

## **PART F. CHAPTER 10. INDIVIDUALS WITH CHRONIC CONDITIONS**

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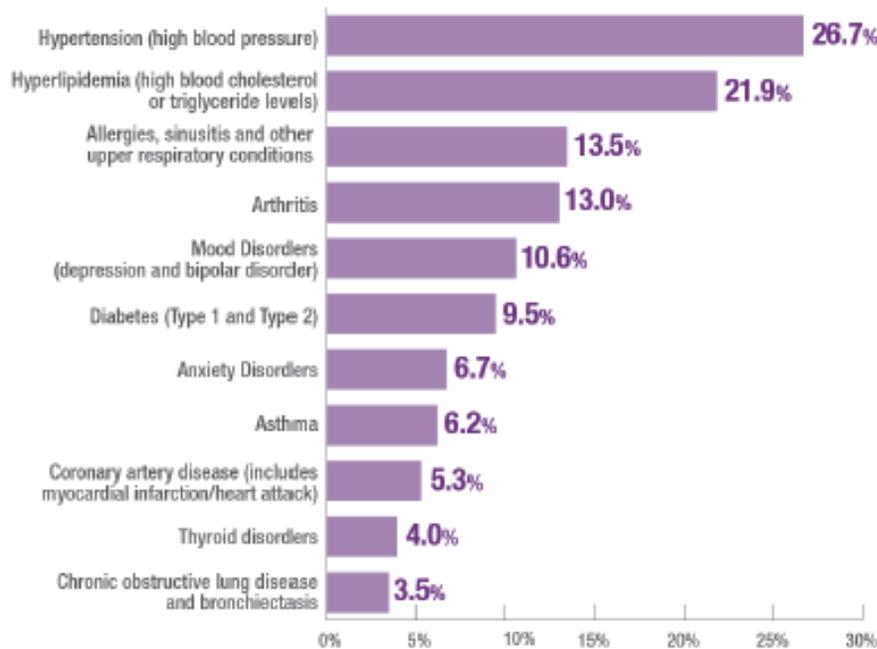
## INTRODUCTION

This chapter reviews evidence related to the preventive effects of physical activity in people with chronic conditions. Chronic conditions can be defined as conditions with duration of at least 1 year, which either require medical care and/or limit activities of daily life.<sup>1</sup> A person has multiple chronic conditions if they have two or more chronic conditions at the same time.

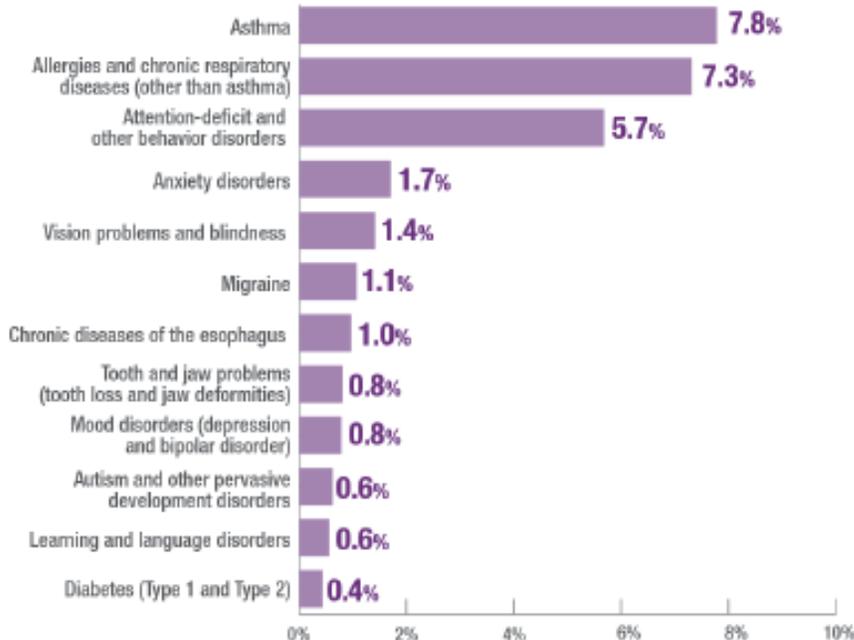
Chronic conditions occur in both children and adults. The prevalence of some common chronic conditions (e.g., hypertension) and groups of chronic conditions (e.g., anxiety disorders) are shown in Figure F10-1.<sup>2</sup> In 2010, about half (51.7%) of all Americans had at least one chronic condition, and about one-third (31.5%) had multiple chronic conditions. The prevalence of most common chronic conditions increases with age, and about 80 percent of adults ages 65 years and older have multiple chronic conditions.<sup>2</sup> Given the aging of the U.S. population, the percent of adults with chronic conditions will thus increase over the next few decades. Chronic conditions that are prevalent in older adults have public health importance, even if they are not included in the figure. For example, in adults ages 50 years and older, the prevalence of osteoporosis is estimated at about 10 percent.<sup>3</sup> Osteoporosis increases risk of hip fracture—an important cause of morbidity and mortality in older adults.

**Figure F10-1. Most Prevalent Chronic Conditions in Adults and Children, 2010**

Most Prevalent Chronic Conditions in Adults (18 and older) – 2010



Most Prevalent Chronic Conditions in Children (17 and younger) – 2010



Source: Gerteis et al., 2014.<sup>2</sup>

Broadly speaking, physical activity has two types of effects in people with chronic conditions: therapeutic and preventive. Therapeutic physical activity is used to treat a disease in the same sense that medication is treatment. An example of therapeutic physical activity is physical activity that is part of formal rehabilitation programs, such as cardiac, stroke, and pulmonary rehabilitation. Generally, therapeutic physical activity is tailored to the medical needs of an individual patient and supervised and/or prescribed by health professionals. The reviews in this chapter do not address therapeutic physical activity per se.

The evidence reviews in this chapter focus on the role of physical activity in prevention in people with an existing chronic condition. Some reviews address primary prevention—not primary prevention of the existing chronic condition, but rather primary prevention of an *additional* chronic condition. For example, evidence reviews in this chapter address whether physical activity reduces risk of cardiovascular mortality in adults with the chronic conditions of type 2 diabetes and hypertension. Questions in this chapter that include the outcome of risk of co-morbid conditions and risk of second primary cancer address primary prevention of additional chronic conditions. Although this chapter does not address primary prevention of type 2 diabetes and hypertension, *Part F. Chapter 5. Cardiometabolic Health and Prevention of Weight Gain* does review the effect of physical activity in reducing risk of incident type 2 diabetes and hypertension.

Other evidence reviews address secondary prevention. Herein, secondary prevention refers to preventing a chronic condition from getting worse over time (i.e., increasing in severity). Worsening of a disease over time is assessed by indicators of disease progression. For example, in the osteoarthritis evidence review of this chapter, indicators of progression are increasing amounts of damaged knee cartilage over time and the need for knee replacement surgery. When a chronic condition progresses, it commonly impairs physical function and lowers health-related quality of life (HRQoL), and may eventually cause mortality. Questions in this chapter that include the outcomes of progression, health-related quality of life, physical function, risk of cancer recurrence, and cancer-specific mortality address secondary prevention.

Admittedly, a clear distinction between therapeutic and preventive effects of physical activity is often not possible. For example, in the evidence review for type 2 diabetes (Question 4 of this chapter), the effects of physical activity on glycated hemoglobin (HbA1C) are regarded as preventive effects, as high levels of HbA1C increase risk of disease progression. Of course, the effects of physical activity on HbA1C

can also be regarded as therapeutic, as a goal medical treatment of type 2 diabetes is to lower HbA1C below an individualized target level.

The evidence reviews of this chapter update information and evidence findings of the *Physical Activity Guidelines Advisory Committee Report, 2008* report.<sup>4</sup> The 2008 Scientific Report<sup>4</sup> addressed, to at least some extent, the effects of physical activity in all the chronic conditions of interest in this chapter: cancer survivors, osteoarthritis, hypertension, type 2 diabetes, multiple sclerosis, spinal cord injury, and intellectual disabilities. However, many fewer scientific studies were available at the time the 2008 Scientific Report<sup>4</sup> was written. The evidence reviews of this chapter located substantially more information, and with one exception (progression outcome of osteoarthritis), the evidence reviews of this chapter relied on existing systematic reviews, meta-analyses, and published analyses of pooled data. Comparisons of the findings of this report with the findings of the 2008 Scientific Report<sup>4</sup> are provided for each question.

The evidence reviews of this chapter have substantial public health importance. As the number of chronic conditions increases in an individual and as existing conditions worsen, the risk of functional limitations increases, quality of life decreases, and costs of medical care increase. In 2010, 65 percent of healthcare spending was for individuals with a chronic condition, and notably, most of this spending (71%) was for people with multiple chronic conditions.<sup>2</sup> Thus, in individuals with a chronic condition, it is of large public health importance to prevent another chronic condition from developing and to prevent the existing condition from getting worse.

Other aspects of the importance of prevention in individuals with chronic conditions are: (1) Individuals with chronic conditions generally engage in less physical activity. To the extent physical activity provides benefits, it emphasizes the importance of promoting physical activity in individuals with chronic conditions. (2) Documenting preventive benefits in individuals with chronic conditions increases the confidence that when a research study reports a preventive effect of physical activity in the general population, it is not because of preventive effects that occur only in relatively healthy people. (3) Documenting preventive benefits increases the confidence that effects of physical activity are not blocked by disease effects. (4) Documenting preventive benefits emphasizes that the same physical activity commonly provides both preventive and therapeutic benefits in individuals with chronic conditions.

## **Prioritization of Chronic Conditions**

Early in its work, the 2018 Physical Activity Guidelines Advisory Committee agreed that Question 1 of this chapter would address effects of physical activity in cancer survivors. To identify the chronic conditions for other questions in this chapter, the Individuals with Chronic Conditions Subcommittee identified four criteria for prioritizing conditions: (1) public health importance as indicated by prevalence of the condition; (2) amount of evidence available as indicated by preliminary literature searches for systematic reviews and meta-analyses; (3) diversity (by organ system) in conditions chosen for review; and (4) no review of effects of physical activity in the condition by another Subcommittee.

A list of chronic conditions for possible review was presented at the Committee's second public meeting and discussed by the Committee publicly and in small group break-out sessions. Information on prevalence of chronic conditions was ascertained from a report by the Agency for Healthcare Research and Quality (Figure F10-1<sup>2</sup>) or from published articles. Preliminary searches were done to estimate the size of the literature of the effects of physical activity for conditions on the list. The search used a standard set of physical activity terms, sought only articles designated as systematic reviews or meta-analyses, and used a list of search terms developed separately for each chronic condition. It was originally thought that, for some conditions, available evidence on the health effects of physical activity in people with that condition would be insufficient. However, the preliminary literature searches located tens, if not hundreds, of possible systematic reviews of effects of physical activity for each condition (Table F10-1). That is, the search did not rule out the possibility that, for any chronic condition, at least a few good quality reviews of effects of physical activity would be available.

A table was created that ranked chronic conditions based upon prevalence and size of published literature (Table F10-1). The purpose of this table was to provide background information for discussions by the Subcommittee; it was not intended to provide a decision rule for selecting chronic conditions. The prevalence of each condition was ranked, as was the number of "hits" in the preliminary search. The sum of the two ranks was calculated, and then the sum was ranked. (This table was revised several times; only one version is shown). As an example of the content of deliberations, consider low back pain. There was concern that low back pain is technically a symptom due to a variety of conditions, rather than a single chronic condition comparable to, for example, hypertension. Because effects of physical activity could vary by the etiology of the back pain, a review would require identifying effects of physical activity for each common condition causing back pain. The preliminary search results might

overestimate the relevant evidence, as trials of therapeutic activity for acute low back pain might be commonly included in reviews. When it was decided to include a review of physical activity and osteoarthritis, part of the rationale was that osteoarthritis is a common cause of back pain, and thus this review might end up addressing effects of physical activity in back pain due to osteoarthritis.

Several conditions were not selected because of evidence reviews by other Subcommittees. The Aging Subcommittee reviewed effects of physical activity on physical function in older adults with cardiovascular disease (CVD), chronic obstructive pulmonary disease, conditions causing cognitive impairment (including Alzheimer's disease), hip fracture, osteoporosis, Parkinson's disease, and stroke. The Brain Health Subcommittee reviewed the effects of physical activity in several additional chronic conditions, including dementia, schizophrenia, attention deficit hyperactivity disorder, major depression, bipolar disorder, anxiety disorders, and obstructive sleep apnea.

The Subcommittee carefully considered an evidence review addressing a chronic condition in children. As of the fourth (next to last) Committee meeting, a review of a chronic condition prevalent in children was still under consideration. With the Brain Health Subcommittee taking the lead on reviews of physical activity in people with mental health conditions, the leading option was a review of asthma in both adults and children. However, children are at low risk of chronic conditions so it was likely that no information on prevention of co-morbidities in children with asthma would be available. The waxing and waning of asthma symptoms and the effects of treatment on disease severity also could make it challenging to tease out effects of physical activity on progression, physical function, and HRQoL.

Thus, it was decided to do a review of the effect of physical activity on intellectual and physical disabilities, in part because intellectual disabilities, such as Down syndrome, are highly relevant to children. Another set of preliminary searches was done and an outside expert consulted. The preliminary search showed insufficient evidence was available for muscular dystrophy, but sufficient evidence would be available for the final three conditions reviewed in this chapter: multiple sclerosis, spinal cord injury, and intellectual disability.

**Table F10-1. Ranking of Chronic Conditions Based on Prevalence and Size of Published Literature**

Chronic Condition	Prevalence Children	Prevalence Adults	Sum of Prevalences	# Search Results	Prevalence rank	Search rank	Sum	Overall Rank
Hypertension	2-3%	26.7%	29.0%	436	1	5	6	1
Mood Disorders	0.80%	10.6%	11.4%	490	6	2	8	2
Cancer Survivors		6.3%	6.3%	785	10	1	11	3 T
Type 2 Diabetes	<.4%	9.5%	9.8%	483	8	3	11	3 T
Low Back Pain		18.1%	18.1%	241	3	9	12	5
Osteoarthritis		13.0%	13.0%	294	5	8	13	6
Lipid Disorder		21.9%	21.9%	84	2	14	16	7
Asthma	7.80%	6.2%	14.0%	83 (125 with Exercise-Induced)	4	13	17	8
Coronary Heart Disease		5.3%	5.3%	294	12	7	19	9
Neuromotor Disease			Low	449 (513 including stroke & AD)	18	4	22	10 T
Congestive Heart Failure		2.3%	2.3%	317	16	6	22	10 T
Chronic Renal Disease		10.0%	10.0%	53	7	16	23	12
COPD		3.5%	3.5%	142 (284 with Rehabilitation)	13	11	24	13
Stroke		3.0%	3.0%	185 (356 with Rehabilitation)	15	10	25	14
Peripheral Artery Disease		3.4%	3.4%	91	14	12	26	15
Anxiety Disorders	1.70%	6.7%	8.4%	27	9	18	27	16

Chronic Condition	Prevalence Children	Prevalence Adults	Sum of Prevalences	# Search Results	Prevalence rank	Search rank	Sum	Overall Rank
ADHD	5.70%		5.7%	11	11	19	30	17
Alzheimer's Disease		2.0%	2.0%	73	17	15	32	18
Cystic Fibrosis	<1%		Low	43	19	17	36	19

Legend: ADHD=attention deficit hyperactivity disorder, COPD=chronic obstructive pulmonary disease, AD=anxiety disorders.

In summary, prioritization was a sequential process based upon discussions at public meetings and various Subcommittee meetings. This sequential process ensured adequate time and resources were available to address the final list of questions. Three prevalent conditions were chosen for Questions 2, 3, and 4: osteoarthritis (musculoskeletal), hypertension (cardiovascular), and type 2 diabetes (metabolic). The resources and time available allowed only a more limited review for the last three conditions, selected in part because of the public health importance of physical activity in people with disabilities: multiple sclerosis, spinal cord injury, and intellectual disability. The selection of cancer types for review in Question 1 is discussed below under Question 1.

### Principles Guiding the Evidence Review and Terminology

In selecting relevant evidence, the Subcommittee was guided by several principles and definitions. (1) The evidence review would rely on existing systematic reviews, rather than de novo reviews of original research articles. This principle was followed for all reviews with one exception—the review of progression in osteoarthritis. (2) Given the focus on prevention, the review would exclude studies of therapeutic exercise, such as the effects of formal rehabilitation programs. (3) The most relevant experimental evidence would come from controlled trials, preferably randomized trials, comparing physical activity (only) to a no-activity control group. (4) In a person with one condition, the term co-morbid condition would refer to any other chronic condition that could be measured by a medical diagnosis (e.g., coronary heart disease) or by events (e.g., cardiovascular mortality). (5) The term physical function would have the same definition as that developed by the Aging Subcommittee, namely “the ability of a person to move around and to perform types of activity.” (6) Given that HRQoL is a multi-dimensional concept that includes physical function, the most relevant HRQoL measures would not be subscale scores, but summary scores aggregating information on quality of life across several

subscales (or domains). (7) The term progression would refer to worsening of an existing disease or chronic condition over time, and be assessed by one or more disease-specific indicators.

## REVIEW OF THE SCIENCE

### Overview of Questions Addressed

This chapter addresses seven major questions and related subquestions:

1. Question 1. Among cancer survivors, what is the relationship between physical activity and (1) all-cause mortality, (2) cancer-specific mortality, or (3) risk of cancer recurrence or second primary 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) Does the relationship vary based on: frequency, duration, intensity, type (mode), and how physical activity is measured?
2. Question 2. In individuals with osteoarthritis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, (4) pain, and (5) disease progression?
  - 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) Does the relationship vary based on frequency, duration, intensity, type (mode), or how physical activity is measured?
3. Question 3: In people with the cardiovascular condition of hypertension, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) cardiovascular disease progression and 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, weight status, or resting blood pressure level?
  - c) Does the relationship vary based on frequency, intensity, time, duration, type (mode), or how physical activity is measured?
4. Question 4. In people with type 2 diabetes, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) disease progression?
  - 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) Does the relationship vary based on: frequency, duration, intensity, type (mode), or how physical activity is measured?
5. Question 5. In people with multiple sclerosis, what is the relationship between physical activity and:
  - 1) risk of co-morbid conditions, 2) physical function, and 3) health-related quality of life?

6. Question 6. In people with spinal cord injury, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?
7. Question 7. In people with intellectual disabilities, what is the relationship between physical activity and: (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

### **Data Sources and Process Used to Answer Questions**

To allow for coverage of the largest number of chronic conditions, the Subcommittee chose to rely exclusively on existing reviews including systematic reviews, meta-analyses, pooled analyses, and reports for its questions, only answering the questions and sub-questions that could be answered with the information from the existing reviews. For all but one question, additional searches for original research were not needed. For Question 2 (individuals with osteoarthritis) the existing reviews did not identify sufficient evidence to answer the question about disease progression. The Subcommittee and expert consultant regarded progression of osteoarthritis as a question that needed to be answered due to the existing relationship between physical activity and osteoarthritis. A supplementary de novo search for original research was conducted on progression in individuals with osteoarthritis.

In an effort to reduce duplication of efforts, the searches for existing reviews and title triage for Question 3 (individuals with hypertension) and Question 4 (individuals with type 2 diabetes) were done concurrently with the Cardiometabolic Health and Weight Management Subcommittee's Question 2 (blood pressure) and Question 3 (incidence of type 2 diabetes). The search strategies for each of these questions were developed to address the needs of both Subcommittees. Title triage addressed the inclusion criteria of both Subcommittees. Abstract and full-text triage were done separately for both Subcommittees.

Across its questions, the Chronic Conditions Subcommittee reviewed original research articles contained in the included systematic reviews, meta-analyses, pooled analyses, and reports to allow for additional specificity in the understanding of the literature. These original research articles are not included as evidence in the evidence portfolio. For complete details on the systematic literature review process, see *Part E. Systematic Literature Search Methodology*.

**Question 1. Among cancer survivors, what is the relationship between physical activity and (1) all-cause mortality, (2) cancer-specific mortality, or (3) risk of cancer recurrence or second primary 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) Does the relationship vary based on: frequency, duration, intensity, type (mode), and how physical activity is measured?

**Sources of evidence:** Systematic reviews, meta-analyses, pooled analyses

**Conclusion Statements**

**Breast Cancer in Women**

Moderate evidence indicates that greater amounts of physical activity after diagnosis are associated with lower risks of breast cancer-specific mortality and all-cause mortality in female breast cancer survivors. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether physical activity after diagnosis is associated with risk of breast cancer recurrence or second primary breast cancer. **PAGAC Grade: Not assignable.**

Moderate evidence indicates that a dose-response relationship exists; as levels of physical activity increase, risks of breast cancer-specific mortality and all-cause mortality decrease in female breast cancer survivors. **PAGAC Grade: Moderate.**

Moderate evidence indicates that greater amounts of physical activity after diagnosis are associated with lower risks of breast-cancer-specific mortality in both pre- and postmenopausal breast cancer survivors, with menopause as a proxy for age, while greater amounts of physical activity are associated with lower risks for all-cause mortality in only postmenopausal breast cancer survivors. **PAGAC Grade: Moderate.**

Moderate evidence indicates that greater amounts of physical activity after diagnosis are associated with lower risks of all-cause mortality in breast cancer survivors with both normal weight and overweight or obesity, while greater amounts of physical activity after diagnosis are associated with lower risks of breast cancer-specific mortality only in breast cancer survivors with overweight or obesity. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether the relationship between physical activity and all-cause mortality or breast cancer-specific mortality differs by sex, race/ethnicity or socioeconomic status in breast cancer survivors. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the frequency, duration, intensity, or type (mode) of physical activity is related to all-cause mortality or breast cancer-specific mortality in breast cancer survivors. **PAGAC Grade: Not assignable.**

### Colorectal Cancer

Moderate evidence indicates that greater amounts of physical activity after diagnosis are associated with lower risks of colorectal cancer-specific mortality and all-cause mortality in colorectal cancer survivors. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether physical activity after diagnosis is associated with risk of colorectal cancer recurrence or second primary colorectal cancer. **PAGAC Grade: Not assignable.**

Moderate evidence indicates that a dose-response relationship exists; as levels of physical activity increase, risks of colorectal cancer-specific mortality and all-cause mortality decrease in colorectal cancer survivors. **PAGAC Grade: Moderate.**

Moderate evidence indicates that the association between physical activity and both colorectal cancer-specific mortality and all-cause mortality does not vary across age groups from middle to older ages. **PAGAC Grade: Moderate.**

Moderate evidence indicates that the association between physical activity and both colorectal cancer-specific mortality and all-cause mortality does not vary between men and women. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether the relationship between physical activity and all-cause mortality or colorectal cancer-specific mortality differs by race/ethnicity, socioeconomic status, or weight status in colorectal cancer survivors. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the frequency, duration, intensity, or type (mode) of physical activity is related to all-cause mortality or colorectal cancer-specific mortality in colorectal cancer survivors. **PAGAC Grade: Not assignable.**

### Prostate Cancer

Limited evidence suggests an inverse association between highest versus lowest levels of physical activity after diagnosis and all-cause mortality in prostate cancer survivors. **PAGAC Grade: Limited.**

Moderate evidence indicates an inverse association between highest versus lowest levels of physical activity after diagnosis and prostate cancer-specific mortality in prostate cancer survivors. **PAGAC Grade: Moderate.**

Insufficient evidence is available on the association between physical activity level and prostate cancer recurrence or progression. **PAGAC Grade: Not assignable.**

Limited evidence suggests that a dose-response relationship exists; as levels of physical activity increase, risks of prostate cancer-specific mortality and all-cause mortality decrease in prostate cancer survivors. **PAGAC Grade: Limited.**

Insufficient evidence is available on the association between physical activity and prostate cancer survival or recurrence by age, race/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Limited evidence suggests that increased frequency, duration, and intensity of physical activity may be associated with decreased risks for all-cause mortality and prostate cancer-specific mortality in prostate cancer survivors. **PAGAC Grade: Limited.**

### **Review of the Evidence**

According to the U.S. National Cancer Institute, a person is considered to be a cancer survivor from the time of diagnosis until the end of life. Currently, almost 15 million people in the United States are cancer survivors.<sup>5</sup> Trends toward earlier detection of cancer and improved treatments have contributed to increased survival; two-thirds of individuals with cancer survive for at least 5 years.<sup>5</sup> This improved survival has shifted focus in survivorship research toward new outcomes, such as studying long-term survival (i.e., over decades). Increasingly, recognition of the role of host factors in cancer survival, such as obesity, metabolic health, inflammation, immune function, and the endocrine system, has supported the increased focus on lifestyle changes to improve these factors.

Systematic literature searches were conducted to answer Question 1, with conclusions possible for breast cancer in women, colorectal cancer, and prostate cancer. The databases searched included

PubMed, Cochrane, and CINAHL. The literature search to address Question 1 was limited to systematic reviews, meta-analyses and pooled analyses. For prostate cancer, the results of the literature search did not provide information on the physical activity association with all-cause mortality. The Subcommittee therefore also reviewed original research articles contained within the one meta-analysis of physical activity and prostate cancer prognosis in order to examine the association between physical activity and all-cause mortality.

In the studies included in the meta-analyses, systematic reviews, and pooled analyses, physical activity was measured through self-report, with different types of validated physical activity questionnaires. In many studies, participants were presented with a list of typical activities (e.g., walking, running, biking), and asked to indicate the frequency and duration of each activity. Other studies used more general questions about time spent in vigorous- or moderate-intensity activities. Most collected information on recreational activities, several also included occupational activities, and only a few included household activities. Some calculated total physical activity, adding up all of these activities; most limited calculation of amount of activity to leisure-time activity. Some of the meta-analyses calculated MET-hours per week of moderate and vigorous physical activities where data were available, but the cut-points for highest versus lowest activity levels varied across studies. Although most studies that calculated MET-hours assigned a MET value of 6 for vigorous activities, some assigned a value of 8.

Although information was available in some meta-analyses and systematic reviews on pre-diagnosis physical activity levels, the Subcommittee examined only post-diagnosis activity levels in relation to prognosis, because the focus of this chapter is on individuals with chronic disease.

Most of the studies included in the meta-analyses and systematic reviews adjusted for possible confounding factors, although few had data on types of treatments and whether full courses of treatment were received. Therefore, none of the meta-analyses was able to examine the confounding or effect modifying effects of treatment. Because receipt of optimal treatment is a key predictor of survival from cancer, the Subcommittee could not rule out a major confounding or modifying effect of this factor.

The remainder of the discussion of the evidence and findings is organized by the three types of cancer addressed by the review: breast cancer in women, colorectal cancer, and prostate cancer. In addition, a section on other cancers comments on results of searches for evidence for other cancer types.

## Breast Cancer in Women

More than three million U.S. women are living with a diagnosis of invasive breast cancer.<sup>6</sup> Breast cancer prognosis is strongly influenced by stage at diagnosis, tumor subtype, and availability and access to appropriate therapies.<sup>7</sup> However, growing evidence suggests that host effects, including weight status, metabolic health, and nutrition influence prognosis.<sup>8-11</sup>

The Subcommittee used information from eight systematic reviews,<sup>12-19</sup> of which six included meta-analyses.<sup>14-19</sup> These reviews included physical activity data collected after diagnosis and between 4 and 14 studies. Sample sizes ranged from several hundred to (in the most recent review) 17,666 breast cancer survivors (1,239 deaths).<sup>14</sup> Median length of follow-up ranged from 3 to 12 years. For recurrence, data were available from four cohort studies and one small randomized controlled trial (RCT). Also reviewed were three reports from a pooling project of four studies with a total of 13,000 breast cancer survivors.<sup>20-22</sup> Where several meta-analyses presented similar risk estimates, the Subcommittee chose to report estimates from the most recent or most comprehensive review. In some cases, subgroup analyses were reported in older reviews, and are therefore presented here.

For this analysis, breast cancer survivors are defined as women who have been diagnosed with invasive breast cancer. All of the systematic reviews and meta-analyses included studies with breast cancer survivors diagnosed at stages I to III, excluding those initially diagnosed with metastatic (stage IV) cancer.

### *Evidence on the Overall Relationship*

Data from this body of evidence show a consistent inverse association between amounts of physical activity after diagnosis and cancer-specific and all-cause mortality in breast cancer survivors. Estimates from a 2015 meta-analysis of eight cohorts found that highest versus lowest levels of physical activity were associated with a 48 percent reduction in risk for all-cause mortality (relative risk (RR)=0.52; 95% confidence interval (CI): 0.43-0.64).<sup>16</sup> A 2016 meta-analysis of ten cohorts found that highest versus lowest levels of post-diagnosis physical activity were associated with a 38 percent reduction in risk of breast cancer-specific mortality (RR=0.62; 95% CI: 0.48-0.80).<sup>14</sup> This latter study found that risk of recurrence was significantly reduced in four cohorts and one trial that collected recurrence data (RR=0.68; 95% CI: 0.58-0.80).<sup>14</sup> It should be noted that the various studies used quite different definitions of recurrence, so it is difficult to interpret the combined effect of these results. The pooling project addressed the association between meeting the 2008 Physical Activity Guidelines<sup>23</sup>

recommended activity levels and breast cancer survival. The project found that engaging in 10 or more MET-hours per week was associated with a 27 percent reduction in all-cause mortality (hazard ratio (HR)=0.73; 95% CI: 0.66-0.82) and a 25 percent reduction in breast cancer-specific mortality (HR=0.75; 95% CI: 0.65-0.85).<sup>20</sup>

**Dose-response:** A meta-analysis of four cohort studies found that, in comparisons of less active to more active individuals, each 5, 10, or 15 MET-hours per week increase in amounts of post-diagnosis physical activity was associated with a 6 percent (95% CI: 3%–8%), 11 percent (95% CI: 6%–15%), and 16 percent (95% CI: 9%–22%) reduction in risk of breast-cancer mortality, respectively.<sup>17</sup> Furthermore, each 5, 10, or 15 MET-hours per week increase in amounts of post-diagnosis physical activity was associated with a 13 percent (95% CI: 6–20%), 24 percent (95% CI: 11%–36%), and 34% (95% CI: 16%–38%) decreased risk of all-cause mortality, respectively.<sup>17</sup>

#### *Evidence on Specific Factors*

**Age:** Although no meta-analyses assessed relationships by age, menopausal status was investigated as an effect modifier in two meta-analyses.<sup>16, 19</sup> In women who were premenopausal at diagnosis, highest versus lowest physical activity was associated with reduced breast cancer death (HR=0.55; 95% CI: 0.37-0.82).<sup>16</sup> In postmenopausal women, highest versus lowest level of physical activity was associated with reduced risk of both breast cancer-specific and all-cause mortality (HR=0.75; 95% CI: 0.58-0.98 and HR=0.44; 95% CI: 0.24-0.80, respectively).<sup>16</sup>

**Cancer subtype:** Two meta-analyses assessed effects by tumor estrogen receptor status.<sup>15, 16</sup> Women with estrogen receptor positive tumors who were in the highest level of physical activity had reduced risk of all-cause mortality compared with women in the lowest level (HR=0.34; 95% CI: 0.14-0.83), but physical activity did not have a similar effect on all-cause mortality in women with estrogen receptor negative tumors. This meta-analysis further found that the subset of survivors at the highest level of physical activity with both estrogen receptor negative and progesterone receptor negative tumors had reduced risk of all-cause mortality (HR=0.56; 95% CI: 0.41-0.77), while those with estrogen and progesterone receptor positive tumors had reduced risk for breast cancer-specific mortality (RR=0.32; 95% CI: 0.12-0.86).<sup>16</sup> Women with stage I and stage II-III disease at diagnosis had reduced risk of all-cause mortality (HR=0.31; 95% CI: 0.10-0.95 and HR=0.57; 95% CI: 0.41-0.79, respectively).<sup>16</sup> These analyses by cancer subtypes were limited to two to three cohort studies, and therefore should be interpreted with caution. The pooling project found that women with estrogen receptor positive tumors

who were in the top two tertiles of post-diagnosis physical activity had significantly reduced mortality (20-30%,  $P_{\text{trend}} < 0.0001$ ) after 5-year follow-up, compared with those with lower activity levels.<sup>21</sup>

**Sex:** Although breast cancer occurs in men, it is 100 times less common than in women. No studies investigated the association between physical activity and survival, recurrence, or second primary in men with breast cancer.

**Race/ethnicity and socioeconomic status:** No conclusions can be made regarding whether the inverse relationship between physical activity and all-cause mortality, as well as cancer-specific mortality, varies by race/ethnicity, or socioeconomic status. The studies lacked sufficient representation of ethnic and minority populations, as well as outcomes based on socioeconomic status, preventing any systematic conclusions related to these factors.

**Weight status:** Three meta-analyses estimated effects of physical activity by body mass index (BMI) level, with similar results.<sup>15, 16, 19</sup> In the latest review, for those with BMI  $< 25$  kg/m<sup>2</sup>, risk of all-cause mortality in those with highest versus lowest physical activity level was reduced (HR=0.44; 95% CI: 0.30-0.64), while risk for breast cancer-specific mortality was not reduced.<sup>16</sup> Among those with BMI  $\geq 25$  kg/m<sup>2</sup>, risks for both breast cancer-specific and all-cause mortality were reduced in those with highest versus lowest physical activity level (HR=0.51; 95% CI: 0.35-0.74 and HR=0.50; 95% CI: 0.32-0.78, respectively).<sup>16</sup>

**Physical activity frequency, duration, intensity, type (mode):** Physical activity in the meta-analyses was measured as either hours per week, or more generally expressed as MET-hours per week of moderate and vigorous physical activities. Beyond the total MET-hours per week of moderate-to-vigorous physical activity, presumed primarily aerobic based on surveys and questionnaires, no specific conclusions can be made regarding the nature of the exercise exposure.

## Colorectal Cancer

### Review of the Evidence

More than 1,317,000 individuals in the United States are colorectal cancer survivors, and about 135,000 new cases occur per year, of which approximately 72 percent are colon and 28 percent are rectal.<sup>24, 25</sup> Colorectal cancer causes approximately 50,260 deaths per year in the United States, accounting for 8.4 percent of cancer deaths as the second leading cause for cancer mortality.

The Subcommittee used information from eight systematic reviews,<sup>12, 14, 17, 26-30</sup> of which six included meta-analyses.<sup>14, 17, 27-30</sup> These reviews included between three and seven studies that assessed post-diagnosis physical activity in relation to survival. Sample sizes in included cohorts ranged from several hundred to (in the most recent review) a total of 9,698 colorectal cancer survivors (1,071 deaths).<sup>14</sup> Median length of follow-up ranged from 4 to 12 years. For recurrence, data were available from only one small cohort study. Where several meta-analyses presented similar risk estimates, the Subcommittee chose to report estimates from the most recent or most comprehensive review. In some cases, subgroup analyses were reported in older reviews, and are therefore presented here.

The studies on physical activity pooled all outcomes for colon and rectal cancer, which are reported at a ratio of approximately two cases of colon cancer for each case of rectal cancer, and adjusted for tumor location, including proximal colon (ascending and transverse), distal colon (descending and sigmoid), and rectal cancer, and for cancer grade. Thus, the conclusions of this report are considered to apply to cancer survivors with a diagnosis of both proximal and distal colon and rectal cancer. Most of the cohort studies included colorectal cancer stages I to III, excluding metastatic stage IV cancer, and the meta-analyses of the cohort studies further excluded stage IV to minimize the bias that could be introduced with its higher mortality. Therefore, this question's conclusions do not apply to stage IV colorectal cancer.

### *Evidence on the Overall Relationship*

Data from this body of evidence show a consistent inverse association between amounts of physical activity after diagnosis and all-cause mortality and colorectal cancer-specific mortality in colorectal cancer survivors. A 2016 meta-analysis including seven cohort studies showed a 42 percent reduced risk of all-cause mortality in survivors with highest versus lowest levels of physical activity (RR=0.58; 95% CI: 0.49-0.68).<sup>30</sup> A different 2016 meta-analysis of six cohorts found that highest versus lowest levels of post-diagnosis physical activity were associated with a 38 percent reduction in risk of colorectal cancer-specific mortality (relative risk (RR)=0.62; 95% CI: 0.45-0.86).<sup>14</sup> This latter study found that risk of recurrence was not statistically significantly related to physical activity, but the data were from only one cohort with 832 survivors (159 deaths).<sup>14</sup>

One meta-analysis assessed dose-response using five cohort studies. In comparisons of less active to more active individuals, each 5, 10, or 15 MET-hours per week increase in post-diagnosis physical activity was associated with a 15 percent (95% CI: 10%-19%), 28 percent (95% CI: 20%-35%), and 35

percent (95% CI: 28%-47%) lower risk for all-cause mortality.<sup>17</sup> Results for colorectal cancer-specific mortality were virtually identical.

### *Evidence on Specific Factors*

**Age:** Most of the prospective cohort studies included in the meta-analyses consisted of individuals with a median age ranging from 60 to 69 years. Although age was included as an adjustment factor in most studies, no meta-analyses conducted analyses by age group. However, the cohorts that enrolled only older individuals<sup>31, 32</sup> found similar effects of physical activity on mortality compared with younger survivor populations.

**Sex:** The recent meta-analyses included two prospective cohort studies with women only<sup>32, 33</sup> that showed statistically significant inverse associations between physical activity and both all-cause mortality and cancer-specific mortality. One study with only men showed a non-statistically significant negative association between highest versus lowest physical activity level and risk for either all-cause mortality or colorectal cancer-specific mortality.<sup>34</sup> Results for remaining cohorts lay between the results for women only and men only. Therefore, it appears likely that physical activity reduces all-cause and colorectal cancer-specific mortality in both men and women.

**Race/ethnicity and socioeconomic status:** No conclusions may be made regarding whether the inverse relationship between physical activity and all-cause mortality or colorectal cancer-specific mortality varies by race/ethnicity, or socioeconomic status. The studies lacked sufficient representation of ethnic and minority populations, as well as outcomes based on socioeconomic status, preventing any systematic conclusions related to these factors.

**Weight status:** Although most of the source cohorts in the meta-analyses adjusted for BMI, the meta-analyses did not provide estimates of effects of physical activity on mortality by categories of BMI. Therefore, the effect of weight status on the role of physical activity in colorectal cancer survivors is unknown.

**Physical activity frequency, duration, intensity, type (mode):** Physical activity in the meta-analyses was measured as either hours per week, or more generally expressed as MET-hours per week of moderate and vigorous physical activities. Sedentary to low activity was defined as less than 3 MET-hours per week, while higher physical activity levels were classified at a range from more than 17 to more than 27 MET-hours per week. Beyond the total MET-hours per week of moderate-to-vigorous physical activity

(which was presumed as primarily aerobic based on surveys and questionnaires), no specific conclusions can be made regarding the nature of the exercise exposure.

## Prostate Cancer

### **Review of the Evidence**

More than three million U.S. men are living with a diagnosis of invasive prostate cancer.<sup>35</sup> Most men diagnosed in older ages (older than age 65 years) do not die of their prostate cancer; rather, the primary cause of death in this survivor population is CVD. Prognosis is influenced by stage at diagnosis and availability and access to appropriate therapies.<sup>36</sup>

The Subcommittee used information from two systematic reviews,<sup>12, 14</sup> of which one included a meta-analysis.<sup>14</sup> The [Ballard-Barbash et al<sup>12</sup>](#) review included only one cohort study of prostate cancer survivors, while the [Friedenreich et al<sup>14</sup>](#) review included four studies. Therefore, estimates for this report are from the latter review. Available information on the association between physical activity and survival in men with prostate cancer is from prospective cohort studies of prostate cancer survivors for whom data were obtained on physical activity levels after diagnosis. Sample sizes in the four cohorts ranged from 830 to 4,600 prostate cancer survivors. Median length of follow-up ranged from 2 to 15 years. For recurrence, data were available from two cohort studies.

### *Evidence on the Overall Relationship*

Data from this body of evidence show an inverse association between amounts of physical activity after diagnosis and cancer-specific mortality in prostate cancer survivors. Estimates from a 2016 meta-analysis of three cohorts found that highest versus lowest levels of physical activity were associated with a 38 percent reduction in risk for prostate cancer-specific mortality (RR=0.62; 95% CI: 0.47-0.82).<sup>14</sup> Overall mortality was not addressed in the [Friedenreich et al<sup>14</sup>](#) meta-analysis. A review of the papers included in the systematic reviews indicates that highest versus lowest levels of total, recreational, non-sedentary occupational, and vigorous physical activity were statistically significantly related to reduced risk for all-cause mortality.<sup>37-39</sup>

Risk of recurrence or progression was not associated with physical activity in a meta-analysis of two cohorts that collected recurrence or progression data (RR=0.77; 95% CI: 0.55-1.08).<sup>14</sup> It should be noted that the various studies used quite different definitions of recurrence, so it is difficult to interpret the combined effect of these results.

A review of the individual papers included in the meta-analysis<sup>14</sup> showed significant dose-response effects, such that men who exercised for greater MET-hours per week or greater numbers of hours per week, or who engaged in vigorous activity, had lower risk for both all-cause mortality and prostate cancer-specific mortality.<sup>37-39</sup> One study found an association between increased walking speed and duration with lower risk of prostate cancer progression,<sup>40</sup> and one study found a statistically significant association between increased walking or biking and both overall and prostate cancer-specific mortality.<sup>38</sup> However, the studies used different categories for gradient of amount of activity, and therefore it is difficult to determine an overall relationship between these components of physical activity and prostate cancer outcomes.

### *Evidence on Specific Factors*

**Age:** Neither the meta-analysis nor the cohort studies assessed relationships by age groups.

**Cancer subtype:** The association between physical activity and prostate cancer progression by Gleason score (cancer aggressiveness) was estimated in one study in a recent meta-analysis.<sup>14</sup> For men with Gleason score less than 7, the hazard ratio for reduced survival for those walking 7 or more hours per week versus less than 0.5 hours per week was 0.39 (95% CI: 0.11-1.41). For those with Gleason score greater than or equal to 7, the hazard ratio for reduced survival for those walking 7 or more hours per week versus less than 0.5 hours per week was 1.33 (95% CI: 0.54-3.29) ( $P_{interaction}$  0.006). Because neither hazard ratio was statistically significant, it is not clear that the prognosis differs by baseline indicator of disease aggressiveness.

**Race/ethnicity and socioeconomic status:** None of the studies provided information on effects of physical activity on survival or progression by race/ethnicity, or socioeconomic status.

**Weight status:** None of the studies provided information on effects of physical activity on survival or progression by weight status.

**Physical activity frequency, duration, intensity, type (mode):** The individual cohort studies assessed relationships between several domains of physical activity and both all-cause mortality and prostate cancer-specific mortality, including vigorous activity, MET-hours per week, walking speed, and mean time walking or biking. Most physical activity domains were associated with improved survival. However, given the variable ways of measuring and presenting data in the source cohort studies, it is

not possible to firmly determine whether the magnitude of effects on prognosis in prostate cancer survivors is similar across these physical activity domains.

### Other Cancers

Although the Subcommittee searched for systematic reviews, meta-analyses, and pooled analyses related to post-diagnosis physical activity and prognosis in any cancer, most of the published studies have focused on breast, colorectal, and prostate cancers. The Subcommittee decided that evidence was too limited for other cancers to draw conclusions or assign an evidence grade.

One 2016 systematic review/meta-analysis identified two cohort studies that included any cancer type.<sup>44</sup> One of these studies showed a statistically significant 38 percent reduction in cancer-specific mortality in men with highest versus lowest levels of physical activity,<sup>41</sup> while the other found no significant association of physical activity with cancer-specific mortality in women.<sup>42</sup> The [Ballard-Barbash et al<sup>12</sup>](#) systematic review included one study of glioma, which showed a statistically significant 36 percent reduction in all-cause mortality in individuals engaging in 9 or more versus less than 9 MET-hours per week of physical activity (HR=0.64; 95% CI: 0.46-0.91;  $P_{trend} < .001$ ).<sup>43</sup> The Subcommittee recognizes that additional single studies of physical activity in relation to cancer survival have been published, but all were published after our systematic search was applied.

***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**

The 2008 Scientific Report<sup>4</sup> reviewed the literature on the association between physical activity and cancer prognosis through 2008. From the limited amount of research available at that time, the 2008 Scientific Report<sup>4</sup> tentatively concluded that increased physical activity is associated with reduced mortality for women with breast cancer and for men and women with colorectal cancer. Since that time, the literature on physical activity and cancer survival has grown enough to warrant meta-analyses of survival cohort data, which can provide more precise estimates of these associations, as well as dose-response estimates and information about effects within subgroups of cancer survivors.

The 2008 Scientific Report<sup>4</sup> also considered evidence of associations between physical activity and late and long-term consequences of cancer treatment and quality of life. The 2018 Committee did not review

these issues, but rather focused on the considerable new literature available on physical activity and survival.

### **Public Health Impact**

In the United States, an estimated 42 percent of men and 38 percent of women will develop cancer in their lifetimes.<sup>44</sup> For several cancers, the projected number of years that affected individuals will live is increasing, such that many cancer survivors can expect to live for decades after their diagnosis.<sup>45</sup> More than 15.5 million children and adults with a history of cancer were alive on January 1, 2016, in the United States, and of these, 8,319,370 had a history of breast, colorectal, or prostate cancer.<sup>46</sup> By January 1, 2026, it is estimated that the population of cancer survivors will increase to 20.3 million: almost 10 million males and 10.3 million females.<sup>46</sup> Of these, an estimated 10,889,250 will be survivors of breast, colorectal, or prostate cancer.

A growing body of literature supports an inverse association between greater amounts of physical activity and decreased all-cause and cancer-specific mortality in individuals with a diagnosis of breast, colorectal, or prostate cancer, with risk reductions ranging from 38 to 48 percent. The lack of information about confounding or effect modification by type and completion of treatment reduced the strength of the findings. However, given the statistical significance and effect sizes of the observed associations, the Subcommittee supports recommendations to breast, colorectal, and prostate cancer survivors to increase physical activity. Given the lack of information on physical activity in relation to survival in individuals with cancers other than breast, colorectal, or prostate cancer, no conclusions or recommendations can be made for these cancer survivors. Physical activity should be encouraged to improve survival in individuals diagnosed with breast, prostate, or colorectal cancer.

### **Question 2. In individuals with osteoarthritis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, (4) pain, and (5) disease progression?**

- 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) Does the relationship vary based on frequency, duration, intensity, type (mode), or how physical activity is measured?

**Sources of evidence:** Systematic reviews, meta-analyses, existing report, original articles

### **Conclusion Statements**

#### **Risk of Co-morbid Conditions**

Insufficient evidence is available to determine whether a relationship exists between greater amounts of physical activity and comorbidities in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

### Physical Function or Pain

Strong evidence demonstrates a relationship between greater amounts of physical activity with decreased pain and improved physical function in adults with osteoarthritis of the knee and hip. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether a dose-response relationship exists between physical activity with pain or physical function in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity with pain or physical function varies by age, sex, race/ethnicity, socioeconomic status, or body weight status in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

Limited evidence suggests that greater intensity or duration of aerobic and muscle-strengthening physical activity is related to improvement in pain and physical function in individuals with osteoarthritis of the knee and hip. **PAGAC Grade: Limited.**

### Health-related Quality of Life

Moderate evidence indicates a relationship between greater amounts of physical activity and improved health-related quality of life in individuals with osteoarthritis of the knee and hip. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether a dose-response relationship exists between physical activity and health-related quality of life in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and health-related quality of life varies by age, sex, race/ethnicity, socioeconomic status, or body weight status in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the frequency, duration, intensity, or type (mode) of physical activity is related to health-related quality of life in individuals with osteoarthritis.

**PAGAC Grade: Not assignable.**

### Disease Progression

Moderate evidence indicates a relationship between physical activity and disease progression in individuals with osteoarthritis. Moderate evidence indicates that up to the range of 10,000 steps per day, ambulatory physical activity does not accelerate osteoarthritis of the knee. **PAGAC Grade:**

**Moderate.**

Moderate evidence indicates a dose-response relationship between physical activity and disease progression in individuals with osteoarthritis. The relationship appears to be U-shaped. **PAGAC Grade:**

**Moderate.**

Insufficient evidence is available to determine whether the relationship between physical activity and progression varies by age, sex, race/ethnicity, socioeconomic status, or body weight status in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the frequency, duration, intensity, or type (mode) of physical activity is related to progression in individuals with osteoarthritis. **PAGAC Grade: Not assignable.**

## **Review of the Evidence**

### *Evidence on the Overall Relationship*

#### Risk of Co-morbid Conditions

Available evidence was insufficient to determine whether a relationship exists between greater amounts of physical activity and comorbidities in individuals with osteoarthritis (OA). A search for systematic reviews, meta-analyses, pooled analyses, and reports failed to locate any reviews of the effects of physical activity on risk of co-morbid conditions. Thus, no additional discussion is provided for the outcome of risk of co-morbid conditions.

#### Osteoarthritis and Pain, Physical Function, and Health-related Quality of Life

The original literature search revealed 18 meta-analyses and systematic reviews meeting the criteria for inclusion in the analysis of OA and pain, physical function, and health-related quality of life (HRQoL).<sup>[47-64](#)</sup>

However, these meta-analyses included significant overlap in the studies included. In an attempt to

minimize redundancy, the Subcommittee reviewed the overlap of studies within all the meta-analyses. Meta-analyses with considerable overlap, with fewer than five unique additional studies, and that did not add additional information to the larger studies were not retained for purposes of the final analyses. This resulted in retention of six meta-analyses.[47-50](#) [52](#), [53](#)

Of these six studies, five covered physical function as an outcome,[47](#), [49](#), [50](#), [52](#), [53](#) five covered pain as an outcome,[47-49](#), [52](#), [53](#) and two dealt with HRQoL as an outcome.[47](#), [52](#)

*Pain:* The meta-analyses examined a variety of physical activity interventions, including land-based therapeutic strength and aerobic exercises,[48](#), [52](#) aquatic activities,[47](#), [48](#) and tai chi.[49](#), [52](#) [Juhl et al](#)<sup>53</sup> examined single or combination exercises, including aerobic, resistance, and performance training. The included reviews[47-49](#), [52](#), [53](#) addressed pain as outcomes using a variety of scales (Western Ontario and McMaster's Osteoarthritis Index, Lequesne Osteoarthritis Index).

*Physical Function:* The meta-analyses examined a variety of physical activity interventions, including land-based strength and aerobic exercises,[50](#), [52](#) aquatic activities,[47](#), [50](#) and tai chi.[49](#), [50](#), [52](#) [Juhl et al](#)<sup>53</sup> examined single or combination exercises, including aerobic, resistance, and performance training. The included reviews addressed physical function and outcomes related to physical function in a variety of ways, including perceived self-efficacy, and cognitive and emotional impairment,[49](#) functional aerobic capacity,[49](#), [50](#) and disability and physical function measured using the Activities of Daily Living Scale, Western Ontario and McMaster's Osteoarthritis Index, and Global Disability Scores.[47](#), [52](#), [53](#)

*Health-related Quality of Life (HRQoL):* [Fransen et al](#)<sup>52</sup> examined the effects of a variety of types of land-based exercise, including muscle strengthening, balance training, aerobic walking, cycling, and tai chi. [Bartels et al](#)<sup>47</sup> assessed various types of exercises (range of motion, strength, aerobics) with HRQoL as an outcome using a variety of scales.[47](#), [52](#)

In sum, these six reviews included:

- 131 individual studies and meta-analyses dealing with knee OA alone, covering 9,798 individuals with physical function as an outcome, 10,948 with pain as an outcome, and 2,771 with HRQoL as an outcome;
- 13 individual studies dealing with hip OA alone, covering 3,021 individuals with physical function as an outcome, 1,320 with pain as an outcome, and 1,190 with HRQoL as an outcome; and

- 13 individual studies dealing with aquatic exercise on knee and hip OA together, covering 1,076 participants with pain as an outcome, 1,059 participants with function as an outcome, and 971 participants with HRQoL as an outcome.

The effect sizes on pain, physical function and quality of life for those with hip OA did not seem to vary from those considering knee OA alone.

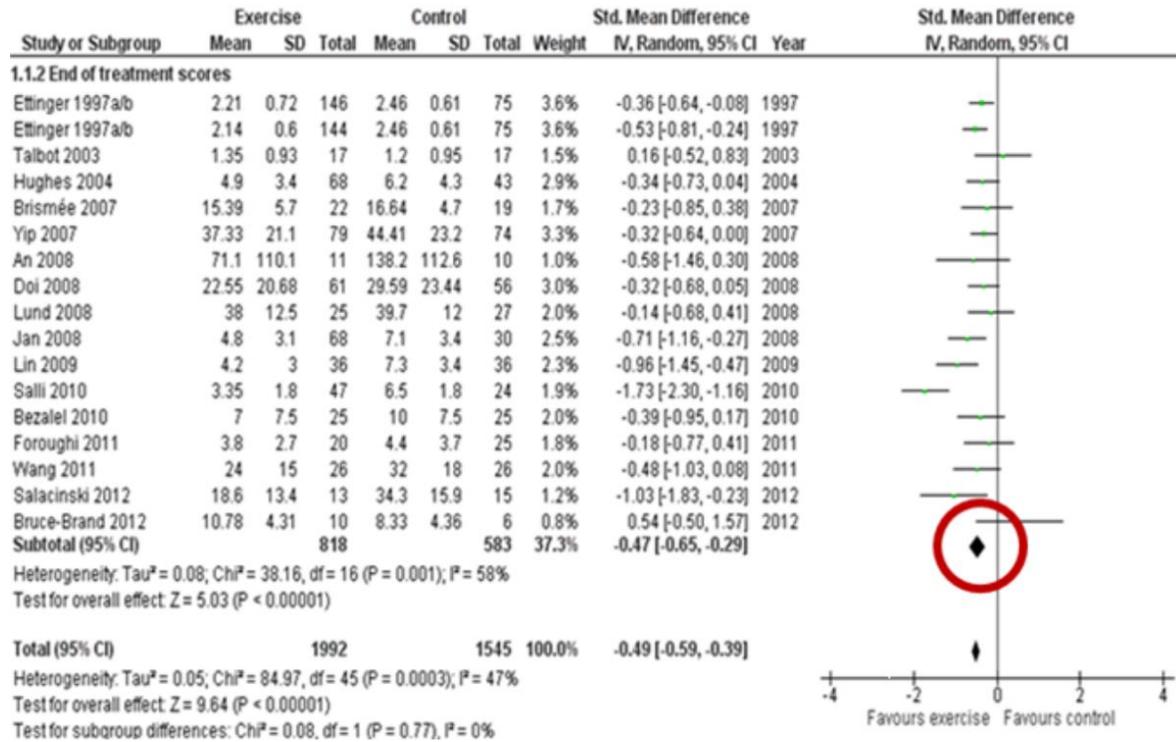
Most of the studies in these meta-analyses consisted of RCTs of the effects of one or more modalities of exercise (land-based and aquatic; aerobic, muscle-strengthening, and tai chi) on knee and hip OA. Most used the Western Ontario and McMaster Arthritis Index (WOMAC) scale—common in the OA research arena—to assess pain, physical function, and quality of life. Some studies examined land-based exercise exclusively.<sup>52</sup> Others examined pool-based exercise effects only.<sup>47</sup> The effect sizes on pain, physical function, and quality of life did not seem to vary whether the exercise was land-based or aquatic exercise.

The findings on pain, physical function, and HRQoL are illustrated in Figures F10-2 and F10-3, which present results from one review dealing with land-based exercise effects on the knee (adapted from [Fransen et al<sup>52</sup>](#)) and one review dealing with aquatic exercise effects on the knee (adapted from [Bartels et al<sup>47</sup>](#)), respectively. In Figure F10-2, the direction to the left favors exercise (decreased pain and improved physical function), whereas, improved HRQoL is to the right. In Figure F10-3, the direction to the left favors exercise (decreased pain, and improved physical function and HRQoL).

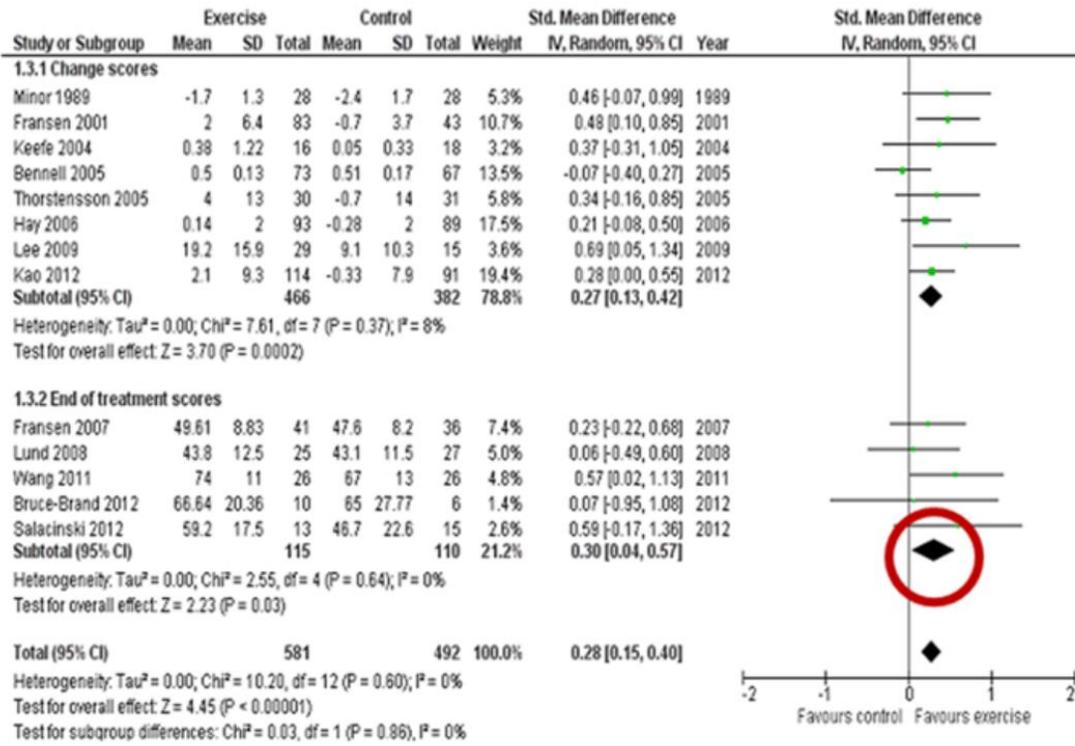
The results of these two reviews reported effect sizes that are roughly equivalent for land-based and aquatic exercise. That is, for the outcomes of pain, physical function, and HRQoL, land-based exercise appears to be as efficacious as water-based exercise. Also, the evidence in these reviews suggests that physical activity effects on pain and physical function persist for up to 6 months following cessation of the intervention.<sup>52</sup>

Figure F10-2. Effects of Land-based Exercise on Pain, Physical Function, and Quality of Life in Knee Osteoarthritis

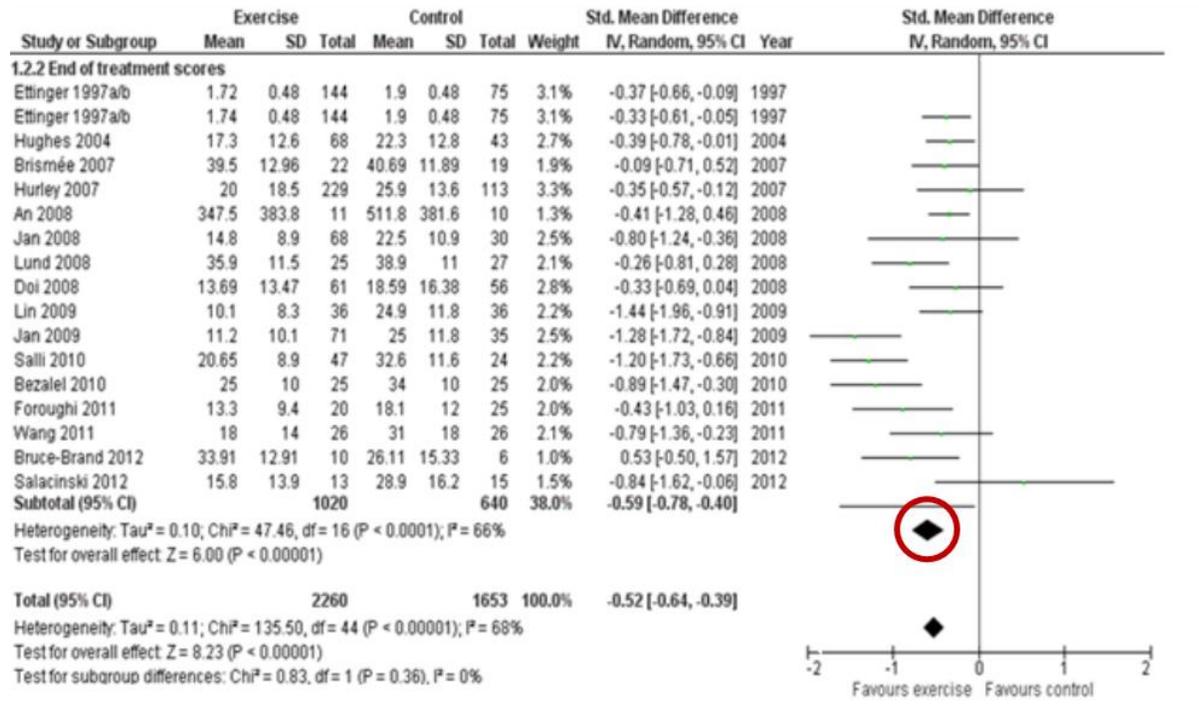
# Pain



# Quality of Life



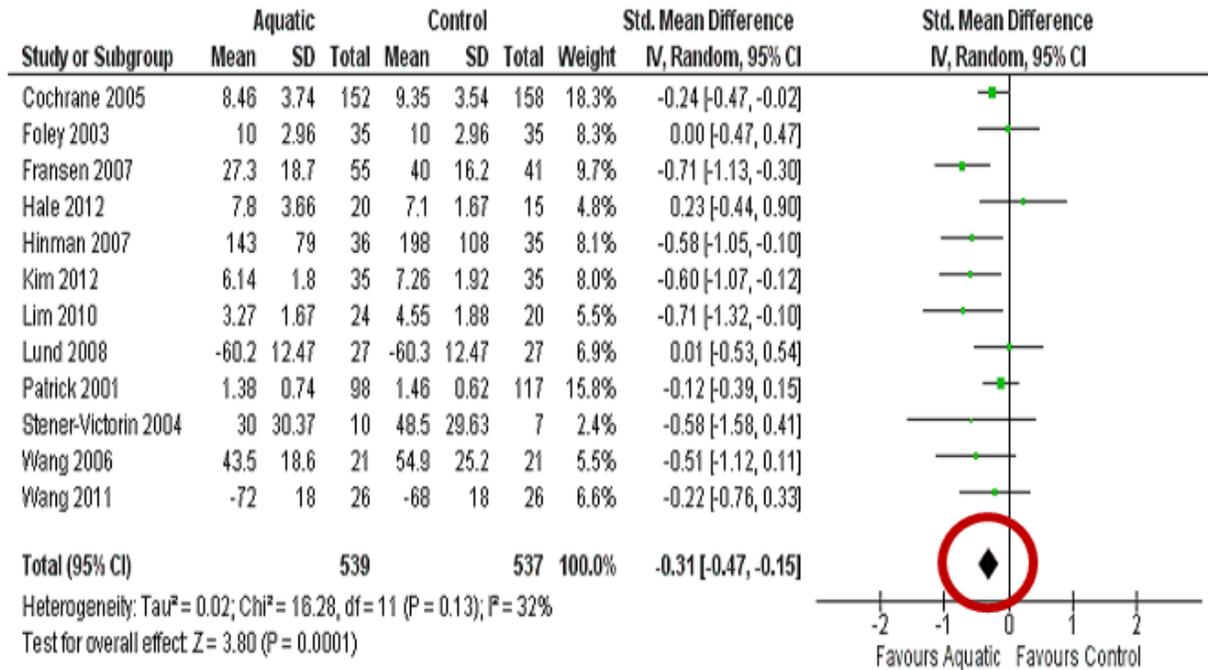
# Physical Function



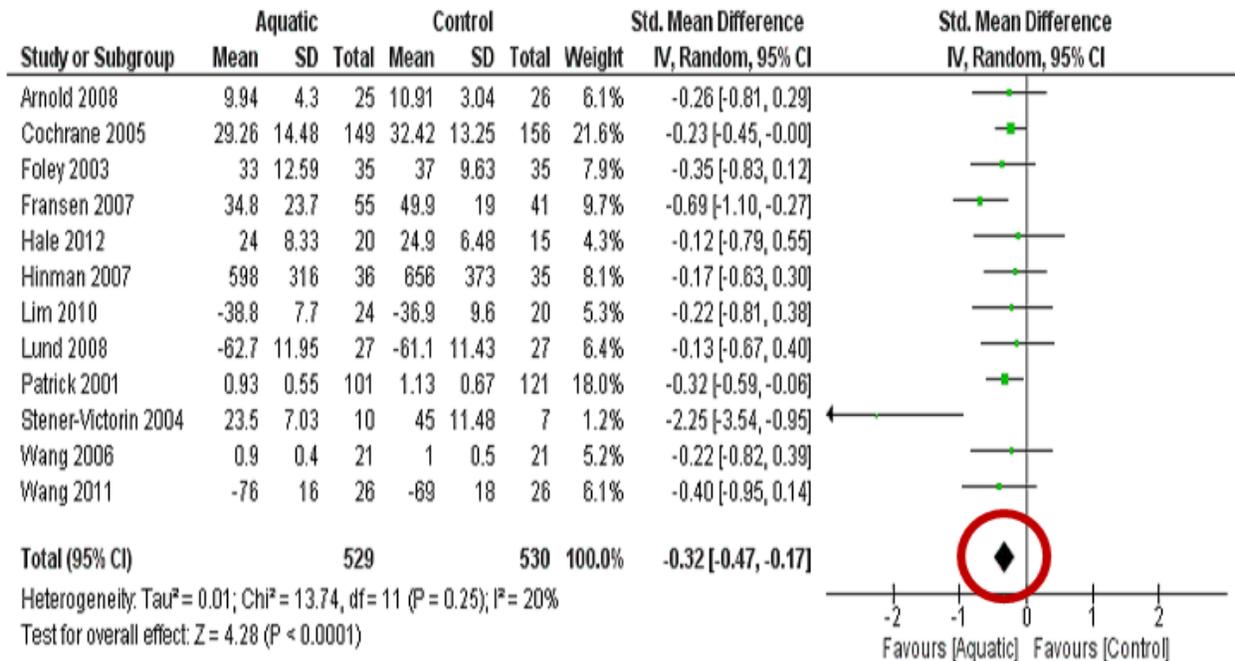
Reproduced from [Exercise for osteoarthritis of the knee: A Cochrane systematic review. Marlene Fransen et al., 49, 2015] with permission from BMJ Publishing Group Ltd.

**Figure F10-3. Effects of Aquatic Exercise on Pain, Physical Function, and Quality of Life in Knee Osteoarthritis**

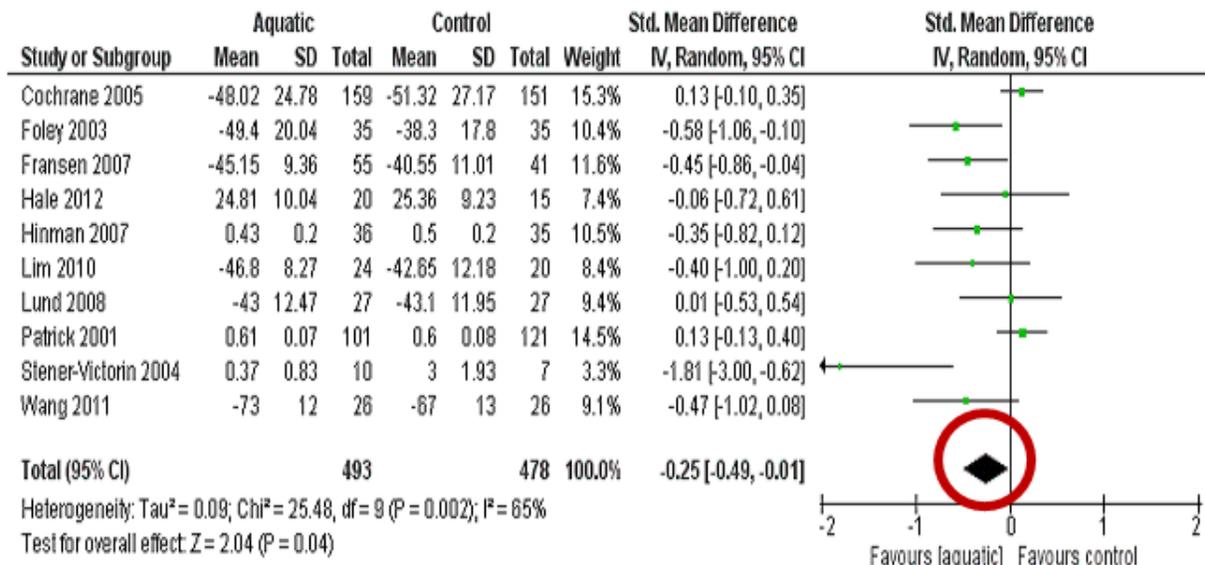
# Pain



# Physical Function



# Quality of Life



Source: Bartels et al.,<sup>47</sup> Aquatic exercise for the treatment of knee and hip osteoarthritis, Cochrane Database of Systematic Reviews, John Wiley and Sons. Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

**Dose-response:** Most studies of the effects of physical activity on pain, physical function and quality of life are RCTs of one mode, intensity, or duration. Further there is significant heterogeneity for these factors in the studies included within each meta-analysis. Therefore, very limited information on dose-response is available and the minimum dose associated with significant response could not be estimated.

### *Evidence on Specific Factors*

The findings of these six reviews were consistent in that physical activity is associated with reductions in pain and improvements in physical function and quality of life for both knee and hip OA, irrespective of the mode (aquatic versus land-based). The relationships with pain relief, physical function, and quality of life appear to be applicable for aerobic physical activity, for muscle-strengthening activity, and for tai chi. However, some modest difference in effect sizes was seen across these exposures. The evidence reviewed did not contain sufficient information to determine if intensity or duration was related to changes in HRQoL. Evidence was also insufficient to determine if the relationship between physical activity and pain, physical function and quality of life varied by age, sex, race/ethnicity, socioeconomic status or body weight.

### Osteoarthritis Disease Progression

Concern that high-intensity physical activity and large amounts of weight-bearing activity may have harmful effects on OA progression prompted the Subcommittee to conduct a targeted review for this outcome. This review required a separate search for evidence from searches related to pain, physical function, and HRQoL. The Subcommittee reviewed the literature addressing the association of physical activity with progression of OA in those with pre-existing disease. For the purposes of this review, progression of OA was defined as worsening of OA as assessed by structural OA imaging (radiograph or magnetic resonance imaging, MRI), or as clinical progression to total knee replacement (TKR). The Subcommittee did not identify any studies examining the effects of physical activity on circulating biomarkers associated with a worsening disease state.

### **Existing Systematic Review and Meta-Analyses**

The Subcommittee identified one systematic review including 49 studies<sup>65</sup> and one meta-analysis<sup>62</sup> including three studies. The systematic review<sup>65</sup> included exposures of low-impact therapeutic physical activity combining muscle-strengthening, stretching, and aerobic elements. All of the primary literature studies in this systematic review dealt with knee OA (no included studies dealt with progression of hip

OA) and used structural OA imaging progression or progression to TKR as outcomes. This systematic review examined 48 longitudinal cohort studies composed of 8,614 total participants.

The systematic review<sup>65</sup> provided no evidence of harmful effects of activity on progression in its comparisons of individuals with greater amounts of low-impact physical activity to individuals with the least amounts of physical activity, when progression was assessed by adverse events of increased pain, decreased physical function, progression of structural OA on imaging or increased TKR at a group level. Of the studies in this review, only six (five of which were RCTs) included objective imaging outcomes or TKR as measures of osteoarthritis progression. Objective measures and need for joint replacement were considered the standards for assessing effects on OA progression. Although the number of joint replacements was small across the five RCTs, these trials found no evidence of more TKRs within physical activity groups (N=8 TKR) compared to groups that did not engage in physical activity (N=10 TKR). Based upon this review, the Subcommittee was not able to comment on the impact of greater intensity physical activity on OA progression.

The meta-analysis<sup>62</sup> assessed self-reported running or jogging (including running-related sports such as triathlon and orienteering). [Timmins et al<sup>62</sup>](#) used radiography, other imaging, and questionnaires to examine diagnosis of knee OA, radiographic markers of knee OA, knee joint surgery for OA, knee pain, and knee-associated disability as markers of OA progression. This review, containing 10 individual studies with a total of 6,962 individuals, examined running and development of knee OA, including joint surgery, as outcomes considered indicative of progression from subclinical to clinical disease.<sup>62</sup> Although this meta-analysis included prevention of primary OA, the data are instructive for understanding the role of running in the development of OA. In this meta-analysis, three studies examined TKR as an outcome. The meta-analysis revealed runners had significantly less risk of having TKR than did non-runners (odds ratio (OR)=0.46; 95% CI: 0.30-0.71;  $P=0.0004$ ).

### **Original Research**

Although providing highly relevant evidence, the Subcommittee did not believe that one systematic review dealing with knee OA alone was adequate to assess the entire range of the literature. Therefore, for the question of the effects of physical activity on OA disease progression, the Subcommittee elected to perform a primary literature review. Five original research studies examining the relationship between physical activity and disease progression were identified.<sup>66-70</sup> All studies were prospective cohort studies, published from 2013 to 2016. The analytical sample size ranged from 100<sup>68</sup> to 2,073<sup>67</sup>;

three were U.S. studies,<sup>67, 69, 70</sup> one Tasmanian,<sup>66</sup> and one did not report. Three studies used self-reported physical activity on the Physical Activity Scale for the Elderly (PASE)<sup>67-69</sup>; two had device-measured physical activity from accelerometer or pedometer.<sup>66, 70</sup> All included studies examined OA progression (knee structural change, cartilage loss) as the outcome.

These five longitudinal cohort studies with imaging or TKR as outcomes were deemed of adequate quality to address the question.<sup>66-70</sup> Two of these studies had device-based measures of physical activity and all used MRI to assess OA progression. Outcome measures included radiographic progression with the Kellgren Lawrence (KL) grading system, MRI with a measure of cartilage damage (T2 relaxation) and, in one study, subchondral bone marrow lesions. Collectively, these five studies focused on one of three longitudinal cohort studies: the Osteoarthritis Initiative,<sup>67-69</sup> the Multicenter Osteoarthritis Study<sup>67, 70</sup> and a longitudinal cohort study of 405 community dwelling adults from Australia.<sup>66</sup> The Osteoarthritis Initiative assessed physical activity with the Physical Activity Scale for the Elderly survey; the Multicenter Osteoarthritis and the Australian cohort assessed exposure by device-based step count measures.

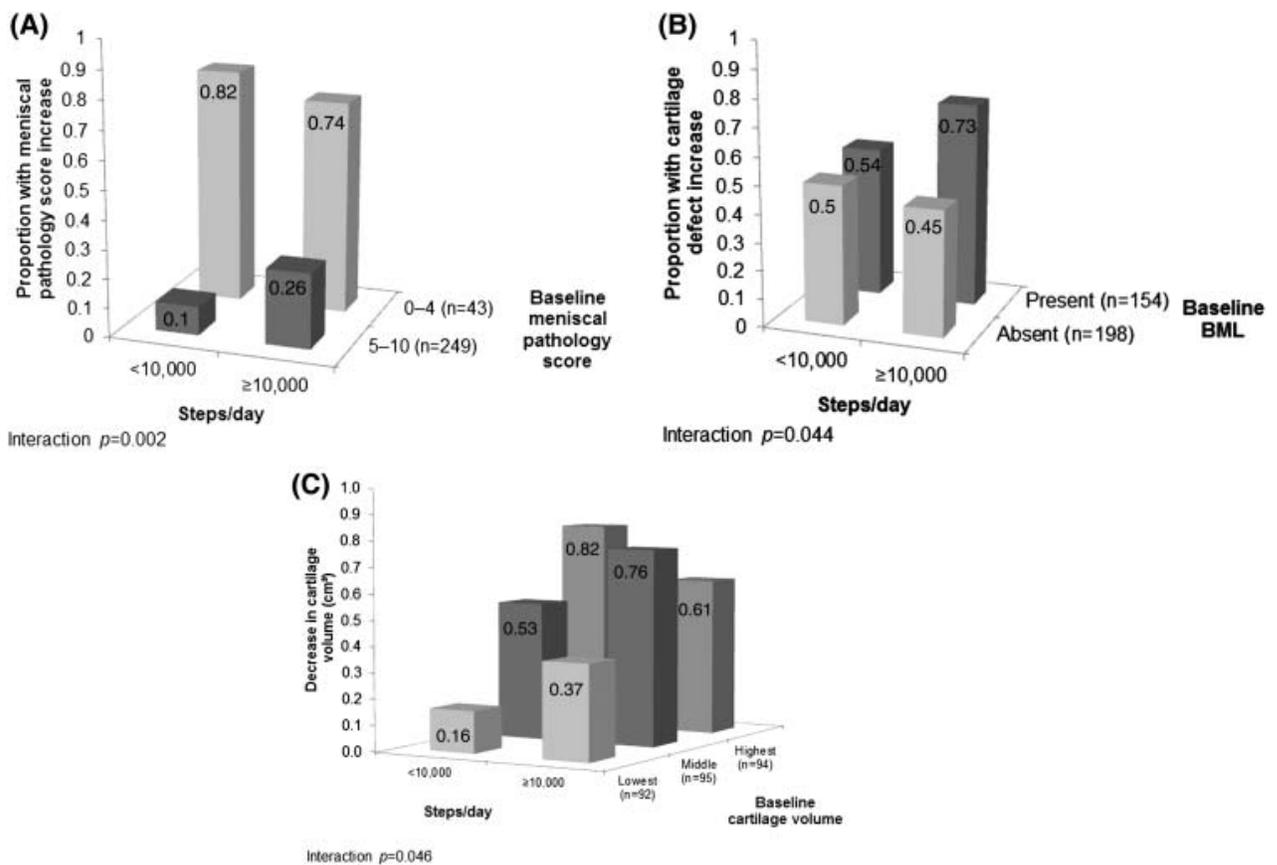
Overall, the findings in these studies were mixed:

- The Osteoarthritis Initiative assessed knee OA in 100 participants using MRI and saw no disease progression with physical activity, as measured by the Physical Activity Scale for the Elderly.<sup>68</sup>
- The Multicenter Osteoarthritis study assessed knee OA in 1,179 participants using radiographic (X-ray) cartilage loss and saw no disease progression with physical activity, as measured by accelerometry (steps).<sup>70</sup>
- The Osteoarthritis Initiative assessed knee OA in 205 individuals with asymptomatic OA using MRI to ascertain cartilage quality. The authors examined large and small amounts of physical activity as measured by high and low Physical Activity Scale for the Elderly scores; they found that 15 percent of the population in each category were associated with OA progression.<sup>69</sup>
- [Felson et al<sup>67</sup>](#) assessed OA in 3,542 knees of 2,073 Osteoarthritis Initiative and Multicenter Osteoarthritis participants with asymptomatic OA; they found that those in the greatest physical activity quartile, as measured by the Physical Activity Scale for the Elderly, showed no OA progression.
- [Dore et al<sup>66</sup>](#) assessed knee OA in 405 Australian individuals using MRI with four structural measures. Steps per day were measured with pedometer counts. Individuals with fewer than 10,000 steps per day showed no knee OA progression; those with more than 10,000 steps per

day showed some progression. The effect of physical activity appeared to be modified by baseline state (Figure F10-4).

Thus, the Subcommittee’s review identified at least two studies demonstrating a U-shaped relationship between aerobic exercise and OA progression in those with pre-existing OA.<sup>66, 69</sup> For land-based exercise, benefit is seen at step counts up to 10,000 steps per day. Greater ambulation (more steps per day) appears to be associated with some OA progression.<sup>66</sup>

**Figure F10-4. Interaction of Underlying Joint Pathology by MRI and Ambulatory Physical Activity Amounts (Step Counts) on Osteoarthritis Progression, as Shown on MRI**



Note: Greater meniscal pathology scores, presence of bone mineral lesions and less cartilage volume all indicate more severe disease. Bone mineral lesions are areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites and indicate more severe joint pathology. All figures show an interaction effect, wherein for those individuals with less baseline meniscal pathology, steps are not related to pathology score increases. In contrast, in adults with greater baseline pathology scores, a greater percent of adults with more than 10,000 steps per day show worsening of pathology scores over time (26%) compare to adults with fewer than 10,000 steps day (10%).

Source: Reproduced from [The association between objectively measured physical activity and knee structural change using MRI, Dawn A Dore et al.,<sup>66</sup> 72, 2013] with permission from BMJ Publishing Group Ltd.

### *Evidence on Specific Factors*

**Demographic factors and weight status:** The issue of effect modification by sex, age, race/ethnicity, and socioeconomic status was not examined in the meta-analyses used as sources of evidence. Although a relationship between BMI and osteoarthritis is generally recognized, no one has investigated through meta-analyses whether these translate to effect modifications of these factors in the physical activity-OA relationship.

Due to exposure heterogeneity, it is not possible estimate an energy expenditure exposure of aerobic exercise associated with effects. Moderate-level evidence indicates that physical activity up to about 10,000 steps per day does not accelerate knee OA. One study indicated that lifetime running was not associated with increased risk of primary OA; in fact, a significant reduction in risk occurred in these cohorts.

**Type of physical activity:** The relationships with pain relief, physical function, and quality of life appear to be applicable for aerobic exercise, muscle-strengthening exercise, and tai chi.<sup>52</sup> In its review, the Subcommittee did not discover any studies investigating the relationships among greater amounts of aquatic exercise and OA progression. It was not possible to determine if effects of physical activity on progression varied by frequency, duration, intensity, or type of physical activity.

***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**

The 2008 Scientific Report<sup>4</sup> included a broad review of physical activity and osteoarthritis, including review of effects of activity on risk of incident OA as well as effects of physical activity in people with OA. That report found clear evidence of benefits of physical activity on pain, HRQoL, and physical function in people with OA.

The findings of this report are generally consistent with those of the 2008 Scientific Report,<sup>4</sup> but expand the information related to these findings. For example, this report comments more extensively on the types of physical activity that provide benefits, e.g., that aquatic exercise can provide benefits similar in magnitude to those of land-based exercise, that tai chi provides benefits in people with OA, and that benefits can persist after cessation of physical activity. This report adds considerably to information on the effects of physical activity on progression of OA. There appears to be U-shaped relationship between

amount of ambulatory physical activity and progression in OA, with moderate evidence that step counts up to the range of 10,000 steps per day do not accelerate progression of OA. However, the Subcommittee located some evidence suggesting that step counts above the range of 10,000 steps per day may have adverse effects on progression.<sup>66, 69</sup>

### **Public Health Impact**

There are approximately 100 different arthritic conditions affecting a total of 54.4 million Americans. Among these, OA is the most common joint disorder in the United States, affecting an estimated 30.8 million adults (13.4 percent of the civilian adult U.S. population).<sup>71</sup> Methodological issues make it highly likely that the real burden of OA has been underestimated.<sup>72</sup> Lower extremity OA is the leading cause of mobility impairment in older adults in the United States.<sup>73</sup> OA affects a broad spectrum of age groups in the United States, including 2 million Americans younger than age 45 years with knee OA.<sup>74</sup> By the year 2040, an estimated 78.4 million (25.9% of the projected total adult population) adults ages 18 years and older are expected to have medically diagnosed arthritis,<sup>75</sup> the majority of whom will have OA. As expected, based on these prevalence and disability figures, OA is associated with an extremely high economic burden—by one national estimate equal to \$185.5 billion in aggregate annual medical care expenditures.<sup>76</sup>

From this review, it is clear that regular exercise at amounts up to those consistent with the 2008 Physical Activity Guidelines<sup>23</sup>—at least 150 minutes per week of moderate-intensity aerobic exercise and 2 days per week of muscle-strengthening exercise—has substantial beneficial effects on the overall population of those with pre-existing OA, and will have a substantial public health impact. Physical activity should be encouraged in the general population of those individuals with pre-existing OA for pain relief, improved physical function, and improved quality of life without concern of causing worsening of the condition for exposures of less than 10,000 steps per day. Measurable benefits of physical activity seem to persist for periods of up to 6 months following cessation of a defined program.

### **Question 3: In people with the cardiovascular condition of hypertension, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) cardiovascular disease progression and 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, weight status, or resting blood pressure level?

- c) Does the relationship vary based on frequency, intensity, time, duration, type (mode), or how physical activity is measured?

**Source of evidence:** Systematic reviews, meta-analyses

## **Conclusion Statements**

### Co-morbid Conditions

Insufficient evidence is available to determine whether a relationship exists between physical activity and risk of co-morbid conditions among adults with hypertension. **PAGAC Grade: Not assignable.**

### Physical Function

Insufficient evidence is available to determine whether a relationship exists between physical activity and physical function among adults with hypertension. **PAGAC Grade: Not assignable.**

### Health-related Quality of Life

Insufficient evidence is available to determine whether a relationship exists between physical activity and health-related quality of life among adults with hypertension. **PAGAC Grade: Not assignable.**

### Disease Progression

Strong evidence demonstrates that physical activity reduces the risk of progression of cardiovascular disease among adults with hypertension. **PAGAC Grade: Strong.**

Strong evidence demonstrates that, among adults with hypertension, physical activity reduces the disease progression indicator of blood pressure. **PAGAC Grade: Strong.**

Moderate evidence indicates an inverse dose-response relationship between physical activity and the disease progression indicator of cardiovascular disease mortality among adults with hypertension.

**PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether a dose-response relationship exists between physical activity and blood pressure among adults with hypertension. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and the disease progression indicators of blood pressure and cardiovascular disease mortality varies by age, sex, race/ethnicity, socioeconomic status, or weight status among adults with hypertension. **PAGAC Grade: Not assignable.**

Limited evidence suggests that, among adults with hypertension, the blood pressure response to physical activity varies by resting blood pressure level, with the greatest blood pressure reductions occurring among those adults who have the highest resting blood pressure levels. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between physical activity and the disease progression indicators of blood pressure and cardiovascular disease mortality varies by the frequency, intensity, time, and duration of physical activity, or how physical activity is measured among adults with hypertension. **PAGAC Grade: Not assignable.**

Moderate evidence indicates the relationship between physical activity and the disease progression indicator of blood pressure does not vary by type of physical activity, with the evidence more robust for traditional types (modes, i.e., aerobic, dynamic resistance, combined) of physical activity than for other types (tai chi, yoga, and qigong) among adults with hypertension. **PAGAC Grade: Moderate.**

### **Review of the Evidence**

Cardiovascular disease is the leading cause of death in the United States and the world, accounting for approximately 1 in 3 deaths (807,775, or 30.8%) in the United States and 17.3 million (31%) worldwide.<sup>77, 78</sup> Hypertension is the most common, costly, and preventable CVD risk factor. According to the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7)<sup>79</sup> blood pressure classification scheme, hypertension affects 86 million (34%) adults in the United States and 1.4 billion (31%) adults globally.<sup>77, 78</sup> The lifetime risk of acquiring hypertension is 90 percent.<sup>79</sup> Furthermore, hypertension is the most common primary diagnosis in the United States, and the leading cause for medication prescriptions among adults older than age 50 years.<sup>80</sup> By 2030, it is estimated that 41 percent of adults in the United States will have hypertension. From 2010 to 2030, the total direct costs attributed to hypertension are projected to triple (\$130.7 to \$389.9 billion), while the indirect costs due to lost productivity will double (\$25.4 to \$42.8 billion).<sup>77</sup> Curbing this growing and expensive public health crisis is a national and global priority.<sup>78, 81</sup>

To answer this question, the Subcommittee reviewed one systematic review,<sup>82</sup> and 14 meta-analyses.<sup>83-96</sup> The coverage dates ranged from inception of the database to 2016, the total number of included studies ranged from 4 to 93, and the total included study sample size consisted of 125,986 adults ranging from 216 to 96,073 participants. The systematic review examined 6 large longitudinal prospective cohort studies, and the 14 meta-analyses included RCTs that examined the blood pressure

response to physical activity among adults with hypertension compared to a control condition among similar adults who were sedentary at baseline.

All studies in the meta-analyses included adults with hypertension,<sup>82-96</sup> six included adults with prehypertension,<sup>82-84, 88, 93, 95</sup> and eight included adults with normal blood pressure.<sup>82-85, 93-96</sup> Because the literature reviewed for this question was based upon the JNC 7 blood pressure classification scheme, the Subcommittee used the JNC 7 blood pressure classification scheme<sup>79</sup> for data extraction purposes. The JNC 7 defines these blood pressure classifications as follows: Hypertension is defined as having a resting systolic blood pressure of 140 mmHg or greater and/or a resting diastolic blood pressure 90 mmHg or greater, or taking antihypertensive medication, regardless of the resting blood pressure level. Prehypertension is defined as a systolic blood pressure from 120 to 139 mmHg and/or diastolic blood pressure from 80 to 89 mmHg. Normal blood pressure is defined as having a systolic blood pressure less than 120 mmHg and diastolic blood pressure less than 80 mmHg. However, it should be noted that during the preparation of this report, the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines released the 2017 *Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults*.<sup>97</sup> The new Guidelines define hypertension as a resting systolic blood pressure of 130 mmHg or greater and/or a resting diastolic blood pressure 80 mmHg or greater, or taking antihypertensive medication, regardless of the resting blood pressure level. Furthermore, the term prehypertension was eliminated and elevated blood pressure was added indicating a resting systolic blood pressure between 120 to 129 mmHg and a diastolic blood pressure <80 mmHg. However, the new hypertension guidelines did not alter the conclusion statements made in this report.

### Co-morbid Conditions, Physical Function, and Health-related Quality of Life

#### *Evidence on the Overall Relationship*

Hypertension co-morbidities include CVD, obesity, diabetes mellitus, chronic kidney disease, congestive heart failure, and the metabolic syndrome, among others. However, because of a lack of evidence, the Subcommittee was unable to draw any conclusions about whether a relationship exists between physical activity and risk of co-morbid conditions among adults with hypertension, or about whether a relationship exists between physical activity and physical function.

The available evidence also was insufficient to determine whether a relationship exists between physical activity and HRQoL among adults with hypertension. Of note, several of the meta-analyses commented

on the potential favorable nature of this relationship ([Xiong et al](#)<sup>89</sup> relating to a type of qigong—Baduanjin). However, few primary level studies in these meta-analyses addressed this relationship.

### Disease Progression

The Subcommittee defined CVD progression in two ways. Because blood pressure is considered a proxy measure of the risk of CVD,<sup>88, 98</sup> the Subcommittee regarded the blood pressure response to physical activity as an indicator of CVD progression, and the outcome of CVD mortality as an indicator of longstanding hypertension. The evidence on the blood pressure response to physical activity is discussed below, and the evidence on CVD mortality outcomes follows in the section on dose-response.

#### *Evidence on the Overall Relationship*

Strong evidence demonstrates that physical activity reduces blood pressure among adults with hypertension. All 14 meta-analyses included RCTs that examined the blood pressure response to physical activity among adults with hypertension compared to a control condition of adults who were inactive.<sup>83-96</sup> Of these, 13 reported a statistically significant reduction in systolic blood pressure and 14 reported a statistically significant reduction in diastolic blood pressure (see Supplementary Table S-F10-1). The magnitude of the reductions ranged from 5 to 17 mmHg for systolic blood pressure and 2 to 10 mmHg for diastolic blood pressure. Blood pressure reductions of this magnitude may be sufficient to reduce risk of coronary heart disease 4 to 22 percent and stroke by 6 to 41 percent among adults with hypertension.<sup>79, 99, 100</sup> Furthermore, the magnitude of these blood pressure reductions to physical activity may be sufficient to reduce the resting blood pressure of some of the samples with hypertension into prehypertensive to normotensive ranges.

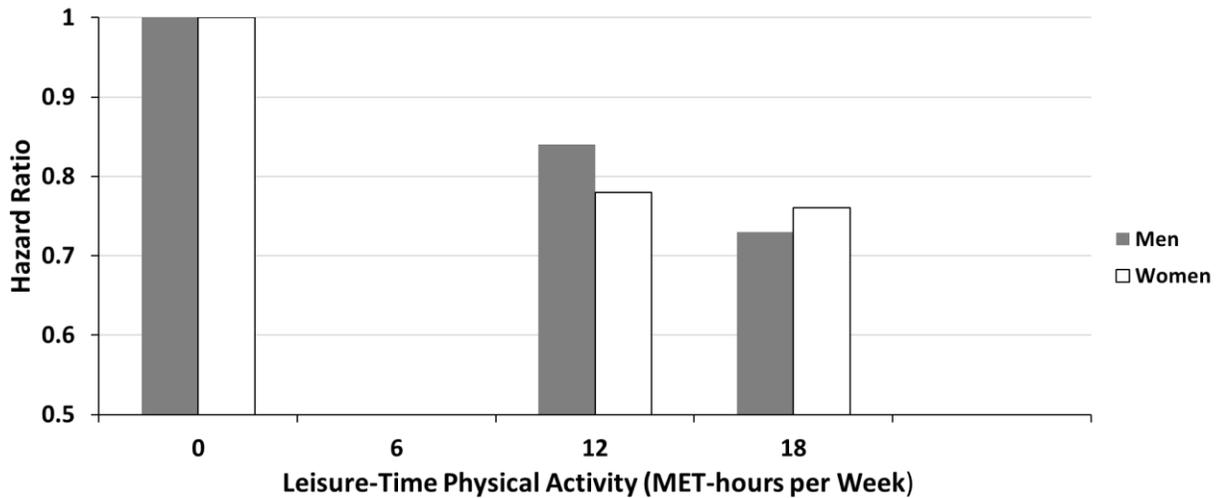
When studies disclosed the information, the frequency of physical activity ranged from 1 to 7 days per week, with 3 days per week most common; the intensity ranged from low to vigorous, with low to moderate most common; the time ranged from 12 to 100 minutes per session, with 30 minutes to 45 minutes per session most common; and the study duration ranged from 4 weeks to 24 years, with 4 weeks to 16 weeks most common. Due to the imprecise disclosure of the frequency, intensity, and time of the physical activity interventions, the dose-response of the blood pressure response to physical activity could not be determined.

**Dose-Response:** Moderate evidence indicates an inverse dose-response relationship between physical activity and CVD mortality among adults with hypertension. One systematic review addressed the impact of self-reported general and leisure-time physical activity on CVD mortality among adults with

hypertension who were followed from 5 to 24 years.<sup>82</sup> This systematic review included six large prospective cohort studies<sup>101-106</sup> of approximately equal numbers of mostly white men and women who had hypertension, prehypertension, and normal blood pressure. Only the findings relating to CVD mortality among the samples with hypertension are discussed here.

[Hu et al<sup>104</sup>](#) investigated the associations among occupational, daily commuting, and leisure-time physical activity and cardiovascular mortality among 26,643 Finnish men and women with overweight and hypertension, ages 25 to 64 years, who were followed for 20 years. The covariate-adjusted hazard ratios of CVD mortality associated with low (almost completely inactive), moderate (some physical activity more than 4 hours per week, about 12 MET-hours per week or more), and high (vigorous physical activity more than 3 hours per week, about 18 MET-hours per week or more) leisure-time physical activity were 1.00, 0.84 (95% CI: 0.77-0.92), and 0.73 (95% CI: 0.62-0.86) among men, respectively; and 1.00, 0.78 (95% CI: 0.70-0.87), and 0.76 (95% CI: 0.60-0.97) among women, respectively (Figure F10-5). The covariate-adjusted hazard ratios of CVD mortality associated with low (very easy physical activity), moderate (standing and walking at work), and high (walking, lifting, or heavy manual labor at work) occupational physical activity were 1.00, 0.84 (95% CI: 0.85-1.05), and 0.86 (95% CI: 0.78-0.96) among men and 1.00, 0.85 (95% CI: 0.74-0.98), and 0.84 (95% CI: 0.73-0.96) among women (see Supplementary Table S-F10-1). Among women only, the hazard ratios for active daily commuting to and from work associated with reduced CVD mortality were 1.00 for motorized transport or no work, 0.83 (95% CI: 0.72-0.96) for walking or bicycling 1 to 29 minutes per day, and 0.86 (95% CI: 0.74-0.99) for 30 or more minutes per day.

**Figure F10-5. The Inverse Relationship Between Cardiovascular Mortality and Leisure-time Physical Activity by MET-hours per Week Among Adults with Hypertension**



Source: Adapted from data found in Hu et al., 2007.<sup>104</sup>

In summary, leisure-time moderate physical activity equating to about 12 MET-hours per week or more reduced CVD mortality by 16 percent among men and 22 percent among women, while higher amounts of leisure-time vigorous physical activity equating to about 18 MET-hours per week or more reduced CVD mortality by 27 percent among men and 24 percent among women, indicating an inverse dose-response relationship between physical activity and cardiovascular mortality among adults with hypertension. However, no dose-response relationship was found between occupational and commuting physical activity and cardiovascular mortality.

Collectively, the prospective cohort studies in the systematic review of [Rossi et al.<sup>82</sup>](#) indicated that greater amounts of physical activity reduced CVD mortality by 16 percent (RR=0.84; 95% CI: 0.73-0.97) to 67 percent (RR=0.33; 95%CI: 0.11-0.94) compared to lower amounts of physical activity or being sedentary. In addition, the greatest amounts of physical activity reduced CVD mortality by 20 percent (HR=0.80; 95% CI: 0.66-0.96) to 67 percent (RR=0.33; 95%CI: 0.11-0.94) compared to lower amounts of physical activity or being sedentary; and low to moderate amounts of physical activity reduced CVD mortality by 16 percent (HR=0.84; 95% CI: 0.73-0.97) to 22 percent (HR=0.78; 95% CI: 0.70-0.87) compared to being physically inactive or sedentary. The protective benefits of physical activity against CVD mortality were similar for men and women. Nonetheless, it was difficult for the Subcommittee to summarize the magnitude and precision of the protective effect based upon the studies of [Engstrom et al.<sup>101</sup>](#), [Fan et al.<sup>102</sup>](#) and [Fossum et al.<sup>103</sup>](#) In these studies there was considerable variation in the definition

of hypertension and measurement of blood pressure, and the self-reported measurements of physical activity did not quantify the frequency, duration, and intensity of physical activity.

[Vatten et al<sup>106</sup>](#) found that among men with a resting systolic blood pressure between 140 to 159 mmHg, those who were highly physically active (RR=1.21; 95% CI: 0.97-1.52) reduced their risk of CVD mortality by 30 percent compared to those who were physically inactive (RR=1.73; 95% CI: 1.37-2.19). Among men with a resting systolic blood pressure >160 mmHg, those who were highly physically active (RR=1.82; 95% CI: 1.46-2.28) reduced their risk of CVD mortality by 19 percent compared to those who were physically inactive (RR=2.24; 95% CI: 1.78-2.83). In addition, among women with a resting systolic blood pressure between 140 to 159 mmHg, those who were highly physically active (RR=1.47; 95% CI: 1.04-2.09) reduced their risk of CVD mortality by 24 percent compared to those who were physically inactive (RR=1.93; 95% CI: 1.39-2.69). Among women with a resting systolic blood pressure >160 mmHg, those who were highly physically active (RR=1.77; 95% CI: 1.26-2.54) reduced their risk of CVD mortality by 27 percent compared to those who were physically inactive (RR=2.41; 95% CI: 1.76-3.30). Therefore, as systolic blood pressure increases within hypertensive ranges, the risk of CVD mortality increases. However, the increased risk is attenuated with higher levels of physical activity.

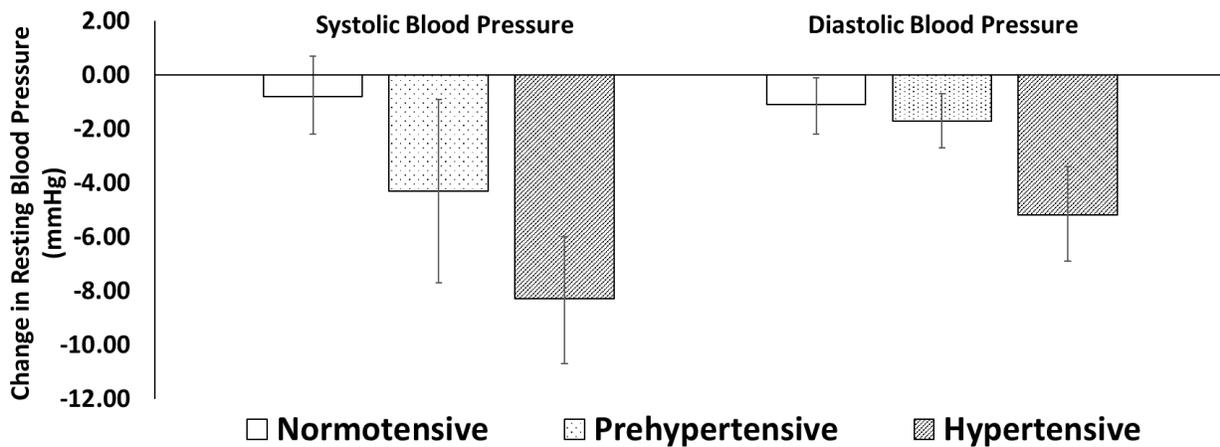
### *Evidence on Specific Factors*

**Demographic characteristics and weight status:** The available evidence is insufficient to determine whether the relationship between physical activity and the disease progression indicators of blood pressure and CVD mortality varies by age, sex, race/ethnicity, socioeconomic status, or weight status among adults with hypertension. In the few instances where these factors were examined, the findings were too disparate to synthesize because they were often not reported separately for adults with hypertension but were reported for the overall sample that included adults with hypertension, prehypertension, and normal blood pressure. Two meta-analyses found age not to be a significant moderator of the blood pressure response to physical activity among samples with mixed blood pressure levels.<sup>83, 84</sup> One meta-analysis reported that men exhibited blood pressure reductions twice as large as women following aerobic exercise training among a sample with mixed blood pressure levels.<sup>84</sup> Race/ethnicity was poorly reported, and when reported in seven of the meta-analyses,<sup>87-92, 95</sup> the samples were largely White or Asian. One meta-analysis reported that nonwhite samples with hypertension experienced greater blood pressure reductions than did White samples with hypertension.<sup>95</sup> [MacDonald et al<sup>95</sup>](#) found reductions of systolic/diastolic blood pressure of -14.3/-10.3 mmHg after moderate-intensity dynamic resistance training among nonwhite samples with

hypertension versus reductions of -9.2/-9.5 mmHg among White samples with hypertension, respectively. No meta-analyses disclosed the socioeconomic status of their samples. Five meta-analyses reported the weight status of their samples, which ranged from normal weight to obese.<sup>83, 87, 88, 93, 95</sup> [Cornelissen and Smart](#)<sup>84</sup> found the systolic blood pressure reductions resulting from aerobic training tended to be larger with greater ( $\beta_1=0.49$ ,  $P=0.08$ ) than less ( $\beta_1=0.45$ ,  $P=0.06$ ) weight loss among 5,223 adults with mixed blood pressure levels.

**Resting blood pressure level:** Limited evidence suggests the disease progression indicator of the blood pressure response to physical activity varies by resting blood pressure level among adults with hypertension (Figure F10-6). Of the six meta-analyses examining blood pressure classification as a moderator of the blood pressure response to physical activity,<sup>83-85, 93, 95, 96</sup> four<sup>84, 85, 93, 95</sup> found that the greatest blood pressure reductions occurred among samples with hypertension (5 to 8 mmHg, 4 to 6 percent of resting blood pressure level) followed by samples with prehypertension (2 to 4 mmHg, 2 to 4 percent of resting blood pressure level), and normal blood pressure (1 to 2 mmHg, 1 to 2 percent of resting blood pressure level) (Supplementary Table S-F10-2). Consistent with the law of initial values,<sup>107, 108</sup> adults with hypertension experience blood pressure reductions from exercise training that are about 2 times greater than the blood pressure reductions among adults with prehypertension and about 4 to 5 times greater than the blood pressure reductions among adults with normal blood pressure (see Supplementary Table S-F10-2). Blood pressure reductions of this magnitude may be sufficient to reduce the resting blood pressure of some of the samples with hypertension into prehypertensive ranges. They may also be sufficient to reduce the risk of coronary heart disease 4 to 22 percent and stroke by 6 to 41 percent among adults with hypertension.<sup>79, 99, 100</sup>

**Figure F10-6. Blood Pressure Response to 16 Weeks of Aerobic Physical Activity, by Resting Blood Pressure Level**



Source: Adapted from data found in Cornelissen and Smart, 2013.<sup>84</sup>

**Frequency:** The frequency of the physical activity interventions was reported by 10 meta-analyses,<sup>83-86, 88-90, 92, 93, 95</sup> and ranged from 1 to 7 days per week. However, no conclusions can be made about the influence of frequency on the blood pressure response to physical activity because the findings were too scarce and too disparate to synthesize.

**Intensity:** The intensity of the physical activity interventions was quantified in nine of the meta-analyses,<sup>83-85, 88, 92-96</sup> and ranged from low to vigorous-intensity. However, no conclusions can be made regarding the influence of intensity on the blood pressure response to physical activity as the magnitude and precision of the effect could not be determined from findings that were too scarce to synthesize.

**Time:** The time of the exercise session was reported in nine of the meta-analyses,<sup>84-86, 88-90, 92, 93, 96</sup> and ranged from 12 minutes to 100 minutes. However, no conclusions can be made regarding the influence of time on the blood pressure response to physical activity as the magnitude and precision of the effect could not be determined from a lack of findings on the time of the exercise session.

**Duration:** All chronic (i.e., training) meta-analyses reported the duration of the physical activity intervention, and they ranged from 1 to 60 months.<sup>83-93, 95, 96</sup> However, no conclusions can be made regarding the influence of duration on the blood pressure response to physical activity as the magnitude and precision of the effect could not be determined from findings that were too scarce to synthesize.

**Type (Mode):** Moderate evidence indicates the relationship between physical activity and the disease progression indicator of blood pressure does not vary by type of physical activity, with the evidence

more robust for traditional types (i.e., aerobic, dynamic resistance, combined) of physical activity than for other types (i.e., tai chi, yoga, qigong) among adults with hypertension.

*Traditional type (mode):* Five meta-analyses examined the blood pressure response to aerobic exercise training,<sup>84-88</sup> three meta-analyses examined the blood pressure response to resistance exercise training (one acute<sup>94</sup> and two chronic<sup>83, 95</sup>), one meta-analysis examined the blood pressure response to combined aerobic and resistance exercise training,<sup>93</sup> and one meta-analysis examined the blood pressure response to isometric resistance training.<sup>96</sup> [Cornelissen and Smart<sup>84</sup>](#) examined aerobic exercise training performed, on average, at moderate- to-vigorous intensity for 40 minutes per session 3 days per week for 16 weeks and reported systolic/diastolic blood pressure reductions of: -8.3 (95% CI: -10.7 to -6.0)/-5.2 (95% CI: -6.9 to -3.4), -4.3 (95% CI: -7.7 to -0.9)/-1.7 (95% CI: -2.7 to -0.7), and -0.8 (95% CI: -2.2 to +0.7)/-1.1 (95% CI: -2.2 to -0.1) mmHg among adults with hypertension, prehypertension, and normal blood pressure, respectively (see Supplementary Table S-F10-1). [MacDonald et al<sup>95</sup>](#) examined dynamic resistance training performed, on average, at moderate intensity for 32 minutes per session 3 days per week for 14 weeks and reported systolic/diastolic blood pressure changes of -5.7 (95% CI: -9.0 to -2.7)/-5.2 (95% CI: -8.4 to -1.9), -3.0 (95% CI: -5.1 to -1.0)/-3.3 (95% CI: -5.3 to -1.4), and 0.0 (95% CI: -2.5 to 2.5)/-0.9 (95% CI: -2.1 to 2.2) mmHg among adults with hypertension, prehypertension, and normal blood pressure, respectively. [Corso et al<sup>93</sup>](#) examined combined aerobic and dynamic resistance exercise training performed, on average, at moderate intensity for 58 minutes per session 3 days per week for 20 weeks and reported systolic/diastolic blood pressure changes of -5.3 (95% CI: -6.4 to -4.2)/-5.6 (95% CI: -6.9 to -3.8), -2.9 (95% CI: -3.9 to -1.9)/-3.6 (95% CI: -5.0 to -0.2), and +0.9 (95% CI: 0.2 to 1.6)/-1.5 (95% CI: -2.5 to -0.4) mmHg among adults with hypertension, prehypertension, and normal blood pressure, respectively.

[Carlson et al<sup>96</sup>](#) investigated the blood pressure response among adults with hypertension (N=61) and normal blood pressure (N=162) to 4 or more weeks of isometric resistance training at 30 to 50 percent maximal voluntary contraction, with four contractions held for 2 minutes with 1 to 3 minutes of rest between contractions. Among the adults with hypertension, all of whom were on medication, training resulted in reductions of systolic, diastolic, and mean arterial blood pressure of -4.3 (95% CI: -6.6 to -2.2)/-5.5 (95% CI: -7.9 to -3.3)/-6.1 (95% CI: -8.0 to -4.0) mmHg, respectively. Among adults with normal blood pressure, training resulted in reductions of systolic, diastolic, and mean arterial blood pressure of -7.8 (95% CI: -9.2 to -6.4)/-3.1 (95% CI: -3.9 to -2.3)/-3.6 (95% CI: -4.4 to -2.7) mmHg, respectively. [Carlson et al<sup>96</sup>](#) were unable to explain the larger reductions in systolic blood pressure among the adults with

normal blood pressure compared to adults with hypertension, and the reverse pattern of blood pressure response for diastolic blood pressure and mean arterial pressure. The sample size of adults with hypertension (N=61), all of whom were on medication, in the meta-analysis by [Carlson et al<sup>96</sup>](#) investigating isometric resistance training was much smaller than the sample size of the adults with hypertension in the meta-analyses investigating aerobic,<sup>84</sup> dynamic resistance,<sup>95</sup> and combined aerobic and dynamic resistance<sup>93</sup> exercise training. For these reason, any conclusions made about the antihypertensive benefits of isometric resistance training should be made with caution.

Collectively, these findings indicate the systolic/diastolic blood pressure reductions following physical activity among adults with hypertension are -8.3/-5.2 mmHg for aerobic, -5.7/-5.2 mmHg for dynamic resistance, and -5.3/-5.6 mmHg for combined aerobic and dynamic resistance exercise training. These blood pressure reductions are about 2 times greater among adults with hypertension than among adults with prehypertension and about 4 to 5 times greater among adults with hypertension than among adults with normal blood pressure, independent of type of exercise. These blood pressure benefits occurred at about 6 MET-hours per week or more of moderate-to-vigorous physical activity.

*Tai chi, yoga, qigong:* Evidence of lower quality suggests that the relationship between physical activity and the disease progression indicator of blood pressure does not vary by for other types of physical activity (i.e., tai chi, yoga, qigong). Four meta-analyses examined these types of physical activity. [Xiong et al<sup>89</sup>](#) investigated the blood pressure response to Baduanjin (a type of qigong), an ancient Chinese mind-body exercise characterized by simple, slow, and relaxing movements, among 572 Asian adults with hypertension, and reported systolic/diastolic blood pressure reductions of -13.0 (95% CI: -21.2 to -4.8)/-6.1 (95% CI: -11.2 to -1.1) mmHg following 3 to 12 months of Baduanjin, respectively. These investigators also found in four trials that Baduanjin plus antihypertensive medications was superior to antihypertensive medications alone in lowering systolic/diastolic blood pressure by a magnitude of -7.5 (95% CI: -11.4 to -3.6)/-3.6 (95% CI: -5.2 to -1.8) mmHg, respectively. The authors acknowledged that the primary levels studies in their meta-analyses were of poor quality.

[Xiong et al<sup>90</sup>](#) investigated the blood pressure response to qigong, an ancient Chinese healing art that consists of breathing patterns, rhythmic movements, and meditation, among 2,349 Asian adults with hypertension, and reported systolic/diastolic blood pressure reductions of -17.4 (95% CI: -21.1 to -13.7)/-10.6 (95% CI: -14.0 to -6.3) mmHg, respectively, following 8 weeks to 1 year of qigong. These investigators also found in two trials that exercise was superior to qigong in lowering systolic blood

pressure by a magnitude of -6.5 (95% CI: -2.8 to -10.2) mmHg, in four trials that qigong was superior to antihypertensive medications in lowering diastolic blood pressure by a magnitude of -6.1 (95% CI: -9.6 to -2.6) mmHg, and in five trials that qigong plus antihypertensive medications was superior to antihypertensive medications alone in lowering systolic/diastolic blood pressure by a magnitude of -12.0 (95% CI: -15.6 to -8.5)/-5.3 (95% CI: -8.1 to -2.4) mmHg, respectively. The authors acknowledged that the primary levels studies in their meta-analyses were of poor quality.

[Wang et al<sup>91</sup>](#) investigated the blood pressure response to tai chi, an ancient Chinese exercise that combines deep diaphragmatic breathing with continuous body movements to achieve a harmonious balance between body and mind, among 1,371 mostly Asian adults with hypertension. They reported systolic/diastolic blood pressure reductions of -12.4 (95% CI: -12.6 to -12.2)/-6.0 (95% CI: -6.2 to -5.9) mmHg, respectively, following 2 to 60 months of all forms and types of tai chi. These investigators also found in 14 trials that tai chi was superior to routine care in lowering systolic/diastolic blood pressure by a magnitude of -12.4 (95% CI: -12.6 to -12.2)/-6.0 (95% CI: -6.2 to -5.9) mmHg, respectively, and in 3 trials that tai chi plus antihypertensive medications was superior to antihypertensive medications alone in lowering systolic/diastolic blood pressure by a magnitude of -9.3 (95% CI: -10.9 to -7.8)/-7.2 (95% CI: -7.7 to -6.6) mmHg, respectively. The authors acknowledged that the primary levels studies in their meta-analyses were of poor quality.

[Park and Han<sup>92</sup>](#) investigated the blood pressure response to yoga, which incorporates meditation with physical movement, among 394 adults with hypertension. They reported systolic/diastolic blood pressure reductions of -11.4 (95% CI: -14.6 to -8.2)/-2.4 (95% CI: -4.3 to -0.4) mmHg, respectively, among older adults ages 60 years and older following 6 to 12 weeks of yoga. In contrast to the other meta-analyses addressing effects of tai chi, yoga, and/or qigong, the primary level studies in this meta-analysis were described by [Park and Han<sup>92</sup>](#) to be of high methodological study quality.

Collectively, the four meta-analyses addressing effects of tai chi, yoga, and/or qigong found blood pressure reductions in systolic blood pressure that ranged from -12 to -17 mmHg and diastolic blood pressure reductions of -2 to -11 mmHg. Except for traditional types of exercise<sup>90</sup> that were superior to qigong in lowering blood pressure, these types of physical activity (tai chi, yoga, and or qigong) proved to be superior to routine care and when combined with antihypertensive medication than compared to antihypertensive medication alone. However, these apparent positive findings of the antihypertensive effects of these types of physical activity types must be interpreted with caution due to the low study

methodological quality of this literature, lack of disclosure of important study design considerations, considerable heterogeneity in this literature, inability to generalize findings to other racial/ethnic groups, and lack of long-term follow-up.

**How physical activity was measured:** All meta-analyses that examined the blood pressure response to physical activity included interventions that were structured by the frequency, intensity, time, duration, and type (mode) of physical activity, but the details of these features of the physical activity interventions were not well disclosed. None of these meta-analyses reported any physical activity measure outside of the structured physical activity intervention. No conclusions can be made regarding how physical activity was measured, as the magnitude and precision of the effect could not be determined from findings that were too scarce to synthesize.

***For additional details on this body of evidence, visit: Supplementary Tables S-F10-1, S-F10-2, and <https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx> for the Evidence Portfolio.***

### **Comparing 2018 Findings with the 2008 Scientific Report**

The 2008 Scientific Report<sup>4</sup> concluded that both aerobic and dynamic resistance exercise training of moderate-to-vigorous intensity produced small but clinically important reductions in systolic and diastolic blood pressure in adults, with the evidence more convincing for aerobic than dynamic resistance exercise. The 2018 Scientific Report extends findings from the 2008 Scientific Report<sup>4</sup> among adults with hypertension in four ways. First, the 2018 Scientific Report provides strong evidence that physical activity reduces the risk of progression of cardiovascular disease, as is evident from its moderate to large reductions in blood pressure. Second, the 2018 Scientific Report provides moderate evidence that an inverse, dose-response relationship exists between physical activity and the risk of cardiovascular disease mortality among adults with hypertension. Third, the 2018 Scientific Report suggests that greater blood pressure reductions occur among adults with hypertension who have the highest resting blood pressure levels. Fourth, reflecting on the accumulating evidence over the past decade, the 2018 Scientific Report indicates that, in the range of physical activity volume effective in lowering blood pressure, aerobic and dynamic resistance exercise may be equally effective in reducing blood pressure at volumes in the lower part of this range.

## Public Health Impact

Hypertension is the most common, costly, and preventable CVD risk factor. According to the JNC 7 blood definition of hypertension, by 2030 it is estimated that 41 percent of adults in the United States will have hypertension. The lifetime risk of acquiring hypertension is 90 percent. Curbing this growing and expensive public health crisis with the adoption and maintenance of lifestyle interventions, such as habitual physical activity, is a national and global priority.<sup>78, 81</sup> Accordingly, professional organizations throughout the world recommend habitual physical activity for the prevention, treatment, and control of hypertension and the associated reduction in risk of CVD progression (Supplementary Table S-F10-1).<sup>79, 108-116</sup> Due to the clinically important role of physical activity in preventing, treating, and controlling hypertension as well as its CVD protective effects, adults with hypertension are encouraged to engage in 90 minutes per week or more of moderate intensity or 45 minutes per week or more of vigorous intensity aerobic and/or dynamic resistance physical activity, or some combination of these. Greater amounts of physical activity confer greater cardiovascular health benefit so that even greater amounts of physical activity should be encouraged. Adults with hypertension may supplement their physical activity programs with tai chi, yoga, or qigong until sufficient evidence exists to make a more precise conclusion.

### **Question 4. In people with type 2 diabetes, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) disease progression?**

- 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) Does the relationship vary based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

**Sources of evidence:** Systematic reviews, meta-analyses, pooled analyses

## Conclusion Statements

### Risk of Co-morbid Conditions

Strong evidence demonstrates an inverse association between volume of physical activity and risk of cardiovascular mortality among adults with type 2 diabetes. **PAGAC Grade: Strong.**

Moderate evidence indicates an inverse, curvilinear dose-response relationship between physical activity and cardiovascular mortality among adults with type 2 diabetes. **PAGAC Grade: Moderate.**

Insufficient evidence was available to determine whether the relationship between physical activity and cardiovascular mortality among adults with type 2 diabetes varies with age, sex, race/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence was available to determine whether the relationship between physical activity and cardiovascular mortality among adults with type 2 diabetes varies with frequency, duration, intensity, or type (mode) of physical activity or how physical activity is measured among people with type 2 diabetes mellitus. **PAGAC Grade: Not assignable.**

### Physical Function

Insufficient evidence was available to determine the relationship between physical activity and physical function in adults with type 2 diabetes. **PAGAC Grade: Not assignable.**

### Health-related Quality of Life

Insufficient evidence was available to determine the relationship between physical activity and health-related quality of life in adults with type 2 diabetes. **PAGAC Grade: Not assignable.**

### Disease Progression: Indicators of Neuropathy, Nephropathy, Retinopathy, and Foot Disorders.

Insufficient evidence was available to determine the relationship between physical activity and indicators of progression of neuropathy, nephropathy, retinopathy, and foot disorders. **PAGAC Grade: Not assignable.**

### Disease Progression: Indicators of HbA1C, Blood Pressure, Body Mass Index, and Lipids

Strong evidence demonstrates an inverse association between aerobic activity, muscle-strengthening activity, and aerobic plus muscle-strengthening activity with risk of progression among adults with type 2 diabetes, as assessed by overall effects of physical activity on four indicators of risk of progression: glycated hemoglobin A1C, blood pressure, body mass index, and lipids. **PAGAC Grade: Strong.**

Insufficient evidence was available to determine the relationship between tai chi, qigong, and yoga exercise on four indicators of risk of progression: hemoglobin A1C, blood pressure, body mass index, and lipids. **PAGAC Grade: Not assignable.**

Moderate evidence indicates an inverse dose-response relationship between volume of aerobic activity and two indicators of risk of progression—blood pressure and hemoglobin A1C—among adults with type 2 diabetes. **PAGAC Grade: Moderate.**

Limited evidence indicates an inverse dose-response relationship between volume of resistance training and one indicator of risk of progression— hemoglobin A1C—among adults with type 2 diabetes. **PAGAC Grade: Limited.**

Limited evidence indicates that longer periods of consistent physical activity have a larger effect on three indicators of risk of progression— hemoglobin A1C, body mass index, and lipids—than do shorter periods among adults with type 2 diabetes. **PAGAC Grade: Limited.**

Moderate evidence indicates that the effects of physical activity on the disease progression indicator of blood pressure are larger in hypertensive individuals with type 2 diabetes than in those without hypertension. Similarly, moderate evidence indicates that the effects of physical activity on the disease progression indicator of hemoglobin A1C are larger in individuals with type 2 diabetes who have higher levels of hemoglobin A1C than in those with lower hemoglobin A1C. **PAGAC Grade: Moderate.**

Insufficient evidence was available to determine whether the effects of physical activity on indicators of risk of progression in adults of type 2 diabetes vary by age, sex, race/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Limited evidence suggests, when adults with type 2 diabetes engage in equal amounts of moderate-intensity and vigorous-intensity aerobic activity, vigorous-intensity activity is more efficient than moderate-intensity activity in improving one indicator of risk of progression— hemoglobin A1C. **PAGAC Grade: Limited.**

Insufficient evidence was available to determine the effects of frequency, bout duration, and method of measuring physical activity on indicators of risk of progression in adults with type 2 diabetes. **PAGAC Grade: Not assignable.**

### **Review of the Evidence**

Type 2 diabetes is characterized by relative insulin deficiency, usually combined with an insufficient cellular response to insulin (insulin resistance), resulting in elevated blood glucose. The extent that blood glucose is persistently elevated is commonly assessed by measuring glycated hemoglobin,

abbreviated as HbA1C. In 2015, an estimated 30.3 million people of all ages in the U.S. population had diabetes, with type 2 diabetes representing 90 to 95 percent of all cases of diabetes and type 1 diabetes representing the other cases.<sup>117</sup> The number of adults diagnosed with diabetes (either type 1 or type 2) has more than tripled in the past 20 years.<sup>118</sup> The estimated prevalence of diabetes is age-related, with prevalence in 2015 of 17.0 percent and 25.2 percent in adults ages 45 to 64 years and ages 65 years and older, respectively.<sup>117</sup>

Type 2 diabetes is a major cause of morbidity and mortality. For example, it is the leading cause of kidney failure, lower limb amputations, and adult-onset blindness.<sup>118</sup> For purposes of this evidence review, the Subcommittee classified morbidity and mortality into two types: (1) morbidity and mortality due to co-morbid conditions and (2) morbidity and mortality related to the progression (or worsening) of type 2 diabetes.

**Co-morbid conditions:** People with type 2 diabetes are at higher risk of co-morbid conditions, with CVD (hypertension, stroke, coronary heart disease, heart failure) as the most common cause of death among people with type 2 diabetes. Because people with type 2 diabetes have a higher prevalence of obesity, they are at increased risk of obesity-related conditions, such as osteoarthritis.<sup>119</sup>

**Progression:** Progression of type 2 diabetes can lead to complications and organ damage, with four well-known conditions regarded as indicators of progression: (1) retinopathy; (2) peripheral neuropathy; (3) nephropathy; and (4) diabetes-related foot infections and foot ulcers. In addition, four conditions were regarded as indicators of risk of progression: HbA1C, blood pressure, BMI, and lipids. For example, hypertension is a strong risk factor for development and progression of diabetic kidney disease.<sup>120</sup> The Subcommittee recognizes that hypertension, lipid disorders such as hypercholesterolemia and obesity can be classified in more than one way, including as co-morbid conditions. However, for the purposes of this evidence review, the Subcommittee focused on these conditions as indicators of risk of progression.

Regular physical activity is recommended for people with type 2 diabetes.<sup>121</sup> Thus, the Subcommittee asked, to what extent does regular physical activity have important preventive effects in people with type 2 diabetes, including reducing risk of co-morbid conditions and reducing risk of disease progression?

To address this question, the Subcommittee considered evidence contained in 40 reviews, which comprised systematic reviews, meta-analyses, and pooled analyses. Individual studies of type 2 diabetes

in children were unusual, so evidence was only sufficient for conclusions in adults. The main focus of the evidence review for three outcomes (physical function, quality of life, and progression) was on evidence provided by meta-analyses of RCTs in adults with type 2 diabetes that compared (only) physical activity or exercise interventions to a no-exercise control group. Such meta-analyses could be included as a source of evidence if the percent of studies with a co-intervention (e.g., a diet intervention) was so small it would not affect the conclusions of the meta-analysis, and the authors deemed their results applied to physical activity-only interventions. However, some additional evidence was provided by meta-analyses comparing effects of different types of physical activity, by systematic reviews, and by pooled analyses.

The main focus of the evidence review for the co-morbidity outcome was a review of cohort studies. Large cohort studies in adults with CVD endpoints were included even though adults with type 1 diabetes were included as well as adults with type 2 diabetes. The rationale was: (1) large cohort studies may measure diabetes by self-report where it is likely difficult to reliably ascertain type of diabetes, (2) type 2 diabetes typically represents about 95 percent of cases of diabetes in the population and inclusion of adults with type 1 diabetes in the cohort would not appreciably affect the strength of association between type 2 diabetes with CVD endpoints; and (3) the results of one analysis limited to people with type 2 diabetes could be compared to other results.

### Risk of Co-morbid Conditions

#### *Evidence on the Overall Relationship*

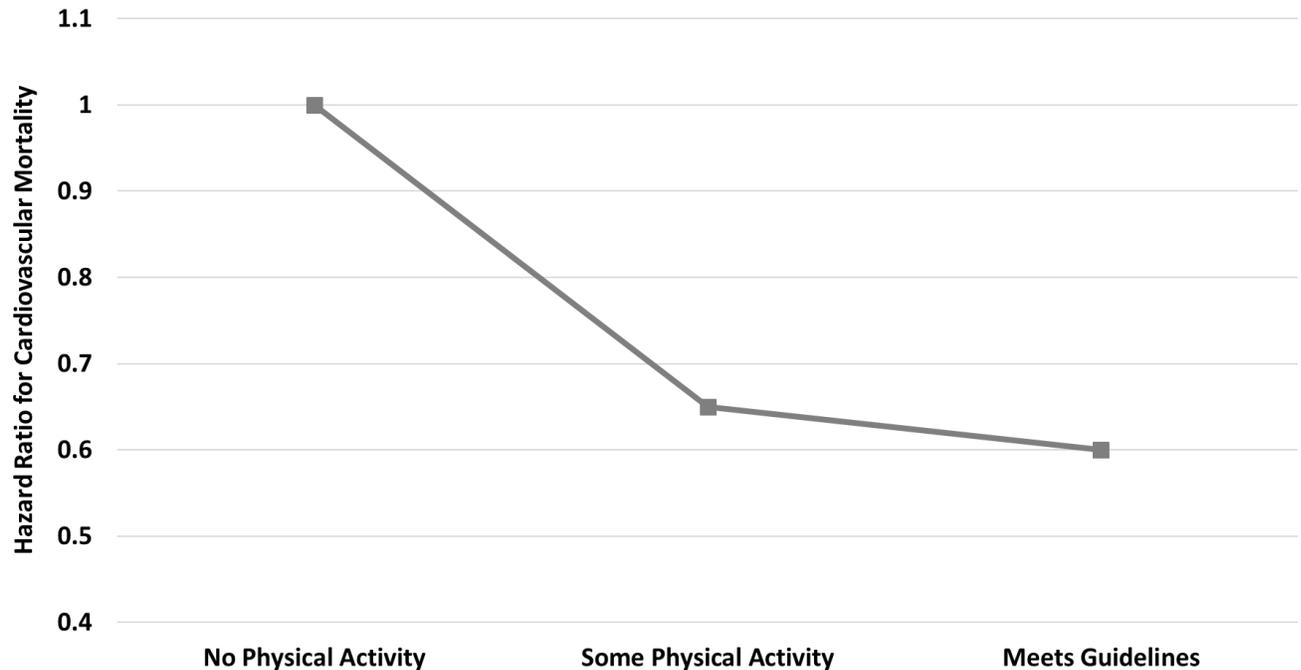
CVD mortality was the only condition for which the Subcommittee located sufficient evidence. The Subcommittee recognized that mortality is not a co-morbidity per se, but included this outcome in its review of co-morbid conditions due to importance and because CVD mortality is related to the prevalence of CVD co-morbidity.

The sources of evidence were two meta-analyses and one pooled analysis. One meta-analysis of CVD mortality included eight cohort studies with a total sample size of nearly 20,000.<sup>122</sup> A second meta-analysis analyzed CVD risk as an outcome, with CVD risk representing a composite outcome of CVD mortality and CVD events (e.g., stroke).<sup>123</sup> This meta-analysis comprised 11 studies, with a total sample size also of about 20,000. Overall, the meta-analyses included 14 individual studies, with five studies included in both meta-analyses. One pooled analyses had a sample size of more than 3,000 adults.<sup>124</sup> The pooled analysis used a single questionnaire assessing leisure-time moderate-to-vigorous physical activity.

These reviews provided strong evidence that regular physical activity reduced risk of CVD mortality in adults with type 2 diabetes. One meta-analysis found a significant and strong inverse relationship between physical activity and CVD mortality, with similar results in comparisons of highest amounts versus lowest amounts of physical activity categories for: total physical activity (HR=0.61; 95% CI: 0.47-0.80); leisure-time physical activity (HR=0.63; 95% CI: 0.48-0.83), and walking (HR=0.58; 95% CI: 0.42-0.79).<sup>122</sup> The other meta-analysis found a significant and strong inverse relationship between high versus low amounts of physical activity with the combined outcome of CVD events or CVD mortality (RR=0.71; 95% CI: 0.60-0.84).<sup>123</sup> When the analysis was limited to six studies known to enroll only adults with type 2 diabetes, the effect was slightly stronger (RR=0.64; 95% CI: 0.56-0.71). The pooled analysis also reported a significant effect of physical activity on CVD mortality in a comparison of highest versus lowest physical activity categories (HR=0.60; 95% CI: 0.44-0.82).<sup>124</sup> In other words, these reviews found that regular physical activity resulted in a 30 to 40 percent reduction in risk of CVD mortality.

**Dose-response:** The pooled analysis reported a substantially reduced risk of CVD mortality in a dose-response manner (Figure F10-7).<sup>124</sup> Compared to no activity, engaging in some activity was associated with a 32 percent reduction in risk of CVD mortality (adjusted HR=0.68; 95% CI: 0.51-0.92), while engaging in higher amounts of activity (meeting physical activity guidelines) was associated with a larger 40 percent reduction in risk of CVD mortality (adjusted HR=0.60; 95% CI: 0.44-0.82) ( $P_{\text{trend}} < .001$ ).<sup>124</sup> The shape of the dose-response curve was similar to that in adults without type 2 diabetes. The [Kodama et al](#)<sup>123</sup> review also reported a significant ( $P < .001$ ) inverse dose-response relationship. The findings of these two reviews were judged to provide moderate evidence of dose-response.

**Figure F10-7. Dose-Response Relationship Between Physical Activity and Cardiovascular Disease Mortality in Individuals with Type 2 Diabetes**



Source: Adapted from data found in Sadarangani et al., 2014.<sup>124</sup>

### *Evidence on Specific Factors*

These three reviews<sup>122-124</sup> did not address how effects of physical activity may vary based upon individual characteristics (e.g., age, sex) or by characteristics of the physical activity (e.g., intensity, type).

### Physical Function

The Subcommittee’s search located only one systematic review of the effects of physical activity on physical function in type 2 diabetes.<sup>125</sup> This review included studies of multicomponent fall prevention programs in people with type 2 diabetes and peripheral neuropathy.

### *Evidence on the Overall Relationship*

The review included insufficient evidence to assess the effect of physical activity on physical function. Only 4 of the 10 included studies had a no-exercise control group, and the author’s quality rating for two of these four trials was low (3/10 and 4/10).<sup>125</sup> The remaining two RCTs enrolled 182 participants for 10 to 12 weeks of exercise. One RCT reported a significant effect of exercise on four out of four measures

of physical function, while the other reported a significant effect of exercise on one out of six measures of physical function. Notably, the authors of the review characterized the evidence as preliminary.

### Health-related Quality of Life

The search located six systematic reviews of the effects of physical activity on HRQoL in adults with type 2 diabetes. The sources of evidence were:

- Two large systematic reviews of controlled trials of various exercise types, including walking, muscle-strengthening activities, video games, tai chi, and yoga.<sup>126, 127</sup> One review included 20 RCTs which enrolled a total of 1,719 participants<sup>127</sup> and the other review included 30 clinical trials (not limited to RCTs) that enrolled a total of 2,785 participants.<sup>126</sup> The two reviews included a total of 37 studies, with 13 studies covered in both reviews. HRQoL was most commonly assessed using the 36-item Short Form Health Survey (SF-36).
- Two reviews of tai chi exercise. As one review<sup>128</sup> was an update of a previous review,<sup>129</sup> only the most recent review was used as a source of evidence. The more recent review included three RCTs, which enrolled a total of 157 participants.
- One review of yoga exercise.<sup>130</sup> This review included three RCTs and one non-randomized trial that enrolled a total of 420 participants.
- One systematic review is not discussed below as it included only one study assessing HRQoL.<sup>131</sup>

### *Evidence on the Overall Relationship*

For physical activity generally, the two large systematic reviews provided conflicting evidence.<sup>126, 127</sup> One review<sup>127</sup> summarized the results of the 16 included studies as: “Between group comparisons showed no significant results for aerobic training with the exception of one study, and mixed results for resistance and combined training.” The abstract of this review characterized overall results as “conflicting.”<sup>127</sup> The other review<sup>126</sup> summarized the results of the 20 included studies quite differently: 15 studies “reported a significant effect of aerobic exercise on quality of life....” The abstract of this review characterized aerobic exercise as “effective,” effects of resistance and combined exercise as “mixed,” and yoga as needing “more research.”<sup>126</sup> The conclusion of conflicting evidence was supported by two additional observations. One of the larger trials reported that HRQoL improved more in the control group than the exercise group.<sup>132</sup> In 13 of 20 studies of aerobic training that assessed HRQoL with the SF-36 in one review, no two studies reported the same pattern of significant changes in SF-36 subscales (except the

negative studies).<sup>126</sup> It was not possible to confidently reconcile the different conclusions of these reviews based upon the information presented in the reviews.

The reviews included insufficient evidence on tai chi and yoga to determine the effect of physical activity on HRQoL in people with type 2 diabetes. The systematic review of tai chi included only three RCTs. Although these RCTs reported positive effects of physical activity on HRQoL, the author's quality scores for these RCTs (on a 7-point scale) was only a 2 or a 3. The authors characterized the evidence as "not convincing enough."<sup>128</sup> The systematic review of yoga included four controlled trials of which three were RCTs. Three of the four trials reported positive effects of physical activity on HRQoL. However, the author's quality scores for these trials (on a 10-point scale) ranged from 1 to 4. The authors concluded that, due to the methodological limitations of existing trials, additional high-quality studies are required to establish effects of yoga on HRQoL in individuals with type 2 diabetes.<sup>130</sup>

### Disease Progression

The Subcommittee used two sets of indicators to assess the effects of physical activity on progression of type 2 diabetes. The first set included the indicators of retinopathy, nephropathy, neuropathy, and diabetes-related foot conditions. However, no reviews were located on the relationship of physical activity to progression, as assessed by these indicators.

The second set of indicators for progression comprised four indicators of risk of progression: HbA1C, blood pressure, BMI, and lipids. These indicators are also referred to as risk factors for progression. A large number of reviews were located on effects of physical activity on these risk factors. The reviews were sorted by mode of physical activity and by risk factor:

- Primary sources of evidence for effects of *aerobic activity, resistance training, or both* on risk factors for progression were meta-analyses of RCTs.
  - **HbA1C.** Twelve meta-analyses included HbA1C as an outcome.<sup>133-144</sup>
  - **Blood Pressure.** Six meta-analyses included blood pressure as an outcome.<sup>134, 136, 137, 140, 144, 145</sup>
  - **BMI.** Six meta-analyses included BMI as an outcome.<sup>133, 134, 136, 137, 140, 146</sup>
  - **Lipids.** Five meta-analyses included lipids as an outcome.<sup>134, 136, 137, 140, 144</sup>

- Secondary sources of evidence for effects of *aerobic activity, resistance training, or both* on risk factors for progression were other types of reviews.
  - Three meta-analyses compared different types of physical activity.[147-149](#)
  - Three meta-analyses which included non-randomized trials.[131](#), [150](#), [151](#)
  - Six systematic reviews (or systematic reviews plus meta-analyses where the meta-analysis part was not used as evidence due to inclusion of non-relevant studies in summary statistics).[152-157](#)
- Primary sources of evidence of the effects of *tai chi, qigong, and yoga* on risk factors for progression were meta-analyses of RCTs.
  - **HbA1C.** Six meta-analyses included HbA1C as an outcome.[128](#), [139](#), [158-161](#)
  - **Blood Pressure.** No meta-analyses included blood pressure as an outcome.
  - **BMI.** No meta-analyses included BMI as an outcome.
  - **Lipids.** One meta-analysis included lipids as an outcome.[161](#)
- Secondary sources of evidence for effects of *tai chi, qigong, and yoga* on risk factors for progression were other reviews.
  - One meta-analyses included comparisons of different types of physical activity.[128](#)
  - Three systematic reviews.[129](#), [130](#), [162](#)

### *Evidence on the Overall Relationship*

#### **Effects of Aerobic Activity, Resistance Training, or Both on Risk Factors for Progression**

Overall, the reviews provided strong evidence that aerobic activity and muscle-strengthening activity reduced risk of progression of type 2 diabetes, though the strength of evidence varied somewhat by risk factor. This evidence is summarized below for each of the four risk factors. Meta-analyses generally summarized the effects of physical activity using the standard measurement units for each indicator. For example, HbA1C is measured in percent of hemoglobin which is glycated, so an effect size of -0.50 percent indicates a net lowering of HbA1C from, for example, 6.5 percent to 6.0 percent. Blood pressure is measured in mm Hg (millimeters of mercury). BMI units are (body weight in kilograms)/(height in meters)<sup>2</sup>. Lipids LDL (low-density lipoprotein), HDL (high-density lipoprotein), total cholesterol, and triglycerides are measured in mg/dL (1 mg/dL=0.01 gram per liter) or in mmol/L. However, some reviews used other measures to quantify exercise effects.

**HbA1C.** Meta-analyses of RCTs consistently reported aerobic activity reduced HbA1C in adults with type 2 diabetes. The five largest meta-analyses involved 19 to 26 comparisons of aerobic exercise with control groups, and reported similar significant effects of aerobic exercise on HbA1C of -0.50 to -0.73 percent: weighted mean difference (WMD)=-0.73 percent (95% CI: -1.06% to -0.40%)<sup>142</sup>; WMD=-0.70 percent (95% CI: -1.02 to -0.38)<sup>143</sup>; mean difference (MD)=-0.71 percent (95% CI: -1.11 to -0.31)<sup>135</sup>; WMD=-0.50 percent (95% CI: -0.78% to -0.21%)<sup>140</sup>; and WMD=-0.60 percent (95% CI: -0.98% to -0.27%).<sup>134</sup> One of these meta-analyses included only studies of walking interventions.<sup>140</sup> Although one meta-analysis of device-based walking interventions reported no effect of walking on HbA1C, the authors essentially attributed this lack of effect to problems with intervention implementation.<sup>141</sup>

Fewer individual studies have been conducted on the effects of muscle-strengthening on HbA1C. Two overlapping meta-analyses involving four and five comparisons of supervised progressive resistance training reported significant effects of WMD=-0.62 percent (95% CI: -1.14% to -0.11%)<sup>143</sup> and WMD=-0.57 percent (95% CI: -1.14% to -0.01%).<sup>142</sup> Another meta-analysis reported a smaller effect of resistance training on HbA1C of WMD=-0.32 percent (95% CI: -0.60% to -0.04%). However, a meta-analysis of seven studies of resistance band exercise reported a non-significant trend on HbA1C of WMD=-0.18 percent (95% CI: -0.49% to 0.14%)<sup>138</sup> and a meta-analysis in which one of seven studies used resistance bands also reported a non-significant trend.<sup>134</sup>

The results of meta-analyses of combined aerobic and resistance training provided further evidence that combined aerobic and muscle-strengthening activity reduces HbA1C in adults with type 2 diabetes. Four meta-analyses, involving 7 to 14 comparisons, reported similar significant effects of combined exercise on HbA1C of -0.47 to -0.74 percent: WMD=-0.74 percent (95% CI: -1.13% to -0.35%)<sup>137</sup>; WMD=-0.51 percent (95% CI: -0.79% to -0.23%)<sup>142</sup>; WMD=-0.47 percent (95% CI: -0.64% to -0.31%)<sup>143</sup>; and WMD=-0.67 percent (95% CI: -0.93% to -0.40%).<sup>134</sup>

Two overlapping meta-analyses involving 14 and 12 RCTs compared exercise types,<sup>148, 149</sup> and both reported aerobic exercise alone lowered HbA1C more than resistance training alone. However, combined aerobic and resistance training had a larger effect on HbA1C than aerobic exercise alone (difference in exercise effect on HbA1C favoring combined training of MD=-0.17 percent; 95% CI: -0.31% to -0.03%).<sup>148</sup> This finding further supports the conclusion that resistance training alone has an effect on HbA1C, and suggests combined training is most effective in lowering HbA1C in adults with type 2 diabetes.

The other meta-analyses not discussed above generally supported the conclusion that aerobic, resistance, or combined activity improves HbA1C. The secondary sources of evidence also generally supported these conclusions. Notably, a systematic review of pedometer-based walking programs found only two of seven programs reported significant improvements in HbA1C,<sup>155</sup> thus supporting the negative findings of the meta-analysis of device-based walking interventions.<sup>141</sup>

**BMI.** Meta-analyses that included at least 10 RCTs reported small but significant effects of physical activity on BMI. The effects were: WMD=-1.05 BMI units (95% CI: -1.31 to -0.80) for free living exercise<sup>133</sup>; effect size (ES)=-0.53 (95% CI: -0.81 to -0.26) for aerobic activity<sup>137</sup>; MD=-1.56 BMI units (95% CI: -2.41 to -0.71) for aerobic activity<sup>135</sup>; WMD=-0.91 BMI units (95% CI: -1.22 to -0.59) for walking<sup>140</sup>; and ES=-0.50 (95% CI: -0.75 to -0.26) for aerobic plus resistance exercise.<sup>137</sup> Meta-analysis including fewer studies generally reported a non-significant trend favoring an effect of activity on BMI.

**Systolic blood pressure.** Meta-analyses of the effects of physical activity on systolic blood pressure in adults with type 2 diabetes consistently reported significant moderate size effects. The summary effects ranged from WMD=-2.42 mmHg (95% CI: -4.39 to -0.45)<sup>137</sup> to WMD=-7.98 mmHg (95% CI: -9.87 to -6.08),<sup>144</sup> with significant effects found for aerobic activity alone (three analyses), resistance exercise alone (two analyses), combined activity (two analyses) and any activity (one analysis)<sup>134, 137, 140, 144, 145</sup> (note the effect on aerobic activity on blood pressure in one study was only significant after an outlier was removed from the analysis<sup>140</sup>).

**Diastolic blood pressure.** Meta-analyses of the effects of physical activity on diastolic blood pressure in adults with type 2 diabetes consistently reported significant small size effects. The summary effects ranged from WMD=-1.97 mmHg (95% CI: -3.94 to -0.00)<sup>140</sup> to WMD=-2.84 mmHg (95% CI: -3.88 to -1.81),<sup>145</sup> with significant effects found for aerobic activity alone (two analyses), resistance exercise alone (one analysis), combined activity (one analysis) and any activity (one analysis).<sup>137, 140, 144, 145</sup>

**Lipids.** Compared to HbA1C, blood pressure, and BMI, less evidence was available that physical activity improved lipids in adults with type 2 diabetes. One large meta-analysis pooled the effects of aerobic, resistance, and combined exercise.<sup>137</sup> This review reported a significant but small benefit of physical activity on HDL (35 studies with N=2,059 participants; WMD=0.4 mmol/L; 95% CI: 0.02-0.07) and LDL (25 studies with N=1,807 participants; WMD=-0.16 mmol/L; 95% CI: -0.30 to -0.01). The effect of exercise on triglycerides (WMD=-0.03 mmol/L; 95% CI: -0.17 to 0.10) was not significant. The review also reported: (1) the effects of physical activity on lipids did not differ by type (aerobic, resistance, combined), and (2)

exercise interventions of longer durations produced significantly ( $P<.03$ ) stronger effects on LDL. Consistent with this latter finding, a meta-analysis found no significant effects of exercise on HDL and triglycerides after 4 months of training, but found significant effects of exercise on HDL and triglycerides in two exercise studies that assessed outcomes at 12 months.<sup>144</sup> Two other meta-analyses with fewer studies generally found non-significant trends,<sup>134, 140</sup> though one reported a significant effect of exercise on triglycerides for both aerobic (WMD=-0.03 mmol/L; 95% CI: -0.48 to -0.11) and combined training (WMD=-0.03 mmol/L; 95% CI: -0.57 to -0.02).<sup>134</sup> It is plausible that smaller meta-analyses will not reliably detect a small effect of physical activity on lipids when the size of the effect depends upon the duration of exercise programs included in the analysis.

### **Effects of Tai Chi, Qigong, and Yoga on Risk Factors for Progression**

**Tai Chi.** Evidence was insufficient to determine the effect of tai chi exercise on risk factors for progression. Three meta-analyses, including a total of five RCTs<sup>128, 139, 161</sup> were found. One reported a significant effect of tai chi on HbA1C (WMD=-0.75 percent; 95% CI: -1.15% to -0.35%) but the analysis included only two comparisons.<sup>139</sup> The other two reviews reported non-significant effects of MD=-1.58 percent (95% CI: -3.83% to 0.67%)<sup>128</sup> and MD=-0.19 percent (95% CI: -0.41% to 0.03%).<sup>161</sup> The mean differences varied considerably among the reviews (-1.58%, -0.75%, and -0.19%), with one analysis including a study with an exercise control group.<sup>161</sup> The meta-analysis of the effects of tai chi on lipids had only two or three comparisons per lipid outcome, and at least one of the studies in the analysis had an exercise control group.<sup>161</sup> No meta-analyses examined the effects of tai chi on blood pressure or BMI.

**Qigong.** Evidence was insufficient to determine the effect of qigong exercise on risk factors for progression. One meta-analysis of 3 RCTs<sup>139</sup> reported a non-significant effect of qigong on HbA1C. No meta-analyses examined the effects of qigong on blood pressure, BMI, or lipids.

**Yoga.** Insufficient evidence was available to determine the types and forms of yoga that may affect risk factors for progression. Three meta-analyses analyzed the effect on yoga exercise on HbA1C, involving a total of 12 RCTs, with each review comprising 5 to 8 studies and 220 to 392 participants.<sup>139, 158, 160</sup> Two reviews reported a significant effect on yoga on HbA1C of WMD=-0.47 percent (95% CI: -0.87% to -0.07%)<sup>158</sup> and WMD=-0.81 percent (95% CI: -1.22 to -0.39 ).<sup>139</sup> One meta-analysis of five RCTs showed significant effects of yoga on total cholesterol (-8.50 mg/dl; 95% CI: -29.88 to -7.11) and LDL cholesterol (- 12.95 mg/dl; 95% CI: -18.84 to -7.06) but not on triglycerides.<sup>158</sup> A fourth meta-analysis did not

contribute any additional evidence, as its analyses included studies that did not compare yoga (only) to a no-exercise control group.<sup>159</sup>

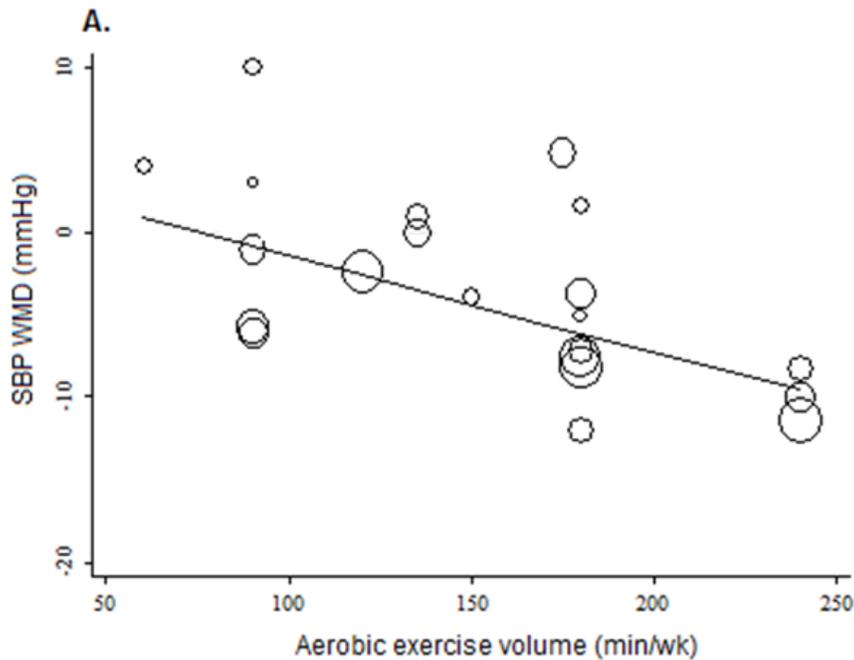
However, the types and forms of yoga studied in the RCTs of yoga varied widely, with substantial heterogeneity in two analyses of the effects of yoga on HbA1C ( $I^2=82\%$ <sup>158</sup> and  $97\%$ <sup>160</sup>). The authors of one review concluded that the appropriate exercise parameters for yoga in adults with type 2 diabetes are unknown.<sup>158</sup> The rating of insufficient evidence reflects that it appears that some forms of yoga are effective while others are not, but current information is insufficient to determine whether this is the case and to identify a subset of effective yoga exercises.

The conclusions of the secondary evidence sources (systematic reviews) were generally consistent with the above conclusions. All three reviews commented that the existing studies of tai chi, qigong, and yoga have methodologic limitations.<sup>129, 130, 162</sup>

**Dose-response:** The evidence reviewed indicates a dose-response relationship between physical activity and some risk factors for progression of type 2 diabetes.

***Aerobic activity and blood pressure.*** Moderate evidence indicates an inverse dose-response relationship of aerobic activity on blood pressure. A weighted regression found a correlation of  $r=-0.59$  ( $P<.005$ ) between systolic blood pressure and weekly exercise volume, over the range of 50 to 250 minutes per week of activity<sup>145</sup> (Figure F10-8).

**Figure F10-8. Dose-response Relationship between Aerobic Activity and Systolic Blood Pressure in Adults with Type 2 Diabetes**



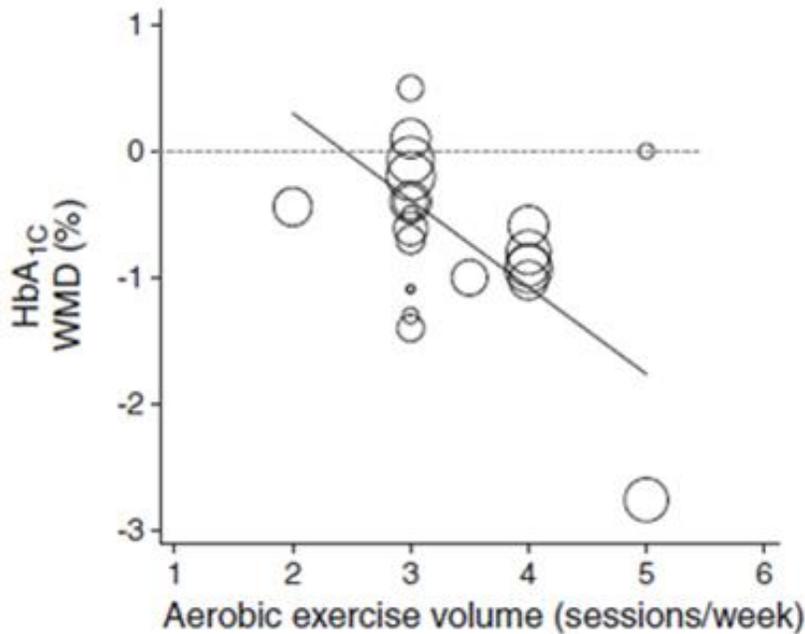
Legend: SBP=systolic blood pressure, WMD=weighted mean difference.

Note: Aerobic exercise volume is measured in minutes per week. The effect on exercise on systolic blood pressure is expressed as the weighted mean difference for each study. The size of the circles is proportional to the inverse variance of each study in the meta-analysis.

Source: Springer Sports Medicine, Association between physical activity advice only or structured exercise training with blood pressure levels in patients with type 2 diabetes: A systematic review and meta-analysis, 44, 2014, 1557-1572, Franciele R. Figueira, Daniel Umpierre, Felipe V. Cureau, Alessandra T. N. Zucatti, Mériane B. Dalzochio, Cristiane B. Leitão, Beatriz D. Schaan,<sup>145</sup> with permission of Springer.

**Aerobic activity and HbA1C.** Moderate evidence also indicates an inverse dose-response relationship between the dose of aerobic activity and HbA1C. A categorical analysis of aerobic exercise studies reported 150 or more minutes per week had a stronger effect on HbA1C (-0.89 percent; 95% CI: -1.26% to -0.51%) than less than 150 minutes per week (-0.36 percent; 95% CI: -0.50% to -0.23%).<sup>142</sup> A weighted regression showed more sessions per week of aerobic exercise were associated with a greater reduction in HbA1C<sup>143</sup> (Figure F10-9). The weighted correlation between volume and change in HbA1C was  $r=-0.64$  ( $P=.002$ ).

**Figure F10-9. Dose-response Relationship between Aerobic Activity and hemoglobin A1c (HbA1C)**



Legend: HbA<sub>1C</sub>=hemoglobin A1c, WMD=weighted mean difference.

Note: Aerobic exercise volume is measured as frequency of sessions per week. The effect on exercise on HbA<sub>1C</sub> is expressed as the weighted mean difference for each study. The size of the circles is proportional to the inverse variance of each study in the meta-analysis.

Source: Springer Diabetologia, Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis, 56, 2012, 242-251, D. Umpierre, P.A.B. Ribeiro, B.D. Schaan, and J.P. Ribeiro,<sup>143</sup> with permission of Springer.

**Muscle-strengthening activity and HbA<sub>1C</sub>.** The Subcommittee found only limited information on dose-response effects in muscle-strengthening training. One meta-regression showed 21 or more sets of resistance training per bout of exercise had greater effects on HbA<sub>1C</sub> (MD=-0.65 percent; 95% CI: -0.97 to -0.32) compared to fewer than 21 sets (MD=-0.16%; 95% CI: -0.38 to -0.05) ( $P=.03$ ).<sup>150</sup>

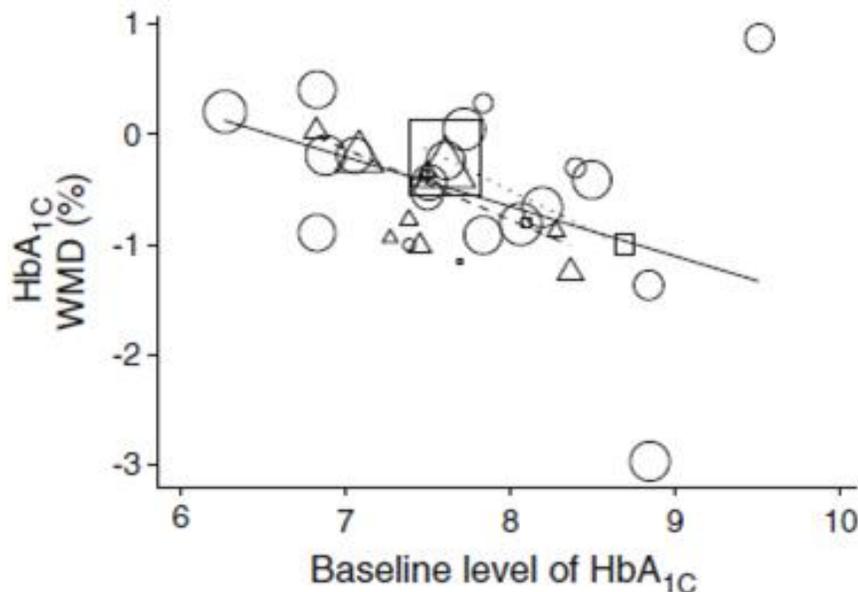
### *Evidence on Specific Factors*

The Subcommittee sought evidence on specific factors related to individual factors (age, sex, race/ethnicity, socioeconomic status, and weight status) and exposure factors (frequency, duration, intensity type, and measurement method). When evidence was located on additional individual factors (blood pressure before physical activity and HbA<sub>1C</sub> level before physical activity), the Subcommittee deemed this evidence was relevant to the intent of question 4b dealing with variation of effects according to individual characteristics.

**Blood pressure before physical activity:** In one meta-analysis, the effects of aerobic and resistance training on systolic blood pressure were significantly larger ( $P<.001$ ) in studies in hypertensive patients with type 2 diabetes compared to normotensive patients with type 2 diabetes. Hypertensive studies were defined as those where more than 70 percent of participants with diabetes had blood pressure readings of  $>140/90$ .<sup>145</sup>

**HbA1C level before physical activity:** In one meta-analysis, the effects of physical activity on HbA1C were greater in adults with type 2 diabetes who had higher levels of HbA1C before the exercise intervention began, than in adults with type 2 diabetes who had lower levels of HbA1C before exercise began.<sup>143</sup> The weighted correlation between baseline HbA1C and change in HbA1C was  $r=-0.52$  ( $P=.001$ ) (Figure F10-10).

**Figure F10-10. Association between HbA1C Before a Supervised Exercise Intervention, with Change in HbA1C After Different Types of Exercise Interventions**



Legend: HbA<sub>1c</sub>=hemoglobin A1c, WMD=weighted mean difference.

Note: The size of the symbols is proportional to the inverse variance calculated for use in a pooled analysis. The continuous line and circles are for aerobic training studies; the dotted line and squares for resistance training studies; and the dashed line and triangles for combined training.

Source: Springer Diabetologia, Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis, 56, 2012, 242-251, D. Umpierre, P.A.B. Ribeiro, B. D. Schaan, and J.P. Ribeiro,<sup>143</sup> with permission of Springer.

**Demographic characteristics and weight status:** Insufficient evidence was available in the studies reviewed to determine whether the effects of physical activity on risk factors for progression in adults of type 2 diabetes vary by age, sex, race/ethnicity, socioeconomic status, or weight status.

**Duration of physical activity programs:** Meta-analyses that analyzed the effects of physical activity programs of varying duration generally found stronger effects on HbA1C, BMI, and lipids with programs that last longer. One analysis reported the effects of free-living activity on HbA1C and BMI increased as follow-up intervals increased.<sup>133</sup> With follow-up intervals of less than 6 months, 6 months, 12 months, and 24 months, the effect of activity on HbA1C increased (-0.18%, -0.33%, -0.33%, -0.56%, respectively) and the effect of activity on BMI also increased (-0.75, -0.77, -1.32, -1.52 BMI units, respectively). One review reported that every additional week of aerobic exercise reduced HbA1C an additional 0.009 percent to 0.04 percent,<sup>135</sup> while another reported long-term studies of 6 or more months showed stronger effects of activity on HbA1C than shorter term studies of less than 6 months.<sup>148</sup> As noted above, longer exercise programs had significantly stronger effects on LDL ( $p < .03$ ).<sup>137</sup> However, one review reported the effect of duration of aerobic exercise on BMI was not significant.<sup>135</sup>

**Intensity of exercise:** Limited evidence suggests that vigorous-intensity aerobic activity is more efficient in reducing HbA1C in individuals with type 2 diabetes compared to moderate-intensity activity. Evidence on effects of intensity on HbA1C was available from a meta-analysis which summarized results of eight RCTs that directly compared effects of moderate-intensity versus high-intensity aerobic activity (either continuous high-intensity or high-intensity interval training).<sup>147</sup> Six of these studies were relevant, as they enrolled adults and matched on volume of aerobic activity. The review reported a stronger effect of vigorous-intensity aerobic activity on HbA1C (WMD=-0.22%; 95% CI: -0.38 to -0.06) across all eight of the trials, which would be similar to the effect in the six relevant trials, as these trials had a total weight of 94.2 percent in the analysis. Although a meta-regression reported no effect of aerobic or resistance training intensity on HbA1C,<sup>143</sup> evidence from RCTs directly comparing effects of different intensities was regarded as preferable and stronger evidence.

**Other characteristics:** Insufficient evidence was available in the reviews located by the search strategy to determine the effects of frequency, bout duration, and method of measuring physical activity on risk factors for progression in adults with type 2 diabetes.

***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**

The Metabolic Health chapter of the *Physical Activity Guidelines Advisory Committee Report, 2008*, which considered the effects of physical activity on diabetes, had a broader scope than this chapter. For example, the chapter addressed both therapeutic and preventive effects of physical activity in individuals with type 1 and type 2 diabetes.<sup>4</sup> The report regarded the cardiovascular health benefits of physical activity as reducing macrovascular risks and regarded the role of physical activity in preventing neuropathy, nephropathy, and retinopathy as reducing micro-vascular risks.<sup>4</sup>

This chapter adds to the conclusions of the 2008 evidence review in three important ways through its focus on the preventive effects of physical activity in adults with type 2 diabetes. First, the 2008 Scientific Report concluded that strong data supported the benefits of physical activity for CVD protection in type 2 diabetes,<sup>4</sup> but lacked a quantitative summary estimate of the effect of physical activity on CVD mortality. Data now exist to quantify the effect of physical activity (mainly aerobic leisure-time physical activity) on risk of CVD mortality—a 30 to 40 percent reduction in risk. Further, moderate evidence indicates a dose-response effect.

Second, strong evidence now demonstrates that aerobic, muscle-strengthening, and combined activity reduce risk factors for progression of type 2 diabetes: HbA1C, blood pressure, BMI, and lipids. Although the 2008 Scientific Report commented on the effects of physical activity on these risk factors, the only evidence grade stated in that report’s Integration chapter was limited evidence for a beneficial effect of physical activity on HbA1C.<sup>4</sup> The evidence available in 2008 on benefits of muscle-strengthening activity was limited, and the report stated resistance training has “shown promise” of beneficial effects in people with type 2 diabetes.<sup>4</sup>

Third, the current findings suggest that for two risk factors for progression—HbA1C and blood pressure—those at greatest risk experience the greatest benefit from physical activity. Further and not surprisingly, evidence is growing that the beneficial effects of physical activity on three risk factors—BMI, HbA1C, and lipids—become larger as adults with type 2 diabetes participate in physical activity over longer periods of time.

## **Public Health Impact**

The public health impact of these findings is large. Type 2 diabetes is prevalent in the population, and the leading cause of death in people with type 2 diabetes is CVD. Physical activity is associated with a 30 to 40 percent reduction in risk of CVD mortality.

Small-to-moderate size beneficial effects of physical activity on HbA1C, blood pressure, BMI, and lipids are consistently reported by randomized trials. Essentially, this finding represents a triple benefit of physical activity in type 2 diabetes: a primary prevention benefit (co-morbidities) as these are risk factors for chronic conditions, a secondary prevention benefit as these are risk factors for progression of type 2 diabetes, and a therapeutic benefit as these are indicators of treatment effectiveness. Importantly, the effects of physical activity on HbA1C and blood pressure appear to be largest in adults with highest levels of risk. Also, the effects of physical activity on some risk factors (BMI, lipids, HbA1C) increase with more months of exercise, and thus may be underestimated by short-term randomized trials.

Overall, the findings emphasize the importance of physical activity in people with type 2 diabetes. There are two main types of physical activity that produced benefit—aerobic and muscle-strengthening—the same two types of activities emphasized in public health guidelines. The volume of activity required to obtain benefits is similar to that in current public health guidelines.

**Question 5. In people with multiple sclerosis, what is the relationship between physical activity and: 1) risk of co-morbid conditions, 2) physical function, and 3) health-related quality of life?**

**Sources of evidence:** Systematic reviews, meta-analyses

**Conclusion Statements**

Risk of Co-morbid Conditions

Insufficient evidence is available to determine the relationship between physical activity and risk of co-morbid conditions in adults with multiple sclerosis. **PAGAC Grade: Not Assignable.**

Physical Function

Strong evidence demonstrates that physical activity—particularly aerobic and muscle-strengthening activities—improves physical function, including walking speed and endurance, in adults with multiple sclerosis. **PAGAC Grade: Strong.**

Health-related Quality of Life

Limited evidence suggests that physical activity improves quality of life, including symptoms of fatigue and depressive symptoms, in adults with multiple sclerosis. **PAGAC grade: Limited.**

## Review of the Evidence

Multiple sclerosis (MS) is a neurological disease involving intermittent episodes of focal inflammation that damage the central nervous system. The frequency and neurological location of these immune-mediated, inflammatory episodes vary among affected individuals, resulting in variation in disease progression over time and a heterogeneous mixture of physical and cognitive impairments among people with MS. Multiple sclerosis is the most prevalent chronic disabling neurological disease among U.S. adults,<sup>163</sup> affecting approximately 400,000 individuals.<sup>164</sup>

In considering the importance of preventive effects of physical activity in MS, several issues raised in recent reviews are relevant to this evidence review. First, more than 80 percent of people with the disease live with it for more than 35 years,<sup>165</sup> so physical activity has the potential to provide long-term benefits. Second, in the past, people with MS were advised not to exercise due to concern that exercise would worsen fatigue or symptoms.<sup>165</sup> Because of growing evidence of its benefits, regular physical activity is now generally recommended for people with MS. People with more severe MS may require adapted exercise training, such as body-weight support treadmill training,<sup>166</sup> but people with mild-to-moderate MS can commonly participate in types of physical activity recommended by public health guidelines, such as walking and muscle-strengthening activity.

Third, effects of physical activity on fatigue and depressive symptoms are important to understand, as these are common symptoms in people with MS<sup>165, 167</sup> and they impair HRQoL.<sup>168</sup> About 80 percent of people with multiple sclerosis experience fatigue<sup>169</sup> and about one-fourth have depression.<sup>170</sup>

Finally, the effects of physical activity on physical function are of importance, as impairments in physical function and mobility are also common.<sup>163</sup> Of particular importance are impairments in walking, as impaired walking is common and life-altering and level of impairment in walking can be used to track disease progression over time.<sup>171</sup>

The Subcommittee considered evidence contained in 16 reviews, which comprised both systematic reviews and meta-analyses. All studies included in the reviews were experimental studies (no cohort studies were included). The Subcommittee focused on studies of physical activity interventions with a no-exercise control group. Studies of formal rehabilitation programs, adapted exercise training, and uncontrolled studies were not included as sources of evidence. All reviews were published between 2011 and 2017 inclusive. Some reviews addressed the effects of specific types of physical activity, including aquatic exercise,<sup>172, 173</sup> yoga,<sup>174</sup> tai chi,<sup>175, 176</sup> and muscle strengthening activity.<sup>177</sup> Most reviews

summarized effects across a variety of activity types, such as walking, muscle-strengthening activity, video game activity, and balance training.<sup>163, 166, 167, 171, 178-183</sup>

Reviews commonly reported a clinical measure of severity of multiple sclerosis, called the Expanded Disability Status Scale (EDDS).<sup>184</sup> The vast majority of existing trials have enrolled people with mild-to-moderate multiple sclerosis, as indicated by an EDDS score of less than 6.5. Only one review focused on people with severe disability,<sup>166</sup> and this review located only one relevant study (i.e., a physical activity intervention with a no-exercise control group).

In considering the evidence, the Subcommittee noted that trials in individuals with multiple sclerosis often have small sample sizes and/or fewer than 10 weeks of exercise. For example, in one of the earlier meta-analyses published in 2012, five of seven exercise trials had an intervention group of fewer than 20 participants.<sup>182</sup> Such trials potentially have low statistical power. Thus, the Subcommittee regarded larger meta-analyses as the primary source of evidence, as these reviews quantify effects and increase statistical power.

Unlike several other questions in this chapter, the review of multiple sclerosis did not focus on effects of physical activity on the outcome of progression. However, the Subcommittee notes one review concluded that some evidence supports the possibility of a disease-modifying effect of exercise on multiple sclerosis.<sup>165</sup>

### *Evidence on the Overall Relationship*

#### Risk of Co-morbid Conditions

The Subcommittee was unable to find sufficient evidence to determine the relationship between physical activity and risk of co-morbid conditions in people with MS. The search did not locate any systematic reviews or meta-analyses that addressed risk of co-morbid conditions, including the co-morbidity of major depressive disorder. Although some trials measured depressive symptoms in all participants, no review addressed the effect of physical activity on the percent of participants with diagnosed depressive illness.

#### Physical Function

Strong evidence demonstrated that physical activity improves physical function in adults with MS. The evidence was strongest for the programs that included moderate-to-vigorous aerobic and/or muscle-strengthening activity, sometimes combined with balance training. A meta-analysis that included 13

RCTs included 5 relevant analyses.<sup>178</sup> First, this review reported that exercise improved walk time in the 10-meter walk test—a measure of gait speed (MD=-1.76 seconds; 95% CI: -2.47 to -1.08).<sup>178</sup> This analysis included 8 comparisons and 234 total participants, and 7 of the 8 interventions tested 4 to 12 weeks of aerobic, resistance, and/or balance training. In the second analysis, the review reported exercise improved walking endurance in the 6-minute walk test (MD=36.46 meters; 95% CI: 15.14-57.79). This analysis included four comparisons and 191 total participants, and all studies tested 12 weeks of aerobic, resistance, and/or balance training. Only one study was included in both of these analyses. In the third analysis, the effect of exercise on 2-minute walk distance involving five comparisons was also significant (MD=12.51 meters; 95% CI: 4.79-20.23).<sup>178</sup> In the fourth analysis, a trend was reported for an exercise effect on the Timed Up and Go test in an analysis including four comparisons (MD=-1.05 seconds; 95% CI: -2.19 to 0.09,  $P=.07$ ). However, the fifth analysis—of the timed 25-foot walk test—found non-significant improvement.

Systematic reviews and another meta-analysis also found some evidence that physical activity improves physical function in people with multiple sclerosis.<sup>163, 171, 177, 183</sup> In some cases, the positive effects were noted for outcomes other than walking, such as balance,<sup>163</sup> and composite measures of physical function.<sup>177</sup> However, these reviews all included fewer RCTs with measures of walking ability than the above meta-analysis (which included 13 trials).<sup>178</sup>

Important supporting evidence that physical activity improves function comes from evidence that physical activity improves measures of physical fitness in adults with MS. Although the Subcommittee did not emphasize reviews of effects of physical activity on fitness, this review of fitness was deemed important in this case because MS has the potential to impair the physiologic effects of exercise. An effect of exercise on physical function is not plausible if exercise has no effect on fitness. It is expected that in individuals with MS, improvements in aerobic capacity and muscular endurance will translate into improvements in walking.<sup>171</sup> For example, one study reported a correlation of  $r=0.62$  between peak aerobic capacity and 6-minute walk distance.<sup>185</sup>

Reviews of the effects of physical activity on fitness consistently reported physical activity improves fitness in people with MS. A meta-analysis that included 20 RCTs reported a small significant effect of exercise on muscular fitness (ES=0.27; 95% CI: 0.17-0.38) and moderate effect on cardiorespiratory fitness (ES=0.47; 95% CI: 0.30-0.65).<sup>179</sup> A meta-analysis of 10 comparisons from 6 studies found strength training increased muscle strength in people with MS (ES=0.31; 95% CI=0.15 to 0.48).<sup>177</sup> A systematic

review concluded that strong evidence shows that moderate-intensity exercise increases aerobic capacity and muscular strength in people with MS.<sup>171</sup> Fitness benefits may occur even in severe MS. In a review of effects of exercise training in adults with EDDS score of at least 6.5, a small controlled trial of aerobic exercise reported that exercise improved peak aerobic capacity.<sup>166</sup>

Insufficient evidence was available to determine whether aquatic exercise improves physical function in people with MS. One systematic review of three trials reported significant positive effects of aquatic exercise on physical function.<sup>172</sup> However, these three trials were described as non-randomized trials and a total of only 36 participants were allocated to aquatic exercise in these trials. A more recent systematic review located three RCTs and three non-randomized controlled trials of aquatic exercise.<sup>173</sup> However, this review did not specify how outcomes in these six trials were measured, making it difficult to determine which trial included tests of physical function. It appeared that only one trial found a significant beneficial effect of exercise on a physical function outcome (walking endurance).

Evidence that yoga or tai chi improves physical function in people with multiple sclerosis also was insufficient. A meta-analysis of effects of yoga on mobility located only two trials with a mobility outcome, and the summary effect of yoga was not significant.<sup>174</sup> One systematic review of tai chi located four trials with a no-exercise control group, with significant between group differences in tests of physical function reported for only one non-randomized trial.<sup>176</sup> Another systematic review of tai chi located two RCTs and five non-randomized controlled trials. However, study quality was rated as low in five of the seven trials, and between-group comparisons on effects of exercise on function were not reported for the remaining two higher quality trials.<sup>175</sup>

### Health-related Quality of Life

Limited evidence suggests that physical activity improves HRQoL in people with MS. The evidence focused on three measures of quality of life: overall HRQoL, depressive symptoms, and fatigue symptoms.

**Overall HRQoL:** One meta-analysis of 13 RCTs with 535 total participants reported significant effects of physical activity on quality of life questionnaires, including the SF-36 and the Multiple Sclerosis Quality of Life (MSQOL).<sup>180</sup> The summary effect of physical activity on measures of overall HRQoL was standardized mean difference (SMD)=0.85 (95% CI: 0.51-1.18). However, the analyses combined diverse physical activity interventions (aquatic, yoga, stretching, treadmill, aerobic, resistance, and combined), with the most common intervention being aquatic exercise. The trials' study populations had limited

diversity in that 90 percent of participants were women who (apparently) all lived in Iran. One meta-analysis of effects of yoga reported a non-significant effect of yoga on measures of HRQoL (5 comparisons in the analysis).<sup>174</sup> The quantitative results of a meta-analysis were not used as source of evidence because its analysis combined effects of physical activity interventions with effects of rehabilitation interventions.<sup>182</sup> However, results of individual exercise studies were reviewed and, consistent with an effect of physical activity on HRQoL, the five individual studies that reported the largest positive effects on HRQoL were all exercise interventions. Also, one small controlled trial of aerobic exercise in adults with severe disability reported a benefit of exercise on HRQoL.<sup>166</sup>

**Depressive symptoms:** The strongest evidence that physical activity improves HRQoL was for the effect of physical activity on depressive symptoms, though the size of the effect was small. Two overlapping meta-analyses examined the effects of physical activity on depressive symptoms, one with 15 RCTs and a total of 591 participants,<sup>167</sup> and one with 13 RCTs and a total of 477 participants.<sup>181</sup> Twelve studies were included in both reviews. The interventions in most of the studies were aerobic training, muscle-strengthening activity, or both. Both reviews reported a small, significant effect of physical activity on depressive symptoms of Hedge's  $g=-0.37$  (95% CI: -0.56 to -0.17) and (when improvement was scored as a positive number) Hedge's  $g=0.36$  (95% CI: 0.18-0.54).<sup>181</sup> A meta-analysis of yoga interventions reported a significant effect of yoga on mood (SMD=-0.55; 95% CI: -0.96 to -0.130), but the analysis included only three studies.<sup>174</sup>

**Fatigue:** One meta-analysis reported a small but significant effect of yoga on measures of fatigue (SMD=-0.52; 95% CI: -1.02 to -0.02; four comparisons).<sup>174</sup> A systematic review located 30 studies of the effects of exercise on fatigue and concluded that the findings from some positive, good quality studies among them suggest that the evidence was promising.<sup>171</sup> A meta-analysis of strength training reported effects on fatigue were assessed by three trials, and all three reported improvements in fatigue.<sup>177</sup> A systematic review noted some high-quality training studies report positive effects on measures of fatigue.<sup>183</sup>

In terms of types of physical activity that improve quality of life in people with MS, the meta-analyses which focused on depressive symptoms indicate that both aerobic and muscle-strengthening activities have benefits.<sup>167, 181</sup> The evidence from a meta-analysis that yoga improved mood and fatigue (summarized above) was based upon only a few studies in each analysis. Evidence for effects of aquatic activity is also limited.

Insufficient evidence was available on the effects of tai chi on measures of HRQoL. One systematic review of tai chi reported a between-group difference in quality of life measures in only one non-randomized controlled trial.<sup>176</sup> As noted in the section on physical function, one systematic review of tai chi included primarily low-quality trials.<sup>175</sup>

***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**

The 2008 Scientific Report reviewed the effects of physical activity in people with MS on the outcomes of cardiorespiratory fitness, muscle strength, mobility (walking speed and distance), and quality of life. For each outcome, only two to four RCTs were located.<sup>4</sup> The evidence was rated as moderate to strong for effects of physical activity on cardiorespiratory fitness, walking speed, and walking distance. The evidence was rated as strong for muscle strength, and very limited for HRQoL. The report did not provide summary measures that quantified the size of the benefits of physical activity on these outcomes.

In comparison, the evidence review and conclusions in this report are based upon a much larger number of RCTs, and meta-analyses are available that quantify effects of physical activity. Strong evidence now exists for a small-to-moderate size effect of physical activity on physical function, as mainly assessed by effects on walking speed and endurance. Systematic reviews provide some evidence that the effects of physical activity are broader than just effects on mobility. For example, it may also improve measures of balance. Although the Subcommittee did not formally rate the evidence of fitness effects, a systematic review done to inform guideline development rated the evidence as strong.<sup>171</sup> A meta-analysis that included 20 RCTs quantified effects of (typically short-term) training studies on fitness as small to moderate. A growing body of evidence is now showing that physical activity improves HRQoL in people with MS, though the evidence for overall quality of life is limited. The Subcommittee did not rate the evidence separately for effects of physical activity on depressive symptoms, and mood is only one component of HRQoL. But clear evidence shows that physical activity has a small beneficial effect on depressive symptoms, as determined by meta-analyses of at least 13 RCTs.

Consistent with the 2008 Scientific Report,<sup>4</sup> evidence is strongest for beneficial effects of conventional aerobic and muscle-strengthening activity. However, data are emerging that other forms of physical activity may have benefits in individuals with MS, particularly on quality of life. This report clarifies that

evidence of benefit is limited to people with mild-to-moderate multiple sclerosis. The 2008 Scientific Report noted it did not locate any evidence “to support the notion that exercise imposes a higher risk of exacerbation or harm in people with Multiple Sclerosis.”<sup>4</sup> Although the 2018 Scientific Report did not have a question addressing adverse events, the included systematic reviews and meta-analyses provided no findings that were inconsistent with the 2008 conclusion.

### **Public Health Impact**

The review supports the importance of promoting physical activity in people with MS. Indeed, people with MS are less physically active than non-disability age-matched populations.<sup>186</sup> The main finding was that physical activity improves physical function in adults with MS. Although meta-analyses summarize effects of physical activity as small to moderate, the duration of exercise in most trials is 12 weeks or less. Potentially, regular physical activity over long periods of time has moderate-to-large benefits. Indeed, a stronger effect of physical activity on walking speed was reported in a meta-analysis when the analysis was limited to studies of at least 12 weeks duration.<sup>178</sup> Although effects on gait speed are modest, effects that may seem small (e.g., an improvement of 0.1 meters per second) are associated with substantial reductions in risk of all-cause mortality in the general population of older adults.<sup>187</sup> Further, walking speed is a key measure of level of disability in people with MS.

The meta-analyses of effects of activity on depressive symptoms indicate that physical activity is a modestly beneficial non-pharmacologic approach to reducing symptoms of depression generally in people with MS. As noted above, depression is common in adults with MS.

### **Question 6. In people with spinal cord injury, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?**

**Sources of evidence:** Systematic reviews, meta-analyses

#### **Conclusion Statements**

##### Risk of Co-morbid Conditions

Limited evidence suggests that physical activity reduces shoulder pain and improves vascular function in paralyzed limbs in individuals with spinal cord injury. **PAGAC Grade: Limited.**

##### Physical Function

Moderate evidence indicates that physical activity improves walking function, muscular strength, and upper extremity function for persons with spinal cord injury. **PAGAC Grade: Moderate.**

### Health-related Quality of Life

Limited evidence suggests physical activity improves health-related quality of life in individuals with spinal cord injury. **PAGAC Grade: Limited.**

### **Review of the Evidence**

The effects of a traumatic spinal cord injury (SCI) on individuals and their families and friends are immediate and enormous.<sup>188</sup> Upon sustaining a SCI, individuals who were previously healthy and independent must suddenly cope with effects of partial or complete paralysis on body movement, as well as cope with partial or complete loss of control over bowel, bladder, and sexual function. SCIs can lead to negative effects on emotions, relationships with family and friends, and on occupational status. In the United States, about 12,000 new cases of SCI occur each year, and about 260,000 individuals are living with a spinal cord injury.<sup>189</sup>

In individuals affected by SCI, prevention of co-morbidities and mitigating effects of SCI on physical function and HRQoL are of great importance. Addressing the effects of physical activity on risk of co-morbidities, physical function, and HRQoL in individuals with SCI is thus important. A review of the effects of physical activity in individuals affected by SCI necessarily deals with different types of physical activity than are common in the general population. Because SCI restricts physical activity behaviors, the types of activity of interest in SCI include arm ergometry, wheelchair-based exercise, underwater treadmills, and adapted forms of physical activity (e.g., adaptations that partially support body weight).

In terms of preventing co-morbidity, measures of improvement in cardiovascular status and CVD risk due to physical activity assume more than the usual importance. With loss of autonomic control due to SCI, the response to physical activity by blood vessels in the areas affected by the injury may not be normal. An impaired cardiovascular response to activity can limit exercise capacity, accelerating development of CVD.<sup>190</sup> Individuals with SCI are at two to four times higher risk of CVD than those without SCI.<sup>191</sup>

In terms of understanding effects of physical activity on physical function, the effects are obviously influenced by the location and severity of the injury. The severity of the injury is commonly described

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using the American Spinal Injury Association’s Standard Neurological Classification of Spinal Cord Injury (ASIA) (Table F10-2).

**Table F10-2. American Spinal Injury Association Impairment and Motor Function Scales**

<b>Impairment Scale</b>	
Group A	Complete: No motor or sensory function is preserved in the sacral segments S4-S5.
Group B	Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segment S4-S5.
Group C	Incomplete: Motor function is preserved below the neurologic level and more than half of key muscles below the neurologic level have a muscle grade <3 (less than full range of motion against gravity).
Group D	Incomplete: Motor function is preserved below the neurologic level and at least half of key muscles below the neurologic level have a muscle grade of 3 or more.
Group E	Normal: Motor and sensory function are normal.
<b>Motor Function Scale</b>	
Grade 0	Total paralysis
Grade 1	Palpable or visible contraction
Grade 2	Active movement, gravity eliminated
Grade 3	Active movement against gravity
Grade 4	Active movement against some resistance
Grade 5	Active movement against full resistance
NT	Not testable

Source: Kirshblum et al., 2011.<sup>192</sup>

In reviews of effects of physical activity located by the search strategy, several outcomes were specific to SCI. This led the Subcommittee to consider how such outcomes should be classified for the three outcomes in Question 6.

1. *Shoulder pain* is an important problem for individuals with SCI, affecting 38 to 67 percent of manual wheelchair users.<sup>193</sup> It is usually related to high workloads placed on the shoulders for transfers and wheelchair mobility in individuals with paraplegia<sup>194</sup> and weakness of shoulder muscles in individuals with quadriplegia. Shoulder pain was deemed to be a co-morbid condition—essentially a surrogate outcome for the group of shoulder conditions that occur commonly with SCI (which including overuse injuries like tendinitis).
2. *Measures of vascular function* are important indicators of CVD risk. Lacking reviews on relationships between greater physical activity and CVD events, measures of vascular function were deemed appropriate as surrogate markers of CVD risk.

3. *Wheelchair skills and propulsion*, including ability to start and stop, change directions, and maneuver through doorways, affect an individual's mobility and hence were regarded as measure of physical function.
4. *Physical fitness outcomes* were included in the review of effects on physical function. Physical fitness (aerobic capacity and muscular strength) are clear determinants of physical function in individuals with SCI. Documenting activity-related improvements in fitness outcomes was regarded as important supporting evidence for a finding of effects of physical activity on physical function.

The evidence reviewed comprised nine systematic reviews<sup>195-203</sup> and two meta-analyses.<sup>204, 205</sup> The number of studies included in each review ranged from seven to 82, with a median of 13. About half of all studies were pre-post designs, and about one-third were experimental designs with a comparison group. Other study designs included cohort and cross-sectional studies, case series and case reports, and a chart review.

### Evidence Identified on Risk of Co-morbid Conditions

Three systematic reviews<sup>196, 198, 202</sup> provided information about physical activity and the development of co-morbid conditions. One review<sup>196</sup> focused on shoulder pain and included 7 studies (3 RCTs, 4 cohort studies), with a total of 197 adult wheelchair users. Another review<sup>202</sup> assessed changes in vascular function associated with either a single acute episode of physical activity or longer term physical activity. The review included 14 studies (8 with a comparison group and 6 with only pre-post-assessments) of a single episode of activity with a total of 215 adults, and 15 studies (1 RCT, 2 case-control, 11 pre-post, and 1 case report) of habitual physical activity, with a total of 179 adults. Lack of mobility, impaired autonomic regulation of the cardiovascular system, and reduced vascular compliance place individuals with SCI at higher risk of CVD.<sup>202</sup>

### Evidence Identified on Physical Function

Six systematic reviews<sup>195, 197, 198, 200, 201, 203</sup> and two meta-analyses<sup>204, 205</sup> provided information about the relationship between physical activity and physical function in individuals with SCI.

**Cardiovascular fitness and muscular strength:** Three systematic reviews<sup>195, 198, 200</sup> provided information about measures of cardiovascular fitness and muscular strength. The review by [Bochkezanian et al](#)<sup>195</sup> included two randomized controlled studies, four pre- post studies, and one case series with a total of

149 adults. The review by [Hicks et al<sup>198</sup>](#) included 12 experimental studies with comparison groups and 70 studies with pre-post designs and a total of 1,207 participants. The review by [Li et al<sup>200</sup>](#) included four experimental studies with comparison groups, two pre-post designs, one case series, and one case report with 143 adults. The physical activity exposures in one of the reviews<sup>200</sup> was limited to aquatic activities, such as swimming or underwater treadmill walking. The physical activity exposures in the more than 80 studies included in the other two reviews<sup>195, 198</sup> were various combinations of aerobic exercise, mostly arm ergometry or wheelchair use, and muscle strengthening exercises with pulleys, bands, and free weights. Outcome measures in all three reviews included VO<sub>2</sub>max, power output, and various task-specific measures of upper body strength.

**Walking:** Four systematic reviews<sup>197, 198, 200, 203</sup> provided information about walking as an outcome. The review by [Gandhi et al<sup>197</sup>](#) included one case series and 11 case reports with a total of 43 children and adolescents of whom 40 were ages 10 to 17 years. The review by [Li et al<sup>200</sup>](#) included one pre-post study and one case report with walking outcomes with a total of 12 adults. The review by [Hicks et al<sup>198</sup>](#) included 3 studies of individuals with acute (≤12 months) and 11 studies of individuals with chronic (>12 months) SCI. The review by [Yang and Musselman<sup>203</sup>](#) included 7 experimental studies with comparison groups, 11 pre-post designs, and 2 case series. The physical activity exposures in one of the reviews<sup>200</sup> was limited to aquatic activities such as swimming or underwater treadmill walking. The exposure in the other three reviews<sup>197, 198, 203</sup> included overground walking, robotic-assisted or body weight supported treadmill training, and muscle-strengthening exercises. Change in walking ability in the four reviews<sup>197, 198, 200, 203</sup> was assessed with measures of walking speed and walking distance.

**Upper extremity function:** One systematic review<sup>201</sup> focused on upper extremity function among individuals with SCI at the cervical level. Of the 16 studies included in the review, 6 RCTs provided physical activity exposures beyond standard physical therapy. The physical activity exposures included arm ergometry, progressive resistance training, or electrical stimulation. Outcomes included tests of hand function, functional independence, and activities of daily living.

**Postural stability:** One meta-analysis<sup>205</sup> examined postural control in sitting and standing. The meta-analysis included six experimental studies with comparison groups, 11 pre-post, and 4 cohort studies. The four studies included in the meta-analyses included 153 participants. Exposures included unsupported sitting, rockerboard, tai chi, balance exercises, and task based training; outcomes included sit and reach test and the Berg Balance Scale.

### Evidence Identified on Health-related Quality of Life

Two systematic reviews<sup>195, 199</sup> provided information about physical activity and quality of life. One<sup>195</sup> included 7 studies, of which two randomized controlled trials, each with 34 total participants, examined the relationship between physical activity and quality of life. The physical activity exposure in both studies included arm ergometry, free weights, and pulleys. Both studies used the Perceived Quality of Life questionnaire and one also used a body satisfaction questionnaire. The other systematic review<sup>199</sup> included six cross-sectional studies and five experimental trials with a total of 634 adults that examined the relationship between physical activity and quality of life. In the cross-sectional studies, the physical activity practices were obtained from six different self-report instruments; in the experimental trials, the physical activity programs included swimming, treadmill, or combined aerobic and strength training.

#### *Evidence on the Overall Relationship*

### Risk of Co-morbid Conditions

**Shoulder Pain:** Evidence that shoulder strengthening and stretching reduces shoulder pain in individuals with SCI comes from a single systematic review that included 3 RCTs and 4 cohort studies with a total of 199 subjects. The exercise exposure included arm ergometry, resistive strengthening with or without electromyogram biofeedback, and stretching the muscles of the shoulder girdle. Training was three times per week and spanned 2 to 6 months. Shoulder pain was assessed with the Wheelchair Users Shoulder Pain Index (WUSPI).<sup>206</sup> All seven studies reported significantly improved (reduced) scores on the WUSPI.<sup>196</sup> Systematic use of WUSPI as a well-validated outcome measure across studies increases the consistency and strength of this relationship, with benefits consistently exceeding the 5.1 points minimal clinical detectable difference on WUSPI, indicating a significant effect size.

**Vascular Function:** A single systematic review examined the effect of both acute episodes of physical activity (14 studies, 215 total subjects) and regular episodes of physical activity (15 studies, 179 total subjects) on arterial function among individuals with SCI.<sup>202</sup> The most common exercise exposure was arm cycling for both acute and non-acute studies, but also included passive arm or leg exercise, electrical stimulation, and, for non-acute only body-weight supported treadmill training. Vascular function in paralyzed limbs was significantly improved in both groups.<sup>202</sup>

### Physical Function

**Walking Function:** Four systematic reviews examined the relationship between physical activity and parameters of walking function; all four reviews reported improved walking function associated with either task-oriented exercise<sup>197, 198, 203</sup> or aquatic treadmill or swimming exercise.<sup>200</sup> [Yang and Musselman<sup>203</sup>](#) reported increased walking speeds ranging from 0.06 to 0.77 meters per second and increased 6-minute walking distances from 24 to 357 meters. In the review by [Hicks et al,<sup>198</sup>](#) 3 of the 13 studies of individuals with acute spinal cord injury reported on walking function as an outcome; 11 of the 69 studies of individuals with chronic spinal cord injuries reported on walking function as an outcome. Quantification was not provided, but all reported general improvements in a variety of assessments of walking. Of the eight studies of aquatic exercise, two examined the effect on walking performance and both reported improvements.<sup>200</sup> [Gandhi et al<sup>197</sup>](#) reported uniform improvements in walking across all 13 studies of children and adolescents with spinal cord injury.

**Upper Extremity Function:** Most studies in the one systematic review that examined upper extremity function reported improvements in muscle strength, arm and hand function, and activities of daily living.<sup>201</sup> However, limited quantitative information was provided, and the outcomes were diverse.

**Postural Stability and Balance:** The meta-analysis<sup>205</sup> suggests that task-oriented training has negligible effect on postural stability and balance during sitting and standing. Two studies with inactive control groups and two studies with active control groups were included in meta-analyses and both comparisons had nonsignificant differences between groups.

**Cardiovascular Fitness and Muscular Strength:** The three systematic reviews all provide evidence indicating a positive relationship between greater amounts of aerobic or muscle-strengthening physical activity and higher cardiovascular or muscular fitness.<sup>195, 198, 200</sup> [Hicks et al<sup>198</sup>](#) report “clear improvements” among individuals with older (>12 months) and newer (≤12 months) SCI. Summarizing the findings reported from 30 studies of interventions of arm or wheelchair ergometry among individuals with older injuries, [Hicks et al<sup>198</sup>](#) report that “it was clear” that the exercise “produced significant improvements in aerobic capacity.” Similarly, 16 studies mostly of combined muscular strengthening and arm ergometry reported improved power output; all 11 studies of muscular strengthening and arm ergometry reported improved muscular strength, and all 9 studies of wheelchair skills and propulsion showed significant improvements.<sup>198</sup> Fewer studies of individuals with newer lesions were identified but findings were similar.<sup>198</sup> [Bochkezanian et al<sup>195</sup>](#) reported that nine of nine

within-group comparisons for aerobic fitness showed improvements associated with the exercise exposure and two of the improvements were statistically significant. Similarly, all 22 within-group comparisons for muscular strength showed improvement and 11 of them were statistically significant. Finally, three of four studies of aquatic exercise (treadmill or swimming) reported improved cardiovascular fitness; the fourth showed no superiority compared with land-based exercise but the review provided no information about whether or how much both aquatic and land-based exercise produced changes in fitness or strength.<sup>200</sup>

### Health-related Quality of Life

The two systematic reviews<sup>195, 199</sup> provide limited support for a beneficial relationship between greater participation in physically active endeavors and higher reported perceptions of quality of life.

[Bochkezanian et al<sup>195</sup>](#) included two RCTs each of which included 32 participants. Of the six comparisons in the two studies, all six showed a beneficial effect of physical activity on quality of life but only one of the six achieved statistical significance. [Kawanishi and Greguol<sup>199</sup>](#) included 11 studies, 6 cross-sectional and 5 experimental studies (4 pre-post, 1 RCT that was also one of the two studies in [Bochkezanian et al<sup>195</sup>](#)), with a total of 634 individuals.<sup>199</sup> Five of the six cross-sectional studies and four of the five experimental studies reported positive associations, but no quantification was provided. Therefore, although these two systematic reviews describe generally positive associations between greater participation in physically active endeavors and greater perceived quality of life, life-satisfaction, or functional independence irrespective of the SCI level or ASIA classification, the evidence is weak.

***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**

The 2008 Scientific Report summarized the evidence that physical activity improves physical function broadly in individuals with disabilities. The report found evidence across several types of disability that physical activity reduces pain, improves fitness, improves physical function and improves quality of life.<sup>4</sup>

In contrast, Question 6 focused on one type of disability—spinal cord injury. This report located more individual studies in individuals with SCI than were available for the 2008 Scientific Report,<sup>4</sup> allowing conclusions specific for SCI and more precise quantification of effects of physical activity. Moderate evidence now indicates that physical activity improves physical function specifically in individuals with SCI. Also specific for SCI, this report found limited evidence that physical activity opposes the elevated

risk of CVD in individuals with SCI, limited evidence that physical activity improves shoulder pain, and limited evidence for benefits of physical activity on HRQoL.

### **Public Health Impact**

This evidence review documents that benefits of physical activity in individuals with chronic conditions extend beyond common age-related chronic conditions such as osteoarthritis and type 2 diabetes. SCI has a different pathogenesis even when compared to other chronic neurological conditions, and yet evidence of limited to moderate strength indicates benefits of physical activity extend to individuals affected by SCI. Notably, these benefits appear to accrue in individuals with both recent ( $\leq 12$  months) and older ( $> 12$  months) injuries, and occur across a range of injury severity. Overall, this review is important to understanding the breadth of beneficial effects of physical activity on health. As about half of individuals with SCI are estimated to have no leisure-time physical activity,<sup>207</sup> the review emphasizes the importance of public health strategies for promoting physical activity in individuals with disabilities.

### **Question 7. In individuals with intellectual disabilities, what is the relationship between physical activity and: (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?**

**Sources of evidence:** Systematic reviews, meta-analyses

#### **Conclusion Statements**

##### Risk of Co-morbid Conditions

Insufficient evidence is available to determine the relationship of physical activity with risk of comorbid conditions in individuals with intellectual disabilities. **PAGAC Grade: Not assignable.**

##### Physical Function

Limited evidence suggests that physical activity improves physical function in children and adults with intellectual disabilities. **PAGAC Grade: Limited.**

##### Health-related Quality of Life

Insufficient evidence is available to determine the relationship of physical activity with health-related quality of life in individuals with intellectual disabilities. **PAGAC Grade: Not assignable.**

#### **Review of the Evidence**

Intellectual disability is historically defined by significant cognitive deficits, most commonly an IQ score of below 70 (two standard deviations below 100, which is the mean IQ of the general population),

significant deficits in functional skills, and reduced adaptive skills to carry out age-appropriate activities of daily life. The Diagnostic and Statistical Manual of Mental Disorders defines intellectual disabilities as neurodevelopmental disorders beginning in childhood and characterized by intellectual difficulties, as well as difficulties in adaptive functioning in conceptual, social, and practical areas of living.<sup>208</sup> When the definition of intellectual disability is based only upon IQ, the prevalence of intellectual disability has been historically 2 to 3 percent of the U.S. population. However, a prevalence of 1.37 percent in children and a prevalence of about 1 percent of the total population are more consistent with the contemporary DSM-5 definition.<sup>208-210</sup> Down syndrome, which occurs in 1 of every 700 births, is the most common genetic cause, with more than 250,000 individuals in the United States affected and prevalence rising, in part due to a major increase in lifespan to a mean of 60 years in age.<sup>211</sup> A majority of the systematic reviews and meta-analyses in this report focused either exclusively or primarily on children and/or adults with Down Syndrome.

### Risk of Co-morbid Conditions

The one systematic review available examined co-morbid conditions among individuals with intellectual disabilities.<sup>212</sup> The systematic review included 20 studies and covered a timeframe from 1980 to May 2013. The studies examined aerobic exercise and muscle-strengthening activities. Aerobic activities included running, jogging, soccer, basketball, and dancing. Studies assessed a variety of co-morbid conditions, including different types of challenging behaviors and hyperactivity.

### *Evidence on the Overall Relationship*

Only 2 of the 20 studies had a control group; 5 were case reports involving a total of 5 individuals with intellectual disability, and the remaining 13 studies included a total of 53 participants. The review showed a small significant beneficial effect consisting of a mean behavioral improvement of 30.9 percent (95% CI: 25.0-36.8) signifying a decrease in challenging behaviors based on observational ratings or questionnaires scoring aggressive/destructive, self-injurious, hyperactive, and stereotypical behaviors. However, the Subcommittee was unable to grade the relationship between physical activity and co-morbid conditions because of limitations in experimental design, with few controlled studies and small sample sizes.

### Physical Function

One meta-analysis<sup>213</sup> and two systematic reviews<sup>214, 215</sup> were available to assess the relationship between physical activity and physical function among individuals with intellectual disabilities.

The [Valentín-Gudiol et al<sup>213</sup>](#) meta-analysis of 7 studies included 175 children younger than age 6 years of age with Down syndrome, cerebral palsy, developmental delay, or at moderate risk for developmental delay. The review studied the effects of treadmill locomotor training on walking function and gross motor function, and in a subset of 30 children with Down syndrome, the age of independent walking onset.

The [Hardee and Fetters<sup>214</sup>](#) systematic review used 19 studies published up to March 2016 to assess effects in 428 children and adults ages 3 to 66 years with Down syndrome. The review examined traditional exercise programs (e.g., aerobic and/or muscle-strengthening training) and non-traditional exercise programs (e.g., bike riding, dancing, swimming, judo) on a function domain (e.g., strength and endurance) and an activity domain (e.g., gross motor activity tests) using appropriate tests by age group (<18 years and ≥18 years).

The [Bartlo and Klein<sup>215</sup>](#) systematic review examined the relationship of physical activity and physical function (walking and balance) using 11 studies over the interval 1990 to 2010 in 310 adults ages 21 to 64 years with intellectual disability.

#### *Evidence on the Overall Relationship*

In the systematic reviews,<sup>214, 215</sup> a variety of physical activity modalities were associated with small improvements in walking velocity in adults. These improvements were typically on the order of 10 to 11 percent. Measures of balance scores increased across a range of 10 percent to 25 percent. However, meta-analyses were not available to determine effects sizes due to variability in the outcome measures used and small sample sizes. In children, a variety of physical activities significantly improved some physical function measures, including walking velocity and Timed Up and Go test.<sup>214</sup> However, no meta-analyses were available to examine effect sizes due to the large variability in outcome measures and small sample sizes. Treadmill locomotor training in children resulted in a small positive effect on walking velocity (MD=0.23; 95% CI: 0.08-0.37). A subset analysis in 30 children with Down syndrome showed earlier age of independent walking onset (MD=-4.00; 95% CI: -6.96 to -1.04), improved walking skills in children with developmental delay and gross motor skills in children with cerebral palsy. Thus, limited evidence suggests that, in children and adults with intellectual disability primarily associated with Down syndrome, greater physical activity improves walking, balance, and gross motor skills. The findings and conclusions, though limited by experimental design issues, provide a promising consistency that greater

physical activity can produce significant and meaningful improvements in mobility function that are of similar magnitude to those we report for other chronic disability populations in this report.

### Health-related Quality of Life

One systematic review of 11 total studies covering a timeframe from 1990 to January 2010 examined relationships between physical activity and health outcomes, including HRQoL in adults with intellectual disabilities, primarily Down syndrome.<sup>215</sup> This study assessed the effects on balance, strength, and cardiovascular fitness of physical activity programs using different modalities, including walking, bicycle ergometer, muscle strengthening, stepping activities, elliptical training, rowing, balance activities, dancing, and plyometric activities. A second systematic review of 11 studies covering a timeframe from 1978 to 2016 examined relationships between greater physical activity and health outcomes, including HRQoL, in children and adults with Down syndrome.<sup>214</sup>

#### *Evidence on the Overall Relationship*

The systematic review in adults included one study in which aerobic training was associated with a significant 50 percent improvement in HRQoL scores and one study that resulted in a small but significant positive effect in life satisfaction.<sup>215</sup> In the systematic review including children and adults with Down syndrome, greater physical activity was associated with increased life satisfaction scale in one study, and improved participation in social and environmental activities in five of eight studies examining this outcome. Both outcomes have been related to HRQoL in this population.<sup>214</sup> However, no other significant changes in HRQoL outcomes were reported. Collectively, these findings in a small number of studies are insufficient to establish a grade for the relationship between physical activity and HRQoL for children and adults with intellectual disabilities.

***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**

The 2008 Scientific Report summarized the evidence that physical activity improves physical function broadly in individuals with disabilities.<sup>4</sup> In contrast, this question focused on one type of disability—intellectual disability. The evidence review located many more individual studies in the sources of evidence than were available for the 2008 Scientific Report,<sup>4</sup> allowing a conclusion specific for intellectual disability. Limited evidence now suggests that physical activity improves physical function specifically in individuals with intellectual disabilities. This conclusion applies to both children and adults

and generalizes to more types of physical activity than just aerobic activity. Some reviews included studies of individuals with intellectual disabilities other than Down syndrome, and provided quantitative estimates of the effects of physical activity. In particular, the finding applies to children with developmental delay, in which greater physical activity has potential to improve walking velocity and lower the age of walking onset.

### **Public Health Impact**

Individuals with intellectual disabilities represent an important and growing population in the United States. Increased prevalence is due in part to increasing longevity for many intellectual disability populations. For Down syndrome, the mean lifespan has risen from 25 in 1983 to a current mean of 60 years in age.<sup>216</sup> The profiles of disability change with aging, typically with delayed motor development in younger years, followed by increasing disability across adulthood that becomes multi-factorial due to changes resembling accelerated aging in many sensory systems, and early onset Alzheimer’s Disease.<sup>217</sup>

The emerging evidence is that greater physical activity has benefits across the lifespan, improving walking function and hastening earliest age of walking onset in children with developmental delay. In adults, a diversity of physical activity modalities is associated with improved walking and gross motor function. Such diversity in physical activity modalities brings choices and many avenues for participation, helping to overcome the many barriers that currently limit the more than 70 percent of adults with disabilities who do not engage in health and wellness programs.<sup>218</sup>

## **NEEDS FOR FUTURE RESEARCH**

This section is organized into two parts. First, five cross-cutting needs for research are discussed that integrate similar research needs relevant to more than one chronic condition (involving conditions reviewed by this chapter or chronic conditions generally). Then, research needs specific to each chronic condition are listed. Research needs within each topic area are listed in order of priority.

### **Priority Research Needs on Preventive Effects of Physical Activity in Individuals with Chronic Conditions**

For the five research priorities in this section, research designs should generally include and compare self-report and device-based measures of physical activity. All the questions in this chapter found

insufficient evidence to determine whether method of measurement of physical activity influences reported relationships between physical activity and health outcomes.

1. Conduct research on how characteristics of aerobic activity, muscle-strengthening activity, balance training, and combined activity (e.g., dose, duration, intensity, frequency, and type) influence the relationship between physical activity and health outcomes in individuals with chronic conditions.

**Rationale:** A basic element of public health recommendations in physical activity is to specify the frequency, duration, intensity, types, and amounts of physical activity that provide health benefits. Hence, it is remarkable that the reviews of this chapter provided so few data on how these characteristics of physical activity influence health effects. For example, in osteoarthritis, no reviews were located comparing the relative effects of different types of physical activity or of different amounts of physical activity. Yet this chapter has some provocative findings illustrating the importance of research in this area. For example, in type 2 diabetes, research indicated (1) muscle-strengthening activity and aerobic activity have independent effects on hemoglobin A1C (indicating the importance of combined activity), and (2) vigorous-intensity activity is more efficient in lowering hemoglobin A1C (larger effect on hemoglobin A1C for a given volume of aerobic activity) than moderate-intensity activity. The increased interest in health benefits of light-intensity activity makes it an even higher priority to conduct randomized trials comparing different intensities and types of physical activity, and to conduct long-term cohort studies that provide dose-response data. For uncommonly performed types of activity (e.g., balance training), cohort studies are not feasible, so dose-response randomized trials are needed. To some extent, such as in individuals with hypertension, studies are needed to understand how characteristics of physical activity influence acute physiologic and health effects of activity.

2. Conduct research in individuals with chronic conditions on the effects of physical activity in reducing risk of developing additional chronic conditions (co-morbidities).

**Rationale:** The introduction of this chapter explains the public health importance of preventing multiple chronic conditions. In essence, as the number of chronic conditions afflicting a person increases, generally physical function worsens, health-related quality of life decreases, and cost of medical care increases. Despite a broad search for preventive effects of physical activity on reduced risk of any co-morbid condition, this chapter could make only a few conclusions related to prevention of co-morbidity. This lack of evidence is despite higher risk of co-morbid conditions in

some chronic diseases, as illustrated by the higher risk of cardiovascular disease in individuals with spinal cord injury. Whereas the incidence of a few chronic conditions may be high enough to study in randomized controlled trials, generally prospective cohort studies are needed of long-term effects of physical activity on risk of common co-morbidities.

3. Conduct research on the secondary prevention effects of physical activity in individuals with chronic conditions, that is, research on how physical activity reduces risk of progression of the chronic condition and mitigates the effects of the chronic condition on physical function and health-related quality of life.

**Rationale:** The amount of information located on secondary prevention by the evidence reviews varied substantially by chronic condition. Except for osteoarthritis, in individuals affected by the chronic conditions of this chapter, high-quality randomized controlled trials of effects of exercise on physical function and health-related quality of life are needed, including longer term studies (e.g., 4-6 months) that have adequate statistical power. For effects of physical activity on progression, generally prospective cohort studies are needed. For example, cohort studies are needed on effects of physical activity in type 2 diabetes on risk of neuropathy, nephropathy, retinopathy, and foot disorders.

4. Conduct systematic and coordinated randomized controlled trials on the health effects of tai chi, qigong, and yoga in individuals with chronic conditions.

**Rationale:** With one exception (osteoarthritis), the evidence for health benefits of tai chi, qigong, and yoga was rated as insufficient by the evidence reviews of this chapter. Although randomized controlled trials of these forms of physical activity were located, often they were few in number, small, and/or of low methodologic quality. Although higher quality randomized controlled trials of these types of physical activity are a priority, it is important that such trials be conducted in a systematic and coordinated fashion. Currently, the types and forms of these physical activity types studied in trials vary substantially, as do reported effects. Public health guidelines need to specify details about physical activity—in this case for each exercise type, to specify the specific movements and minimal dose that are effective in improving health. Such information is not currently available, and systematic and coordinated randomized controlled trials are necessarily to provide this information.

5. Conduct research on whether or not individual characteristics influence the effects of physical activity interventions on health outcomes in individuals with chronic conditions.

**Rationale:** The evidence reviews of this chapter found little information on whether or not the effects of physical activity vary by individual characteristics, such as age, sex, race/ethnicity, body weight, socioeconomic status, and severity of the chronic condition. The importance of such information is illustrated by findings in type 2 diabetes. The evidence suggested effects of physical activity on hemoglobin A1C were larger in individuals with the highest levels of hemoglobin A1C, thus emphasizing those at higher risk of progression with more severe disease were not less likely to benefit from physical activity. From the standpoint of evidence needed for public health guidelines, this is a lower priority need for research because beneficial effects of physical activity have been demonstrated across a wide variety of populations. However, it is desirable for prevention guidelines be appropriately tailored to individuals. Thus, this topic remains a research priority.

### **Priority Research Needs on Preventive Effects of Physical Activity in Individuals with a Specific Chronic Condition**

#### **Question 1: Cancer Survivors**

6. Continue long-term follow-up of cohorts of cancer survivors, with repeated self-report and device-based measures of physical activity, to determine long-term effects of physical activity on recurrence and survival.

**Rationale:** Although survival from breast cancer is improving, the risk of mortality continues for 20 years or more, especially for women with hormone receptor positive tumors. Survival from prostate cancer tends to be long-term for most men, but for some, progression occurs in spite of optimal treatment. Furthermore, many men with prostate cancer have increased risk for cardiovascular disease, and the primary cause of death in these patients is cardiovascular disease. Therefore, the effect of physical activity on long-term all-cause mortality in prostate cancer survivors will need to be assessed. Colorectal cancer survival is increased with lower stage at diagnosis, and many individuals survive long-term. However, little is known about effects of physical activity on long-term colorectal cancer survival. Continued follow-up of large cohorts will allow for identification of individuals with less common cancers, who can then be followed to determine associations between physical activity level and survival from these other cancers.

7. Conduct randomized controlled trials and cohort studies of physical activity and cancer survival, recurrence, and second primary cancer, aimed at eliminating effects of possible confounders.

**Rationale:** Treatment type, adherence, and completion are strong predictors of cancer outcomes and can reduce physical activity levels. Fatigue from the cancer and its treatments can reflect adverse clinical processes, and can also reduce physical activity interest and ability. Therefore, randomized controlled trials to test the effect of physical activity on survival, recurrence, and second primary cancer are needed. In addition, cohort studies with appropriate adjustment for clinical sources of confounding can provide additional information, especially if randomized controlled trials are not feasible.

8. Conduct prospective cohort studies and randomized controlled trials to determine effects of physical activity on cancer survival, recurrence, and second primary cancer in understudied groups, such as survivors from diverse races, ethnicities, and socioeconomic groups; individuals with metastatic cancer; men with breast cancer; individuals with cancers other than breast, colorectal, and prostate cancer; and patients treated with cardiotoxic drugs (such as doxorubicin and trastuzumab), radiotherapy, and hormonal treatments.

**Rationale:** Few studies have investigated the effects of physical activity on cancer prognosis and survival within specific race, ethnic, or socioeconomic groups. Some of these groups have high risk for poor survival, and are also less likely to meet recommended levels of physical activity. Therefore, determining whether physical activity can improve survival and reduce recurrence and second primary cancers in specific groups is important. Patients treated with cardiotoxic drugs, radiotherapy, or hormonal therapies may have increased risk for cardiac events; it is not known whether physical activity could be cardioprotective in such patients, or whether some forms of physical activity could increase risk of cardiac events.

### **Question 2: Osteoarthritis**

9. Conduct prospective cohort and longer-term randomized controlled trials on osteoarthritis disease progression, with device-based measures used to quantify physical activity exposures and with molecular and imaging disease status biomarkers as outcomes.

**Rationale:** There is great confusion in the field on whether physical activity and exercise causes osteoarthritis in the absence of underlying injury and whether specific physical activity and exercise

exposure amounts and intensities lead to disease progression. Studies are needed to address these critical issues. Because it takes years for disease activity to result in structural, detectable radiographic changes in the joint, sophisticated imaging modalities, such as magnetic resonance imaging, and biological biomarkers of disease activity (circulating systemic or intra-articular) are required to measure the outcomes.

10. Conduct research to clarify how osteoarthritis progression is modified by baseline demographic and disease characteristics.

**Rationale:** For the outcome of disease progression induced by physical activity, some evidence suggests that baseline disease status plays a role in modifying the effect of physical activity, but this role has not yet been fully explained. In addition, although a relationship between body mass index and osteoarthritis is generally recognized, no studies have investigated through meta-analyses whether body mass index modifies the physical activity-osteoarthritis relationship.

11. Conduct direct head-to-head comparisons of the relative effectiveness of physical activity and analgesics for pain control in individuals with osteoarthritis.

**Rationale:** The current of the literature revealed that the effect sizes of pain control for exercise therapy is very similar to that of analgesics, including narcotic analgesics.<sup>54</sup> If true, this would be a critical observation with profound implications for patient care, especially as the effects of physical activity on osteoarthritis-related pain seem to be durable for up to six months following cessation of an intervention. Determining the comparative effects of physical activity and analgesics on osteoarthritis pain could contribute greatly to effective clinical management of osteoarthritis.

### **Question 3: Hypertension**

12. Conduct research in people with hypertension on the relationships among physical activity and risk of co-morbid conditions, physical function, health-related quality of life, and cardiovascular disease progression and mortality, which compares effects of physical activity in African Americans to effects in other racial/ethnic groups.

**Rationale:** Due to the disproportionate burden of hypertension among African Americans, large trials are needed that are sufficiently powered to perform stratified analyses between African Americans and other racial/ethnic groups. Gaining this information will inform public health recommendations about demographic characteristics that influence the relationship between

physical activity and blood pressure, and provide insight into the populations that will experience the greatest cardiovascular health benefits from physical activity.

13. Conduct research that discloses the standard criteria and methods that were used to determine the blood pressure status of the study sample to better isolate samples with hypertension from those with normal blood pressure and prehypertension.

**Rationale:** Limited evidence suggests the magnitude of the blood pressure response to physical activity varies by resting blood pressure level, with the greatest blood pressure reductions occurring among adults with hypertension that have the highest resting blood pressure levels. Study sample often include mixed samples of adults with hypertension, prehypertension, and normal blood pressure, and findings are frequently not reported separately by blood pressure classification. Consistent with the law of initial values, this practice underestimates the antihypertensive benefits of physical activity. Reporting findings by blood pressure classification will inform public health recommendations on the magnitude and precision of the blood pressure reductions that result from physical activity among adults with hypertension.

14. Conduct research that discloses and quantifies medication use, particularly antihypertensive medication use among samples with hypertension.

**Rationale:** Medication use is poorly reported and is a significant confounder in interpreting the clinical significance of the blood pressure response to physical activity. In addition, evidence is lacking on the interactive effects of physical activity and antihypertensive medication use, another important clinical outcome on that has insufficient evidence. Gaining this information is important to determine whether the influence of physical activity on blood pressure varies by antihypertensive medication use.

#### **Question 4: Type 2 Diabetes**

15. Conduct randomized controlled trials comparing the effects of shifting time from sedentary behavior to low-intensity aerobic activity, moderate-intensity aerobic activity, low-intensity muscle-strengthening activity, and moderate-intensity muscle-strengthening activity on indicators of risk of progression of type 2 diabetes.

**Rationale:** Evidence is growing of the benefits of reducing sedentary behavior, particularly in individuals with chronic conditions affecting metabolic health. Research is needed on whether

shifting sedentary time to light-intensity activities affects progression of type 2 diabetes. If light-intensity activities are beneficial, it is important to compare the efficiency and effectiveness of light-intensity versus moderate-intensity activity. Given the well-documented health benefits of shifting time to moderate-intensity aerobic and muscle-strengthening activities, randomized controlled trials are needed that answer questions such as: Does it require shifting, say, 2 to 3 hours from sedentary to light-intensity activity to obtain the same benefits? Or does it take more like 6 to 8 hours?

16. Conduct randomized controlled trials of fall prevention exercise in adults with type 2 diabetes who are at increased risk of falls and fall injuries.

**Rationale:** A major finding in the Older Adults chapter (see *Part F. Chapter 9. Older Adults*) is that fall prevention exercise programs can substantially reduce risk of serious fall injuries in the general aging population. However, the risk factor profile for falls in adults with type 2 diabetes may differ substantially from the profile in the general population, due to effects specific to type 2 diabetes-related on fall risk factors (e.g., neuropathy, myopathy, impaired vision, and foot disorders). The search for evidence located one small review of fall prevention programs in type 2 diabetes. Thus, RCTs are needed on effects of fall prevention exercise in individuals with type 2 diabetes at increased fall risk.

### **Question 5: Multiple Sclerosis**

17. Conduct randomized controlled trials to determine the effects of physical activity on basic and instrumental activities of daily living, participation, and community engagement for individuals with multiple sclerosis.

**Rationale:** Strong evidence now exists that greater physical activity can improve walking function, strength, and fitness for individuals with multiple sclerosis. This supports a rationale for further research to determine whether this translates into improved basic and instrumental activities of daily living, increased free-living physical activity, and improved safety in mobility.

18. Conduct longitudinal cohort studies to determine the potential for physical activity to serve as a moderator of disease progression and changes in brain health in individuals with multiple sclerosis.

**Rationale:** Systematic reviews of controlled studies find no evidence that physical activity alters disease progression, in contrast to epidemiological studies that indicate possible disease-modifying

effects.<sup>165</sup> However, these controlled studies are limited by relatively brief intervention lengths, small sample sizes, and lack of measures of brain disease activity; factors that multi-site studies of disease-modifying medications show are needed to fully explore the natural history of multiple sclerosis. This discrepancy between epidemiological and controlled studies, and bench neuroscience findings that physical activity can provide neuroprotective effects and stimulate neuroplasticity, including for brain white matter, support a rationale for further research into disease modification.

### **Question 6: Spinal Cord Injury**

19. Conduct randomized controlled trials in children and adolescents with spinal cord injury to determine effects of physical activity on psychosocial and social environmental development and participation.

**Rationale:** A knowledge gap exists regarding health benefits in this population, which differs from adults in terms of mechanisms for injury and greater potential for neuroplasticity and recovery. Future research in pediatric spinal cord injury is needed to determine age-appropriate modalities and prescriptions for physical activity to facilitate recovery of mobility, optimize functional recovery and independence in daily activities, prevent or reduce comorbid and secondary complications, and optimize psychosocial and psychological development across the formative childhood and adolescent years.

20. Conduct research in individuals with spinal cord injury to determine effects of physical activity on basic and instrumental activities of daily living, free-living physical activity, social participation and engagement, balance and risk for injurious falls and fractures.

**Rationale:** The evidence in this report that selected modes of physical activity can produce clinically significant improvements in physical function supports a rationale for randomized studies to determine whether such gains translate into improved daily function, participation, and engagement in activities in the living space and social environment. Systematic analyses of relationships between age, race/ethnicity, socioeconomic status, and weight status need to be built into all such research recommendations. Generally, randomized controlled trials are necessary to address the research need.

### Question 7: Intellectual Disabilities

21. Conduct randomized controlled trials to determine the effects of physical activity on cognitive function, neurodevelopmental profiles, instrumental activities of daily living, and adaptive functioning that are related to neuropsychological status in individuals with intellectual disabilities.

**Rationale:** Only limited evidence is available on the effects of physical activity on four important outcomes in people with intellectual disabilities: cognitive function, neurodevelopmental profiles, instrumental activities of daily living, and adaptive functioning. Randomized studies are needed to determine whether physical activity can improve cognition for individuals with intellectual disabilities across the age spectrum. Likewise, future research is needed to investigate effects of greater physical activity on neurodevelopment and adaptive functioning. In addition, research should also consider these broader outcomes in an age- and intellectual disability-specific fashion.

22. Conduct randomized controlled trials and cohort studies on effects of physical activity in individuals with a variety of etiologies for intellectual disabilities, and determine whether health effects vary by age, race/ethnicity, socioeconomic status, and weight status.

**Rationale.** As the most common genetic cause of intellectual disability in the United States, Down syndrome has received the most research attention. Major gaps exist on the potential health benefits of physical activity in most other conditions, including autism spectrum disorder and autistic traits, Fragile X syndrome, tuberous sclerosis, neurologic sequelae of toxins (e.g., alcohol, lead), maternal and fetal infections, and nutritional deficiencies (e.g., iodine, protein-calorie malnutrition), and neurological sequelae associated with prematurity. Future research is needed to address race/ethnicity, socioeconomic status, and weight status as factors that influence relationships between physical activity and health outcomes for individuals with disabilities.

## REFERENCES

1. U.S. Department of Health and Human Services. Multiple chronic conditions initiative. 2016. [https://www.hhs.gov/ash/about-ash/multiple-chronic-conditions/about-mcc/index.html#\\_edn3](https://www.hhs.gov/ash/about-ash/multiple-chronic-conditions/about-mcc/index.html#_edn3). Accessed January 4, 2018.
2. Gerteis J, Izrael D, Deitz D, et al. Multiple chronic conditions chartbook. AHRQ Publications No, Q14-0038. Rockville, MD: Agency for Healthcare Research and Quality; April 2014.
3. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29(11):2520-2526.

4. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: US Department of Health and Human Services; 2008. <https://health.gov/paguidelines/guidelines/report.aspx>. Published 2008. Accessed January 4, 2018.
5. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: cancer of any site. <https://seer.cancer.gov/statfacts/html/all.html>. Accessed January 4, 2018.
6. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: female breast cancer. <https://seer.cancer.gov/statfacts/html/breast.html>. Accessed January 4, 2018.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. Version 3.2017. [https://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp#breast](https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast). Published November 10, 2017. Accessed December 5, 2017.
8. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25(10):1901-1914. doi:10.1093/annonc/mdu042.
9. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol*. 2009;27(21):3437-3444. doi:10.1200/JCO.2008.18.9068.
10. Yao S, Kwan ML, Ergas IJ, et al. Association of serum level of vitamin D at diagnosis With breast cancer survival: a case-cohort analysis in the pathways study. *JAMA Oncol*. 2017;3(3):351-357. doi:10.1001/jamaoncol.2016.4188.
11. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol*. 2011;29(1):40-46. doi:10.1200/JCO.2009.27.3011.
12. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012;104(11):815-840. doi:10.1093/jnci/djs207.
13. Fontein DB, de Glas NA, Duijm M, et al. Age and the effect of physical activity on breast cancer survival: a systematic review. *Cancer Treat Rev*. 2013;39(8):958-965. doi:10.1016/j.ctrv.2013.03.008.
14. Friedenreich CM, Neilson HK, Farris MS, Courneya KS. Physical activity and cancer outcomes: a precision medicine approach. *Clin Cancer Res*. 2016;22(19):4766-4775.
15. Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol*. 2011;28(3):753-765. doi:10.1007/s12032-010-9536-x.
16. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies. *Acta Oncol*. 2015;54(5):635-654. doi:10.3109/0284186X.2014.998275.
17. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol*. 2014;25(7):1293-1311. doi:10.1093/annonc/mdu012.

18. World Cancer Research Fund International. Continuous update project report: systematic review on diet, nutrition, physical activity and survival and second cancers in breast cancer survivors. [www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-SLR-2014-Report.pdf](http://www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-SLR-2014-Report.pdf). Published June 2014. Accessed September 22, 2017.
19. Zhong S, Jiang T, Ma T, et al. Association between physical activity and mortality in breast cancer: a meta-analysis of cohort studies. *Eur J Epidemiol*. 2014;29(6):391-404. doi:10.1007/s10654-014-9916-1.
20. Beasley JM, Kwan ML, Chen WY, et al. Meeting the physical activity guidelines and survival after breast cancer: findings from the after breast cancer pooling project. *Breast Cancer Res Treat*. 2012;131(2):637-643. doi:10.1007/s10549-011-1770-1.
21. Nechuta S, Chen WY, Cai H, et al. A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis. *Int J Cancer*. 2016;138(9):2088-2097. doi:10.1002/ijc.29940.
22. Nelson SH, Marinac CR, Patterson RE, et al. Impact of very low physical activity, BMI, and comorbidities on mortality among breast cancer survivors. *Breast Cancer Res Treat*. 2016;155(3):551-557. doi:10.1007/s10549-016-3694-2.
23. U.S. Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans*. Washington, DC: U.S. Department of Health and Human Services; 2008.
24. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: colorectal cancer. <https://seer.cancer.gov/statfacts/html/colorect.html>. Accessed January 3, 2018.
25. American Cancer Society. Key statistics for colorectal cancer. <https://www.cancer.org/cancer/colorectal-cancer/about/key-statistics.html>. Accessed January 4, 2018.
26. Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: a systematic review. *Physiother Can*. 2010;62(1):25-34. doi:10.3138/physio.62.1.25.
27. Des Guetz G, Uzzan B, Bouillet T, et al. Impact of physical activity on cancer-specific and overall survival of patients with colorectal cancer. *Gastroenterol Res Pract*. 2013;340851. doi:10.1155/2013/340851.
28. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies. *Int J Cancer*. 2013;133(8):1905-1913. doi:10.1002/ijc.28208.
29. Otto SJ, Korfage IJ, Polinder S, et al. Association of change in physical activity and body weight with quality of life and mortality in colorectal cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2015;23(5):1237-1250. doi:10.1007/s00520-014-2480-0.
30. Wu W, Guo F, Ye J, et al. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. *Oncotarget*. 2016;7(32):52095-52103. doi:10.18632/oncotarget.10603.
31. Arem H, Pfeiffer RM, Engels EA, et al. Preand postdiagnosis physical activity, television viewing, and mortality among patients with colorectal cancer in the National Institutes of Health-AARP Diet and Health study. *J Clin Oncol*. 2015;33(2):180–188. doi:10.1200/JCO.2014.58.1355.

32. Kuiper JG, Phipps AI, Neuhouser ML, et al. Recreational physical activity, body mass index, and survival in women with colorectal cancer. *Cancer Causes Control*. 2012;23(12):1939–1948. doi:10.1007/s10552-012-0071-2.
33. Meyerhardt JA, Giovannucci EL, Holmes MD, et al. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol*. 2006;24(22):3527–3534. doi:10.1200/JCO.2006.06.0855.
34. Meyerhardt JA, Giovannucci EL, Ogino S, et al. Physical activity and male colorectal cancer survival. *Arch Intern Med*. 2009;169(22):2102–2108. doi:10.1001/archinternmed.2009.412.
35. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: prostate cancer. <https://seer.cancer.gov/statfacts/html/prost.html>. Accessed January 4, 2018.
36. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer. Version 2.2017. [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Published February 21, 2017. Accessed December 5, 2017.
37. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the Health Professionals Follow-Up study. *J Clin Oncol*. 2011;29(6):726–732. doi:10.1200/JCO.2010.31.5226.
38. Bonn SE, Sjolander A, Lagerros YT, et al. Physical activity and survival among men diagnosed with prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):57–64. doi:10.1158/1055-9965.EPI-14-0707.
39. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical activity and survival after prostate cancer. *Eur Urol*. 2016;70(4):576–585. doi:10.1016/j.eururo.2015.12.032.
40. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the Cancer of the Prostate Strategic Urologic Research Endeavor. *Cancer Res*. 2011;71(11):3889–3895. doi:10.1158/0008-5472.CAN-10-3932.
41. Lee IM, Wolin KY, Freeman SE, Sattlemair J, Sesso HD. Physical activity and survival after cancer diagnosis in men. *J Phys Act Health*. 2014;11(1):85–90. doi:10.1123/jpah.2011-0257.
42. Inoue-Choi M, Robien K, Lazovich D. Adherence to the WCRF/AICR guidelines for cancer prevention is associated with lower mortality among older female cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2013;22(5):792–802. doi:10.1158/1055-9965.EPI-13-0054.
43. Ruden E, Reardon DA, Coan AD, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. *J Clin Oncol*. 2011;29(21):2918–2923. doi:10.1200/JCO.2011.34.9852.
44. National Cancer Institute. SEER Cancer Statistics Review 1975–2012, table 12. [https://seer.cancer.gov/archive/csr/1975\\_2012/browse\\_csr.php?sectionSEL=2&pageSEL=sect\\_02\\_table\\_12.html](https://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=2&pageSEL=sect_02_table_12.html). Accessed January 4, 2018.
45. National Cancer Institute. SEER Cancer Statistics Review 1975–2012, table 9. [https://seer.cancer.gov/archive/csr/1975\\_2012/browse\\_csr.php?sectionSEL=2&pageSEL=sect\\_02\\_table\\_09.html](https://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=2&pageSEL=sect_02_table_09.html). Accessed January 4, 2018.

46. American Cancer Society. Cancer treatment and survivorship facts and figures, 2016–2017. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2016-2017.pdf>. Accessed January 4, 2018.
47. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2016;Cd005523. doi:10.1002/14651858.CD005523.pub3.
48. Beumer L, Wong J, Warden SJ, Kemp JL, Foster P, Crossley KM. Effects of exercise and manual therapy on pain associated with hip osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med*. 2016;50(8):458–463. doi:10.1136/bjsports-2015-095255.
49. Chang WD, Chen S, Lee CL, Lin HY, Lai PT. The effects of tai chi chuan on improving mind-body health for knee osteoarthritis patients: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2016;1813979. doi:10.1155/2016/1813979.
50. Escalante Y, Garcia-Hermoso A, Saavedra JM. Effects of exercise on functional aerobic capacity in lower limb osteoarthritis: a systematic review. *J Sci Med Sport*. 2011;14(3):190–198. doi:10.1016/j.jsams.2010.10.004.
51. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev*. April 2014;(4):Cd007912. doi:10.1002/14651858.CD007912.pub2.
52. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med*. 2015;49(24):1554–1557. doi:10.1136/bjsports-2015-095424.
53. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol*. 2014;66(3):622–636. doi:10.1002/art.38290.
54. Henriksen M, Hansen JB, Klokke L, Bliddal H, Christensen R. Comparable effects of exercise and analgesics for pain secondary to knee osteoarthritis: a meta-analysis of trials included in Cochrane systematic reviews. *J Comp Eff Res*. 2016;5(4):417–431. doi:10.2217/ce-2016-0007.
55. Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJ, de Bie RA. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review. *J Physiother*. 2011;57(1):11–20. doi:10.1016/S1836-9553(11)70002-9.
56. Li Y, Su Y, Chen S, et al. The effects of resistance exercise in patients with knee osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil*. 2016;30(10):947–959. doi:10.1177/0269215515610039.
57. Regnaud JP, Lefevre-Colau MM, Trinquart L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. *Cochrane Database Syst Rev*. Oct 2015;(10):Cd010203. doi:10.1002/14651858.CD010203.pub2.

58. Sampath KK, Mani R, Miyamori T, Tumilty S. The effects of manual therapy or exercise therapy or both in people with hip osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil*. 2016;30(12):1141–1155. doi:10.1177/0269215515622670.
59. Tanaka R, Ozawa J, Kito N, Moriyama H. Does exercise therapy improve the health-related quality of life of people with knee osteoarthritis? A systematic review and meta-analysis of randomized controlled trials. *J Phys Ther Sci*. 2015;27(10):3309–3314. doi:10.1589/jpts.27.3309.
60. Tanaka R, Ozawa J, Kito N, Moriyama H. Effect of the frequency and duration of land-based therapeutic exercise on pain relief for people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *J Phys Ther Sci*. 2014;26(7):969–975. doi: 10.1589/jpts.26.969.
61. Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil*. 2013;27(12):1059–1071. doi:10.1177/0269215513488898.
62. Timmins KA, Leech RD, Batt ME, Edwards KL. Running and knee osteoarthritis: a systematic review and meta-analysis. *Am J Sports Med*. 2016;45(6):1447–1457. doi: 10.1177/0363546516657531.
63. Zhang Y, Huang L, Su Y, Zhan Z, Li Y, Lai X. The effects of traditional Chinese exercise in treating knee osteoarthritis: a systematic review and meta-analysis. *PLoS One*. 2017;12(1):e0170237. doi:10.1371/journal.pone.0170237.
64. Uthman OA, van der Windt DA, Jordan JL, et al. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. *BMJ*. Sept 2013;347:f5555. doi:10.1136/bmj.f5555.
65. Quicke JG, Foster NE, Thomas MJ, Holden MA. Is long-term physical activity safe for older adults with knee pain? A systematic review. *Osteoarthritis Cartilage*. 2015;23(9):1445–1456. doi:10.1016/j.joca.2015.05.002.
66. Dore DA, Winzenberg TM, Ding C, et al. The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis*. 2013;72(7):1170–1175. doi:10.1136/annrheumdis-2012-201691.
67. Felson DT, Niu J, Yang T, et al. Physical activity, alignment and knee osteoarthritis: data from MOST and the OAI. *Osteoarthritis Cartilage*. 2013;21(6):789–795. doi:10.1016/j.joca.2013.03.001.
68. Kwee RM, Wirth W, Hafezi-Nejad N, Zikria BA, Guermazi A, Demehri S. Role of physical activity in cartilage damage progression of subjects with baseline full-thickness cartilage defects in medial tibiofemoral compartment: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage*. 2016;24(11):1898–1904. doi:10.1016/j.joca.2016.06.009.
69. Lin W, Alizai H, Joseph GB, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage*. 2013;21(10):1558–1566. doi:10.1016/j.joca.2013.06.022.
70. Oiestad BE, Quinn E, White D, et al. No association between daily walking and knee structural changes in people at risk of or with mild knee osteoarthritis. Prospective data from the Multicenter Osteoarthritis Study. *J Rheumatol*. 2015;42(9):1685–1693. doi:10.3899/jrheum.150071.

71. Cisternas MG, Murphy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG. Alternative methods for defining osteoarthritis and the impact on estimating prevalence in a U.S. population-based survey. *Arthritis Care Res (Hoboken)*. 2016;68(5):574-580. doi:10.1002/acr.22721.
72. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-1330. doi:10.1136/annrheumdis-2013-204763.
73. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(9):1145-1153. doi:10.1016/j.joca.2013.03.018.
74. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. *Arthritis Care Res (Hoboken)*. 2016;68(12):1743-1750. doi:10.1002/acr.22897.
75. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among U.S. adults, 2015-2040. *Arthritis Rheumatol*. 2016;68(7):1582-1587. doi:10.1002/art.39692.
76. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data. *Arthritis Rheum*. 2009;60(12):3546-3553. doi:10.1002/art.24984.
77. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485.
78. World Health Organization. A Global Brief on Hypertension Silent Killer Global Public Health Crisis. Geneva, Switzerland: WHO Press; 2013.
79. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
80. Staessen JA, Wang JG, Birkenhager WH. Outcome beyond blood pressure control? *Eur Heart J*. 2003;24(6):504-514.
81. Egan BM, Li J, Hutchison FN, Ferdinand KC. Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. *Circulation*. 2014;130(19):1692-1699. doi:10.1161/CIRCULATIONAHA.114.010676.
82. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. *J Hypertens*. 2012;30(7):1277-1288. doi:10.1097/HJH.0b013e3283544669.
83. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. *Hypertension*. 2011;58(5):950-958. doi:10.1161/HYPERTENSIONAHA.111.177071.
84. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2(1):e004473. doi:10.1161/JAHA.112.004473.

85. Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. *Eur J Cardiovasc Prev Rehabil*. 2007;14(1):12-17.
86. Conceição LS, Neto MG, do Amaral MA, Martins-Filho PR, Carvalho O. Effect of dance therapy on blood pressure and exercise capacity of individuals with hypertension: a systematic review and meta-analysis. *Int J Cardiol*. 2016;220:553-557. doi:10.1016/j.ijcard.2016.06.182.
87. Wen H, Wang L. Reducing effect of aerobic exercise on blood pressure of essential hypertensive patients: a meta-analysis. *Medicine (Baltimore)*. 2017;96(11):e6150. doi:10.1097/MD.00000000000006150.
88. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens*. 2006;24(2):215-233.
89. Xiong X, Wang P, Li S, Zhang Y, Li X. Effect of baduanjin exercise for hypertension: a systematic review and meta-analysis of randomized controlled trials. *Maturitas*. 2015a;80(4):370-378. doi:10.1016/j.maturitas.2015.01.002.
90. Xiong X, Wang P, Li X, Zhang Y. Qigong for hypertension: a systematic review. *Medicine (Baltimore)*. 2015b;94(1):e352. doi:10.1097/MD.0000000000000352.
91. Wang J, Feng B, Yang X, et al. Tai Chi for essential hypertension. *Evid Based Complement Alternat Med*. 2013;2013:215254. doi:10.1155/2013/215254.
92. Park SH, Han KS. Blood pressure response to meditation and yoga: a systematic review and meta-analysis. *J Altern Complement Med*. 2017;doi:10.1089/acm.2016.0234.
93. Corso LM, Macdonald HV, Johnson BT, et al. Is concurrent training efficacious antihypertensive therapy? A meta-analysis. *Med Sci Sports Exerc*. 2016;48(12):2398-2406.
94. Casonatto J, Goessler KF, Cornelissen VA, Cardoso JR, Polito MD. The blood pressure-lowering effect of a single bout of resistance exercise: a systematic review and meta-analysis of randomised controlled trials. *Eur J Prev Cardiol*. 2016;23(16):1700-1714.
95. MacDonald HV, Johnson BT, Huedo-Medina TB, et al. Dynamic resistance training as stand-alone antihypertensive lifestyle therapy: a meta-analysis. *J Am Heart Assoc*. 2016;5(10): e003231. doi:10.1161/JAHA.116.003231.
96. Carlson DJ, Dieberg G, Hess NC, Millar PJ, Smart NA. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. *Mayo Clin Proc*. 2014;89(3):327-334. doi:10.1016/j.mayocp.2013.10.030.
97. The American College of Cardiology. 2017 guideline for the prevention, detection, evaluation and management of high blood pressure in adults. *Hypertension*. Nov 2017. doi:10.1161/HYP.0000000000000065.
98. Semlitsch T, Jeitler K, Hemkens LG, et al. Increasing physical activity for the treatment of hypertension: a systematic review and meta-analysis. *Sports Med*. 2013;43(10):1009-1023. doi:10.1007/s40279-013-0065-6.

99. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies. *BMJ*. May 2009;338:b1665. doi:10.1136/bmj.b1665.
100. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA*. 2002;288(15):1882-1888.
101. Engstrom G, Hedblad B, Janzon L. Hypertensive men who exercise regularly have lower rate of cardiovascular mortality. *J Hypertens*. 1999;17(6):737-742.
102. Fan J, Wylie-Rosett J, Alderman MH. Exercise and cardiovascular outcomes by hypertensive status: NHANES I epidemiological follow-up study, 1971-1992. *Am J Hypertens*. 2005;18(6):751-758. doi:10.1016/j.amjhyper.2004.12.020.
103. Fossum E, Gleim GW, Kjeldsen SE, et al. The effect of baseline physical activity on cardiovascular outcomes and new-onset diabetes in patients treated for hypertension and left ventricular hypertrophy: the LIFE study. *J Intern Med*. 2007;262(4):439-448. doi:10.1111/j.1365-2796.2007.01808.x.
104. Hu G, Jousilahti P, Antikainen R, et al. Occupational, commuting, and leisure-time physical activity in relation to cardiovascular mortality among Finnish subjects with hypertension. *Am H Hypertens*. 2007;20(12):1242-1250. doi:10.1016/j.amjhyper.2007.07.015.
105. Paffenbarger RS Jr, Lee I. Intensity of physical activity related to incidence of hypertension and all-cause mortality: an epidemiological view. *Blood Press Monit*. 1997;2(3):115-123.
106. Vatten LJ, Nilsen TI, Holmen J. Combined effect of blood pressure and physical activity on cardiovascular mortality. *J Hypertens*. 2006;24(10):1939-1946. doi:10.1097/01.hjh.0000244941.49793.f9.
107. Wilder J. The law of initial value in neurology and psychiatry; facts and problems. *J Nerv Ment Dis*. 1957;125(1):73-86.
108. Pescatello LS, MacDonald HV, Ash GI, et al. Assessing the existing professional exercise recommendations for hypertension: A review and recommendations for future research priorities. *Mayo Clin Proc*. 2015;90(6):801-812. doi:10.1016/j.mayocp.2015.04.008.
109. Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc*. 2004;36(3):533-553.
110. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520; doi: 10.1001/jama.2013.284427.
111. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2960-2984. doi:10.1016/j.jacc.2013.11.003.
112. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. *Hypertension*. 2013;61(6):1360-1383. doi:10.1161/HYP.0b013e318293645f.

113. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. *Blood Press*. 2014;23(1):3-16. doi:10.3109/08037051.2014.868629.
114. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol*. 2014;30(5):485-501. doi:10.1016/j.cjca.2014.02.002.
115. Chiang CE, Want TD, Li YH, et al. 2010 guidelines of the Taiwan Society of Cardiology for the management of hypertension. *J Formos Med Assoc*. 2010;109(10):740-773. doi:10.1016/S0929-6646(10)60120-9.
116. Sharman JE, Stowasser M. Australian Association for Exercise and Sports science position statement on exercise and hypertension. *J Sci Med Sport*. 2009;12(2):252-257. doi:10.1016/j.jsams.2008.10.009.
117. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>. Accessed January 4, 2018.
118. Centers for Disease Control and Prevention. Diabetes quick facts. <https://www.cdc.gov/diabetes/basics/quick-facts.html>. Accessed January 4, 2018.
119. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. *Obes Rev*. 2014;15(7):578-586. doi:10.1111/obr.12173.
120. American Diabetes Association. Microvascular complications and foot care. Sec 10. In Standards of Medical Care in Diabetes—2017. *Diabetes Care*. 2017;40(suppl 1):S88-S98. doi:10.2337/dc17-er07c.
121. American Diabetes Association. Lifestyle management. Sec. 4. In Standards of Medical Care in Diabetes--2017. *Diabetes Care*. 2017;40(suppl 1):S33–S43.
122. Sluik D, Buijsse B, Muckelbauer R, et al. Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. *Arch Intern Med*. 2012;172(17):1285-1295. doi:10.1001/archinternmed.2012.3130.
123. Kodama S, Tanaka S, Heianza Y, et al. Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes: a meta-analysis. *Diabetes Care*. 2013;36(2):471-479. doi:10.2337/dc12-0783.
124. Sadarangani KP, Hamer M, Mindell JS, Coombs NA, Stamatakis E. Physical activity and risk of all-cause and cardiovascular disease mortality in diabetic adults from Great Britain: pooled analysis of 10 population-based cohorts. *Diabetes Care*. 2014;37(4):1016-1023. doi:10.2337/dc13-1816.
125. Gu Y, Dennis SM. Are falls prevention programs effective at reducing the risk factors for falls in people with type-2 diabetes mellitus and peripheral neuropathy: a systematic review with narrative synthesis. *J Diabetes Complications*. 2017;31(2):504-516. doi:10.1016/j.jdiacomp.2016.10.004.
126. Cai H, Li G, Zhang P, Xu D, Chen L. Effect of exercise on the quality of life in type 2 diabetes mellitus: a systematic review. *Qual Life Res*. 2017;26(3):515-530. doi:10.1007/s11136-016-1481-5.

127. van der Heijden MM, van Dooren FE, Pop VJ, Pouwer F. Effects of exercise training on quality of life, symptoms of depression, symptoms of anxiety and emotional well-being in type 2 diabetes mellitus: a systematic review. *Diabetologia*. 2013;56(6):1210-1225. doi:10.1007/s00125-013-2871-7.
128. Lee MS, Jun JH, Lim HJ, Lim HS. A systematic review and meta-analysis of tai chi for treating type 2 diabetes. *Maturitas*. 2015;80(1):14-23. doi:10.1016/j.maturitas.2014.09.008.
129. Lee MS, Choi TY, Lim HJ, Ernst E. Tai chi for management of type 2 diabetes mellitus: a systematic review. *Chin J Integr Med*. 2011;17(10):789-793. doi:10.1007/s11655-011-0812-1.
130. Innes KE, Selfe TK. Yoga for adults with type 2 diabetes: a systematic review of controlled trials. *J Diabetes Res*. 2016;6979370. doi:10.1155/2016/6979370.
131. Plotnikoff RC, Costigan SA, Karunamuni ND, Lubans DR. Community-based physical activity interventions for treatment of type 2 diabetes: a systematic review with meta-analysis. *Front Endocrinol (Lausanne)*. 2013;4:3. doi:10.3389/fendo.2013.00003.
132. Reid RD, Tulloch HE, Sigal RJ, et al. Effects of aerobic exercise, resistance exercise or both, on patient-reported health status and well-being in type 2 diabetes mellitus: a randomised trial. *Diabetologia*. 2010;53(4):632-640. doi:10.1007/s00125-009-1631-1.
133. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care*. 2012;35(12):2681-2689. doi:10.2337/dc11-2452.
134. Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. *Diabetes Care*. 2011;34(5):1228-1237. doi:10.2337/dc10-1881.
135. Grace A, Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2017;16(1):37. doi:10.1186/s12933-017-0518-6.
136. Hovanec N, Sawant A, Overend TJ, Petrella RJ, Vandervoort AA. Resistance training and older adults with type 2 diabetes mellitus: strength of the evidence. *J Aging Res*. 2012;284635. doi:10.1155/2012/284635.
137. Hayashino Y, Jackson JL, Fukumori N, Nakamura F, Fukuhara S. Effects of supervised exercise on lipid profiles and blood pressure control in people with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*. 2012;98(3):349-360. doi:10.1016/j.diabres.2012.10.004.
138. McGinley SK, Armstrong MJ, Boule NG, Sigal RJ. Effects of exercise training using resistance bands on glycaemic control and strength in type 2 diabetes mellitus: a meta-analysis of randomised controlled trials. *Acta Diabetol*. 2015;52(2):221-230. doi:10.1007/s00592-014-0594-y.
139. Pai LW, Li TC, Hwu YJ, Chang SC, Chen LL, Chang PY. The effectiveness of regular leisure-time physical activities on long-term glycemic control in people with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2016;113:77-85. doi:10.1016/j.diabres.2016.01.011.
140. Qiu S, Cai X, Chen X, Yang B, Sun Z. Step counter use in type 2 diabetes: a meta-analysis of randomized controlled trials. *BMC Med*. 2014;36. doi:10.1186/1741-7015-12-36.

141. Qiu S, Cai X, Schumann U, Velders M, Sun Z, Steinacker JM. Impact of walking on glycemic control and other cardiovascular risk factors in type 2 diabetes: a meta-analysis. *PLoS One*. 2014b;9(10):e109767. doi:10.1371/journal.pone.0109767.
142. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *Jama*. 2011;305(17):1790-1799. doi:10.1001/jama.2011.576.
143. Umpierre D, Ribeiro PA, Schaan BD, Ribeiro JP. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. *Diabetologia*. 2013;56(2):242-251. doi:10.1007/s00125-012-2774-z.
144. Zou Z, Cai W, Cai M, Xiao M, Wang Z. Influence of the intervention of exercise on obese type II diabetes mellitus: a meta-analysis. *Prim Care Diabetes*. 2016;10(3):186-201. doi:10.1016/j.pcd.2015.10.003.
145. Figueira FR, Umpierre D, Cureau FV, et al. Association between physical activity advice only or structured exercise training with blood pressure levels in patients with type 2 diabetes: a systematic review and meta-analysis. *Sports Med*. 2014;44(11):1557-1572. doi:10.1007/s40279-014-0226-2.
146. Huang XL, Pan JH, Chen D, Chen J, Chen F, Hu TT. Efficacy of lifestyle interventions in patients with type 2 diabetes: a systematic review and meta-analysis. *Eur J Intern Med*. 2016;27:37-47. doi:10.1016/j.ejim.2015.11.016.
147. Liubaoerjijin Y, Terada T, Fletcher K, Boule NG. Effect of aerobic exercise intensity on glycemic control in type 2 diabetes: a meta-analysis of head-to-head randomized trials. *Acta Diabetol*. 2016;53(5):769-781. doi:10.1007/s00592-016-0870-0.
148. Schwingshackl L, Missbach B, Dias S, König J, Hoffmann G. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetologia*. 2014;57(9):1789-1797. doi:10.1007/s00125-014-3303-z.
149. Yang Z, Scott CA, Mao C, Farmer AJ. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. *Sports Med*. 2014;44(4):487-499. doi:10.1007/s40279-013-0128-8.
150. Ishiguro H, Kodama S, Horikawa C, et al. In search of the ideal resistance training program to improve glycemic control and its indication for patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Sports Med*. 2016;46(1):67-77. doi:10.1007/s40279-015-0379-7.
151. Lee J, Kim D, Kim C. Resistance training for glycemic control, muscular strength, and lean body mass in old type 2 diabetic patients: a meta-analysis. *Diabetes Ther*. 2017;8(3):459-473. doi:10.1007/s13300-017-0258-3.
152. Baskerville R, Ricci-Cabello I, Roberts N, Farmer A. Impact of accelerometer and pedometer use on physical activity and glycaemic control in people with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2017;34(5):612-620. doi:10.1111/dme.13331.

153. Bhurji N, Javer J, Gasevic D, Khan NA. Improving management of type 2 diabetes in South Asian patients: a systematic review of intervention studies. *BMJ Open*. 2016;6(4):e008986. doi:10.1136/bmjopen-2015-008986.

154. Byrne H, Caulfield B, De Vito G. Effects of self-directed exercise programmes on individuals with type 2 diabetes mellitus: a systematic review evaluating their effect on HbA1c and other metabolic outcomes, physical characteristics, cardiorespiratory fitness and functional outcomes. *Sports Med*. 2017;47(4):717-733. doi:10.1007/s40279-016-0593-y.

155. Funk M, Taylor EL. Pedometer-based walking interventions for free-living adults with type 2 diabetes: a systematic review. *Curr Diabetes Rev*. 2013;9(6):462-471. doi:10.2174/15733998113096660084.

156. Rohling M, Herder C, Roden M, Stemper T, Mussig K. Effects of long-term exercise interventions on glycaemic control in type 1 and type 2 diabetes: a systematic review. *Exp Clin Endocrinol Diabetes*. 2016;124(8):487-494. doi:10.1055/s-0042-106293.

157. Sukala WR, Page R, Cheema BS. Exercise training in high-risk ethnic populations with type 2 diabetes: a systematic review of clinical trials. *Diabetes Res Clin Pract*. 2012;97(2):206-216. doi:10.1016/j.diabres.2012.02.001.

158. Cui J, Yan JH, Yan LM, Pan L, Le JJ, Guo YZ. Effects of yoga in adults with type 2 diabetes mellitus: a meta-analysis. *J Diabetes Investig*. 2017;8(2):201-209. doi:10.1111/jdi.12548.

159. Kumar V, Jagannathan A, Philip M, Thulasi A, Angadi P, Raghuram N. Role of yoga for patients with type II diabetes mellitus: a systematic review and meta-analysis. *Complement Ther Med*. 2016;25:104-112. doi:10.1016/j.ctim.2016.02.001.

160. Vizcaino M, Stover E. The effect of yoga practice on glycemic control and other health parameters in type 2 diabetes mellitus patients: a systematic review and meta-analysis. *Complement Ther Med*. 2016;28:57-66. doi:10.1016/j.ctim.2016.06.007.

161. Yan JH, Gu WJ, Pan L. Lack of evidence on tai chi-related effects in patients with type 2 diabetes mellitus: a meta-analysis. *Exp Clin Endocrinol Diabetes*. 2013;121(5):266-271. doi:10.1055/s-0033-1334932.

162. Freire MD, Alves C. Therapeutic Chinese exercises (Qigong) in the treatment of type 2 diabetes mellitus: a systematic review. *Diabetes Metab Syndr*. 2013;7(1):56-59. doi:10.1016/j.dsx.2013.02.009.

163. Sosnoff JJ, Sung J. Reducing falls and improving mobility in multiple sclerosis. *Expert Rev Neurother*. 2015;15(6):655-666. doi:10.1586/14737175.2015.1046377.

164. Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD. Multiple sclerosis prevalence in the United States commercially insured population. *Neurology*. 2016;86(11):1014-1021. doi:10.1212/WNL.0000000000002469.

165. Dalgas U, Stenager E. Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? . *Ther Adv Neurol Disord*. 2012;5(2):81-95. doi:10.1177/1756285611430719.

166. Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: a systematic review and future research directions. *Mult Scler Relat Disord*. 2017;16:31–39. doi:10.1016/j.msard.2017.06.003.
167. Dalgas U, Stenager E, Sloth M, Stenager E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. *Eur J Neurol*. 2015;22(3):443-e34. doi:10.1111/ene.12576.
168. Göksel Karatepe A, Kaya T, Günaydn R, Demirhan A, Ce P, Gedizlioğlu M. Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability. *Int J Rehabil Res*. 2011;34(4):290-298. doi:10.1097/MRR.0b013e32834ad479.
169. National Multiple Sclerosis Society. Fatigue. <https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Fatigue>. Accessed January 4, 2018.
170. Viner R, Fiest KM, Bulloch AG, et al. Point prevalence and correlates of depression in a national community sample with multiple sclerosis. *Gen Hosp Psychiatry*. 2014;36(3):352-354. doi:10.1016/j.genhosppsy.2013.12.011.
171. Latimer-Cheung AE, Pilutti AE, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013;94(9):1800–1828.e3. doi:10.1016/j.apmr.2013.04.020.
172. Methajarunon P, Eitivipart C, Diver C, Foongchomcheay A. Systematic review of published studies on aquatic exercise for balance in patients with multiple sclerosis, Parkinson's disease, and hemiplegia. *HKPJ*. 2016;35:12–20. doi:10.1016/j.hkpj.2016.03.002.
173. Corvillo I, Varela E, Armijo F, Alvarez-Badillo A, Armijo O, Maraver F. Efficacy of aquatic therapy for multiple sclerosis: a systematic review. *Eur J Phys Rehabil Med*. 2017;17. doi:10.23736/S1973-9087.
174. Cramer H, Lauche R, Azizi H, Dobos G, Langhorst J. Yoga for multiple sclerosis: a systematic review and meta-analysis. *PLoS One*. 2014;9(11):e112414. doi:10.1371/journal.pone.0112414.
175. Zou L, Wang H, Xiao Z, et al. Tai chi for health benefits in patients with multiple sclerosis: a systematic review. *PLoS One*. 2017;12(2):e0170212. doi:10.1371/journal.pone.0170212.
176. Taylor E, Taylor-Piliae RE. The effects of tai chi on physical and psychosocial function among persons with multiple sclerosis: a systematic review. *Complement Ther Med*. 2017;31:100–108. doi:10.1016/j.ctim.2017.03.001.
177. Cruickshank TM, Reyes AR, Ziman MR. A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. *Medicine (Baltimore)*. 2015;94(4):e411. doi:10.1097/MD.0000000000000411.
178. Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. *Arch Phys Med Rehabil*. 2015;96(7):1339–1348.e7. doi:10.1016/j.apmr.2015.02.011.
179. Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of exercise training on fitness in multiple sclerosis: a meta-analysis. *Arch Phys Med Rehabil*. 2016;97(9):1564–1572. doi:10.1016/j.apmr.2016.01.023.

180. Afkar A, Ashouri A, Rahmani M, Emami Sigaroudi A. Effect of exercise therapy on quality of life of patients with multiple sclerosis in Iran: a systematic review and meta-analysis. *Neurol Sci*. 2017;doi:10.1007/s10072-017-3047-x.
181. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. *J Psychosom Res*. 2014;76(6):465–471. doi:10.1016/j.jpsychores.2014.03.014.
182. Kuspinar A, Rodriguez AM, Mayo NE. The effects of clinical interventions on health-related quality of life in multiple sclerosis: a meta-analysis. *Mult Scler*. 2012;18(12):1686–1704. doi:10.1177/1352458512445201.
183. Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. *J Neurol*. 2014;261(9):1651–1661. doi:10.1007/s00415-013-7183-9.
184. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.
185. Sandroff BM, Sosnoff JJ, Motl RW. Physical fitness, walking performance, and gait in multiple sclerosis. *J Neurological Sciences*. 2013;328(1-2):70-76. doi:<http://dx.doi.org/10.1016/j.jns.2013.02.021>.
186. Kinnett-Hopkins D, Adamson B, Rougeau K, Motl RW. People with MS are less physically active than healthy controls but as active as those with other chronic diseases: an updated meta-analysis. *Mult Scler Relat Disord*. April 2017;13:38-43. doi:10.1016/j.msard.2017.01.016.
187. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, Nevitt M, Visser M, Kritchevsky S, Badinelli S, Harris T, Newman AB, Cauley J, Ferrucci L, Guralnik J. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-8.
188. Kelsey JL in Maxcy-Rosenau-Last, Public Health & Preventive Medicine [Ed. Wallace RB]. Appleton & Lange, Stamford, Connecticut, 1993. pp 1010-1011.
189. Brainandspinalcord.org. Spinal cord injury statistics. <http://www.brainandspinalcord.org/spinal-cord-injury-statistics>. Accessed January 4, 2018.
190. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil*. 2007;86(2):142-152. doi:10.1097/PHM.0b013e31802f0247.
191. Cragg JJ, Noonan VK, Krassioukov A, Borisoff JF. Cardiovascular disease and spinal cord injury: results from a national population health survey. *Neurology*. 2013;81(8):723-728. doi:10.1212/WNL.0b013e3182a1aa68.
192. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *J Spinal Cord Med*. 2011;34(6):535-546. doi:10.1179/204577211X13207446293695.
193. Jain NB, Higgins LD, Katz JN, Garshick E. Association of shoulder pain with the use of mobility devices in persons with chronic spinal cord injury. *PMR*. 2010;2(10):896-900. doi:10.1016/j.pmrj.2010.05.004.

194. Samuelsson KA, Tropp H, Gerdle B. Shoulder pain and its consequences in paraplegic spinal cord injured, wheelchair users. *Spinal Cord*. 2004;42(1):41-46. doi:10.1038/sj.sc.310-1490.
195. Bochekezanian V, Raymond J, de Oliveira CQ, Davis GM. Can combined aerobic and muscle strength training improve aerobic fitness, muscle strength, function and quality of life in people with spinal cord injury? A systematic review. *Spinal Cord*. 2015;53(6):418-431. doi:10.1038/sc.2015.48.
196. Cratsenberg KA, Deitrick CE, Harrington TK, et al. Effectiveness of exercise programs for management of shoulder pain in manual wheelchair users with spinal cord injury. *J Neurol Phys Ther*. 2015;39(4):197-203. doi:10.1097/NPT.000000000000103.
197. Gandhi P, Chan K, Verrier MC, Pakosh M, Musselman KE. Training to improve walking after pediatric spinal cord injury: a systematic review of parameters and walking outcomes. *J Neurotrauma*. 2017;34(9):1713-1725. doi:10.1089/neu.2016.4501.
198. Hicks AL, Martin Ginis KA, Pelletier CA, Ditor DS, Foulon B, Wolfe DL. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. *Spinal Cord*. 2011;49(11):1103-1127. doi:10.1038/sc.2011.62.
199. Kawanishi CY, Greguol M. Physical activity, quality of life, and functional autonomy of adults with spinal cord injuries. *Adapt Phys Activ Q*. 2013;30(4):317-337.
200. Li C, Khoo S, Adnan A. Effects of aquatic exercise on physical function and fitness among people with spinal cord injury: a systematic review. *Medicine (Baltimore)*. 2017;96(11):e6328. doi:10.1097/MD.0000000000006328.
201. Lu X, Battistuzzo CR, Zoghi M, Galea MP. Effects of training on upper limb function after cervical spinal cord injury: a systematic review. *Clin Rehabil*. 2015;29(1):3-13. doi:10.1177/0269215514536411.
202. Phillips AA, Cote AT, Warburton DE. A systematic review of exercise as a therapeutic intervention to improve arterial function in persons living with spinal cord injury. *Spinal Cord*. 2011;49(6):702-714. doi:10.1038/sc.2010.193.
203. Yang JF, Musselman KE. Training to achieve over ground walking after spinal cord injury: a review of who, what, when, and how. *J Spinal Cord Med*. 2012;35(5):293-304. doi:10.1179/2045772312Y.0000000036.
204. Mehrholz J, Harvey LA, Thomas S, Elsner B. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. *Spinal Cord*. 2017;55(8):722-729. doi:10.1038/sc.2017.31.
205. Tse CM, Chisholm AE, Lam T, Eng JJ. A systematic review of the effectiveness of task-specific rehabilitation interventions for improving independent sitting and standing function in spinal cord injury. *J Spinal Cord Med*. 2017;1-13. doi:10.1080/10790268.2017.1350340.
206. Curtis KA, Roach KE, Applegate EB, et al. Development of the Wheelchair User's Shoulder Pain Index (WUSPI). *Paraplegia*. 1995;33(5):290-293. doi:10.1038/sc.1995.65.
207. Ginis KA, Latimer AE, Arbour-Nicitopoulos KP, et al. Leisure time physical activity in a population-based sample of people with spinal cord injury part I: demographic and injury-related correlates. *Arch Phys Med Rehabil*. 2010;91(5):722-728. doi:10.1016/j.apmr.2009.12.027.

208. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
209. Van Naarden Braun K, Christensen D, Doernberg N, et al. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, metropolitan Atlanta, 1991–2010. *PLoS ONE*. 2015;10(4):e0124120. doi:10.1371/journal.pone.0124120.
210. Boat TF, Wu JT. Prevalence of intellectual disabilities. In: Boat TF, Wu JT, eds. *Mental Disorders and Disabilities Among Low-Income Children*. Washington, DC: The National Academies Press; 2015:267.
211. Presson AP, Partyka G, Jensen KM, et al. Current estimate of Down syndrome population prevalence in the United States. *J Pediatr*. 2013;163(4):1163-1168. doi:10.1016/j.jpeds.2013.06.013.
212. Ogg-Groenendaal M, Hermans H, Claessens B. A systematic review on the effect of exercise interventions on challenging behavior for people with intellectual disabilities. *Res Dev Disabil*. 2014;35(7):1507–1517. doi:10.1016/j.ridd.2014.04.003.
213. Valentín-Gudiol M, Mattern-Baxter K, Girabent-Farrés M, Bagur-Calafat C, Hadders-Algra M, Angulo-Barroso RM. Treadmill interventions in children under six years of age at risk of neuromotor delay. *Cochrane Database Syst Rev*. 2017(7):CD009242. doi:10.1002/14651858.CD009242.pub3.
214. Hardee JP, Fetters L. The effect of exercise intervention on daily life activities and social participation in individuals with Down syndrome: a systematic review. *Res Dev Disabil*. 2017;62:81–103. doi:10.1016/j.ridd.2017.01.011.
215. Bartlo P, Klein PJ. Physical activity benefits and needs in adults with intellectual disabilities: systematic review of the literature. *Am J Intellect Dev Disabil*. 2011;116(3):220–232. doi:10.1352/1944-7558-116.3.220.
216. National Association for Down Syndrome. Facts about down syndrome. [www.nads.org/resources/facts-about-down-syndrome](http://www.nads.org/resources/facts-about-down-syndrome). Accessed January 4, 2018.
217. National Down Syndrome Society. Aging and down syndrome: a health and well-being guidebook. <http://www.ndss.org/wp-content/uploads/2017/11/Aging-and-Down-Syndrome.pdf>. Accessed January 4, 2018.
218. Office of Disease Prevention and Health Promotion. 2020 topics and objectives: disability and health. <https://www.healthypeople.gov/2020/topics-objectives/topic/disability-and-health/national-snapshot>. Accessed January 4, 2018.