Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women

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ABSTRACT

Objective To examine the combined associations and relative contributions of leisure-time physical activity (PA) and cardiorespiratory fitness (CRF) with all-cause mortality.

Design Prospective cohort study.

Setting Aerobics centre longitudinal study.

Participants 31 818 men and 10 555 women who received a medical examination during 1978–2002.

Assessment of risk factors Leisure-time PA assessed by self-reported questionnaire; CRF assessed by maximal treadmill test.

Main outcome measures All-cause mortality until 31 December 2003.

Results There were 1492 (469 per 10 000) and 230 (218 per 10 000) deaths in men and women, respectively. PA and CRF were positively correlated in men (r=0.49) and women (r=0.47) controlling for age (p<0.001 for both). PA was inversely associated with mortality in multivariable Cox regression analysis among men, but the association was eliminated after further adjustment for CRF. No significant association of PA with mortality was observed in women. CRF was inversely associated with mortality in men and women, and the associations remained significant after further adjustment for PA. In the PA and CRF combined analysis, compared with the reference group "not meeting the recommended PA (<500 metabolic equivalent-minute/week) and unfit", the relative risks (95% CIs) of mortality were 0.62 (0.54 to 0.72) and 0.61 (0.44 to 0.86) in men and women "not meeting the recommended PA and fit", 0.96 (0.61 to 1.53) and 0.93 (0.33 to 2.58) in men and women "meeting the recommended PA and unfit" and 0.60 (0.51 to 0.70) and 0.56 (0.37 to 0.85) in men and women "meeting the recommended PA and fit", respectively.

Conclusions CRF was more strongly associated with all-cause mortality than PA; therefore, improving CRF should be encouraged in unfit individuals to reduce risk of mortality and considered in the development of future PA guidelines.

Regular physical activity (PA) and moderate to high levels of cardiorespiratory fitness (CRF) are associated with health benefits and reduced risk of mortality.[1–10] The protective effects of higher levels of PA or CRF on mortality are evident regardless of age, sex, fatness, smoking, alcohol consumption and other clinical factors.[3 7 8 10] The 2008 Physical Activity Guidelines for Americans recommends 150 min of moderate-intensity PA or 75 min of vigorous-intensity PA a week,[11] and 49.5% of the US adults met the recommended levels of PA in 2007.[12]

PA is a behaviour, defined as any body movement that increases energy expenditure, including leisure-time activities and sports, whereas CRF is a physiologic attribute, usually measured by a maximal or submaximal exercise test. Although PA is a principal determinant of CRF, PA and CRF may be differentially influenced by age, sex, genotypes, subclinical disease and behavioural, social and environmental factors.[13–15] Therefore, some physically active individuals may have relatively low CRF, whereas some inactive individuals may be fit. In fact, the cross-sectional relationship between self-reported PA and CRF is modest (r=0.1–0.4),[5 6 14 16] and objective measures of PA by doubly labelled water or motion sensors also were not highly correlated with CRF (r=0.15–0.37).[17 18] Thus, it is possible that PA and CRF are, to some extent, independent in relation to health outcomes.

Although several studies have simultaneously examined PA and CRF with mortality,[1 3 5–7 9 10 19 20] the combined associations and relative contributions of PA and CRF with mortality are still unclear. In addition, most published studies on this issue are in men, and further research is required in women. The present study aimed to address the following scientific questions:

- Does the magnitude of the association with mortality risk differ between PA and CRF?
- Do PA and CRF contribute to mortality risk independently of each other?
- Does mortality risk differ between "less active-fit" and "active-unfit"?
- Are the combined effects of PA and CRF with mortality stronger than either exposure by itself?

The information gained from this study may help define more clearly the benefits of PA and CRF to reduce mortality risk, and may be useful in developing future PA guidelines.

METHODS

Study population

This is a prospective observational study of men and women who received preventive medical examinations during 1978–2002. Mortality follow-up was completed until the date of death for decedents or 31 December 2003 for survivors using the National Death Index. Most of the study participants were college graduates from middle to upper socioeconomic strata, and were employed in or retired from professional or executive positions.[8 10] More than 95% of them were non-Hispanic whites, and were referred by their employers, or personal physicians, or were self-referred.

Among 50 244 participants aged 20–82 years at baseline, we selected relatively healthy participants without a history or clinical evidence of cardiovascular disease (CVD) or cancer (n=3588), or abnormal resting or exercise electrocardiogram (n=4027). In addition, participants who did not achieve at least 85% of their age-predicted maximal heart rate (220 minus age in years) on the treadmill test (n=1004) or had <1 year of follow-up (n=39) were excluded, leaving 31 818 men and 10 555 women. The study was approved annually by the Cooper Institute Institutional Review Board, and all participants gave written informed consent.

Clinical examination

All participants completed a clinical evaluation including an exercise test, body composition assessments, blood chemistry analyses, blood pressure measurement, electrocardiography, physical examination and detailed medical history questionnaire. Blood chemistry analyses were performed with automated bioassays after at least 12 h of overnight fasting. Diabetes was defined as fasting glucose ≥126 mg/dl, current therapy with insulin or history of diabetes. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dl or history of hypercholesterolemia.

Resting blood pressure was measured by standard auscultatory methods after at least 5 min of seated rest and recorded as the average of at least two readings separated by 2 min. Hypertension was defined as systolic or diastolic blood pressure ≥140/90 mm Hg or history of hypertension. Body mass index (BMI) (kg/m^2) was calculated from measured weight and height, and classified into three groups: underweight or normal weight, BMI <25.0 kg/m^2; overweight, BMI 25.0–29.9 kg/m^2; and obese, BMI ≥30.0 kg/m^2. Personal history of physician-diagnosed CVD, cancer, hypertension, diabetes and hypercholesterolemia, family history of CVD and smoking status were obtained from the medical history questionnaire.

Physical activity

PA was assessed on the medical history questionnaire by self-reported leisure-time or recreational activities during the past 3 months. We created PA categories based on responses to 10 specific activities: walking, jogging, running, treadmill exercise, cycling, stationary cycling, swimming, racquet sports, aerobic dance and other sports-related activities (eg, basketball or soccer). If individuals indicated that they were participating in activities, additional questions about the frequency (number of workouts per week), duration (minutes of workouts per session) were asked. For walking, jogging, running, treadmill exercise and cycling, they also were asked to report speed (eg, average time per mile). The intensities of activities were estimated via speed-specific or activity-specific metabolic equivalent (MET) values from the Compendium of Physical Activities.[21] To calculate the total volume of PA, the MET value for a given speed or activity was multiplied by the frequency and the duration, and then summed over all activities resulting in total MET-minutes/week of PA, which is the principal metric used in the 2008 PA Guidelines.

Advisory Committee Report

All participants were classified into three PA categories based on the PA Guidelines Advisory Committee Report[22]: "inactive (0 MET-minutes/week)", "insufficient (1–499 MET-minutes/week)" and "recommended (≥500 MET-minutes/week)". In the combined analysis of PA and CRF with mortality, we reduced the three PA categories to either "not meeting the recommended PA (<500 MET-minutes/week)" or "meeting the recommended PA (≥500 MET-minutes/week)". In our previous study, this PA questionnaire has been formerly validated.[23]

Cardiorespiratory fitness

CRF was defined as the total duration of a maximal treadmill test using a modified Balke protocol.[24] Detailed information on the test has been described in earlier reports.[8 23] This treadmill time is highly correlated with measured maximal oxygen uptake (r≥0.92) in men[25] and women.[26] Participants were assigned to three categories based on their age (20–39, 40–49, 50–59 and ≥60 years) and sex-specific treadmill time distributions of the entire ACLS cohort: "low (least fit 20%)", "moderate (next fit 40%)" and "high (most fit 40%)". CRF was dichotomised as either "unfit (low fitness)" or "fit (moderate or high fitness)" in the combined analysis of PA and CRF with mortality. We have used these cut points as a standardised fitness classification method,[1 8 10] given that there is no consensus for the clinical definition of fitness level.

Statistical analysis

Baseline group differences were examined by using χ^2 test for categorical variables and t test for continuous variables. The partial correlation between PA (MET-minutes/week) and CRF (treadmill time in minutes) controlling for age was analysed using Pearson correlation coefficients. Baseline age- and examination year-adjusted mortality were computed per 10 000 person-years of follow-up.

We used Cox proportional hazard models to estimate the relative risk and 95% confidence interval of mortality across categories of PA, CRF and each group of confounders. Tests for linear trends across exposure categories were calculated using general linear models. In the combined analysis of PA and CRF with mortality, we used dichotomised PA and CRF to preserve adequate numbers of participants for the analysis and simplify the complicated joint associations of PA and CRF with mortality. Cox regression models were adjusted for age (years), year of baseline examination, BMI (kg/m^2), smoking status (never, former or current), presence or absence of hypertension, diabetes, hypercholesterolemia and parental CVD at baseline based on earlier studies.[3 8 10] The proportional hazards assumption was examined and satisfied by comparing the log–log survival plots grouped on exposure categories. For the interaction test between PA and CRF with mortality, we entered interaction terms into the multivariable Cox regression models, and no significant interactions were found. All statistical tests were two-sided, and p<0.05 was accepted to indicate statistical significance using SAS software (V.9.2).

RESULTS

There were 1492 (469 per 10 000) and 230 (218 per 10 000) deaths in men and women during the average follow-up of 14.6 and 12.8 years, respectively. PA and CRF were positively correlated in men (r=0.49) and women (r=0.47) controlling for age (p<0.001 for both). At baseline, decedents were older, less active, less fit and more likely to be current smokers compared to survivors in both men and women (table 1). Also, decedents had significantly higher blood pressure, fasting glucose, total cholesterol and family history of CVD. There was no significant difference in BMI between survivors and decedents.

PA and CRF and all confounders were identified as significant mortality predictors in men (table 2). In women, moderate or high fitness level and current smoking were identified as significant mortality predictors, and the other factors were not significant in spite of mostly similar trends in men, probably due to the small number of deaths in women. PA was inversely associated with all-cause mortality in multivariable Cox regression analysis among men, but the association was eliminated after further adjustment for CRF (table 3). No significant association of PA with mortality was observed in women. CRF was inversely associated with all-cause mortality in both men and women, and the associations remained significant after further adjustment for PA.

In the CRF stratified analyses (table 4), PA was not associated with all-cause mortality within both unfit and fit CRF categories. On the other hand, in the PA stratified analyses, CRF was associated inversely with mortality within men and women not meeting the recommended PA category. Relative risks of dying were lower in fit men and women in the recommended PA category, but the risks were not significant. In the combined associations of PA and CRF with mortality (table 5), fit men and women had significantly lower death risk whether or not they met the PA recommendations; however, if men and women met the PA recommendations, but were unfit, mortality risk was not lower compared with the reference group that did not meet the recommended PA and were unfit.

When we additionally excluded for mortality within the first 3 years of follow-up, the independent and combined associations of PA and CRF with mortality were similar, indicating that the results were not likely to be biased by subclinical disease present at baseline (data not shown).

DISCUSSION

We addressed four specific questions in this study regarding the independent and combined associations of PA and CRF with all-cause mortality. For each of the questions, we will discuss the results in the context of other relevant studies.

Does the magnitude of the association with mortality risk differ between PA and CRF?

Yes, it does. The mortality risk reduction was larger in men with high CRF than in men who met the recommended PA after adjusting for the same set of confounders (table 3). Among women, those who met the recommended PA did not

Table 1 Baseline characteristics by survival status

	Men				Women			
	All (n=31 818)	Survivors (n=30 326)	Decedents (n=1492)	p Value*	All (n=10 555)	Survivors (n=10 325)	Decedents (n=230)	p Value*
Age (years)	43.3 (9.2)	43.0 (9.0)	49.8 (10.3)	<0.001	42.8 (10.1)	42.6 (10.0)	51.1 (10.6)	<0.001
Physical activity†								
Inactive	39.5	38.9	52.2	<0.001	37.6	37.2	56.1	<0.001
Insufficient	17.3	17.3	18.7		18.7	18.6	20.0	
Recommended	43.2	43.8	29.1		43.7	44.2	23.9	
MET-minutes/week	759.8 (1205.6)	773.8 (1216.8)	477.0 (904.6)	<0.001	766.8 (1197.3)	775.4 (1203.8)	380.5 (764.2)	<0.001
Cardiorespiratory fitness‡								
Low	13.4	12.9	23.7	<0.001	10.6	10.2	24.8	<0.001
Moderate	39.9	39.9	40.9		34.5	34.4	38.7	
High	46.7	47.2	35.4		54.9	55.4	36.5	
Treadmill time (min)	18.4 (4.9)	18.5 (4.8)	15.7 (5.0)	<0.001	13.9 (4.5)	14.0 (4.5)	10.8 (4.6)	<0.001
Maximal METs	11.9 (2.4)	11.9 (2.4)	10.6 (2.4)	<0.001	9.7 (2.1)	9.8 (2.1)	8.3 (2.2)	<0.001
Body mass index (kg/m^2)	26.5 (3.8)	26.5 (3.8)	26.7 (4.0)	0.20	23.1 (4.2)	23.1 (4.2)	23.4 (4.4)	0.38
<25.0	37.8	37.8	37.3	0.12	76.2	76.2	75.2	0.86
25.0–29.9	47.2	47.3	45.8		17.0	16.9	18.3	
≥30.0	15.0	14.9	16.9		6.8	6.9	6.5	
Smoking status								
Never	71.1	71.3	67.4	<0.001	78.8	78.8	76.5	<0.001
Former	11.4	11.8	5.0		11.5	11.7	5.7	
Current	17.5	16.9	27.6		9.7	9.5	17.8	
Systolic blood pressure (mm Hg)	120.7 (12.9)	120.5 (12.8)	124.8 (15.0)	<0.001	111.7 (13.9)	111.6 (13.8)	118.1 (15.6)	<0.001
Diastolic blood pressure (mm Hg)	80.9 (9.5)	80.8 (9.5)	82.5 (10.4)	<0.001	75.4 (9.5)	75.4 (9.5)	76.8 (9.7)	0.02
Hypertension	29.0	28.3	41.3	<0.001	15.4	15.2	23.5	<0.001
Fasting glucose (mg/dl)	99.5 (16.1)	99.3 (15.2)	104.3 (29.1)	<0.001	93.3 (13.3)	93.2 (13.0)	96.8 (21.3)	<0.001
Diabetes	4.1	3.9	7.3	<0.001	3.5	3.5	3.9	0.73
Total cholesterol (mg/dl)	207.4 (39.9)	206.9 (39.7)	216.3 (42.7)	<0.001	196.9 (37.7)	196.7 (37.7)	208.3 (38.8)	<0.001
Hypercholesterolemia	27.5	27.3	31.5	<0.001	20.3	20.2	23.5	0.22
Parental cardiovascular disease	26.5	25.8	40.5	<0.001	25.5	25.1	43.0	<0.001

Data are means (SD) for continuous variables or percentage for categorical variables.
*For comparison of survivors and decedents.
†Inactive, insufficient and recommended was defined as 0, 1–499 and ≥500 MET-minutes/week, respectively.
‡Low, moderate and high was defined as the least fit 20%, the next fit 40% and the most fit 40%, respectively.
MET, metabolic equivalent.

Table 2 Relative risk of all-cause mortality across each exposure and confounder categories

	Men					Women				
	No	Deaths (n)	Person-years	Rate*	RR† (95% CI)	No	Deaths (n)	Person-years	Rate*	RR† (95% CI)
Physical activity‡										
Inactive	12 572	779	203 666	37.0	1.00 (referent)	3968	129	60 155	19.3	1.00 (referent)
Insufficient	5518	279	83 598	30.9	0.84 (0.73 to 0.96)	1970	46	26 457	16.4	0.85 (0.61 to 1.20)
Recommended	13 728	434	178 189	27.0	0.73 (0.65 to 0.82)	4617	55	48 201	14.6	0.76 (0.55 to 1.05)
p Trend					<0.001					0.22
Cardiorespiratory fitness§										
Low	4277	354	65 438	58.1	1.00 (referent)	1115	57	16 903	29.1	1.00 (referent)
Moderate	12 697	610	187 408	31.9	0.55 (0.48 to 0.63)	3640	89	50 996	16.3	0.56 (0.40 to 0.78)
High	14 844	528	212 715	24.2	0.42 (0.36 to 0.48)	5800	84	66 932	14.6	0.50 (0.36 to 0.71)
p Trend					<0.001					<0.001
Body mass index, kg/m^2										
<25.0	12 017	557	195 997	27.3	1.00 (referent)	8041	173	108 714	16.3	1.00 (referent)
25.0–29.9	15 014	683	211 998	31.2	1.14 (1.02 to 1.28)	1791	42	19 003	19.2	1.18 (0.84 to 1.66)
≥30.0	4787	252	57 492	51.1	1.87 (1.61 to 2.18)	723	15	7100	23.5	1.45 (0.85 to 2.46)
p Trend					<0.001					0.29
Smoking status										
Never	22 622	1005	341 140	28.0	1.00 (referent)	8318	176	107 219	15.1	1.00 (referent)
Former	3643	75	39 417	29.4	1.05 (0.81 to 1.37)	1217	13	12 535	17.7	1.17 (0.64 to 2.17)
Current	5553	412	84 850	49.7	1.77 (1.58 to 1.99)	1020	41	15 086	30.6	2.03 (1.44 to 2.86)
p Trend					<0.001					<0.001
Hypertension										
No	22 607	876	342 044	27.4	1.00 (referent)	8932	176	116 027	16.7	1.00 (referent)
Yes	9211	616	123 520	45.0	1.65 (1.48 to 1.83)	1623	54	18 778	19.6	1.17 (0.86 to 1.61)
Diabetes										
No	30 527	1383	452 105	31.1	1.00 (referent)	10 186	221	131 807	16.9	1.00 (referent)
Yes	1291	109	13 336	65.8	2.12 (1.74 to 2.58)	369	9	2993	25.6	1.52 (0.78 to 2.95)
Hypercholesterolemia										
No	23 077	1022	347 540	30.7	1.00 (referent)	8416	176	110 923	17.5	1.00 (referent)
Yes	8741	470	117 916	36.0	1.17 (1.05 to 1.31)	2139	54	23 871	14.9	0.85 (0.62 to 1.17)
Parental cardiovascular disease										
No	23 391	888	335 427	30.9	1.00 (referent)	7860	131	98 879	16.8	1.00 (referent)
Yes	8427	604	130 029	35.1	1.14 (1.02 to 1.26)	2695	99	35 924	17.8	1.06 (0.81 to 1.39)

*Death rate per 10 000 person-years adjusted for age and examination year.
†Adjusted for age and examination year.
‡Inactive, insufficient and recommended was defined as 0, 1–499, and ≥500 MET-minutes/week, respectively.
§Low, moderate and high was defined as the least fit 20%, the next fit 40% and the most fit 40%, respectively.
MET, metabolic equivalent.

Table 3 Relative risk of all-cause mortality by PA and CRF

	Men		Women	
	Model 1*	Model 2†	Model 1*	Model 2†
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
PA‡				
Inactive	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Insufficient	0.91 (0.79 to 1.05)	0.99 (0.86 to 1.14)	0.92 (0.65 to 1.29)	0.98 (0.69 to 1.38)
Recommended	0.87 (0.77 to 0.99)	1.05 (0.91 to 1.20)	0.83 (0.59 to 1.15)	0.95 (0.67 to 1.35)
p Trend	0.07	0.76	0.52	0.95
Not recommended PA (inactive or insufficient)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Recommended PA (recommended)	0.90 (0.80 to 1.01)	1.05 (0.92 to 1.19)	0.85 (0.62 to 1.16)	0.95 (0.68 to 1.33)
CRF§				
Low	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Moderate	0.64 (0.56 to 0.74)	0.64 (0.56 to 0.74)	0.61 (0.44 to 0.86)	0.62 (0.44 to 0.87)
High	0.56 (0.47 to 0.65)	0.55 (0.46 to 0.66)	0.59 (0.40 to 0.85)	0.61 (0.41 to 0.90)
p Trend	<0.001	<0.001	0.01	0.02
Unfit (low)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Fit (moderate or high)	0.62 (0.54 to 0.71)	0.62 (0.54 to 0.72)	0.60 (0.44 to 0.83)	0.62 (0.44 to 0.86)

*Adjusted for age, examination year, body mass index, smoking status, hypertension, diabetes, hypercholesterolemia and parental cardiovascular disease.
†Further adjusted for PA for CRF or CRF for PA.
‡Inactive, insufficient and recommended was defined as 0, 1–499 and ≥500 MET-minutes/week, respectively.
§Low, moderate and high was defined as the least fit 20%, the next fit 40% and the most fit 40%, respectively.
CRF, cardiorespiratory fitness; MET, metabolic equivalent; PA, physical activity.

Table 4 Relative risk (95% CI)* of all-cause mortality by PA in CRF stratified analysis and by CRF in PA stratified analysis

	Men		Women	
	CRF†		CRF†	
	Unfit	Fit	Unfit	Fit
Recommended PA (MET-minutes/week)				
No (0–499)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Yes (≥500)	0.90 (0.56 to 1.45)	0.96 (0.85 to 1.09)	0.85 (0.29 to 2.44)	0.92 (0.65 to 1.29)
	Men		**Women**	
	Recommended PA (MET-minutes/week)			
	No (0–499)	**Yes (≥500)**	**No (0–499)**	**Yes (≥500)**
CRF†				
Unfit	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Fit	0.61 (0.53 to 0.71)	0.64 (0.39 to 1.04)	0.63 (0.45 to 0.89)	0.49 (0.16 to 1.46)

*Adjusted for age, examination year, body mass index, smoking status, hypertension, diabetes, hypercholesterolemia and parental cardiovascular disease.
†Unfit was defined as the least fit 20% and fit was defined as the most fit 80% based on maximal treadmill test time.
CRF, cardiorespiratory fitness; MET, metabolic equivalent; PA, physical activity.

Table 5 Combined association of recommended PA and CRF with all-cause mortality

	Unfit*				Fit*			
	No	Deaths (n)	Death rate†	RR‡ (95% CI)	No	Deaths (n)	Death rate†	RR‡ (95% CI)
Men								
Recommended PA (MET-minutes/week)								
No (0–499)	3792	335	84.0	1.00 (referent)	14 298	723	41.7	0.62 (0.54 to 0.72)
Yes (≥500)	485	19	76.0	0.96 (0.61 to 1.53)	13 243	415	37.3	0.60 (0.51 to 0.70)
Women								
Recommended PA (MET-minutes/week)								
No (0–499)	975	53	41.4	1.00 (referent)	4963	122	22.6	0.61 (0.44 to 0.86)
Yes (≥500)	140	4	36.9	0.93 (0.33 to 2.58)	4477	51	20.0	0.56 (0.37 to 0.85)

*Unfit was defined as the least fit 20% and fit was defined as the most fit 80% based on maximal treadmill test time.
†Death rate per 10 000 person-years adjusted for age and examination year.
‡Adjusted for age, examination year, body mass index, smoking status, hypertension, diabetes, hypercholesterolemia and parental cardiovascular disease.
MET, metabolic equivalent; PA, physical activity; CRF, cardiorespiratory fitness.

have significantly lower risk, but women in the high CRF category had 41% lower risk.

In similar studies that examined both PA and CRF with mortality, the association of CRF with mortality was stronger than those of self-reported PA (approximately 40% to 70% lower mortality risk in CRF and 20% to 50% in PA).[1 3 5–7 9 10 19 20] A review paper on self-reported PA and all-cause mortality in women reported convincing evidence that PA can postpone premature death in women, and the magnitude of benefit experienced by women was similar to that seen in men.[27] Thus, we believe no association of PA with mortality in women may be related to the inappropriate design of the PA questionnaire for women and also to the small number of deaths compared to men. The traditional leisure-time PA questionnaire was developed for studies in men, then later was applied to studies in women.[1] Therefore, it did not include some PA such as childcare, housework or dance. In fact, in recent studies with specific PA questionnaires for women, active women had lower risk of mortality than inactive women.[28 29]

Do PA and CRF contribute to mortality risk independently of each other?

In the multivariable analyses (table 3), the association of CRF with mortality remained significant after further adjustment for PA in both men and women, but the association of PA with mortality was no longer significant after controlling for CRF in men, and no association was observed in women.

No significant relations of PA with mortality were observed within either unfit or fit categories in men or women, whereas CRF was significantly associated with mortality for both men and women who did not meet the recommended PA (table 4). However, for men and women who met the recommended PA, the relative risks of mortality in fit men (0.64) and women (0.49) did not reach statistical significance. Although the relative risk estimates suggest evidence for an association, the lack of statistical significance is likely explained by the small number of deaths in unfit men (n=19) and unfit women (n=4), respectively. These findings are in line with a recent study that reported an inverse association between CRF and mortality among inactive men but not among active men.[20] However, another study showed contradictory results, with CRF significantly associated with mortality in the active category, but not in the sedentary category.[7] Therefore, whether the CRF effects on risk reduction for mortality differ between PA levels is still unresolved.

Does mortality risk differ between less active-fit and active-unfit?

According to the PA and CRF combined analysis with mortality (table 5), individuals who did not meet the recommended

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level of PA, but were fit, had lower risks of all-cause mortality. However, if men or women who met the recommended level of PA were unfit, the relative risks of mortality were not significantly lower than the reference group that did not meet the recommended PA and was unfit. None of the earlier observational studies that simultaneously examined PA and CRF compared the relative contribution to mortality between less active-fit and active-unfit using combined stratification analysis.

Are the combined effects of PA and CRF with mortality stronger than either exposure by itself?

Compared with the single relative risks of mortality in fit men and women (table 3), the combined effects of PA and CRF with mortality were somewhat stronger, but almost similar to the effect of CRF alone (table 5). This finding parallels the previous reports that indicated all-cause and ischemic heart disease mortalities in active and fit men were slightly lower than those in fit men.

On the basis of our findings, we attempted to interpret the interactive role of PA or CRF with mortality. PA is one of the behavioural factors that influence the effects of physiological mediators (blood pressure, lipids, glucose, immune function, inflammation and hormones), including CRF, on various health outcomes. From the results of the attenuated association of PA with mortality after additional adjustment for CRF in men, it is likely that the effect of PA on mortality would be mediated largely by CRF. Because PA was defined as leisure-time exercise or sports, intensity of PA may reach a certain threshold to affect CRF; therefore, it may be more likely that CRF lie on the causal pathway between PA and mortality. Several investigators have stated that leisure-time PA not resulting in an increase in CRF may not provide any protective effect against CVD.[5 30] On the other hand, the significant inverse associations of CRF with mortality after adjustment for PA suggest that the association between CRF and mortality may be explained by PA and by other factors such as genotypes and other behaviour, social or environmental factors, as proposed by earlier reports.[13–15]

Strengths and limitations

The principal strength of the present study is the large population and extensive database generated over 30 years.

The primary limitation is the use of self-reported PA. People tend to over-report their PA level,[31] and the random measurement error from self-reported PA is likely to be more pronounced than that for CRF, inducing an underestimation of the true association between PA and mortality. Therefore, it is possible that self-reported PA compared to objectively measured CRF may show a weaker association of PA with mortality. However, because of a complicated multifaceted human behaviour, an accurate measure of true daily PA is more challenging than the measure of CRF.

The proportion of those who met the recommended PA may be underestimated because PA from other domains such as occupation, home or active commuting was not included. However, most participants were employed in professional or executive positions. Thus, it is unlikely that occupational PA was a major contributor to overall levels of PA in our cohort, and between-individual differences are likely to be minor. Approximately 43% to 44% of participants met the recommended level of PA in this study, and it is similar to the national estimates of 46.1% in 2001.[32]

This study population is mainly college graduates, non-Hispanic whites from middle to upper socioeconomic strata, but physiologic characteristics were similar with representative population groups.[23] The homogeneity of the cohort on socioeconomic variables may reduce the possibility of confounding by education, occupation and income. We assessed PA and CRF at baseline once and did not assess the changes over the follow-up; thus, individual changes in PA or CRF could not be taken into account in the analysis. Another limitation is the confounding effect of dietary habits such as fat consumption on the association of PA or CRF with mortality.

Implications

Although recent review papers have highlighted stronger associations between CRF and health outcomes than PA and health outcomes,[27 33] the 2008 Physical Activity Guidelines focus entirely on physical inactivity as a health risk factor.[11] However, individuals with low CRF should be encouraged to increase their CRF because they are more likely to reduce the risk of mortality if they are at least moderately fit based on the current findings.

PA is a primary modifiable factor to improve CRF despite that other factors such as genotypes also influence CRF. Therefore, healthcare providers should encourage their patients to become more fit by participating in regular PA that is sufficient to improve CRF to reduce risk of mortality. In addition, increasing CRF should be considered in the development of

What is already known about this topic

- It is well known that regular physical activity (PA) and moderate to high levels of cardiorespiratory fitness (CRF) are associated with reduced risk of mortality.
- The combined associations and relative contributions of leisure-time PA and CRF with all-cause mortality have not been fully investigated.

What this study adds

- The mortality risk reduction was larger in men with high CRF than in men who met the recommended PA.
- The association of CRF with mortality remained significant after further adjustment for PA in both men and women, but the association of PA with mortality was no longer significant after controlling for CRF in men.
- The mortality risk was lower in less active-fit individuals but not in active-unfit compared with less active-unfit reference.
- The combined effects of PA and CRF with mortality were somewhat stronger but almost similar to the effect of CRF alone.
- It is likely that the effect of PA on mortality is mediated largely by CRF.

future PA guidelines. Further studies using objective measures of PA in combination with measured CRF are needed to elucidate the combined associations and relative contributions of PA, its subcomponents and CRF with mortality risk.

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