ORIGINAL ARTICLE

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Objectively Assessed Cardiorespiratory Fitness and All-Cause Mortality Risk: An Updated Meta-analysis of 37 Cohort Studies Involving 2,258,029 Participants

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Abstract

Objective: To detail the magnitude and specificity of the association between cardiorespiratory fitness (CRF) and all-cause mortality risk.

Methods: Cohort studies with at least 1 year of follow-up were sought from inception until December 2021 in MEDLINE, Embase, Web of Science, and a manual search of relevant articles. Relative risks (RRs) with 95% CIs were pooled using random-effects models. Quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation tool.

Results: A total of 37 unique studies comprising of 2,258,029 participants with 108,613 all-cause mortality events were eligible. The pooled multivariable-adjusted RR for all-cause mortality comparing the top vs bottom tertiles of CRF levels was 0.55 (95% CI, 0.50 to 0.61). When CRF was expressed in metabolic equivalent task (MET) units, the corresponding pooled RR was 0.56 (95% CI, 0.50 to 0.62). For every 1-MET increase in CRF, the RR for all-cause mortality was 0.89 (95% CI, 0.86 to 0.92). Strength of the association did not differ by publication year, age, sex, follow-up duration, CRF assessment method, or risk of bias.

Conclusion: Aggregate analysis of observational cohort studies confirms a strong inverse and independent association between CRF and all-cause mortality risk. The results suggest that guideline bodies should consider the inclusion of CRF in standard risk panels for mortality risk assessment.

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Regular physical activity (PA) has several health benefits and it is a well-established way to reduce the risk of cardiovascular disease (CVD) outcomes and mortality.[1-8] Measured physical fitness, which is a strong predictor of health status,[9] has cardiorespiratory and muscular fitness as its main components.[10] Cardiorespiratory fitness (CRF) is an indicator of cardiopulmonary and body muscular function and largely reflects the level of PA in addition to its genetic contribution. A wide variation of methods is used to assess CRF, and these range from directly measured maximal oxygen uptake during cardiopulmonary exercise testing (CPX),[11,12] to estimation from exercise tests and non-exercise prediction equations. Maximal oxygen uptake is one of the most accurate measures of CRF assessment and considered the gold standard for assessing aerobic exercise capacity. Similar to PA, objectively defined CRF (directly measured or estimated from exercise tests) has also been consistently shown to be inversely associated with several chronic disease outcomes, CVD, severe coronavirus disease 2019 (COVID-19) outcomes, and all-cause mortality.[13-17] Given that CRF has been shown to provide additional prognostic value beyond conventional risk factors in predicting vascular outcomes including all-cause mortality,[9,13,18,19] its inclusion in classic risk algorithms has been considered as it may improve the classification of an individuals' risk and optimize prevention, especially

in individuals at high risk.[12,13] However, the adoption of CRF as a crucial risk assessment tool in clinical practice has not become a reality yet. Most risk prediction scores still rely only on conventional risk factors and do not usually consider CRF in their risk equations, although it is a prognostic measurable marker that can be assessed in clinical practice.[20,21]

A major reason why CRF is not applied in routine clinical practice is because the use of CPX for defining CRF involves skills, equipment, and relatively high costs compared with the assessment of other risk factors such as blood pressure, blood lipid levels, and smoking status. The use of CPX allows for the most accurate and standardized quantification of CRF.[12] There is a need to make a strong case for the inclusion of CRF in standard risk prediction tools and this includes providing the most updated evidence on the association between CRF and relevant outcomes. Because mortality is the most reliable and consistently defined measure of population health, our focus was on all-cause mortality outcomes. Kodama et al[9] published a meta-analysis of 33 studies on the association between CRF and all-cause mortality risk in 2009. Since then, several relevant large individual studies with varying results have been published on the topic. In a recent elegant literature review, Harber et al[22] highlighted the major published CRF and mortality studies that have contributed to the literature and clinical practice in the field since 2009. However, this review did not pool the existing evidence as a formal meta-analysis.[22] Therefore, there is a need to provide an updated synthesis of the existing literature to reflect current clinical practice. To re-evaluate the association in a larger representative group of participants than previously, we aimed to evaluate the nature, magnitude, and specificity of the association between objectively measured CRF and all-cause mortality risk using an updated meta-analysis.

METHODS

Data Sources and Searches

This systematic review and meta-analysis was conducted based on a predefined protocol and in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Mate rials 1-2, available online at http://www.mayoclinicproceedings.org).[23,24] MEDLINE and Embase databases were searched from inception to December 6, 2021, with no restriction on language. The computer-based searches used a combination of key words or terms relating to CRF (eg, cardiorespiratory fitness, aerobic capacity, and exercise test) and all-cause mortality (eg, mortality and death). The detailed search strategy is presented in Supplementary Material 3 (available online at http://www.mayoclinicproceedings.org).

Study Selection and Eligibility

Titles and abstracts of retrieved citations were initially screened by one author (NMI) to assess their suitability for potential inclusion. This was then followed by full-text evaluation which was independently conducted by two authors (NMI and SKK) with involvement of a third author (JAL) to reach consensus when there were disagreements. The reference lists of key studies and review articles were manually scanned for additional studies and citing references were also checked in Web of Science. We only included population-based observational cohort (retrospective or prospective, case-cohort, or nested case-control) studies if they had at least 1 year of follow-up and examined the relationship of CRF with the risk of all-cause mortality in adult general populations. We included only studies where CRF was directly measured or estimated following an exercise stress test (maximal or submaximal) on a cycle ergometer or treadmill. The following study types were excluded: 1) cross-sectional or case-control study designs; 2) those based on athletes and/or evaluated competitive or endurance sports; 3) those evaluating the associations between PA and risk of mortality; 4) studies that estimated CRF using an algorithm and did not undertake an exercise

stress test; and 5) those that enrolled only patients with specific diseases that were major risk factors for all-cause mortality such as diabetes, hypertension, CVD, or heart failure.

Data Extraction and Quality Assessment

Using a predesigned data collection form, one author (NMI) initially extracted data from eligible studies, and a second author (SKK) independently checked the data with that in original articles. Inconsistencies were discussed and resolved by mutual agreement and with involvement of a third author (JAL). Data on the following variables were extracted from the publications: first author surname and year of publication, study name, study design, country, year of baseline enrollment, demographic characteristics (age, sex), total number of participants, details on CRF exposure (assessment methods, unit of measurement, and modelling), duration of follow-up, number of all-cause mortality events, and the most fully adjusted relative risks (RRs), hazard ratios, or odds ratios (with corresponding 95% CIs). When we identified multiple publications of studies using data from the same cohort, study selection was limited to a single set of most comprehensive results to avoid double counting of participants in the pooled analysis. The most relevant factor used for selection was the most up-to-date and/or comprehensive results (most extended follow-up or analysis covering the largest number of participants). We assessed the risk of bias within individual observational studies using the Cochrane Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool.[25] It assesses the risk of bias for the following domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements, and selective reporting. Risk is quantified in each domain as low, moderate, serious, or critical, with an overall judgement of the risk of bias provided for each study. To assess the quality of the body of evidence for the outcome, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is based on study limitations, inconsistency of effect, imprecision, indirectness, and publication bias.[26]

Data Synthesis and Analysis

The summary measures of association were presented as RRs with 95% CIs. To enable a consistent approach to the meta-analysis and facilitate pooling and comparisons, reported study-specific risk estimates were transformed to comparisons involving the top vs bottom tertiles of CRF using well-established standard statistical methods,[27,28] which have been described in previous reports.[29,30] For comparisons that could not be transformed, the extreme groups (ie, maximum vs minimal value of CRF) were used for the analyses, as done in previous reports.[4,5,31,32] This approach is considered reliable as it has been shown that pooled estimates from transformed and untransformed data are qualitatively similar.[33] When the top CRF category was used as a referent, we converted the reported risk estimate into its reciprocal. Risk estimates were pooled using a random effects model to minimize the effect of between-study heterogeneity.[34] For studies that reported estimates of the association, according to subgroups (eg, by sex), we obtained a within-study summary estimate using a fixed effect model. Because of the variation in expression of CRF units across studies, we adopted two pooling approaches. First, we pooled all studies irrespective of the unit of CRF measurement, as we have performed in previous systematic reviews and meta-analyses.[5,31,32,35,36] Second, we pooled all studies that expressed CRF in metabolic equivalent task (MET) units; values of CRF reported in mL/kg per minute were converted to METs by dividing by 3.5.[37] To clarify the dose-response relationship, the pooled risk per 1-MET increase in CRF was also reported. The extent of statistical heterogeneity across studies was quantified using standard χ^2 tests and the I^2 statistic.[38,39] Using stratified analysis and random effects meta-regression,[40] we explored for sources of heterogeneity based on prespecified study-level characteristics such as publication year, geographical

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location, sex, the average age at baseline, average follow-up period, CRF assessment method, number of all-cause mortality events, and overall risk of bias. To test the robustness of the observed association, we conducted a sensitivity analysis by investigating the influence of omitting each study in turn on the overall result (stata module metaninf). To assess the potential for small study effects such as publication bias, we visually inspected constructed Begg's funnel plots[41] and performed Egger's regression symmetry test.[42] Finally, we adjusted for the effect of publication bias by the use of the Duval and Tweedie's nonparametric trim-and-fill method which imputes hypothetical small missing null or negative studies.[43] All analyses were conducted using Stata version MP 16 (Stata Corp, College Station, TX, USA).

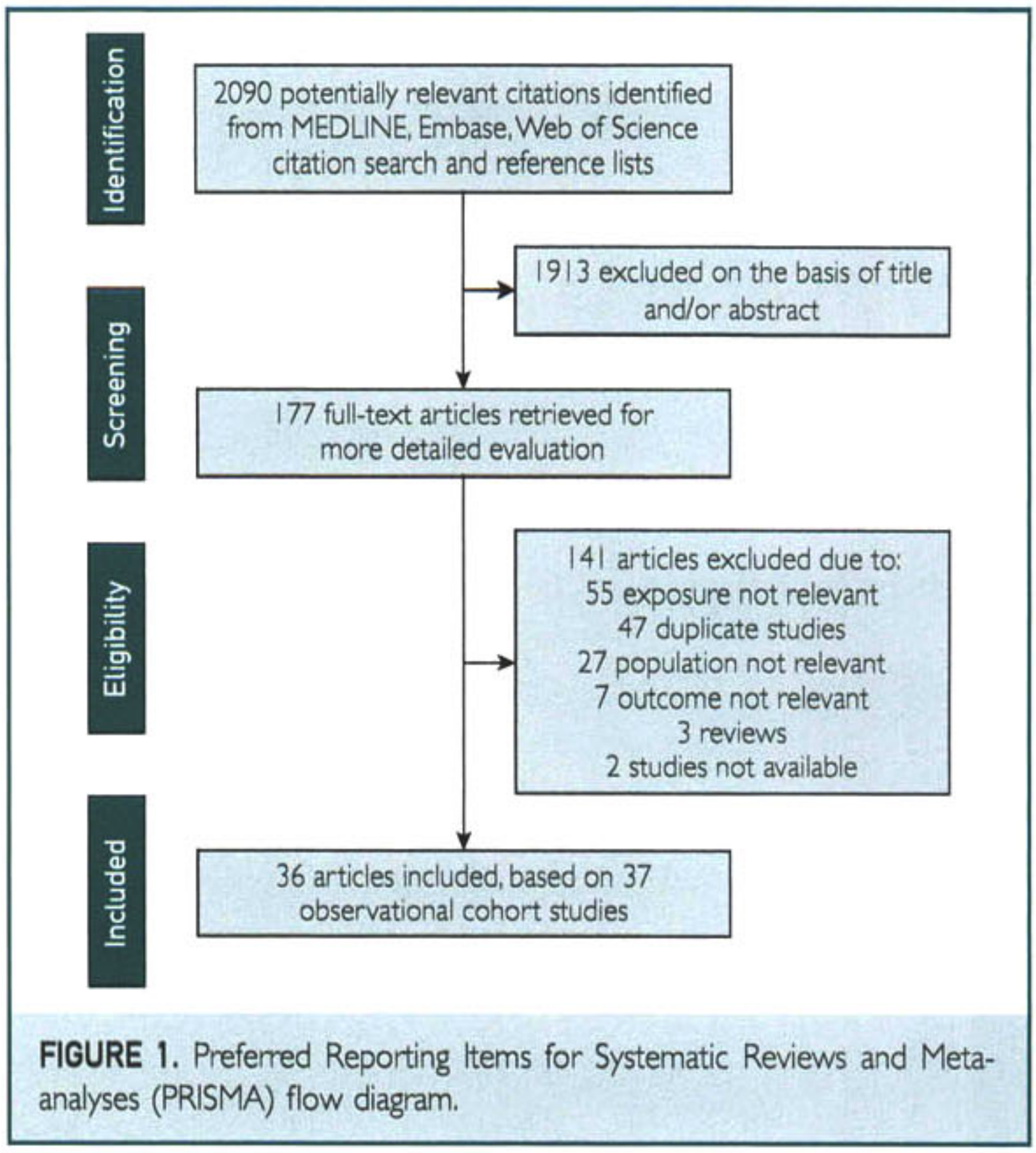

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

RESULTS

Study Identification and Selection

The study selection process is shown in Figure 1. Our search of databases and manual screening of relevant articles identified 2090 potentially relevant citations. Following the screening of titles and abstracts, 1913 citations were excluded with 177 remaining for full-text evaluation. On full-text evaluation, 141 articles were excluded because 1) exposure was not relevant (n=55); 2) they duplicated a previous publication using the same cohort (n=47); 3) population was not relevant (n=27); 4) outcome was not relevant (n=7); 5) they were based on reviews (n=3); and 6) studies were not available (n=2). In total, we included 36 articles[44-79] representing 37 unique observational cohort studies comprising of 2,258,029 general population participants and 108,613 all-cause mortality events.

Study Characteristics and Risk of Bias

The Table summarizes the characteristics of the eligible studies evaluating the associations between CRF and all-cause mortality. Twenty-six studies were based on prospective cohort designs and 11 on retrospective cohort designs. Publication years ranged from 1992 to 2020. The average age of participants at baseline ranged from approximately 25 to 77 years, with a weighted mean of 48.3 years. Nineteen studies were based in North America (USA), 13 in Europe (Denmark, Finland, Germany, Norway, Russia, Sweden, and United Kingdom), 3 in Asia (Hong Kong, Japan, and Korea), and 2 in South America (Brazil and Trinidad). The average duration of follow-up ranged from 3.2 to 47.4 years, with a weighted mean of 35.4 years. Thirty-one studies assessed CRF using a maximal/symptom-limited exercise test and six studies were based on a submaximal CRF assessment during the exercise test. Although there was a slight variation in the degree of covariate adjustment, all except three studies adjusted for a comprehensive panel of established and/or available risk factors such as age, sex, body mass index, smoking, alcohol consumption, blood pressure, lipids, and comorbidities such as hypertension, diabetes, or coronary heart disease. Using the ROBINS-I tool, 29 studies were at moderate risk of bias (ie, at low or moderate risk of bias for

TABLE. Baseline Characteristics of Included Studies[a,b]

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
Kohl, 1992	Preventive Medicine Clinic in Dallas	USA	1971-1985	42.0	8.2	Maximal	153	8108	Age, serum cholesterol, resting systolic blood pressure, age, BMI, smoking habit, family history of heart disease, and follow-up interval
Sandvik, 1993	5 companies in Oslo	Norway	1972-1975	50.0	16.0	Maximal	271	1960	Age, smoking status, serum lipids, blood pressure, resting heart rate, vital capacity, BMI, level of physical activity and glucose tolerance
Erikssen, 1998	NR	Norway	1980-1982	56.6	13.0	Maximal	238	1428	Age
Roger, 1998	Olmsted County, MN	USA	1987-1989	48.4	6.3	Submaximal	123	2193	Age, presence of symptoms, history of MI, coronary disease risk factors (hypertension, diabetes mellitus, smoking, hyperlipidemia, familial coronary disease), obesity (by use of BMI), Charlson index, angina on the TMET (treadmill exercise testing), and positive exercise ECG
Lee, 1999	Cooper Clinic in Dallas	USA	1971-1989	43.8	8.0	Maximal	428	21,925	Age (single year), examination year, smoking habit, alcohol intake, and parental history of ischemic heart disease.
Sawada, 1999	NR	Japan	1982-1984		14.0	Maximal	247	9986	Age, BMI, hypertension, and urinary protein
Goraya, 2000	The Rochester Epidemiology Project	USA	1987-1989	48.6	6.3	Maximal	224	3107	Age, sex, presence of symptoms, history of myocardial infarction, history of congestive heart failure, coronary disease risk factors (history of hypertension, diabetes mellitus, smoking, hyperlipidemia, familial

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TABLE. Continued

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
									coronary disease), obesity (BMI. 27.3 kg/m^2 for women and .27.8 kg/m^2 for men), Charlson comorbidity index score, angina with treadmill exercise testing, positive exercise electrocardiogram
Farrell, 2002	ACLS (Females)	USA	1970-1996	42.9	11.4	Maximal	195	9925	Age, BMI, baseline health status, smoking status
Gulati, 2003	St James Women Take Heart Project	USA	1992	52.4	8.4	Maximal	180	5721	The Framingham Risk Score (involving total cholesterol, HDL-cholesterol, age, systolic blood pressure, diastolic blood pressure, the presence or absence of diabetes mellitus, and current smoking) (as a continuous variable)
Evenson, 2004	Lipids Research Clinics (LRC) Prevalence Study	USA	1972-1976	43.4	25.0	Maximal	639	3995	Age, smoking, education, alcohol, BMI, race, and hyperlipidemic sampling strata
Lai, 2004	Long Beach Veteran Affairs and Palo Alto Veterans Affairs	USA	1987-2000	58.6	6.0	Maximal	1064	5625	ECG findings, resting heart rate, maximal heart rate, CABG history, smoking
Stevens, 2004	US-Russia LRC study	USA	1972-1976	49.0	17.6	Maximal	460	1716	Age, smoking, education, alcohol, and Keys score
Stevens, 2004	US-Russia LRC study	Russia	1975-1977	49.0	17.6	Maximal	211	1359	Age, smoking, education, alcohol, and Keys score
Miller, 2005	St James Study	Trinidad	1977-1981	52.1	7.3	Maximal	83	626	Age and fat-free mass
Park, 2009	Health Promotion Center at Seoul National University Hospital	Korea	1995-2003	56.0	6.4	Maximal	547	18,775	Age, study year, BMI, total cholesterol, alcohol consumption, smoking status (never, former, or

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TABLE. Continued

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
									current) and diagnosis of hypertension or diabetes
Byun, 2010	ACLS (Men)	USA	1974-2002	44.0	16.0	Maximal	2642	38,110	Age (single year), examination year, hypertension, diabetes, hypercholesterolemia, and other positive health factors (BMI, smoking, alcohol intake, physical activity
Daugherty, 2011	Kaiser Permanente of Colorado	USA	2001-2004	56.0	3.2	Maximal	142	9569	Age, smoking status, ectopy in recovery, maximal heart rate, and history of diabetes, coronary artery disease, COPD, cancer, obstructive sleep apnea, and family history of CAD
Shuval, 2015	CCLS	USA	1982	45.0	28.7	Maximal	581	3141	Age, sex, current smoking, alcohol, personal history of hypertension, personal history of diabetes, family history of CVD, CRF or sedentary time, physical activity, BMI, total cholesterol, systolic blood pressure and glucose
Blaha, 2016	The FIT Project	USA	1991-2009	53.0	10.4	Maximal	6356	57,085	Age, sex, race, resting heart rate, resting systolic and diastolic blood pressure, history of diabetes, hypertension, obesity, smoking, family history of CAD, medications for treatment of hypertension, hyperlipidemia and COPD, and indication for stress testing

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TABLE. Continued

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
Korpelainen, 2016	Oulu Deaconess Institute	Finland	1988-1994	51.3	19.0	Maximal	525	3033	Age, BMI, heart rate reserve defined as a difference in heart rate between rest and maximum (beats/min)
Ladenvall, 2016	The Study of Men Born in 1913	Sweden	1962-1967	54.0	45.0	Maximal	653	792	Smoking habits, mean arterial blood pressure, serum cholesterol, and body height
Shah, 2016	CARDIA Study	USA	1985-1986	24.8	26.9	Maximal	273	4872	Age, race, sex, parental history of MI (at younger than 60 years), BMI, systolic blood pressure, diabetes mellitus, smoking exposure (cigarettes per day), and HDL and total cholesterol levels.
Crump, 2017	Swedish Military Conscription Registry	Sweden	1969–1997	47.4	47.4	Maximal	64,343	1,547,478	Year of the military conscription examination, aerobic fitness, muscular strength, BMI, education level, neighborhood SES, and family history of CVD
Jensen, 2017	Copenhagen Male Study	Denmark	1970-1971	48.8	44.1	Submaximal	4486	5131	Age, smoking, grams of tobacco per day, systolic and diastolic blood pressure, previous MI, diabetes, self-reported physical activity, alcohol and social group
Ramos, 2017	CLINIMEX exercise medicine clinic	Brazil	1996-2013	58.0	6.4	Maximal	237	3331	Age, sex, BMI and FEV1/FVC ratio
Bahls, 2018	Study of Health in Pomerania (SHIP-1)	Germany	2002-2006	53.0	8.2	Maximal	332	2935	Age, sex, years of schooling, income, smoking, BMI
Davidson, 2018	The VETS	USA	1983	58.3	8.7	Maximal	1349	8171	Age; BMI; smoking status; history of stroke; use of medications; and presence or absence of hypertension,

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TABLE. Continued

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
									diabetes, hypercholesterolemia, CVD, and family history of risk factors
Hussain, 2018	Mayo Clinic Integrated Stress Center in Rochester	USA	1993-2010	52.1	14.0	Maximal	1590	12,043	Age, sex, hypertension, COPD, current smokers, past smokers, sleep apnea, CAD, indication for test, diabetes, hyperlipidemia, chronic kidney disease, and use of β blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium-channel blockers, alpha adrenergic blockers, long-acting nitrates, statins, levothyroxine, aspirin, antiplatelet, anticoagulants, and bronchodilators. BMI (kg/m^2) as a continuous variable
Imboden, 2018	BALL ST study	USA	1968-2016	42.8	24.2	Maximal	727	4137	Age, sex, examination year, obesity, hypertension, dyslipidemia, impaired fasting glucose, physical inactivity, and smoking status
Kunutsor, 2018	KIHD study	Finland	1984-1989	53.0	26.1	Maximal	1124	2277	Age, BMI, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, history of type 2 diabetes, prevalent coronary heart disease, alcohol consumption, SES and C-reactive protein

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TABLE. Continued

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
Lu, 2018	MrOs and MsOs cohort	Hong Kong	2001	76.6	5.3	Maximal	99	1242	Age, sex, BMI and medical history of stroke, hypertension, diabetes, angina, heart attack, and heart failure
Mandsager, 2018	Cleveland Clinic Foundation	USA	1991-2014	53.4	8.4	Maximal	13,637	122,007	Age, sex, body mass index, history of CAD, hyperlipidemia, hypertension, diabetes, smoking, ESRD, year of testing, and current use of aspirin, β-blockers, or statin
Ekblom-Bak, 2019	Health Profile Assessments	Sweden	1995-2015	18-74	7.6	Submaximal	2750	266,109	Performed year, sex (when not stratified for), age, length of education, exercise, smoking, diet and overall stress
Letnes, 2019	HUNT 3 Fitness Study	Norway	2006-2008	48.2	8.8	Maximal	91	4527	Sex, smoking status, alcohol use, and family history of CVD
Sipila, 2019	Finnish Cardiovascular Study	Finland	2001-2008	56.0	10.0	Maximal	573	3456	Age, systolic blood pressure change, heart rate recovery, female sex, diabetes, history of MI, smoking, resting blood pressure, history of coronary heart disease, any cardiovascular medication, BMI, usage of beta-adrenergic blocking agents and medication for hypercholesterolemia
Cao, 2020	The NHANES study	USA	1999-2004	33.8	13.8	Submaximal	104	3242	Age, sex (overall only), race/ethnicity, smoking status, alcohol intake, and total

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TABLE. Continued

Author, year of publication	Study name or source	Country	Baseline year	Mean/median age, years	Average follow-up, years	CRF assessment	All-cause mortality cases	No. of participants	Adjustment factors
									energy intake, sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia
Laukkanen, 2020	UK Biobank study	United Kingdom	2006-2010	58.1	5.8	Submaximal	936	58,892	Age, sex, systolic blood pressure, BMI (nonlinear spline), smoking status, high cholesterol level, number of medications, and prevalent cancer, CVD, or diabetes at baseline

[a]ACLS = Aerobics Center Longitudinal Study; BALL ST = Ball State Adult fitness program Longitudinal Lifestyle Study; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CARDIA = Coronary Artery Risk Development in Young Adults; CLINIMEX = Exercise Medicine Clinic; CCLS = Cooper Center Longitudinal Study; COPD = chronic obstructive pulmonary disease; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; ECG = electrocardiogram; ESRD = end-stage renal disease; FEV1 = forced expiratory volume in the first one second; FIT = Henry Ford Exercise Testing Project; FVC = forced vital capacity; HDL = high-density lipoprotein; HUNT = Nord-Trøndelag Health Study; KIHD = Kuopio Ischemic Heart Disease; LRC = Lipids Research Clinics; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey study; NR = not reported; SES = socioeconomic status; TMET = treadmill exercise testing; VETS = Veterans Exercise Testing Study.

[b]From source studies.[44-79]

all domains) and eight were at serious risk of bias (ie, were judged to be at serious risk of bias in at least one domain, but no study was judged to be at critical risk of bias in any domain) (Supplementary Material 4, available online at http://www.mayoclinicproceedings.org).

Cardiorespiratory Fitness and Risk of All-cause Mortality

The pooled multivariable-adjusted RR for all-cause mortality comparing the top vs bottom thirds of CRF levels was 0.55 (95% CI, 0.50 to 0.61) (Figure 2). There was substantial heterogeneity between the contributing studies (I^2>90%, P<.001), which was partly explained by location (P for meta-regression=.04); the associations were significant in all locations, but the strongest association was observed in North American populations with a RR of 0.46 (95% CI, 0.35 to 0.60) (Figure 3). After excluding the studies that could be potentially biased by reverse causation (excluding those with ≤5 years of follow-up), regression dilution bias (excluding those with ≥12 years of follow-up), or studies that assessed CRF using submaximal tests, the RRs of all-cause mortality comparing the top vs bottom thirds of CRF levels were 0.55 (95% CI, 0.50 to 0.61; I^2>90%; P<.001), 0.48 (95% CI, 0.38 to 0.61; I^2>90%; P<.001), and 0.52 (95% CI, 0.46 to 0.60; I^2>90%; P<.001), respectively; these pooled results were similar to the overall pooled finding. Exclusion of any single study one at a time from the meta-analysis did not change the direction of the association, yielding pooled RRs which ranged from 0.53 (95% CI, 0.48 to 0.60) to 0.57 (95% CI, 0.52 to 0.63) (Supplementary Material 5, available online at http://www.mayoclinicproceedings.org). In a pooled analysis of studies with CRF estimated as METs (23 studies, 638,708 participants, 37,435 all-cause mortality events), the RR for all-cause mortality comparing the top vs bottom thirds of CRF levels was 0.56 (95% CI, 0.50 to 0.62; I^2>90%; P<.001) (Figure 4). In a pooled analysis of studies with CRF reported or estimated as per 1-MET increase in CRF (10 studies, 360,131 participants, 13,437 all-cause mortality events), the RR for all-cause mortality was 0.89 (95% CI, 0.86 to 0.92; I^2>90%; P<.001) (Supplementary Material 6, available online at http://www.mayoclinicproceedings.org).

Publication Bias

A funnel plot of the 37 studies reporting on the associations between CRF and risk of all-cause mortality showed visual evidence of asymmetry (Supplementary Material 7, available online at http://www.mayoclinicproceedings.org), which was consistent with Egger's regression symmetry test (P<.001). The trim-and-fill technique, which was used to adjust for publication bias, did not impute additional studies (Supplementary Material 8, available online at http://www.mayoclinicproceedings.org). The pooled RR after adjustment for publication bias was unchanged: 0.55 (95% CI, 0.50-0.61).

GRADE Summary of Findings

Ratings via the GRADE tool for the overall population and findings based on studies reporting CRF in METs are reported in Supplementary Material 9 (available online at http://www.mayoclinicproceedings.org). The quality of the evidence per GRADE was very low.

DISCUSSION

Summary of Main Findings

In this updated meta-analysis of 37 distinct studies involving a total of 2.2 million adult general population men and women with objective assessments of CRF, we found that the participants in the top third of CRF levels had a 45% reduced risk of all-cause mortality compared with those in the bottom third. The association was similar in pooled analysis of 23 studies with CRF estimated as METs. In dose-response analysis, a 1-MET higher level of CRF was associated with an 11% decrement in the risk of all-cause mortality. The association was independent of established risk factors and remained consistent in several sensitivity analyses. In a detailed subgroup analysis, the

association was not modified by various relevant study characteristics except for location of study; the association was strongest for North American populations which could be due to the wealth of published CRF studies with significant associations in this location. There was evidence of publication bias, which was not unexpected given that we excluded studies that estimated CRF using an algorithm or did not use data from an exercise stress test, in addition to exclusion of several duplicate studies conducted on the topic. Despite evidence of publication bias, application of trim-and-fill techniques did not impute additional studies and the significant inverse association persisted. The GRADE quality of the evidence was very low.

Comparison With Previous Work

To the best of our knowledge, there has only been one previous comprehensive aggregation of the existing data on the relationship between CRF and all-cause mortality, which was published in 2009; therefore we saw the need for an updated report. Kodama et al[9] combined the results of 33 studies comprising more than 100,000 participants, including 6910 deaths. Their study results showed that a 1-MET higher level of CRF was associated with a 13% decrement in all-cause mortality and individuals with low CRF had a 70% increased risk of all-cause mortality compared with those with high CRF. The mortality risk reductions (per 1-MET higher level of CRF) observed were consistently significant in their subgroup analyses. A recent meta-analysis by Han et al[80] focused on a dose-response analysis of CRF with mortality from all-causes, CVD, and cancer, and this only included studies that reported CRF as at least three levels or per incremental increase. This study included a total of 24 studies that provided information on the association between CRF and all-cause mortality. Their pooled analysis for the risk of all-cause mortality per 1-MET increase in CRF included 14 unique studies; the results showed that a 1-MET higher level of CRF was associated with a 12% decrement in all-cause mortality. We included all studies that have assessed the association between CRF and all-cause mortality to date irrespective of the risk comparison reported. Our pooled analysis per 1-MET higher level of CRF showed an 11% decrement in the risk of all-cause mortality. In addition to this, we were able to transform the risk comparisons reported by the studies into consistent comparisons (top vs bottom tertiles) to ensure all studies were included, enhance pooling and comparability, and to increase the clinical usefulness of the CRF data. To further address the specificity of the CRF-mortality association, we conducted subgroup analyses by several relevant study-level characteristics including publication year, geographical location, sex, the average age at baseline, average follow-up period, CRF assessment method, number of all-cause mortality events, and overall risk of bias. We also replicated the findings of Kodama et al[9] which showed that studies with longer follow-durations ($\geq$12 years) had weaker associations compared with those that had shorter follow-up durations (<12 years); these findings on longer-term CRF studies are likely due to regression dilution bias. However, it seems that a single baseline assessment of CRF is a strong risk marker for at least 10-years mortality risk assessment; this is the common timescale widely used in validated CVD risk calculators. We also showed that the association was stronger in North American populations. Our findings, which are based on the most up-to-date evidence on general population participants, highlight a robust and strong relationship between CRF and all-cause mortality.

Possible Explanations for Findings

Although even half of the variation in CRF is heritable,[81] habitual PA is the major pathway by which CRF can be increased.[82,83] Physical activity or structured exercise training generally improves cardiovascular function, lowers the risk of CVD, and promotes longevity. Both aerobic and resistance training are effective for glycemic control, blood pressure reduction, weight loss, and dyslipidemia, in addition to improving

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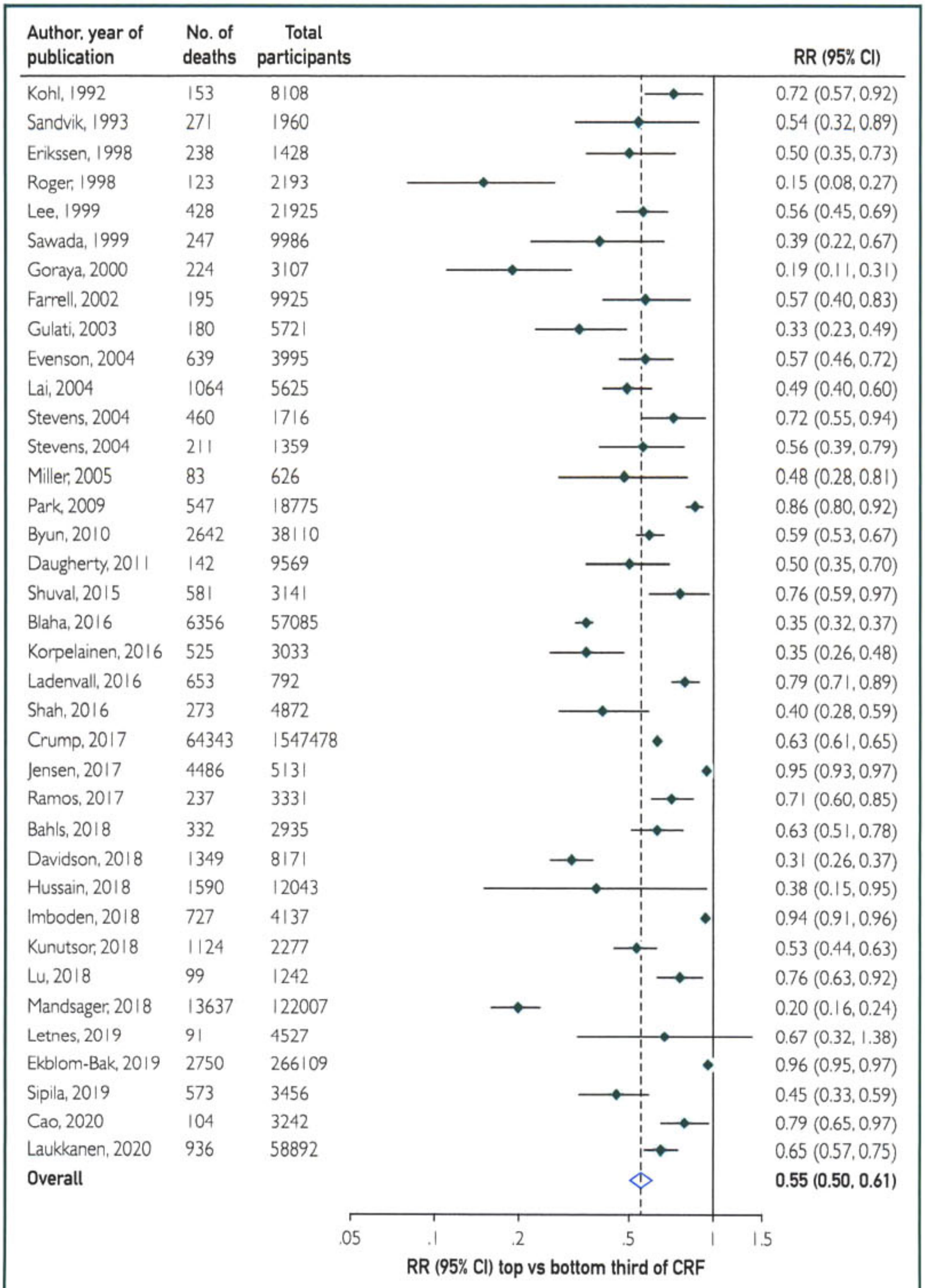

FIGURE 2. Association of cardiorespiratory fitness with all-cause mortality in pooled analysis of all eligible studies. The summary estimate presented was calculated using random effects models and was based on fully adjusted estimates; sizes of data markers are proportional to the inverse of the variance of the relative ratio. 95% CI shown with bars. RR = relative risk.

CRF. The specific mechanisms postulated to underpin the protective effects of PA on CVDs and all-cause mortality outcomes include beneficial modulation in cardiometabolic risk factors and markers such as blood pressure, lipid and glucose levels, natriuretic

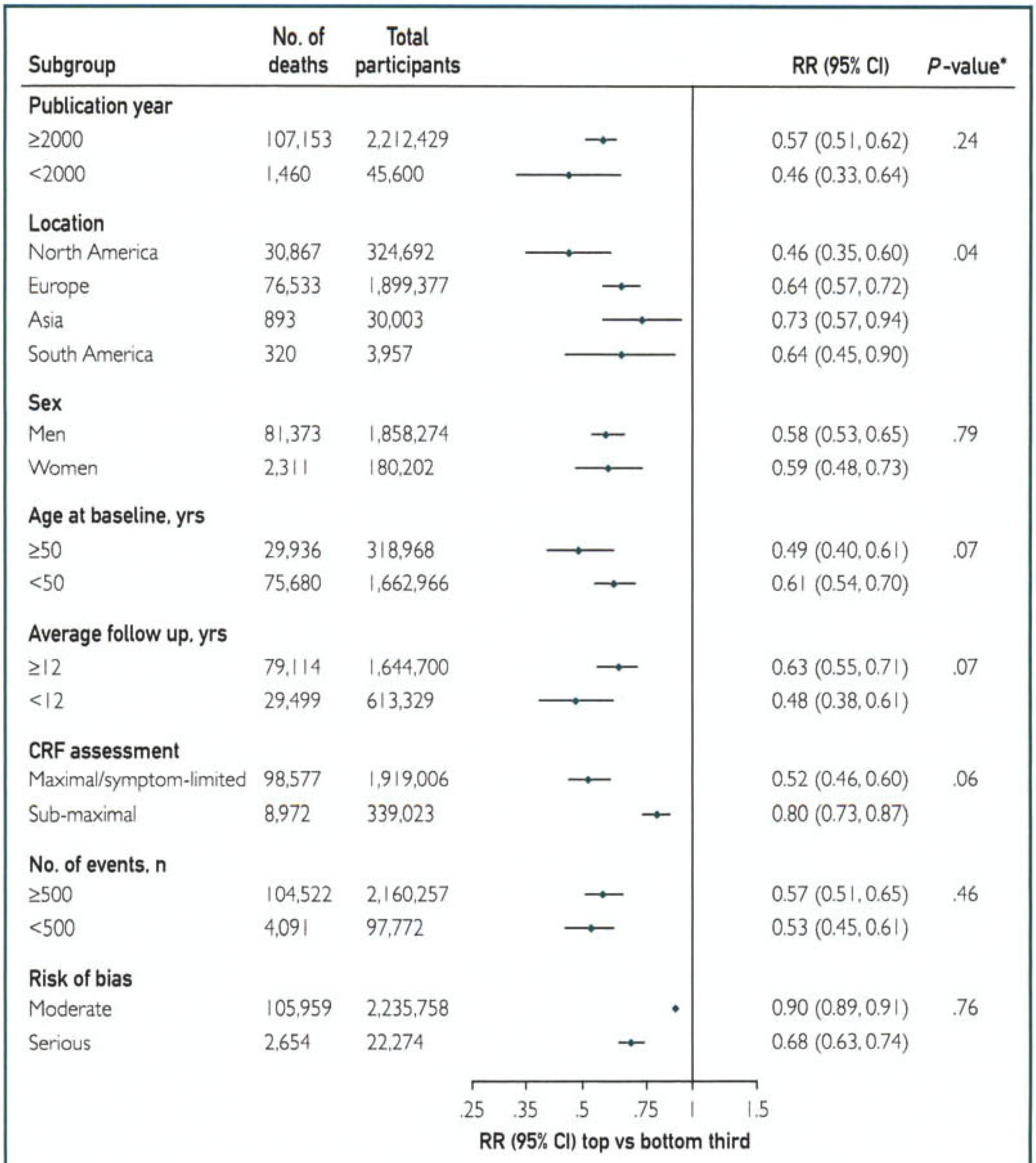

FIGURE 3. Association between cardiorespiratory fitness (CRF) and all-cause mortality, grouped according to several relevant study-level characteristics. The summary estimates presented were calculated using random effects models 95% CI shown with bars. An asterisk (*) indicates *P* value for meta-regression. RR = relative risk.

peptides, and cardiac troponin T[84-86]; reduction in inflammation[87,88]; improvement in endothelial function[89,90]; and regulation of cardiac autonomic function and vagal control of heart rate.[91] Physical activity has favorable effects on lipid metabolism by reducing serum triglycerides by up to 50% and increasing high-density lipoprotein cholesterol by 5% to 10%. Regular exercise may also reduce low-density lipoprotein (LDL) cholesterol by up to 5% and shift the more atherogenic small, dense LDL fraction towards larger LDL particles in a dose-dependent fashion. These metabolic improvements can be achieved through 3.5 to 7 hours of moderate-to-vigorous PA per week or 30 to 60 minutes of exercise on most days.[92] Aerobic exercise intervention is associated with a mean reduction in blood pressure of 5 to 7 mm Hg.[93] The European Society of Cardiology guidelines have recommended participating in at least 30 minutes

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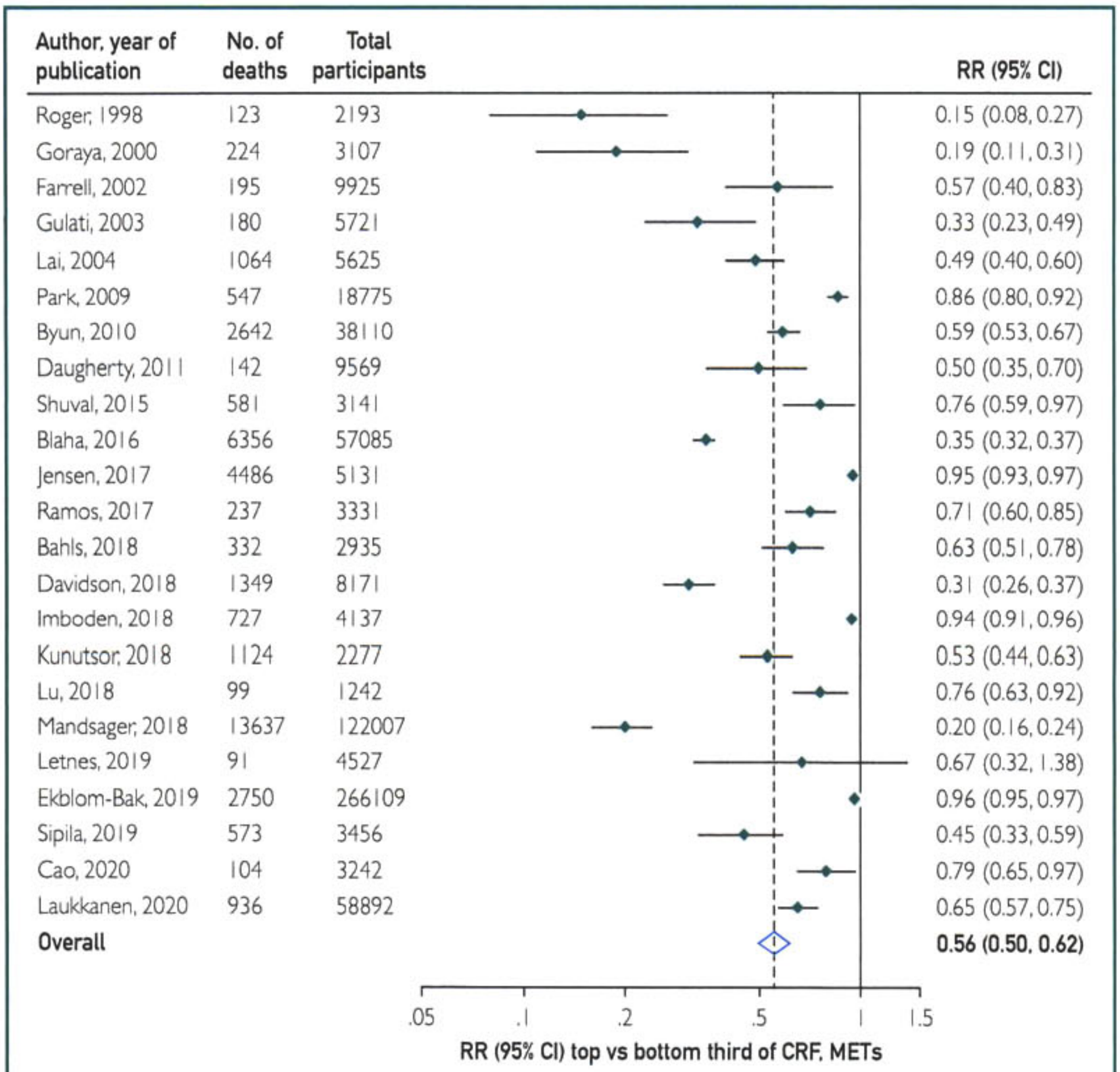

FIGURE 4. Association of cardiorespiratory fitness (CRF) with all-cause mortality in pooled analysis of studies with CRF reported or estimated as metabolic equivalent task (MET) units. The summary estimate presented was calculated using random effects models and was based on the most fully adjusted estimates. Sizes of data markers are proportional to the inverse of the variance of the relative ratio. 95% CI is shown with bars. RR = relative risk.

of moderate-intense aerobic exercise for 5 to 7 days per week for hypertensive individuals, as this is associated with a mean reduction in systolic blood pressure of 7 mm Hg and diastolic blood pressure of 5 mm Hg.[92] Regular exercise training reverses the left ventricular (LV) stiffening associated with healthy but sedentary aging, reduces LV myocardial stiffness, and improves LV diastolic function, in addition to improving LV systolic function.[94,95] The exact mechanism of the increased vascular and LV compliance cannot be determined; however, better compliance is consistent with activation of physiological growth pathways that antagonize the pathological growth initiated by both sedentary behavior and the presence of LV hypertrophy with elevated biomarkers.[94] These pathways may underline the association between CRF and all-cause mortality.

Implications of Findings

These findings confirm the already existing evidence on a strong and independent association between CRF and all-cause mortality. Habitual PA (particularly regular aerobic exercise training) is essential for achieving good CRF levels and the evidence on the vascular health and mortality benefits

attributed to regular PA is overwhelming. In addition, PA also promotes mental well-being. Despite the knowledge on its plentiful benefits, the majority of adult populations do not yet achieve the established guideline recommended levels — 150 to 300 min/wk of moderate-intensity or 75 to 150 min/wk of vigorous-intensity aerobic PA or exercise training for adults.[96] Notwithstanding the implementation of various strategies for promoting PA, such as policy and environmental changes that improve access to PA and information and promote use of communication technology, among others, PA levels are still too low. This is especially very important in the era of the COVID-19 pandemic, where infection control measures have had the unintended consequence of reducing PA even more. It has been shown that patients who were consistently physically inactive were at greater risk of severe disease or death due to COVID-19.[97] Conversely, consistently meeting PA guidelines was strongly associated with a reduced risk for severe COVID-19 outcomes among infected adults.[97] Physical or sports activities that are feasible, attractive, and accessible to the wider population must be identified and promoted to enable engagement for the improvement in CRF. Cardiorespiratory fitness can be estimated in a relatively rapid and accurate way and will be useful for the prediction of all-cause mortality risk in routine clinical care. We suggest that guideline bodies should take the overall evidence into context and consider updating guideline recommendations with inclusion of CRF in the standard risk assessment panel (eg, risk score calculators).

Study Strengths and Limitations

The present study has several strengths, which deserve consideration. Our review of the literature was up-to-date and comprehensively conducted, which to the best of our knowledge covers all of the relevant original research work related to the topic to date. Our meta-analysis includes more than 2.2 million participants (more than 100,000 deaths), which is approximately 19 times higher than the number in the previously published largest review paper on the topic.[9] Other strengths include 1) the inclusion of only studies that assessed CRF using objective methods (exercise stress tests on a cycle ergometer or treadmill with or without respiratory gas exchange analyses); 2) exclusion of studies that recruited only patients with specific diseases such as diabetes, hypertension, CVD, or heart failure that are well known major risk factors for all-cause mortality to minimize reverse causation bias; and 3) transformation of risk estimates to uniform comparisons (top vs bottom third) which enhanced the pooling process for easy interpretation in addition to the reporting of dose-response estimates. In addition, several sensitivity analyses were performed to confirm the reliability of the results, exploration for small study effects, investigation for potential sources of heterogeneity using several study-level characteristics previously not used and assessing the risk of bias, and the GRADE quality of the evidence using validated tools.

There were also some study limitations, which were all inherent and cannot be completely avoided in meta-analysis of aggregate data. We could not have access to participant-level data, which is a typical feature of most study-level meta-analyses; therefore, we could not adopt a uniform approach to statistical adjustment to avoid all possible confounding factors. However, the majority of included CRF studies adjusted for established, well known risk factors. We also cannot rule out residual confounding due to other unmeasured variables and potential underestimation of the cause-effect relationship due to adjustment for mediators by individual studies. There was variance in the assessment methodology of CRF across studies, which could have caused biases in the overall estimates. However, a subgroup analysis by CRF assessment method did not suggest evidence of effect modification, and the objective assessment of CRF is generally accepted, irrespective of exercise testing mode or method.

CONCLUSION

In the most updated comprehensive meta-analysis, high levels of objectively assessed CRF were strongly and independently

associated with reduced risk of all-cause mortality. Guideline bodies should consider the inclusion of CRF in mortality risk assessment panels in clinical practice.

POTENTIAL COMPETING INTERESTS

The authors report no potential competing interests.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CPX**, cardiopulmonary exercise testing; **CRF**, cardiorespiratory fitness; **CVD**, cardiovascular disease; **HR**, hazard ratio; **LV**, left ventricular; **MET**, metabolic equivalent; **OR**, odds ratio; **PA**, physical activity; **RR**, relative risk

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