OPEN ACCESS

Cardiorespiratory fitness is a strong and consistent predictor of morbidity and mortality among adults: an overview of meta-analyses representing over 20.9 million observations from 199 unique cohort studies

Justin J Lang [1,2,3] Stephanie A Prince [1,2] Katherine Merucci,[4] Cristina Cadenas-Sanchez [5,6] Jean-Philippe Chaput [2,7,8] Brooklyn J Fraser [3,9] Taru Manyanga [10] Ryan McGrath,[3,11,12,13] Francisco B Ortega [5,14] Ben Singh [3] Grant R Tomkinson [3]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bjsports-2023-107849).

For numbered affiliations see end of article.

Correspondence to
Dr Justin J Lang, Public Health Agency of Canada, Ottawa, Canada; justin.lang@phac-aspc.gc.ca

JJL and SAP are joint first authors.

Accepted 18 March 2024
Published Online First 9 April 2024

Check for updates

To cite: Lang JJ, Prince SA, Merucci K, *et al. Br J Sports Med* 2024;**58**:556–566.

ABSTRACT

Objective To examine and summarise evidence from meta-analyses of cohort studies that evaluated the predictive associations between baseline cardiorespiratory fitness (CRF) and health outcomes among adults.

Design Overview of systematic reviews.

Data source Five bibliographic databases were searched from January 2002 to March 2024.

Results From the 9062 papers identified, we included 26 systematic reviews. We found eight meta-analyses that described five unique mortality outcomes among general populations. CRF had the largest risk reduction for all-cause mortality when comparing high versus low CRF (HR=0.47; 95% CI 0.39 to 0.56). A dose–response relationship for every 1-metabolic equivalent of task (MET) higher level of CRF was associated with a 11%–17% reduction in all-cause mortality (HR=0.89; 95% CI 0.86 to 0.92, and HR=0.83; 95% CI 0.78 to 0.88). For incident outcomes, nine meta-analyses described 12 unique outcomes. CRF was associated with the largest risk reduction in incident heart failure when comparing high versus low CRF (HR=0.31; 95% CI 0.19 to 0.49). A dose–response relationship for every 1-MET higher level of CRF was associated with a 18% reduction in heart failure (HR=0.82; 95% CI 0.79 to 0.84). Among those living with chronic conditions, nine meta-analyses described four unique outcomes in nine patient groups. CRF was associated with the largest risk reduction for cardiovascular mortality among those living with cardiovascular disease when comparing high versus low CRF (HR=0.27; 95% CI 0.16 to 0.48). The certainty of the evidence across all studies ranged from very low-to-moderate according to Grading of Recommendations, Assessment, Development and Evaluations.

Conclusion We found consistent evidence that high CRF is strongly associated with lower risk for a variety of mortality and incident chronic conditions in general and clinical populations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many systematic reviews have examined the prospective link between baseline cardiorespiratory fitness and health outcomes, but no study has compiled all the evidence to help identify important gaps in the literature.

WHAT THIS STUDY ADDS

⇒ This study identified 26 systematic reviews with meta-analysis representing over 20.9 million observations from 199 unique cohort studies. Cardiorespiratory fitness was strongly and consistently protective of a variety of incident chronic conditions and mortality-related outcomes.

⇒ Gaps in the literature continue to exist, with limited evidence available among women, and certain clinical populations. Several health outcomes could benefit from future meta-analyses, including specific cancer types, especially among women (eg, breast cancer) and mental health conditions beyond depression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the strength of the predictive utility of cardiorespiratory fitness across many health outcomes, cardiorespiratory fitness would be a valuable risk stratification tool in clinical practice.

INTRODUCTION

Cardiorespiratory fitness (CRF) is a physical trait that reflects the integrated function of numerous bodily systems to deliver and use oxygen to support muscle activity during sustained, rhythmic, whole-body, large muscle physical activity.[1] CRF can be objectively measured using direct (usually by maximal exercise testing with concomitant gas exchange analysis)[2] or indirect (exercise predicted equations)[3 4] methods with a variety of maximal or submaximal protocols using different modalities (eg, stationary cycling, treadmill running/walking, bench stepping, field-based running/walking). Non-exercise prediction equations with reasonable validity are also available when direct CRF measurement is not feasible.[5 6] CRF is commonly expressed as the maximum or peak rate of oxygen consumption per kilogram of body mass (common units: mL/kg/min) or metabolic equivalents of task (METs). Nearly half of the variance in CRF is attributable to genetics, with the remainder modified primarily

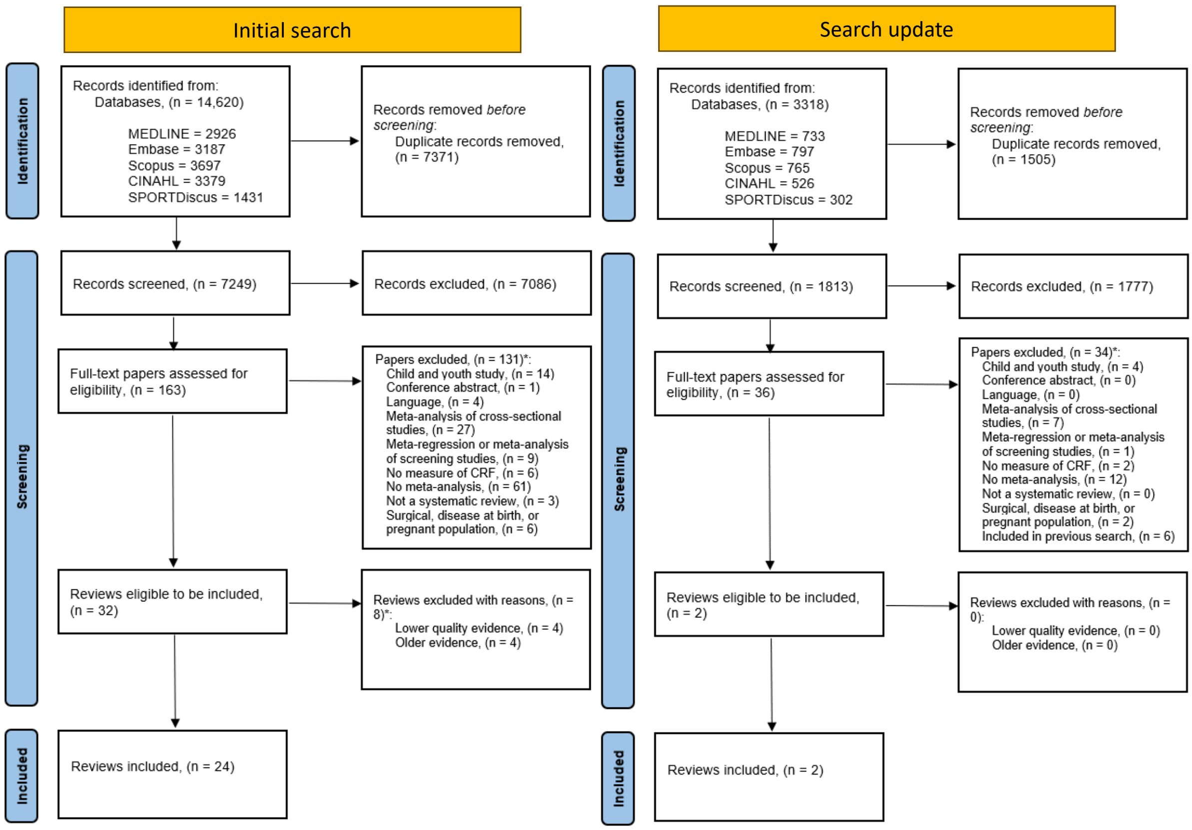

Figure 1 PRISMA flow chart depicting the number of papers identified, screened and included in the overview. *A list of excluded studies with reasons are provided in online supplemental appendix 2.

through habitual physical activity.[7] For example, brisk walking for approximately 150 min per week can result in large relative improvements in CRF among sedentary and unfit individuals.[8 9] Even those with severe chronic disease can improve CRF through well-planned aerobic physical activity programmes.[10]

Low CRF is considered a strong chronic disease risk factor that is not routinely assessed in clinical practice.[11] Evidence suggests that the inclusion of CRF as a clinical vital sign would enhance patient management by improving the classification of those at high risk of adverse outcomes.[11] The evidence supporting CRF as an important risk factor has accumulated since the 1980s through large cohort studies that investigated the prospective risk of all-cause mortality and cardiovascular events associated with CRF.[12–14] Research has linked CRF to the incidence of some cancers (eg, colon/rectum, lung),[15] type 2 diabetes,[16] metabolic syndrome,[17] stroke[18] and depression.[19] Higher CRF may even improve the prognosis in those with chronic conditions such as cancer,[20] peripheral artery disease,[21] heart failure[22] and chronic kidney disease.[23]

Given the mounting evidence supporting CRF as an important risk factor, numerous systematic reviews with meta-analyses summarising results of primary studies for various health outcomes have been published. Kodama *et al*[24] published the first meta-analysis on the health-related predictive validity of CRF and found that a 1-MET (3.5 mL/kg/min) higher level of CRF was associated with a 13% and 15% reduction in the risk of all-cause mortality and cardiovascular disease (CVD) events, respectively. This study helped to establish the meaningful clinically important difference (MCID) of 1-MET for exercise trials. Since Kodama's study, there have been several systematic reviews with meta-analyses, with several published in recent years (ie, 2020+). Most systematic reviews have focused on a single health outcome. To date, there has not been a systematic synthesis of the relationships between CRF and a broad range of health outcomes. To help summarise the breadth of evidence, an overview of reviews provides a systematic method to examine evidence across a range of outcomes for a specific exposure.[25] Thus, the objective of this study was to conduct an overview of systematic reviews with meta-analyses from cohort studies that investigated relationships between CRF and prospective health-related outcomes among adults. We also aimed to assess the certainty of the evidence for each identified health outcome.

METHODS

This overview followed the methods outlined in the Cochrane handbook,[25] and additional methods that were published elsewhere.[26] We adhered to both the Preferred Reporting Items for Overviews of Reviews statement[27] and the Meta-analyses of Observational Studies in Epidemiology reporting standards.[28] The overview was prospectively registered with the PROSPERO international prospective register of systematic reviews (#CRD42022370149). Here, we present a condensed methods section with the full methods available in online supplemental methods.

Eligibility criteria

Population

Adult populations (≥18 years) including apparently healthy and clinical populations with diagnosed chronic conditions. Studies

Table 1 Study characteristics for general populations without known disease at baseline and mortality outcomes

First author, year	Population description	Exposure description(s)	Range of follow-up*	Outcome(s)	Number of studies included in meta-analysis)	Sample size included in meta-analysis	AMSTAR2 rating†
Aune, 2020[36]	General populations of adults	High versus low	14.7–22 years	Sudden cardiac mortality	2	57 813	Critically low quality
		Per 1-MET increase			2	57 813	
Barry, 2014[52] Data only presented in supplement	General populations of adults	Normal weight fit versus normal weight unfit, overweight unfit, overweight fit, obese unfit and obese fit	7.7–16 years	All-cause mortality	10	92 986	Low quality
Barry, 2018[53] Data only presented in supplement	General populations of adults	Normal weight fit versus normal weight unfit, overweight unfit, overweight fit, obese unfit and obese fit	8.1–19.8 years	CVD mortality	8	137 406	Low quality
Han, 2022[35]	General populations of adults	High versus low	5.0–44.1 years	All-cause mortality	19	2 187 550	Moderate quality
		Per 1-MET increase			14	625 400	
		High versus low		CVD mortality	13	1 952 352	
		Per 1-MET increase			10	392 240	
		High versus low		All cancer mortality	11	409 422	
		Per 1-MET increase			10	409 594	
Kodama, 2009[24]	General populations of adults	High versus low	1.1–26 years	All-cause mortality	15	31 010	Critically low
		Per 1-MET increase			18	85 315	
Laukkanen, 2022[54]	General populations of adults	High versus low	3.2–47.4 years	All-cause mortality	37	2 255 441	High quality
		Per 1-MET increase			10	360 131	
Lee, 2020[55]	General populations of adults	High versus low	11.5–49.8 years	Lung cancer mortality	5	12 758	Low quality
Qiu, 2021[6]	General populations of adults	Per 1-MET increase (eCRF)	8.8–24 years	All-cause mortality	7	154 015	Moderate quality
				CVD mortality	6	174 075	

*Data presented are for all the papers included in the systematic reviews and may include exposures other than CRF.
†Details on the AMSTAR2 quality assessment are available from Shea *et al*.[31]
AMSTAR2, A MeaSurement Tool to Assess systematic Reviews 2; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; MET, metabolic equivalent of task.

that focused on certain special populations were excluded (ie, those recovering from surgery, athletes, disease at birth, pregnant individuals).

Exposure
The primary exposure was CRF measured using the following approaches: (1) maximal exercise testing with gas analysis (ie, directly measured $\dot{V}O_{2max/peak}$), (2) maximal or submaximal exercise testing without gas analysis, which used either exercise prediction equations to estimate CRF or the measured exercise performance (ie, indirect measures) or (3) non-exercise prediction equations for estimating CRF.

Outcome
Any health-related outcome such as all-cause or cause-specific mortality, incident conditions related to physical risk factors, chronic conditions or mental health issues were included. Among populations with diagnosed chronic conditions, we included evidence on outcomes such as mortality or disease severity.

Study design
Only systematic reviews with meta-analyses that searched a minimum of two bibliographic databases and provided a sample search strategy were included. We also included meta-analyses that pooled data from primary prospective/retrospective cohort or case-control studies. These studies were the focus because of their ability to assess causality for observational research.

Publication status and language restriction
Only systematic reviews published in peer-reviewed journals in English, French or Spanish (based on authors' language capacity) were eligible. Conference abstracts or papers, commentaries, editorials, dissertations or grey literature were ineligible.

Time frame
Systematic reviews published during the past 20 years for the initial search.

Information sources
Five bibliographic databases, including OVID Medline, OVID Embase, Scopus, CINAHL and EBSCOhost SPORTDiscus, were searched from 1 January 2002 to 21 November 2022. The search was later updated from 1 November 2022 to 8 March 2024.

Search strategy
A research librarian (KM) created the search strategy in collaboration with the authorship team, and the final search was peer-reviewed by an independent research librarian using the Peer Review of Electronic Search Strategies guidelines.[29] The search strategies for each database are available in online supplemental appendix 1. The reference lists of included papers were also searched for additional relevant systematic reviews.

Selection process
All records were imported into RefWorks where duplicates were removed using automated and manual methods. Records were

Table 2 Study characteristics for general populations without known disease at baseline and incident outcomes

First author, year	Population description	Exposure description(s)	Range of follow-up*	Outcome(s)	Number of studies included in meta-analysis)	Sample size included in meta-analysis	AMSTAR2 rating†
Aune, 2021[38]	General populations of adults	High versus low	6.5–19.1 years	Incidence of heart failure	6	1 505 114	Moderate quality
		Per 1-MET increase			5	173 678	
Cheng, 2022[37]	General populations of adults	High versus low	4.3–25.7 years	Incidence of hypertension	9	1 618 067	Moderate quality
		Per 1-MET increase			9	1 618 067	
Kandola, 2019[56]	General populations of adults	High versus low	8 weeks to 42 years	Incidence of depression	3	1 145 655	Critically low quality
Kunutsor, 2023[57]	General populations of adults	High versus low	7.2–27.9 years	Incidence of chronic kidney disease	5	32 447	Moderate quality
Lee, 2021[58]	General populations of adults	High versus low	6–38 years	Incidence of dementia	3	11 694	Critically low quality
Pozuelo-Carrascosa, 2019[40] Data only presented in supplement	General populations of adult men only	High versus low	5–40 years	Incidence of colon/rectum, prostate, skin and all site cancer	4–5	23 350–28 262	Moderate quality
Tarp, 2019[59]	General populations of adults	Per 1-MET increase	3–29 years	Incidence of type 2 diabetes	10	1 601 490	High quality
Wang, 2020[39]	General populations of adults	High versus low	3.9–25.2 years	Incidence of stroke	14	1 409 340	Moderate quality
		Per 1-MET increase			9	Not reported	
Xue, 2020[60]	General populations of adults	High versus low	5.0–28.2 years	Incidence of atrial fibrillation	7	2 168 739	Critically low quality
		Per 1-MET increase			7	222 124	

*Data presented are for all the papers included in the systematic reviews and may include exposures other than CRF.
†Details on the AMSTAR2 quality assessment are available from Shea *et al*.[31]
AMSTAR2, A MeaSurement Tool to Assess systematic Reviews 2; CRF, cardiorespiratory fitness; MET, metabolic equivalent of task.

imported into Covidence for further deduplication and record screening. Reviewers were not blinded to the study metadata when screening. The title and abstract from each record were screened by two of the following independent reviewers (JJL, SAP, CC-S, J-PC, BJF, TM, BS and GRT) against the inclusion criteria. Full-text papers were obtained for each record that met the inclusion criteria or provided insufficient evidence to make a conclusive decision at the title and abstract stage. Conflicts during title and abstract screening automatically advanced to full-text screening. Each full-text record was screened by two of the following independent reviewers (JJL, SAP, CC-S, J-PC, BJF, TM, BS and GRT) against the inclusion criteria. Conflicts at the full-text stage were resolved through discussion by two reviewers (JJL and SAP), with a third reviewer resolving disagreements (GRT).

Data collection process

Data extraction was completed in Covidence using a form that was piloted by the authorship group for accuracy. Data from the included studies were extracted by two of the following independent reviewers (JJL, SAP, CC-S, J-PC, BJF, TM, FBO, BS and GRT). Conflicts were resolved by one reviewer (JJL), who contacted the reviewers who extracted the data when necessary to resolve conflicts.

Data items

The data extraction form included several items related to the demographic characteristics of the primary studies, the meta-analyses effect estimates and related statistics, and details for risk of bias and subgroup analyses.

Review quality

We extracted the original risk of bias assessment for each primary study, as reported by the study authors. Most of the included studies used the Newcastle-Ottawa Scale (NOS) to assess risk of bias for cohort studies.[30] In the event that risk of bias was not assessed, a new assessment was conducted and verified by two reviewers using the NOS. We also assessed quality of the systematic reviews using the second edition of A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR2) checklist.[31] Two of the following independent reviewers (JJL, SAP, CC-S, J-PC, BJF, TM, FBO, BS and GRT) assessed review quality. Conflicts were resolved by one reviewer (JJL), with the reviewers who extracted the data contacted to resolve outstanding conflicts.

Effect measures

We presented pooled hazard ratios (HRs) or relative risks (RRs) for an incident event (ie, mortality or morbidity) across the included systematic reviews. We extracted data from models that compared high versus low CRF and those that examined the impact of a 1-MET higher level of CRF.

Synthesis of data

We followed an outcome-centric approach, as outlined by Kho *et al*.[26] Our goal was to identify systematic reviews with

Table 3 Study characteristics for clinical populations with diagnosed chronic disease at baseline and mortality outcomes

First author, year	Population description	Exposure description(s)	Range of follow-up*	Outcome(s)	Number of studies included in meta-analysis)	Sample size included in meta-analysis	AMSTAR2 rating†
Barbagelata, 2022[41]	Patients with pulmonary hypertension	High versus low	1.6–6.2 years	Mortality or heart/lung transplantation	9	986	Critically low quality
Cantone, 2023[61]	Patients with amyloid cardiomyopathy	Per 1-MET increase	1.7–3.2 years	All-cause mortality	3	233	Moderate quality
Ezzatvar, 2021[42]	Patients with CVD	High versus low	1.0–14.0 years	All-cause mortality	11	22 274	Critically low quality
				CVD mortality	4	5821	
Ezzatvar, 2021[62]	Patients with cancer	High versus low	1–10 years	All-cause mortality	9	4343	Low quality
Fuentes-Abolafio, 2020[63]	Patients with heart failure	High versus low	1 month to 20 years	All-cause mortality	5	5170	High quality
				Heart failure mortality	4	982	
Lachman, 2018[64]	Patients with coronary artery disease	Delayed HRR versus not delayed HRR	2.0–9.8 years	All-cause mortality and hospitalisation	3	2146	Critically low quality
Morris, 2014[65]	Patients with peripheral artery disease	High versus low	3.7–11.3 years	5-year all-cause mortality	3	2793	Critically low quality
				5-year CVD mortality	3	2793	
Rocha, 2022[66]	Patients with interstitial lung disease	High versus low	23 days to 15.5 years	All-cause mortality	3	1908	Critically low quality
Yang, 2023[67]	Patients with chronic kidney disease and end-stage renal disease	High versus low	3.3 months to 12 years	All-cause mortality	2	415	Critically low quality

*Data presented are for all the papers included in the systematic reviews and may include exposures other than CRF.
†Details on the AMSTAR2 quality assessment are available from Shea *et al*.[31]
AMSTAR2, A MeaSurement Tool to Assess systematic Reviews 2; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HRR, heart rate recovery.

non-overlapping primary studies for each outcome to avoid double counting evidence. When more than one eligible systematic review was identified for a single outcome, we calculated the corrected covered area (CCA) to assess the degree of overlap in the primary studies.[32]

$$CCA = \frac{N-r}{(r*c)-r}$$

Where, N is the total number of times a primary study appeared across reviews (inclusive of double counting), r is the number of unique primary studies and c is the number of systematic reviews included for the outcome.

The CCA was interpreted as slight (0%–5%), moderate (6%–10%), high (11%–15%) or very high (>15%). If the CCA was slight or moderate, we included multiple systematic reviews per outcome. If the CCA was high or very high, we selected the highest quality systematic review according to the AMSTAR2 assessment. We included the most recent systematic review when reviews of the same outcome were rated as equal in quality.

Synthesis of results

For each health outcome, we reported evidence for apparently healthy and clinical populations separately. We summarised results using a narrative synthesis approach using summary of findings tables. Results were reported as described by the systematic review authors. Meta-analytical results, including the effect, confidence limits, number of studies and number of participants, were presented by outcome using a forest plot to allow for easy comparison between studies. RR values were taken to approximate the HR. When comparing high versus low CRF, we inverted the scale when studies compared low versus high by taking the reciprocal (ie, HR=2.00 was changed to HR=0.50). Dose−response values were rescaled to a 1-MET higher level of CRF when more than 1-MET was used or if the unit increase was in VO_2. We rescaled by taking the natural log of the HR, dividing or multiplying it to correspond with 1-MET, and exponentiating the result. Subgroup analyses for sex were described when available.

Certainty of the evidence assessment

For each outcome, the certainty of the evidence was assessed using a modified Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[33] Observational cohort evidence began at 'high' certainty because randomised controlled trials were deemed not feasible for our research question.[34] The certainty of the evidence could be rated down based on five domains (ie, risk of bias, imprecision, inconsistency, indirectness and publication bias). See online supplemental table 1 for a GRADE decision rules table.

Equity, diversity and inclusion statement

Our research team included diversity across genders with representation from researchers at all career stages. We stratified our results by sex which allowed use to identify the potential need for more diversity in this area of the literature. This stratification allowed us to discuss the overall generalisability of our results. The GRADE evaluation carried out in this study assessed the indirectness of the results. We downgraded evidence that did not demonstrate good global representation or did not provide a gender-balanced sample. Reducing indirectness is important for ensuring the results are representative of the target population.

Lang JJ, *et al*. *Br J Sports Med* 2024;**58**:556–566. doi:10.1136/bjsports-2023-107849

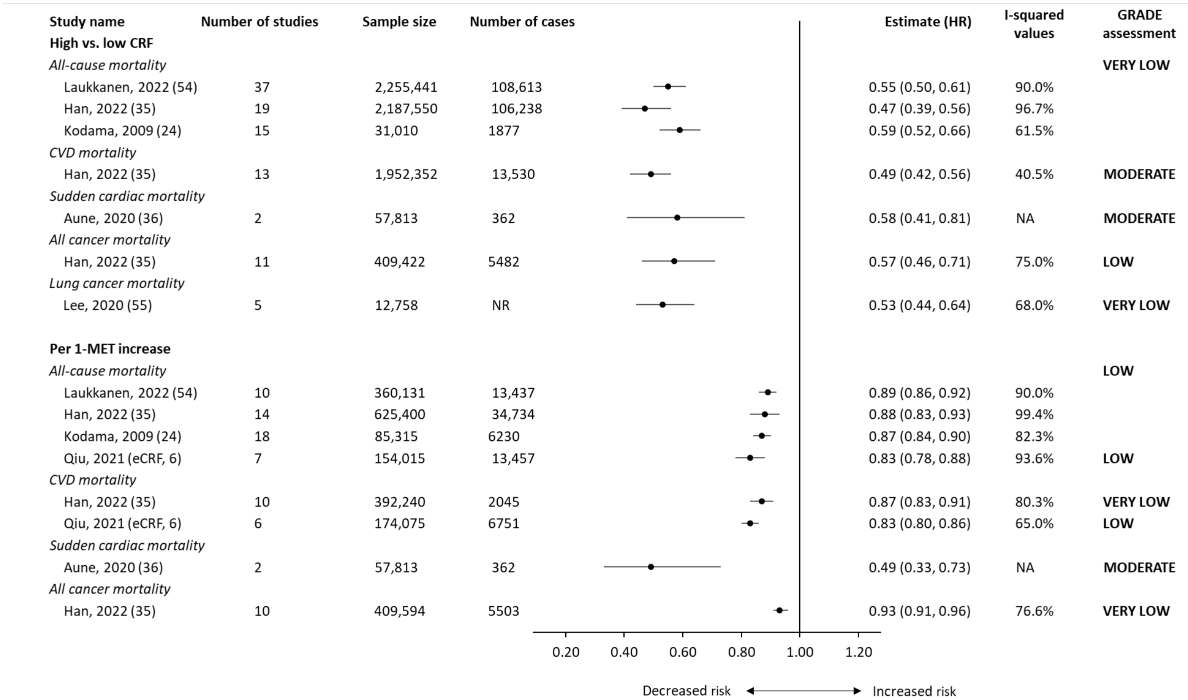

Figure 2 HRs for each mortality outcome in apparently healthy populations at baseline for high versus low CRF and per 1-MET increase in CRF. Estimates from Laukkanen (2022), Han (2022), Kodama (2009) and Aune (2020) were reported as RR, the remaining studies were reported as HR. Qui (2021) reported estimates from self-reported CRF. Kodama (2009) reported low versus high CRF which were inverted for this study. CRF, cardiorespiratory fitness; CVD, cardiovascular disease; eCRF, estimated non-exercise cardiorespiratory fitness; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; MET, metabolic equivalent of task; NA, not applicable; NR, not reported; RR, relative risk.

RESULTS

We identified 9062 records after removing duplicates, assessed 199 full-text papers, and excluded 165 papers during full-text screening, and 8 papers because of high or very high overlap based on the CCA calculation (see figure 1 and online supplemental appendix 2 for full texts with reasons for exclusion). The proportion of agreement between reviewers for title and abstract screening ranged from 95% to 100% while the agreement for full-text screening ranged from 75% to 100%. We included 26 systematic reviews with meta-analyses representing over 20.9 million observations from 199 unique cohort studies, including 21 mortality or incident chronic disease outcomes. We identified CCA values in the high or very high range for sudden cardiac mortality (CCA=33%; n=2), incident heart failure (33%; n=2), incident depression (50%; n=2), incident type 2 diabetes (25%; n=4) and all-cause mortality among those living with heart failure (14%; n=3; see online supplemental appendix 2 for more details). We included multiple systematic reviews for all-cause mortality because the CCA was moderate (10%; n=3).

Tables 1–3 describe the study characteristics. We identified 8 systematic reviews that investigated mortality outcomes, with pooled data from 95 unique primary cohort studies. Nine systematic reviews investigated incident outcomes, pooling data from 63 unique primary cohort studies. The remaining 9 systematic reviews investigated health-related outcomes among populations living with chronic conditions, which represented data from 51 unique primary cohort studies. 11 reviews were of critically low quality, 4 were low, 8 were moderate and 3 were of high quality as assessed using the AMSTAR2 (see online supplemental table 2). See online supplemental table 3 for a detailed summary of findings with the certainty of the evidence for each outcome.

Figure 2 illustrates results for CRF as a predictor of mortality outcomes, which included all-cause, CVD, sudden cardiac, all cancer and lung cancer mortality. When comparing high versus low CRF across all outcomes, there was a 41% (HR for all-cause mortality[24]=0.59; 95% CI 0.52 to 0.66) to 53% (HR for all-cause mortality[35]=0.47; 95% CI 0.39 to 0.56) reduction in the risk of premature mortality. The certainty of the evidence was assessed as very low-to-moderate, mainly due to serious indirectness (ie, most studies only included male participants). In assessing the dose–response relationship, a 1-MET higher level of CRF was associated with a 7% (HR for all cancer mortality[35]=0.93; 95% CI 0.91 to 0.96) to 51% (HR for sudden cardiac mortality[36]=0.49; 95% CI 0.33 to 0.73) reduction in the risk of premature mortality. The certainty of the evidence ranged from very low-to-moderate, largely due to serious indirectness from a large proportion of male-only studies. Sex differences were similar between outcomes with larger CIs for females because of smaller samples (see online supplemental figure 1). For example, there were 1 858 274 male participants compared with 180 202 female participants for all-cause mortality.

Figure 3 describes results for CRF as a predictor of newly diagnosed chronic conditions, including: hypertension, heart failure, stroke, atrial fibrillation, dementia, chronic kidney disease, depression and type 2 diabetes. Online supplemental figure 2 describes results for all cancer (male only), lung cancer (male only), colon/rectum cancer (male only) and prostate cancer. When comparing high versus low CRF, there was a 37% (HR for incident hypertension[37]=0.63; 95% CI 0.56 to 0.70) to 69% (HR for incident heart failure[38]=0.31; 95% CI 0.19 to 0.49) reduction in the risk of incident conditions. The certainty of this evidence was rated as very low-to-low

Study name	Number of studies	Sample size	Number of cases	Estimate (HR)	I-squared values	GRADE assessment
High vs. low CRF						
Incidence of hypertension						
Cheng, 2022 (37)	9	1,618,067	110,638	0.63 (0.56, 0.70)	80.7%	LOW
Incidence of heart failure						
Aune, 2021 (38)	6	1,505,114	19,693	0.31 (0.19, 0.49)	96.1%	VERY LOW
Incidence of stroke						
Wang, 2020 (39)	14	1,409,340	23,894	0.58 (0.51, 0.66)	64.8%	VERY LOW
Incidence of atrial fibrillation						
Xue, 2020 (60)	7	2,168,739	NR	0.60 (0.51, 0.72)	97.0%	VERY LOW
Indicence of dementia						
Lee, 2021 (58)	3	11,694	NR	0.36 (0.27, 0.49)	69.6%	VERY LOW
Incidence of chronic kidney disease						
Kunutsor, 2023 (57)	5	32,447	4,043	0.58 (0.46, 0.73)	76.0%	VERY LOW
Incidence of depression						
Kandola, 2019 (56)	3	1,145,655	NR	0.61 (0.48, 0.78)	73.7%	VERY LOW
Per 1-MET increase						
Incidence of hypertension						
Cheng, 2022 (37)	9	1,618,067	110,638	0.92 (0.90, 0.94)	89.4%	LOW
Incidence of heart failure						
Aune, 2021 (38)	5	173,678	9059	0.82 (0.79, 0.84)	70.0%	VERY LOW
Incidence of stroke						
Wang, 2020 (39)	9	NR	4419	0.97 (0.96, 0.98)	68.1%	VERY LOW
Incidence of atrial fibrillation						
Xue, 2020 (60)	7	222,124	NR	0.91 (0.86, 0.95)	94.0%	VERY LOW
Incidence of type 2 diabetes						
Tarp, 2019 (59)	10	1,601,490	40,286	0.92 (0.90, 0.94)	83.1%	VERY LOW

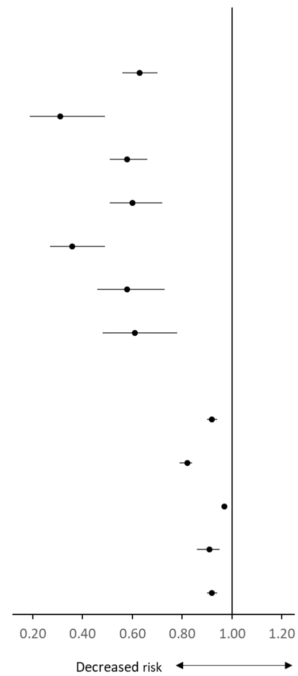

Figure 3 HRs for each incident outcome in apparently healthy populations at baseline for high versus low CRF and per 1-MET increase in CRF. Note: Estimates from Cheng (2022), Aune (2021), Wang (2020), Xue (2020), Tarp (2019) and Kunutsor (2023) were reported as RR, the remaining studies were reported as HR. Kandola (2019) reported estimates for low versus high which were inverted for this study. The estimates from Tarp (2019) are fully adjusted for adiposity. Aune (2021) was reported per 5-MET increase which we converted to 1-MET increase for this study. CRF, cardiorespiratory fitness; CVD, cardiovascular disease; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; MET, metabolic equivalent of task; NA, not applicable; NR, not reported; RR, relative risk.

largely due to inconsistency and indirectness (ie, high heterogeneity that could not be described by subgroup analysis and largely male populations). The dose–response relationship per 1-MET higher level of CRF was associated with a 3% (HR for incident stroke[39]=0.97; 95% CI 0.96 to 0.98) to 18% (HR for incident heart failure[38]=0.82; 95% CI 0.79 to 0.84) reduction in the risk of incident conditions. The certainty of the evidence ranged from very low-to-low due to inconsistency and indirectness. Only two studies reported results for females separately. High versus low CRF was more protective for incident stroke and type 2 diabetes among females compared with males (online supplemental figure 2). Among men, there was a null association between high versus low CRF for prostate cancer (HR=1.15; 95% CI 1.00 to 1.30).[40]

Figure 4 highlights results comparing high versus low CRF among individuals living with chronic conditions. There was a 19% (HR for adverse events among those living with pulmonary hypertension[41]=0.81; 95% CI 0.78 to 0.85) to 73% (HR for cardiovascular mortality among those living with CVD[42]=0.27; 95% CI 0.16 to 0.48) reduction in the risk of all-cause and type-specific mortality. Comparing delayed versus not delayed heart rate recovery was associated with an 83% reduced risk of adverse events among those living with coronary artery disease. The certainty of the evidence for mortality in those living with a chronic condition was rated as very low-to-low largely due to risk of bias, indirectness and imprecision (ie, low-quality studies, mainly male participants and small sample sizes). No evidence examining sex differences were available. See online supplemental table 3 for a detailed summary of findings.

DISCUSSION

This overview of systematic reviews demonstrated that CRF is a strong and consistent predictor of risk across many mortality outcomes in the adult general population. Among populations living with chronic conditions such as cancer, heart failure and CVD, this study showed better prognosis for those with higher CRF. We also demonstrated that low CRF is an important risk factor for developing future chronic conditions such as hypertension, heart failure, stoke, atrial fibrillation, dementia and depression. Given that we summarised evidence from cohort studies, and randomised controlled trials cannot be used in our investigation, the results of this study may signal a causal relationship between CRF and future health outcomes. We also found a significant dose–response effect showing protection for every 1-MET higher level of CRF. This evidence further supports 1-MET as an MCID for CRF and could be considered as a target for interventions. The strength and consistency of the evidence across a wide range of outcomes supports the importance of CRF for clinical assessment and public health surveillance.

Several studies have identified the need for the routine measurement of CRF in clinical and public health practice.[11 43] For instance, a scientific statement from the American Heart Association concluded that healthcare providers should assess CRF during annual routine clinical visits using submaximal tests (eg, treadmill, cycling or bench stepping tests) or self-report estimates and that patients living with chronic conditions should have CRF measured regularly using a symptom-limited direct measure.[11] There are several benefits to regular measurement of CRF in clinical practice. First, CRF is an important risk factor

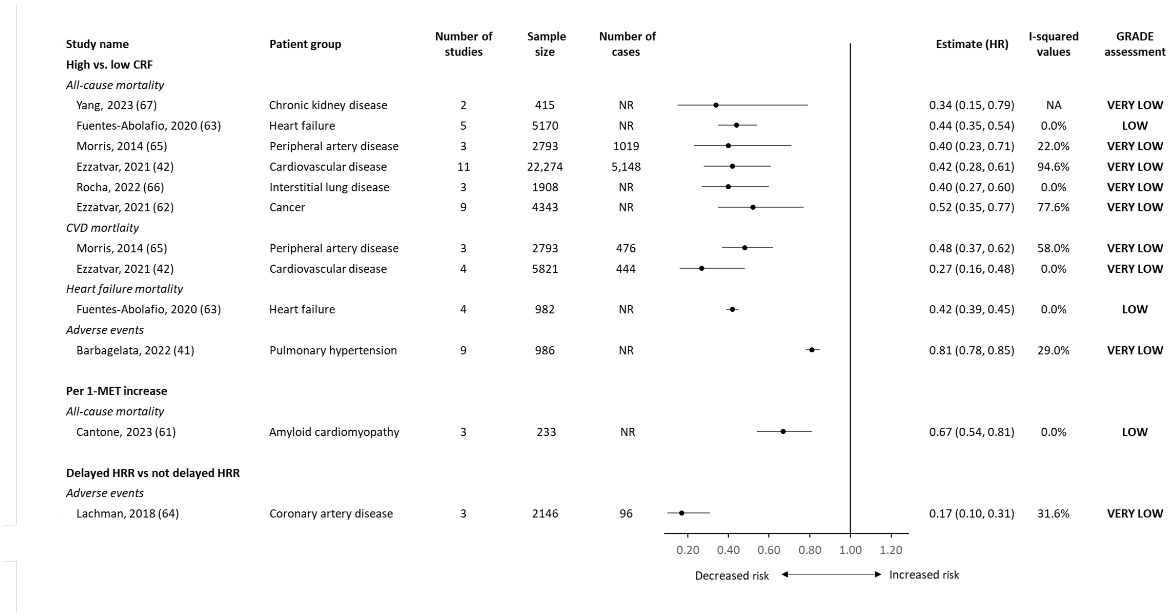

Figure 4 HRs for health outcomes in patients living with chronic conditions at baseline for high versus low CRF and delayed versus not delayed HRR. Estimates from Morris (2014) were reported as RR, the remaining estimates were reported as HR. Yang (2023), Fuentes-Abolafio (2020), Morris (2014), Rocha (2022) and Lachman (2018) reported estimates as low versus high which were inverted for this study. Cantone (2023) was reported per 1-unit VO_2 increase which we converted to 1-MET increase for this study. Adverse events for Lachman (2018) were all-cause mortality, cardiovascular mortality and hospitalisations for congestive heart failure. CRF, cardiorespiratory fitness; CVD, cardiovascular disease; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HRR, heart rate recovery; MET, metabolic equivalent of task; NA, not applicable; NR, not reported; RR, relative risk.

that provides additional information beyond traditional risk factors such as blood pressure, total cholesterol and smoking status.[44] Second, given the strong link with habitual physical activity, CRF could be a valuable tool to help guide exercise prescription. In those with low CRF (defined based on age, sex and health status), large relative improvements can be attained through additional moderate physical activity (ie, brisk walking at a heart rate of 50% of peakO_2).[45] The largest health benefits have been observed when individuals move from being unfit to fit.[46] Lastly, CRF measured using field-based tests are easy to implement with a variety of tests that could be adapted to suit space and time limitations.

Areas of future work

Applying the GRADE approach to evaluate the certainty of the evidence helped identify several important gaps in the literature. Nearly all the outcomes identified in this study were downgraded due to the evidence being generated largely from samples comprising males. Although an increase in female samples would help improve the certainty of the evidence, it likely would not impact the magnitude of the observed effects because the benefits of CRF were similar for males and females in our study (see online supplemental figures 1,2) and other large cohort studies.[47] There is also a need for higher-quality studies with larger samples sizes in clinical populations, as many of the outcomes were downgraded due to primary studies with high risk of bias, low sample sizes (<4000 participants), and inconsistencies in the measurement of CRF across studies. Improving the evidence for CRF in clinical populations remains an important research gap. For instance, outcomes in clinical populations with a serious or very serious risk of bias were often rated this way due to a lack of adequate control for confounding, including a lack of adjustment for age, sex, and body mass.

In addition to the need for higher-quality studies with greater samples in more diverse populations including females, we did not identify any systematic reviews that explored the association between CRF and breast cancer[48] or mental health outcomes beyond incident depression and dementia, as an example. These outcomes present important areas for future work. Finally, future studies would benefit from repeated longitudinal measures of CRF to further establish causality.

Implications for clinical practice

This study further demonstrates the importance of including CRF measurement in regular clinical practice. For every 1-MET (3.5 mL/kg/min) higher level of CRF, we identified substantial reductions in the risk of all-cause, CVD and cancer mortality. We also identified significant reductions in the risk of incident hypertension, heart failure, stroke, atrial fibrillation and type 2 diabetes per higher MET. For most, a 1-MET higher level of CRF is attainable through a regular aerobic exercise programme. For example, in a large population-based observational study of over 90 000 participants, nearly 30% were able to increase their CRF by 1-MET (median follow-up was 6.3 years) without intervention.[49] However, for some, improvements as small as 0.5-METs may substantially benefit health.[50 51]

Given the strength of the predictive utility of CRF across many health outcomes, CRF would be a valuable risk stratification tool in clinical practice. Furthermore, the predictive strength of CRF is maintained regardless of age, sex and race.[47] Through regular CRF measurement, clinicians could better identify patients at greater risk of premature mortality, initiating the need for targeted exercise prescription. Improvements in CRF through regular physical activity results in a proportional reduction in mortality risk, regardless of the presence of other major risk factors such as higher body mass index, hypertension, type

2 diabetes, dyslipidaemia, or smoking.[49] There is an important need for clinical and public health guidelines around the assessment, interpretation of results and MCID of CRF across age, sex and clinical populations.

Strengths and limitations

Our paper has several strengths, including a focus on pooled meta-analyses from cohort studies, assessment of the certainty of the evidence using a modified GRADE, and an evaluation of the systematic review quality using AMSTAR2. Our study identifies gaps where new evidence is needed across a broad range of health outcomes. However, this study is not without limitations. As in any overview, the quality of the data is restricted to the included papers. In our case, heterogeneity was high for many of the included meta-analyses and was often not explained by subgroup analyses. We also identified low-to-very low certainty of the evidence for most outcomes, suggesting the need for higher-quality studies in this research area including adequate adjustment for confounding and greater representation of females. The evidence was also limited to studies examining associations between a single measure of CRF and prospective health outcomes.

CONCLUSION

Our findings showed that high CRF is strongly associated with lower risk of premature mortality, incident chronic conditions (ie, hypertension, heart failure, stroke, atrial fibrillation, dementia and depression), and poor prognosis in those with existing chronic conditions. The consistency of the evidence across a variety of health outcomes demonstrates the importance of CRF and the need to incorporate this measure in routine clinical and public health practice. Future studies should focus on outcomes with limited evidence and where the certainty of the evidence was rated as very low by improving study quality.

Author affiliations
[1]Centre for Surveillance and Applied Research, Public Health Agency of Canada, Ottawa, Ontario, Canada
[2]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3]Alliance for Research in Exercise, Nutrition and Activity (ARENA), Allied Health and Human Performance, University of South Australia, Adelaide, South Australia, Australia
[4]Health Library, Health Canada, Ottawa, Ontario, Canada
[5]Department of Physical Education and Sports, Faculty of Sport Sciences, Sport and Health University Research Institute (iMUDS), University of Granada; CIBEROBN, ISCIII, Granada, Andalucía, Spain
[6]Stanford University, Department of Cardiology; and Veterans Affair Palo Alto Health Care System, Palo Alto, California, USA
[7]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
[8]Department of Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[9]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
[10]Division of Medical Sciences, University of Northern British Columbia, Prince George, British Columbia, Canada
[11]Fargo VA Healthcare System, Fargo, North Dakota, USA
[12]Department of Health, Nutrition, and Exercise Sciences, North Dakota State University, Fargo, North Dakota, USA
[13]Department of Geriatrics, University of North Dakota, Grand Forks, North Dakota, USA
[14]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

X Justin J Lang @JustinJLang, Stephanie A Prince @SPrinceWare and Ben Singh @bensinghphd

Acknowledgements We would like to acknowledge the support of Valentine Ly, MLIS, Research Librarian at the University of Ottawa for her help with translating and conducting the search strategy in CINAHL and SPORTDiscus. We would also like to acknowledge the Health Library at Health Canada and the Public Health Agency of Canada for their support in constructing and carrying out the search strategy for MEDLINE, Embase and Scopus. The PRESS peer-review of the search strategy was carried out by Shannon Hayes, MLIS, research librarian, from the Health Library at Health Canada and the Public Health Agency of Canada. We would also like to thank Joses Robinson and Iryna Demchenko for their help with the paper.

Contributors JJL, GRT and SAP conceptualised and planned the study design. JJL and SAP led the study. JJL accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. All coauthors contributed to article screening. JJL and SAP wrote the first draft of the article. All coauthors reviewed, revised and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Dr. Ortega is supported by the Grant PID2020-120249RB-I00 funded by MCIN/AEI/10.13039/501100011033 and by the Andalusian Government (Junta de Andalucía, Plan Andaluz de Investigación, ref. P20_00124). Dr. Cadenas-Sanchez is supported by a grant from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska Curie grant agreement No 101028929. Dr. Fraser is supported by a National Heart Foundation of Australia Postdoctoral Fellowship (106588).

Disclaimer The content and views expressed in this articles are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Justin J Lang http://orcid.org/0000-0002-1768-319X
Stephanie A Prince http://orcid.org/0000-0001-6729-5649
Cristina Cadenas-Sanchez http://orcid.org/0000-0002-4513-9108
Jean-Philippe Chaput http://orcid.org/0000-0002-5607-5736
Brooklyn J Fraser http://orcid.org/0000-0002-1752-5431
Taru Manyanga http://orcid.org/0000-0001-5461-5981
Francisco B Ortega http://orcid.org/0000-0003-2001-1121
Ben Singh http://orcid.org/0000-0002-7227-2406
Grant R Tomkinson http://orcid.org/0000-0001-7601-9670

REFERENCES

1 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100:126–31.
2 Balady GJ, Arena R, Sietsema K, *et al*. American heart Association exercise, cardiac rehabilitation and prevention committee of the Council on clinical cardiology; Council on epidemiology and prevention; Council on peripheral vascular disease; Interdisciplinary Council on quality of care and outcomes research. clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American heart Association. *Circulation* 2010;22:191–225.
3 Pollock ML, Foster C, Schmidt D, *et al*. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J* 1982;103:363–73.
4 Kaminsky LA, Whaley MH. Evaluation of a new standardized ramp protocol: the BSU/Bruce ramp protocol. *J Cardiopulm Rehabil* 1998;18:438–44.
5 Nes BM, Vatten LJ, Nauman J, *et al*. A simple Nonexercise model of cardiorespiratory fitness predicts longterm mortality. *Med Sci Sports Exerc* 2014;46:1159–65.
6 Qiu S, Cai X, Sun Z, *et al*. Is estimated cardiorespiratory fitness an effective Predictor for cardiovascular and all-cause mortality? A meta-analysis. *Atherosclerosis* 2021;330:22–8.

7 Bouchard C, Daw EW, Rice T, *et al*. Familial resemblance for Vo2Max in the sedentary state: the HERITAGE family study. *Medicine &Amp Science in Sports &Amp Exercise* 1998;30:252–8.
8 Stofan JR, DiPietro L, Davis D, *et al*. Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the aerobics center longitudinal study. *Am J Public Health* 1998;88:1807–13.
9 Garber CE, Blissmer B, Deschenes MR, *et al*. American college of sports medicine position stand. quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and Neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334–59.
10 Sandercock G, Hurtado V, Cardoso F. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: a meta-analysis. *International Journal of Cardiology* 2013;167:894–902.
11 Ross R, Blair SN, Arena R, *et al*. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American heart Association. *Circulation* 2016;134:e653–99.
12 Bruce RA, DeRouen TA, Hossack KF. Value of maximal exercise tests in risk assessment of primary coronary heart disease events in healthy men: five years' experience of the Seattle heart watch study. *Am J Cardiol* 1980;46:371–8.
13 Cumming GR, Samm J, Borysyk L, *et al*. Electrocardiographic changes during exercise in asymptomatic men: 3-year follow-up. *Can Med Assoc J* 1975;112:578–81.
14 Blair SN, Kohl HW, Paffenbarger RS, *et al*. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 1989;262:2395–401.
15 Robsahm TE, Falk RS, Heir T, *et al*. Cardiorespiratory fitness and risk of site-specific cancers: a long-term prospective cohort study. *Cancer Med* 2017;6:865–73.
16 Sieverdes JC, Sui X, Lee D, *et al*. Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men. *Br J Sports Med* 2010;44:238–44.
17 Kim S, Kim JY, Lee DC, *et al*. Combined impact of cardiorespiratory fitness and visceral Adiposity on metabolic syndrome in overweight and obese adults in Korea. *PLoS ONE* 2014;9:e85742.
18 Hooker SP, Sui X, Colabianchi N, *et al*. Cardiorespiratory fitness as a Predictor of fatal and nonfatal stroke in asymptomatic women and men. *Stroke* 2008;39:2950–7.
19 Åberg MAI, Waern M, Nyberg J, *et al*. Cardiovascular fitness in males at age 18 and risk of serious depression in adulthood: Swedish prospective population-based study. *Br J Psychiatry* 2012;201:352–9.
20 Groarke JD, Payne DL, Claggett B, *et al*. Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. *Eur Heart J Qual Care Clin Outcomes* 2020;6:315–22.
21 Leeper NJ, Myers J, Zhou M, *et al*. Exercise capacity is the strongest Predictor of mortality in patients with peripheral arterial disease. *J Vasc Surg* 2013;57:728–33.
22 Ferreira JP, Metra M, Anker SD, *et al*. Clinical correlates and outcome associated with changes in 6-minute walking distance in patients with heart failure: findings from the BIOSTAT-CHF study. *Eur J Heart Fail* 2019;21:218–26.
23 Roshanravan B, Robinson-Cohen C, Patel KV, *et al*. Association between physical performance and all-cause mortality in CKD. *J Am Soc Nephrol* 2013;24:822–30.
24 Kodama S, Saito K, Tanaka S, *et al*. Cardiorespiratory fitness as a quantitative Predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;301:2024–35.
25 Pollock M, Fernandes RM, Becker LA, *et al*. Chapter V: Overviews of reviews. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane, 2022. Available: www.training.cochrane.org/handbook
26 Kho ME, Poitras VJ, Janssen I, *et al*. Development and application of an outcome-centric approach for conducting Overviews of reviews. *Appl Physiol Nutr Metab* 2020;45:S151–64.
27 Gates M, Gates A, Pieper D, *et al*. Reporting guideline for Overviews of reviews of Healthcare interventions: development of the PRIOR statement. *BMJ* 2022;378:e070849.
28 Brooke BS, Schwartz TA, Pawlik TM. MOOSE reporting guidelines for meta-analyses of observational studies. *JAMA Surg* 2021;156:787.
29 McGowan J, Sampson M, Salzwedel DM, *et al*. PRESS peer review of electronic search strategies: 2015 guideline statement. *Journal of Clinical Epidemiology* 2016;75:40–6.
30 Wells G, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2013. Available: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
31 Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of Healthcare interventions, or both. *BMJ* 2017;358:j4008.
32 Pieper D, Antoine S-L, Mathes T, *et al*. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014;67:368–75.
33 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
34 Iorio A, Spencer FA, Falavigna M, *et al*. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.
35 Han M, Qie R, Shi X, *et al*. Cardiorespiratory fitness and mortality from all causes, cardiovascular disease and cancer: dose-response meta-analysis of cohort studies. *Br J Sports Med* 2022;56:733–9.
36 Aune D, Schlesinger S, Hamer M, *et al*. Physical activity and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies. *BMC Cardiovasc Disord* 2020;20:318.
37 Cheng C, Zhang D, Chen S, *et al*. The Association of cardiorespiratory fitness and the risk of hypertension: a systematic review and dose-response meta-analysis. *J Hum Hypertens* 2022;36:744–52.
38 Aune D, Schlesinger S, Leitzmann MF, *et al*. Physical activity and the risk of heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2021;36:367–81.
39 Wang Y, Li F, Cheng Y, *et al*. Cardiorespiratory fitness as a quantitative Predictor of the risk of stroke: a dose-response meta-analysis. *J Neurol* 2020;267:491–501.
40 Pozuelo-Carrascosa DP, Alvarez-Bueno C, Cavero-Redondo I, *et al*. Cardiorespiratory fitness and site-specific risk of cancer in men: A systematic review and meta-analysis. *Eur J Cancer* 2019;113:58–68.
41 Barbagelata L, Masson W, Bluro I, *et al*. Prognostic role of cardiopulmonary exercise testing in pulmonary hypertension: a systematic review and meta-analysis. *Adv Respir Med* 2022;90:109–17.
42 Ezzatvar Y, Izquierdo M, Núñez J, *et al*. Cardiorespiratory fitness measured with cardiopulmonary exercise testing and mortality in patients with cardiovascular disease: A systematic review and meta-analysis. *Journal of Sport and Health Science* 2021;10:609–19.
43 Myers J, Kokkinos P, Arena R, *et al*. The impact of moving more, physical activity, and cardiorespiratory fitness: why we should strive to measure and improve fitness. *Prog Cardiovasc Dis* 2021;64:77–82.
44 Gander JC, Sui X, Hébert JR, *et al*. Association of cardiorespiratory fitness with coronary heart disease in asymptomatic men. *Mayo Clinic Proceedings* 2015;90:1372–9.
45 Church TS, Earnest CP, Skinner JS, *et al*. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA* 2007;297:2081–91.
46 Blair SN, Kohl HW, Barlow CE, *et al*. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA* 1995;273:1093–8.
47 Kokkinos P, Faselis C, Samuel IBH, *et al*. Cardiorespiratory fitness and mortality risk across the spectra of age. *J Am Coll Cardiol* 2022;80:598–609.
48 Katsaroli I, Sidossis L, Katsagoni C, *et al*. The association between cardiorespiratory fitness and the risk of breast cancer in women. *Med Sci Sports Exerc* 2024.
49 Kokkinos P, Faselis C, Samuel IBH, *et al*. Changes in cardiorespiratory fitness and survival in patients with or without cardiovascular disease. *J Am Coll Cardiol* 2023;81:1137–47.
50 Bonafiglia JT, Preobrazenski N, Islam H, *et al*. Exploring differences in cardiorespiratory fitness response rates across varying doses of exercise training: a retrospective analysis of eight randomized controlled trials. *Sports Med* 2021;51:1785–97.
51 Grace SL, Poirier P, Norris CM, *et al*. Pan-Canadian development of cardiac rehabilitation and secondary prevention quality indicators. *Can J Cardiol* 2014;30:945–8.
52 Barry VW, Baruth M, Beets MW, *et al*. Fitness vs. fatness on all-cause mortality: a meta-analysis. *Prog Cardiovasc Dis* 2014;56:382–90.
53 Barry VW, Caputo JL, Kang M. The joint Association of fitness and fatness on cardiovascular disease mortality: A meta-analysis. *Prog Cardiovasc Dis* 2018;61:136–41.
54 Laukkanen JA, Isiozor NM, Kunutsor SK. Objectively assessed cardiorespiratory fitness and all-cause mortality risk: an updated meta-analysis of 37 cohort studies involving 2,258,029 participants. *Mayo Clin Proc* 2022;97:1054–73.
55 Lee J. Cardiorespiratory fitness physical activity, walking speed, lack of participation in leisure activities, and lung cancer mortality: A systematic review and meta-analysis of prospective cohort studies. *Cancer Nurs* 2021;44:453–64.
56 Kandola A, Ashdown-Franks G, Stubbs B, *et al*. The association between cardiorespiratory fitness and the incidence of common mental health disorders: A systematic review and meta-analysis. *J Affect Disord* 2019;257:748–57.
57 Kunutsor SK, Isiozor NM, Myers J, *et al*. Baseline and usual cardiorespiratory fitness and the risk of chronic kidney disease: A prospective study and meta-analysis of published observational cohort studies. *GeroScience* 2023;45:1761–74.
58 Lee J. Influence of cardiorespiratory fitness on risk of dementia and dementia mortality: A systematic review and meta-analysis of prospective cohort studies. *J Aging Phys Act* 2021;29:878–85.
59 Tarp J, Støle AP, Blond K, *et al*. Cardiorespiratory fitness, muscular strength and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetologia* 2019;62:1129–42.
60 Xue Z, Zhou Y, Wu C, *et al*. Dose-response relationship of cardiorespiratory fitness with incident atrial fibrillation. *Heart Fail Rev* 2020;25:419–25.
61 Cantone A, Serenelli M, Sanguettoli F, *et al*. Cardiopulmonary exercise testing predicts prognosis in Amyloid cardiomyopathy: a systematic review and meta-analysis. *ESC Heart Fail* 2023;10:2740–4.

62 Ezzatvar Y, Ramírez-Vélez R, Sáez de Asteasu ML, *et al*. Cardiorespiratory fitness and all-cause mortality in adults diagnosed with cancer systematic review and meta-analysis. *Scand J Med Sci Sports* 2021;31:1745–52.
63 Fuentes-Abolafio IJ, Stubbs B, Pérez-Belmonte LM, *et al*. Physical functional performance and prognosis in patients with heart failure: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2020;20:512.
64 Lachman S, Terbraak MS, Limpens J, *et al*. The Prognostic value of heart rate recovery in patients with coronary artery disease: A systematic review and meta-analysis. *Am Heart J* 2018;199:163–9.
65 Morris DR, Rodriguez AJ, Moxon JV, *et al*. Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2014;3:e001105.
66 Rocha V, Paixão C, Marques A. Physical activity, exercise capacity and mortality risk in people with interstitial lung disease: A systematic review and meta-analysis. *J Sci Med Sport* 2022;25:903–10.
67 Yang L, He Y, Li X. Physical function and all-cause mortality in patients with chronic kidney disease and end-stage renal disease: a systematic review and meta-analysis. *Int Urol Nephrol* 2023;55:1219–28.