

5-7-2019

Cardiorespiratory Fitness and the Risk of First Acute Myocardial Infarction: The HUNT Study

Rajesh Shigdel

Håvard Dalen

Xuemei Sui

Carl J. Lavie

Ulrik Wisløff

See next page for additional authors

Follow this and additional works at: https://scholarcommons.sc.edu/sph_physical_activity_public_health_facpub



Part of the Exercise Science Commons

Author(s)

Rajesh Shigdel, Håvard Dalen, Xuemei Sui, Carl J. Lavie, Ulrik Wisløff, and Linda Ernsten

Cardiorespiratory Fitness and the Risk of First Acute Myocardial Infarction: The HUNT Study

Rajesh Shigdel, MPH, PhD; Håvard Dalen, MD, PhD; Xuemei Sui, MD, MPH, PhD; Carl J. Lavie, MD; Ulrik Wisløff, PhD; Linda Ernstsén, RN, PhD

Background—The majority of studies evaluating cardiorespiratory fitness (CRF) as a cardiovascular risk factor use cardiovascular mortality and not cardiovascular disease events as the primary end point, and generally do not include women. The aim of this study was to investigate the association of estimated CRF (eCRF) with the risk of first acute myocardial infarction (AMI).

Methods and Results—We included 26 163 participants (51.5% women) from the HUNT study (Nord-Trøndelag Health Study), with a mean age of 55.7 years, without cardiovascular disease at baseline. Baseline eCRF was grouped into tertiles. AMI was derived from hospital records and deaths from the Norwegian Cause of Death Registry. We used Fine and Gray regression modeling to estimate subdistribution hazards ratio (SHR) of AMI, accounting for competing risk of death. During a mean (range) follow-up of 13 (0.02–15.40) years (347 462 person-years), 1566 AMI events were recorded. In fully adjusted models men in the 2 highest eCRF had 4% (SHR: 0.96, 95% CI: 0.83–1.11) and 10% (SHR: 0.90, 95% CI: 0.77–1.05) lower SHR of AMI, respectively, when compared with men in the lowest tertile. The corresponding numbers in women were 12% (SHR: 0.88, 95% CI: 0.72–1.08) and 25% (SHR: 0.75, 95% CI: 0.60–0.95).

Conclusions—eCRF was inversely associated with risk of AMI event among women but not in men. Our data suggest that high eCRF may have substantial benefit in reducing the risk of AMI. Therefore, our data suggest that an increased focus on eCRF as a cardiovascular disease risk marker in middle-aged and older adults is warranted. (*J Am Heart Assoc.* 2019;8:e010293. DOI: 10.1161/JAHA.118.010293.)

Key Words: cardiovascular disease risk factors • epidemiology • myocardial infarction • physical exercise

Cardiovascular diseases (CVDs) are the number 1 cause of morbidity and mortality worldwide.^{1–3} Acute myocardial infarction (AMI) is among the most frequent underlying causes of hospital admissions among older adults,⁴ and the increasing number of older people is expected to result in a substantial increase in AMI incidence, healthcare demands, and premature mortality.^{1,5}

Cardiorespiratory fitness (CRF) refers to the ability of the circulatory and respiratory system to supply oxygen to skeletal muscles during sustained physical activity (PA) and it is considered as a key marker of cardiovascular health.^{6,7}

Several prospective cohort studies have reported a consistent, inverse association between CRF and CVD events,^{6,8–11} CVD mortality,¹² and all-cause mortality^{6,7,13–21} even after adjustment for potential risk factors. Furthermore, most of studies evaluating the association between CRF and fatal/non-fatal CVD events are limited to men.^{8,10,22–24} However, CVD is more common in women than in men, and more knowledge on CVD risk in women is needed.²⁵

A study on the association between CRF and risk of AMI (non-fatal and fatal) in healthy Finnish men (aged 42–60 years) observed a strong inverse association between CRF

From the Department of Public Health and Nursing (R.S., L.E.), and K.G. Jebsen Center for Exercise in Medicine, Department of Circulation and Medical Imaging (H.D., U.W.), Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; Clinic of Cardiology, St. Olav's University Hospital, Trondheim, Norway (H.D.); Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway (H.D.); Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC (X.S.); Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA (C.J.L.); School of Human Movement & Nutrition Sciences, University of Queensland, Australia (U.W.).

An accompanying Table S1 is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010293>

Correspondence to: Rajesh Shigdel, MPH, PhD, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU-Norwegian University of Science and Technology, Trondheim, Norway. E-mail: shigdelrajesh@gmail.com

Received July 17, 2018; accepted February 26, 2019.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Clinical Perspective

What Is New?

- Data from the Nord-Trøndelag Health Study showed that cardiorespiratory fitness is associated with decreased risk of first myocardial infarction.
- Higher level of cardiorespiratory fitness is even more protective against incident myocardial infarction in middle-aged and older women than in men.

What Are the Clinical Implications?

- Middle-aged and older adults, especially women, need to be informed about the cardioprotective effects from higher levels of cardiorespiratory fitness.
- Cardiorespiratory fitness is an important measurement that can be easily estimated in routine clinical practices with efforts to increase fitness in patients with low levels as a strategy to prevent a first heart attack.

and AMI.²⁶ Another study of 43 356 Americans aged 20 to 84 years (21% women) from the Aerobic Center Longitudinal Study also found an inverse association between CRF and non-fatal CVD events (defined as AMI, stroke, or coronary revascularization procedure, self-reported from 65% to 75% respondents).¹³ Unfortunately, previous studies did not report separate results for AMI for either women or men. Whether the protective effect from high CRF persists in relationship to risk for AMI (non-fatal and fatal) in women and men from the general population has not been previously evaluated. Thus, long-term follow-up studies are needed to evaluate the association between CRF and AMI that includes both sexes. We therefore aimed to investigate the prospective association between CRF and first AMI in middle-aged and older men and women from a large Norwegian population-based study.

Methods

Data from the HUNT study (Nord-Trøndelag Health study) used in research projects will, when reasonably requested by others, be made available upon request to the HUNT data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (available here <https://www.ntnu.edu/hunt/data>) describes in detail the policy on data availability.

The HUNT Study

The HUNT study is one of the largest health studies ever performed.²⁷ The surveys called HUNT1, HUNT2, and HUNT3 were conducted in 1984 to 1986, 1995 to 1997, and 2006 to 2008, respectively. In all the HUNT surveys, the data were collected in each of the 24 municipalities in the county

Nord-Trøndelag by using temporarily located health examination sites staffed by certified fieldwork teams. HUNT has largely been publicly funded.²⁸ For HUNT2 all residents of Nord-Trøndelag County, aged ≥ 20 years (reaching 20 years during the year of the screening in their municipality) were invited to the health survey.²⁷ Detailed information about the HUNT can be found elsewhere.^{27,28} HUNT data are linked to the unique personal identification number assigned to every Norwegian citizen at birth. This makes it possible to link data between the HUNT surveys and the Norwegian Cause of Death Registry. In Norway, all deaths are required to be reported by a physician to the National Cause of Death Registry with a cause of death diagnosis.²⁹ The official cause of death statistics are based on these death certificates and are prepared in accordance with the *International Classification of Diseases, Tenth Revision (ICD-10)*. The Norwegian Institute of Public Health has been responsible for processing data for the Causes of Death Registry since 2001.²⁹

The present study is a part of a project on middle-aged and older people, thus 42 313 middle-aged and older individuals who did not die until after they reached the age of 50 years in HUNT2 were selected. The exclusion criteria included the following: participants who reported ischemic heart disease or stroke ($n=4983$) at baseline, and those with missing values on ischemic heart disease or stroke ($n=648$); those who were underweight (body mass index <18.5 kg/m²) ($n=150$); those with missing data on the exposure variables for estimated CRF (eCRF) or those who had missing information on any of the potential confounders ($n=10287$). After this exclusion, 26 163 participants (51.5% women and 48.5% men) free from CVD and with complete data on physical activity (PA), waist circumference (WC), resting heart rate (rHR) and the confounders that were included in the final analyses (Figure 1).

Cardiorespiratory fitness

A non-exercise prediction model developed from HUNT2 was used to determine non-exercise estimated cardiorespiratory fitness (eCRF)¹⁸ in the current study. The sex-specific algorithms used in our cohort from HUNT2 were developed from data collected in the HUNT Fitness study (2006–2008). This sub-study was designed to obtain normal values from VO_{2peak} in a healthy population through a maximal treadmill test and 4631 participants in the age range 19 to 90 years participated. The participants also went through clinical examinations and provided self-reported information through several questionnaire as a part of the ordinary HUNT3 study. Because the difference in the questions on PA in HUNT1 (1984–1996) and HUNT2 (1995–1997) participants in HUNT3 were asked about their PA level by the use of the questions used in the 2 former HUNT surveys. And for the same reason it has been developed different prediction models for non-

exercise estimation of CRF from the HUNT population, where 1 includes the 3 PA questions on intensity, frequency, and duration used in HUNT1 and HUNT3. The other model includes the 2 PA question from HUNT2 on weekly duration of hard PA (being sweat and breathless) and light PA (not being sweat and breathless).¹⁸ According to the authors,¹⁸ the accuracy of the last model is comparable with the first model, and both non-exercise models have been validated against CVD mortality where the results have been published.^{18,19} As the cohort in the current study consists of middle-aged and older people who participated in HUNT2, we used the sex-specific non-exercise algorithms based on the PA questions from HUNT2. These algorithms predict CVD mortality beyond the inclusion of classical CVD risk factors.¹⁸

Several other studies using non-exercise prediction models also support the association between eCRF and cardiovascular health,^{13,20} and mortality.^{19,20}

The sex-specific model consists of age, WC, PA and rHR. The following algorithms were used to calculate each individual's eCRF:

Men:

$$105.91 - (0.334 \times \text{Age}) - (0.402 \times \text{WC}) - (0.144 \times \text{rHR}) + (3.102 \times \text{PA})$$

Women:

$$78.00 - (0.297 \times \text{Age}) - (0.270 \times \text{WC}) - (0.110 \times \text{rHR}) + (2.674 \times \text{PA})$$

WC were measured to the nearest cm, horizontally at the level of the umbilicus with the participants standing and arms hanging relaxed. The rHR was measured by palpating the radial pulse over a period of 15 seconds with a stopwatch, after at least 4 minutes of seated rest. PA was measured as the weekly average of hours of PA the past year and was measured through the question "How has your leisure-time physical activity been the last year?" with 1 answering category for light PA (not sweating/not being out of breath) and 1 for moderate/vigorous (sweating and being out of breath). The 4 response options were "none," "less than an hour," "1–2 hours" and "3 hours or more." The participants were classified as physically active if they met the recommended weekly level of 150 minutes of moderate PA, 75 minutes of vigorous PA, or a combination of both.³⁰ These PA question have been validated against directly measured cardiorespiratory fitness and accelerometer data.³⁰

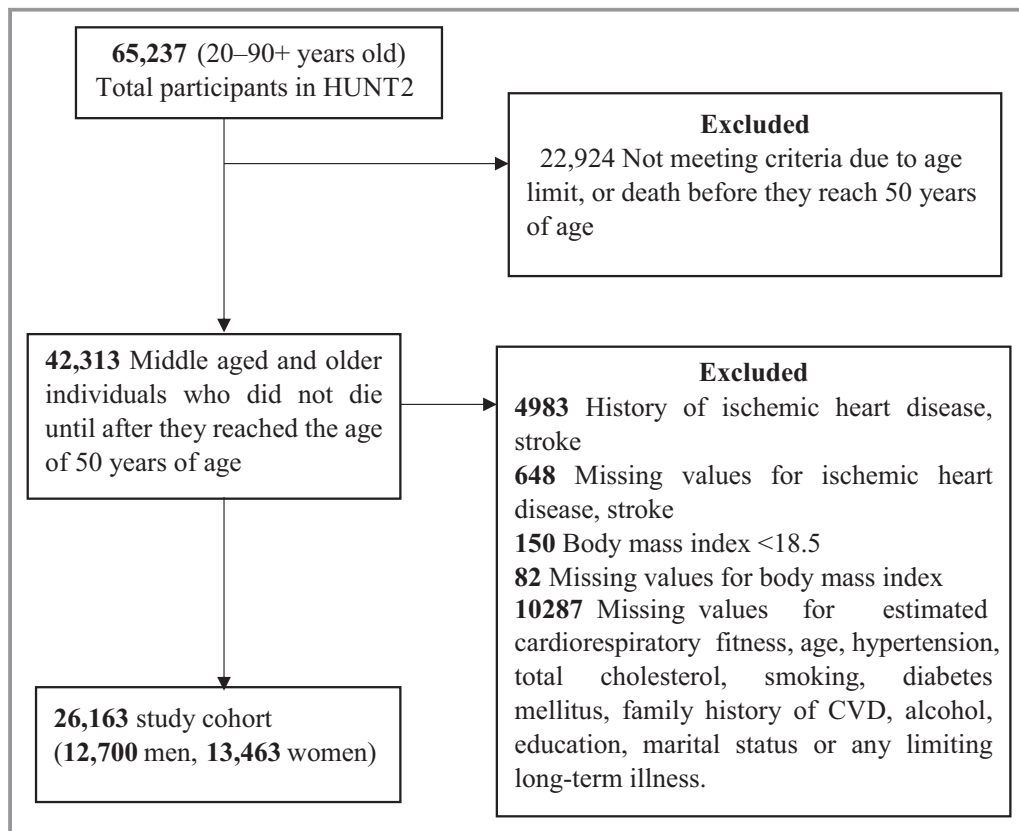


Figure 1. Participant flowchart. CVD indicates cardiovascular death. HUNT, The Nord-Trøndelag Health Study.

The participants were further classified into eCRF tertiles; low, medium, and high groups based on age (10-year categories) and sex.

Assessment of covariates

In HUNT2 information was collected through self-reported questionnaires and clinical measurements, and the objective and methods are previously described in detail by Holmen et al²⁷ Height and weight were measured with the participants wearing light clothes without shoes, height to the nearest 1.0 cm and weight to the nearest 0.5 kg. Resting systolic and diastolic blood pressure were measured by specially trained nurses or technicians using a Dinamap 845XT (Critikon) based on oscillometry. Blood pressure and heart rate were measured automatically 3 times at 1-minute intervals. Blood pressure reported is the mean of the second and third systolic and diastolic blood pressures. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or as self-report of current use of antihypertensive medication. According to European guidelines for CVD prevention,³¹ the concentration of total cholesterol was measured in accordance with the standards of the Centers for Disease Control and Prevention's Lipid Standardization Program.²⁷ Other covariates such as, smoking (current, former, non-smoker), diabetes mellitus (yes, no), family history of CVD (no, yes, I don't know), alcohol drinking past 14 days (abstainers, 0 times or not abstainers, 1–4 times, ≥ 5 times), marital status (unmarried, married, widow, divorced), limiting long-term illness (no, yes) were collected from questionnaires. Data on the highest achieved education level were based on the 1995 census and retrieved from the Norwegian Standard Classification of Education by Standard Classification of Education³² and categorized into 3 education levels: primary (primary and lower secondary school), secondary (upper secondary and post-secondary school) and tertiary (first and second stage of tertiary education).

First AMI

The Nord-Trøndelag county are served by 2 local hospitals only in addition to 1 invasive center at the regional Trondheim University Hospital, all patients admitted to the hospital in central Norway will be included in the regional (from 2012–2013 national) AMI registry. Thus, only patients not admitted to the regional hospitals because of death out of hospital or being admitted to hospitals in other health regions or countries may be missing. For patients admitted to other Norwegian hospitals the local hospitals will receive the reports, and if the event was an AMI the patient will be included in the registry. Even patients admitted to foreign hospitals with AMI would most often be followed by the local hospitals and included in the registry. AMI patients dying out of hospital do not have any data in the registry, but these patients will be registered with

AMI as the cause of death. Naturally, the diagnostic accuracy (AMI as the cause of death) may not be as valid as the in-hospital AMIs as the diagnostic workflow differ. As for other countries, the validity of the cause of death may be suboptimal.³³ The validation process was done in 2 steps. First, all AMIs are entered in to the registry by the caregiving cardiologist or physician. All AMI diagnoses from the hospitals are followed by an obligatory registration by the caregiving cardiologist or physician. If the diagnosis is judged not to be valid, the event is deleted from the registry. Secondly, we have validated $>50\%$ of all AMIs from 1995, and of these, 97% have been judged as valid AMIs by experienced cardiologists (according to the third universal definition of MI).

Incidence of AMI was identified through linkage with medical records from the 2 hospitals of Nord-Trøndelag county. AMI was defined and diagnosed by the caregiving cardiologist and physicians according to the European Society of Cardiology/American College of Cardiology consensus guidelines.³⁴ Criteria for AMI included: specific clinical symptoms according to case history information, changes in blood levels of cardiac enzymes, and ECG changes as defined in American and European consensus guidelines.^{34,35} Some of the AMI diagnosis from the medical records have been validated,³⁶ and an ongoing validation study (unpublished) found that 92% of the cases ($n=1194$) was type 1 AMI, implying that the underlying pathological process is plaque erosion, fissuring, or rupture with thrombus formation.³⁷ Using the unique 11-digit identification number of Norwegian citizens, individual information was linked to the Norwegian Cause of Death Registry. *International Classification of Diseases, Ninth Revision (ICD-9)*, code 410; (*ICD-10*) codes I21, I22, and I23. The date of the first non-fatal AMI events was defined as the date of admission to hospital. The date of a fatal AMI event was defined as the date of death on the death certificate. In participants with >1 non-fatal events, the earliest event was used for analysis. Each of the 26 163 participants was followed from the date of participation in HUNT2 (1995–1997) to the date of hospital admission, death, emigration, and/or until study end, 27th December 2010. In the current study, the number of deaths from AMI were 319 and 1175 were non-fatal AMI.

Ethical Considerations

Ethical approval for the HUNT study was provided by the Data Inspectorate of Norway and recommended by the Regional Committee for Medical Research Ethics. Participation in the HUNT study was voluntary, and each participant signed a written consent about the use of data for research purpose. The study was conducted in conformity with the Declaration of Helsinki, 1964.

Statistical Analysis

Participant's baseline characteristics are summarized as mean, standard deviation, numbers, and percentages by eCRF categories. We used 2 approaches to evaluate the hazards of AMI attributable to each level of eCRF, we used 2 approach : 1) Cox proportional hazards regression model that treat mortality as censored observation; and 2) We also performed a competing risk analysis using Fine and Gray survival modeling^{38,39} to estimate unadjusted and multivariable adjusted subdistribution hazard ratio (SHR) and 95% CIs for first AMI accounting for non-CVD death as a competing risk. Due to the high competing risk of non-CVD death among elderly people we presented main results are based on the competing risk analysis. We presented both univariate and multivariable adjusted models, and in the multivariable model, we adjusted for age (in years), education (low, medium, high) marital status (unmarried/married/widow/divorce), diabetes mellitus (yes/no), any limiting-long standing illness (yes/no), smoking (current smoker/former smoker/non-smoker), alcohol drinking past 14 days (abstainers, 0 times or not abstainers, 1–4 times, ≥ 5 times), hypertension (yes/no), hypercholesterolemia (yes/no), and family history of CVD (yes/no). Confounders were adjusted based on previous studies,^{10,13,24} and available data.

We also examined eCRF as a continuous variable so that each SHR represents the risk associated with a 1-metabolic equivalent (MET 3.5 mL/kg per min) increase in the exposure variable. Person-time for each participant was computed from the date of the baseline examination to the date of report of first AMI, death, emigration or to December 27, 2010. Incidence rates were calculated as the number of cases divided by person-time follow-up separately in men and women. There was significant statistical interaction between the sex and eCRF in relation to AMI ($P < 0.05$), we therefore, stratified the analyses according to sex. The assumption of proportionality was based on Schoenfeld residuals. The proportionality of the model as a whole, and for each variable, was checked. One of the confounders (family history of CVD) was not proportional, so we stratified on the non-proportional confounder. Data analyses were performed using STATA statistical analyses software package (version 14; Stata Corp.) A 2-sided $P \leq 0.05$ was accepted to indicate statistical significance.

Multiple imputations

The primary analyses were repeated using multiple imputations for the variables with missing information at baseline using chained equation (MICE) under the assumption that data were missing at random.⁴⁰ We introduced a wide range of variables into the imputation modes, which we thought could predict incomplete variables. Fifteen duplicate

completed data sets were created in order to reduce sampling variability from the imputation simulation. Parameter estimates from analyzing the imputed data sets were pooled according to Rubin's rules.⁴¹ However, the result based on multiple imputation data (n=31 155) did not differ as compared with complete case analyses. Our main results are based on complete case analyses whereas multiple imputation-based analyses are displayed in Table S1.

Results

Baseline Characteristics

The mean age (SD) of participants was 55.7 (11.4) years and 51.5% were women. Mean age (SD) of men and women were 55.8 (11.2) and 55.6 (11.6) years, respectively. During a mean (range) of 13 (0.02–15.40) years (347 462 person-years) of follow up of exposure, there were 1566 incident AMI events. The death rate from AMI in our sample was 1.67 per 1000 for men and 0.96 per 1000 for women. Table 1 presents baseline characteristic of study participants by eCRF categories stratified by sex. Mean low eCRF for men was 36.6 mL/kg per min range (13.6–46.8) and 28.1 mL/kg per min range (10.1–38.0) for women. As expected, men and women with low eCRF had higher body mass index, WC, systolic and diastolic blood pressure than those with medium and high eCRF levels. During the follow-up 3226 non-CVD related deaths were recorded (1446 women and 1780 men).

Incident AMI

The incidence rate of AMI was 506 per 18, 2366 person-years for women and 1060 per 16, 5096 person-years for men. There was an inverse association between eCRF and incident AMI rates (Figure 2).

Association Between CRF and AMI with Competing Mortality

eCRF and AMI in total cohort

Table 2 presents the association between eCRF and AMI in total cohort. In unadjusted analysis, (model 1), those with medium and high eCRF had 16% (SHR; 0.84; 95% CI, 0.75–0.95) and 31% (SHR; 0.69; 95% CI, 0.61–0.78) lower rates of AMI, than those who had low eCRF, respectively. This inverse association remains statistically significant for those with high eCRF in the fully adjusted model. In the multivariable analysis, those with medium and higher eCRF had 7% (SHR; 0.93; 95% CI, 0.82–1.05) and 15% (SHR; 0.85; 95% CI, 0.75–0.97) lower rates of AMI, than those who had low eCRF, respectively.

Table 1. Baseline Characteristics of Middle-Aged and Older Participants in the Nord-Trøndelag Health Study 2 (1995–1997) by Sex and eCRF Group in Tertiles

Variables	Men (n=12 700)			Women (n=13 463)		
	Low eCRF Level, (n=4150)	Medium eCRF Level, (n=4259)	High eCRF Level, (n=4291)	Low eCRF Level, (n=4391)	Medium eCRF Level, (n=4485)	High eCRF Level, (n=4587)
Age, y	56.4 (11.1)	56 (11.3)	55.1 (11.3)	56.5 (11.6)	55.8 (11.6)	54.8 (11.6)
Height, cm	177.8 (6.6)	177 (6.5)	176 (6.4)	163.7 (6.2)	163.7 (6)	163.3 (6)
Weight, kg	88.3 (13.5)	83.9 (10.8)	79.1 (8.6)	80.7 (12.8)	69.7 (8.7)	63.5 (7.5)
BMI, kg/m ²	29.2 (3.4)	26.4 (2.4)	24.7 (3.3)	30.1 (4.6)	26 (3)	23 (2.6)
WC, cm	100.8 (7.8)	92.3 (5.1)	85.7 (5.4)	92.8 (10.3)	81.1 (6.8)	73.9 (5.9)
Resting heart rate, bpm	75.9 (12.9)	67.9 (10.3)	61.3 (9.5)	78.7 (13.2)	72.0 (10.7)	66.7 (9.5)
eCRF (peak oxygen consumption mL/kg per min)	36.6 (5.56)	42.0 (4.5)	46.8 (4.7)	28.1 (5.1)	32.7 (4.5)	36.5 (4.4)
eCRF (MET)	10.4 (1.6)	12.0 (1.3)	13.4 (1.3)	8.0 (1.5)	9.3 (1.3)	10.4 (1.3)
Weekly recommended PA, n (%)						
No	2889 (69.6)	1914 (45)	765 (18)	3448 (78.5)	2575 (57.4)	1092 (23.8)
Yes	1261 (30.4)	2345 (55)	3526 (82.2)	943 (21.5)	1910 (42.6)	3495 (76.2)
Smoker, n (%)						
Current	1210 (29.1)	1241 (29.1)	1181 (27.5)	1294 (29.5)	1315 (29.3)	1290 (28.1)
Former	1800 (43.4)	1691 (39.7)	1427 (33.3)	1021 (23.2)	1098 (24.5)	1070 (23.3)
Non smoker	1140 (27.5)	1327 (31.2)	1683 (39.2)	2076 (47.3)	2072 (46.2)	2227 (48.6)
Alcohol consumption, n (%)						
Abstainers	354 (8.5)	353 (8.3)	350 (8.2)	911 (20.7)	710 (15.8)	651 (14.2)
0 times, not abstainers	1018 (24.5)	921 (21.6)	891 (20.8)	1708 (38.9)	1529 (34.1)	1428 (31.1)
1 to 4 times	2246 (54.1)	2329 (54.7)	2385 (55.6)	1576 (35.9)	1945 (43.4)	2062 (44.9)
5 times	532 (12.8)	656 (15.4)	665 (15.5)	196 (4.5)	301 (6.7)	446 (9.7)
Diabetes mellitus, n (%)						
No	3978 (95.9)	4147 (97.4)	4211 (98.1)	4209 (95.9)	4391 (97.9)	4537 (98.9)
Yes	172 (4.1)	112 (2.6)	80 (1.9)	182 (4.1)	94 (2.1)	50 (1.1)
Limiting long-term illness, n (%)						
No	2837 (68.4)	3135 (73.6)	3298 (76.9)	2918 (66.4)	3266 (72.8)	3591 (78.3)
Yes	1313 (31.6)	1124 (26.4)	993 (23.1)	1473 (33.6)	1219 (27.2)	996 (21.7)
Hypertension, n (%)						
No	1374 (33.1)	1889 (44.4)	2428 (56.6)	1698 (38.7)	2451 (54.7)	2963 (64.6)
Yes	2776 (66.9)	2370 (55.6)	1863 (43.4)	2693 (61.3)	2034 (45.3)	1624 (35.4)
Total cholesterol (mmol/L), n (%)						
Low	460 (11.1)	586 (13.8)	761 (17.7)	459 (10.5)	608 (13.6)	887 (19.34)
High	3690 (88.9)	3673 (86.2)	3530 (82.3)	3932 (89.5)	3877 (86.4)	3700 (80.6)
Blood pressure, mm Hg						
Systolic	145.8 (20.1)	141.7 (19)	137.8 (18.5)	145.5 (23.3)	138.3 (22.8)	133.2 (21.5)
Diastolic	88.2 (11.3)	84.8 (10.6)	81.5 (10.2)	84.8 (12.2)	80.6 (11.1)	77.3 (10.8)
Family history of CVD, n (%)						
No	2235 (53.9)	2340 (54.9)	2333 (54.4)	2118 (48.2)	2248 (50.1)	2316 (50.5)
Yes	1648 (39.7)	1675 (39.3)	1719 (40.1)	2028 (46.2)	2028 (45.2)	2084 (45.4)

Continued

Table 1. Continued

Variables	Men (n=12 700)			Women (n=13 463)		
	Low eCRF Level, (n=4150)	Medium eCRF Level, (n=4259)	High eCRF Level, (n=4291)	Low eCRF Level, (n=4391)	Medium eCRF Level, (n=4485)	High eCRF Level, (n=4587)
I don't know	267 (6.4)	244 (5.7)	239 (5.57)	245 (5.6)	209 (4.7)	187 (4.1)
Education, n (%)						
Primary	1325 (31.9)	1137 (26.7)	968 (28.2)	1754 (40)	1479 (33)	1277 (27.8)
Secondary	2275 (54.8)	2374 (55.7)	2323 (33.3)	2168 (49.4)	2268 (50.6)	2206 (48.1)
Tertiary	550 (13.3)	748 (17.6)	1000 (43.5)	469 (10.7)	738 (16.5)	1104 (24.1)
Marital status, n (%)						
Unmarried	503 (12.1)	392 (9.2)	414 (9.6)	231 (5.3)	192 (4.3)	229 (5.0)
Married	3121 (75.2)	3384 (79.5)	3442 (80.2)	3161 (72.0)	3313 (73.9)	3381 (73.7)
Widow	188 (4.5)	127 (3.0)	121 (2.8)	638 (14.5)	594 (13.2)	560 (12.2)
Divorced	338 (8.1)	356 (8.4)	314 (7.3)	361 (8.2)	386 (8.6)	417 (9.1)

Values are presented as mean (SD), number (n), percentage (%) of participants. BMI indicates body mass index; bpm, beats per minute; CVD, cardiovascular disease; eCRF, estimated cardiorespiratory fitness; MET, metabolic equivalent; WC, waist circumference.

eCRF and AMI in men

In unadjusted analysis, (model 1), men with medium and high eCRF had 11% (SHR; 0.89; 95% CI, 0.77–1.02) and 25% (SHR; 0.75; 95% CI, 0.65–0.88) lower rates of AMI, than men who had low eCRF, respectively. This inverse association did not remain statistically significant in the fully adjusted model. In the multivariable analysis, men with medium and higher eCRF had 4% (SHR; 0.96; 95% CI, 0.83–1.11) and 10% (SHR; 0.90; 95% CI, 0.77–1.05) lower rate of first AMI, than men who had low eCRF, respectively.

Unadjusted analysis exhibited a 23% lower risk of first AMI for each 1-unit higher MET (SHR; 0.77; 95% CI, 0.75–0.79). After adjustment of all confounders, each 1-unit MET increase was associated with 3% lower rate of first AMI (SHR; 0.97; 95% CI, 0.92–1.01).

eCRF and AMI in women

In unadjusted analyses (Table 2), women with medium and high eCRF had 25% (SHR; 0.75; 95% CI, 0.62–0.93) and 44% (SHR; 0.56; 95% CI, 0.45–0.70) lower risk of first AMI than women with low eCRF, respectively. In multivariable analysis, women with medium and high level of eCRF had 22% (SHR; 0.88; 95% CI, 0.72–1.08) and 25% (SHR; 0.75; 95% CI, 0.60–0.95) lower risk of first AMI than women who had low eCRF, respectively.

Unadjusted analysis exhibited a 41% lower risk of first AMI for each 1-unit higher MET (SHR; 0.59; 95% CI, 0.56–0.61). In multivariable analysis, each 1-unit MET increase was associated with 11% lower risk of first AMI (SHR; 0.89; 95% CI, 0.82–0.96).

There was a similar substantial increase in the estimated hazard ratio (HR) of AMI when using traditional Cox regression

versus competing risk model. (Table 2) Using the competing risk approach (Figure 1), the absolute probability of AMI was higher among those with low eCRF and medium eCRF as compared with those with high eCRF in both men and women.

Discussion

In this prospective study of a general population, we observed that women with high CRF had a protective effect against AMI as compared with those with low eCRF level, even after adjustment for well-known CVD risk factors and other potential confounders.

The findings of the present study are in agreement with previous research in the general population, which demonstrates that higher level of measured CRF is associated with a lower risk of CVD outcomes,^{8,15} including AMI.^{11,13,26,42} Our findings based on traditional analytical approach (Cox proportional hazard regression) are also in line with previous findings from the HUNT cohort¹⁸ and the National Health and Nutrition Examination Survey,²¹ which reports a statistical significant inverse association between estimated CRF from non-exercise algorithms and CVD mortality in men and women. However, CVD mortality is not quite comparable with first AMI, where also first non-fatal CVD events are included, meaning that our results are better suited for assessing disease risk. To our knowledge, this is the first study to show the association between eCRF and risk of first AMI making use of information of both non-fatal and fatal events in men and women.

Artero et al¹³ found that both medium and high eCRF was associated with lower CVD related mortality and non-fatal CVD in men. In women, only high eCRF was significantly

Table 2. Subdistribution Models and Tradition Cox Proportional Hazards Models for Association of Different Categories of eCRF With Risk of AMI in Middle-Aged and Older Men and Women Participating in HUNT2 (1995–1997), 15.4 Years' Follow-Up

Total		Cox Proportional Hazards Models		Fine and Gray, Sub Distribution Models	
		HR (95% CI)		SHR (95% CI)	
eCRF	Non-fatal/fatal AMI	Model 1	Model 2	Model 1	Model 2
Low	434/169	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium	401/125	0.83 (0.74–0.93)	0.90 (0.80–1.01)	0.84 (0.75–0.95)	0.93 (0.82–1.05)
High	340/97	0.66 (0.59–0.75)	0.81 (0.71–0.92)	0.69 (0.61–0.78)	0.85 (0.75–0.97)
<i>P</i> linear trend		<0.001	<0.05	<0.001	<0.05
Maximal oxygen uptake, mL/kg per min		0.95 (0.95–0.96)	0.98 (0.97–0.99)	0.96 (0.95–0.97)	0.99 (0.97–0.99)
Per 1 MET		0.85 (0.83–0.87)	0.93 (0.90–0.97)	0.87 (0.85–0.89)	0.95 (0.92–0.99)
Men (n=12 700)					
Low	288/102	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium	282/78	0.87 (0.76–1.01)	0.93 (0.80–1.07)	0.89 (0.77–1.02)	0.96 (0.83–1.11)
High	247/63	0.73 (0.63–0.85)	0.87 (0.74–1.01)	0.75 (0.65–0.88)	0.90 (0.77–1.05)
<i>P</i> linear trend		<0.001	0.067	<0.001	0.195
Maximal oxygen uptake, mL/kg per min		0.91 (0.90–0.92)	0.98 (0.97–0.99)	0.93 (0.92–0.93)	0.99 (0.98–1.00)
Per 1 MET		0.72 (0.70–0.74)	0.95 (0.91–0.99)	0.77 (0.75–0.79)	0.97 (0.92–1.01)
Women (n=13 463)					
Low	146/67	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium	119/47	0.74 (0.60–0.91)	0.85 (0.69–1.04)	0.75 (0.62–0.93)	0.88 (0.72–1.08)
High	93/34	0.55 (0.44–0.68)	0.71 (0.56–0.88)	0.56 (0.45–0.70)	0.75 (0.60–0.95)
<i>P</i> linear trend		<0.001	<0.05	<0.001	<0.05
Maximal oxygen uptake, mL/kg per min		0.84 (0.83–0.85)	0.96 (0.94–0.98)	0.86 (0.85–0.87)	0.97 (0.94–0.99)
Per 1 MET		0.54 (0.52–0.57)	0.87 (0.80–0.94)	0.59 (0.56–0.61)	0.89 (0.82–0.96)

Model 1: Unadjusted. Model 2: Adjusted for age, education, marital status, diabetes mellitus, any limiting-long standing illness, smoking, alcohol intake, hypertension, hypercholesterolemia, family history of CVD. eCRF indicates estimated cardiorespiratory fitness; HUNT, The Nord-Trøndelag Health Study; MET, metabolic equivalent; Ref, Reference group; SHR, subdistribution hazard ratio.

associated with non-fatal CVD risk (HR; 0.38; 95% CI, 0.22–0.70). However, in their study, neither medium (HR; 0.70; 95% CI, 0.35–1.37) or high (HR; 0.65; 95% CI, 0.32–1.31) eCRF were statistically significantly associated with CVD-related mortality in women. The reasons for this dissimilarity to our finding might be because of differences in the population characteristics, and relatively low statistical power in their study, as there was a smaller number of CVD-related mortality (50/9145) and non-fatal CVD cases (72/3635) among women. Moreover, in the former study, the assessment of incidence of non-fatal CVD was based on self-report while non-fatal AMI events in our study were identified through medical diagnoses from hospital records. In the current study, we observed that the risk for first AMI decreased more with higher levels of CRF among women than for men. It appears that women gain more benefit than men in the reduction of AMI when increasing CRF from low to medium levels. In support of our findings previous literature reports that differences between men and women emerge when PA

increase beyond low intensity.⁴³ Similarly, a meta-analysis shows that the relative risk for coronary disease reduce more rapidly with a lower level of PA for women than for men.⁴⁴ A recent prospective study of 29, 854 male participants from the Aerobics Center Longitudinal Study found that those with high eCRF had a 28% (HR=0.72; 95% CI 0.57, 0.91) lower CHD-mortality risk compared with those with low eCRF. However, no association was found among men with moderate eCRF.⁴⁵

Our data underscore that substantive protective effect against incident AMI can be achieved among women even by maintaining high eCRF (5–12 MET). However, in our study high levels of eCRF were not statistically significant associated with protection against incident AMI among men. In addition, when eCRF, was defined as a continuous variable, we observed 3% and 5% lower risk of AMI for each 1-unit increase in MET in men and women, respectively. These associations were in agreement with previous findings showing^{13,18,21} that for each MET of higher eCRF there was

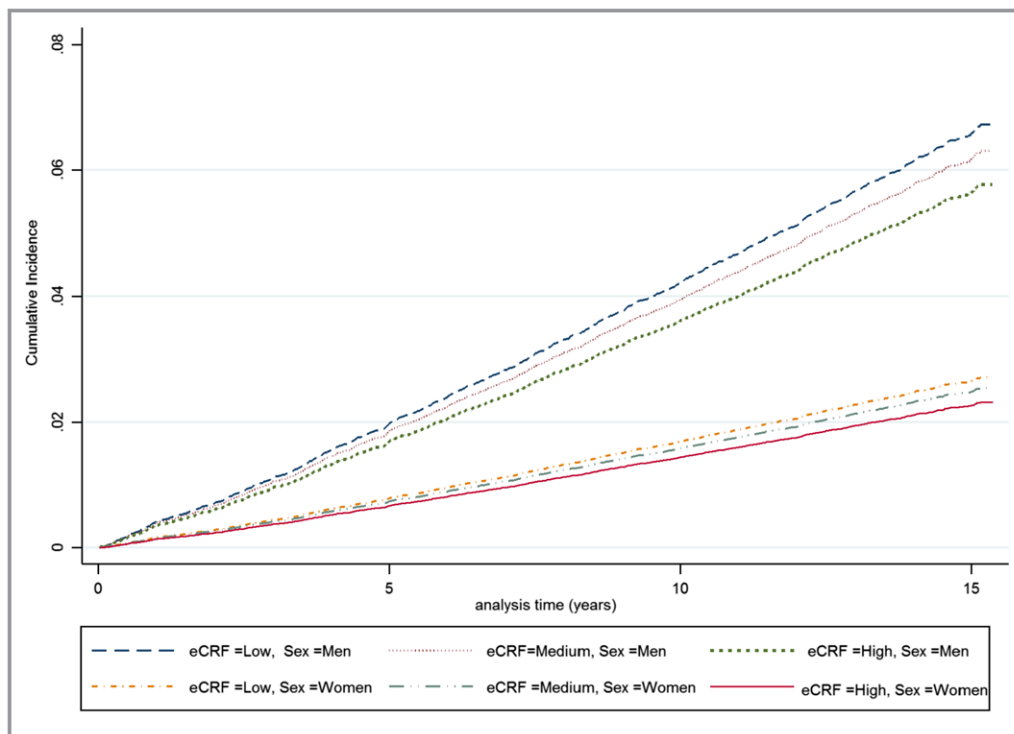


Figure 2. Cumulative absolute probability of AMI by eCRF categories using cumulative incidence function (competing risk approach). AMI indicates acute myocardial infarction; eCRF, estimated cardiorespiratory fitness.

an 18% to 25% lower risk for CVD mortality in men and 15% to 25% lower risk in women even after adjusting for age, clinical risk factors, lifestyle factors, and disease status. A meta-analysis showed that the risk reduction associated with 1-MET higher non-exercise eCRF was 13% and 15% for all-cause and CVD mortality, respectively.¹⁷ However, this meta-analysis did not report sex-specific results. Data from the National Health and Nutrition Examination Survey III showed that each 1-MET higher eCRF was associated with a 19% and 24% lower CVD mortality hazard risk in men and women, respectively, suggesting that the protective effect was slightly larger among women as observed in our study. The higher risk reduction in the National Health and Nutrition Examination Survey III study compared with the present study could be explained by their inclusion of individuals with existing heart disease and cancer.

The specific casual mechanism of lower risk for first AMI among those with high eCRF remains to be investigated. However, it is known that both genetic and behavioral factors influence levels of CRF.⁴⁶ The contribution of genetic factors on CRF is estimated to vary from 20% to 40%^{47,48} thus, modifiable factors such as PA, body composition, and lifestyle factors play potentially important roles to maintain CRF.⁴⁹ Several physiological and metabolic mechanisms favorable to cardiovascular health have been explained in previous reports.^{12,21,24} Biological plausibility for the presented

association may be through PA with high eCRF leads to lower blood pressure, lower level of serum lipids, cholesterol, and inflammation markers like interleukin, C-reactive protein and several other factors,⁵⁰ which predispose to development of AMI.

The main strength of the present study lies in the prospective design and large representative sample size of middle-aged and older individuals. To our knowledge, this is the first and largest study to relate the association of eCRF with first AMI accounting for the competing risk in asymptomatic middle-aged and older men and women. We believe that previous studies failing to account for competing risk may have overestimated CVD risk among the older population, as there is evidence that Cox regression models may overestimate the risk if incorrectly used in the presence of competitive risk.³⁹

Additionally, the HUNT cohort is recognized for having valid data and a high participation rate.²⁸ The eCRF was calculated by using non-exercise algorithms developed from the same cohort, which can provide a better estimation of CRF. We have reliable data on AMI as the major outcome, which were prospectively ascertained by medical records from the 2 hospitals of the Nord-Trøndelag County and cause-specific deaths from the Norwegian Cause of Death Registry. We excluded those with CVD at baseline and broad ranges of potential confounders were taken into account in the

analyses. However, there are some limitations in our study. PA, the main variable in the algorithm, was self-reported, and people could tend to overestimate PA. Furthermore, we calculated the eCRF at baseline but the variation in PA and other components that are used to determine eCRF might have occurred over this follow-up period thus, potentially leading to an underestimation of the study association. There may be some residual confounding, such as, information about diet and medications were not available. Non-response bias is a concern in epidemiologic surveillance, and participation in HUNT2 was strongly age-dependent, with the highest participation in the age group, 60 to 69 years, for both sexes (84.3% in men and 87.0% in women), and gradually lower participation rate in younger and older age groups.²⁷ Heavy alcohol drinker and people with mental distress were also less likely to participate in HUNT2.⁵¹ As the population of the HUNT study is homogeneous with respect to ethnicity and genetics, the findings of this study have high internal validity, but this may limit generalization to other populations with different ethnicity. Clearly, further studies are needed to investigate the association of eCRF with AMI in other cohorts.

Although CRF is an important risk marker for AMI, it is not routinely measured in the clinical practice because of the high associated costs, time and requirement of trained personnel and specialized equipment. Therefore, eCRF obtained from non-exercise algorithms can be a more cost-effective way of assessing CRF for the wide use in the routine clinical practice.^{18,52} Moreover, eCRF can be calculated by using easily available health indicator variables, many of which are potentially available in electronic health records. Therefore, eCRF could potentially add clinical value in routine clinical practice as a simple tool to identify individuals who are at high risk of first AMI. In fact, last year a scientific statement from the American Heart Association underscores the importance of assessing CRF in clinical practice as a clinical vital sign.

Conclusions

eCRF, estimated by using easily available health indicators was strongly associated with lower risk of first AMI in women when accounting for competing risk of mortality. The eCRF could be useful in the routine clinical practice as a feasible means to estimate CRF and to predict the AMI risk in the general population. Population-based interventions designed to reduce CVD risk should promote smoking cessation and PA, to maintain ideal weight and to increase or maintain high eCRF levels.

Acknowledgments

The Nord-Trøndelag Health Study (the HUNT study) is a collaboration between HUNT Research Center Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology,

Nord-Trøndelag County Council, Central Regional Health Authority, and the Norwegian Institute of Public Health.

Author Contributions

Ernstsen and Shigdel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ernstsen and Shigdel; Drafting of the manuscript: Shigdel; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: Shigdel; Obtained funding: Ernstsen.

Sources of Funding

Dr. Ernstsen was funded by grant 2011–2–0161 by the Norwegian Extra Foundation for Health and Rehabilitation and by the Liaison Committee between the Central Norway Regional Health Authority. Prof. Wisløff has received research grants from the K.G Jebsen Foundation in Norway. The funders had no role in the design and conduct of the study nor the collection, management, analysis, and interpretation of the data preparation, review, or approval of the manuscript, or decision to submit the manuscript for publication.

Disclosures

None.

References

- Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, Murray CJ, Naghavi M. The global burden of ischemic heart disease in 1990 and 2010: the global burden of disease 2010 study. *Circulation*. 2014;129:1493–1501.
- O'Flaherty M, Bandosz P, Critchley J, Capewell S, Guzman-Castillo M, Aspelund T, Bennett K, Kabir K, Bjorck L, Bruthans J, Hotchkiss JW, Hughes J, Laatikainen T, Palmieri L, Zdrojewski T. Exploring potential mortality reductions in 9 European countries by improving diet and lifestyle: a modelling approach. *Int J Cardiol*. 2016;207:286–291.
- Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Arnlov J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Barnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castaneda-Orjuela CA, Castillo-Rivas J, Catala-Lopez F, Choi JY, Christensen H, Cirillo MJ, Cooper L Jr, Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C, Kasaeian A, Khader Y, Khan A, Khang YH, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin MJ, Shishehbor M, Shore H, Silva DAS, Sobngwi E, Stranges S, Swaminathan S, Tabares-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T,

- Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70:1–25.
4. Braunwald E. The war against heart failure: the lancet lecture. *The Lancet*. 2015;385:812–824.
5. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, Naghavi M, Mensah GA, Murray CJL. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med*. 2015;372:1333–1341.
6. Blair SN, Kampert JB, Kohl HW III, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276:205–210.
7. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U. 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:e653–e699.
8. Gander JC, Sui X, Hébert JR, Hazlett LJ, Cai B, Lavie CJ, Blair SN. Association of cardiorespiratory fitness with coronary heart disease in asymptomatic men. *Mayo Clin Proc*. 2015;90:1372–1379.
9. Khan H, Kella D, Rauramaa R, Savonen K, Lloyd MS, Laukkanen JA. Cardiorespiratory fitness and atrial fibrillation: a population-based follow-up study. *Heart Rhythm*. 2015;12:1424–1430.
10. Kokkinos PF, Faselis C, Myers J, Narayan P, Sui X, Zhang J, Lavie CJ, Moore H, Karasik P, Fletcher R. Cardiorespiratory fitness and incidence of major adverse cardiovascular events in us veterans: a cohort study. *Mayo Clin Proc*. 2017;92:39–48.
11. Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness as a predictor of nonfatal cardiovascular events in asymptomatic women and men. *Am J Epidemiol*. 2007;165:1413–1423.
12. 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;262:263–272.
13. Artero EG, Jackson AS, Sui X, Lee DC, O'Connor DP, Lavie CJ, Church TS, Blair SN. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality. *J Am Coll Cardiol*. 2014;63:2289–2296.
14. Fishman EI, Steeves JA, Zippunnikov V, Koster A, Berrigan D, Harris TA, Murphy R. Association between objectively measured physical activity and mortality in nhanes. *Med Sci Sports Exerc*. 2016;48:1303–1311.
15. Harber MP, Kaminsky LA, Arena R, Blair SN, Franklin BA, Myers J, Ross R. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. *Prog Cardiovasc Dis*. 2017;60:11–20.
16. Jackson AS, Sui X, O'Connor DP, Church TS, Lee DC, Artero EG, Blair SN. Longitudinal cardiorespiratory fitness algorithms for clinical settings. *Am J Prev Med*. 2012;43:512–519.
17. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301:2024–2035.
18. Nauman J, Nes BM, Lavie CJ, Jackson AS, Sui X, Coombes JS, Blair SN, Wisloff U. Prediction of cardiovascular mortality by estimated cardiorespiratory fitness independent of traditional risk factors: the hunt study. *Mayo Clin Proc*. 2017;92:218–227.
19. Nes BM, Vatten LJ, Nauman J, Janszky I, Wisloff U. A simple nonexercise model of cardiorespiratory fitness predicts long-term mortality. *Med Sci Sports Exerc*. 2014;46:1159–1165.
20. 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;34:750–758.
21. Zhang Y, Zhang J, Zhou J, Ernsten L, Lavie CJ, Hooker SP, Sui X. Nonexercise estimated cardiorespiratory fitness and mortality due to all causes and cardiovascular disease: the NHANES III study. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*. 2017;1:16–25.
22. Laukkanen JA, Makikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study. *J Am Coll Cardiol*. 2010;56:1476–1483.
23. Farrell SW, Kampert JB, Kohl HW III, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW, Blair SN. Influences of cardiorespiratory fitness levels and other predictors on cardiovascular disease mortality in men. *Med Sci Sports Exerc*. 1998;30:899–905.
24. Khan H, Jaffar N, Rauramaa R, Kurl S, Savonen K, Laukkanen JA. Cardiorespiratory fitness and nonfatalcardiovascular events: a population-based follow-up study. *Am Heart J*. 2017;184:55–61.
25. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis*. 2015;241:211–218.
26. Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *The New England journal of medicine*. 1994;330:1549–1554.
27. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg G, Vatten LJ, Larsen PG. The Nord-Trøndelag Health Study 1995–97 (HUNT2). Objectives, contents, methods and participation. *Nor Epidemiol*. 2003;13:19–32.
28. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort profile: the hunt study, norway. *Int J Epidemiol*. 2013;42:968–977.
29. Pedersen AG, Ellingsen CL. Data quality in the causes of death registry. *Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny række*. 2015;135:768–770.
30. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the nord-trondelag health study (hunt 2). *Eur J Epidemiol*. 2007;22:379–387.
31. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knappton M, Perk J, Priori SG, Pyörälä K, Reiner Z, Ruijlo L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellems I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Altnier A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen ML, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil*. 2007;14(Suppl 2):S1–S113.
32. OECD. *OECD Handbook for Internationally Comparative Education Statistics: Concepts, Standards, Definitions and Classifications*, OECD Publishing: Paris 2017. <https://doi.org/10.1787/9789264279889-en>.
33. Gulsvik AK, Gulsvik A, Svendsen E, Mæhle BO, Thelle DS, Wyller TB. Diagnostic validity of fatal cerebral strokes and coronary deaths in mortality statistics: an autopsy study. *Eur J Epidemiol*. 2011;26:221–228.
34. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the joint european society of Cardiology/American College Of Cardiology committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959–969.
35. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, Levy D, Manolio T, Mendis S, Mensah G, Pajak A, Prineas RJ, Reddy KS, Roger VL, Rosamond WD, Shahar E, Sharrett AR, Sorlie P, Tunstall-Pedoe H. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108:2543–2549.
36. Olson KA, Beatty AL, Heidecker B, Regan MC, Brody EN, Foreman T, Kato S, Mehler RE, Singer BS, Hveem K, Dalen H, Sterling DG, Lawn RM, Schiller NB, Williams SA, Whooley MA, Ganz P. Association of growth differentiation factor 11/8, putative anti-ageing factor, with cardiovascular outcomes and overall mortality in humans: analysis of the heart and soul and HUNT3 cohorts. *Eur Heart J*. 2015;36:3426–3434.
37. Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. *Cardiovascular diagnosis and therapy*. 2017;7:348–358.
38. Austin PC, Fine JP. Practical recommendations for reporting fine-gray model analyses for competing risk data. *Stat Med*. 2017;36:4391–4400.
39. Abdel-Qadir H, Fang J, Lee DS, Tu JV, Amir E, Austin PC, Anderson GM. Importance of considering competing risks in time-to-event analyses: application to stroke risk in a retrospective cohort study of elderly patients with

- atrial fibrillation. *Circulation. Cardiovascular quality and outcomes*. 2018;11:e004580.
40. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
 41. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10:585–598.
 42. Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness and risk of nonfatal cardiovascular disease in women and men with hypertension. *Am J Hypertens*. 2007;20:608–615.
 43. Hands B, Parker H, Larkin D, Cantell M, Rose E. Male and female differences in health benefits derived from physical activity: implications for exercise prescription. *J Womens Health Issues Care*. 2016;5:4.
 44. Sattelmair J, Pertman J, Ding EL, Kohl HW III, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation*. 2011;124:789–795.
 45. Gander JC, Sui X, Hebert JR, Lavie CJ, Hazlett LJ, Cai B, Blair SN. Addition of estimated cardiorespiratory fitness to the clinical assessment of 10-year coronary heart disease risk in asymptomatic men. *Preventive medicine reports*. 2017;7:30–37.
 46. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC, Earnest CP, Church TS, O'Keefe JH, Milani RV, Blair SN. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circ Res*. 2015;117:207–219.
 47. Erikssen G, Bodegard J, Bjornholt JV, Liestol K, Thelle DS, Erikssen J. Exercise testing of healthy men in a new perspective: from diagnosis to prognosis. *Eur Heart J*. 2004;25:978–986.
 48. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001;33:754–761.
 49. Bouchard C, Daw EW, Rice T, Perusse L, Gagnon J, Province MA, Leon AS, Rao DC, Skinner JS, Wilmore JH. Familial resemblance for VO2max in the sedentary state: the heritage family study. *Med Sci Sports Exerc*. 1998;30:252–258.
 50. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015 Jun 26;4(7). pii: e002014. doi: 10.1161/JAHA.115.002014.
 51. Torvik FA, Rognmo K, Tambs K. Alcohol use and mental distress as predictors of non-response in a general population health survey: the hunt study. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47:805–816.
 52. Nes BM, Janszky I, Vatten LJ, Nilsen TI, Aspenes ST, Wisloff U. Estimating VO2peak from a nonexercise prediction model: the hunt study, Norway. *Med Sci Sports Exerc*. 2011;43:2024–2030.