Nonexercise Estimated Cardiorespiratory Fitness and Mortality Due to All Causes and Cardiovascular Disease: The NHANES III Study

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Abstract

Objective: To investigate associations of estimated cardiorespiratory fitness (eCRF) and all-cause and cardiovascular disease (CVD) mortality in a representative US population.

Participants and Methods: A total of 12,834 participants, aged 20 to 86 years at baseline, were included in the Third National Health and Nutrition Examination Survey. They were followed up from October 18, 1988, through December 31, 2011, for all-cause and CVD death. Cardiorespiratory fitness was estimated from a nonexercise algorithm and further grouped into tertiles. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs.

Results: A total of 3439 deaths (999 due to CVD) occurred during median follow-up of 19.2 years. After adjusting for race/ethnicity, education, age, hypertension, diabetes, hypercholesterolemia, baseline CVD, and cancer status, each metabolic equivalent increase of eCRF was associated with an 18% (range, 15%-21%) lower risk of all-cause mortality and a 19% (range, 15%-24%) lower risk of CVD mortality in men and a 24% (range, 20%-28%) lower risk of all-cause mortality and a 24% (18%-30%) lower risk of CVD mortality in women. Compared with the lower eCRF group, the HRs (95% CIs) of the middle and upper groups were 0.72 (0.61-0.85) and 0.56 (0.47-0.67) for all-cause mortality and 0.76 (0.57-1.01) and 0.48 (0.34-0.66) for CVD mortality in men; and 0.80 (0.66-0.97) and 0.49 (0.40-0.60) for all-cause mortality and 0.84 (0.60-1.17) and 0.46 (0.33-0.66) for CVD mortality in women (trend \( P < .001 \) for all).

Conclusion: High eCRF was associated with lower risk of all-cause and CVD mortality in a national representative population. The eCRF method has great potential for initial clinical risk stratification and mortality prediction.

Cardiorespiratory fitness (CRF) measures the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity (PA); CRF is inversely associated with the risk of all-cause and cardiovascular disease (CVD) mortality.1-10 The measurement of CRF often requires specialized equipment and trained personnel, and it is time-consuming and relatively expensive, especially in clinical settings.11 The development of nonexercise algorithms provides a cost-effective way to estimate CRF from easily obtained health indicators.

Several nonexercise algorithms have been developed based on different studies.12-19 Most were derived from cross-sectional data, and estimated CRF (eCRF) was based on linear regression of age. Recent longitudinal studies demonstrated that CRF declines nonlinearly with aging.13,20,21 To achieve more accurate estimation of CRF, Jackson et al13 developed longitudinal nonexercise algorithms based on age, quadratic age, sex, body mass index (BMI)/percentage fat, waist circumference (WC), resting heart rate (RHR), PA, and smoking status. The results based on longitudinal nonexercise eCRF revealed a significant association with all-cause and CVD mortality in the study using 1999-2006 National Health and Nutrition Examination Survey (NHANES) data22 and in the Aerobics Center Longitudinal Study (ACLS),23 which were comparable with studies using directly measured
CRF. Another study that applied the longitudinal nonexercise algorithm to estimate CRF was from a Spanish cohort of men and women 60 years or older followed up for mortality. It reported an inverse association between higher eCRF and lower risk of all-cause death in women but not in men and, therefore, questioned the feasibility of this nonexercise eCRF in the prediction of mortality in elderly adults.

The present study aimed to investigate the association between eCRF and mortality due to all causes and CVD in men and women with a wide age range in the Third NHANES (NHANES III).

PARTICIPANTS AND METHODS

Study Population
The NHANES III (1988-1994) uses a complex multistage, stratified, clustered, probability sample design and is a nationally representative sample of the civilian, noninstitutionalized US population. Conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, the NHANES III collects information on the health and nutritional status by personal interview, physical examination, and laboratory testing after obtaining signed consent forms from participants. Although CRF was not measured in the NHANES III, all the variables needed in the longitudinal nonexercise algorithm were collected, which enables us to estimate CRF. This study was followed up from October 18, 1988, through December 31, 2011.

Of the 20,050 adult participants from the NHANES III, we excluded those meeting the following criteria: (1) age beyond the range for which the algorithms were developed (men: 20-86 years; women: 20-78 years) (n=3903); (2) race/ethnicity other than non-Hispanic white, non-Hispanic black, or Mexican American (n=655); (3) BMI less than 18.5 (n=241); (4) the first 2 years of follow-up (n=410); and (5) missing values on calculating eCRF (n=1215) and on other covariates (n=792). Therefore, 12,834 participants were included in the final analysis. All these participants have complete information about race/ethnicity, education, smoking status, physical examination findings (including height, weight, WC, and RHR), self-reported PA during the past month, and laboratory test results (including blood pressure [BP], cholesterol, and glucose).

eCRF Assessment
Sex-specific algorithms were used to determine eCRF in metabolic equivalents (METs; 1 MET=3.5 mL O$_2$·kg$^{-1}$·min$^{-1}$)$^{13}$. eCRF(Women)=$21.2870+(Age^{2}×0.0023)−(BMI×0.2318)−(WC×0.0337)−(RHR×0.0390)+(Active×0.6351)−(Current Smoker×0.4263)$
eCRF(Men)=14.1783+(Age×0.1159)−(Age^{2}×0.0017)−(BMI×0.1534)−(WC×0.0088)−(RHR×0.0364)+(Active×0.5987)−(Current Smoker×0.2994)$

Age was calculated by computing the number of months between the date of birth and the interview date and then dividing by 12. The BMI was calculated as the weight in kilograms divided by the height in meters squared; WC was recorded in centimeters; RHR was measured by pulse rate in beats per minute. Current smoker was defined as participants who smoke cigarettes, cigars, or pipes or use chew tobacco/snuff now.

Physical activity included walking a mile or more at a time without stopping, jogging or running, riding a bicycle, swimming, doing aerobics, doing other dancing, calisthenics, gardening or yard work, lifting weights, and doing other activities. For each of these activities, 3 questions were asked. For example, did you swim in the past month? How often did you swim? Intensity ratings of activities in units of METs were assigned according to the standardized coding scheme developed by Ainsworth et al.$^{28}$ A list of the intensity ratings can be found in the Household Adult File, Appendix 2, at the Centers for Disease Control and Prevention website.$^{29}$ Based on the self-reported information, PA was divided into 2 levels: active and not active. The active group comprised those who met the recommended levels of PA (ie, moderate activity [METs of 3-6] $\geq$5 times per week or vigorous activity [METs >6] $\geq$3 times per week).$^{30}$ The not active group included people who did not achieve the recommended levels of PA. Once the algorithms were implemented, participants were classified into lower, middle, and upper groups on the basis of age- (20-39, 40-49,
50-59, or ≥60 years) and sex- (men or women) specific tertiles of the estimated MET distribution.

**Potential Confounders**

Race/ethnicity groups are non-Hispanic white, non-Hispanic black, and Mexican American. Education was categorized into 2 levels according to the highest grade completed: 12 years or more (high school and above) and fewer than 12 years (less than high school).

Hypertension was defined based on previous physician diagnosis, taking prescribed medicine to decrease BP, or BP of 140/90 mm Hg or greater; diabetes was defined based on physician diagnosis, taking diabetes pills, insulin use, or glucose level greater than 6.9 mmol/L. Glucose level was the average of the first and second venipuncture plasma glucose measurements, or serum glucose if plasma glucose was missing; and hypercholesterolemia was defined based on physician diagnosis, taking prescribed medicine to lower the cholesterol level, or a serum cholesterol level greater than 6.2 mmol/L. Cardiovascular disease status was defined based on physician diagnosis of congestive heart failure, stroke, heart attack, or any pain or discomfort in the chest. Cancer status was defined based on physician diagnosis of cancer. All information was collected by trained examiners using standardized procedures. Details of the questionnaires and examination components can be found in the NHANES III reference manuals and report.

**Assessment of Mortality**

The mortality of participants was ascertained by linkage to the National Center for Health Statistics survey, which used multiple sources of information to determine the final mortality status of a participant. Mortality sources include death certificate records from the National Death Index, the Death Master File, or the Numerical Identification System file from the Social Security Administration; mortality status obtained from the Centers for Medicare and Medicaid Services; death certificates; and information collected during the Second Longitudinal Study of Aging follow-up period. The follow-up time was months calculated from the baseline interview date until the registered date of death or the end of follow-up (December 31, 2011), whichever came first.

A new underlying cause of death (UCOD) coding variable, UCOD-113, was developed to achieve comparability of the International Classification of Diseases (ICD) 9th and 10th revisions. The UCOD-113 recodes cause of death under ICD-9 coding rules into ICD-10–based groups. CVD mortality was defined by UCOD-113 codes 54-64, 70. Its corresponding ICD-9 and ICD-10 coding can be found in the report.

**Statistical Analyses**

Baseline characteristics were summarized based on nonexercise cCRF groups for men and women. Mean ± SE was used for continuous variables, and frequency and weighted percentage for categorical variables. Differences in means or percentages among the 3 cCRF groups were tested using linear regressions and χ² tests, respectively. Considering the complex design of NHANES III, sampling weight, strata, and cluster were considered in all the analyses.

Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs for all-cause and CVD mortality according to cCRF (both as continuous and categorical variables). The proportional hazards (PH) assumptions were examined graphically by plotting the logarithm of the cumulative hazard function vs time or by examining the association between the Schoenfeld residual and time. Covariates that did not satisfy the PH assumption were adjusted as strata in stratified PH models.

Three multivariable models were analyzed. Model 1 adjusted for race/ethnicity, education, and age (we dichotomized age into <60 vs ≥60 years because entering it as a continuous variable did not satisfy the PH assumption); model 2 adjusted for all the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia; and model 3 adjusted for all the variables in model 2 plus CVD and cancer status. The linear trend test was calculated by modeling cCRF groups as an ordinal variable. Interactions between cCRF groups, age (<60 vs ≥60 years) and sex were also checked. Because they were statistically significant, we also presented the age×sex subgroup analyses. Sensitivity analyses were also conducted in...
relatively healthy individuals, who were without a reported history of CVD, cancer, or diabetes. Data management and statistical analyses were performed using a software program (SAS, version 9.4; SAS Institute Inc). An α level of .05 was considered significant.

RESULTS

After median follow-up of 19.2 years (interquartile range, 17.4-21.0 years), 3439 participants died (999 of CVD). Baseline characteristics are shown by eCRF tertiles in men (Table 1) and in women (Table 2). In general, a large proportion of people in the higher eCRF groups were younger; were non-Hispanic white; had completed high school or more; were not current smokers; had a lower weight, lower BMI, smaller WC, and lower level of RHR; were physically active; and had a lower percentage of reporting hypertension, diabetes, and history of CVD.

eCRF and Mortality in Men

Higher eCRF was associated with lower risk of all-cause mortality in men. Compared with model 1, HRs increased only slightly in models 2 and 3 and remained statistically significant. After adjusting for race/ethnicity, education, age, hypertension, diabetes, hypercholesterolemia, CVD, and cancer status, each MET increase of eCRF was associated with an 18% (range, 15%-21%) decrease in hazard risk. Considering the lower eCRF group as the referent, HRs (95% CIs) in the middle and upper eCRF groups for all-cause mortality were 0.72 (0.61-0.85) and 0.56 (0.47-0.67), respectively. Trend tests showed significant trends across ascending categories of eCRF groups (Table 3). The magnitude and pattern of the association between eCRF and CVD mortality were consistent with all-cause mortality. Each MET increase of eCRF was associated with a 19% (range, 15%-24%) decrease in hazard risk for CVD mortality. The HRs (95% CIs) in the middle and upper eCRF groups for CVD mortality were 0.76 (0.57-1.01) and 0.48 (0.34-0.66), respectively (Table 3). Results in relatively healthy participants without a reported history of CVD, cancer, or diabetes were consistent (Table 4).

Table 1.

| Variable                   | All men (N=6248) | Lower (n=2081) | Middle (n=2084) | Upper (n=2083) | P value |
|----------------------------|-----------------|---------------|-----------------|---------------|---------|
| Age (y)                    | 43.0±0.4        | 43.6±0.5      | 43.2±0.6        | 43.4±0.6      | <.001   |
| Height (cm)                | 176.2±0.1       | 176.4±0.3     | 176.4±0.2       | 175.8±0.3     | .23     |
| Weight (kg)                | 83±0.3          | 97.5±0.6      | 81.5±0.3        | 72.1±0.3      | <.001   |
| BMI                        | 26.7±0.1        | 31.3±0.1      | 26.1±0.1        | 23.3±0.1      | <.001   |
| WC (cm)                    | 95.8±0.3        | 107.7±0.4     | 94.6±0.3        | 86.5±0.3      | <.001   |
| RHR (bpm)                  | 72.3±0.3        | 78.4±0.6      | 72.4±0.4        | 66.7±0.4      | <.001   |
| eCRF (METs)                | 11.5±0.1        | 9.6±0.1       | 11.6±0.0        | 13±0.1        | <.001   |
| Physically active (%)      | 2892 (50.3)     | 642 (32.9)    | 923 (47.4)      | 1327 (69.0)   | <.001   |
| Current smoker (%)         | 2281 (38.9)     | 809 (45.3)    | 778 (40.7)      | 694 (31.3)    | <.001   |
| Race/ethnicity (%)         |                 |               |                 |               | <.001   |
| Non-Hispanic white         | 2626 (83.6)     | 887 (82.8)    | 909 (85.0)      | 830 (82.7)    |         |
| Non-Hispanic black         | 1710 (10.4)     | 519 (10.2)    | 525 (9.1)       | 666 (12.1)    |         |
| Mexican American           | 1912 (6.0)      | 675 (7.0)     | 650 (5.9)       | 587 (5.2)     |         |
| Education ≥12 y (%)        | 3649 (76.4)     | 1131 (71.5)   | 1215 (77.5)     | 1303 (79.6)   | <.001   |
| Hypertension (%)           | 2316 (32.0)     | 980 (42.5)    | 739 (30.2)      | 597 (24.3)    | <.001   |
| Hypercholesterolemia (%)   | 3897 (65.1)     | 1345 (66.0)   | 1274 (63.9)     | 1278 (65.6)   | .64     |
| Diabetes (%)               | 1212 (15.0)     | 496 (19.2)    | 402 (13.8)      | 314 (12.4)    | <.001   |
| Cancer (%)                 | 412 (6.0)       | 156 (5.8)     | 149 (6.1)       | 107 (6.1)     | .94     |
| CVD (%)                    | 1929 (32.2)     | 736 (37.7)    | 627 (31.8)      | 566 (27.7)    | <.001   |

*BMI = body mass index; CVD = cardiovascular disease; eCRF = estimated cardiorespiratory fitness; MET = metabolic equivalent; PA = physical activity; RHR = resting heart rate; WC = waist circumference.

Data are shown as mean ± SD for continuous variables. For categorical variables, the first number is the observed count and the parenthetical number is the weighted percentage.
eCRF and Mortality in Women

Similar to men, the association between higher eCRF and lower risk of all-cause mortality was observed in women. After adjusting for race/ethnicity, education, age, hypertension, diabetes, hypercholesterolemia, CVD, and cancer status, each MET increase of CRF was associated with a 24% (range, 20%-28%) decrease in hazard risk. Considering the lower eCRF group as the referent, HRs (95% CIs) in the middle and upper eCRF groups for all-cause mortality were 0.80 (0.66-0.97) and 0.49 (0.40-0.60), respectively. Trend tests showed significant trends across ascending categories of eCRF groups (Table 3). The magnitude and pattern of the association between eCRF and CVD mortality were similar as for all-cause mortality. Each MET increase of eCRF was associated with a 24% (range, 18%-30%) decrease in hazard risk of CVD mortality. The HRs (95% CIs) in the middle and upper eCRF groups for CVD mortality were 0.84 (0.60-1.17) and 0.46 (0.33-0.66), respectively (Table 3). In relatively healthy women, reduced risk was significant for all-cause mortality. The HR (95% CI) per MET was 0.75 (0.58-0.99) for CVD mortality, although the HRs (95% CIs) in the middle and upper eCRF groups for CVD mortality were nonsignificant (Table 4).

Subgroup Analysis

Interactions among eCRF groups, age (<60 vs ≥60 years), and sex were significant (P< .001). Results of the age×sex-specific subgroup analyses also showed the inverse association between eCRF and mortality due to all causes and CVD (Figure), except for CVD mortality in men younger than 60 years. The HRs (95% CIs) in the middle and upper eCRF groups for all-cause mortality were 0.71 (0.49-1.01) and 0.74 (0.53-1.04), respectively, in men younger than 60 years. But when eCRF was modeled as a continuous variable, the HR (95% CI) per MET is 0.84 (0.78-0.91). Similarly, HRs (95% CIs) in the middle and upper eCRF groups for CVD mortality were 0.45 (0.20-1.00) and 0.54 (0.27-1.08), respectively, in women younger than 60 years.

### TABLE 2. Baseline Characteristics of Women by eCRF Group

| Variable          | All women (N=6586) | Lower (n=2194) | Middle (n=2196) | Upper (n=2196) | P value |
|-------------------|--------------------|----------------|----------------|----------------|---------|
| Age (y)           | 44.0±0.4           | 45.3±0.6       | 44.2±0.7       | 43.0±0.6       | <.001   |
| Height (cm)       | 162.5±0.2          | 161.8±0.3      | 162.2±0.3      | 163.1±0.2      | <.001   |
| Weight (kg)       | 70.8±0.4           | 89.3±0.7       | 93.9±0.3       | 60.0±0.2       | <.001   |
| BMI               | 26.8±0.2           | 34.1±0.3       | 26.3±0.1       | 22.5±0.1       | <.001   |
| WC (cm)           | 89.3±0.4           | 105.8±0.6      | 88.8±0.3       | 79.0±0.3       | <.001   |
| RHR (bpm)         | 76.3±0.5           | 83.4±0.6       | 77.8±0.5       | 70.7±0.5       | <.001   |
| eCRF (METs)       | 8.7±0.1            | 6.9±0.1        | 8.6±0.0        | 9.8±0.0        | <.001   |
| Physically active | 2198 (39.8)        | 381 (19.3)     | 630 (30.2)     | 1187 (60.0)    | <.001   |
| Current smoker    | 1550 (26.9)        | 556 (31.3)     | 530 (28.7)     | 464 (22.8)     | <.001   |
| Race/ethnicity (%)| Non-Hispanic white | 2708 (82.6)    | 745 (76.1)     | 845 (80.1)     | 1118 (88.6) |
|                  | Non-Hispanic black | 2004 (12.2)    | 803 (17.2)     | 685 (13.9)     | 516 (7.7)   |
|                  | Mexican American   | 1874 (5.2)     | 646 (6.7)      | 666 (6.0)      | 562 (3.7)   |
| Education ≥12 y (%)| 4211 (78.8)        | 1250 (70.2)    | 1349 (77.5)    | 1612 (85.3)    | <.001     |
| Hypertension (%)  | 2339 (30.7)        | 1005 (45.5)    | 779 (31.4)     | 555 (20.6)     | <.001     |
| Hypercholesterolemia (%) | 4549 (74) | 1511 (73.6) | 1494 (73.6) | 1544 (74.6) | .86       |
| Diabetes (%)      | 1400 (16.9)        | 633 (25.4)     | 457 (17.0)     | 310 (11.3)     | <.001     |
| Cancer (%)        | 422 (8.5)          | 133 (8.0)      | 139 (8.5)      | 150 (8.8)      | .87       |
| CVD (%)           | 2033 (30.1)        | 756 (35.3)     | 668 (31.7)     | 609 (25.6)     | <.001     |

*BMI = body mass index; CVD = cardiovascular disease; eCRF = estimated cardiorespiratory fitness; MET = metabolic equivalent; RHR = resting heart rate; WC = waist circumference.

Data are shown as mean ± SD for continuous variables. For categorical variables, the first number is the observed count and the parenthetical number is the weighted percentage.
the HR (95% CI) per MET was 0.74 (0.63-0.86), which is statistically significant.

**DISCUSSION**

In this relatively large representative US study, nonexercise eCRF was inversely associated with mortality due to all causes and CVD in men and women. To our knowledge, only 3 studies have investigated the association between the longitudinal model-derived eCRF and all-cause and CVD mortality. A short report using 1999-2006 NHANES data showed that for per-MET increase, HRs (95% CIs) were 0.76 (0.72-0.80) for all-cause mortality and 0.71 (0.61-0.82) for CVD mortality in all the participants, which were comparable with HRs observed from the NHANES III (Table 3). The slightly quantifiable difference might be explained by the sample size, length of follow-up, death occurrences, and characteristics of participants. The NHANES III has a larger sample size (12,834 vs 9974) and longer follow-up (median, 19.2 years vs 8.8 years), which provides more deaths (3439 deaths [999 of CVD] vs 490 deaths [79 of CVD]).

The ACLS reported that the HRs (95% CIs) associated with each MET increase of eCRF were 0.85 (0.82-0.88) for all-cause mortality and 0.81 (0.77-0.86) for CVD mortality in men and 0.87 (0.75-0.99) for all-cause mortality in women, which was consistent to the present study. However, we found a significant inverse association between eCRF and CVD mortality in women, whereas the HR (95% CI) was 0.84 (0.64-1.12) and not quite significant statistically in the ACLS study. This inconsistency might also be explained by the fact that the NHANES III has longer follow-up (median, 19.2 years vs 14.5 years

| TABLE 3. Association Between eCRF and Mortality Due to All Causes and CVD in Men and Women |  |
|---|---|---|---|
| Mortality type and eCRF level | Deaths/patients (No.) | HR (95% CI) |  |
|  |  | Model 1 | Model 2 | Model 3 |
| Men (n=6248) |  |  |  |  |
| All-cause mortality |  |  |  |  |
| Lower | 790/2081 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Middle | 671/2084 | 0.69 (0.59-0.82) | 0.72 (0.61-0.84) | 0.72 (0.61-0.85) |
| Upper | 571/2083 | 0.52 (0.45-0.61) | 0.56 (0.48-0.65) | 0.56 (0.47-0.67) |
| P linear trend | <.001 | <.001 | <.001 |  |
| Per 1 MET | 0.81 (0.78-0.83) | 0.82 (0.79-0.85) | 0.82 (0.79-0.85) |  |
| CVD mortality |  |  |  |  |
| Lower | 260/2081 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Middle | 212/2084 | 0.73 (0.53-1.02) | 0.76 (0.55-1.06) | 0.76 (0.57-1.01) |
| Upper | 147/2083 | 0.43 (0.31-0.61) | 0.47 (0.34-0.66) | 0.48 (0.34-0.66) |
| P linear trend | <.001 | <.001 | <.001 |  |
| Per 1 MET | 0.78 (0.74-0.82) | 0.80 (0.76-0.85) | 0.81 (0.76-0.85) |  |
| Women (n=6586) |  |  |  |  |
| All-cause mortality |  |  |  |  |
| Lower | 579/2194 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Middle | 490/2196 | 0.75 (0.62-0.92) | 0.81 (0.66-0.99) | 0.80 (0.66-0.97) |
| Upper | 338/2196 | 0.44 (0.36-0.54) | 0.50 (0.41-0.61) | 0.49 (0.40-0.60) |
| P linear trend | <.001 | <.001 | <.001 |  |
| Per 1 MET | 0.74 (0.70-0.77) | 0.77 (0.73-0.81) | 0.76 (0.72-0.80) |  |
| CVD mortality |  |  |  |  |
| Lower | 153/2194 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Middle | 142/2196 | 0.76 (0.54-1.06) | 0.85 (0.61-1.16) | 0.84 (0.60-1.17) |
| Upper | 85/2196 | 0.39 (0.28-0.55) | 0.47 (0.34-0.65) | 0.46 (0.33-0.66) |
| P linear trend | <.001 | <.001 | <.001 |  |
| Per 1 MET | 0.72 (0.66-0.78) | 0.77 (0.71-0.83) | 0.76 (0.70-0.82) |  |

*CVD = cardiovascular disease; eCRF = estimated cardiorespiratory fitness; HR = hazard ratio; MET = metabolic equivalent.
Model 1 was adjusted for race/ethnicity, education, and age.
Model 2 was adjusted for all the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia.
Model 3 was adjusted for all the variables in model 2 plus CVD and cancer status.
in the ACLS), which provides more CVD deaths (among 6586 women, 380 died of CVD vs among 9145 ACLS women, 50 died of CVD). In addition, more than 90% of the ACLS women were non-Hispanic white, whereas the NHANES III women included almost 20% people who reported as non-Hispanic black or Mexican American.

The second major finding was the lower risk of all-cause and CVD mortality associated with incremental eCRF in men 60 years and older. A previous study with elderly women in Spain found that eCRF was associated with 20% lower all-cause mortality per MET, which was in accordance with the present study. However, their results did not support the predictive validity of these algorithms in elderly men. The inconsistency from the Spanish study might be explained by differences in population characteristics (US population vs Spanish population) and follow-up period (median, 14.6 years vs 9.4 years for elder adults). However, we did not find an association between eCRF and CVD mortality in men who were younger than 60 years.

In addition, the present findings were comparable with those of studies using other non-exercise algorithms. One is a pooled analysis of 8 cohorts from the Health Survey for England and the Scottish Health Survey. A 1-SD increase in eCRF (corresponding to 1.6-1.7 METs) was associated with 15% (range, 7%-22%) and 25% (10%-33%) decreases for all-cause mortality and CVD mortality, respectively, in men and 12% (range, 2%-20%) and 27% (range, 8%-40%) decreases, respectively, in women. Another is the Nord-Trøndelag Health Study (the HUNT study). After adjusting for age, clinical risk factors, lifestyle factors, and disease status, HRs (95% CIs) associated with each MET increase of eCRF were 0.87 (0.84-0.90) for all-cause mortality and 0.82 (0.78-0.87) for CVD mortality in men and 0.89 (0.86-0.93) for all-cause mortality and 0.85 (0.78-0.92) for CVD mortality in women.

Note that the present study results were consistent with those of studies with directly measured CRF. In general, mortality decreases by 10% to 20% with each 1-MET increase of CRF. A meta-analysis of 33 eligible studies showed that pooled relative risks (95% CIs) of all-cause mortality and coronary heart disease or CVD per 1-MET increase were 0.87 (0.84-0.90) for all-cause mortality and 0.82 (0.78-0.87) for CVD mortality in men and 0.89 (0.86-0.93) for all-cause mortality and 0.85 (0.78-0.92) for CVD mortality in women.

The potential mechanisms for the protective role of eCRF might be achieved through healthy lifestyle habits, which, in turn, reduce

| TABLE 4. Association Between eCRF and Mortality Due to All Causes and CVD in Relatively Healthy Men and Women Without a History of CVD, Cancer, or Diabetesa |
|---|---|---|---|---|---|
| | Sex and eCRF level | All-cause mortalityb | CVD mortalityb |
| | Deaths/patients (No.) | HR (95% CI) | Deaths/patients (No.) | HR (95% CI) |
| Men (n=3429) | Lower 239/1010 1.00 (Reference) 72/1010 1.00 (Reference) | 0.69 (0.48-1.00) 0.71 (0.36-1.43) | 0.52 (0.39-0.69) 0.29 (0.14-0.60) | <.001 | <.001 |
| | Middle 236/1146 0.69 (0.48-1.00) 0.71 (0.36-1.43) | 0.52 (0.39-0.69) 0.29 (0.14-0.60) | <.001 | <.001 |
| | Upper 233/1273 0.52 (0.39-0.69) 0.29 (0.14-0.60) | 0.80 (0.74-0.86) 0.75 (0.68-0.83) | 0.75 (0.68-0.83) 0.75 (0.68-0.83) |
| Women (n=3513) | Lower 131/1041 1.00 (Reference) 29/1041 1.00 (Reference) | 1.05 (0.70-1.57) 0.76 (0.36-1.59) | 0.66 (0.46-0.94) 0.67 (0.35-1.30) | .01 | .25 |
| | Middle 153/1175 1.05 (0.70-1.57) 0.76 (0.36-1.59) | 0.66 (0.46-0.94) 0.67 (0.35-1.30) | 0.75 (0.58-0.95) 0.75 (0.58-0.95) |
| | Upper 123/1297 0.66 (0.46-0.94) 0.67 (0.35-1.30) | 0.75 (0.58-0.95) 0.75 (0.58-0.95) |
| aCVD = cardiovascular disease; eCRF = estimated cardiorespiratory fitness; HR = hazard ratio; MET = metabolic equivalent. |
| The model was adjusted for race/ethnicity, education, age, hypertension, and hypercholesterolemia. |

MAYO CLINIC PROCEEDINGS: INNOVATIONS, QUALITY & OUTCOMES

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levels of BP and cholesterol, improve insulin sensitivity and control body weight, and enhance cardiopulmonary function and cognitive ability.\textsuperscript{23,39,40} Health benefits can be achieved by encouraging people to improve PA and CRF levels, which has been demonstrated by numerous reports.\textsuperscript{41-45} The American College of Sports Medicine has provided scientific evidence-based recommendations to improve CRF and health.\textsuperscript{46}

The present study examines the association between eCRF and mortality using a US representative sample of adult men and women. The sample size was relatively large, and an adequate number of deaths was observed during a long follow-up. The non-exercise algorithms we applied were derived from a longitudinal study, taking the nonlinear role of age into account, which can provide a more precise estimation of CRF. All questionnaires, physical examinations, and laboratory tests were conducted by trained examiners in the NHANES III. Limitations of this study, however, must also be acknowledged. First, PA was from self-report, which could introduce recall or social desirability bias into the estimation of CRF. Second, we included only non-Hispanic white, non-Hispanic black, and Mexican American adults. Therefore, the findings might not be generalized to other race/ethnicity populations. Last, eCRF was obtained at baseline only, so it is possible that eCRF might change during follow-up because components used to determine eCRF may
change, which primarily would lead to an underestimation of the study association.

In conclusion, by using nonexercise algorithms to determine eCRF based on the commonly collected health indicators in the NHANES III database, we found that a higher level of eCRF is associated with lower risk of all-cause and CVD mortality. The estimated method of CRF is feasible for clinicians and others to use to reflect CRF levels and predict risk of all-cause and CVD mortality.

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Abbreviations and Acronyms: ACLS = Aerobics Center Longitudinal Study; BMI = body mass index; BP = blood pressure; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; eCRF = estimated cardiorespiratory fitness; HR = hazard ratio; ICD = International Classification of Diseases; MET = metabolic equivalent; NHANES = National Health and Nutrition Examination Survey; NHANES III = Third National Health and Nutrition Examination Survey; PA = physical activity; PH = proportional hazards; RHR = resting heart rate; UCD = underlying cause of death; WC = waist circumference

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REFERENCES

1. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation. 2016;134(24):e653-e699.
2. Blair SN, Kampert JB, Kohl HW III, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA. 1996;276(3):205-210.
3. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024-2035.
4. Laukkanen JA, Lakka TA, Rauramaa R, et al. Cardiorespiratory fitness as a predictor of mortality in men. Arch Intern Med. 2001;161(6):825-831.
5. Ekelund UG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: the Lipid Research Clinics Mortality Follow-up Study. N Engl J Med. 1988;319(21):1379-1384.
6. Farrell SW, Finley CE, Radford NB, Haskell WL. Cardiorespiratory fitness, body mass index, and heart failure mortality in men: Cooper Center Longitudinal Study. Circ Heart Fail. 2013;6(5):898-905.
7. Kampert JB, Blair SN, Barlow CE, Kohl HW III. Physical activity, physical fitness, and all-cause and cancer mortality: a prospective study of men and women. Ann Epidemiol. 1996;6(5):452-457.
8. Laukkanen JA, Rauramaa R, Salonen JT, Kurl S. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. J Intern Med. 2007;262(2):263-272.
9. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. N Engl J Med. 1993;328(8):533-537.
10. Kokkinos PF, Faselis C, Myers J, et al. Cardiorespiratory fitness and incidence of major adverse cardiovascular events in US veterans: a cohort study. Mayo Clin Proc. 2017;92(1):39-48.
11. Balady GJ, Arena R, Setserna K, et al. Clinician’s Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225.
12. Bradshaw DL, George JD, Hyde A, et al. An accurate VO2max nonexercise regression model for 18-65-year-old adults. Res Q Exerc Sport. 2005;76(4):426-432.
13. Jackson AS, Sui X, O’Connor DP, et al. Longitudinal cardiorespiratory fitness algorithms for clinical settings. Am J Prev Med. 2012;43(5):S12-S19.
14. Matthews CE, Hei DP, Freedson PS, Paszko H. Classification of cardiorespiratory fitness without exercise testing. Med Sci Sports Exerc. 1999;31(3):486-493.
15. Nes BM, Januszy I, Vatten LJ, Nilsen TI, Aspnes ST, Waloff U. Estimating VO2peak from a nonexercise prediction model: the HUNT Study, Norway. Med Sci Sports Exerc. 2011;43(11):2024-2030.
16. O’Donovan G, Bakrana K, Ghouri N, et al. Nonexercise equations to estimate fitness in white European and South Asian men. Med Sci Sports Exerc. 2016;48(5):854-859.
17. Jurca R, Jackson AS, LaMonte MJ, et al. Assessing cardiorespiratory fitness without performing exercise testing. Am J Prev Med. 2005;29(3):185-193.
18. George JD, Stone WJ, Burkett LN. Non-exercise VO2max estimation for physically active college students. Med Sci Sports Exerc. 1997;29(3):415-423.
19. Maranhao Neto GA, Oliveira RB, Myers JN, Farinati PT. Prediction of peak oxygen pulse (O2Ppeak) without exercise testing in older adults. Arch Gerontol Geriatr. 2014;59(3):562-567.
20. Fleg JL, Morrell CH, Bos AG, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. Circulation. 2005;112(5):674-682.
21. Jackson AS, Sui X, Hebert JR, Church TS, Blair SN. Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. Arch Intern Med. 2009;169(19):1781-1787.
22. Addoh O, Edwards MK, Loprinzi PD. Predictive validity of a medical-related cardiorespiratory fitness algorithm in predicting cardiovascular disease and all-cause mortality: implications for integration into clinical practice. Mayo Clin Proc. 2016;91(9):1320-1321.
23. Artero EG, Jackson AS, Sui X, et al. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal
cardiovascular disease and disease-specific mortality. J Am Coll Cardiol. 2014;63(21):2289-2296.

24. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the Lipid research clinics preva-

cence study. JAMA. 2003;290(12):1600-1607.

25. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.

26. Martinez-Gomez D, Guallar-Castillon P, Hallal PC, Lopez-Garcia E, Rodriguez-Artalejo F. Nonexercise cardiorespiratory fitness and mortality in older adults. Med Sci Sports Exerc. 2015;47(3):568-574.

27. National Center for Health Statistics. NHANES III (1988-1994): survey methods and analytic guidelines. CDC website. https://www.cdc.gov/Nchs/Nhanes/Nhanes3/SurveyMethods.aspx. Accessed December 31, 2016.

28. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993;25(1):71-80.

29. National Center for Health Statistics. NHANES III (1988-1994): data files. CDC website. https://www.cdc.gov/Nchs/Nhanes/Nhanes3/DataFiles.aspx. Accessed December 31, 2016.

30. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical activity and mortality in chronic kidney disease (NHANES III). Clin J Am Soc Nephrol. 2009;4(12):1901-1906.

31. Diabetes: tests and diagnosis. Mayo Clinic website. http://www.mayoclinic.org/diseases-conditions/diabetes/basics/tests-diagnosis/con-20033091. Accessed December 31, 2016.

32. High cholesterol: diagnosis. Mayo Clinic website. http://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/diagnosis-treatment/diagnosisidoc/20181913. Accessed December 31, 2016.

33. National Center for Health Statistics. NHANES III (1988-1994) - Reference Manuals and Report. CDC website. https://www.cdc.gov/nchs/nhanes/nhanes3/manualsandreports.aspx. Accessed December 31, 2016.

34. National Center for Health Statistics. NCHS Data Linkage, 2011 Public-Use Linked Mortality Files. CDC website. https://www.cdc.gov/nchs/data-linkage/mortality-public.htm. Accessed December 31, 2016.

35. Anderson RN, Minina AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. Natl Vital Stat Rep. 2001; 49(2):1-32.

36. Stamatakis E, Hamer M, O’Donovan G, Batty GD, Kivimaki M. A non-exercise testing method for estimating cardiorespiratory fitness: associations with all-cause and cardiovascular mortality in a pooled analysis of eight population-based cohorts. Eur Heart J. 2013;34(10):750-758.

37. Nauman J, Nes BM, Lavie CJ, et al. Prediction of cardiovascular mortality by estimated cardiorespiratory fitness independent of traditional risk factors: the HUNT study. Mayo Clin Proc. 2017; 92(2):218-227.

38. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular mortality in men: the Aerobics Center Longitudinal Study. Circulation. 2011;124(23):2483-2490.

39. Physical activity guidelines for Americans. Health.gov website. https://health.gov/paguidelines/guidelines. Accessed December 31, 2016.

40. Lee DC, Artero EG, Sui X, Blair SN. Mortality trends in the general population: the importance of cardiorespiratory fitness. J Psychopharmacol. 2010;24(4 suppl):27-35.

41. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. JAMA. 1995;273(14):1093-1098.

42. Laukkanen JA, Zaccardi F, Khan H, Karl S, Jae SY, Rauramaa R. Long-term change in cardiorespiratory fitness and all-cause mortality: a population-based follow-up study. Mayo Clin Proc. 2016;91(9):1183-1188.

43. Kokkinos P, Myers J, Faselis C, et al. Exercise capacity and mortality in older men: a 20-year follow-up study. Circulation. 2010;122(8):790-797.

44. Lavie CJ, Arena R, Blair SN. A call to increase physical activity across the globe in the 21st century. Future Cardiol. 2016;12(6):605-607.

45. Lavie CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res. 2015;117(2):207-219.

46. Garber CE, Blissmer B, Deschenes MR, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-1359.