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Part G. Section 1: All-Cause Mortality

Introduction

This chapter examines the relation between physical activity and all-cause mortality. Two leading causes of mortality, both in the United States as well as globally, are cardiovascular disease and cancer, with both diseases estimated to be responsible for 43% of all deaths globally (1). From a biological perspective, the evidence is strongly persuasive that physical activity reduces the occurrence of these leading causes of death (discussed in the individual chapters on these diseases); thus, it is also biologically plausible for physical activity to postpone the occurrence of all-cause mortality. (Because we all die eventually, when the phrase "lower risk of all-cause mortality" is used in this chapter, it refers to lower risk during the period of follow-up in a study; i.e., postponed mortality.)

Review of the Science

Overview of Questions Addressed

This chapter addresses 5 specific questions:

1. Is there an association between physical activity and all-cause mortality? If so, what is the magnitude of this association?

2. What is the minimum amount of physical activity associated with significantly lower risk of all-cause mortality?

3. Is there a dose-response relation between physical activity and all-cause mortality?

4. What is the shape of the dose-response relation between physical activity and all-cause mortality?

5. Is the relation between physical activity and all-cause mortality independent of adiposity?

Data Sources and Process Used to Answer Questions

To provide evidence-based answers to the above questions, the All-cause Mortality subcommittee obtained data from a search of the *Physical Activity Guidelines for Americans* Scientific Database (see *Part F: Scientific Literature Search Methodology*, for a full description of the database). The Database contains studies published in 1995 and later. The

selection criteria were broad and included searching for studies of all age groups, all study designs, and all physical activity types that had the outcome of all-cause mortality. This retrieved 83 publications, of which 7 were excluded for the following reasons: 3 studies of exercise-related mortality were covered in another chapter; 2 studies of survival among cancer patients were covered in another chapter; 1 study provided essentially duplicate results on physical activity and all-cause mortality as another; and 1 study did not provide results on the specific association of physical activity with all-cause mortality. An additional 3 studies of cardiovascular or muscular fitness in relation to all-cause mortality were excluded because, although they provided important information, they did not directly inform on the amount of physical activity associated with decreased risk of premature mortality (additional discussion of studies on physical fitness and all-cause mortality is provided later in this chapter). This left 73 studies that provide the evidence based for the conclusions of this chapter. (Table G1.A1, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.)

Question 1: Is There an Association Between Physical Activity and All-Cause Mortality? If So, What Is the Magnitude of This Association?

Conclusions

The data very strongly support an inverse association between physical activity and all-cause mortality. Active individuals — both men and women — have approximately a 30% lower risk of dying during follow-up, compared with inactive individuals. This inverse association has been observed among persons residing in the United States, as well as in other countries, older persons (aged 65 years and older), and persons of different race/ethnic groups. In one study of persons with impaired mobility (unable to walk 2 km and climb 1 flight with no difficulty), physical activity also appeared to be associated with lower all-cause mortality rates.

Rationale

Description of Studies in Evidence Base

Of the 73 studies included in the evidence base (Table G1.A1), 71 were prospective cohort studies, 1 was a retrospective cohort study, and 1 was a case-control study. These studies were conducted in many countries in North America, Europe, the Middle East, Asia, and Australia. Twenty-seven studies, or 37%, were studies in the United States; the remaining 46 (63%) were conducted in other countries. The length of follow-up in the studies ranged from 10 months to 28 years, apart from the one retrospective cohort study of Finnish Olympic athletes, in which follow-up was 71 years (2). Across all studies, the median follow-up was 11.7 years.

Population Subgroups

These studies provide a large database that included 312,554 observations in men and 690,671 observations in women, with a total of 140,114 deaths. Because several studies published updated results in the same subjects, unique observations totaled 254,514 men and 576,574 women, and 113,358 deaths. Although the total number of women is larger than the total number of men, this is skewed by 3 large studies of women (3-5); actually, fewer studies included women (n=51), compared with studies that included men (n=62).

The youngest subjects included were aged 16 years (6), though most studies (44 of 73 studies, or 60%) included middle-aged subjects aged 40 years and older. A reasonable body of evidence was specific to older persons aged 65 years and older, with 15 studies including such subjects. With regard to race/ethnicity, among the US studies, most included only small proportions of persons belonging to race/ethnic minority groups. However, 3 included nationally representative samples of subjects (7-9) and another comprised 48.3% blacks (10). In addition, 2 studies specifically enrolled Hispanic-American (11) and Japanese-American men (12); 5 studies conducted in Asia enrolled Chinese and Japanese subjects (4;13-16).

Most of the studies enrolled ostensibly healthy subjects who were free of cardiovascular disease and cancer. However, several studies did select patient groups, including patients with coronary artery disease (17) or at high risk (9;18), and patients with diabetes. (7;19-22). In one study, subjects with impaired mobility were examined separately (23).

Main Findings

The available data strongly support an inverse relation between physical activity and all-cause mortality rates during follow-up, with 67 of the 73 studies reporting a significant, inverse relation for at least one group of subjects (e.g., men versus women) and/or one domain of activity (e.g., all activity, exercise activity, or commuting activity).

With regard to the strength of association, the median relative risk (RR), comparing most with least active subjects was 0.69 across all studies, indicating a 31% risk reduction with physical activity. This was similar for men (median RR = 0.71) and women (median RR = 0.67), and for studies where both sexes were analyzed together (median RR = 0.68). The magnitude of association in this evidence base, which included studies published in 1995 and later, is similar to that reported in a 2001 review that included studies published before 1995 (24).

An inverse association also existed among persons aged 65 years and older, with a median relative risk of 0.56 when comparing most with least active persons. No significant interaction was observed with race/ethnic groups in a study that included nationally representative subjects (i.e., results did not differ across race/ethnic groups) (7). Inverse associations also were noted among Puerto Rican men (11), Japanese-American men (12), and Chinese and Japanese men and women living in Asia (4;13-16). Additionally, inverse

relations between physical activity and all-cause mortality were reported among patients with coronary artery disease (17) or at high risk (9;18), and among patients with diabetes (7;19-22). One study examined subjects with and without impaired mobility separately. Among persons with impaired mobility, mortality rates also appeared lower among active than inactive persons (this was not directly tested for statistical significance) (23).

Validity of Findings

Because all of the studies in the evidence base were observational epidemiologic studies with no randomized controlled trials, the data cannot prove causality of effect. However, the totality of evidence does support a cause-and-effect relation between physical activity and lower all-cause mortality rates for the following reasons. First, as mentioned above, plausible biological mechanisms — demonstrated in randomized clinical trials — exist for physical activity to decrease the occurrence of cardiovascular disease and cancer, the leading causes of mortality worldwide.

Second, bias due to decreased physical activity from ill health (i.e., a spurious inverse relation, with ill health causing decreased physical activity, rather than physical activity causing lower mortality rates) is unlikely. Many of the studies in Table G1.A1 included only ostensibly healthy subjects and excluded persons with cardiovascular disease and cancer. Studies that did include subjects with chronic diseases typically adjusted for the presence of these conditions, and continued to observe inverse associations between physical activity and all-cause mortality rates. Several studies also allowed for a lag period (i.e., excluding initial years of follow-up) in analyses to minimize the potential bias from ill health leading to decreased physical activity (as ill persons are likely to die early in follow-up); physical activity was significantly related to lower all-cause mortality rates in these analyses. Finally, if the follow-up period is long (which was typically the case, with the median follow-up being 11.7 years), the impact of this bias will be diluted, with ill persons dying early in follow-up.

Third, bias due to systematic misclassification of physical activity is unlikely. It is true that almost all of the studies collected physical activity information using self-reports by subjects, and this is likely to be imprecise. However, because physical activity was assessed prospectively in almost all the studies, any misclassification is likely to be random (leading to dilution of results, rather than a systematic bias). Additionally, one study assessed physical activity using doubly-labeled water, considered a gold standard for measuring energy expenditure. This study did report an inverse relation between physical activity and all-cause mortality rates (10).

Fourth, bias resulting from large losses to follow-up is unlikely. Although many studies did not report follow-up rates, many of these studies used national systems to ascertain deaths (e.g., National Death Index in the United States), which tend to be complete. Of the studies that did report follow-up rates, these tended to be very high.

Finally, physically active persons tend to have other healthy habits as well, which may confound the association of physical activity with all-cause mortality rates. This is unlikely to have explained the inverse relation observed because the association persisted after controlling for several potential confounders (including age, sex, race, education, smoking, body mass index [BMI], alcohol, diet, personal and family medical history, and reproductive variables in women) listed in Table G1.A1.

Physical Fitness and All-Cause Mortality

Studies of physical fitness and all-cause mortality were not reviewed in the same detail as studies of physical activity because the former studies do not provide direct information that can be translated to public health recommendations for physical activity (e.g., How much? What intensity? What duration? What frequency?). However, physical fitness, which includes cardiorespiratory fitness, is closely related to physical activity. In particular, among most individuals and particularly in those who are sedentary, increases in physical activity result in increases in cardiorespiratory fitness. Thus, cardiorespiratory fitness is an objective and reproducible marker of recent physical activity patterns. The findings from studies of cardiorespiratory fitness mirror those from studies of physical activity in showing inverse associations with all-cause mortality (see *Part G. Section 2: Cardiorespiratory Health* for a detailed discussion of this issue). In fact, the magnitude of association is stronger for studies of cardiorespiratory fitness, which may be due in part to the higher precision of measurement, as, most of these studies use objective measurements of fitness (instead of, typically, self-reported physical activity). For example, in the Aerobics Center Longitudinal Study, the relative risks for mortality among the most fit men and women were 0.49 and 0.37, respectively, while the associations for physical activity were much weaker (25). In a recent review (26), the median relative risk for all-cause mortality, comparing most fit with least fit men in 10 studies was 0.55; for women in 6 studies, this also was 0.55. Thus, the findings from studies of physical fitness support those from studies of physical activity, with regard to an inverse relation with all-cause mortality.

Question 2: What Is the Minimum Amount of Physical Activity Associated With Significantly Lower Risk of All-Cause Mortality?

Conclusions

The studies in the evidence base have assessed different domains of physical activity (including one of more of the following: leisure-time activity, occupational activity, household activity, and commuting activity), with most assessing primarily leisure-time physical activity (LTPA), including walking. Some evidence indicates that it may be the overall **volume** of energy expended — regardless of which activities produce this energy expenditure — that is important to lower the risk of mortality. The studies also have used different measures or units, such as kilocalories per week, metabolic equivalent (MET)-hours per week, or hours per week to categorize physical activity levels in analyses. Thus, combining the findings across studies posed a challenge.

In synthesizing the data across studies and expressing their findings in a fashion that can be readily translated for public health purposes, the evidence base is clear in showing that the equivalent of at least 2 to 2.5 hours per week of moderate-intensity physical activity is sufficient to significantly decrease all-cause mortality rates (see Table G1.1, below). Several studies investigated walking specifically, and it is reasonably clear that walking 2 or more hours per week is associated with a significantly lower risk of all-cause mortality (see Table G1.2, below). Additionally, faster pace of walking, compared with slower pace, is associated with lower risk.

Table G1.1.   Minimum Amounts of Physical Activity Associated With Significantly Lower Risks of All-Cause Mortality

The data are presented according to different classifications of physical activity in the studies reviewed. Within each classification scheme, studies are ordered according to their findings regarding the minimum amount of activity observed to be associated with significantly lower risk of all-cause mortality (lowest to highest).

Studies with subjects classified by **energy expended** in physical activity:

Reference	Men	Women	Both Sexes Analyzed Together
Yu et al., 2003 (27)	23.9-2142.9 kcal/day vigorous LTPA (vs. 0-0.6 kcal/day)	–	–
Lee et al., 1995 (28)	750-1499 kcal/wk vigorous LTPA (vs. <150 kcal/wk)	–	–
Tanasescu et al., 2003 (22)	12.1-21.7 MET-hr/wk LTPA (vs. 0-5.1 MET-hr/wk); ≥16.1 MET-hr/wk walking (vs. 0-1.4)	–	–
Bucksch 2005 (29)	–	14-<33.5 kcal/kg/wk LTPA; i.e., ~910-2200 kcal/wk (65 kg woman) (vs. 0 kcal/kg/wk)	–
Fried et al., 1998 (30)	–	–	980-1890 kcal/wk LTPA (vs. ≤67.5 kcal/wk)
Lee & Paffenbarger 2000 (31)	1000-1999 kcal/wk LTPA (vs. < 1000 kcal/wk)	–	–
Janssen & Jolliffe 2006 (17)	–	–	1000-1999 kcal/wk LTPA (vs. < 500 kcal/wk)

Table G1.1. Minimum Amounts of Physical Activity Associated With Significantly Lower Risks of All-Cause Mortality (continued)

Studies with subjects classified by **energy expended** in physical activity (continued):

Reference	Men	Women	Both Sexes Analyzed Together
Lan et al., 2006 (15)	–	–	1000-1999 kcal/wk LTPA (vs. < sedentary)
Haapanen et al., 1996 (32)	>2100 kcal/wk LTPA, household activities, commuting (vs. <800 kcal/wk)	–	–
Matthews et al., 2007 (4)	–	10.0-13.6 MET-hr/day LTPA, work, household, walking/ cycling commute (vs. ≤9.9 MET-hr/day)	–
Manini et al., 2006 (10)	–	–	>770 kcal/day all activities (doubly-labeled water) (vs. <521 kcal/day)
Carlsson et al., 2006 (33)	–	>50 MET-hr/day LTPA, work, household, walking/cycling (vs. <35 MET-hr/day)	–

Studies with subjects classified by **duration** of physical activity:

Reference	Men	Women	Both Sexes Analyzed Together
Bijnen et al.,1999 (34)	At least 20 min/day, 3 day/wk walking and cycling (vs. lesser amount)	–	–
Rockhill et al., 2001 (35)	–	1-1.9 hr/wk moderate- to vigorous LTPA (vs. <1 hr/wk)	–
Gregg et al., 2003 (7)	–	–	≥2 hr/wk walking (vs. none) ≥2 hr/wk LTPA (vs. none)
Landi et al., 2004 (36)	–	–	≥2 hr/wk LTPA and chores (vs. <2 hr/wk)

Table G1.1. Minimum amounts of physical activity associated with significantly lower risks of all-cause mortality (continued)

Studies with subjects classified by **duration** of physical activity (continued):

Reference	Men	Women	Both Sexes Analyzed Together
Mensink et al., 1996 (37)	>2 hr/wk sports (vs. none)	–	–
Leon et al., 1997 (18)	140 min/day LTPA (vs. 4.9 min/day)	–	–
Schooling et al., 2006 (16)	–	–	≤30 min/day LTPA (vs. none)
Hu et al., 2004a (3)	–	≥3.5 hr/wk moderate-to vigorous LTPA (vs. ≤0.5 hr/wk)	–
Fujita et al., 2004 (13)	–	≥1 hr/day walking (vs. ≤0.5 hr/day)	–

Studies with subjects classified by **frequency** of physical activity:

Reference	Men	Women	Both Sexes Analyzed Together
Sundquist et al., 2004 (38)	–	–	Occasional LPTA (vs. none)
Lam et al., 2004 (14)	1/mo to 1-3/wk LTPA of ≥30 min (vs. <1/mo)	1/mo to 1-3/wk LTPA of ≥30 min (vs. <1/mo)	–
Kushi et al., 1997 (39)	–	Few/mo to 1/wk to moderate LPTA (vs. never/rarely)	–
Hillsdon et al., 2004 (40)	–	–	1/wk vigorous sports/recreation (vs. <1/mo)

LTPA, leisure-time physical activity

Table G1.2. Walking and All-Cause Mortality

For each study, the data* presented are for the lowest walking level significantly associated with decreased relative risk of all-cause mortality. For studies without significant results, the non-significant relative risk (shown in ***bold italics***) associated with the highest walking level is given.

Further, the studies are grouped according to different classifications of walking in the studies reviewed. Within each classification scheme for walking, studies are ordered from lowest to highest walking level.

Table G1.2.   Walking and All-Cause Mortality (continued)

Studies with subjects classified by **energy expended** on walking:

Reference	Men	Women	Both Sexes Analyzed Together
Tanasescu et al., 2003 (22)	≥16.1 MET-hr/wk (vs. 0-1.4): RR = 0.60 (0.41-0.88)	–	–
Matthews et al., 2007 (4)	–	≥7.1 MET-hr/day (vs. 0.3.4): RR = 0.86 (0.75-1.05)	–

Studies with subjects classified by **time** spent walking:

Reference	Men	Women	Both Sexes Analyzed Together
Gregg et al., 2003 (7)	≥2 hr/wk (vs. 0): RR = 0.61 (0.48-0.78)	≥2 hr/wk (vs. 0): RR = 0.71 (0.59-0.87)	–
Stessman et al., 2000 (41)	–	–	~4 hr/wk (vs. <4 hr/wk): RR = 0.41 (0.19-0.91)
LaCroix et al., 1996 (42)	–	–	>4 hr/wk: ***RR = 0.91 (0.58-1.42)***
Fujita et al., 2004 (13)	≥1 hr/day (vs. ≤0.5): ***RR = 0.91 (0.80-1.04)***	≥1 hr/day (vs. ≤0.5): RR = 0.75 (0.62-0.90)	–
Wannamethee et al., 1998 (43)	>60 min/day (vs. 0): ***RR = 0.62 (0.37-1.05)***	–	–
Schnohr et al., 2007 (44)	>2 hr/day (vs. <0.5): ***RR = 0.80 (0.59-1.10)***	>2 hr/day (vs. <0.5): ***RR = 0.89 (0.69-1.14)***	–

Studies with subjects classified by **distance** walked:

Reference	Men	Women	Both Sexes Analyzed Together
Smith et al., 2007 (21)	–	–	≥1 mile/day (vs. 0): ***RR = 0.89 (0.67-1.18), normoglycemics*** RR = 0.54 (0.33-0.88), diabetics
Hakim et al., 1998 (12)	1.0-2.0 miles/day (vs. <1) RR = 0.68 (no CI provided)	–	–

Table G1.2.   Walking and All-Cause Mortality (continued)

Studies with subjects classified by **distance** walked (continued):

Reference	Men	Women	Both Sexes Analyzed Together
Lee & Paffenbarger 2000 (31)	≥12.5 miles/wk (vs. <3.1): RR = 0.84 (0.75-0.94)	–	–

Studies with subjects classified by **pace** of walking:

Reference	Men	Women	Both Sexes Analyzed Together
Davey Smith et al., 2000; (45) Batty et al., 2002; (19) Batty et al., 2003 (46)	P, trend across slower, the same, faster pace (compared to others) all < 0.01	–	–
Schnohr et al., 2007 (44)	Average walking pace (vs. slow): RR = 0.75 (0.61-0.92)	Average walking pace (vs. slow): RR = 0.54 (0.45-0.67)	–

Studies with subjects classified by **walking/cycling** combined:

Reference	Men	Women	Both Sexes Analyzed Together
Bijnen et al., 1998 (47)	≥20 min, 3 days/wk: RR = 0.71 (0.58-0.88)	–	–
Barengo et al., 2004 (48)	≥30 min/day commute (vs. <15): ***RR = 1.07 (0.98-1.17)***	≥30 min/day commute (vs. <15): ***RR = 0.98 (0.88-1.09)***	–
Hu et al., 2004b (20)	–	–	≥30 min/day commute (vs. 0): ***RR = 0.88 (0.75-1.04)***
Carlsson et al., 2006 (33)	–	>1.5 hr/day (vs. almost never): RR = 0.58 (0.45-0.75)	–

*Data shown are relative risk, RR (95% CI).

It is important to note that this amount — 2 to 2.5 hours per week of moderate-intensity physical activity — does not represent a threshold level for risk reduction. Rather, the data consistently support an inverse dose-response relation for the total volume of energy expended, supporting a "some is good; more is better" message (see discussion under Question 3 below).

Rationale

Assessment of Physical Activity

The different studies reviewed in this chapter primarily have used questionnaires to assess physical activity. These questionnaires were different across the various studies and assessed one or more domains of physical activity — leisure-time, household, occupation, and commuting activity — with most assessing primarily leisure-time physical activity. In analyses, the studies classified subjects using different classification schemes, such as by energy expended, duration of activity, and frequency of activity. Several studies classified subjects by ordinal groupings of physical activity (e.g., groups denoted as "sedentary," "light," "moderate," and "heavy"), but the amount of activity attributable to each category was unclear. Thus, combining the data across studies and translating the findings into a fashion that could be readily translated for public health purposes was challenging. Future studies should attempt to collect detailed information on physical activity, as well as categorize this in ways that make comparison across studies feasible. One helpful strategy may be to use standardized units, such as energy expenditure (e.g., MET-hours per week) of duration in activities of specified intensity (e.g., hours per week of moderate-intensity physical activity).

Minimum Amount of Physical Activity Needed

Table G1.1 lists the studies with quantifiable amounts of physical activity, and shows that most of the physical activity assessments were derived from leisure-time activities. For studies classifying subjects by energy expended, it appears that some 1,000 kilocalories per week or 10 to 12 MET-hours per week (approximately equivalent to 2.5 hours per week of moderate-intensity activity) or more is needed to significantly lower the risk of all-cause mortality. For studies classifying subjects by the duration of their physical activity, it appears that some 2 hours per week or more is needed for significantly lower risks. A few studies classified subjects by the frequency of physical activity (with or without duration built in). These sparse data show that even 1 per month to 1 to 3 times per week of physical activity, lasting at least 30 minutes in duration, is significantly associated with lower risk. Across all studies, the minimum amount of activity did not appear to differ for men and women.

Walking

Many studies have included walking in their assessment of physical activity, although several combined this activity into an overall estimate of physical activity (e.g., as kilocalorie energy expenditure). In recent years, however, investigators have been interested

in walking as an activity to be promoted for public health, and several studies have presented data specifically on walking in relation to all-cause mortality rates.

Table G1.2 summarizes the findings from studies that have specifically investigated walking. In these studies, investigators classified walking according to the energy expended on walking, the time spent walking, the distance walked, the pace of walking, and walking combined with bicycling, primarily for the purpose of commuting. Only 2 studies examined the energy expended on walking and all-cause mortality rates; the data are inconsistent. With regard to the time spent walking, for which most data are available, the findings are reasonably consistent in showing that walking some 2 or more hours per week is associated with a significantly lower risk. A small body of data suggests that walking 1 to 2 miles per day is associated with lower risk. Additionally, faster pace of walking, compared with slower pace, is consistently associated with lower risk. Few data are available on walking or cycling as part of active commuting in relation to all-cause mortality, with investigators typically examining 30 minutes or more per day of active commuting versus lesser levels. These data are inconsistent and do not indicate that 30 minutes or more per day of active commuting is associated with lower risk.

What Activities "Count"?

As mentioned previously, the studies reviewed in this chapter that have shown an inverse relation between physical activity and all-cause mortality primarily have assessed leisure-time physical activity, including walking. However, some evidence indicates that it may be the overall **volume** of energy expended — regardless of where this energy is derived —that is important to lower the risk of mortality. Studies that have attempted to assess the total amount of energy expended in leisure-time, occupational, household activity, and commuting activity have reported significant inverse associations with the overall volume of physical activity, as well with most of the individual domains analyzed separately (except for commuting activity). These studies have included the Swedish Mammography Cohort Study (33) and the Shanghai Women's Health Study (4). In the Shanghai Women's Health Study (Figure G1.1), as amounts of energy expended on what investigators termed "nonexercise activities" (i.e., activities other than leisure-time activity, including household chores, walking and cycling as part of commuting, and climbing stairs) increased, rates of all-cause mortality declined steadily.

Within each category of "nonexercise activities," the addition of "regular exercise" (i.e., regular leisure-time physical activity) further reduced risk, except at the highest level of nonexercise energy expenditure. This observation is compatible with the postulated dose-response relation between physical activity and all-cause mortality, described in detail under Questions 3 and 4 below. That is, the dose-response is likely curvilinear such that at higher levels of energy expended, the curve flattens out. So in the Shanghai Women's Health Study, women at the highest level of nonexercise activities may have been at the upper end of the dose-response curve, and the addition of further amounts of energy expended on exercise activities did not appreciably reduce all-cause mortality rates further.

Figure G1.1. Relative risks of all-cause mortality according to exercise and nonexercise activities, Shanghai Women's Health Study
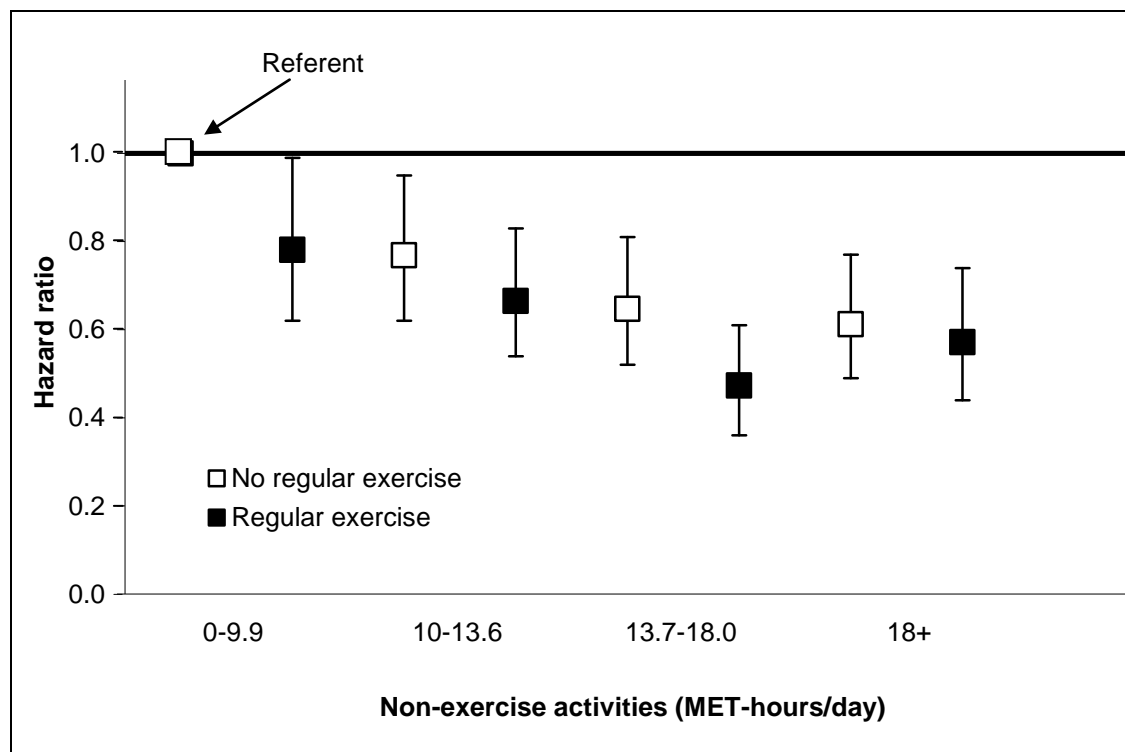
Source: Matthews et al., 2007 (4), with permission

Values are hazard ratios and 95% confidence intervals.

Adjusted for age (years), marital status (yes, no), education (elementary school or less, junior high school, high school, college/post-high school), household income (low, middle, high), smoking (ever, never), alcohol drinking (ever, never), number of pregnancies, oral contraceptive use (ever, never), menopausal status (yes, no), and several chronic medical conditions, such as diabetes (yes, no), hypertension (yes, no), respiratory disease (yes, no; asthma, chronic bronchitis, or tuberculosis), and chronic hepatitis (yes, no).

Figure G1.1. Data Points

Non-exercise activities (MET-hrs/d)	No regular exercise Hazard Ratio	No regular exercise (95% CI)	Regular exercise Hazard Ratio	Regular exercise (95% CI)
0–9.9	1.00	–	0.78	(0.62–0.99)
10–13.6	0.77	(0.62–0.95)	0.67	(0.54–0.83)
13.7–18.0	0.65	(0.52–0.81)	0.47	(0.36–0.61)
18.1+	0.61	(0.49–0.77)	0.57	(0.44–0.74)

Further support for the premise that all activities "count," and that it is the total amount of energy expended that is relevant for all-cause mortality, comes from the Health ABC study (10). In this study, which objectively measured total energy expenditure using doubly-labeled water, the relative risk for all-cause mortality was significantly lower (0.65) among men and women who expended more than 770 kilocalories per day in physical activity, compared with less than 521 kilocalories per day. (The energy expended in physical activity was estimated as: [total energy expenditure*0.90] — resting metabolic rate; i.e., assuming the thermic effect of food to be 10%.) Among those expending 521 to 770 kilocalories per day, the relative risk was 0.64, well below 1.0 but not statistically significant, which is a likely consequence of reduced power due to the small number of deaths (n=55) in this study.

Findings from Studies of Physical Fitness That Can Inform on the Minimum Amount of Physical Activity Needed

As stated previously, studies of cardiorespiratory fitness and all-cause mortality do not provide direct information on the minimum amount of physical activity needed. However, these studies can provide indirect information, in that the physical activity levels of groups of fit subjects, who have lower mortality rates compared with unfit subjects, can be ascertained. In a large prospective cohort study where moderate and high levels of cardiorespiratory fitness were associated with lower rates of all-cause mortality, compared with low levels of fitness in both men and women, the physical activity levels of subjects were obtained by questionnaire (49). Men in the moderate and high cardiorespiratory fitness groups reported an average of 130 and 138 minutes per week of walking, respectively. Among women, the corresponding amounts were 148 and 167 minutes per week, respectively. Thus, these data are compatible with data from the overall body of literature on physical activity and all-cause mortality, which suggest that walking at least 2 hours per week is needed to significantly lower mortality rates.

Question 3: Is There a Dose-Response Relation Between Physical Activity and All-Cause Mortality?

Conclusions

The dose-response relation can be assessed with respect to specific dimensions of physical activity, such as the total volume of energy expended, the intensity of the physical activity carried out, the duration of physical activity, or the frequency of physical activity. The largest amount of data, as well as the clearest, pertains to the total volume of energy expended. These data consistently show an inverse dose-response relation between volume of energy expended and all-cause mortality. Thus, while the answer to Question 2 above indicates that at least 2 to 2.5 hours per week of moderate-intensity physical activity is needed to significantly decrease all-cause mortality rates, this amount does not represent a minimum threshold level for risk reduction. Rather, the dose-response relation for the total volume of energy expended supports a "some is good; more is better" message. Some data indicate that among populations where physical activity levels are likely to be low (e.g., middle-aged and older women, older men), significantly lower mortality rates are observed

at levels below 2 to 2.5 hours per week of moderate-intensity physical activity. Taken as a whole, the data support a target of 2 to 2.5 hours per week of moderate-intensity physical activity for lowering all-cause mortality rates, yet also encourage any level of activity below the target for inactive groups of individuals.

Limited data suggest that vigorous-intensity physical activity is associated with additional risk reduction compared with lower-intensity activities, beyond its contribution to the total energy expended. There are no data to clarify dose-response relations for duration and frequency of physical activity that are independent of their contributions to the total volume of energy expended. In other words, it is unknown whether multiple, short bouts of physical activity versus a single, long bout that expends the same energy are differentially associated with all-cause mortality rates.

Rationale

The concept of "physical activity" is complex, in that it includes many different aspects, such as the kinds of activities carried out, the intensity with which they are conducted, and their duration and frequency. In examining the dose-response relation between physical activity and all-cause mortality, we can investigate the association with regard to several specific dimensions of physical activity: the total volume of energy expended, the intensity, the duration, or the frequency. The dose-response relation for each of these dimensions is discussed separately below.

Dose-Response Relation for Total Volume of Physical Activity

As Table G1.A1 indicates, the studies reviewed have used different methods (primarily questionnaires, which differed across studies) to assess physical activity. However, all of them possessed a measure that reflected the total volume of energy expended. This is because any assessment of physical activity, no matter how simple, provides some indication of the total volume of energy expended. For example, in the NHANES I Epidemiologic Follow-up Study (50), physical activity during recreation was assessed by asking, "Do you get much exercise in things you do for recreation, or hardly any exercise, or in between?" Response options were: much exercise, moderate exercise, and little or no exercise. Although it is impossible to equate the different activity categories to actual kilocalories or MET-hours of energy expended, it is clear that the categories represent ordered levels representing the total volume of physical activity.

Of the studies reviewed, 59 of the 73 studies classified subjects according to at least 3 levels of physical activity, allowing for assessment of dose-response related to the total volume of energy expended. Among these 59 studies, 33 reported significant, inverse trends between physical activity and all-cause mortality rates. Another 21 studies showed apparent inverse trends that were not formally tested for statistical significance. The remaining 5 studies showed a non-significant trend (n=1) or apparent lack of trends that were not formally tested for significance (n=4).

As discussed above under Question 2, at least 2 to 2.5 hours per week of moderate-intensity physical activity is needed to significantly decrease all-cause mortality rates. However, rather than representing a minimum threshold level for risk reduction, the dose-response relation for the total volume of energy expended indicates that though this is a desired minimum level of physical activity, risk reductions already begin to occur below this level, supporting a message of "some is good; more is better." Additionally, some data indicate that among populations where physical activity levels are likely to be low (e.g., middle-aged and older women, older men) significantly lower mortality rates are observed at levels below 2 to 2.5 hours per week of moderate-intensity physical activity. In a study of middle-aged and older women, significantly lower rates of mortality were observed among women engaging in 1 to 1.9 hours per week of moderate-to-vigorous intensity leisure-time physical activity (35). In another study of older men and women aged 65 years and older, "occasional" leisure-time physical activity also was associated with significantly lower mortality rates (38). This association also held true for walking or cycling for at least 20 minutes, 3 days a week, among men aged 64 to 84 years (47).

Further support for the "some is good; more is better" message comes from a recent randomized clinical trial of physical activity to increase cardiorespiratory fitness levels — higher levels of which are associated with lower all-cause mortality rates — among sedentary, postmenopausal women (51). In this trial, a dose-response relation was observed such that graded increased in fitness were observed for 3 groups exercising at 50%, 100%, and 150% of the Surgeon-General's recommendation (with 100% being equivalent to 150 minutes per week of moderate-intensity physical activity). Thus, these data support a target of 2 to 2.5 hours per week of moderate-intensity physical activity for lowering all-cause mortality rates, yet also encouraging any level of activity below the target for inactive groups of individuals.

Dose-Response Relation for Intensity of Physical Activity

In 11 studies, investigators examined the dose-response relation for intensity of physical activity. All but one reported significantly reduced risks for vigorous-intensity activity compared with lesser-intensity physical activity. However, the interpretation of these findings is not straightforward because the intensity of physical activity is related to the total volume of energy expended. That is, when carried out for the same total duration, higher-intensity physical activities expend more total energy than do lower-intensity physical activities. Thus, if studies do not account for this correlation, it is unclear whether the significantly reduced risk associated with vigorous-intensity physical activity can be attributed to the **intensity** of the activity, or whether it is merely due to the increase in the total **volume** of energy expended (i.e., confounding of intensity by volume of energy expended). In other words, for the same volume of energy expended, does vigorous intensity activity confer additional benefits compared to moderate- or light-intensity activity?

Of the 11 studies, 4 did attempt to account for confounding by the volume of energy expended. All 4 reported significant, inverse dose-response relations with intensity of physical activity. Thus, these limited data suggest that higher intensities of physical activity

are associated with additional risk reductions for all-cause mortality, beyond their contribution to greater total volume of energy expended.

Dose-Response Relation for Duration and Frequency of Physical Activity

Longer duration of physical activity, as well as greater frequency of physical activity, results in greater total volume of energy expended, compared with shorter durations or lower frequencies of activity. However, just as with the dose-response relation to the intensity of physical activity, the relation between dose and duration or frequency has the potential to be confounded by the total volume of energy expended. Therefore, the total volume must be taken into account in order to make conclusions regarding duration and frequency that are independent of the total volume of energy expended.

Ten studies examined the dose-response relation between duration of physical activity and all-cause mortality. These studies indicated that longer durations of activity were associated with lower mortality rates. However, these studies did not adjust for confounding by volume of physical activity and so the data on duration may be reflecting the dose-response relation between the total volume of energy expended and risk of all-cause mortality. These data cannot provide any conclusion regarding whether multiple, short bouts of physical activity versus a single, long bout that expends the same energy are differentially associated with all-cause mortality rates.

Three studies examined the dose-response relation for frequency of physical activity. Again, these studies did not adjust for confounding by volume of physical activity; thus, the data on frequency may be reflecting findings for the dose-response of total volume of energy expended and all-cause mortality rates. These data also cannot clarify the relative benefits of multiple, short bouts of physical activity versus a single, long bout that expends the same energy for all-cause mortality rates.

Finally, 1 study examined the association of all-cause mortality and physical activity carried out 1 to 2 days a week and that generates sufficient energy expenditure to meet current physical activity recommendations (i.e., the so-called "weekend warrior" pattern) (52). Overall, the relative risk for mortality among weekend warriors, compared with sedentary men, was 0.85 (95% confidence interval [CI], 0.65, 1.11). In stratified analysis, however, among men without major cardiovascular risk factors, weekend warriors had a significantly lower risk of dying, compared with sedentary men (RR = 0.41 [0.21, 0.81]). This was not seen among men with at least 1 major risk factor (corresponding RR = 1.02 [0.75, 1.38]).

Question 4: What Is the Shape of the Dose-Response Relation Between Physical Activity and All-Cause Mortality?

Conclusions

The dose-response curve relating different amounts of physical activity to all-cause mortality rates appears curvilinear. On average across studies, compared to less than

0.5 hours per week of moderate-to-vigorous physical activity, engaging in approximately 1.5 hours per week of such activity is associated with about a 20% reduction in risk. Additional amounts of activity are associated with additional risk reductions, but at smaller magnitudes, such that an additional approximately 5.5 hours per week is required to observe a further 20% in risk (i.e., approximately 7.0 hours per week is associated with about a 40% reduction in risk, compared with less than 0.5 hour per week).

Rationale

To describe the dose-response curve in detail, studies in which subjects were classified into at least 5 categories of physical activity were selected. Eleven studies defined 5 levels of physical activity; one defined 6 levels. Figure G1.2 shows the dose-response curve for each of the 12 studies. These categories were defined according to ordinal levels of activity (5;43), the frequency of activity (38), the time per week spent in physical activity (35), or the energy expended on physical activity (either as kilocalories per week, MET-hours per week, or MET-hours per day)(15;17;22;28;30;31;33;53). In a first analysis, we did not attempt to quantify the amount of physical activity, but merely designated these categories as 1 to 6, and plotted the relative risks of all-cause mortality associated with each of these categories. In general, these studies support a curvilinear shape to the dose-response curve.

Next, we attempted to synthesize the results across the different studies to obtain an "average" shape of the dose-response curve. Because the physical activity categories represented different amounts of physical activity, we translated them, where possible, into a common measure of hours per week spent on moderate-to-vigorous physical activity. We excluded from the analysis the one study that had 6 categories of physical activity because it used ordinal groupings that did not allow interpretation of the amount of physical activity. For the remaining studies, we assigned to each of their 5 categories of physical activity the median value of that category, in hours per week of moderate-to-vigorous physical activity. We plotted the median relative risk of all-cause mortality against each of these 5 categories of physical activity.

Figure G1.3 shows that this analysis supports the curvilinear shape observed for most of the individual studies in Figure G1.2. The largest risk reduction is seen at the lowest end of the physical activity spectrum, and additional risk reductions — at smaller magnitudes — are seen at higher levels of physical activity. On average, it appears that compared to less than 0.5 hour per week of moderate-to-vigorous physical activity, engaging in approximately 1.5 hours per week of such activity is associated with about a 20% reduction in risk of all-cause mortality. Additional amounts of physical activity are associated with additional risk reductions, but at smaller magnitudes, such that an additional approximately 5.5 hours per week are required to observe a further 20% decline in risk (i.e., approximately 7.0 hours per week is associated with approximately 40% reduction in risk, compared with less than 0.5 hour per week).

Figure G1.2. Shape of the Dose-Response Curve: Relative Risks of All-Cause Mortality by Physical Activity Level (Studies With at Least 5 Levels of Physical Activity)
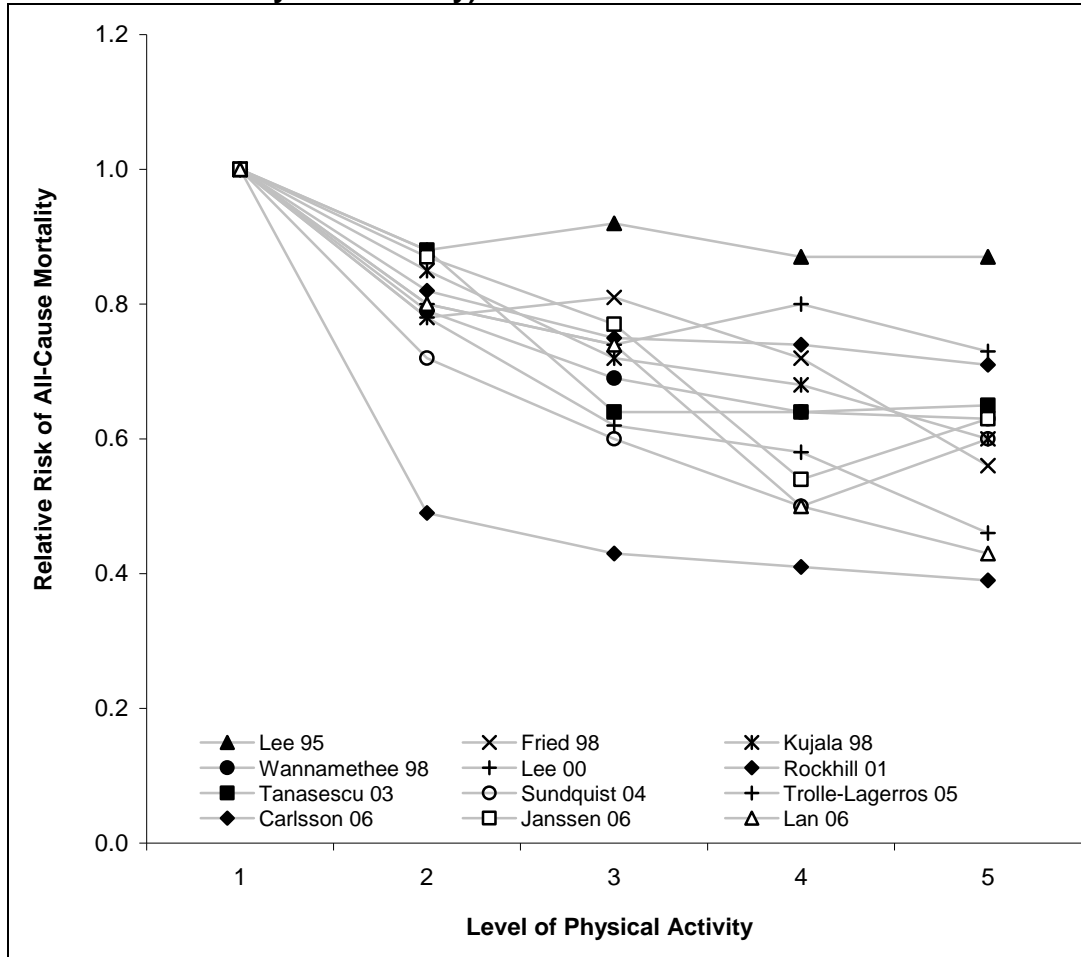

Figure G1.2. Data Points

Author/Year	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Lee 95	1	0.88	0.92	0.87	0.87	
Fried 98	1	0.78	0.81	0.72	0.56	
Kujala 98	1	0.85	0.72	0.68	0.6	
Wannamethee 98	1	0.79	0.69	0.64	0.63	0.54*
Lee 00	1	0.8	0.74	0.8	0.73	
Rockhill 01	1	0.82	0.75	0.74	0.71	
Tanasescu 03	1	0.88	0.64	0.64	0.65	
Sundquist 04	1	0.72	0.6	0.5	0.6	
Trolle-Lagerros 05	1	0.78	0.62	0.58	0.46	
Carlsson 06	1	0.49	0.43	0.41	0.39	
Janssen 06	1	0.87	0.77	0.54	0.63	
Lan 06	1	0.8	0.74	0.5	0.43	

*Not shown.

Figure G1.3. "Median" Shape of the Dose-Response Curve
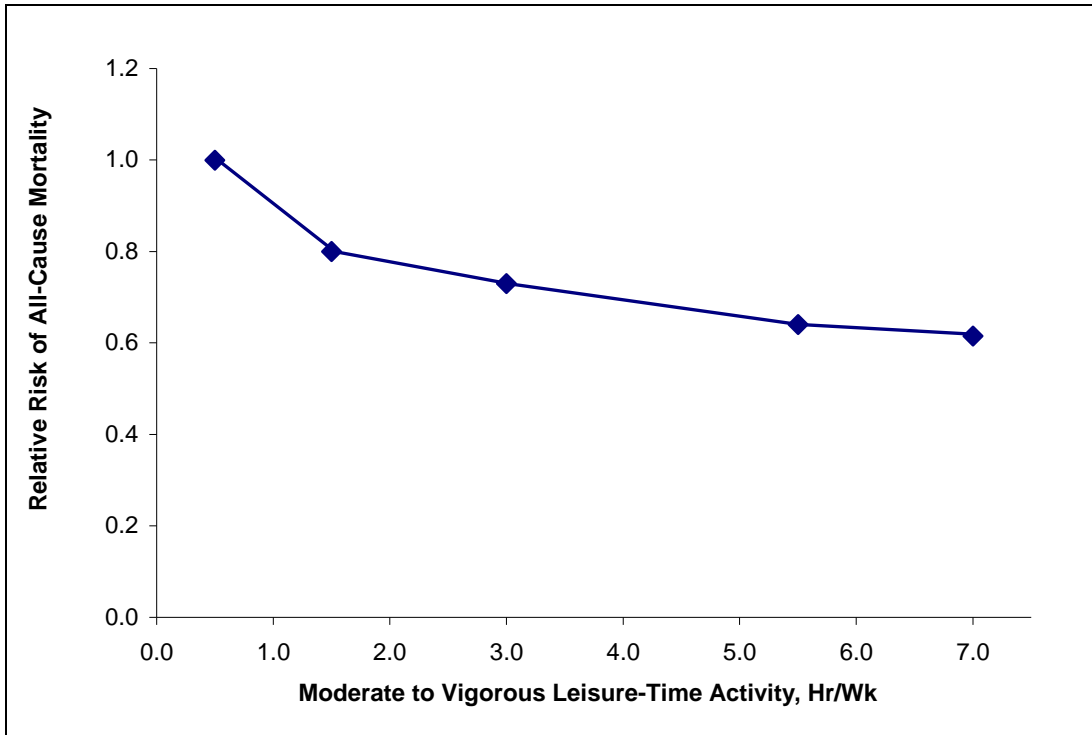
Figure G1.3. Data Points

Hr/wk	RR
0.5	1
1.5	0.8
3	0.73
5.5	0.64
7	0.615

Question 5: Is the Relation Between Physical Activity and All-Cause Mortality Independent of Adiposity?

Conclusions

The inverse relation between physical activity and all-cause mortality appears independent of adiposity. Further, this inverse relation appears to hold regardless of whether subjects are normal weight, overweight, or obese.

Rationale

Debate exists regarding whether adiposity should be adjusted for when examining the relation between physical activity and all-cause mortality rates. The argument against adjusting is that adiposity represents one pathway through which physical activity favorably influences mortality rates; thus, adjustment for adiposity minimizes the effect of physical activity. Nonetheless, almost 60% of the studies (43 of 73) adjusted their results for BMI or some other measure of adiposity (e.g., weight or waist-hip ratio). These studies, after adjustment for adiposity, continued to observe significant, inverse associations between physical activity and all-cause mortality.

Additionally, a few studies have stratified their findings by BMI, to examine the relation between physical activity and all-cause mortality among subjects with different BMI (3;11;31;54). These studies indicate that the inverse association between physical activity and all-cause mortality holds for persons who are normal weight, overweight, and obese. For example, among men in the Harvard Alumni Health Study (31), compared with inactive and **overweight** men, those who were active but overweight had a relative risk of 0.80 (95% CI, 0.71-0.91). Corresponding results were 0.90 (0.79-1.02) for men who were inactive but of **normal weight**, and 0.67 (0.60-0.75) for active and normal weight men. Among women in the Nurses' Health Study (3), using **normal weight**, active women as referent, normal weight women who were inactive had an elevated relative risk of dying during follow-up, 1.55 (1.42-1.70). Using the same referent, the relative risk for **overweight**, active women was 1.28 (1.12-1.46); for overweight, inactive women, this was 1.64 (1.46-1.83). For **obese**, active women, the relative risk was 1.91 (1.60-2.30); for obese and inactive women, this was 2.42 (2.14-2.73).

Overall Summary and Conclusions

The overall conclusions of this chapter on physical activity and all-cause mortality may be summarized as the following:

- A large body of scientific evidence, all from observational epidemiologic studies, exists on the association of physical activity with all-cause mortality rates.

- The data very consistently show an inverse relation, with the most active individuals — both men and women — experiencing approximately a 30% reduction in risk of mortality during follow-up, compared with the least active.

- The inverse relation extends to older persons, aged 65 years and older.

- Although this inverse relation has been observed in many countries throughout the world, the data that are specific to non-white populations are limited compared to those on white populations. The inverse relation appears to be similar for both white and non-white populations.

- Studies primarily have assessed leisure-time physical activity, including walking. There is, however, some evidence to indicate that it may be the overall **volume** of energy expended — regardless of which activities produce this energy expenditure — that is important to lower the risk of mortality.

- With regard to the minimum amount of physical activity needed, it appears that at least 2 to 2.5 hours per week of moderate-intensity physical activity are required to significantly lower all-cause mortality rates. Walking has been specifically investigated in several studies, and it also appears that walking at least 2 hours per week is associated with significantly lower all-cause mortality rates.

- However, this amount — 2 to 2.5 hours per week of moderate-intensity physical activity — does not represent a minimum threshold level for risk reduction. The data consistently support an inverse dose-response relation for the total volume of energy expended, which supports a "some is good; more is better" message. In particular, the data support a target of 2 to 2.5 hours per week of moderate-intensity physical activity for lowering all-cause mortality rates, and encourage any level of activity below this target for inactive groups of individuals.

- It appears that the shape of the dose-response curve is curvilinear (see Figure G1.2). On average across studies, compared to less than 0.5 hour per week of moderate-to-vigorous physical activity, engaging in approximately 1.5 hours per week of such activity is associated with about a 20% reduction in risk. Additional amounts of activity are associated with additional risk reductions, but at smaller magnitudes, such that another approximately 5.5 hours per week is required to observe a further 20% decline in risk (i.e., approximately 7.0 hours per week is associated with about a 40% reduction in risk, compared with the risk associated with less than 0.5 hour per week).

- Limited data support vigorous-intensity physical activity being associated with additional risk reduction, compared with lower intensity activities, beyond its contribution to the total volume of energy expended.

- No data are available to inform whether multiple, short bouts of physical activity versus a single, long bout that expends the same energy are differentially associated with all-cause mortality rates.

- Finally, the inverse relation between physical activity and all-cause mortality appears independent of adiposity. Importantly, this inverse relation appears to hold regardless of whether subjects are normal weight, overweight, or obese.

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