Physical activity and all-cause mortality: what is the dose-response relation?

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ABSTRACT

LEE, I-M., and P. J. SKERRETT. Physical activity and all-cause mortality: what is the dose-response relation? *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S459–S471. **Purpose:** The purpose of this review is to assess the dose-response relation between physical activity and all-cause mortality. We examined these parameters of physical activity dose: volume, intensity, duration, and frequency. **Methods:** We used a computer-assisted literature search to identify papers on this topic. After excluding papers examining only two levels of physical activity or fitness, papers investigating specific causes of mortality, reviews, and those not written in English, 44 papers satisfying all criteria were included in this review. **Results:** There is clear evidence of an inverse linear dose-response relation between volume of physical activity and all-cause mortality rates in men and women, and in younger and older (≥60 yr) persons. Minimal adherence to current physical activity guidelines, which yield an energy expenditure of about 1000 $kcal \cdot wk^{-1}$ (4200 $kJ \cdot wk^{-1}$), is associated with a significant 20-30% reduction in risk of all-cause mortality. Further reductions in risk are observed at higher volumes of energy expenditure. It is unclear whether a volume of <1000 $kcal \cdot wk^{-1}$ also may be associated with lower risk; there are some data supporting this. Due to limited data, it is also unclear whether vigorous-intensity activity confers additional benefit beyond its contribution to volume of physical activity when compared with moderate-intensity activity. No data are available on duration and frequency of physical activity in relation to all-cause mortality rates after controlling for volume of physical activity. **Conclusions:** All studies in this review are observational studies, so conclusions are based on Evidence Category C. There is an inverse linear dose-response relation between volume of physical activity and all-cause mortality. Further research is needed to clarify the contributions of its components—intensity, duration, and frequency—to decreased all-cause mortality rates. **Key Words:** CARDIORESPIRATORY FITNESS, DEATH, EPIDEMIOLOGY, EXERCISE, PHYSICAL FITNESS

The hypothesis that physical activity and physical fitness promote health and longevity is not new. As far back as 2500 BC in ancient China, we find records of organized exercise for health promotion (28). Today, there is clear evidence to support this hypothesis (48). What is less clear is the shape of the dose-response relation between physical activity or fitness and all-cause mortality rates. Clarifying this relation is important in light of a widely cited and heavily promoted recommendation (33,37,48) that calls for at least 30 min of moderate-intensity physical activity (e.g., brisk walking at 3–4 mph) on most days of the week. We refer to this as the "current" recommendation. It contrasts with previous recommendations that advocated vigorous-intensity exercise (e.g., jogging or running) for at least 20 min continuously three times a week (1).

Although the volume of energy expended by minimal adherence to current or previous recommendations is similar (on the order of 1000 $kcal \cdot wk^{-1}$ [4200 $kJ \cdot wk^{-1}$]), two major differences exist between the current and previous recommendations. They are: 1) the current emphasis on moderate, rather than vigorous, activity; and 2) the current allowance for the accumulation of short sessions of activity, instead of one longer, continuous session. These concessions were made partly to encourage physical activity among sedentary individuals because the previous, more difficult prescription was believed to pose a barrier (48). With the high prevalence of sedentary behavior today, it is important to ascertain the minimum dose of physical activity required to decrease all-cause mortality rates. From a public health perspective, advocating small (effective) doses of physical activity is likely to be more palatable to the many physically inactive persons.

The purpose of this review is to describe the shape of the dose-response curve between physical activity or fitness and all-cause mortality. Because of the large number of sedentary individuals, we are particularly interested in the minimum dose of physical activity required to decrease all-cause mortality rates. In the broadest sense, "dose" can be defined as the volume of physical activity. We also will examine the parameters that characterize volume of physical activity: intensity, frequency, and duration. The specific questions we will address are:

1. What are the available data for a dose-response relation between physical activity or fitness and all-cause mortality rates?

2. What is the minimum *volume* of physical activity associated with decreased all-cause mortality rates? With increasing dose, do mortality rates decline commensurately, or is there a threshold effect (i.e., an L-shaped curve)?

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3. What is the minimum *intensity* of physical activity associated with decreased all-cause mortality rates? Holding the volume of physical activity constant, do mortality rates decline commensurately with increasing intensity, or is there a threshold effect?

4. Holding the volume of physical activity constant, what is the minimum *duration* of physical activity associated with decreased all-cause mortality rates? With increasing duration, do mortality rates decline commensurately, or is there a threshold effect?

5. Holding the volume of physical activity constant, what is the minimum *frequency* of physical activity associated with decreased all-cause mortality rates? With increasing frequency, do mortality rates decline commensurately, or is there a threshold effect?

METHODS

We used a computer-assisted literature search to identify papers published between 1966 and July 2000 by using the National Library of Medicine's Medical Subject Heading (MeSH) keywords related to physical activity (physical fitness, exercise, physical education and training, exertion, sports, running, walking, recreation, and leisure activities) and all-cause mortality (mortality and death). We excluded papers examining only two levels of physical activity or fitness, because this would not allow assessment of a dose-response relation, papers investigating only specific causes of mortality, review papers, and papers not written in English, because we did not have the means to translate them. We also checked the reference list of papers for additional papers not identified by the computerized literature search. By these means, we identified 44 papers. Both authors reviewed each of these papers, which are summarized in Table 1.

RESULTS

Of the 44 papers identified, the majority investigated physical activity. Five studies assessed physical fitness (6,10,39,41,45), whereas two assessed both activity and fitness (14,49). For this review, we have assumed equivalence between physical activity and physical fitness, because regular physical activity improves physical fitness. Moreover, from a practical perspective, public health recommendations target physical activity, a behavior, rather than physical fitness, an attained physiologic condition. Of the 38 papers examining physical activity, most assessed only leisure-time physical activity (LTPA), three assessed only occupational physical activity (OPA) (7,29,32), and nine assessed both LTPA and OPA (2,3,8,15,31,40,42,43,51).

Evidence for a dose-response relation. The primary parameter analyzed in the 44 studies was volume of physical activity (see below). There was evidence of an inverse linear dose-response relation between physical activity (or fitness) and all-cause mortality rates: 34 of the 44 studies showed an apparent dose-response relation in at least one subgroup (Table 1). A formal test of linear trend was conducted in only 17 studies, with 15 reporting a statistically significant inverse linear trend in at least one subgroup of subjects (Table 1).

Volume of physical activity. All 44 papers assessed the relation between volume of physical activity (or fitness) and all-cause mortality rates. Several investigators estimated energy expenditure, whereas others used proxies of energy expenditure (Table 1). These proxies included ordinal groupings, quantiles of physical activity, frequency of physical activity, and duration of physical activity.

As described above, 34 of the 44 studies reviewed showed an apparent inverse linear dose-response relation between volume of physical activity and all-cause mortality rates in at least one subgroup of subjects (Table 1). Of the remaining 10 studies, five noted a threshold effect, with a decline in all-cause mortality rates between the least active and second least active group but no diminution of rates at higher levels of physical activity (i.e., an L-shaped curve) (9,25,26,40,49). The other five reported no significant association between physical activity and all-cause mortality rates (15,19,20,29,52).

For a more stringent evaluation of the dose-response relation, we examined only studies that formally tested for a significant linear trend of declining all-cause mortality rates with increasing volume of physical activity (or fitness). This formal test was carried out in 17 studies; 15 observed significant, inverse linear trends in at least one subgroup (3,4,6,8,11–14,17,18,21,22,34,35,39), whereas two reported no significant trend (15,20).

An inverse linear dose-response relation between volume of physical activity and all-cause mortality rates was observed in both men and women. Of the 44 studies, 20 included men and women, 20 included men only, and 4 included women only. Of the 24 that included female subjects, 20 presented findings specifically for women (2,4,6,8,14–19,27,30,31,38,39,42,43,49,51,52). Findings for women generally paralleled those for men (Table 1).

The ages of subjects in most of the studies spanned a wide range, from young adulthood to old age. In 10 studies, results for adults aged 60 yr and older were presented separately (2,3,13,19,20,26,31,38,43,47). All but two (19,20) showed apparent linear inverse dose-response associations (i.e., formal statistical tests for trend were not always carried out) between volume of physical activity and all-cause mortality rates. In the Seventh-day Adventist Study, a significant benefit of physical activity was observed up to attained age of 80 yr (26).

Few studies quantified volume of physical activity in a manner that allows for direct translation to public health recommendations. Statistically significant decreased all-cause mortality rates occurred during follow-up among subjects who expended >1000 kcal·wk^{-1} (22,34), >980 kcal·wk^{-1} (11), an average of 518 kcal·wk^{-1} (25), >500 kcal·wk^{-1} (35); walked 1–2 miles·d^{-1} (13); or who exercised moderately or vigorously at least a few times a month to once a week (18). Risk reductions on the order of 20–30% were observed. This suggests that minimal adherence to either the current or previous physical activity guidelines,

TABLE 1. Summary of epidemiologic studies on the dose-response relation between physical activity or fitness and all-cause mortality.

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Andersen et al., 2000, Denmark (2)	3 prospective cohorts, 17,265 men and 13,375 women aged 20–93 yr	14.5 yr; 8549	4 levels of LTPA and OPA in the previous year, assessed by questionnaire	vs inactive LTPA Light: RR = 0.68 (0.64–0.71) Moderate: RR = 0.61 (0.57–0.66) Heavy: RR = 0.53 (0.41–0.68) Among subjects with light, moderate, and heavy LTPA, sports participation in men: RR = 0.63 (0.51–0.79) in women: RR = 0.47 (0.34–0.66) OPA: inverse association in women, no association in men.	Adjusted for age and sex. Adjustment for chronic disease did not change findings. Inverse association observed for individuals aged 20–44, 45–64, and ≥65 yr, and in men and women.
Bijnen et al., 2000, The Netherlands (3)	Prospective cohort (Zutphen Elderly Study), 472 Dutch men aged 70–90 yr	5 yr; 118	Physical activity assessed by questionnaire in 1985 and 1990 asking about walking, bicycling, hobbies, odd jobs, and sports, converted to a "total physical activity" score	vs lowest tertile (T1) of activity in 1990 T2: RR = 0.56 (0.35–0.89) T3: RR = 0.44 (0.25–0.80) *P* for trend, <0.01 Bicycling, but not gardening, walking, or other activities, showed an inverse association with mortality. Changing from an active to a sedentary lifestyle between 1985 and 1990, compared with remaining active: RR = 1.72 (1.04–2.85).	Adjusted for age, disease, functional status, and lifestyle factors.
Lee and Paffenbarger, USA (22)	Prospective cohort (Harvard Alumni Health Study), 13,485 men, mean age 57.5 yr, free of CVD, COPD, and cancer	15 yr; 2539	LTPA energy expenditure derived from questionnaire asking about walking, stair climbing, and sports/recreation	vs <4200 kJ·wk^{-1} in LTPA: 4200–<8400 kJ·wk^{-1}: RR = 0.80 (0.72–0.88) 8400–<12,600 kJ·wk^{-1}: RR = 0.74 (0.65–0.83) 12,600–<16,800 kJ·wk^{-1}: RR = 0.80 (0.69–0.93) ≥16,800 kJ·wk^{-1}: RR = 0.73 (0.64–0.84) *P* for trend, <0.001	Adjusted for age, BMI, smoking, alcohol use, and early parental death.
				P for trend: across categories of walking, 0.004 across categories of stair climbing, <0.001 across categories of light (<4 METs) sports/recreation, 0.72 across categories of moderate (4–<6 METs) sports/recreation, 0.07 across categories of vigorous (≥6 METs) sports/recreation, <0.001	Analyses of each of the components of LTPA simultaneously adjusted for the other components of LTPA, in addition to the variables above.
Stessman et al., 2000, Israel (47)	Prospective cohort (Jerusalem 70-Year-Olds Longitudinal Study), 456 men and women born in 1920–21	6 yr; 240	4 levels of LTPA at baseline—no exercise (walks less than 4 h weekly), moderate activity (walks approx. 4 h weekly), sports participation at least twice weekly, and regular activity (walks at least 1 h a day)	vs no activity: Moderate: RR = 0.41 (0.19–0.91) Sports: RR = 0.73 (0.33–1.62) Regular: RR = 0.14 (0.04–0.50)	Adjusted for sex, smoking, subjective economic hardship, and preexisting medical conditions.
Dorn et al., 1999, USA (8)	Prospective cohort (Buffalo Blood Pressure Study), 698 men and 763 women aged 15–96	29 yr; 578	LTPA and OPA assessed by 28 questions regarding time spent sleeping, sitting, driving, standing, carrying or lifting, walking, gardening, exercising, and playing sports.	For every 1 kcal·kg^{-1}·h^{-1} of physical activity, men: Nonobese: RR = 0.55 (0.36–0.84) Obese: RR = 1.44 (0.86–2.43) No significant association seen in women.	Adjusted for age, education, smoking, and mean arterial blood pressure.
Erikssen et al., 1998, Norway (10)	Prospective cohort, 1428 healthy men aged 50–70 yr	13 yr; 238	Physical fitness determined by bicycle test in 1972–75 and 1980–82	vs lowest quartile (Q1) in 1980–82: Q2: RR = 0.72 (0.52–0.99) Q3: RR = 0.48 (0.33–0.71) Q4: RR = 0.45 (0.29–0.69) Regardless of baseline level of fitness, improved fitness over 5–10 yr resulted in decreased all-cause mortality rate.	Adjusted for age, systolic blood pressure, heart rate, lipids, BMI, physical activity, and smoking status.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Fried et al., 1998, USA (11)	Prospective cohort (Cardiovascular Health Study), 5201 men and women aged ≥65 yr	5 yr; 646	Kcal/week in moderate or vigorous LTPA estimated from interview	vs ≤67.5 kcal·wk^{-1} >67.5–472.5: RR = 0.78 (0.60–1.00) >472.5–980: RR = 0.81 (0.63–1.05) >980–1890: RR = 0.72 (0.55–0.93) >1890: RR = 0.56 (0.43–0.75) *P* for trend, <0.005	Adjusted for age, smoking, BMI, and numerous other factors, including alcohol use, blood pressure, serum cholesterol, and chronic diseases.
Hakim et al., 1998, USA (13)	Prospective cohort (Honolulu Heart Study), 707 physically capable, nonsmoking men aged 61–81 yr	12 yr; 208	Daily distance walked	vs <1 mile·d^{-1} 1.0–2.0: RR = 0.68 2.1–8.0: RR = 0.59 *P* for trend, 0.002	Adjusted for age.
Kujala et al., 1998, Finland (17)	Prospective cohort (Finnish Twin Cohort), 15,902 men and women aged 25–64 yr free of various chronic diseases	18 yr; 1253	3 levels of LTPA plus calculated MET index assessed by questionnaire on activity, frequency, duration, and intensity	vs sedentary Occasional exercisers: RR = 0.80 (0.69–0.91) Conditioning exercisers: RR = 0.76 (0.59–0.98) vs lowest MET quintile (Q1) Q2: RR = 0.85 Q3: RR = 0.72 Q4: RR = 0.68 Q5: RR = 0.60 *P* for trend, 0.04 Participation in vigorous activities, RR = 0.79 (0.56–1.10)	Adjusted for age, sex, smoking, occupation, and alcohol use. Inverse association observed for men and women. Inverse association remained after taking into account genetic factors (twin status).
Roger et al., 1998, USA (39)	Retrospective cohort (Olmsted County), 1452 men, mean age 47 yr, and 741 women, mean age 51 yr, referred for treadmill testing	6.3 yr; 123	Physical fitness determined by maximal exercise test on treadmill	For each 1 MET increase in workload men: RR = 0.80 (*P* < 0.001) women: RR = 0.75*P* < 0.0002)	Adjusted for age and comorbidity. Similar findings seen when excluding first 3 years of follow-up.
Villeneuve et al., 1998, Canada (49)	Prospective cohort (Canada Fitness Survey), 6246 men and 8196 women aged 20–69 yr	7 yr; 1116	Average daily energy expenditure (KKD = kcal·kg^{-1} body weight·d^{-1}) on LTPA estimated from modified Minnesota LTPA questionnaire	vs lowest KKD (<0.5), men 0.5 to <1.5 KKD: RR = 0.81 (0.59–1.11) 1.5 to <3.0 KKD: RR = 0.79 (0.54–1.13) ≥3.0 KKD: RR = 0.86 (0.61–1.22) vs lowest KKD (<0.5), women 0.5 to <1.5 KKD: RR = 0.94 (0.69–1.30) 1.5 to <3.0 KKD: RR = 0.92 (0.64–1.34) ≥3.0 KKD: RR = 0.71 (0.45–1.11) Among subjects without vigorous (<6 METs) LTPA, vs lowest KKD (<0.5) in nonvigorous LTPA, men 0.5 to <1.5 KKD: RR = 0.81 (0.59–1.17) 1.5 to <3.0 KKD: RR = 0.70 (0.44–1.13) ≥3.0 KKD: RR = 0.82 (0.53–1.27) Among subjects without vigorous (<6 METs) LTPA, vs lowest KKD (<0.5) in nonvigorous LTPA, women 0.5 to <1.5 KKD: RR = 0.97 (0.69–1.36) 1.5 to <3.0 KKD: RR = 0.87 (0.57–1.33) ≥3.0 KKD: RR = 0.72 (0.43–1.21) Participation in vigorous (≥6 METs) LTPA men: RR = 0.72 (0.53–0.96) women: RR = 0.71 (0.48–1.05)	Adjusted for age and smoking
			3 levels of fitness based on Canadian Aerobic Fitness Test	vs recommended fitness level minimum: RR = 1.02 (0.69–1.51) undesirable: RR = 1.52 (0.72–3.18)	
Weller and Corey 1998, Canada (51)	Prospective cohort (Canada Fitness Survey), 6620 women aged ≥30 yr	7 yr; 449	Average daily energy expenditure (KKD = kcal·kg^{-1} body weight·d^{-1}) on all activities estimated from modified Minnesota LTPA questionnaire	vs lowest KKD quartile (Q1) of leisure activity Q2: RR = 0.91 (0.66–1.25) Q3: RR = 0.94 (0.72–1.23) Q4: RR = 0.89 (0.67–1.17) vs lowest KKD quartile (Q1) of nonleisure activity Q2: RR = 0.66 (0.50–0.87) Q3: RR = 0.68 (0.51–0.89) Q4: RR = 0.71 (0.50–0.87)	Adjusted for age.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Wannamethee et al., 1998, UK (50)	Prospective cohort (British Regional Heart Study), 7735 men aged 40–59 yr free of CVD and diabetes	15 yr; 1064	6 categories of physical activity based on physical activity score derived from intensity and frequency of activities reported on questionnaire	vs inactive Occasional: RR = 0.79 (0.64–0.96) Light: RR = 0.69 (0.56–0.86) Moderate: RR = 0.64 (0.50–0.81) Moderately vigorous: RR = 0.63 (0.48–0.82) Vigorous: RR = 0.54 (0.38–0.77)	Adjusted for age, smoking, alcohol use, and BMI.
Kushi et al., 1997, USA (18)	Prospective cohort (Iowa Women's Health Study), 40,417 women aged 55–69 yr	7 yr; 2260	Frequency of moderate and vigorous LTPA assessed by questionnaire	vs rarely/never participating in moderate activity 1/wk–few/mo: RR = 0.71 (0.63–0.79) 2–4 times/wk: RR = 0.63 (0.56–0.71) >4 times/wk: RR = 0.59 (0.51–0.67) *P* for trend, <0.001 vs rarely/never participating in vigorous activity 1/wk–few/mo: RR = 0.83 (0.69–0.99) 2–4 times/wk: RR = 0.74 (0.59–.093) >4 times/wk: 0.62 (0.42–0.90) *P* for trend, 0.009	Adjusted for age; reproductive factors; alcohol use; total energy intake; smoking; estrogen use; BMI at baseline and 18 yr; waist-to-hip ratio; high blood pressure; diabetes; education level; marital status; and family history of cancer. Similar findings observed when excluding women with CVD or cancer and first 3 yr of follow-up.
			3-level LTPA index based on frequency and intensity of activity	low activity index Medium: RR = 0.77 (0.69–0.86) High: RR = 0.68 (0.60–0.77) *P* for trend, <0.001	
Morgan and Clarke, 1997, UK (31)	Prospective cohort (Nottingham longitudinal study of aging and activity), 406 men and 635 women aged ≥65 yrs	10 yr; 568	3 levels of physical activity assessed by interview using detailed inventory of activities	vs high activity, men Intermediate: RR = 1.35 (0.96–1.89) Low: RR = 1.59 (1.12–2.25) vs high activity, women Intermediate: RR = 1.53 (1.12–2.09) Low: RR = 2.07 (1.53–2.79)	Adjusted for age, health index score, and smoking.
Rosengren and Wilhelmsen, 1997, Sweden (40)	Prospective cohort (Göteborg study), 7142 men aged 47–55 yr at baseline	20 yr; 684	4 levels of LTPA and OPA assessed by questionnaire. Few men fell into the highest level of LTPA so top 3 levels combined	vs sedentary LTPA Moderately active: RR = 0.84 (0.77–0.93) Regular exercise: RR = 0.83 (0.77–0.90) No significant association with OPA.	Adjusted for age, diastolic blood pressure, serum cholesterol, smoking, alcohol use, BMI, diabetes, and occupation.
Haapanen et al., 1996, Finland (12)	Prospective cohort, 1072 men aged 35–63 yr	10.8 yr; 168	Energy expenditure index assessed by questionnaire asking 23 questions on LTPA, household chores, and commuting	vs >2100 kcal·wk^{-1} 1500.1–2100 kcal·wk^{-1}: RR = 1.74 (0.87–3.50) 800.1–1500 kcal·wk^{-1}: RR = 1.10 (0.55–2.21) <800 kcal·wk^{-1}: RR = 2.74 (1.46–5.14) *P* for trend, <0.0001 Specific activities showing independent inverse associations were leisure time forestry work, gardening, and repair work	Adjusted for age. Men who were unable to participate in physical activity because of ill health were excluded.
Kampert et al., 1996, USA (14)	Prospective cohort (Aerobics Center Longitudinal Study), 25,341 men and 7080 women aged 20–88 yr	8 yr; 690	Physical fitness determined by maximal exercise test on treadmill	vs lowest fitness quintile (Q1), men Q2: RR = 0.55 (0.44–0.70) Q3: RR = 0.61 (0.48–0.78) Q4: RR = 0.52 (0.41–0.66) Q5: RR = 0.49 (0.37–0.64) *P* for trend, <0.001 vs lowest fitness quintile (Q1), women Q2: RR = 0.53 (0.30–0.95) Q3: RR = 0.56 (0.31–1.01) Q4: RR = 0.22 (0.10–0.49) Q5: RR = 0.37 (0.19–0.72) *P* for trend, <0.001	Adjusted for age, examination year, smoking, chronic illness, and ECG abnormalties.
Kaplan et al., 1996, USA (16)	Prospective cohort (Alameda County Study), 2832 men and 3299 women aged 16–94 yr	28 yr; 1226	LTPA index assessed using answers to three questions on physical exercise, sports participation, and swimming	vs lowest LTPA tertile (T1), men T2: RR = 0.46 T3: RR = 0.31 vs lowest LTPA tertile (T1), women T2: RR = 0.42 T3: RR = 0.22	Unadjusted. Adjustment for age, sex, ethnicity, education, health conditions, and social isolation still yielded significant inverse associations.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
LaCroix et al., 1996, USA (19)	Prospective cohort study, 615 men and 1030 women aged ≥65 without severe disability or CHD	4.2 yr; 128	Modified Minnesota LTPA	vs walked <1 h·wk^{-1} 1–4 h·wk^{-1}: RR = 0.83 (0.53–1.29) >4 h·wk^{-1}: RR = 0.91 (0.58–1.42)	Adjusted for age, sex, functional status, smoking, BMI, chronic disease score, self-rated health, and alcohol use. Inverse association significant for women but not men, and for ≥75 yr but not 65–74 yr.
Lissner et al., 1996, Sweden (27)	Prospective cohort (Gothenborg Prospective Study of Women), 1405 healthy women aged 38–60 yr free of CVD, cancer, and diabetes	20 yr; 424	LTPA and OPA in the 12 months before baseline assessed from questionnaire in 1968–69 and 1974–75	vs low OPA in 1968–69 Medium: RR = 0.28 (0.17–0.46) High: RR = 0.24 (0.14–0.43) vs low LTPA in 1968–69 Medium: RR = 0.56 (0.39–0.82) High: RR = 0.45 (0.24–0.86) Women who increased their LTPA between 1968–69 and 1974–75, compared with no change: RR = 1.11 (0.67–1.86); those who decreased LTPA, compared with no change, RR = 2.07 (1.39–3.09)	Adjusted for age. Findings little changed with additional adjustment for smoking, alcohol use, education, BMI, waist-to-hip ratio, diet, blood pressure, blood lipids, and peak expiratory flow.
Mensink et al., 1996, Germany (30)	Prospective cohort (German Cardiovascular Prevention Study), 7689 men and 7747 women aged 25–69 yr	5–8 yr; 110	Questionnaire assessed 18 leisure activities; one question on OPA. Total activity, LTPA, conditioning activities (all except walking, cycling, gardening) and sports examined separately	vs low total activity, men Moderate: RR = 0.56 (0.30–1.04) High: RR = 0.78 (0.42–1.44) vs low LTPA, men Moderate: RR = 0.61 (0.35–1.05) High: RR = 0.79 (0.48–1.31) vs low conditioning activity, men Moderate: RR = 0.76 (0.44–1.34) High: RR = 0.67 (0.36–1.25) vs no sports activity, men <1 h·wk^{-1}: RR = 0.49 (0.26–0.95) 1–2 h·wk^{-1}: RR = 0.57 (0.30–1.09) >2 h·wk^{-1}: RR = 0.36 (0.16–0.79) vs low total activity, women Moderate: RR = 1.24 (0.60–2.58) High: RR = 1.29 (0.58–2.85) vs low LTPA, women: Moderate: RR = 0.94 (0.51–1.75) High: RR = 0.81 (0.44–1.49) vs low conditioning activity, women: Moderate: RR = 0.38 (0.13–1.06) High: RR = 0.80 (0.42–1.54) vs no sports activity, women: <1 h·wk^{-1}: RR = 0.38 (0.12–1.23) 1–2 h·wk^{-1}: RR = 0.52 (0.23–1.17) >2 h·wk^{-1}: RR = 0.28 (0.07–1.17)	Adjusted for age, systolic blood pressure, total serum cholesterol, BMI, and smoking.
Eaton et al., 1995, Israel (9)	Prospective cohort (Israeli Ischemic Heart Disease Study), 8463 men aged ≥40 yr free of CVD	21 yr; 2593	LTPA and OPA assessed by interview using 2 questions with 4 responses each	vs sedentary LTPA Light: RR = 0.84 (0.74–0.94) Light daily: RR = 0.81 (0.73–0.90) Heavy: RR = 0.84 (0.72–0.98) vs sitting OPA Standing: RR = 0.99 (0.88–1.12) Walking: RR = 1.09 (0.99–1.20) Physical labor: RR = 1.16 (1.03–1.30)	Adjusted for age.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Lee et al., 1995, USA (21)	Prospective cohort (Harvard Alumni Health Study), 17,321 men, mean age 46 yr free of CVD, COPD, and cancer	22–26 yr; 3728	Nonvigorous (<6 METs) and vigorous (≥6 METs) LTPA energy expenditure derived from questionnaire asking about walking, stair climbing, and sports/recreation	vs lowest nonvigorous activity (energy expenditure <630 kJ·wk^{-1}) 630–1679 kJ·wk^{-1}: RR = 0.89 (0.79–1.01) 1680–3149 kJ·wk^{-1}: RR = 1.00 (0.89–1.12) 3150–6299 kJ·wk^{-1}: RR = 0.98 (0.88–1.12) ≥6300 kJ·wk^{-1}: RR = 0.92 (0.82–1.02) *P* for trend, 0.36 vs lowest vigorous activity (energy expenditure <630 kJ·wk^{-1} 630–1679 kJ·wk^{-1}: RR = 0.88 (0.82–0.96) 1680–3149 kJ·wk^{-1}: RR = 0.92 (0.82–1.02) 3150–6299 kJ·wk^{-1}: RR = 0.87 (0.77–0.99) ≥6300 kJ·wk^{-1}: RR = 0.87 (0.78–0.97) *P* for trend, 0.007	Adjusted for age, BMI, smoking, hypertension, diabetes, and early parental death; mutually adjusted for the 2 kinds of energy expenditure.
Sherman et al., 1994, USA (42)	Prospective cohort (Framingham Heart Study), 1404 women aged 50–74 yr free of CVD	16 yr; 319	Time spent sleeping, resting, or engaged in light, moderate, or heavy physical activity assessed by interview	vs lowest activity quartile (Q1) Q2: RR = 0.93 (0.70–1.23) Q3: RR = 0.65 (0.47–0.90) Q4: RR = 0.68 (0.49–0.94)	Adjusted for age, systolic blood pressure, serum cholesterol, smoking, weight, and presence or absence of glucose intolerance, LVH, COPD, and cancer. Excluding first 6 years of follow-up yielded similar results.
Sherman et al., 1994, USA (43)	Prospective cohort (Framingham Heart Study), 96 men and 189 women aged ≥75 yr free of CVD	10 yr; (N/A)	Time spent sleeping, resting, or engaged in light, moderate, or heavy physical activity assessed by interview	vs lowest activity quartile (Q1), men Q1: RR = 0.67 (0.32–1.38) Q3: RR = 0.59 (0.26–1.34) Q4: RR = 0.46 (0.20–1.03) vs lowest activity quartile (Q1), women Q2: RR = 0.70 (0.38–1.29) Q3: RR = 0.26 (0.12–0.55) Q4: RR = 0.39 (0.20–0.77)	Adjusted for age, systolic blood pressure, serum cholesterol, smoking, weight, and presence or absence of glucose intolerance, LVH, COPD, and cancer. Excluding first 3 years of follow-up yielded similar results.
Blair et al., 1993, USA (4)	Prospective cohort (Aerobics Center Longitudinal Study), 10,224 men, mean age 41.7 yr, and 3120 women, mean age 40.9 yr	8 yr; 283	LTPA assessed by questionnaire asking about 18 common activities. Subjects with no activities were classified as inactive, those who walked, jogged, or ran as highly active, and all others as moderately active	vs high LTPA, men Moderate: RR = 1.48 (0.9–2.42) Low: RR = 1.70 (1.06–2.74) *P* for trend, <0.001 vs high LTPA, women Moderate: RR = 0.75 (0.41–1.39) Low: RR = 0.95 (0.54–1.70) *P* for trend, 0.31	Adjusted for age.
Paffenbarger et al., 1993, USA (35)	Prospective cohort (Harvard Alumni Study), 10,269 men aged 45–84 yr	9 yr; 476	LTPA index (kcal·wk^{-1}) derived from questionnaires in 1962 or 1966 and 1977 asking about walking, climbing stairs, and participating in sports/recreation	vs <500 kcal·wk^{-1} in 1977 500–999 kcal·wk^{-1}: RR = 0.73 (0.54–0.95) 1000–1499 kcal·wk^{-1}: RR = 0.71 (0.53–0.96) 1500–1999 kcal·wk^{-1}: RR = 0.64 (0.46–0.92) 2000–2499 kcal·wk^{-1}: RR = 0.57 (0.40–0.87) 2500–2999 kcal·wk^{-1}: RR = 0.74 (0.50–1.12) 3000–3499 kcal·wk^{-1}: RR = 0.81 (0.52–1.32) ≤3500 kcal·wk^{-1}: RR = 0.52 (0.39–0.75) *P* for trend, <0.001	Adjusted for age.
				Taking up activities of ≥4.5 METs between 1962/1966 and 1977, compared with not engaging in these activities at both times RR = 0.77 (0.58–0.96)	Adjusted for age, smoking, BMI, hypertension, and total energy expenditure.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Sandvik et al., 1993, Norway (41)	Prospective cohort, 1960 healthy men aged 40–59 yr	16 yr; 271	Physical fitness determined by maximal exercise test on bicycle ergometer	vs lowest fitness quartile (Q1) Q2: RR = 0.59 (0.28–1.22) Q3: RR = 0.45 (0.22–0.92) Q4: RR = 0.41 (0.20–0.84)	Adjusted for age, smoking, systolic blood pressure, lipids, vital capacity, glucose tolerance, resting heart rate, BMI, and physical activity level. Physical activity unrelated to mortality after accounting for physical fitness.
Simonsick et al., 1993, USA (44)	3 prospective cohorts (Established Populations for Epidemiologic Studies of the Elderly), 2264 men and 2913 women aged ≤65 yr	6 yr; (N/A)	LTPA assessed by interview; different questions used at different sites. In all sites, "highly active" persons participated in vigorous exercise or active sports	vs inactive, East Boston Moderately active: RR = 0.85 (0.63–1.15) Highly active: RR = 0.73 (0.48–1.11) vs inactive, New Haven Moderately active: RR = 0.81 (0.60–1.11) Highly active: RR = 0.66 (0.45–0.95) vs inactive, Iowa Moderately active: RR = 1.06 (0.77–1.46) Highly active: RR = 0.59 (0.37–0.92)	Adjusted for age, sex, education, work status, smoking, respiratory symptoms, MI, stroke, diabetes, angina, self-rated health, and modified depression score.
Weyerer, 1993, Germany (52)	Prospective cohort, 1536 men and women aged ≥15 yr	5 yr; 79	LTPA assessed by interview with the question, "How often do you currently exercise for sports (never, occasionally, or regularly)?"	vs regular LTPA, men Occasional: RR = 1.50 (0.46–4.89) Never: RR = 1.76 (0.65–4.75) vs regular LTPA, women Occasional: RR = 1.14 (0.24–5.30) Never: RR = 1.51 (0.41–5.54)	Adjusted for age, social class, physical and psychiatric disorders.
Rakowski and Mor, 1992, USA (38)	Prospective cohort (Longitudinal Study of Aging), 2222 men and 3679 women aged ≥70 yr	4 yr; 1098	LTPA assessed by responses to questions: "How often do you walk a mile or more at a time?" and "Compared with other persons your age, would you say you are physically more active, less active, or the same?"	vs walk 4+ $d \cdot wk^{-1}$, men 2–3 $d \cdot wk^{-1}$: RR = 1.15 (0.70–1.90) 1 $d \cdot wk^{-1}$: RR = 1.20 (0.74–1.94) <1 d/never: RR = 1.23 (0.93–1.62) vs walk 4+ $d \cdot wk^{-1}$, women 2–3 $d \cdot wk^{-1}$: RR = 1.72 (1.01–2.05) 1 $d \cdot wk^{-1}$: RR = 1.48 (0.70–3.10) <1 d/never: RR = 2.49 (1.64–3.80) vs more/much more activity than peers, men Same: RR = 1.29 (0.99–1.67) Less/much less: RR = 1.77 (1.16–2.70) vs more/much more activity than peers, women Same: RR = 1.31 (1.05–1.63) Less/much less: RR = 1.48 (1.05–2.09)	Adjusted for age, sex, race, education, living arrangement, self-rated health, social involvement, heart condition, hypertension, stroke, diabetes, functional status, and BMI.
Leon et al., 1991, USA (24)	Prospective cohort (Multiple Risk Factor Intervention Trial [MRFIT]), 12,138 men aged 35–57 yr at high risk for CHD	10.5 yr; 958	LTPA assessed by Minnesota LTPA questionnaire	vs lowest tertile of LTPA (T1) T2: RR = 0.89 (0.77–1.04) T3: RR = 0.92 (0.79–1.07)	Adjusted for age, treatment group assignment, baseline serum cholesterol, diastolic blood pressure, and smoking.
Lindsted et al., 1991, USA (26)	Prospective cohort (Adventist Mortality Study), 9484 men aged ≥30 yr	26 yr; 4000	Total LTPA and OPA assessed by the question, "How much exercise do you get (work or play)?"	vs low total activity, attained age 50 Moderate: RR = 0.61 (0.50–0.74) High: RR = 0.66 (0.50–0.87) vs low total activity, attained age 60 Moderate: RR = 0.68 (0.59–0.78) High: RR = 0.76 (0.63–0.92) vs low total activity, attained age 70 Moderate: RR = 0.76 (0.69–0.83) High: RR = 0.89 (0.78–1.01) vs low total activity, attained age 80 Moderate: RR = 0.85 (0.78–0.92) High: RR = 1.03 (0.91–1.16) vs low total activity, attained age 90 Moderate: RR = 0.94 (0.84–1.06) High: RR = 1.19 (0.99–1.43)	Adjusted for race, smoking, education, medical illness, BMI, marital status, and diet.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Lee and Markides, 1990, USA (20)	Prospective cohort, 508 men and women aged ≥60 yr	8 yr; 119	LTPA scale derived from answers to 10-item questionnaire	No significant trend for increasing LTPA, $P > 0.05$	Adjusted for age, sex, ethnicity, education, and self-rated health.
Blair et al., 1989, USA (6)	Prospective cohort (Aerobics Center Longitudinal Study), 10,224 men, mean age 41.7 yr, and 3120 women, mean age 40.9 yr	8 yr; 283	Physical fitness determined by maximal treadmill exercise test	vs highest fitness quintile (Q5), men Q4: RR = 1.17 (0.63–2.17) Q3: RR = 1.46 (0.81–2.63) Q2: RR = 1.37 (0.76–2.50) Q1: RR = 3.44 (2.05–5.77) *P* for trend, <0.05 vs highest fitness quintile (Q5), women Q4: RR = 0.76 (0.27–2.11) Q3: RR = 1.43 (0.60–3.44) Q2: RR = 2.42 (1.09–5.37) Q1: RR = 4.65 (2.22–9.75) *P* for trend, <0.05	Adjusted for age.
Slattery et al., 1989, USA (46)	Prospective cohort (U.S. Railroad Study), 3043 middle-aged men free of CVD	17–20 yr; (N/A)	Weekly energy expended in LTPA, derived from Minnesota LTPA questionnaire	vs >2000 $kcal \cdot wk^{-1}$ 1001–1999 $kcal \cdot wk^{-1}$: RR = 1.04 (1.01–1.08) 251–1000 $kcal \cdot wk^{-1}$: RR = 1.08 (1.01–1.15) ≤250 $kcal \cdot wk^{-1}$: RR = 1.21 (1.03–1.42)	Adjusted for age, systolic blood pressure, serum cholesterol level, and smoking. In simultaneous analyses of light/moderate and vigorous activities, only vigorous activity was significantly and inversely related to all-cause mortality.
Slattery and Jacobs, 1988, USA (45)	Prospective cohort (US Railroad Study), 2431 men aged 22–79 yr free of CVD	17–20 yr; 630	Physical fitness assessed by heart rate on submaximal 3-minute treadmill test	vs ≤105 $beats \cdot min^{-1}$ 106–115 $beats \cdot min^{-1}$: RR = 1.07 (1.02–1.13) 116–127 $beats \cdot min^{-1}$: RR = 1.15 (1.10–1.21) ≥127 $beats \cdot min^{-1}$: RR = 1.23 (1.17–1.30)	Adjusted for age, systolic blood pressure, serum cholesterol, and smoking. Similar associations seen among men with <1000 $kcal \cdot wk^{-1}$ or ≥1000 $kcal \cdot wk^{-1}$ in LTPA.
Leon et al., 1987, USA (25)	Prospective cohort (Multiple Risk Factor Intervention Trial [MRFIT]), 12,138 men aged 35–57 yr at high risk of CHD	7 yr; 488	LTPA assessed by Minnesota LTPA questionnaire	vs lowest tertile (T1) T2: RR = 0.73 (0.59–0.91) T3: RR = 0.87 (0.70–1.07)	Adjusted for age, diastolic blood pressure, serum cholesterol, smoking, and treatment group.
Paffenbarger, et al., 1986, USA (34)	Prospective cohort (Harvard Alumni Study), 16,936 men aged 35–74 yr and free of CHD	12–16 yr; 1413	LTPA index ($kcal \cdot wk^{-1}$) derived from questionnaire asking about walking, climbing stairs, and participating in sports/ recreation	vs <500 $kcal \cdot wk^{-1}$ 500–999 $kcal \cdot wk^{-1}$: RR = 1.00 1000–1499 $kcal \cdot wk^{-1}$: RR = 0.73 1500–1999 $kcal \cdot wk^{-1}$: RR = 0.63 2000–2499 $kcal \cdot wk^{-1}$: RR = 0.62 2500–2999 $kcal \cdot wk^{-1}$: RR = 0.52 3000–3499 $kcal \cdot wk^{-1}$: RR = 0.46 ≤3500 $kcal \cdot wk^{-1}$: RR = 0.62 *P* for trend, <0.0001	Adjusted for age.
Menotti and Seccareccia, 1985, Italy (29)	Prospective cohort (Italian Railroad Study), 99,049 men aged 40–59 yr	5 yr; 2661	OPA based on estimated energy cost of task performed	vs. sedentary OPA Moderate: RR = 1.03 ($P > 0.05$) Heavy: RR = 1.04 ($P > 0.05$)	
Kannel and Sorlie, 1979, USA (15)	Prospective cohort (Framingham Heart Study), 1909 men and 2311 women aged 35–69	14 yr; 552	Physical activity index derived from interview on hours resting and various job and extracurricular activities	No significant trend for increasing physical activity index in men and women, $P > 0.05$	Adjusted for age, systolic blood pressure, smoking, serum cholesterol, glucose intolerance, and LVH. Physical activity significantly associated with lower CHD rates in men.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Breslow and Buell, 1960, USA (7)	Proportional mortality study, 2,984,867 male California workers aged 20–64	(not applicable); 72,664	OPA derived from Census Bureau occupational list	vs sedentary OPA Light: RR = 1.10 Medium: RR = 1.21 Heavy nonfarm: RR = 1.52 Heavy farm: RR = 1.11	Data from death certificates. Did not adjust for smoking. CHD mortality lower among workers with heavy OPA.
Morris and Heady, 1953, UK (32)	Mortality study, ≈2.5 million male British workers aged 45–64	(not applicable); 5,037	OPA estimated from job descriptions	vs light OPA, smoking possible occupations Intermediate/doubtful: RR = 1.00 Heavy: RR = 0.75 vs light OPA, smoking prohibited occupations Intermediate/doubtful: RR = 0.52 Heavy: RR = 0.37	Data from death certificates. Smoking prohibited occupations included miners, textile workers, those in chemical processes, policemen, and printers.

* Figures in parentheses are 95% confidence limits. If not provided, they were not available. *P*-values for trend come from tests of linear trend.
BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; LTPA, leisure time physical activity; LVH, left ventricular hypertrophy; MET, metabolic equivalent; MI, myocardial infarction; N/A, not available; OPA, occupational physical activity; RR, relative risk.

both of which will generate a volume of energy expenditure on the order of 1000 kcal·wk^{-1}, is likely to decrease all-cause mortality rates. However, we cannot rule out that a lesser volume of physical activity may be associated with benefit for all-cause mortality (18,25,35).

Intensity of physical activity. To ascertain the dose response between intensity of physical activity and all-cause mortality, activities of different intensity must be simultaneously considered to prevent confounding by volume of physical activity. As discussed earlier, a larger volume of physical activity is clearly associated with decreased all-cause mortality rates, and vigorous-intensity activities generate higher levels of energy expenditure than moderate-intensity activities when time is held constant. Alternately, investigators can examine select populations that engage only (or primarily) in moderate-intensity or vigorous-intensity activity. Although such studies can answer the question of whether moderate-intensity or vigorous-intensity physical activity is associated with decreased all-cause mortality rates, they do not allow direct comparison of the merits of moderate-intensity activity with vigorous-intensity activity; i.e., dose-response with intensity.

Only four studies examined intensity of physical activity, simultaneously considering physical activity of other intensities; one reported that moderately vigorous (≥4.5 METs) activities were beneficial compared with activities of lesser intensity (35), whereas three noted that only vigorous physical activity (≥6 METs), but not less-intense physical activity, predicted lower all-cause mortality rates (21,22,46).

Some of the studies examined intensity of physical activity in relation to all-cause mortality rates but did not simultaneously adjust for activities of different intensities. Among Danish subjects with any LTPA, participation in sports conferred further risk reduction for all-cause mortality (2). Participation in vigorous activities of ≥ 6 METs was associated with a lower risk of all-cause mortality in Finnish subjects (17). In German subjects, participation in sports but not other activities reduced rates of all-cause mortality (30). In all three of these studies, it is unclear whether the findings reflect additional benefit with greater volume of physical activity from participation in sports or vigorous activities. In three other studies where subjects engaged primarily in moderate-intensity physical activity, investigators did observe a benefit for all-cause mortality with increasing levels of participation in these activities (13,18,25).

Duration and frequency of physical activity. To isolate the effect of duration or frequency of physical activity on all-cause mortality rates, it is imperative to hold volume of physical activity constant to prevent confounding by volume of activity. In other words, if two individuals expend the same volume of energy, does it matter whether one expends this volume in several, shorter bouts of physical activity or in fewer, longer bouts?

None of the 44 studies addressed this question in relation to all-cause mortality. One recent study did examine this issue in relation to coronary heart disease (CHD) (23). The investigators concluded that duration (examined in 15-min intervals) and frequency did not predict CHD rates once volume of physical activity was accounted for. That is,

shorter sessions of exercise had similar effects on CHD risk compared with longer sessions, as long as the total energy expended was similar.

Four of the studies in Table 1 examined duration (19) or frequency (18,30,38) of physical activity in relation to all-cause mortality rates. However, because the analyses did not control for volume of physical activity, the findings essentially reflect the association between volume of physical activity and all-cause mortality.

DISCUSSION

There is a sufficient body of evidence to evaluate the dose-response relation between physical activity and all-cause mortality rates. We identified 44 studies conducted in Canada, Denmark, Finland, Germany, Israel, Italy, the Netherlands, Norway, Sweden, the United Kingdom, and United States that addressed this issue. Based on these studies, there is clear evidence of an inverse dose-response relation between volume of physical activity (or level of physical fitness) and all-cause mortality rates. The preponderance of evidence suggests that risk of dying during a given period continues to decline with increasing levels of physical activity rather than displaying a threshold or L-shaped relation. This inverse dose-response relation has been shown in men and women, and in younger and older (≥60 yr) subjects.

Fewer data are available regarding the volume of physical activity needed to reduce all-cause mortality rates. It appears that minimal adherence to current or previous physical activity recommendations, which will generate energy expenditure on the order of 1000 $kcal \cdot wk^{-1}$, results in decreased all-cause mortality rates with risk reductions on the order of 20–30%. In addition, three studies suggest that an even lower volume of physical activity may be associated with benefit (18,25,35).

Sparse data exist regarding the components that contribute to the volume of physical activity: intensity, duration, and frequency. Studies conducted in populations engaged primarily in moderate-intensity physical activity show that higher levels of moderate-intensity physical activity are associated with lower all-cause mortality rates, presumably because of higher volume of physical activity. However, hardly any data are available to determine for two individuals expending the same volume of physical activity whether there is additional benefit for the one who expends all of it in vigorous-intensity physical activity compared with the other who expends all of it in moderate-intensity activity.

No data are available to answer the questions on duration and frequency. That is, it is unknown whether a given volume of physical activity expended in shorter, more frequent bouts has different effects on all-cause mortality rates than that same volume expended in longer, less frequent bouts.

Although not directly relevant to the issue of dose response, an important public health issue is determining whether changing from a sedentary lifestyle to an active one (or from an unfit cardiorespiratory profile to a fit one) is associated with lower all-cause mortality rates. The studies reviewed suggest that increasing physical activity or fitness is associated with benefit (3,10,35), whereas decreasing levels is associated with harm (27). Two other studies that did not satisfy the criteria for this review also support the benefit of increasing physical activity or fitness levels (5,36).

Evidence category. All studies investigating dose-response associations between physical activity and all-cause mortality have been observational studies. No randomized clinical trial data are available. Therefore, the above conclusions are based on Evidence Category C.

Because the conclusions are based on observational studies, two potential limitations need to be considered. First, are the observed associations the result of bias? If poor health caused subjects to decrease their physical activity level before the start of the study, this would cause investigators to observe a spurious inverse relation between higher levels of physical activity and lower all-cause mortality rates. Such a bias is unlikely to account for the results because the inverse associations have been noted in studies that included only healthy subjects. It is also possible that apparently healthy subjects with undiagnosed, serious illnesses (who are likely to die in the early years of follow-up) may have decreased their physical activity before study entry. Employing a built-in lag period minimizes this bias. Several studies that considered a lag period observed an inverse association between physical activity and all-cause mortality rates. Finally, the effect of this bias is diluted with longer follow-up periods; many of the studies that reported an inverse association had periods of follow-up lasting 10 or more yr.

A second potential limitation is confounding by other health habits. Individuals who are physically active are likely to be health conscious in other ways as well, such as not smoking, eating a healthier diet, and maintaining a healthy weight. However, the inverse association between physical activity level and all-cause mortality rates are unlikely to be due to these other health habits, because studies that controlled for these potential confounders continued to observe an inverse association.

RESEARCH RECOMMENDATIONS

Although the most rigorous data for a cause-and-effect relation come from well-designed and conducted randomized clinical trials, it is simply not feasible to conduct such trials in the context of examining the dose-response relation between physical activity and all-cause mortality. Thus, answers concerning this relation must come from observational epidemiologic studies. These observational data will be strengthened by data from randomized clinical trials of physical activity and short-term health outcomes that in themselves predict mortality (e.g., blood pressure, lipid profile, glucose tolerance), as well as by data from laboratory studies on plausible biologic mechanisms linking physical activity with decreased mortality rates.

With regard to observational epidemiologic studies that directly assess the dose-response relation between physical

activity and all-cause mortality rates, we propose the following areas for future research:

1. Studies must assess physical activity in sufficient detail to permit translation of findings to public health recommendations. For example, studies asking subjects whether they get none, some, or a lot of physical activity during work or leisure-time are difficult to interpret with respect to the dose of physical activity. Assessment of the kinds of activity, the intensity (both on an absolute scale and relative to the capacity of the individual subject, the latter being especially relevant for older persons), duration, and frequency are desirable.

2. The existing data suggest that current and previous physical activity recommendations will generate sufficient volume of physical activity to decrease all-cause mortality rates. However, there are some provocative, but not definitive, data suggesting that an even lower volume of physical activity—perhaps half of what is currently recommended—may be all that is needed. This is important to ascertain because recommending an even lower volume of physical activity for health surely will be more palatable to the many sedentary individuals in the world.

3. It is unclear whether there is a dose-response relation between intensity of physical activity and all-cause mortality rates above the contribution of intensity to volume of physical activity. Future studies should analyze data on intensity of physical activity while controlling for volume of physical activity. Although expending the minimum volume of energy for health, whether from moderate- or vigorous-intensity physical activity, may be all that is relevant to the public, recommendations for higher-intensity activity may be more attractive to busy individuals because they deliver greater volume of activity in shorter time periods. They may be even more attractive if they engender additional benefit for all-cause mortality.

4. There are no data on whether duration and frequency of physical activity are important to all-cause mortality beyond their contribution to volume of physical activity. This area has direct bearing on the current physical activity recommendation that allows for accumulation of short bouts of physical activity. Future studies should analyze the associations of duration and frequency with all-cause mortality rate, controlling for the volume of energy expended.

5. There are no data on whether patterns of physical activity conforming to previous physical activity recommendations ("structured exercise") offer commensurate benefit for all-cause mortality rates as patterns of physical activity conforming to current physical activity guidelines ("lifestyle physical activity"), when the same volume of physical activity is generated. Studies that satisfy research recommendation (1) should have adequate information to classify subjects according to both patterns of physical activity and be capable of examining mortality rates in both groups.

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