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The Influence of Change in Cardiorespiratory Fitness With Short-Term Exercise Training on Mortality Risk From The Ball State Adult Fitness Longitudinal Lifestyle Study

Mary T. Imboden, PhD; Matthew P. Harber, PhD; Mitchell H. Whaley, PhD; W. Holmes Finch, PhD; Derron A. Bishop, PhD; Bradley S. Fleenor, PhD; and Leonard A. Kaminsky, PhD

Abstract

Objective: To assess the influence of changes in cardiorespiratory fitness (CRF) after exercise training on mortality risk in a cohort of self-referred, apparently healthy adults.

Patients and Methods: A total of 683 participants (404 men, 279 women; mean age: 42.7±11.0 y) underwent two maximal cardiopulmonary exercise tests (CPX) between March 20, 1970, and December 11, 2012, to assess CRF at baseline (CPX1) and post-exercise training (CPX2). Participants were followed for an average of 29.8±10.7 years after their CPX2. Cox proportional hazards models were performed to determine the relationship of CRF change with mortality, with change in CRF as a continuous variable, as well as a categorical variable. A Wald chi-square test was used to compare the coefficients estimating the relationship of peak oxygen consumption (VO_{2peak}) at CPX1 with VO_{2peak} measured at CPX2 with time until death for all-cause mortality.

Results: During the follow-up period there were 180 deaths. When assessed independently, there were 20% (95% CI, 10−49%) and 38% (95% CI, 7−66%) lower mortality risks per 1 metabolic equivalent improvement in CRF ($P<.01$) in men and women, respectively, after multivariable adjustment. Those that remained unfit had ∼2-fold higher risk for all-cause mortality compared with those that remained fit and CRF at CPX2 was a stronger predictor of all-cause mortality than at CPX1 ($P=.02$).

Conclusion: Improving CRF through exercise training lowers mortality risk. Clinicians should encourage individuals to participate in exercise training to improve CRF to lower risk of mortality.

Low cardiorespiratory fitness (CRF) has been established as an important predictor of cardiovascular disease (CVD), cancer, and all-cause mortality since the late 1980s.[1-6] This has been studied in various populations using a variety of methods to assess CRF,[3] more recently including cardiopulmonary exercise testing (CPX), which is widely considered to be the gold standard method for measuring CRF.[7,8]

Aerobic exercise training is widely recommended, particularly in those with low CRF, to improve CRF. Exercise training programs typically result in improvements in CRF of 1 to 2 metabolic equivalents (METs) following 3 to 6 mo of moderate to vigorous exercise, which may influence mortality risk.[9,10] Most investigations of the relationship between CRF and mortality have only observed the relationship from a baseline measure of CRF.[6,11-18] It is presently unknown if assessing CRF after a short-term exercise training program would be more effective in determining a patient's risk, as is commonly done with other risk factors following prescribed therapies to determine effectiveness in improving patient health and reducing risk for adverse health outcomes.

The association between short-term (<1 year) changes in CRF post-exercise training

and mortality risk has only been studied in patients with established CVD attending cardiac rehabilitation. Martin et al[19] showed that participation in a 12-week cardiac rehabilitation program resulted in a 13% reduction in mortality with each MET increase in CRF estimated from an exercise test (CRF_e) in the overall sample, and a 30% reduction in those CVD patients categorized as low fit at baseline. However, there have been no studies that have assessed the association between change in directly measured CRF, obtained from CPX with short-term exercise training and all-cause mortality in apparently healthy men and women.

Therefore, the primary aim of this study was to assess the association between changes in CPX–derived CRF following a short-term aerobic exercise training program and the risk for all-cause mortality in apparently healthy men and women. Secondly, this study aimed to compare CPX–derived CRF measured at baseline (CPX1) to that measured after short-term exercise training (CPX2) in predicting mortality risk.

METHODS

A sample of 683 apparently healthy participants (404 men, 279 women), ranging from 20 to 77 years of age (mean age at CPX1 for total sample, 42.7±11.0 y; mean age for men, 42.2±10.6 y, mean age for women, 43.5±11.5 y) was obtained from the Ball State Adult Fitness Longitudinal Lifestyle Study (BALL ST) cohort between March 20, 1970, and December 11, 2012. Participants were residents of east-central Indiana who were self-referred to this university-based exercise program and were considered apparently healthy, defined as free from known CVD (history of cardiac arrest, coronary artery disease, heart failure, myocardial infarction, symptomatic valvular heart disease, peripheral artery disease, and stroke) and cancer at baseline (n=17). CVD diagnosis was self-reported and verified by written physician confirmation in 24 participants; therefore, these individuals were excluded from all analyses. Participants were included if they were 18 years of age or older when they joined the program and performed two CPXs using the same mode of exercise, with CPX2 occurring after 3 to 8 months of exercise training. Participants were excluded if they did not meet the defined maximal effort criteria of a respiratory exchange ratio of ≥1.0 during both exercise tests (n=44), or had <5.0 years of mortality follow-up from the second test (n=16) in an attempt to control for unknown underlying disease. This study was reviewed by the Ball State University Institutional Review Board and determined exempt as only de-identified data were used.

Clinical Measurements

A full description of the procedures involved in the resting clinical measurements performed before both CPXs has been provided previously.[20,21] In summary, participants completed a health history questionnaire, providing demographic information, personal and family medical history, medication usage, and lifestyle behaviors. Information gained from the questionnaire was used to screen for medical contraindications and/or physical limitations to CPX.

Lifestyle behaviors of physical activity (PA) and smoking were self-reported. PA status was classified as inactive or active, with active being designated if participants reported engagement in regular PA, meeting the 2008 US PA recommendations for aerobic activity for adults.[22] Smoking status was categorized as current smoker, including those who used cigarettes or quit within the past year, or nonsmoker at baseline.

Clinical measurements including resting heart rate, blood pressure, anthropometrics (height, weight, and waist circumference), 12-lead electrocardiogram, and blood chemistry (≥8 h post-prandial), were performed by trained technicians using standardized laboratory procedures.[20,21] These measurements were used to determine the presence of risk factors, including obesity, hypertension, dyslipidemia, and impaired fasting glucose, defined according to current accepted atherosclerotic CVD risk factor criteria.[23]

Assessment of CRF

CPXs were performed using a treadmill or cycle, to determine peak oxygen consumption

(VO_{2peak}). The mode of exercise was chosen based on participant preference, comfort, and the presence of functional limitations as determined through health history questionnaire. The protocol was chosen to target achieving peak effort within 8 to 12 minutes based on the participant's self-reported PA level or CRF_e obtained using a validated non-exercise prediction equation.[21] Throughout the CPX, gas exchange measurements were collected using an open-circuit spirometry metabolic testing system. Standardized procedures were followed for metabolic cart calibration and all tests were supervised by trained clinical exercise physiologists, with additional medical supervision when appropriate. Participants were encouraged to exercise to volitional fatigue and a respiratory exchange ratio $\geq$1.0 was used as an objective indicator of peak effort. CRF was expressed as VO_{2peak} in units of $mL \cdot kg^{-1} \cdot min^{-1}$. VO_{2peak} was determined by averaging the highest two to three consecutive measured VO_2 values within 2 $mL \cdot kg^{-1} \cdot min^{-1}$, occurring in the last 2 minutes of the CPX.

Exercise Training

Following CPX1, participants were provided an individualized exercise prescription developed by clinical exercise physiologists based on their CPX results. The program consistently followed the at-the-time current recommendations first established by the American Heart Association[24] and later by the American College of Sports Medicine which are updated approximately every 5 years.[23,25] The exercise prescription was created with the goal of improving CRF by progressively increasing PA volume (intensity, duration, and frequency), which has previously been shown in this cohort.[26] All participants who attended the program regularly, operationally defined as approximately >75% of the sessions, were reassessed after 3 to 8 months of exercise training. CPX2 was performed using the same mode of exercise and following the same protocol as performed with CPX1.

Outcomes and Follow-up

All participants were followed from the date of CPX2 through November 2017 or until their date of death. The National Death Index was the primary data source for obtaining vital status between 1979 and 2016. Those identified by the National Death Index as deceased due to accidental causes (n=6) were excluded from analyses.

Statistical Analysis

SPSS V. 24 (SPSS, Inc., Chicago, IL), was used for all statistical analyses. Descriptive statistics were performed to summarize baseline characteristics of the participants and a univariate analysis of variance and chi-square goodness of fit test were used when appropriate to test for significant differences between sexes, CRF level (low fit [quartile I] vs fit [quartiles II, III, IV]), and vital status. A paired *t* test was used to assess the differences between baseline CRF and CRF after exercise training, both expressed as a continuous variable ($mL \cdot kg^{-1} \cdot min^{-1}$). Cox proportional hazards models were used to determine hazard ratios and 95% CIs associated with the change in CRF as related to all-cause mortality for both sexes. The change in CRF was computed as the difference between baseline and post-training VO_{2peak}, and was used as a continuous variable in analyses. Additional models were performed with change in CRF level, as a categorical variable, as the covariate. CRF levels were initially grouped into quartiles based on the Fitness Registry and the Importance of Exercise National Database (FRIEND),[27,28] which provides age- and sex-specific reference values for CPX−derived CRF for adults in the United States. Analyses were performed to determine if there were significant differences between fitness quartiles in mortality risk at baseline and post-training test. As there were no significant differences in risk between quartiles II-IV, these were grouped together and categorized as the fit group ($\geq 26^{th}$ percentile). Quartile I was classified as the low-fit group ($\leq 25^{th}$ percentile). The change in CRF level was then categorized into three groups, those that remained low-fit, those that remained fit, and those that improved their CRF level moving from the low-fit to fit group. The Cox proportional hazards models were fit to the data and the continuous models

TABLE 1. Descriptive Characteristics of BALL ST Cohort at CPX1 and After CPX2[a]

	All (N=683)		Women (n=279)		Men (n=404)	
	CPX 1	CPX 2	CPX 1	CPX 2	CPX 1	CPX 2
Characteristics						
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)[b]	32.3±8.6	37.2±9.2	27.5±7.0	31.6±7.5	37.2±9.2	41.1±8.2
VO_{2peak} ($L \cdot min^{-1}$)[b]	2.55±0.8	2.86±0.9	1.88±0.4	2.11±0.5	2.86±0.9	3.38±0.7
METs[*]	9.2±2.5	10.6±2.6	7.9±2.0	9.0±2.1	10.6±2.6	11.7±2.3
FRIEND (percentile)	54	64	50	68	59	63
Weight (kg)	79.2±17.0	76.7±16.3	69.6±15.8	68.3±14.4	82.7±15.0	77.2±16.4
BMI ($kg \cdot m^{-2}$)[b]	26.0±4.7	25.5±4.8	25.7±5.8	25.1±5.2	26.1±4.0	25.7±4.8
WC (cm)[b]	88.9±14.2	85.5±13.0	80.6±13.7	78.9±12.4	92.1±10.3	86.5±13.0
SBP/DBP (mm Hg)[b]	120/77±13/10	117/76±13/10	118/76±14/10	115/72±13/12	121/77±12/12	117/76±13/10
RHR (bpm)[b]	68±23	64±10	70±9	67±9	64±10	61±9
Total cholesterol ($mg \cdot dL^{-1}$)[b]	211.2±45.5	206.3±42.3	205.3±42.7	200.1±37.9	212.0±45.6	207.1±43.3
Blood glucose ($mg \cdot dL^{-1}$)	93.9±19.2	94.2±18.6	91.8±20.0	92.2±20.9	96.1±16.6	94.3±18.7
Risk factors						
Obesity (%)[b]	24	18	26	20	17	18
Hypertension (%)[*]	20	17	18	14	20	18
Dyslipidemia (%)[b]	55	50	41	37	62	52
Pre-diabetes /diabetes (%)[b]	30	29	21	19	41	31
Physical inactivity (%)	78	—	79	—	78	—
Smoking (%)	11	10	7	6	13	11

[a]BALL ST = Ball State Adult Fitness Longitudinal Lifestyle Study; CPX1/2 = cardiopulmonary exercise testing before/after; BMI = body mass index, bpm = beats per minute, DBP = diastolic blood pressure, FRIEND = Fitness Registry and the Importance of Exercise National Database, METs =metabolic equivalents, RHR = resting heart rate; SBP = systolic blood pressure, VO_{2peak} = peak oxygen consumption, WC = waist circumference.

[b]Significantly different results between CPX1 and CPX2 within sexes; $P \leq .05$.

were analyzed unadjusted (model 1), adjusted for VO_{2peak} at baseline (model 2), and then with further adjustment for baseline age, examination year, and the change in confounding CVD risk factors (model 3; body mass index, systolic blood pressure, fasting blood glucose, total cholesterol, expressed continuously, and smoking status), which were computed as the change in each variable between CPX1 and CPX2. The categorical models were analyzed unadjusted (model 1), adjusted for change in VO_{2peak} (model 2), and then with further adjustment for all variables listed in the multivariable model above (model 3). A Wald chi-square test was used to compare the coefficients estimating the relationship of VO_{2peak} at CPX1 to VO_{2peak} measured at CPX2 with time until death for all-cause mortality. These models were analyzed with VO_{2peak} at both tests as covariates only and then further adjusted for age and sex. To assess the assumption of proportional hazards, which underlies the Cox model, Schoenfeld residuals were examined.[29] The relationships between these residuals and the model covariates were not statistically significant ($P>.05$), indicating that the proportional hazards assumption was met.

RESULTS

VO_{2peak} was 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$ (~15%) higher ($P=.04$) after short-term training compared with baseline for the overall sample. Further, the overall risk factor profile of subjects was improved following participation in the exercise training program (Table 1). In addition to becoming physically active, the prevalence of obesity, hypertension, and dyslipidemia were reduced ($P=.01$).

Participants were followed for an average of 29.8 ± 10.7 y. During this period 180 subjects died (129 men, 51 women).

The Cox proportional hazards models showed an inverse relationship between per unit increase in VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) and risk for all-cause mortality ($P<.05$) (Table 2). The relationship remained significant after adjustment for baseline VO_{2peak} and in the multivariable adjusted model. Specifically, a 1 $mL \cdot kg^{-1} \cdot min^{-1}$improvement was found to be associated with a 7% (95% CI, 2−11%) lower risk for all-cause mortality ($P=.02$) after multivariable adjustment. This corresponded to a 25% lower risk per 1 MET improvement. The relationship between change in VO_{2peak} and all-cause mortality remained significant when men and women were assessed independently (Table 2). In men, there was a 6% (95% CI, 3−14%) lower risk for all-cause mortality per 1 $mL \cdot kg^{-1} \cdot min^{-1}$ VO_{2peak} ($P=.01$), after multivariable adjustment. However, the risk reduction increase was found to be greater in women, with an 11% (95% CI, 2−19%) lower risk per each 1 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in VO_{2peak} (hazard ratio per $mL \cdot kg^{-1} \cdot min^{-1}$ improvement, 0.89; 95% CI, 0.81−0.98); $P=.04$). The inverse relationship between per unit increase in CRF and risk for all-cause mortality was also significant with absolute VO_{2peak} ($L \cdot min^{-1}$) ($P<.05$).

TABLE 2. Hazard Ratios for All-Cause Mortality According to per 1 $mL \cdot kg^{-1} \cdot min^{-1}$ change in VO_{2peak}[a]

All	HR (95% CI)
Model 1[b]	0.955 (0.92−0.99)
Model 2[c]	0.935 (0.90−0.97)
Model 3[d]	0.929 (0.89−0.98)
Men	
Model 1	0.968 (0.93−1.01)
Model 2	0.937 (0.90−0.98)
Model 3	0.944 (0.86−0.97)
Women	
Model 1	0.904 (0.84−0.98)
Model 2	0.840 (0.77−0.92)
Model 3[e]	0.890 (0.81−0.98)

[a]CRF = cardiorespiratory fitness, HR = hazard ratio; VO_{2peak} = peak oxygen consumption.
[b]Model 1 unadjusted.
[c]Model 2 adjusted for baseline VO_{2peak}.
[d]Model 3 adjusted for age, sex, examination year, baseline VO_{2peak}, and change in risk factors (continuous variables include body mass index, systolic blood pressure, fasting blood glucose, and total cholesterol, as well as the categorical variable smoking status).
[e]As there were fewer deaths in women, the analysis was adjusted for age, gender, examination year, baseline VO_{2peak}, and change in risk factors (continuous variables include body mass index, fasting blood glucose, and total cholesterol).

At baseline, 181 subjects (130 men, 51 women) were characterized as low-fit ($\leq 25^{th}$ percentile). After 4.2 ± 1.5 months of participation in an exercise training program, 132 of these subjects (93 men, 39 women) improved their CRF to the fit category. The cumulative hazard over the follow-up period of the three CRF categories associated with the short-term training for all-cause mortality is shown in the Figure 1. Results from the Cox proportional hazards models for all-cause mortality showed those who did not improve their CRF above the low-fit threshold had an approximately 2-fold higher risk of dying from all causes compared with those who were above the low-fit threshold at both CPX1 and CPX2 ($P<.001$). The strength of the association with mortality remained significant after further adjustment for change in VO_{2peak}, as well as in the multivariable adjusted model. Those who improved their CRF above the low-fit threshold had no difference in mortality rates compared with those who maintained their level in the fit classification.

Results from the Wald chi-square test of equality comparing CPX-derived CRF at baseline versus after short-term exercise training showed the value measured at CPX2 was a stronger predictor of all-cause mortality than at CPX1 ($P=.02$) (Table 3). This relationship remained significant after further adjustment for age and sex ($P=.05$).

DISCUSSION

This study found a strong, inverse relationship between the change in CRF after short-term exercise training and all-cause mortality equating to a 25% (95% CI, 7−38%) lower mortality risk per MET improvement. This suggests greater improvement in CRF following short-term exercise training results in larger reductions in risk of all-cause mortality in apparently healthy adults. This

association was independent of sex and baseline CRF and was observed over a long follow-up period of more than 28 years on average. This relationship remained significant when adjusted for changes in other risk factors, including body mass index, and when VO_{2peak} was expressed as L/min. The exercise training resulted in a 15% increase in CRF in our cohort, which is consistent with the expected improvement that is considered to be 5% to 30%.[18] These findings further support the importance of CRF and lifestyle modifications designed to improve CRF for long-term health outcomes.

The findings from the current study also showed that CRF after short-term exercise training is a stronger predictor of mortality than a single baseline measure of CRF. This emphasizes the importance of screening for low CRF as a risk factor and subsequently prescribing an exercise training program to improve CRF. This is similar to how clinicians screen for and address other risk factors, through an initial assessment, prescription of a therapy for the risk factor, and subsequent follow-up to determine the effectiveness of the prescription in improving health outcomes.

The only other study to date that has assessed the association of changes in CRF analyzed the changes in CRF_e following a 12-week exercise training program with mortality risk was performed in cardiac patients (76% men; mean age, 60±10 y).[19] The patients' improvement in CRF_e was (~14%) similar to what we observed in the BALL ST cohort. They also found an inverse relationship between CRF_e change and mortality risk; however, their observed reduction in mortality risk of 13% per MET increase was notably lower than the 25% per MET value observed in the current study. One explanation for the greater reduction in risk observed in the current study may be due to the differences in the characteristics of the cohorts (apparently healthy vs cardiac disease). However, the differences may also be due to the use of CPX to directly measure CRF in the current study versus the estimation method used in the previous study. The increased accuracy of CPX allows for a more precise determination of the change in CRF in response to exercise training, which may provide a more sensitive risk stratification.[30,31]

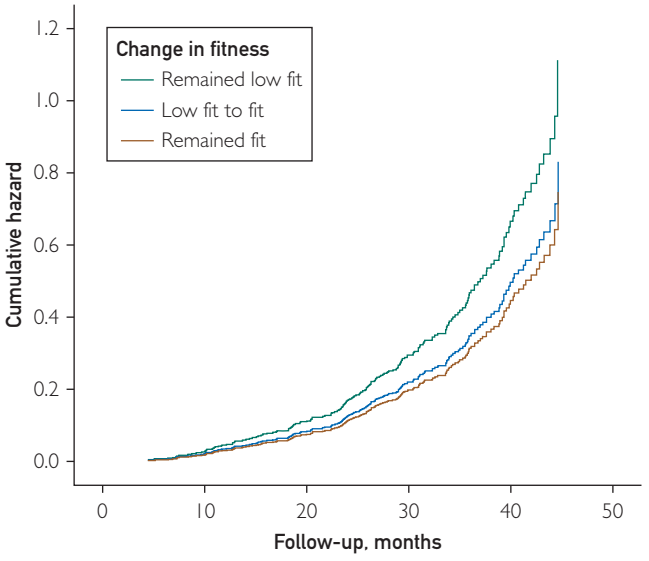

FIGURE 1. Cumulative hazard of change in cardiorespiratory fitness group with mortality during follow-up period.

The current cohort was also categorized into fitness groups based on age- and sex-specific normative data from the FRIEND registry.[27,28] Those who did not improve their fitness level above the 25th percentile had an approximately 2-fold greater risk,

TABLE 3. Comparison the Relationship Between VO_{2peak} Measured at Baseline (CPX1) and After Short-Term Training (CPX2) With Mortality Outcomes[a]

	Wald chi-square test of equality	Absolute parameter estimate
Model 1[b]		
CPX2 VO_{2peak}		0.047[c]
CPX1 VO_{2peak}		0.013
Model 2[d]		
CPX2 VO_{2peak}		0.035[c]
CPX1 VO_{2peak}		0.007

[a]CPX1/2 = cardiopulmonary exercise at baseline/after; Vo_{2peak} = peak oxygen uptake.
[b]Model 1 unadjusted.
[c]$P \leq .05$.
[d]Model 2 adjusted for age and sex.

compared with those who were above the 25th percentile at both CPX1 and CPX2. The mortality risk of those who improved their fitness at CPX2 above the 25th percentile was no different than the group who were above the 25th percentile on both CPX. It is known that the training effect is variable for different individuals,[32] and it is also understood that the rate of improvement is not uniform.[10] A strength of this cohort is the wide range of demographic characteristics which likely contributed to this variation in CRF response to short-term exercise training. These findings suggest that improvement of CRF, at least above the 25th percentile, is important to achieve reduction in mortality risk. This shows the importance of performing periodic CRF assessments, in this case to evaluate response to short-term exercise training. Those who have not responded adequately would require modifications to their exercise prescription, as increasing exercise volume and intensity have been shown to improve CRF in individuals with a below-normal initial response.[32]

Several cohorts have also assessed the association between long-term changes in CRF and mortality (>4 years between assessments).[33-38] All of these studies reported that maintaining or improving CRF or CRF_e resulted in lower risk of mortality. However, these previous longitudinal studies did not directly assess the influence of exercise training—induced improvements in CRF on mortality risk. The current study assessed this relationship after a short-term exercise training program in apparently healthy adults and our findings support that exercise-related increase in CRF decreases mortality risk.

Strengths and Limitations

The primary strengths of this study include assessing CRF after a short-term exercise training program, examining a population of apparently healthy men and women, and directly measuring CRF with CPX. Presently there is only one other report of the CRF-mortality relationship after short-term exercise training, and that was performed with cardiac patients and assessment of CRF_e. The BALL ST cohort also consists of men and women across a wide distribution of ages and number of risk factors and therefore may be representative of the population that many clinicians see on a regular basis. The long follow-up period is another notable strength, as it permits the understanding of how post-training improvements in CRF may alter mortality risk over time, as this study had a mean follow-up of approximately 30 years with a range of 5 to 46 years. Additionally, the use of population-specific CRF groups based on the FRIEND registry, which standardizes CRF across age- and sex-specific percentiles,[27,28] increases the generalizability of our results to the US adult population, and provides clinicians with a tool to more easily interpret mortality by age and sex.

The limitations of the present study include a convenience sample of a self-referred cohort comprised of more than 90% non-Hispanic white persons, all of whom could achieve maximal effort on an exercise test. As such, caution should be used when generalizing these results. Additionally, the low number of deaths in each CRF group, when further divided by sex, decreased statistical power for the sex-specific analyses and therefore were not performed for the categorical models. Future studies should assess the relationship between the change in directly measured CRF after short-term exercise training and all-cause mortality in men and women with a greater number of mortality outcomes, as well as in a greater distribution of racial and ethnic backgrounds. Another limitation was that lifestyle behaviors used in analyses including smoking and physical activity were self-reported. Finally, information on exercise habits and further changes in CRF following CPX2 were not available. Therefore, future studies should assess the association between changes in CRF and mortality in a large diverse cohort that has long-term exercise training adherence.

CONCLUSION

This is the first study to quantify the influence of short-term exercise training—induced changes in CRF on mortality risk in

apparently healthy men and women. These findings show the importance of adopting exercise training as an effective method to improve CRF and decrease mortality risk. Clinicians should screen patients for low CRF, similar to their screening of other CVD risk factors and prescribe exercise training for those with low CRF and to all as a healthy lifestyle intervention. Reassessment of CRF after exercise training is important to establish if the response is adequate or if additional modifications are needed for the individual's exercise prescription.

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Abbreviations and Acronyms: **BALL ST** = Ball State Adult Fitness Longitudinal Lifestyle Study; **CPX** = cardiopulmonary exercise testing; **CRF** = cardiorespiratory fitness; **CRF_e** = estimated cardiorespiratory fitness; **CVD** = cardiovascular disease; **FRIEND** = Fitness Registry and the Importance of Exercise National Database; **MET** = metabolic equivalent; **PA** = physical activity; **VO_{2peak}** = peak oxygen consumption

Dr. Imboden is now with George Fox University. Newberg, OR.
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