PART F. CHAPTER 2. SEDENTARY BEHAVIOR

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INTRODUCTION

In general, sedentary behavior refers to any waking behavior characterized by an energy expenditure of 1.5 METs or less while in a sitting, reclining, or lying posture.[1] Most previous physical activity research has focused on the association between higher intensity (i.e., moderate-to-vigorous) physical activity and health outcomes. However, sedentary behavior has received an increasing amount of attention as a public health problem because: 1) it appears to have negative associations with health outcomes, and 2) it is a highly prevalent behavior in the U.S. population. Data collected by accelerometry in the U.S. National Health and Nutrition Examination Survey indicate that children and adults spend approximately

7.7 hours per day (55% of their monitored time) being sedentary.[2] Thus, the potential population health impact of sedentary behavior is substantial.

Given that much of the scientific evidence for an association between sedentary behavior and health has been published after 2008, the 2008 Physical Activity Guidelines Advisory Committee did not systematically assess the effects of sedentary behavior on health outcomes. Since then, a considerable amount of research has been conducted, and the 2018 Physical Activity Guidelines Advisory Committee decided to systematically review this literature to assess the effect of sedentary behavior on health outcomes.

The Sedentary Behavior Subcommittee operationalized the definition of sedentary behavior to include self-reported sitting (leisure-time, occupational, total), television (TV) viewing or screen time, and data from objective, device-based assessments (accelerometry or inclinometry). Although these operational definitions do not capture all aspects of the definition of sedentary behavior (i.e., both posture and energy expenditure), they are widely used in the scientific literature as measures of time spent in sedentary behavior.

The Subcommittee examined the relationship between sedentary behavior and major causes of mortality and also assessed the relationship between sedentary behavior and weight status in addition to the incidence of common chronic diseases, including type 2 diabetes, cardiovascular disease, and cancer. In addition to the relationship between the total duration of daily or weekly sedentary behavior and health outcomes, it is of interest to understand the associations between patterns of sedentary behavior, including bouts and breaks, and health outcomes. A bout of sedentary behavior can be operationalized as a period of uninterrupted sedentary time, whereas a break in sedentary behavior can be operationalized as a non-sedentary bout in between two sedentary bouts.[1] The potential health effects associated with sedentary bouts and breaks are also addressed in this chapter.

REVIEW OF THE SCIENCE

Overview of Questions Addressed

This chapter addresses five major questions:

1. What is the relationship between sedentary behavior and all-cause mortality?

2. What is the relationship between sedentary behavior and cardiovascular disease mortality?
3. What is the relationship between sedentary behavior and cancer mortality?
4. What is the relationship between sedentary behavior and (1) type 2 diabetes, (2) weight status, (3) cardiovascular disease, and (4) cancer?
5. Does the effect of moderate-to-vigorous physical activity on all-cause mortality vary by amount of sedentary behavior?

Questions 1 through 4 each have the following subquestions:

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?
c) Is the relationship independent of amounts of light, moderate, or vigorous physical activity?
d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Data Sources and Process Used to Answer Questions

A single literature search strategy was conducted to answer Questions 1, 2, and 3. Subsets of the resulting body of evidence were used to answer each question or subquestion. The databases searched included PubMed, Cochrane, and CINAHL. The systematic literature search to address Questions 1, 2, and 3 was conducted in three steps. Step 1 involved a search for existing systematic reviews and meta-analyses that could address the question. Step 2 involved reviewing the original research articles contained in the systematic reviews and meta-analyses to identify those that could provide evidence to address the questions, especially the subquestions related to dose-response and variation in the relationship by age, sex, race/ethnicity, socioeconomic status, or weight status. Original research articles contained in the systematic reviews and meta-analysis identified in Step 2 are not included as evidence in the evidence portfolio. Step 3 involved a de novo literature search of more recent original research studies published after the systematic reviews and meta-analyses.

The systematic literature search to address Question 4 was conducted in two steps. The databases searched included PubMed, Cochrane, and CINAHL. Step 1 involved a search for existing systematic reviews and meta-analyses that could address the question. Step 2 involved a de novo literature search of more recent original research studies published after the systematic reviews and meta-analyses.

The evidence used to address Question 5 was obtained from the evidence base compiled for Question 1.

Question 1. What is the relationship between sedentary behavior 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?
c) Is the relationship independent of amounts of light, moderate, or vigorous physical activity?
d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Sources of evidence: Systematic reviews, meta-analyses, original research articles

Conclusion Statements

Strong evidence demonstrates a significant relationship between greater time spent in sedentary behavior and higher all-cause mortality rates. **PAGAC Grade: Strong.**

Strong evidence demonstrates the existence of a direct, curvilinear dose-response relationship between sedentary behavior and all-cause mortality, with an increasing slope at higher amounts of sedentary behavior. **PAGAC Grade: Strong.**

Limited evidence suggests that the relationship between sedentary behavior and all-cause mortality does not vary by age, sex/ethnicity, or weight status. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and all-cause mortality varies by socioeconomic status. **PAGAC Grade: Not assignable.**

Strong evidence demonstrates that the relationship between sedentary behavior and all-cause mortality varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and all-cause mortality. **PAGAC Grade: Not assignable.**

Review of the Evidence

Sources of evidence included: 1) systematic reviews and meta-analyses published from January 2000 to December 5, 2016, 2) the relevant original research articles cited by the systematic reviews and meta-analyses, and 3) recent original research articles published between January 2014 and January 30, 2017.

The search for systematic reviews and meta-analyses returned a total of 201 articles and the titles were reviewed by two members of the Subcommittee. A total of 48 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 16 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified

nine systematic reviews and meta-analyses that addressed Question 1 (Supplementary Table S-F2-1). These 9 systematic reviews included information on 25 original research articles that included all-cause mortality as an outcome. After excluding one study in breast cancer survivors,[3] one study of occupational sitting and physical activity that included a mix of sitting and physical activity exposures,[4] one study that only presented data on changes in sitting time,[5] and two studies that presented only baseline descriptions of cohorts,[6, 7] the Subcommittee was able to identify 20 original articles that addressed Question 1 (Supplementary Table S-F2-2).

The de novo literature search of original research studies returned a total of 1,214 articles and the titles were reviewed by two members of the Subcommittee. A total of 62 articles were deemed potentially relevant based on the title search, and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 38 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified 30 original studies that addressed Question 1. Note that three of the papers[8-10] identified in the search for original articles were duplicates of those identified from the systematic reviews and meta-analyses and they appear only in Supplementary Table S-F2-2. Supplementary Table S-F2-3 presents the 27 new original studies that address Question 1.

Evidence on the Overall Relationship

A total of nine systematic reviews and meta-analyses[11-19] that reviewed a total of 20 original studies have addressed the relationship between sedentary behavior and all-cause mortality, and they provide strong evidence demonstrating a significant relationship. The number of studies that addressed all-cause mortality encompassed by each of the reviews ranges from 3 to 16, with newer reviews reporting on a greater number of studies as they appear in the literature. The meta-analysis of Biswas et al[18] analyzed 14 prospective cohort studies and reported a hazard ratio of 1.22 (95% confidence interval (CI): 1.09-1.41) for the relationship between sedentary behavior and all-cause mortality. The available studies represent several population cohorts that apply broadly to the U.S. population and the results are consistent in direction and the size of the effect.

Based on the review of the more recent original research articles, 9 of 10 studies found a significant relationship between self-reported total or leisure sitting time and all-cause mortality, 3 out of 5 studies of TV viewing or screen time found a significant relationship between TV viewing or screen time and all-

cause mortality, and 0 out of 2 studies found a significant relationship between occupational sitting time and all-cause mortality.

Thirteen studies have reported on relationships between device-based objectively measured sedentary behavior (using accelerometry) and all-cause mortality. Of these, 11 studies relied on data from the National Health and Nutrition Examination Survey (NHANES). Although the analytical strategies differed, 10 of the 13 studies reported a significant relationship (1 in men only) between sedentary time and all-cause mortality (8 out of the 11 NHANES studies). Among the 3 NHANES studies that did not find a significant relationship, one stratified their analysis by level of visual acuity,[20] one compared risk for below-median to above-median sedentary time,[21] and the third compared risk across quartiles of sedentary time.[22] The 8 NHANES studies that reported a significant association between sedentary behavior and all-cause mortality used a variety of analysis strategies, including comparisons of quartiles of sedentary behavior,[23] comparing above-median to below-median sedentary time,[24] continuous variable analysis,[25, 26] latent class analysis,[27] and isotemporal substitution analysis.[28-30]

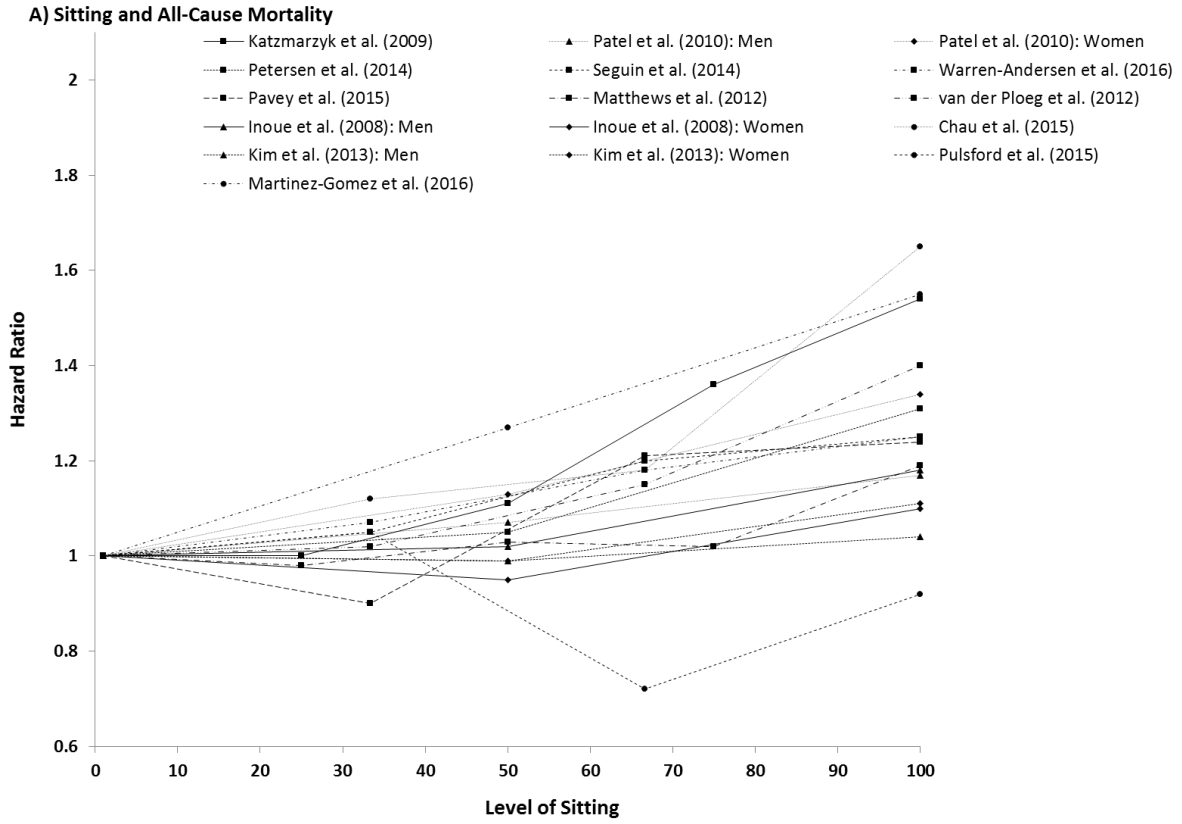
Given the confines of the 24-hour period, interest is increasing in understanding inter-relationships among time spent in different aspects of daily living, such as sleep, sedentary behavior, and light-, moderate-, and vigorous-intensity physical activity, with outcomes such as all-cause mortality. To this end, several studies have used isotemporal substitution analyses to model the effects of replacing time spent in sedentary behavior with time spent in other behaviors such as standing, light-intensity activity, moderate-to-vigorous physical activity, or exercise.[28-33] The results invariably show a reduction in mortality risk when sedentary behavior is replaced with higher intensity activities. Models in which an equivalent duration of sedentary behavior is replaced with light-intensity physical activity predict a reduction in mortality, and models in which sedentary behavior is replaced with moderate- or vigorous-intensity physical activity predict an even greater reduction in mortality. Because the models are "isotemporal," it cannot be determined whether the increase in predicted benefit is due to the higher intensity of the physical activity per se or the higher volume of energy expended.

Dose-response: Strong evidence also demonstrates the existence of a dose-response relationship between sedentary behavior and all-cause mortality. Two meta-analyses were used to provide evidence for dose-response relationships between daily sitting[15] or TV viewing,[17] and all-cause mortality. Chau et al[15] found that a spline model of best fit had hazard ratios of 1.00 (95% CI: 0.98-1.03), 1.02 (95% CI: 0.99-1.05) and 1.05 (95% CI: 1.02-1.08) for every 1-hour increase in daily sitting time in intervals between 0 to

3, more than 3 to 7, and more than 7 hours per day total sitting, respectively. Thus, the dose-response curve was curvilinear, and the slope of the relationship increased beyond 7 hours per day of sitting. Similarly, Sun et al[17] reported that TV viewing time was statistically significantly associated with all-cause mortality risk in a curvilinear, direct fashion that increases steadily and more rapidly as length of exposure increases ($P_{nonlinearity}$=0.001).[17]

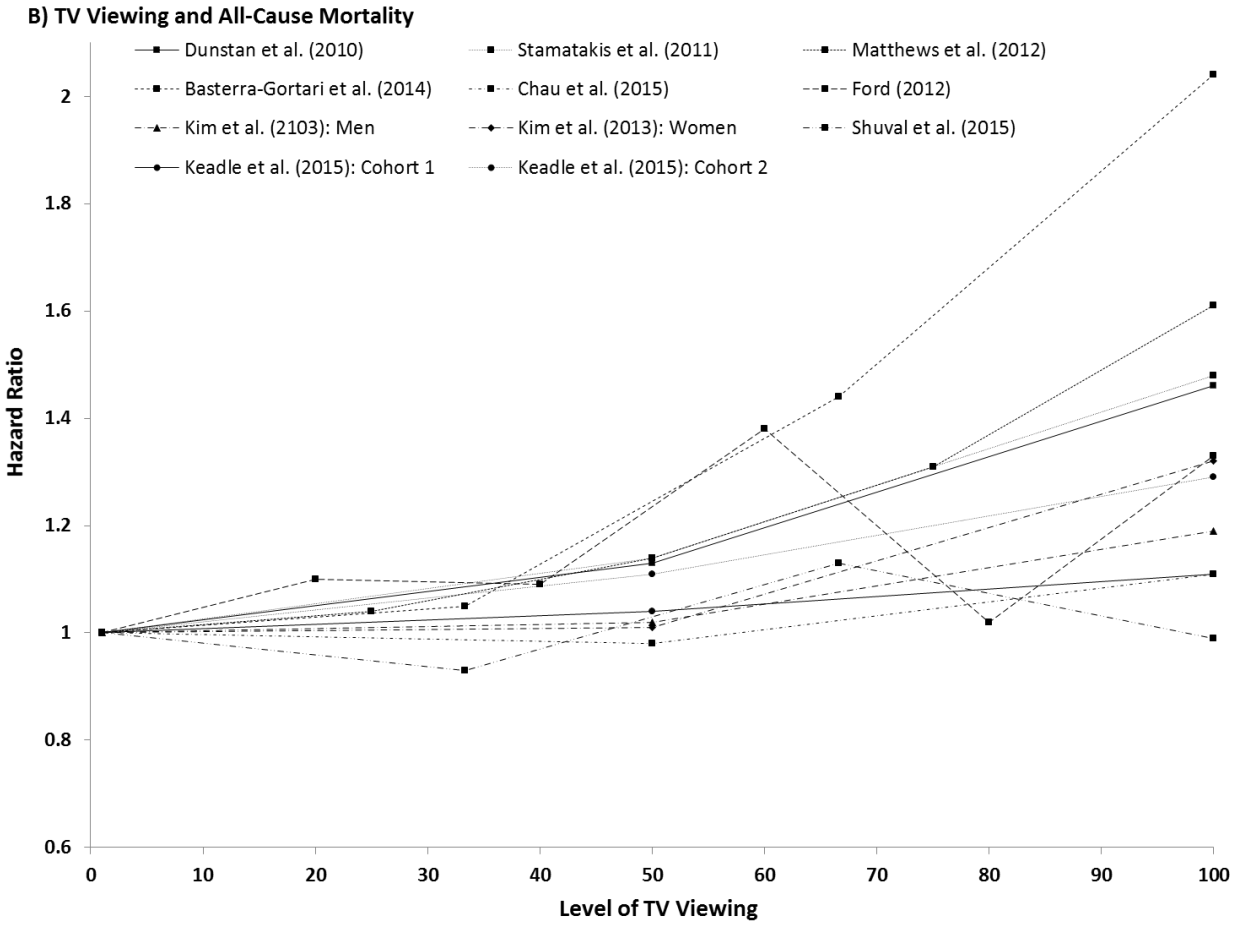
Of the 47 original studies identified through the systematic reviews and meta-analyses and the de novo search, 29 tested for the existence of a dose-response relationship, and 24 studies found a significant dose-response relationship. Figure F2-1 presents the dose-response curves from studies of self-reported sitting (Panel A) and TV viewing (Panel B) that included at least three amounts of sedentary behavior as the exposure. The pattern of results generally mirrors those of the two previous meta-analyses,[15, 17] with increasing risk at higher amounts of sedentary behavior following a curvilinear relationship.

Figure F2-1. Dose-Response Curves Showing Relationship Between Sedentary Behavior and All-Cause Mortality



Note: The figure shows the reported hazard ratio for each category of sitting with the lowest category of sitting assigned as the referent at zero on the X-axis and the highest value assigned at 100. The original categories of

sitting from the studies (tertiles, quartiles, quintiles, etc.) have been rescaled from 0 to 100 using an ordinal scale. For example, for a study with three categoires, the points were plotted at 0, 50 and 100.
Source: Adapted from data found in Katzmarzyk et al., 2009,[34] Patel et al., 2010,[35] Petersen et al., 2014,[10] Seguin et al., 2014,[36] Warren Andersen et al., 2016,[37] Pavey et al., 2015,[9] Matthews et al., 2012,[38] van de Ploeg et al., 2012,[39] Inoue et al., 2008,[40] Chau et al., 2015,[8] Kim et al., 2013,[41] Pulsford et al., 2015,[42] and Martinez-Gomez et al., 2016.[43]



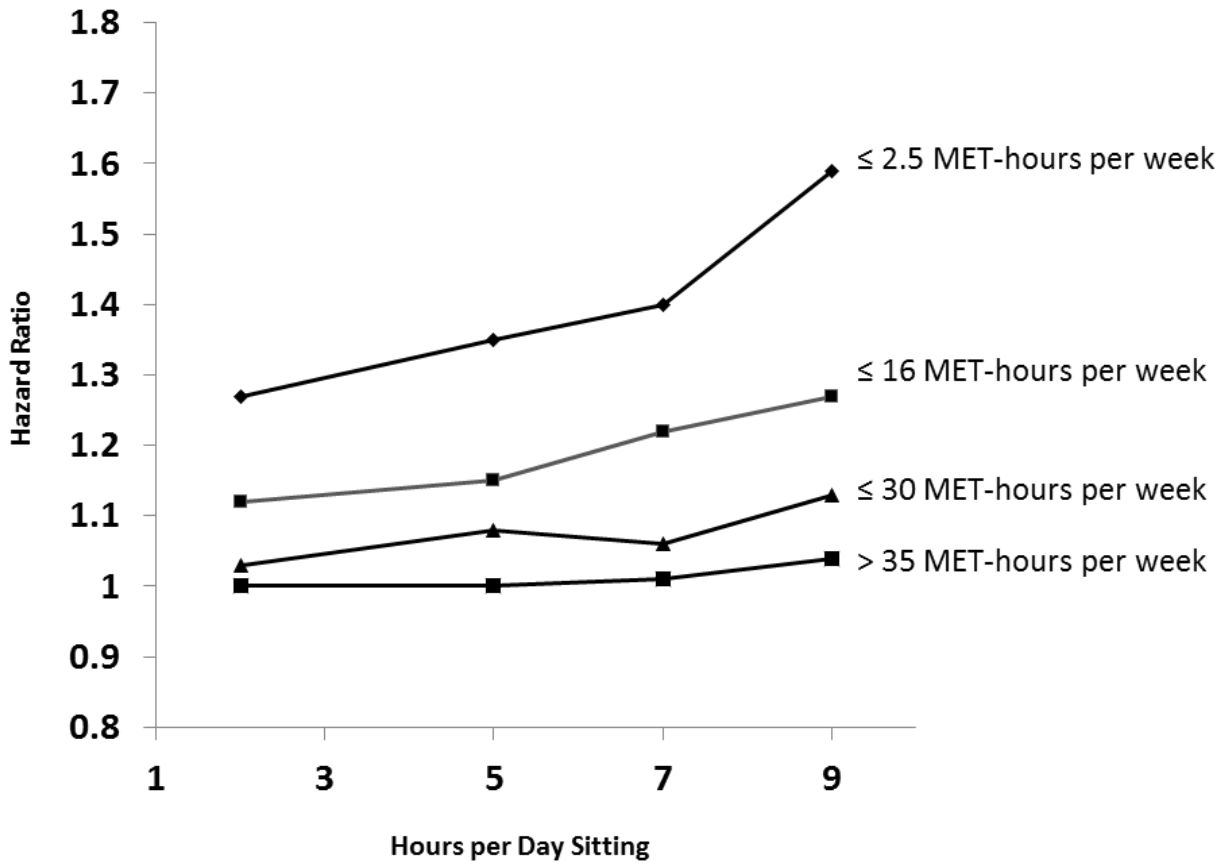
Note: The figure shows the reported hazard ratio for each category of TV viewing with the lowest category of TV viewing assigned as the referent at zero on the X-axis and the highest value assigned at 100. The original categories of TV viewing from the studies (tertiles, quartiles, quintiles, etc.) have been rescaled from 0 to 100 using an ordinal scale. For example, for a study with three categoires, the points were plotted at 0, 50 and 100.
Source: Adapted from data found in Dunstan et al., 2010,[44] Stamatakis et al., 2011,[32] Matthews et al., 2012,[38] Basterra-Gortari et al., 2014,[45] Chau et al., 2015,[8] Ford, 2012,[46] Kim et al., 2013,[41] Shuval et al., 2015,[47] and Keadle et al., 2015.[48]

Evidence on Specific Factors

Demographic factors and weight status: Limited evidence suggests that the relationship between sedentary behavior and all-cause mortality does not vary by age, sex, race/ethnicity, or weight status. Available evidence is insufficient to determine whether the relationship between sedentary behavior and all-cause mortality varies by socioeconomic status. In general, studies reported no significant effect modification by age,[35, 36, 44, 49, 50] sex,[31, 35, 44, 49] or weight status,[35, 36, 44, 49] and stratified analyses generally showed similar results across age,[28, 38, 39, 41, 49] sex,[28, 34, 37, 39, 41, 49] race/ethnicity,[37, 38, 41, 51] and weight status,[28, 34, 35, 38, 39, 41, 49] with varying levels of significance. In general, data are lacking on the variation in the observed associations by level of socioeconomic status. The available evidence suggests that the observed relationship between sedentary behavior and all-cause mortality applies broadly to the general adult population of the United States.

Amount of physical activity: Strong evidence demonstrates that the relationship between sedentary behavior and all-cause mortality varies by the amount of moderate-to-vigorous physical activity. The effect of sedentary behavior on all-cause mortality is stronger among people who have low amounts of moderate-to-vigorous physical activity. For example, in the meta-analysis of Biswas et al[18] the risk of all-cause mortality was 1.16 (95% CI: 0.84-1.56) among those with high physical activity and 1.46 (95% CI: 1.22-1.75) among those with low physical activity. Further, Ekelund et al[19] conducted a harmonized meta-analysis using individual-level data from more than 1 million adults and reported that increasingly higher amounts of moderate-to-vigorous physical activity attenuated the relationship between sedentary behavior and all-cause mortality (Figure F2-2), and the relationship between self-reported sitting and mortality was not significant among those who reported participating in at least moderate-intensity physical activity for 60 to 75 minutes per day. Similar results were observed for TV viewing, although high amounts of physical activity did not completely attenuate the relationship between TV viewing and all-cause mortality. Evidence is insufficient to determine whether the association between sedentary behavior and all-cause mortality varies by level of light- or vigorous-intensity activity.

Figure F2-2. Relationship Between Sitting and All-Cause Mortality, Stratified by Amount of Moderate-to-Vigorous Physical Activity



Source: Adapted from data found in Ekelund et al., 2016.[19]

Bouts and breaks: Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and all-cause mortality. Only one study was identified that included bouts of sedentary behavior in their definition of the exposure. Using accelerometry data from NHANES, Evenson et al[27] defined sedentary bouts as 30 or more minutes with at least 80 percent of the minutes falling below 100 counts per minute, allowing for less than 5 consecutive minutes above the threshold. Based on latent class analysis, the class with the highest percentage of the day in sedentary bouts had a higher risk of all-cause mortality compared to the class with fewer sedentary bouts (hazard ratio (HR)=2.10; 95% CI: 1.11-3.97). However, further research is required to replicate these results. No studies were identified that examined the associations between breaks in sedentary behavior and all-cause mortality. Thus, a grade was not assignable for this question.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for Supplementary Tables S-F2-1, S-F2-2, and S-F2-3 and the Evidence Portfolio.

Question 2. What is the relationship between sedentary behavior 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?
c) Is the relationship independent of amounts of light, moderate, or vigorous physical activity?
d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Sources of evidence: Systematic reviews, meta-analyses, original research articles

Conclusion Statements

Strong evidence demonstrates a significant relationship between greater time spent in sedentary behavior and higher mortality rates from cardiovascular disease. **PAGAC Grade: Strong.**

Strong evidence demonstrates the existence of a direct, positive dose-response relationship between sedentary behavior and mortality from cardiovascular disease. **PAGAC Grade: Strong.**

Limited evidence suggests that the relationship between sedentary behavior and cardiovascular disease mortality does not vary by age, sex, race/ethnicity, or weight status. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and mortality from cardiovascular disease varies by socioeconomic status. **PAGAC Grade: Not assignable.**

Moderate evidence indicates that the relationship between sedentary behavior and mortality from cardiovascular disease varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and mortality from cardiovascular disease. **PAGAC Grade: Not assignable.**

Review of the Evidence

Sources of evidence included: 1) systematic reviews and meta-analyses published from January 2000 to December 5, 2016, 2) the relevant original research articles cited by the systematic reviews and meta-analyses, and 3) recent original research articles published between January 2014 and January 30, 2017.

The search for systematic reviews and meta-analyses returned a total of 201 articles and the titles were reviewed by two members of the Subcommittee. A total of 48 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 16 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified five systematic reviews and meta-analyses that addressed Question 2 (Supplementary Table S-F2-4). These 5 systematic reviews and meta-analyses included information on 12 original research articles that included cardiovascular disease mortality as an outcome. After excluding one study that presented only a baseline description of a cohort,[7] 11 original articles addressed Question 2 (Supplementary Table S-F2-5).

The de novo literature search of original research studies returned a total of 1,214 articles and the titles were reviewed by two members of the Subcommittee. A total of 62 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 38 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified seven original studies that addressed Question 2 (Supplementary Table S-F2-6).

Evidence on the Overall Relationship

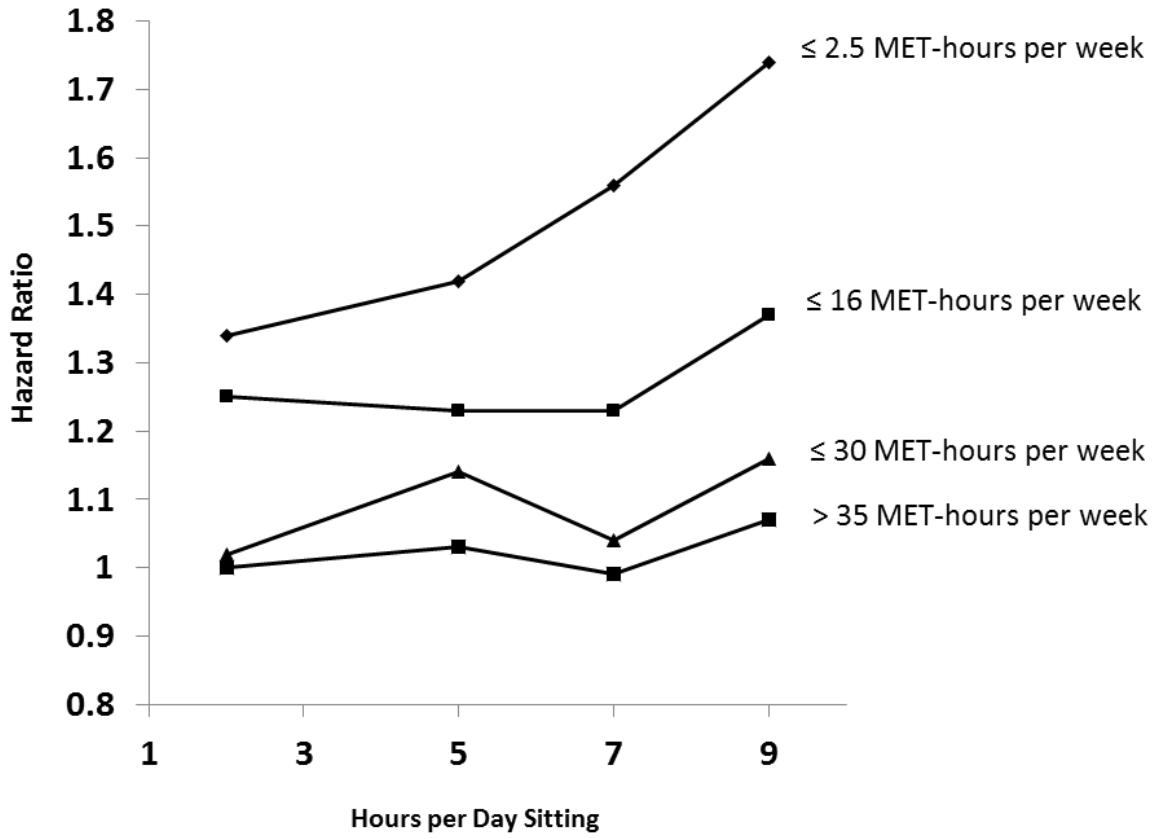
A total of 5 systematic reviews and meta-analyses that reviewed 11 original studies have addressed the relationship between sedentary behavior and cardiovascular disease mortality, and they provide strong evidence demonstrating a significant relationship between sedentary behavior and cardiovascular disease mortality. The meta-analysis of Biswas et al[18] analyzed seven prospective cohort studies and reported a hazard ratio of 1.15 (95% CI: 1.11-1.20) for the relationship between sedentary behavior and cardiovascular disease mortality. Further, a meta-analysis by Wilmot et al[14] reported a relative risk of 1.90 (95% CI: 1.36-2.66) for the relationship between sedentary behavior and cardiovascular disease mortality. Both meta-analyses reported a statistically significant summary risk estimate. However, the magnitude of the effect was quite different. The main reasons for the difference in the summary hazard

ratios between these two meta-analyses relate to the selection of studies included in each review and differences in the exposure categories and types of sedentary behavior among the included studies.

A total of 18 original studies were identified through the meta-analyses and systematic reviews (N=11) and the de novo search (N=7). Nine studies reported on the association with sitting or total sedentary time, eight reported on the association with TV or screen time, and three studies used device-based measures of sedentary time (accelerometry or arm band). A total of 13 of these 18 studies found a significant positive relationship between sedentary time and cardiovascular disease mortality. The available studies represent several population cohorts that apply broadly to the U.S. population and the results are consistent in direction and the size of the effect.

Dose-response: Strong evidence also demonstrates the existence of a dose-response association between sedentary behavior and cardiovascular disease mortality. Seventeen original research studies tested for the existence of a dose-response association, and 10 reported a significant association. Except for one study of TV viewing among Japanese adults,[52] the studies that did not detect a significant dose-response association had small sample sizes (N< 10,000).[22, 28, 46, 50, 53, 54] The results of the pooled analysis of 11 prospective cohort studies by Ekelund et al[19] demonstrated that the associations among sedentary behavior, moderate-to-vigorous physical activity, and cardiovascular disease mortality were similar to those observed for all-cause mortality. Figure F2-3 presents the dose-response associations between sedentary time and cardiovascular disease mortality, stratified by amount of moderate-to-vigorous physical activity.[19]

Figure F2-3. Relationship Between Sitting and Cardiovascular Disease Mortality, Stratified by Amount of Moderate-to-Vigorous Physical Activity



Source: Adapted from data found in Ekelund et al, 2016.[19]

Evidence on Specific Factors

Demographic factors and weight status: Limited evidence suggests that the relationship between sedentary behavior and cardiovascular disease mortality does not vary by age, sex, race/ethnicity or weight status. Among the available studies that tested for interaction effects,[34, 36, 44, 49] no significant effect modification was observed for age,[36, 44, 49] sex,[34, 36, 44, 49] race/ethnicity,[36] or weight status.[36, 44, 49] In general, data are lacking on variation in the observed associations by level of socioeconomic status. The available evidence suggests that the observed relationship between sedentary behavior and mortality from cardiovascular disease applies broadly to the general adult population of the United States.

Amount of physical activity: Moderate evidence suggests that the relationship between sedentary behavior and cardiovascular disease mortality varies by amount of moderate-to-vigorous physical activity. Several individual studies reported the interaction between sedentary behavior and physical activity was not significant. However, the meta-analysis of Ekelund et al[19] provided convincing evidence

that the association between sedentary time and cardiovascular disease mortality was influenced by moderate-to-vigorous physical activity. Some of the individual studies may have been underpowered to detect significant interaction effects, whereas the pooled analysis overcomes this limitation. Figure F2-3 presents the relationship between sedentary behavior and mortality rates from cardiovascular disease, stratified by amount of moderate-to-vigorous physical activity.[19] The strongest association between sitting and cardiovascular disease mortality is observed among those who are physically inactive (moderate-to-vigorous physical activity ≤ 2.5 MET-hours per week), and the slope of the association diminishes across increasing categories of moderate-to-vigorous physical activity. Evidence is insufficient to determine whether the association between sedentary behavior and cardiovascular disease mortality varies by amount of light- or vigorous-intensity activity.

Bouts and breaks: Insufficient evidence is available that bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and mortality from cardiovascular disease. No studies were identified that examined the relationship between breaks and/or bouts of sedentary behavior and mortality rates from cardiovascular disease.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for Supplementary Tables S-F2-4, S-F2-5, and S-F2-6 and the Evidence Portfolio.

Question 3. What is the relationship between sedentary behavior and cancer 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?
c) Is the relationship independent of amounts of light, moderate, or vigorous physical activity?
d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Sources of evidence: Systematic reviews, meta-analyses, original research articles

Conclusion Statements

Limited evidence suggests a direct relationship between greater time spent in sedentary behavior and higher mortality rates from cancer. **PAGAC Grade: Limited.**

Limited evidence suggests the existence of a direct, positive dose-response relationship between sedentary behavior and mortality from cancer. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and cancer mortality varies by age, sex, race/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and mortality from cancer varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and mortality from cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Sources of evidence included: 1) systematic reviews and meta-analyses published from January 2000 to December 5, 2016, 2) the relevant original research articles cited by the systematic reviews and meta-analyses, and 3) recent original research articles published between January 2014 and January 30, 2017.

The search for systematic reviews and meta-analyses returned a total of 201 articles and the titles were reviewed by two members of the Subcommittee. A total of 48 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 16 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified five systematic reviews and meta-analyses that addressed Question 3 (Supplementary Table S-F2-7). These 5 systematic reviews included information on 10 original research articles that included cancer mortality as an outcome. After excluding one study in colorectal cancer survivors[55] and one study that presented a baseline description of a cohort,[7] eight original articles addressed Question 3 (Supplementary Table S-F2-8).

The de novo literature search of original research studies returned a total of 1,214 articles and the titles were reviewed by two members of the Subcommittee. A total of 62 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 38 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified five original studies that addressed Question 3 (Supplementary Table S-F2-9).

Evidence on the Overall Relationship

The five systematic reviews/meta-analyses suggest that only a weak association exists between sedentary behavior and all-cancer mortality. For example, the meta-analysis of eight studies by Biswas et al[18] reported a summary hazard ratio of 1.13 (95% CI: 1.05-1.21). A total of 13 original research studies were identified that addressed the association between sedentary behavior and cancer mortality. Five of the 13 studies reported a significant association, and the results were not always consistent (one in women only; one for TV viewing but not sitting; one in current smokers only). Cancer is a heterogeneous disease, and the major risk factors differ by cancer site. Further, associations between specific risk factors and cancer mortality are affected by cancer screening and treatment availability and efficacy. A limitation of most studies of sedentary behavior and cancer mortality is a failure to take these factors into account.

Dose-response: Limited evidence suggests the existence of a dose-response association between sedentary behavior and cancer mortality. Thirteen original research studies tested for the existence of a dose-response association, and five reported a significant dose-response association in the total sample or in one or more subgroups.

Evidence on Specific Factors

Demographic factors and weight status: Insufficient evidence is available to determine whether the relationship between sedentary behavior and cancer mortality varies by age, sex, race/ethnicity, socioeconomic status, or weight status. Of the five studies that reported a significant association between sedentary behavior and cancer mortality,[35, 36, 38, 53, 56] only one tested for effect modification, and the results indicated no significant interactions with body mass index (BMI) and race/ethnicity.[36] The study showed a significant interaction with age, with a significant association observed in women ages 50 to 69 years but not in women ages 70 to 79 years. However, this finding needs to be replicated in other studies before any definitive statements can be made about the effects of age on the observed associations. In general, data on variations in the observed associations by level of socioeconomic status are lacking.

Amount of physical activity: Insufficient evidence is available to determine whether the relationship between sedentary behavior and cancer mortality is modified by physical activity. The pooled meta-analysis by Ekelund et al[19] did not specifically test for an interaction between sedentary behavior and moderate-to-vigorous physical activity on cancer mortality, and there did not appear to be a relationship

between sedentary behavior (either sitting or TV time) and cancer mortality within quartiles of moderate-to-vigorous physical activity. Further, the study by Seguin et al[36] reported no significant interaction between sedentary time and physical activity (*P*=0.51). Evidence is insufficient to determine whether the association between sedentary behavior and mortality from cancer varies by amount of light or vigorous activity.

Bouts and breaks: Available evidence is insufficient to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and mortality from cancer. No studies were identified that examined the relationship between breaks and/or bouts of sedentary behavior and mortality rates from cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for Supplementary Tables S-F2-7, S-F2-8, and S-F2-9 and the Evidence Portfolio. For information on the relationship of physical activity and cancer, see Part F. Chapter 4: Cancer Prevention.

Question 4. What is the relationship between sedentary behavior and (1) type 2 diabetes, (2) weight status, (3) cardiovascular disease, and (4) cancer?

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?
c) Is the relationship independent of amounts of light, moderate, or vigorous physical activity?
d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Sources of evidence: Systematic reviews, meta-analyses, original research articles

Conclusion Statements

Type 2 Diabetes

Strong evidence demonstrates a significant relationship between greater time spent in sedentary behavior and higher risk of type 2 diabetes. **PAGAC Grade: Strong.**

Limited evidence suggests the existence of a direct, graded dose-response relationship between sedentary behavior and risk of type 2 diabetes. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and type 2 diabetes varies by age, sex/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and type 2 diabetes varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incidence of type 2 diabetes. **PAGAC Grade: Not assignable.**

Weight Status

Limited evidence suggests a positive relationship between greater time spent in sedentary behavior and higher levels of adiposity and indicators of weight status. **PAGAC Grade: Limited.**

Limited evidence suggests the existence of a direct, graded dose-response relationship between greater sedentary behavior and higher levels of adiposity and indicators of weight status. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and weight status varies by age, sex/ethnicity, socioeconomic status, or baseline weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and weight status varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and weight status. **PAGAC Grade: Not assignable.**

Cardiovascular Disease

Strong evidence demonstrates a significant relationship between greater time spent in sedentary behavior and higher risk of incident cardiovascular disease. **PAGAC Grade: Strong.**

Strong evidence demonstrates the existence of a direct, graded dose-response relationship between sedentary behavior and risk of incident cardiovascular disease. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident cardiovascular disease varies by age, sex/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident cardiovascular disease varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incidence of cardiovascular disease. **PAGAC Grade: Not assignable.**

Cancer

Moderate evidence indicates a significant relationship between greater time spent in sedentary behavior and higher risk of incident endometrial, colon, and lung cancers. **PAGAC Grade: Moderate.**

Limited evidence suggests the existence of a direct dose-response relationship between sedentary behavior and incident endometrial, colon, and lung cancers. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident cancer varies by age, sex/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident cancer varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incident cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Sources of evidence included: 1) systematic reviews and meta-analyses published from January 2000 to February 21, 2017, and 2) recent original research articles published between January 2014 and April 25, 2017.

The systematic literature search to address Question 4 was conducted in two steps. Step 1 involved a search for existing systematic reviews and meta-analyses that could address the question. The search strategy (from January 1, 2000 to February 21, 2017 returned a total of 201 articles and the titles were reviewed by two members of the Subcommittee. A total of 48 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 22 articles were deemed to be potentially relevant and the full papers were retrieved. A review of the full texts of these papers by two members of the Subcommittee identified 11 systematic reviews and meta-analyses that addressed Question 4 (five for type 2 diabetes, two for weight status, five for cardiovascular disease, and eight for cancer) (Supplementary Table S-F2-10).

Step 2 involved a de novo literature search of original research studies published between January 1, 2014, and April 25, 2017. The search strategy returned a total of 1,877 articles and the titles were reviewed by two members of the Subcommittee. A total of 200 articles were deemed potentially relevant based on the title search and the abstracts of these papers were reviewed by two members of the Subcommittee. Of these, 44 articles were deemed to be potentially relevant and the full papers were retrieved. A review the full texts of these papers by two members of the Subcommittee identified 34 original studies that addressed Question 4 (Supplementary Table S-F2-11).

Type 2 Diabetes

Evidence on the Overall Relationship

Two systematic reviews[12, 13] and three meta-analyses[11, 14, 18] addressed the issue of sedentary behavior and the incidence of type 2 diabetes (Supplementary Table S-F2-10). All three meta-analyses reported significant pooled estimates of risk for incident type 2 diabetes associated with sedentary behavior. The pooled relative risk per 2 hours of TV viewing per day was 1.20 (95% CI: 1.14-1.27) among four original papers analyzed by Grontved and Hu.[11] The summary relative risk (from five cross-sectional and five prospective studies) for type 2 diabetes reported by Wilmot et al[14] was 2.12 (95% CI: 1.61-2.78) for highest versus lowest sedentary time. Finally, the summary hazard ratio for type 2 diabetes was 1.91 (95% CI: 1.64-2.22) from five studies analyzed by Biswas et al.[18]

Eight original research articles were retrieved from the de novo literature search for incident type 2 diabetes (Supplementary Table S-F2-11).[57-64] Three[57, 59, 61] of the eight studies reported significant effects of higher sedentary behavior and greater risk of type 2 diabetes from fully adjusted models. An additional three studies[58, 62, 64] reported significant effects of sedentary behavior on risk of type 2

diabetes in minimally adjusted models (e.g., age, sex) but the effects were attenuated to the null when additional covariates, including BMI, were added to the models. These results are supported by the meta-analysis of Grontved and Hu[11] who reported a that pooled relative risk per 2 hours of TV viewing per day on risk of type 2 diabetes was 1.20 (95% CI: 1.14-1.27), which was reduced to a relative risk of 1.13 (95% CI: 1.08-1.18) when the relative risk was calculated from models that included BMI or another obesity measure. These results suggest that BMI may be on the causal pathway between sedentary behavior and increased risk of type 2 diabetes. In other words, the effects of sedentary behavior on risk of type 2 diabetes may be operating, in part, through its association with BMI.

Dose-response: Limited evidence suggests a graded, positive association between sedentary behavior and incident type 2 diabetes. The meta-analysis of Grontved and Hu[11] reported a significant, positive linear dose-response association between TV viewing and type 2 diabetes. Further, two[57, 61] of four original research studies[57, 58, 60, 61] that tested for linear dose-response associations reported a significant finding.

Evidence on Specific Factors

Demographic factors and weight status: Available evidence is insufficient to determine whether the relationship between sedentary behavior and incident type 2 diabetes varies by age, sex, race/ethnicity, socioeconomic status, or weight status. A single study stratified the analysis by race/ethnicity and reported a significant graded association only among Non-Hispanic Whites and not in Chinese Americans, African Americans, or Hispanic Americans.[61] Two studies reported a significant interaction between sedentary behavior and BMI on risk of diabetes,[57, 62] with significant effects of sedentary behavior observed only among individuals with obesity. On the other hand, a single study[64] reported no significant interaction between sedentary behavior and BMI on risk of diabetes (*P*=0.65).

Amount of physical activity: Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident type 2 diabetes varies by amount of moderate-to-vigorous physical activity. Four of the original research studies considered the potential interactions between sedentary behavior and physical activity on incident type 2 diabetes.[57, 58, 62, 64] Manini et al[57] reported significant effects of daily sitting on incident type 2 diabetes among people with different amounts of physical activity (all *P*-values for trends <0.01). On the other hand, Smith and Hamer[58] reported that active participants who reported high TV viewing were not at elevated risk of type 2 diabetes, in comparison to inactive participants who reported high TV viewing, who were at significantly elevated

risk. Petersen et al[62] reported a non-significant interaction between sitting time and moderate-to-vigorous physical activity (*P*=0.68). However, the association between sitting time and incident type 2 diabetes was only significant in those who were inactive. Asvold et al[64] reported a significant interaction between daily sitting time and leisure-time physical activity (*P*=0.01), with a significant effect observed only in inactive participants. Thus, the evidence from these four studies is not consistent.

Bouts and breaks: Insufficient evidence is available that bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incident type 2 diabetes. No studies were identified that addressed this topic.

Weight Status

Evidence on the Overall Relationship

Two systematic reviews[12, 13] each reviewed 10 original research studies and concluded that evidence was insufficient or limited, respectively, that sedentary behavior was related to changes in body weight or other indicators of weight status, such as BMI, waist circumference, body fat, or overweight (BMI ≥25 kg/m^2) or obesity (BMI ≥30 kg/m^2) (Supplementary Table S-F2-10). Fourteen original research articles were identified that were published between 2014 and 2017[65-78] (Supplementary Table S-F2-11) that explored associations between sedentary behavior and indicators of adiposity or weight status.

Of the 14 original studies, 11 reported a significant positive association between at least one sedentary behavior and at least one indicator of adiposity or weight status,[67, 68, 70-78] whereas three studies reported no significant results.[65, 66, 69] However, the relationships observed among the studies that reported significant effects showed considerable heterogeneity. For example, among adults in the United Kingdom, the relationship between TV viewing and incident abdominal obesity (high waist circumference) was significant, but the relationship with incident obesity (high BMI) was not.[72] Among Swedish adults followed for 5 years, the association between computer gaming and incident overweight was significant in women, but not in men.[73] Among Finnish adults, the association between screen time and 6-year weight change was significant in men ages 24 to 27 years but not in men ages 30 to 39 years or in women.[74] Saidj et al[76] reported that occupational sitting time was associated with changes in waist circumference over 5 years, but not with changes in BMI. In the same study, the authors found no association between leisure-time sitting and either BMI or waist circumference.[76] Finally, among Chinese adults, the relationship between daily sedentary time and the incidence of obesity was significant in

men but not in women.[78] However, the association with weight change per se was significant in both men and women.

Several indicators of adiposity and weight status have been employed as outcomes in the available studies. Many studies included multiple analyses of subgroups (e.g., in men, in women, and total sample). Significant results were reported in five[70, 71, 74, 78] out of seven analyses[65, 70, 71, 74, 78] for body weight; four[67, 68, 73, 75] out of nine analyses[67, 68, 73, 75, 76] for BMI; 3[67, 68, 77] out of 10 analyses[65, 67-69, 71, 75-77] for waist circumference; one out of one analysis[71] for fat mass; one[75] out of two analyses[71, 75] for percent body fat; one[71] out of one analysis[71] for fat mass index; 2[73, 78] out of 10 analyses[66, 72, 73, 78] for incident overweight or obesity; and one out of one analysis[72] for incident central obesity (high waist circumference).

The results for weight status differed by the exposure variable used to measure sedentary behavior. However, some significant results were reported regardless of the exposure variable used. For example, significant results were reported for one or more of the indicators of weight status in one[71] out of two analyses[69, 71] in studies that used accelerometry to measure sedentary time; significant results were reported for one or more of the indicators of weight status in three[76, 78] out of six analyses[65, 66, 76, 78] in studies that relied on self-reported measures of sitting time or total sedentary time; and significant results were reported for one or more indicators of weight status for 8[67, 68, 70, 72-74, 77] out of 10 analyses[67-70, 72-75, 77] in studies that used TV viewing or screen time as the exposure.

The associations between measures of sedentary behavior and indicators of adiposity are complex. For example, four studies explored the existence of a reciprocal relationship between sedentary behavior and weight status[67, 71, 75, 76]—i.e., does weight status at baseline predict changes in sedentary behavior? Three of the four studies reported significant reciprocal effects[71, 75, 76] and one did not.[67] Helajarvi et al[67] reported that consistently low TV viewing was associated with a smaller increase in BMI and waist circumference over approximately 10 years of follow-up in young Finnish adults, with no evidence of a reciprocal relationship. On the other hand, Menai et al[75] also reported a significant association between increased TV viewing over follow-up and increases in BMI and percent fat. However, a reciprocal relationship also was observed, with positive associations between baseline BMI, percent fat, and waist circumference and increases in TV viewing. Positive associations between accelerometer-determined sedentary time and increases in weight, fat mass, and fat mass index were observed among U.K. adults, and significant positive associations also were seen between the obesity indicators at baseline and

increases in sedentary time over follow-up.[71] Similarly, association between baseline leisure-time sitting and changes in BMI or waist circumference was seen over 5 years of follow-up in Danish adults. However, higher BMI and waist circumference were both positively associated with greater increases in leisure-time sitting (P<0.0001).[76]

Dose-response: The issue of dose-response was addressed in 12 of the original research studies, mainly by testing for linear associations in regression models, or testing for linear trends across categorical exposures.[65-72, 74-77] A statistically significant linear dose-response association was observed in 9 of the 12 studies for at least one subgroup for one of the weight-related outcomes.[67, 68, 70-72, 74-77]

Evidence on Specific Factors

Demographic factors and weight status: Insufficient evidence is available to determine whether age, sex, race/ethnicity, or baseline weight status are important factors in the relationship between sedentary behavior and weight status.

Amount of physical activity: Insufficient evidence is available to determine whether the association between sedentary behavior and weight status varies by amount of moderate-to-vigorous physical activity. Shibata et al[77] found no significant interaction between change in moderate-to-vigorous physical activity and change in TV viewing on 12-year changes in waist circumference among Australian adults. Although Bell et al[66] found no main effect of leisure-time sitting on incident obesity in the study of U.K. adults, a significant interaction between sitting time and physical activity was seen at a 5-year (P=0.02) but not at a 10-year (P=0.37) follow-up. At the 5-year follow-up, the combination of high physical activity and low sedentary time was associated with an odds ratio of 0.26 (95% CI: 0.11-0.64) for incident obesity.[66]

Bouts and breaks: Insufficient evidence is available that bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and weight status. No studies were identified that addressed this topic.

Cardiovascular Disease

Evidence on the Overall Relationship

One systematic review[13] and four meta-analyses[11, 14, 18, 79] were identified that addressed the association between sedentary behavior and incident cardiovascular disease (Supplementary Table S-F2-10). All four meta-analyses reported a statistically significant pooled estimate of risk. Grontved and Hu[11] reported a

pooled relative risk of 1.15 (95% CI: 1.06-1.23) per 2 hours of TV viewing per day. Similarly, Biswas et al[18] and Pandey et al[79] reported summary hazard ratios of 1.14 (95% CI: 1.00-1.30) and 1.14 (95% CI: 1.09-1.19), respectively, for high versus low sedentary behavior and incident cardiovascular disease. Finally, Wilmot et al[14] reported a significant summary relative risk for cardiovascular events of 2.47 (95% CI: 1.44-4.24). Taken together, the results of these meta-analyses indicate that sedentary behavior is significantly associated with incident cardiovascular disease risk.

Three[10, 80, 81] of the six original research studies[10, 80-84] published between 2014 and 2017 found a significant association between sedentary behavior and incident cardiovascular disease (Supplementary Table S-F2-11). Petersen et al[10] reported that daily sitting time was significantly associated with incident myocardial infarction but not with incident coronary heart disease. Young et al[80] reported a significant association between sedentary time and incident heart failure in U.S. men, and Borodulin et al[81] reported a significant association between daily sitting time and incident fatal and nonfatal cardiovascular disease among Finnish adults.

Dose-response: Two meta-analyses addressed the issue of dose-response in the association between sedentary behavior and incident cardiovascular disease.[11, 79] Grontved and Hu[11] reported a significant linear dose-response association between TV viewing and incident fatal and nonfatal cardiovascular disease. In a similar vein, Pandey et al[79] reported a significant, curvilinear dose-response association with increasing slope of risk at increasingly higher levels of sedentary time. Three of the recent research studies published between 2014 and 2017 reported significant dose-response associations between sedentary behavior and incident cardiovascular disease.[10, 80, 81]

Evidence on Specific Factors

Demographic factors and weight status: Insufficient evidence is available to determine whether the relationship between sedentary behavior and cardiovascular disease varies by age, sex, race/ethnicity, socioeconomic status, or weight status, as few studies examined these interactions. Young et al[80] reported that the association between sedentary time and incidence of heart failure was elevated in all ethnic groups, but was statistically significant only in Non-Hispanic White and Hispanic men. The association also was significant in men with normal weight, overweight, and obesity. McDonnell et al[83] reported no significant interactions between TV viewing and age, race or sex on risk of incident stroke.

Amount of physical activity: Available evidence is insufficient to determine whether the relationship between sedentary behavior and cardiovascular disease varies by amount of moderate-to-vigorous

physical activity. Two of the original research studies identified in the de novo literature search considered the potential interactions between sedentary behavior and physical activity on incident cardiovascular disease. Petersen et al[10] found no significant interaction between sitting time and leisure-time physical activity for myocardial infarction or coronary heart disease. On the other hand, Young et al[80] reported a small additive interaction effect between low physical activity and high sedentary time on incident heart failure (relative risk (RR)=0.08; 95% CI: 0.03-0.14).

Bouts and breaks: Insufficient evidence is available that bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incident cardiovascular disease. No studies were identified that addressed this topic.

Cancer

Evidence on the Overall Relationship

Four systematic reviews[12, 13, 85, 86] and four meta-analyses[18, 87-89] addressed the relationship between sedentary behavior and cancer incidence (Supplementary Table S-F2-10). Two meta-analyses addressed associations with total cancer incidence,[18, 88] two meta-analyses examined associations with incidence of several-site-specific cancers,[87, 88] and one meta-analysis addressed breast cancer incidence only.[89] The research studies included in the meta-analyses generally reported relative risks that were adjusted for several covariates, including physical activity. Six original research studies, published between 2014 and 2017, that addressed the relationship between sedentary behavior and incident cancer were identified[90-95] (Supplementary Table S-F2-11). These studies considered the relationship between sedentary behavior and total cancer and site-specific cancers,[94] breast cancer,[91, 93] ovarian cancer,[92] prostate cancer,[90] and lung cancer.[95]

Total Cancer: Two meta-analyses examined the association between sedentary behavior and total cancer incidence.[18, 88] Shen et al[88] reported a summary relative risk of 1.20 (95% CI: 1.12-1.28) and Biswas et al[18] reported a summary hazard ratio of 1.13 (95% CI: 1.05-1.21) for highest versus lowest levels of sedentary behavior and all-cancer incidence. Further, an original research study in a large cohort (American Cancer Prevention Study II Nutrition Cohort) reported a significant association between leisure-time sitting and total cancer incidence in women but not in men.[94] The results of studies that use total cancer incidence as the outcome should be interpreted with caution, given that cancer is a heterogeneous disease and specific cancers vary widely in their etiology and progression, as well as geographic distribution.

Breast Cancer: Three meta-analyses examined the association between sedentary behavior and breast cancer incidence.[87-89] Zhou et al[89] reported non-significant associations between highest and lowest amounts of sitting time and breast cancer incidence (odds ratio (OR)=1.05; 95% CI: 0.99-1.11) and highest versus lowest amounts of TV viewing and breast cancer (OR=1.07; 95% CI: 0.96-1.20), respectively. Similarly, Schmid and Leitzmann[87] also reported no relationship between highest versus lowest amounts of sedentary behavior and breast cancer incidence in their meta-analysis (RR=1.03; 95% CI: 0.95-1.12). On the other hand, Shen et al[88] reported a significant association between the highest versus the lowest amounts of sedentary behavior and breast cancer incidence (RR=1.17; 95% CI: 1.03-1.33). The Shen et al[88] meta-analysis used three prospective cohort studies in their analysis, whereas Schmid and Leitzmann[87] relied on 13 case-control and prospective studies, and Zhou et al[89] also relied on both case-control and prospective studies (9 studies for sitting and 6 studies for TV viewing). Of the two newer original research studies that were found, one reported a significant association with breast cancer[93] and the other did not.[91]

Endometrial Cancer: Two meta-analyses examined the association between sedentary behavior and endometrial cancer, and both reported a significant association.[87, 88] Comparing the highest versus lowest levels of sedentary time, Schmid and Leitzmann[87] reported a summary relative risk of 1.36 (95% CI: 1.15-1.60); whereas Shen et al[88] reported a summary relative risk of 1.28 (95% CI: 1.08-1.53).

Colorectal Cancer: The meta-analysis by Shen et al[88] reported a significant association comparing the highest versus lowest amounts of sedentary behavior and combined colorectal cancer (RR=1.30; 95% CI: 1.12-1.49); whereas Schmid and Leitzmann[87] reported a significant association for the highest versus lowest amounts of sedentary behavior and colon cancer (relative risk = 1.28; 95% CI: 1.13-1.45) but not for rectal cancer (RR=1.03; 95% CI: 0.89-1.19).

Lung Cancer: Two meta-analyses examined the association between sedentary behavior and lung cancer, and both reported a significant association.[87, 88] Comparing the highest versus lowest levels of sedentary time, Schmid and Leitzmann[87] reported a summary relative risk of 1.21 (95% CI: 1.03-1.43); whereas Shen et al[88] reported a summary relative risk of 1.27 (95% CI: 1.06-1.52).

Other Cancers: The two meta-analyses that examined site-specific cancers[87, 88] did not find significant associations between sedentary behavior and risk of ovarian cancer, prostate cancer, stomach cancer, testicular cancer, renal cell carcinoma, or non-Hodgkin lymphoid neoplasms. In a more recent original research study using data from the American Cancer Prevention Study II Nutrition Cohort, the authors

reported significant associations between leisure-time sitting and risk of multiple myeloma, invasive breast cancer, and ovarian cancer in women, but found no associations in men between sedentary behavior and site-specific cancers.[94]

Dose-response: One meta-analysis examined dose-response associations between sedentary behavior and cancer risk by modelling the association according to 2-hour increments per day of time spent being sedentary.[87] Each 2-hour per day of sitting time was related to significantly increased risk of colon cancer (RR=1.08; 95% CI: 1.04-1.11), endometrial cancer (RR=1.10; 95% CI: 1.05-1.15), and a borderline statistically increased risk of lung cancer (RR=1.06; 95% CI: 1.00-1.11).

Evidence on Specific Factors

Demographic factors and weight status: None of the identified meta-analyses stratified its analysis by demographic factors or weight status. Only three original studies tested for interactions between sedentary behavior and BMI, with varying results.[90, 93, 94] Therefore, the evidence is insufficient to determine whether the association between sedentary behavior and cancer risk varies by age, sex/ethnicity, socioeconomic status, or weight status.

Amount of physical activity: None of the identified meta-analyses stratified its analysis by amount of physical activity. Three of the six original research studies tested for an interaction between sedentary behavior and physical activity, and none was significant.[90, 93, 94] Therefore, the evidence is insufficient to determine whether the association between sedentary behavior and cancer risk varies by amount of moderate-to-vigorous physical activity.

Bouts and breaks: Insufficient evidence is available that bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incident cancer. No studies were identified that addressed this topic.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for Supplementary Tables S-F2-10 and S-F2-11, and the Evidence Portfolio. For information on the relationship of physical activity and cancer, see Part F. Chapter 4: Cancer Prevention.

Question 5. Does the effect of moderate-to-vigorous physical activity on all-cause mortality vary by amount of sedentary behavior?

Sources of evidence: Meta-analyses, original research articles

Conclusion Statement

Moderate evidence indicates that the beneficial effect of moderate-to-vigorous physical activity on all-cause mortality varies by amount of sedentary behavior. Importantly, the relative reductions in risk are larger for those who are the most sedentary. **PAGAC Grade: Moderate.**

Review of the Evidence

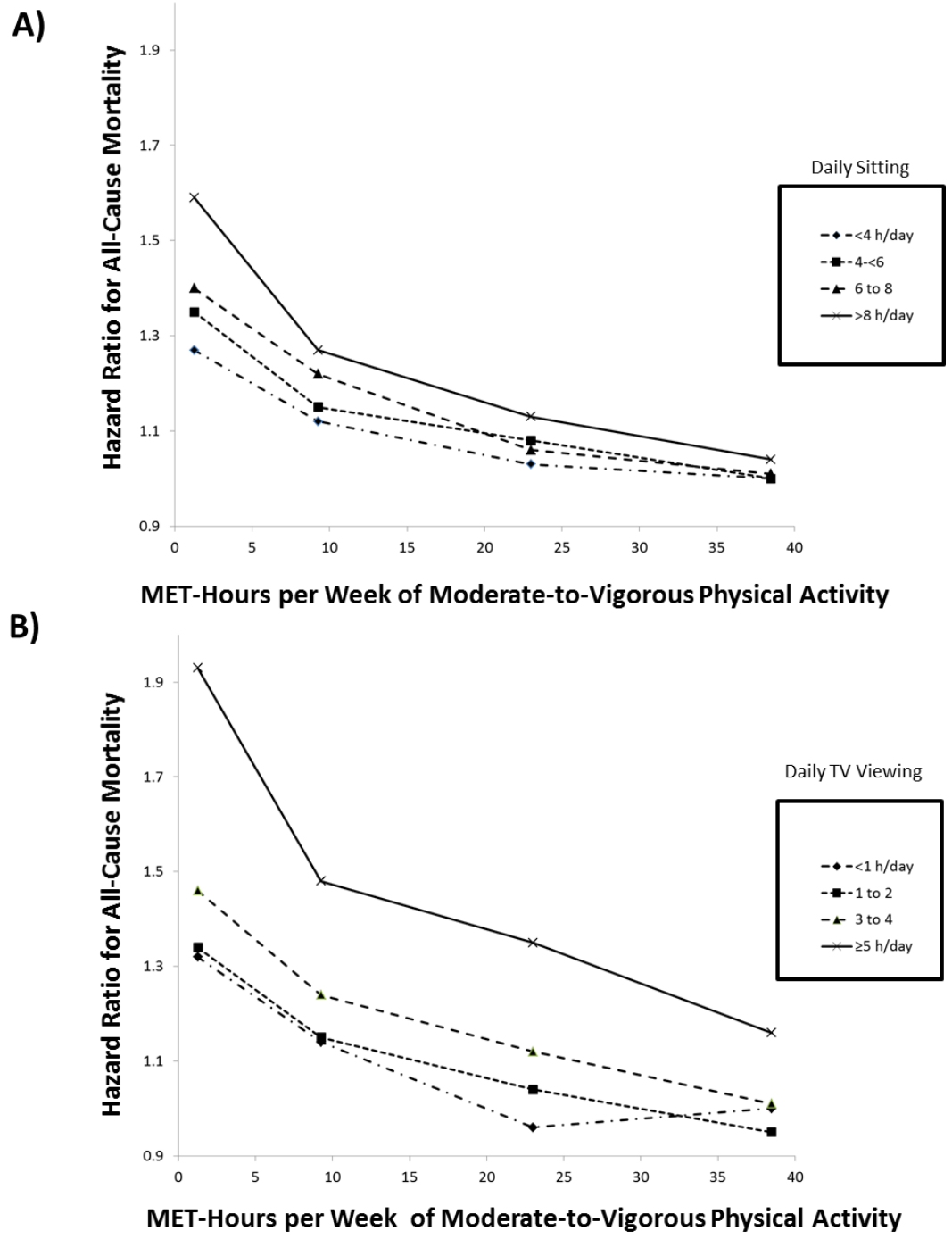
The evidence used to address Question 5 was obtained from the evidence compiled for Question 1. The evidence base is described in greater detail in the section for Question 1. All systematic reviews/meta-analyses and original research articles were reviewed for potential inclusion in the evidence for Question 5. Cohort studies that included multiple amounts of moderate-to-vigorous physical activity as the exposure, in addition to at least two categories of sedentary time, were included in the evidence base. One meta-analysis of data from more than 1 million participants from 16 cohort studies was identified[19] in addition to two original research articles.[35, 38] An additional three original research studies[36, 39, 51] provided graphical representations of death rates or hazard ratios across combined categories of sedentary behavior and moderate-to-vigorous physical activity. However, the purpose of these figures was to examine the shape of the association between sedentary behavior within different amounts of moderate-to-vigorous physical activity, and the point estimates were not provided in the figures. Finally, one study reported similar non-linear associations between moderate-to-vigorous physical activity in those who had more than 10.9 hours per day of sedentary behavior versus those who had 10.9 hours or less per day of sedentary behavior. However, estimates of relative risk were not provided.[26]

The joint associations of moderate-to-vigorous physical activity with daily sitting and TV viewing from the meta-analysis of Ekelund et al[19] are plotted in Figure F2-4. In general, the overall shapes of the dose-response relationships between moderate-to-vigorous physical activity and all-cause mortality are generally similar when stratified by level of sitting or TV viewing. However, the relative risks at every level of moderate-to-vigorous physical activity are consistently higher in the high sitting and high TV viewing groups. The reduction in risk of all-cause mortality is relatively greater for those who are the most sedentary. This is especially apparent at the lower amounts of moderate-to-vigorous physical

activity. For example, among those who sit more than 8 hours per day, the risk for individuals in the second quartile (about 9.25 MET-hours per week) is 20 percent lower than the risk for individuals in the first quartile (≤2.5 MET-hours per week). In contrast, among those who sit less than 4 hours per day, the risk for individuals in the second quartile is 12 percent lower than the risk for individuals in the first quartile.

The level of risk associated with accumulating approximately 20 to 25 MET-hours per week of moderate-to-vigorous physical activity in the low sitting (<4 h/day) group is similar to the risk associated with accumulating 35 to 40 MET-hours per week in the high sitting (>8 h per day) group (Figure 4a). Similar results are observed across categories of TV viewing, except that the level of relative risk associated with high amount of moderate-to-vigorous physical activity in the high TV viewing (≥5 h/day) never achieves that of moderate or high amounts of moderate-to-vigorous physical activity in the low TV viewing (<1 h/day) group (Figure F2-4B). These observations are supported by the results of two original research studies in U.S. adults.[38, 94] It should be noted that both original research studies contributed data to the pooled meta-analysis by Ekelund et al.[19] Further research is required to determine why the associations differ somewhat for self-reported sitting versus self-reported TV viewing.

Figure F2-4. Relationship Between Moderate-to-Vigorous Physical Activity and All-cause Mortality, Stratified by Amounts of A) Sitting Time and B) TV Viewing



Source: Adapted from data found in Ekelund et al., 2016.[19]

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

Strong scientific evidence demonstrates that exposure to high amounts of sedentary behavior significantly increases the risk of all-cause mortality, cardiovascular disease incidence and mortality, and type 2 diabetes incidence. Moderate evidence indicates that high amounts of sedentary behavior are associated with the incidence of cancer, particularly for endometrial, colon and lung cancer. Further, limited evidence exists that sedentary behavior is associated with cancer mortality and weight status. Currently, sedentary behavior is highly prevalent in the U.S. population. Therefore, limiting excessive time spent sitting would reduce the population health impact associated with premature mortality and several major chronic diseases such as type 2 diabetes, cardiovascular disease, and cancer. For physically inactive adults, replacing sedentary behavior with light intensity physical activities is likely to produce some health benefits. Among all adults, replacing sedentary behavior with higher intensity (moderate-to-vigorous) physical activities may produce even greater benefits.

Strong evidence demonstrates that the association between sedentary behavior and all-cause mortality varies by amount of moderate-to-vigorous physical activity, such that the hazardous effects of sedentary behavior are more pronounced in physically inactive people. Moderate evidence also indicates that the effects of moderate-to-vigorous physical activity vary by amount of sedentary behavior, such that those who are the most sedentary experience the greatest relative reductions in mortality risk associated with increases in physical activity. Further, individuals who are highly sedentary appear to require even higher amounts of physical activity to achieve the same level of absolute mortality risk as people who are less sedentary. Therefore, moderate-to-vigorous physical activity should be part of every adult's lifestyle, especially for those who sit for large portions of the day.

NEEDS FOR FUTURE RESEARCH

1. Conduct research using prospective cohorts on the interactive effects of physical activity and sedentary behavior on all-cause and cardiovascular disease mortality and incident cardiovascular disease, especially on the role of light-intensity physical activity on attenuating the relationship between sitting and mortality.

   Rationale: Evidence on the role of physical activity in displacing the mortality risks associated with sedentary behavior is limited. A better understanding of these interactive effects will allow for more

specific recommendations regarding the amount and intensity of physical activity required to maximize health benefits among people with higher or lower levels of sedentary behavior. Given that associations between specific risk factors and cancer mortality are affected by cancer screening and treatment availability and efficacy, studies of the associations between sedentary behavior and all-cancer mortality are not a priority.

2. Conduct research using prospective cohorts on the role of bouts and breaks in sedentary behavior in relation to all-cause and cardiovascular disease mortality.

   Rationale: The preponderance of the existing evidence on prospective associations between sedentary behavior and health is based on the association between daily or weekly duration of sedentary behavior. More research is needed on the relationship between patterns of sedentary behavior and mortality and other health outcomes, especially the role of sedentary bouts and breaks. This information will contribute to the development of recommendations on how sedentary behavior patterns should be modified to maximize related health benefits. Given that associations between specific risk factors and cancer mortality are affected by cancer screening and treatment availability and efficacy, studies of the associations between sedentary behavior and all-cancer mortality are not a priority.

3. Conduct research on how factors such as sex, age, race/ethnicity, socioeconomic status, and weight status relate to the association between sedentary behavior and cardiovascular disease incidence and cardiovascular disease mortality.

   Rationale: Compared to the evidence base for all-cause mortality, fewer studies have addressed issues of effect modification by these factors on the relationship between sedentary behavior and cardiovascular disease incidence and mortality. This information will help determine how generalizable the potential benefits of reducing sedentary behavior are in preventing cardiovascular disease and whether different recommendations are required based one's sex, age, race/ethnicity, socioeconomic status, or weight status. Given that associations between specific risk factors and cancer mortality are affected by cancer screening and treatment availability and efficacy, studies of the associations between sedentary behavior and all-cancer mortality are not a priority.

4. Conduct research using prospective cohorts to disentangle the independent effects of sedentary behavior and adiposity on risk of type 2 diabetes.

Rationale: Given that the association between sedentary behavior and type 2 diabetes is attenuated when body mass index is a covariate in the statistical models, this suggests that body mass index may be in the causal pathway between sedentary behavior and risk of type 2 diabetes. However, further research is required to understand the nature and direction of this relationship to better understand whether the relationship between sedentary behavior and type 2 diabetes is truly causal.

5. Conduct randomized controlled trials to test the health effects of interventions to replace time spent in sedentary behaviors with standing and light-, moderate-, and vigorous-intensity physical activity.

   Rationale: The preponderance of the evidence on the health effects of sedentary behavior has come from observational epidemiological studies. To develop public health guidelines and develop effective intervention strategies, more evidence is required on the positive and negative consequences associated with replacing sedentary behavior with greater intensity activities for short or long durations.

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