 0.87-0.92). Thus, only 33 percent of the maximal benefit was achieved at the 2008 Guidelines[2] amount. Thus, for heart failure, it appears that the dose-response relationship is linear, and not the curvilinear relationship observed for the other outcomes discussed in this chapter.

Figure F6-7. Dose-Response Relationships Between Moderate-to-Vigorous Physical Activity and Risk of Incident Heart Failure



Note: For reference, shown are the lower end (8.5 MET-hours/week) and upper bounds (17 MET-hours/week) of the 2008 Guidelines for moderate-to-vigorous physical activity. Also indicated is the moderate-to-vigorous physical activity amount associated with normalization of the risk from greater than 8 hours per day of sedentary activity from Ekelund et al., 2016 (17 MET-hours/week).

Source: Used with permission, Pandey et al., 2015[22] 2016, Dose–Response Relationship Between Physical Activity and Risk of Heart Failure, a Meta-Analysis, Circulation, 132: 1786-1794. https://doi.org/10.1161/CIRCULATIONAHA.115.015853. Lines added from Ekelund et al., 2016.[5]

Evidence on Specific Factors

Demographic factors and weight status: No effect modifications by age, sex, or weight status were reported for the two reviews that studied incident heart failure. Socioeconomic status and race/ethnicity were not reported in these studies.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

OVERALL SUMMARY, CONCLUSIONS, AND PUBLIC HEALTH IMPACT

The effects of moderate-to-vigorous physical activity on atherosclerotic CVDs of coronary heart disease, ischemic stroke and heart failure are very similar to those of all-cause mortality and CVD mortality. The evidence continues to support the conclusion that increasing moderate-to-vigorous physical activity levels by even small amounts in the inactive U.S. population has the potential to have an important and substantial impact on these outcomes in the adult population. With respect to reductions in risk for these endpoints, the following points are clear:

- Any amount of physical activity has greater benefit than no physical activity at all;
- More moderate-to-vigorous physical activity is better than none;
- Meeting current moderate-to-vigorous physical activity guidelines will result in an all-cause mortality risk reduction that is about 75 percent of the maximal benefit;
- More physical activity results in greater benefit, although the incremental benefit is less; and
- There is no evidence of excess risk over the maximal effect observed at about three to five times the moderate-to-vigorous physical activity of the current guidelines.

When the activity is quantified by volume in terms of energy expenditure of task (MET-hours per week), these relationships seem to hold for several modes and intensities of physical activity, including walking, running, and biking.

NEEDS FOR FUTURE RESEARCH

Several advances in our understanding of the relationships among physical activity and these outcomes have occurred since the Physical Activity Guidelines Advisory Committee Report, 2008.[1] Most of the literature upon which the conclusions were based used survey data and questionnaire data; physical activity exposures were assessed using self-reported estimates of time spent in aerobic continuous moderate-to-vigorous physical activity accumulated in bouts of at least ten minutes. Therefore, all other components across the physical activity spectrum – sedentary behavior, light-intensity physical activity, and any moderate-to-vigorous physical activity in bouts less than 10 minutes – was considered "baseline" physical activity. Researchers have begun to incorporate device-based measures of physical activity into their measurement armamentarium. This has permitted assessments of the relationship of activity of less than moderate-to-vigorous intensity with health outcomes; it has permitted the assessment of the effects of episodes of moderate-to-vigorous physical activity of less than 10 minutes on health outcomes. These issues are addressed in *Part F. Chapter 1. Physical Activity Behaviors: Steps, Bouts, and High Intensity Training*.

More research is needed in these areas:

1. Conduct research on the role of light intensity physical activities in risk reduction for all-cause mortality, cardiovascular disease mortality, and incident cardiovascular disease (coronary heart disease, stroke and heart failure). This can most economically and efficiently be accomplished by incorporating devices (pedometers or wearables) to measure physical activity into all clinical drug trials with all-cause mortality, cardiovascular disease mortality, or incident cardiovascular disease as outcomes.

   Rationale: As reported in this chapter, the benefits of moderate-to-vigorous physical activity on all-cause mortality, cardiovascular disease mortality, and incident cardiovascular disease (coronary heart disease, stroke and heart failure) are well-documented and strong. However, these studies ignore the effects of physical activity that are not characterized as moderate-to-vigorous in intensity (i.e., light intensity). The development of device-based measures of physical activity (pedometers, accelerometers, and other wearables) provides the scientific imperative to begin to explore the relations of all intensities and amounts of physical activity—light- to vigorous-intensity; small to large total amounts. These studies are beginning to appear.[27-31] Unfortunately, there are not enough studies on the relation of light-intensity physical activity, total physical activity, or step counts per

day to provide enough information for meta-analyses to be performed in these areas for the outcomes of interest here. Therefore, this is a major future research need in this area.

2. Conduct research on the possibility of increased risk associated with high amounts of physical activity.

   Rationale: Whether high amounts (volumes) of aerobic physical exercise lead to increased cardiac morbidity or mortality is an important, yet open question. As discussed in this chapter, there is a hint in some studies of an increase in cardiovascular risk in high-volume aerobic athletes. Recent reports document increased coronary calcium scores in masters athletes[32, 33]; however, there seems to be a U-shaped relationship with life-long volume of training.[33] These findings may explain the hint of an increased cardiovascular risk in long-term athletes. Clearly, this issue demands more study in athletic populations.

3. Conduct research on the relative importance of the various characteristics of physical activity exposure (total volume, intensity, frequency and mode) on all-cause mortality, cardiovascular disease mortality, and incident cardiovascular disease (coronary heart disease, stroke and heart failure).

   Rationale: The second edition of the Physical Activity Guidelines Advisory Committee Scientific Report, continues to rely on studies of aerobic ambulatory moderate-to-vigorous physical activity, primarily collected via survey, to understand the relationship of physical activity to all-cause mortality, cardiovascular disease mortality, and incident cardiovascular disease. Underexplored are the importance of frequency and intensity relative to volume of aerobic exercise; the importance of muscle strengthening to these clinical outcomes; whether swimming, biking, and rowing contribute to cardiovascular health equally to aerobic ambulatory exercise; and what the energy expenditures and programs are for these aerobic activities for equivalent clinical outcomes. If we are going to prescribe exercise of all modalities as options for individuals who want to exercise for health, we need better understanding of the relative contributions of a general range of options.

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