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Original Contribution

Cardiovascular Disease and All-Cause Mortality in Male Twins With Discordant Cardiorespiratory Fitness: A Nationwide Cohort Study

Marcel Ballin, Anna Nordström, and Peter Nordström*

* Correspondence to Prof. Peter Nordström, Department of Community Medicine and Rehabilitation, Unit of Geriatric Medicine, Umeå University, 901 87 Umeå, Sweden (e-mail: peter.nordstrom@umu.se).

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Whether genetic and familial factors influence the association between cardiorespiratory fitness (CRF) and cardiovascular disease (CVD) is unknown. Two cohorts were formed based on data from 1,212,295 men aged 18 years who were conscripted for military service in Sweden during 1972–1996. The first comprised 4,260 twin pairs in which the twins in each pair had different CRF (≥1 watt). The second comprised 90,331 nonsibling pairs with different CRF and matched on birth year and year of conscription. Incident CVD and all-cause mortality were identified using national registers. During follow-up (median 32 years), there was no difference in CVD and mortality between fitter twins and less fit twins (246 vs. 251 events; hazard ratio (HR) = 1.00, 95% confidence interval (CI): 0.83, 1.20). The risks were similar in twin pairs with ≥60-watt difference in CRF (HR = 0.96, 95% CI: 0.57, 1.64). In contrast, in the nonsibling cohort, fitter men had a lower risk of the outcomes than less fit men (4,444 vs. 5,298 events; HR = 0.83, 95% CI: 0.79, 0.86). The association was stronger in pairs with ≥60-watt difference in CRF (HR = 0.65, 95% CI: 0.59, 0.71). These findings indicate that genetic and familial factors influence the association of CRF with CVD and mortality.

aerobic fitness; cardiovascular disease; physical activity; twin study

Abbreviations: CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HR, hazard ratio; ICD, *International Classification of Diseases*; MI, myocardial infarction; PA, physical activity; SD, standard deviation.

Today, it is widely accepted that being physically active and fit is fundamental to one's overall health. This notion is also supported by a compelling body of evidence showing that physical activity (PA) and cardiorespiratory fitness (CRF) are inversely associated with a wide spectrum of adverse health outcomes including cardiovascular disease (CVD), type 2 diabetes mellitus, common types of cancer, dementia, and mortality (1–7). In addition to having adverse effects on individuals, a sedentary lifestyle and low CRF place a substantial economic burden on society (8, 9). In contrast, high CRF has been associated with reduced health-care expenses (10).

Despite all this knowledge, the prevalence of inactivity and low CRF remains high (11, 12), and a decline in CRF has been observed especially among young men during the past 2 decades (13). In light of this finding, it is interesting that the incidence of CVD decreased during the same time period (14, 15). This is partly due to enhanced treatment and primary and secondary prevention, such as improvements in hypertension treatment and control, reductions in cholesterol levels, and declines in smoking prevalence (16). Even so, given the trends in CRF, the question of whether the association of CRF with CVD is causal or whether it is influenced by other factors remains.

Early research suggested that hereditary factors substantially influence CRF (17). Since then, maternal heritage specifically has been shown to significantly influence CRF (18, 19), and large twin studies show that at least 65% to 78% of the variance in CRF among young men is attributable to genetic factors (20, 21). Interestingly, it is suggested that certain factors linked to CRF, such as peroxisome proliferator-activated receptor α gene and vascular endothelial growth factor gene expression, also play a role in atherosclerosis (22–24). Thus, there are grounds to believe that genetic and familial factors might influence the association between CRF and incident CVD. One way to examine the influence

of genetic and familial factors is to compare twins with discordant levels of CRF; a lower risk of adverse outcomes in twins with higher CRF would suggest that the association is attributable to behavioral factors, such as PA, rather than genetic predisposition and familial resemblance. In the present study, we therefore examined the association of CRF in late adolescence with incident CVD and all-cause mortality later in life in male twins with discordant levels of CRF.

METHODS

Study design and cohorts

The present study was a retrospective cohort study approved by the Regional Ethical Review Board in Umeå, Sweden (No. 2010–13-31M) and by the Swedish National Board of Health and Welfare. It was based on register data from 1.4 million Swedish men who participated in compulsory national military conscription during 1972–1996. Only 2%–3% of all Swedish men were relieved from conscription due to severe chronic conditions. In connection to conscription, all conscripts took part in highly standardized physical and mental tests for 2 days. A medical doctor examined the participants, using the *International Classification of Diseases* (ICD), *Eighth Revision*, and all conscripts underwent a resting electrocardiogram to evaluate heart function. To be considered for inclusion in this study, participants had to have partaken in a bicycle-ergometer test assessing their CRF in connection with conscription and obtained a test result of ≥100 watts. From these participants (n = 1,212,295), 2 study cohorts were created. The primary study cohort included twins, defined as full siblings born within 1 week of each other, with discordant CRF (difference of ≥1 watt). The twins were identified by linking the conscription registry data with family data from Statistics Sweden. Initially, 6,113 twin pairs were identified, of which 4,260 pairs had undergone CRF testing and had discordant CRF. Thus, the primary study cohort comprised a total of 8,520 men. The second study cohort was a nonsibling cohort selected from the same population. The purpose of this cohort was to form pairs that would have twin-like characteristics without the actual genetic component. Thus, nonsiblings with discordant CRF (difference of ≥1 watt) were matched 1:1 on birth year, year of conscription, body height (within 3 cm), and body weight (within 5 kg). This nonsibling cohort comprised 90,331 matched pairs, resulting in a total cohort of 180,662 men.

Exposure measurement

CRF was assessed using a validated and reliable electrically braked bicycle-ergometer test, previously described (25). Prior to testing, participants were required to present normal findings from a resting electrocardiogram before being given permission to perform the bicycle test. The test began with a 5-minute submaximal warmup where the resistance was set at a point from 75 to 150 watts depending on the participant's body weight. During the test, participants were instructed to pedal at a cadence of 60–70 revolutions per minute. When the warmup was completed, the workload was progressively increased by 25 watts/minute. The test was finished when the participant fatigued and was unable to continue pedaling at the prespecified cadence. The final work rate in watts was then recorded as the participant's level of CRF, which served as the primary exposure in the subsequent analysis. Given that a higher body weight contributes to higher absolute watts, which could lead to overestimation of CRF among heavier people, an additional exposure in terms of weight-adjusted CRF (watts/kg) was used. This was calculated by dividing the absolute watts by body weight for each participant.

CVD and mortality ascertainment

Participants were followed until the first of the following: an initial diagnosis of CVD (myocardial infarction (MI), stroke, or angina pectoris), death, or December 31, 2016. The primary study outcome was the composite endpoint of CVD and all-cause mortality. As secondary outcomes, CVD and all-cause mortality were analyzed separately. Data on mortality were retrieved from the Swedish Cause of Death Registry. All cases of incident CVD were tracked through the Swedish National Inpatient Register. ICD codes from the Ninth and Tenth Revisions were used to identify diagnoses of MI (ICD-9: 410; ICD-10: I61), stroke (ICD-9: 431–434; ICD-10: I61-I64), and angina pectoris (ICD-9: 413; ICD-10: I20). The Inpatient Register is managed by the Swedish National Board of Health and Welfare and contains information on approximately 90% of all inpatient care in Sweden since 1971 and 100% since 1987. Diagnoses recorded in the Inpatient Register have been shown to have a positive predictive value of 85%–95% in general (86%–100% for MI, 69%–99% for stroke, 95% for angina pectoris) (26–28).

Confounding and additional variable measurements

Body weight was measured using a standardized scale and height was measured using a wall-mounted gauge. The body mass index was calculated by dividing body weight by height squared. Blood pressure was measured using a mercury sphygmomanometer with the participant in a supine position. Data on smoking and cardiometabolic blood markers were not available. As previously described (29), smoking status among conscripts was registered only in a small subcohort during 1969–1978, from which nearly all data were obtained during 1969–1970, and thus not eligible for inclusion in the present study. Socioeconomic data, including disposable annual household income, relationship status, and level of education, were retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies, initiated in 1990. To maximize sufficient availability of socioeconomic data for conscripts, we retrieved socioeconomic data from 2000 for all participants. Data on disposable annual household income was missing for 167 participants in the twin cohort and 4,544 participants in the nonsibling cohort. All the registers used in the present study were linked using personal identification numbers, which all Swedish residents have.

Statistical analysis

Baseline differences between more and less fit individuals were tested using independent-samples *t* tests for continuous variables and Pearson's χ^2 tests for categorical variables. To compare more and less fit individuals with respect to the study outcomes, hazard ratios and confidence intervals were estimated using conditional Cox regression models that were stratified by matched pairs. The proportional hazards assumption was not violated according to an analysis of Schoenfeld residuals. In the main analysis, CRF discordance was analyzed as a categorical variable (0, 1), and the models were adjusted for confounders in 2 steps. First, adjustments were made for socioeconomic factors including annual household disposable income, relationship status (unmarried, married, divorced, registered partner), and level of education (≤9 years of elementary school, ≤2 years of high school, ≥3 years of high school, <3 years of university, ≥3 years of university, doctoral studies). Next, the models additionally adjusted for body mass index, systolic blood pressure, and diastolic blood pressure. The models did not adjust for age at baseline or year of conscription because the subjects were matched on these variables. Given that the ≥1-watt within-pair difference in CRF might have been insufficient to detect differences in risks, the associations of CRF with the composite endpoint was investigated in subgroups defined by larger within-pair discordances in CRF. Previous research has shown that that an increase in CRF equivalent to 17.5 watts is associated with 13%–15% lower risk of CVD and mortality (30). Hence, we performed subgroup analyses where the within-pair difference in CRF was ≥10 watts, ≥20 watts, ≥30 watts, ≥40 watts, ≥50 watts, and ≥60 watts. Further analyses based on even larger within-pair differences were not performed because there was an insufficient number of events for adequate statistical power.

In a secondary analysis, CRF was placed into a conditional Cox model as a continuous variable to estimate the increase in risk per 10-watt increment in within-pair difference in CRF. Adjustments were made according to the same procedure as in the main analysis.

In the twin cohort, a sensitivity analysis was performed to evaluate whether CRF was associated with CVD and mortality when not accounting for genetic and familial factors. In this analysis, one twin in each pair was excluded, and the associations were evaluated per standard-deviation increase in CRF using unconditional Cox regression. These analyses were adjusted in the same way as the main analysis. All analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, New York), and Stata, version 15 (StataCorp LLC, College Station, Texas). Statistical significance was determined based on confidence intervals for the hazard ratios, where confidence intervals that did not overlap 1.0 were considered statistically significant.

RESULTS

Baseline characteristics

In the twin cohort (Table 1), the mean age at baseline was 18.3 years (standard deviation (SD), 0.6 years). The median difference in CRF between twins was 25 watts (interquartile range, 12–47), with a mean difference of 33 watts. There were small differences in anthropometrics and systolic blood pressure between more and less fit twins. In the matched nonsibling cohort (Table 1), the mean age at baseline was 18.3 (0.7) years. The median difference in CRF between nonsiblings was 36 watts (interquartile range, 18–62), with a mean difference of 44 watts. There were small differences in age, anthropometrics, blood pressure, and socioeconomic variables between more and less fit men.

CVD and mortality in twins

During a median follow-up time of 32.3 years (interquartile range, 27.0–37.6), a total of 497 outcome events (angina, 93; MI, 94; stroke, 70; death, 294) occurred in the twin cohort (Figure 1). The incidence rate of the composite endpoint of CVD and mortality was 17.8/10,000 person-years in fitter twins compared with 18.2 per 10,000 person-years in less fit twins. As shown in Table 2, fitter twins did not have a lower risk of CVD and mortality before adjustment for confounders (hazard ratio (HR) = 1.00, 95% confidence interval (CI): 0.83, 1.20) or after adjustment (HR = 0.90, 95% CI: 0.72, 1.12). The association was weaker in twin pairs discordant for CRF/body weight (HR = 0.99, 95% CI: 0.80, 1.24) (Table 3). When analyzed as a continuous variable, each 10-watt increment in within-pair difference in CRF was not associated with CVD and mortality either before adjustment for confounders (HR = 1.01, 95% CI: 0.97, 1.06) or after (HR = 1.00, 95% CI: 0.94, 1.05).

Subgroup analyses showed that CRF was not associated with CVD and mortality in twin pairs with a difference in CRF of at least 10 watts (HR = 0.94, 95% CI: 0.76, 1.15) or in twin pairs with a difference in CRF of at least 60 watts (HR = 0.96, 95% CI: 0.57, 1.64) (Figure 2).

CVD and mortality in nonsiblings

In the matched nonsibling cohort, 9,742 outcome events (angina, 1,980; MI, 2,322; stroke, 1,658; death, 6,194) occurred during a median follow-up time of 32.3 years (interquartile range, 27.1–38.3) (Figure 3). The incidence rate of CVD and mortality was 15.0/10,000 person-years in fitter men compared with 18.0/10,000 person-years in less fit men. As shown in Table 2, fitter men had a lower risk of CVD and mortality, both before adjustment for confounders (HR = 0.83, 95% CI: 0.79, 0.86) and after adjustment (HR = 0.87, 95% CI: 0.83, 0.92). Similar results were observed for the secondary outcomes (Table 2), and the associations remained in pairs discordant for CRF/body weight (HR = 0.89, 95% CI: 0.84, 0.93) (Table 3). When analyzed as a continuous variable, each 10-watt increment in within-pair difference in CRF among nonsiblings was associated with CVD and mortality after adjustment for confounders (HR = 0.97, 95% CI: 0.96, 0.98).

Subgroup analyses showed that higher CRF was associated with lower risk of CVD and mortality in nonsibling pairs with a difference in CRF of at least 10 watts (HR = 0.81,

Table 1. Baseline Characteristics of the 2 Study Cohorts Including 18-Year-Old Men Conscripted for Military Service in Sweden, 1972–1996

Variables	Twin Cohort				*P* Value	Matched Nonsibling Cohort				*P* Value
	Less Fit (*n* = 4,260)		More Fit (*n* = 4,260)			Less Fit (*n* = 90,331)		More Fit (*n* = 90,331)		
	Mean (SD)	%	Mean (SD)	%		Mean (SD)	%	Mean (SD)	%	
Age, years	18.3 (0.6)		18.3 (0.6)		0.9	18.3 (0.7)		18.3 (0.7)		0.007
Body weight, kg	66.5 (9.0)		68.9 (9.2)		<0.001	67.9 (6.6)		68.3 (6.4)		<0.001
Body height, cm	178.2 (6.5)		179.0 (6.5)		<0.001	178.9 (4.8)		178.9 (4.8)		0.8
BMI[a]	20.9 (2.5)		21.5 (2.5)		<0.001	21.2 (1.8)		21.3 (1.7)		<0.001
CRF, watt	262.7 (49.0)		295.8 (51.6)		<0.001	256.8 (43.2)		300.7 (48.8)		<0.001
CRF/body weight, watt/kg	4.0 (0.7)		4.3 (0.7)		<0.001	3.8 (0.6)		4.4 (0.7)		<0.001
Systolic blood pressure, mm Hg	129.0 (11.0)		129.5 (11.2)		0.029	128.0 (10.8)		128.5 (10.8)		<0.001
Diastolic blood pressure, mm Hg	65.7 (10.1)		65.8 (10.2)		0.8	66.8 (9.9)		66.4 (10.0)		<0.001
Annual household income, in 1,000 SEK	283.4 (897.1)		296.5 (915.6)		0.5	267.0 (448.6)		288.4 (538.5)		<0.001
Relationship status					0.2					<0.001
Unmarried		67.2		65.8			64.6		62.2	
Married		27.3		28.8			29.4		32.5	
Divorced		5.4		5.4			5.9		5.3	
Registered partner		0.1		<0.1			0.1		<0.1	
Level of education					0.2					<0.001
≤9 years of elementary school		10.8		10.2			15.0		9.7	
≤2 years of high school		37.2		35.2			38.0		31.5	
≥3 years of high school		19.3		19.5			19.9		20.6	
<3 years of university		16.1		17.2			14.9		19.8	
≥3 years of university		15.8		17.1			11.6		17.5	
Doctoral studies		0.8		0.8			0.6		0.9	

Abbreviations: BMI, body mass index; CRF, cardiorespiratory fitness; SD, standard deviation; SEK, Swedish krona.
[a] Weight (kg)/height $(m)^2$.

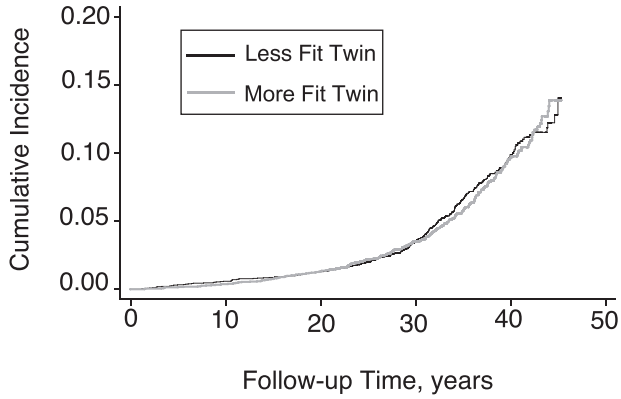

Figure 1. Cumulative incidence of cardiovascular disease and mortality in the twin cohort among Swedish men who were 18 years of age in 1972–1996. The hazard ratio for fitter twins compared with less fit twins was 1.00 with a 95% confidence interval of 0.83, 1.20.

95% CI: 0.78, 0.85) up to at least 60 watts (HR = 0.65, 95% CI: 0.59, 0.71) (Figure 2).

Sensitivity analyses

In the twin cohort, using unconditional Cox regression, CRF was associated with lower risk of CVD and mortality when excluding the less fit twin in each pair (HR for 1-SD increase in CRF = 0.74, 95% CI: 0.64, 0.85) or when excluding the fitter twin in each pair (HR for 1-SD increase in CRF = 0.83, 95% CI: 0.73, 0.96), before adjustment. Fully adjusting models showed similar associations when excluding the less fit twin (HR for 1-SD increase in CRF = 0.75, 95% CI: 0.63, 0.89) or when excluding the fitter twin (HR for 1-SD increase in CRF = 0.86, 95% CI: 0.73, 1.02).

In the twin cohort, a post-hoc power calculation was performed under the assumptions of no matching, a cohort size of 8,520, 497 outcomes, and a 2-sided 5% significance level. The statistical power was estimated to be 21.6%, 44.1%, 70.1%, and 89.4% for expected hazard ratios of 0.90, 0.85, 0.80, and 0.75, respectively.

DISCUSSION

In this nationwide study, higher CRF was associated with a lower risk of early CVD and mortality in matched pairs of nonsiblings, which corroborates the results of previous studies (4, 29, 31, 32). However, no association was observed in twin pairs, and the results remained in twin pairs with greater-than-average differences in CRF. These findings were even more pronounced when analyzing CRF relative to body weight. Together, these findings suggest that genetic and familial factors exert a sizeable influence on the association of CRF with the risk of early CVD and mortality in young men.

The relationship between CRF and adverse events, including CVD and mortality, has been subject to rigorous investigation (3–7). Not long ago, the American Heart Association highlighted emerging evidence suggesting that low CRF might be as strong a predictor of mortality as, if not stronger than, traditional risk factors such as smoking, obesity, and cardiometabolic abnormalities (33). In a meta-analysis, the pooled estimates of risk reduction of CVD and all-cause mortality per increase in CRF equivalent to 17.5 watts for a 70-kg person were 13% and 15%, respectively (30). However, there was a substantial heterogeneity in risk estimates across the individual studies. In previous studies, Högström et al. (29, 31) demonstrated that the risk of stroke and MI was reduced by 16%–24% per 1-standard-deviation increase in CRF among military conscripts, who constituted the study population in the present study as well. Thus, the mean difference of 33 watts between conscripted twins in the present study is clinically relevant and should have been associated with a similar risk reduction in CVD and mortality if the association was independent of genetic and familial factors. Yet, the fitter twins did not have a lower risk of CVD and mortality compared with the less fit twins. We then further explored the association of CRF with CVD and mortality in twin pairs with increasing differences in CRF; still, the absence of association persisted. While this could partly be due to the relatively low number of events in the subgroups, the results of these analyses, as well as the sensitivity analysis, suggest that genetic and familial factors play an important role in the association of CRF with CVD and mortality. Given that behavioral factors likely explain the difference in CRF within twin pairs, the results also suggest that higher levels of lifestyle-acquired CRF, including gene-behavior interactions, might not be effective in reducing the risk of early CVD and mortality in young men.

To our knowledge, no previous study used a twin design to explore the association between CRF and both CVD and mortality. However, the association between self-reported PA and mortality has previously been evaluated in twin studies with somewhat inconclusive results. In studies based on the Finnish Twin Cohort, lower risk of mortality was observed in twins with higher levels of self-reported PA (34, 35). However, the associations were significant only in the subcohort of dizygotic twins, which might indicate residual genetic confounding or lack of statistical power. The latter explanation is more likely; Carlsson et al. (36) observed lower all-cause and cardiovascular mortality in a larger twin cohort of monozygotic twins with discordant levels of self-reported PA. Thus, together these results and the results of the present study indicate that PA might influence the risk of CVD and mortality through mechanisms other than a higher CRF.

It would also be of interest to explore other behavioral pathways that could influence the association between CRF and the risk of disease and mortality. One possible mediating factor is obesity. In a previous study, a co-twin design was used to explore whether a higher body mass index would contribute to a lower risk of MI, diabetes, and mortality among 4,046 monozygotic twins (37). Interestingly, the twins with lower body mass index did not have a lower risk of MI or mortality, although they did have a lower risk of diabetes. Overall, more studies are needed on the topic of CRF in relation to the risk of disease and mortality.

Beyond the observational design, the present study has some additional limitations that should be considered. First,

Table 2. Risks of Cardiovascular Disease and Mortality During a Median Follow-up of 32 Years in Pairs of 18-Year-Old Men with Discordant Cardiorespiratory Fitness (>1 watt) Who Were Conscripted for Military Service in Sweden During 1972–1996

	Twin Cohort						Matched Nonsibling Cohort					
	Less Fit (*n* = 4,260)		More Fit (*n* = 4,260)		HR	95% CI	Less Fit (*n* = 90,331)		More Fit (*n* = 90,331)		HR	95% CI
	IR per 10,000 PY	No. of Events	IR per 10,000 PY	No. of Events			IR per 10,000 PY	No. of Events	IR per 10,000 PY	No. of Events		
Unadjusted												
Angina	3.6	50	3.1	43	0.98	0.64, 1.50	3.7	1,080	3.0	900	0.83	0.76, 0.91
MI	3.6	50	3.2	44	0.95	0.62, 1.47	4.3	1,257	3.6	1,065	0.83	0.76, 0.90
Stroke	2.8	39	2.2	31	0.72	0.44, 1.17	3.1	918	2.5	740	0.80	0.72, 0.88
Death	10.0	139	11.2	155	1.15	0.91, 1.46	11.4	3,377	9.5	2,817	0.83	0.79, 0.88
CVD and death	18.2	251	17.8	246	1.00	0.83, 1.20	18.0	5,298	15.0	4,444	0.83	0.79, 0.86
Adjusted for socioeconomic factors												
Angina					0.99	0.62, 1.58					0.87	0.79, 0.96
MI					0.82	0.49, 1.37					0.86	0.79, 0.94
Stroke					0.75	0.43, 1.31					0.84	0.75, 0.93
Death					1.07	0.79, 1.45					0.90	0.84, 0.96
CVD and death					0.94	0.76, 1.16					0.88	0.83, 0.92
Additionally adjusted for BMI and blood pressure												
Angina					0.92	0.56, 1.53					0.86	0.78, 0.94
MI					0.77	0.44, 1.35					0.86	0.78, 0.94
Stroke					0.58	0.29, 1.35					0.84	0.75, 0.93
Death					1.05	0.77, 1.44					0.90	0.84, 0.97
CVD and death					0.90	0.72, 1.12					0.87	0.83, 0.92

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PY, person-years.

Table 3. Risks of Cardiovascular Disease and Mortality During a Median Follow-up of 32 Years in Pairs of 18-Year-Old Men with Discordant Weight-Adjusted Cardiorespiratory Fitness (watt/kilogram) Who Were Conscripted for Military Service in Sweden During 1972–1996

	Twin Cohort						Matched Nonsibling Cohort					
	Less Fit (n = 4,260)		More Fit (n = 4,260)		HR	95% CI	Less Fit (n = 90,331)		More Fit (n = 90,331)		HR	95% CI
	IR per 10,000 PY	No. of Events	IR per 10,000 PY	No. of Events			IR per 10,000 PY	No. of Events	IR per 10,000 PY	No. of Events		
Unadjusted												
Angina	3.3	46	3.4	47	1.24	0.81, 1.92	3.7	1,093	3.0	887	0.81	0.74, 0.88
MI	3.8	52	3.0	42	0.95	0.62, 1.47	4.2	1,249	3.6	1,073	0.84	0.77, 0.91
Stroke	2.7	38	2.3	32	0.76	0.47, 1.24	3.1	927	2.5	731	0.79	0.71, 0.87
Death	10.4	145	10.7	149	1.04	0.82, 1.31	11.4	3,378	9.5	2,816	0.83	0.79, 0.87
CVD and death	18.1	250	17.9	247	1.02	0.85, 1.23	18.0	5,294	15.1	4,448	0.83	0.80, 0.86
Adjusted for socioeconomic factors												
Angina					1.27	0.79, 2.05					0.86	0.78, 0.94
MI					0.89	0.54, 1.46					0.89	0.81, 0.97
Stroke					0.86	0.50, 1.48					0.82	0.74, 0.91
Death					0.95	0.70, 1.28					0.90	0.85, 0.97
CVD and death					0.97	0.78, 1.19					0.88	0.84, 0.93
Additionally adjusted for BMI and blood pressure												
Angina					1.49	0.87, 2.55					0.87	0.79, 0.96
MI					0.94	0.55, 1.60					0.89	0.82, 0.98
Stroke					0.88	0.49, 1.60					0.82	0.74, 0.91
Death					0.93	0.67, 1.28					0.91	0.85, 0.97
CVD and death					0.99	0.80, 1.24					0.89	0.84, 0.93

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PY, person-years.

Cohort and Difference in Cardiorespiratory Fitness, W	Less Fit		More Fit		HR (95% CI)
	IR	No. of Events	IR	No. of Events	
Twins					
≥1	18.2	251	17.8	246	1.00 (0.83, 1.20)
≥10	18.1	206	16.6	189	0.94 (0.76, 1.15)
≥20	17.1	142	17.0	141	1.05 (0.82, 1.34)
≥30	17.9	108	17.0	103	1.02 (0.77, 1.35)
≥40	16.8	72	15.6	67	1.05 (0.74, 1.49)
≥50	14.3	43	15.3	46	1.07 (0.70, 1.64)
≥60	14.6	29	14.6	29	0.96 (0.57, 1.64)
Nonsiblings					
≥1	18.0	5,298	15.0	4,444	0.83 (0.79, 0.86)
≥10	17.8	4,542	14.6	3,745	0.81 (0.78, 0.85)
≥20	17.6	3,687	13.8	2,893	0.77 (0.73, 0.81)
≥30	17.6	2,971	13.1	2,223	0.73 (0.69, 0.78)
≥40	17.0	2,252	12.1	1,611	0.70 (0.66, 0.75)
≥50	17.2	1,751	11.4	1,162	0.65 (0.60, 0.70)
≥60	16.8	1,308	11.0	856	0.65 (0.59, 0.71)

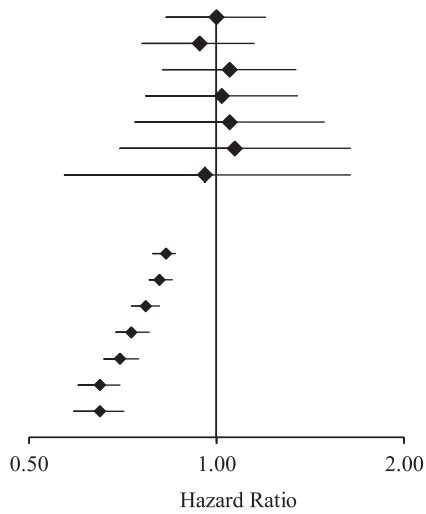

Figure 2. Cardiovascular disease and mortality in twins and matched nonsiblings with increasing difference in cardiorespiratory fitness among Swedish men who were 18 years of age in 1972–1996. CI, confidence interval; HR, (unadjusted) hazard ratio; IR, incidence rate (per 10,000 person-years); W, watts.

because CRF was measured only once in young adulthood, follow-up measurements later in life could have led to different results. However, it should be noted that higher CRF was associated with a lower risk of the outcomes when genetic and familial factors were not accounted for, as demonstrated by our nonsibling analysis as well as by our sensitivity analysis, in which one twin in each pair was excluded from the analysis. Together, these findings are consistent with previous research in young men (29, 31, 32) and other age groups (4, 30). In addition, while long-term studies on changes in CRF throughout life are lacking, there was a study with a 36-year follow-up that showed that physical capacity in adolescence is a fairly stable predictor of physical capacity in middle age (38). Second, the present study cohort included only men, so no inferences can be made for women. Third, the lack of associations in the twin cohort could be due to a lack of statistical power. As mentioned above, however, the mean difference of 33 watts between more and less fit twins was expected to result in 16%–24% lower CVD and mortality, and a post-hoc power analysis suggested that the statistical power to detect such differences was sufficient. Fourth, the twin cohort comprised both monozygotic and dizygotic twins. In a previous evaluation of the conscription cohort, 46% of twin pairs were found to be monozygotic (39), with a substantial chance of residual genetic confounding. Yet, our twin model appeared to adequately adjust for genetic and familial factors given that the fitter twin did not have a lower risk of CVD and mortality. Furthermore, the present study lacked certain behavioral confounders, including smoking, which is a major cause of CVD and mortality (40, 41). However, because smoking is associated with lower CRF (42), smoking status, and any residual genetic confounding, would likely have further attenuated the regression estimates. The primary strengths of this study include the unique design with a large nationwide twin population, objectively measured CRF, and a comprehensive set of analyses. These strengths increase the internal and external validity of the results.

In conclusion, the novel results of the present study suggest that CRF is not associated with CVD and mortality

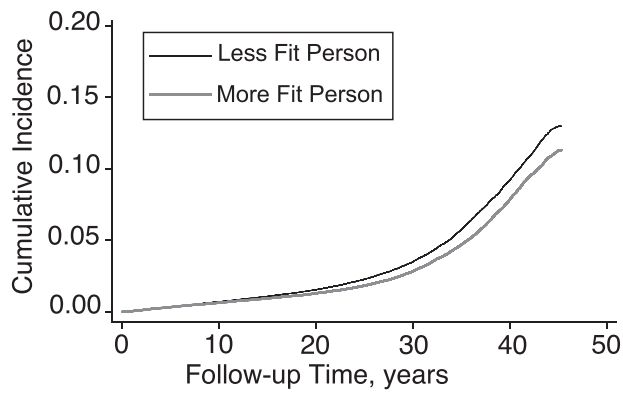

Figure 3. Cumulative incidence of cardiovascular disease and mortality in the matched nonsibling cohort among Swedish men who were 18 years of age in 1972–1996. The hazard ratio for fitter men compared with less fit men was 0.83 with a 95% confidence interval of 0.79, 0.86.

when controlling for genetic and familial factors using a male twin model. Given that the difference in CRF in the twin cohort most likely is caused by behavioral factors, these findings suggest that genetic and familial factors play an important role in the association of CRF with CVD and mortality and, by implication, that higher levels of lifestyle-acquired CRF might not be effective in reducing the risk of early CVD and mortality in men. Given the lack of previous reports, it would be of value if these associations can be confirmed in other twin cohorts, including cohorts of women and older individuals.

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Author affiliations: Department of Community Medicine and Rehabilitation, Unit of Geriatric Medicine, Umeå University, Umeå, Sweden (Marcel Ballin, Peter Nordström); Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden (Marcel Ballin, Anna Nordström); and School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway (Anna Nordström).

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