

# Dose–Response Relationship between Exercise and Respiratory Disease Mortality

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## ABSTRACT

WILLIAMS, P. T. Dose–Response Relationship between Exercise and Respiratory Disease Mortality. *Med. Sci. Sports Exerc.*, Vol. 46, No. 4, pp. 711–717, 2014. **Purpose:** The objective of this study is to assess prospectively the dose–response relationship between respiratory disease (ICD<sub>10</sub>: J1–99), pneumonia (ICD<sub>10</sub>: J12.0–18.9), and aspiration pneumonia mortality (ICD<sub>10</sub>: J69) versus baseline walking and running energy expenditure (MET·h·d<sup>-1</sup>, 1 MET = 3.5 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>). **Methods:** We conducted Cox proportional hazard analyses of 109,352 runners and 40,798 walkers adjusted for age, sex, smoking, diet, alcohol, and education. **Results:** There were 236 deaths with respiratory disease listed as the underlying cause, and 833 deaths were respiratory disease related (entity axis diagnosis). Included among these were 79 deaths with pneumonia listed as the underlying cause and 316 pneumonia-related deaths, and 77 deaths were due to aspiration pneumonia. There was no significant difference in the effect of running compared with walking (per MET-hour per day) on mortality; thus, runners and walkers were combined for analysis. Respiratory disease mortality decreased 7.9% per MET-hour per day as the underlying cause (95% CI, 1.6%–14.0%;  $P = 0.01$ ) and 7.3% for all respiratory disease-related deaths (95% CI, 4.2%–10.4%;  $P = 10^{-5}$ ). Pneumonia mortality decreased 13.1% per MET-hour per day as the underlying cause (95% CI, 2.6%–23.2%;  $P = 0.01$ ) and 10.5% per MET-hour per day for all pneumonia-related deaths (95% CI, 5.4%–15.5%;  $P = 0.0001$ ). The risk for aspiration pneumonia mortality also did not differ between running and walking, and it decreased 19.9% per MET-hour per day run or walked (95% CI, 8.9%–30.2%;  $P = 0.0004$ ). These results remained significant when additionally adjusted for body mass index. **Conclusions:** Higher doses of running and walking were associated with lower risk of respiratory disease, pneumonia, and aspiration pneumonia mortality in a dose-dependent manner, and the effects of running and walking appear equivalent. These effects appear to be independent of the effects of exercise on cardiovascular disease. **Key Words:** PHYSICAL ACTIVITY, PNEUMONIA, PREVENTION, COHORT

Pneumonia is the leading cause of death from infection in the United States, and in combination with influenza, it ranks eighth among all underlying causes of death (6,14). Hospitalization is required for 40% to 50% of those infected, with approximately 10% requiring intensive care (24). By 2020, the annual number of hospitalizations for community-acquired pneumonia is expected to rise to 1 million in the United States as the population ages (26). In the elderly, the risk for community-acquired pneumonia is increased by heart disease, chronic lung disease, immunosup-

pressive drugs, alcoholism, and increasing age (9). Long-term survival of community-acquired pneumonia is diminished by age, male sex, low educational achievement, and comorbid illnesses (14), with age and comorbid conditions being stronger predictors of survival than abnormal acute physiologic or laboratory findings (13).

Less common are nosocomial (hospital-acquired) and aspiration pneumonia. Treatment of nosocomial pneumonia is becoming increasingly problematic because of increases in antibiotic resistance of Gram-negative bacteria (22), and it has greater mortality (38% to over 70% (15)) than community-acquired pneumonia. Aspiration pneumonia, which is an infection of the lung caused by the inhalation of vomit or food, currently ranks as the 15th leading cause of death in the United States (6). Its occurrence may indicate impaired ability to remove food or vomit by coughing due to age, inebriation, a complication of general anesthesia, or debilitation, as, for example, because of stroke (21).

Public health guidelines recommend 150 min·wk<sup>-1</sup> of moderate-intensity or 75 min·wk<sup>-1</sup> of vigorous-intensity aerobic physical activity (20). Multiple health benefits have

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been ascribed to physical activity (20). However, these benefits do not currently include decreased respiratory disease risk. Two reports from the Nurses' Health Study II suggest that the risk for community-acquired pneumonia decreases with greater leisure-time and recreational physical activity in women, but not when adjusted for body mass index (BMI) (1,17), and, to our knowledge, there have been no significant risk reductions reported for men. However, reductions in pneumonia risk would be consistent with evidence suggesting that regular exercise improves immune function and attenuates its decline with age (3,7,8,11,12,19,35,37).

This report examines the association of running and walking with mortality due to respiratory disease in the National Walkers' and Runners' Health Studies, prospective epidemiological cohorts of over 150,000 walkers and runners whose mortality follow-up has been completed through 2008. The runners and walkers reported usual distance run or walked per week as part of their baseline questionnaire, which has been shown to be superior to the more traditional time-based physical activity assessments for testing epidemiological hypotheses (32–34). The large sample size, and the superior quantification of physical activity, provides a unique opportunity to test whether greater exercise energy expenditure predicts lower risk for respiratory diseases in general and for pneumonia and aspiration pneumonia in particular.

## MATERIALS AND METHODS

The National Walkers' and Runners' Health Studies have been described in detail (27–34). Walkers were recruited between 1999 and 2001, whereas runners were recruited in two waves, between 1991 and 1993 (phase I) and between 1998 and 2001 (phase II), through solicitation of subscribers of activity-targeted publications and participants at footrace events. The three cohorts may be more accurately characterized as a single cohort that targeted the runners and walkers, because all three used the same questionnaire (modified slightly for the different activities), the same sampling domain (subscription lists to running and walking publications, and running and walking events), as well as the same survey staff, and were funded by the same grants.

Participants completed a four-page survey on running and walking history, height, weight, diet, smoking, and history of diseases. Intakes of meat and fruit were based on the questions "During an average week, how many servings of beef, lamb, or pork do you eat," and "... pieces of fruit do you eat?" Alcoholic beverage consumption was ascertained from the corresponding questions for 4-oz (112 mL) glasses of wine, 12-oz (336 mL) bottles of beer, and mixed drinks and liqueurs, and alcohol intake was estimated from 10.8-g/4-oz glass of wine, 13.2-g/12-oz bottle of beer, and 15.1-g/mixed drink. Running energy expenditure was expressed in units of METs, in which 1 MET is the energy expended sitting at rest ( $3.5 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) (4). Running MET values were calculated as

$1.02 \text{ MET} \cdot \text{h} \cdot \text{km}^{-1}$  (34). Previously, we reported strong correlations between repeated questionnaires for self-reported running distance ( $r = 0.89$ ) (29). Walking energy expenditure ( $\text{MET} \cdot \text{h} \cdot \text{d}^{-1}$ ) was computed by converting the reported usual weekly distance into duration (i.e., distance divided by mph for their usual walking pace) and then calculating the product of the average hours walked per day and the MET value corresponding to their reported pace (32,33). The study protocol was approved by the University of California Berkeley committee for the protection of human subjects, and all subjects provided a signed statement of informed consent.

Mortality surveillance was completed through 2008 using the National Death Index plus (16). International Classification of Disease codes versions 9 (ICD<sub>9</sub>) and 10 (ICD<sub>10</sub>) (36) were used to identify deaths due to respiratory disease (ICD<sub>9</sub>: 460–519, 799.1, ICD<sub>10</sub>: J1–99), pneumonia (ICD<sub>9</sub>: 480–489, ICD<sub>10</sub>: J12.0–18.9), and aspiration pneumonia (ICD<sub>9</sub>: 507, ICD<sub>10</sub>: J69). The underlying cause of death is "the disease or injury that initiated the chain of morbid events that led directly and inevitably to death" (25). Other contributing causes of death are "all other significant diseases, conditions, or injuries that contributed to death but which did not result in the underlying cause of death" (25). "All pneumonia-related mortality" and "all respiratory disease-related mortality" refer to pneumonia or respiratory disease listed as either underlying or other contributing causes of death. Aspiration pneumonia was seldom listed as a contributing cause of death (nine deaths), and therefore, only the underlying cause of death was analyzed.

Cox proportional hazard analyses (JMP version 5.1; SAS Institute, Cary, NC) were used to test whether total and cause-specific mortalities were significantly related to MET-hour per day run or walked when adjusted for baseline age (age and age<sup>2</sup>), sex, years of education, baseline smoking status (current smoker vs nonsmoker), cohort, and intakes of meat, fruit, and alcohol. Results are presented as HR and their percent risk reduction (calculated as  $100(\text{HR} - 1)$ ) per MET-hour per day run or walked, and for five categories of exercise energy expenditure: 1) falling short of the current exercise recommendations for health ( $450 \text{ MET} \cdot \text{min} \cdot \text{wk}^{-1} = 1.07 \text{ MET} \cdot \text{h} \cdot \text{d}^{-1}$  (4)), 2) achieving the exercise recommendations ( $450$  to  $750 \text{ MET} \cdot \text{min} \cdot \text{wk}^{-1} = 1.07$  to  $1.8 \text{ MET} \cdot \text{h} \cdot \text{d}^{-1}$  (4)), and 3) exceeding the recommendations by one- to twofold ( $1.8$  to  $3.6 \text{ MET} \cdot \text{h} \cdot \text{d}^{-1}$ ), two- to threefold ( $3.6$ – $5.4 \text{ MET} \cdot \text{h} \cdot \text{d}^{-1}$ ), or threefold or more of the recommended levels ( $\geq 5.4 \text{ MET} \cdot \text{h} \cdot \text{d}^{-1}$ ). Deaths occurring within 1 yr of the baseline survey were excluded.

The primary hypothesis was that MET-hours per day of exercise would be inversely related to all pneumonia-related mortality, with a significance level of  $P \leq 0.05$ . Secondary hypotheses were that MET-hours per day of exercise was significantly related to pneumonia as an underlying cause of death, all respiratory disease-related mortality, respiratory disease as an underlying cause of death, and aspiration pneumonia as an underlying cause of death. Analyses were repeated excluding all cardiovascular disease (CVD)-related

mortality (ICD<sub>9</sub>: 390–448, ICD<sub>10</sub>: I00–78) to ensure the observed associations with respiratory diseases were not due to their associations with CVD. Schoenfeld residuals were checked for serious departures from proportionality. The significance for the decreased mortality with MET-hour per day of running or walking was verified in every case by logistic regression analyses, which included follow-up duration as a covariate (one exception,  $P = 0.06$  for pneumonia as an underlying cause in females, results not displayed).

## RESULTS

The baseline characteristics of the cohorts and the numbers of death by respiratory disease end points during the 11.4-yr average follow-up are displayed in Tables 1 and 2, respectively.

Table 2 presents the HR for the covariates used in the analyses when all were included simultaneously in the model and adjusted for age and exercise level. Compared with men, women had significantly lower risk for all respiratory disease end points studied. Runners, as a group, were also at lower risk for respiratory disease mortality than walkers. Other variables showing significant associations with mortality were 1) years of education with lower risk of respiratory disease as an underlying cause of death and all respiratory disease related deaths, 2) smoking with all respiratory disease- and pneumonia-related deaths and deaths with pneumonia as an underlying cause, 3) greater fruit intake with lower risk of respiratory deaths as an underlying cause, and 4) greater BMI with increased risk for all respiratory disease-related deaths and decreased risk for pneumonia as an underlying cause.

**Respiratory disease deaths as the underlying cause.** There was no significant difference in the decrease in respiratory disease deaths per MET-hours per day run versus MET-hours per day walked ( $P = 0.58$ ), so their energy expenditures were combined and the analyses adjusted for cohort effects. The risk for respiratory disease mortality decreased 7.9% per MET-hour per day, which remained essentially unaffected by adjustment for BMI (Table 3). Figure 1 shows that compared with falling short of the recommended exercise level ( $<1.07 \text{ MET}\cdot\text{h}\cdot\text{d}^{-1}$ ), there was no significant reduction in risk for merely satisfying the exercise recommendations (10% decrease), whereas the risk for

respiratory disease mortality decreased 34.5% for exceeding the recommendations by one- to twofold and 45.3% for exceeding the recommendations by twofold or higher (HR, 0.55; 95% CI, 0.36–0.83;  $P = 0.005$ ). Very similar risk reductions were experienced in men and women (Table 3), with their difference in statistical significance reflecting more their differences in the number of deaths (163 men and 73 women) rather than their effect size.

**All respiratory disease-related deaths.** The estimated effects of exercise energy expenditure on all respiratory disease-related deaths were also not significantly different between walking and running ( $P = 0.10$ ). Table 3 shows that for running and walking combined, the risk for all respiratory disease-related deaths decreased 7.3% per MET-hour per day, which persisted when adjusted for BMI, and was significant in both males and females separately (Table 3). Forty-nine percent of the respiratory disease deaths had CVD listed as a contributing cause, a mortality end point known to decrease with running (30,31). However, the reduction in the risk for all respiratory disease-related deaths persisted when all CVD-related deaths were excluded (Table 3). Only two-thirds of the potential risk reduction was achieved by meeting the current exercise guidelines (Fig. 1). Exceeding the current exercise guidelines was associated with a significantly greater decrease in all respiratory disease-related deaths than merely satisfying the guidelines (i.e.,  $>1.8$  vs  $1.07$  to  $1.8 \text{ MET}\cdot\text{h}\cdot\text{d}^{-1}$ ; HR, 0.79; 95% CI, 0.63–0.98;  $P = 0.04$  for all respiratory disease-related deaths).

**Pneumonia as the underlying cause.** The risk for pneumonia decreased 13.1% per MET-hour per day run or walked, and was significant both with and without adjustment for BMI and when the analyses were restricted to women (Table 3,  $P = 0.07$  for men). Compared with not achieving the current exercise recommendation, the risk for pneumonia as an underlying cause of death decreased 21% for meeting the guidelines, 31% by exceeding the guidelines by one- to twofold, 35% by exceeding the guidelines by two- to threefold, and 37% by exceeding the guidelines by threefold or more when all CVD-related deaths were excluded (not displayed).

**All pneumonia-related deaths.** The risk for all pneumonia-related deaths decreased 10.5% per MET-hour per day run or walked, and was significant both with and

TABLE 1. Baseline characteristics of the cohorts.

	Males		Females	
	Runners	Walkers	Runners	Walkers
Sample (N)	63,267	8103	46,085	32,695
Age (yr)*	40.40 ± 10.85	61.16 ± 13.07	38.18 ± 10.10	50.39 ± 10.85
Education (yr)*	16.42 ± 2.50	15.92 ± 2.80	16.04 ± 2.55	15.02 ± 2.52
Current smokers (%)	1.58	4.76	2.30	5.52
Alcohol (g·d <sup>-1</sup> )*	11.52 ± 16.21	10.40 ± 16.77	7.10 ± 10.43	5.50 ± 10.46
Meat (servings per day)*	0.42 ± 0.40	0.46 ± 0.41	0.26 ± 0.31	0.37 ± 0.49
Fruit (pieces per day)*	1.51 ± 1.25	1.52 ± 1.19	1.50 ± 1.11	1.57 ± 1.30
BMI (kg·m <sup>-2</sup> )*	24.16 ± 2.82	27.20 ± 4.72	21.65 ± 2.74	25.83 ± 5.55
Running and walking (MET·h·d <sup>-1</sup> )*	4.43 ± 3.31	2.23 ± 1.66	4.89 ± 3.08	2.20 ± 1.60

\*Means ± SD.

TABLE 2. HR from Cox proportional hazard analyses (95% CI) for respiratory disease, pneumonia, and aspiration pneumonia mortality versus other risk factors.

	Respiratory Disease ICD <sub>9</sub> : 460-519, 799.1, ICD <sub>10</sub> : J1-99		Pneumonia ICD <sub>9</sub> : 480-489, ICD <sub>10</sub> : J12.0-18.9		Aspiration Pneumonia ICD <sub>9</sub> : 507, ICD <sub>10</sub> : J69	
	Underlying	All Related Mortality	Underlying	All Related Mortality	Underlying	All Related Mortality
Deaths	81	349	33	141	28	28
Runners	155	484	46	175	49	49
Walkers						
Female	0.420 (0.308, 0.569), $P = 10^{-8}$	0.561 (0.476, 0.660), $P = 10^{-11}$	0.403 (0.229, 0.693), $P = 0.0009$	0.458 (0.347, 0.601), $P = 10^{-8}$	0.222 (0.118, 0.398), $P = 10^{-7}$	0.222 (0.118, 0.398), $P = 10^{-7}$
Education ( $yr^{-1}$ )	0.948 (0.904, 0.995), $P = 0.03$	0.967 (0.942, 0.992), $P = 0.01$	0.990 (0.911, 1.050), $P = 0.82$	0.996 (0.956, 1.034), $P = 0.86$	0.975 (0.898, 1.049), $P = 0.54$	0.975 (0.898, 1.049), $P = 0.54$
Smokers	1.728 (0.818, 3.188), $P = 0.14$	3.362 (2.518, 4.397), $P = 10^{-12}$	3.367 (1.166, 7.697), $P = 0.03$	2.723 (1.542, 4.442), $P = 0.001$	0.740 (0.042, 3.365), $P = 0.75$	0.740 (0.042, 3.365), $P = 0.75$
Meat (per servings per day)	1.105 (0.923, 1.157), $P = 0.19$	1.003 (0.824, 1.121), $P = 0.97$	1.006 (0.509, 1.187), $P = 0.99$	0.782 (0.549, 1.085), $P = 0.15$	1.139 (0.727, 1.222), $P = 0.42$	1.139 (0.727, 1.222), $P = 0.42$
Fruit (per pieces per day)	0.849 (0.749, 0.955), $P = 0.006$	0.956 (0.903, 1.012), $P = 0.12$	0.845 (0.678, 1.027), $P = 0.10$	0.957 (0.870, 1.039), $P = 0.34$	0.964 (0.791, 1.072), $P = 0.69$	0.964 (0.791, 1.072), $P = 0.69$
Alcohol ( $g \cdot d^{-1}$ ) <sup>-1</sup>	1.000 (0.991, 1.008), $P = 0.95$	1.000 (0.995, 1.004), $P = 0.88$	0.984 (0.962, 1.002), $P = 0.08$	0.994 (0.985, 1.001), $P = 0.11$	0.987 (0.967, 1.004), $P = 0.14$	0.987 (0.967, 1.004), $P = 0.14$
Runner	0.364 (0.206, 0.622), $P = 0.0002$	0.769 (0.599, 0.987), $P = 0.04$	0.940 (0.390, 2.149), $P = 0.89$	1.049 (0.705, 1.547), $P = 0.81$	0.544 (0.205, 1.313), $P = 0.18$	0.544 (0.205, 1.313), $P = 0.18$
BMI ( $kg \cdot m^{-2}$ ) <sup>-1</sup>	0.994 (0.960, 1.028), $P = 0.73$	1.018 (1.000, 1.036), $P = 0.05$	0.915 (0.848, 0.982), $P = 0.01$	0.990 (0.959, 1.022), $P = 0.55$	1.023 (0.961, 1.081), $P = 0.46$	1.023 (0.961, 1.081), $P = 0.46$

HR when all variables are included simultaneously in the model with age (age<sup>2</sup>) and cohort effect.

without adjustment for BMI and when the analyses were restricted to men and women. Compared with not achieving the current exercise recommendation, the risk for all pneumonia-related deaths decreased 36.2% for meeting the guidelines, 50.6% by exceeding the guidelines by one- to twofold, 55.9% by exceeding the guidelines by two- to threefold, and 54.0% by exceeding the guidelines by threefold or more (Fig. 1, middle). The reductions in risk for all pneumonia-related mortality were somewhat weakened by excluding CVD-related deaths but remained significant except for merely meeting the guidelines.

**Aspiration pneumonia as the underlying cause.**

There was no difference in the per MET-hour per day reduction in aspiration pneumonia mortality between running and walking ( $P = 0.89$ ). Its risk decreased 19.9% per MET-hour per day run or walked before adjustment for BMI and 19.1% after adjustment. Figure 1 (bottom) shows that aspiration pneumonia was less likely to occur in those that exceeded 1.8 MET·h·d<sup>-1</sup> run or walked (i.e., exceeded the current recommendations).

**Other respiratory disease-related deaths.**

The remaining 441 deaths included 180 respiratory failures of an unspecified nature and 261 deaths involving other respiratory causes. Neither the respiratory failures (HR, 0.985; 95% CI, 0.924–1.045;  $P = 0.62$ ) nor the other respiratory causes (HR, 0.943; 95% CI, 0.885–1.002;  $P = 0.06$ ) were significantly related to MET-hours per day run or walked.

**DISCUSSION**

These analyses show that the risks for respiratory diseases and pneumonia as underlying and contributing causes of mortality decreased significantly in association with greater baseline exercise energy expenditure (MET·h·d<sup>-1</sup>), and it did not differ significantly between running (a vigorously intense exercise) and walking (a moderately intense exercise). Exceeding physical activity recommendations beyond that currently recommended appeared to produce substantial reductions in risk. Aspiration pneumonia mortality also decreased significantly with greater METs run or walked, with those who exceeded the recommendations having ≥60% lower risk for aspiration pneumonia as those who fell short of the recommendations.

The current results substantially strengthen the evidence linking pneumonia risk to physical activity in women. Specifically, the women's risk for pneumonia as an underlying cause decreased significantly per MET-hour per day both before (Table 3) and after adjustment for BMI (HR, 0.644; 95% CI, 0.420–0.916;  $P = 0.01$ ). At best, prior reports suggest a weak association that loses its statistical significance when adjusted for BMI. In particular, a 2-yr follow-up of 78,062 women who participated in the Nurses' Health Study showed that the risk for community-acquired pneumonia decreased 6% for the second, 21% for the third, 26% for the fourth, and 34% for the fifth quintile of recreational



TABLE 3. HRs from Cox proportional hazard analyses (95% CI) for respiratory disease, pneumonia, and aspiration pneumonia mortality versus MET-hours per day run or walked.

	Sexes Combined			Sex Specific	
	No BMI Adjustment	Adjusted for BMI	Males Only	Females Only	
Respiratory disease-underlying cause					
All cases	0.921 (0.860, 0.984), <i>P</i> = 0.01	0.915 (0.853, 0.979), <i>P</i> = 0.009	0.926 (0.859, 0.996), <i>P</i> = 0.04	0.918 (0.776, 1.067), <i>P</i> = 0.27	
All respiratory disease-related deaths					
All cases	0.927 (0.896, 0.958), <i>P</i> = 10 <sup>-5</sup>	0.932 (0.901, 0.965), <i>P</i> = 0.0001	0.938 (0.902, 0.974), <i>P</i> = 0.0007	0.894 (0.832, 0.958), <i>P</i> = 0.001	
Excluding CVD-related deaths	0.941 (0.900, 0.983), <i>P</i> = 0.005	0.936 (0.895, 0.978), <i>P</i> = 0.003	0.953 (0.905, 1.001), <i>P</i> = 0.06	0.920 (0.840, 1.002), <i>P</i> = 0.06	
Pneumonia-underlying cause					
All cases	0.869 (0.768, 0.974), <i>P</i> = 0.01	0.833 (0.848, 0.915), <i>P</i> = 0.002	0.896 (0.786, 1.009), <i>P</i> = 0.07	0.623 (0.456, 0.974), <i>P</i> = 0.03	
All pneumonia-related deaths					
All cases	0.895 (0.845, 0.946), <i>P</i> = 0.0001	0.891 (0.840, 0.943), <i>P</i> = 0.0001	0.918 (0.863, 0.975), <i>P</i> = 0.005	0.796 (0.685, 0.914), <i>P</i> = 0.0008	
Excluding CVD-related deaths	0.896 (0.831, 0.961), <i>P</i> = 0.002	0.890 (0.824, 0.956), <i>P</i> = 0.001	0.934 (0.863, 1.006), <i>P</i> = 0.07	0.721 (0.581, 0.875), <i>P</i> = 0.0006	
Aspiration pneumonia-underlying cause					
All cases	0.801 (0.698, 0.911), <i>P</i> = 0.0004	0.809 (0.703, 0.920), <i>P</i> = 0.0009	0.779 (0.670, 0.894), <i>P</i> = 0.0002		
Excluding CVD-related deaths	0.795 (0.661, 0.939), <i>P</i> = 0.006	0.798 (0.661, 0.945), <i>P</i> = 0.008	0.782 (0.639, 0.937), <i>P</i> = 0.006		

HR adjusted for baseline age (age and age<sup>2</sup>), years of education, baseline smoking status (current smoker vs nonsmoker), cohort, and intakes of meat, fruit, and alcohol. Sex was also included as a covariate in the analyses of the sexes combined. There were only 15 deaths from aspiration pneumonia in women, and therefore, those results are not included.

or leisure-time physical activity relative to the least active quintile (1). This trend was significant when adjusted for age, smoking, and alcohol intake (*P* = 0.02), but not when further adjusted for BMI. Subsequent 12-yr follow-up of this cohort (*N* = 83,185) showed that nurses in the highest activity quintile had 28% lower risk of nonfatal community-acquired pneumonia compared with those in the lowest quintile when adjusted for age, smoking, and alcohol use (*P* < 0.0001 for trend), but again, not when adjusted for BMI (17). The highest quintile of walking had 18% lower risk of

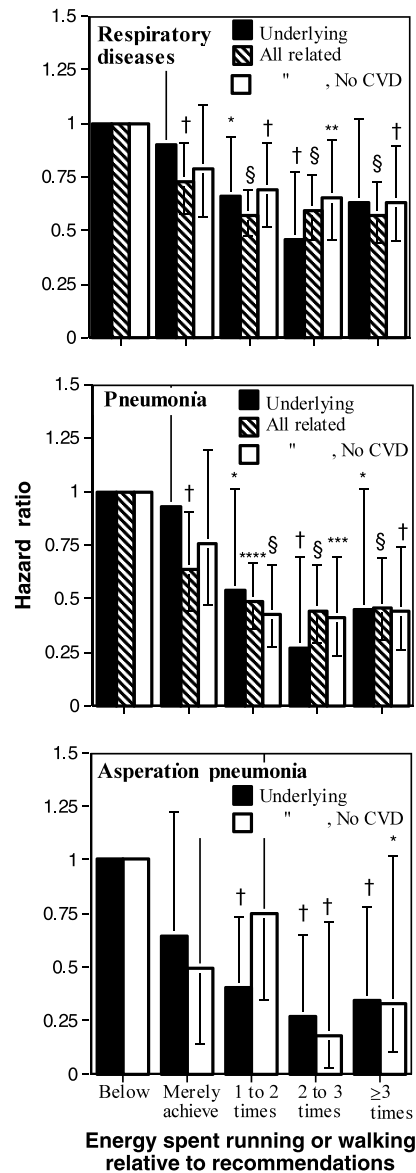


FIGURE 1—Decrease in the risk for respiratory disease mortality as underlying cause and for all related mortality (underlying and contributing combined) relative to falling below (<1.07 MET·h·d<sup>-1</sup>) or merely meeting the recommendations (1.07 to 1.8 MET·h·d<sup>-1</sup>), and running or walking at one to two times (1.8 to 3.6 MET·h·d<sup>-1</sup>), two to three times (1.8 to 3.6 MET·h·d<sup>-1</sup>), or three times or more (≥3.6 MET·h·d<sup>-1</sup>) the recommended levels. Brackets represent 95% CI. Significance levels relative to not meeting the current exercise recommendations (<1.07 MET·h·d<sup>-1</sup>) are coded: \**P* ≤ 0.05; †*P* ≤ 0.01; ‡*P* ≤ 0.001; §*P* ≤ 0.0001.

community-acquired pneumonia compared with the lowest quintile, but there was no significant trend across quintiles. Running or jogging  $>2 \text{ h}\cdot\text{wk}^{-1}$  had 54% lower risk than a woman who neither ran nor jogged (17). The effects of BMI adjustment on the walking, jogging, or running associations were not reported.

The current results provide the only evidence linking pneumonia risk to physical activity in men. A 6-yr follow-up of 26,429 men age 44 to 79 in the Health Professionals Follow-up Study showed no significant risk reduction for community-acquired pneumonia from the lowest quintile of recreational or leisure-time physical activity to the second (7% increase), third (31% decrease), fourth (20% decrease), and fifth quintiles of activity (4% decrease) (1). Although Paffenbarger et al. (18) reported that lower physical activity predicted a 3.9-fold increased risk of deaths due to pneumonia in their 22-yr follow-up of 3686 San Francisco longshoremen, the increased risk was not statistically significant. In addition, moderate and heavy physical activities were not found to decrease the incidence of hospital-treated pneumonia in 50- to 69-yr-old male smokers participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (5).

The effects of running and walking we observed on pneumonia risk are consistent with other research, suggesting that exercise may improve immune function (3,11,35) and attenuate its decline with age (8). Regular exercise in adults has been associated with higher amounts of antiinfluenza IgG and IgM after immunization (7) and attenuates the decline in natural killer cell activity with age (37). Chronic resistance training is reported to improve natural killer cell activity in older women (12).

The reduction respiratory disease and pneumonia risk per MET-hours per day run or walked remained significant when CVD-related deaths were excluded. Over one-half of older community-acquired pneumonia patients have preexisting chronic cardiac conditions, and acute infections such as pneumonia can precipitate acute cardiac events (2). Although running reduces the risk for CHD (31) and stroke (30), our results suggest that the reductions respiratory disease and pneumonia risk were not simply the consequence of lowered CVD risk due to running or walking.

Whether obesity increases the risk for infectious pneumonia is controversial (10). Contrary to the Nurses Health Study (1), we did not find BMI was related to increased risk for pneumonia, but this might be explained by the study differences, e.g., our focus on fatal rather than nonfatal pneumonia and our lack of specificity on the origin of the infections (community vs hospital acquired). Our cohort was also leaner than either the men of the Health Professionals' Follow-up Study (mean BMI,  $24.2 \text{ kg}\cdot\text{m}^{-2}$  for our males vs  $25.5 \text{ kg}\cdot\text{m}^{-2}$ ) or the women of the Nurses' Health Study (mean BMI,  $21.7 \text{ kg}\cdot\text{m}^{-2}$  for our females vs  $24.45 \text{ kg}\cdot\text{m}^{-2}$ ), and it included fewer obese subjects (3.5% obese males vs 8.2% for the Health Professionals Follow-up Study; 1.5% obese females vs 12.1% in the Nurses' Health Study), and therefore, many have included too few subjects at risk for their obesity.

We considered all respiratory-related and all pneumonia-related deaths in addition to deaths due to respiratory disease and pneumonia as underlying causes to increase statistical power. Concurrent infections, and the contraction of hospital-acquired pneumonia while being treated for other conditions, are examples of pneumonia's contribution to mortality without necessarily being listed as the underlying cause. Moreover, the mechanism by which physical activity reduces mortality may not simply involve its effect on pneumonia as the underlying cause, but also by affecting whether pneumonia contributes to the fatal consequence of other underlying causes.

Finally, we hypothesize that the observed reduction of aspiration pneumonia with increased exercise may represent a lower risk for stroke or conditions requiring general anesthesia, less loss of vitality with aging, or the sustained ability to cough or otherwise prevent the aspiration of food or vomit. We have previously demonstrated that the risk for stroke decreases with greater running mileage (30). Greater running may also be associated with reduced susceptibility to lung inflammation when food or vomit is aspirated. The association was unexpected and requires confirmation.

**Limitations.** There are important limitations to these analyses. Running, walking, and other baseline variables were self-reported from the participants' baseline questionnaires. Exercise levels and other subject characteristics could have changed before infection. Our use of mortality is both a strength and weakness—a strength in its ease of ascertainment, lack of subjectivity, and broad importance to patients and the critical care community, and a weakness in that it is not known whether the risk reduction is due to a lower risk of infection, a lower risk of mortality among those infected, or both. Another important limitation of these analyses is the lack of information on the circumstances of the infections. Death certificate diagnoses do not distinguish pneumonias acquired in the community, nursing homes, and health care facilities. Almost all of the diagnoses were pneumonia, unspecified (ICD<sub>9</sub>: 486, ICD<sub>10</sub>: J18.9). Differential mortality could represent differences in susceptibility to infection and well as the adequacy, timeliness, and response to antibiotic treatment (23). Additional studies are required that track incidence, circumstances of infection, and treatment to determine whether the relationships observed are affected by patient physiology, behavior, or access to quality treatment in addition to exercise. Vital status is known only from the National Death Index, and therefore, some subjects who have died are likely to be misclassified as alive. Finally, we caution with regard to implying cause and effect in that individuals with greater susceptibility to respiratory disease may choose to exercise less.

In conclusion, the current results provide strong evidence that greater levels of physical activity may reduce the risk for respiratory disease-related deaths in a dose-dependent manner, including pneumonia and aspiration pneumonia. These effects appear to be independent of the effects of exercise on CVD risk.

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