Association of muscle strength and cardiorespiratory fitness with all-cause and cancer-specific mortality in patients diagnosed with cancer: a systematic review with meta-analysis

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Abstract

Objectives: To examine the association between muscle strength and cardiorespiratory fitness (CRF) with all-cause and cancer-specific mortality in patients diagnosed with cancer, and if these associations are affected by type and/or stage of cancer.

Design: Systematic review with meta-analysis.

Data source: Five bibliographic databases were searched to August 2023.

Results: Forty-two studies were included (*n* = 46,694). Overall, cancer patients with high muscle strength or CRF levels (when dichotomised as high *vs.* low) presented a significant reduction in risk of all-cause mortality by 31 to 46% compared to those with low physical fitness levels. Similarly, a significant 11% reduction was found for change per unit increments in muscle strength. In addition, muscle strength and CRF were associated with a 8 to 46% reduced risk of all-cause mortality in patients with advanced cancer stages, and a 19 to 41% reduced risk of all-cause mortality was observed in lung and digestive cancers. Lastly, unit increments in CRF were associated with a significant 18% reduced risk of cancer-specific mortality.

Conclusion: High muscle strength and CRF were significantly associated with lower all-cause mortality risk. In addition, increases in CRF were associated with a reduced risk in cancer-specific mortality. These fitness components were especially predictive in patients with advanced cancer stages as well as in lung and digestive cancers. This highlights the importance of assessing fitness measures for predicting mortality in cancer patients. Given these findings, tailored exercise prescriptions to improve muscle strength and CRF in patients with cancer may contribute to reducing cancer-related mortality.

Keywords: Muscle strength, cardiorespiratory fitness, mortality, survival, cancer

What is already known

- Many systematic reviews have examined the association between muscle strength and/or cardiorespiratory fitness (CRF) and the risk of all-cause cancer mortality in apparently healthy individuals. These reviews followed participants prospectively from baseline to cancer diagnosis and death to evaluate the association. To date, there is no available research investigating whether these physical fitness components are associated with a lower risk of mortality in individuals who have been diagnosed with cancer. Additionally, the associations between these components and cancer-specific mortality remain to be determined.

What are the new findings

- This review identified 42 prospective observational cohort studies, including 47,000 patients with any form of cancer and stage, examining muscle strength and CRF.
- Cancer patients diagnosed with any form of cancer and stage with high muscle strength or cardiorespiratory fitness levels presented a significant reduction of the risk of all-cause mortality compared to those with low physical fitness levels. In addition, physical fitness components were significant predictors of all-cause mortality in patients with advanced cancer stages as well as in lung and digestive cancers.
- Increments in cardiorespiratory fitness were associated with a significant reduced risk of cancer-specific mortality.
- Gaps in the current literature includes the limited evidence available for cancer-specific mortality and for certain forms of cancer (e.g., brain).

1. Introduction

Cancer is a major global health challenge, contributing significantly to both morbidity and mortality [1]. In 2022, there were 20 million new cases and 9.7 million cancer deaths worldwide, with a trend expected to increase in the coming decades [1]. Progress in cancer prevention, diagnosis and treatment have reduced overall mortality rates, however side-effects of cancer treatments (e.g., cardiotoxicity and muscle loss), presence of comorbidities (e.g., cardiovascular diseases [CVD]), increases in body fatness, and lack of physical activity, are thought to contribute to mortality in patients with cancer [2-4].

To determine the risk of mortality, measures of physical fitness have been widely investigated in different clinical populations, including cancer [5-7]. Indeed, muscle strength and cardiorespiratory fitness (CRF) are two of the most studied components of physical fitness due to their strong association with CVD and all-cause cancer mortality [8, 9], and therefore, widely used for observational prospective studies [10, 11]. When considering assessments for muscle strength, several assessment modes have been employed. The most commonly used are the handgrip strength (HGS) and knee extension tests, which are both time- and cost-effective, provide estimates of overall muscle strength, and strong predictive values for mortality [12], making these ideal for large-scale epidemiological research. Other studies have also utilised assessment modes such as isokinetic dynamometry, which can provide quantification of muscle strength over the entire range of motion at a set velocity, although this requires specialized equipment, and therefore, is less used in cohort studies [13]. For CRF, both maximal and submaximal tests have been utilized. These include the cardiopulmonary exercise test (CPET), which is considered the gold standard, offering a direct measure of maximal oxygen uptake (VO2max) and also a robust indicator of CRF and mortality risk [8]. Similarly, submaximal tests such as the 6-minute walking test (6MWT) have also been widely employed and provide valuable insights of CRF, especially for those with lower fitness levels initially [14]. This test is suitable because it is easier to administer and is indicated in populations where maximal testing may not be feasible.

When examining physical fitness and mortality risk, higher muscle strength has been associated with a significant reduction in the risk of all-cause mortality in healthy adults by 21%, CVD mortality by 15%, and chronic obstructive pulmonary disease (COPD) mortality by 27% [5, 10, 15]. When cancer is considered, Garcia-Hermoso et al. [12] found a very low (i.e., 2-3%), and barely significant, association between muscle strength and cancer mortality. However, it should be noted that muscle strength assessment was performed before the diagnosis of cancer in healthy subjects who were followed prospectively over time. Subsequently, Ezzatvar et al. [16] observed in patients with cancer that higher muscle strength levels were significantly associated with a 39% lower risk of all-cause mortality. In

addition, they found that a 5 kilogram (kg) increase in muscle strength was significantly correlated with a lower risk of all-cause mortality by 15%. Of note though, the study included only older cancer patients (i.e., > 60 years of age), limiting the translation of these findings to other age ranges.

In line with the findings observed in muscle strength, higher CRF levels have been shown to be correlated with a significant lower risk of all-cause, CVD, as well as COPD mortality by 42%, 56% and 62%, respectively, in healthy adults [17, 18]. When investigating the relationship between CRF and risk of cancer death, Schmid et al. [9] found that the risk of mortality was significantly reduced in healthy individuals with higher CRF. Subsequently, and to the best of our knowledge, only one systematic review has examined the relationship between CRF and cancer mortality in adult patients already diagnosed with cancer [19]. The authors observed a significant 48% reduced risk of all-cause mortality when comparing patients with higher *vs.* lower CRF. Furthermore, they also found a significant 18% decrease in all-cause mortality risk per 1-metabolic equivalent (MET) increment. However, it should be acknowledged that some limitations including population (e.g., childhood cancer) and data analysis were noted which, in turn, may have limited the interpretation of the results.

Therefore, it remains unknown whether higher muscle strength and CRF are associated with lower risk of mortality in patients already diagnosed with cancer. Furthermore, considering the lack of studies investigating cancer-specific mortality, it has still to be determined the association between physical fitness components and death caused by cancer. Indeed, previous systematic reviews that have explored the association between muscle strength and/or CRF with all-cause cancer mortality [15, 20, 21] were conducted in apparently healthy individuals before the diagnosis of cancer. In fact, such studies followed prospectively individuals to cancer diagnosis and death to estimate the risk of cancer mortality. As a result, we undertook the first meta-analysis to investigate the association between physical fitness components measured after cancer diagnosis with all-cause and cancer-specific mortality. Moreover, no studies have investigated the association between muscle and/or CRF and mortality in different cancer types (e.g., breast, lung, prostate, etc.) or stages (e.g., early-stage *vs.* advanced). This is of utmost relevance when considering the increased risk of mortality in advanced cancer stages [22]. Consequently, exploring the association between physical fitness, cancer stage and mortality may help to inform how exercise interventions are conducted to mitigate the risk of mortality at different stages. Thus, the aims of this systematic review with meta-analysis were two-fold: 1) to examine the association between muscle strength and CRF with all-cause and cancer-specific mortality in adults already diagnosed with any form of cancer; 2) to determine whether the association of muscle strength and CRF with all-cause and cancer-specific mortality were affected by type and/or stage of cancer.

2. Methods

All procedures undertaken in the present study were conducted in compliance with the guidelines outlined by the Cochrane Back Review Group [23], adhering to the reporting standards established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [24, 25], and registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023448143).

2.1. Search strategy and study selection procedure

A systematic search was conducted in PubMed, CINAHL, SPORTDiscus, Web of Science, and Embase from inception to August 1st, 2023. The search strategy is presented in the supplementary materials. In addition, a manual search of references in all retrieved studies was undertaken to detect potentially eligible articles for inclusion. During the screening phase, titles and abstracts were first independently evaluated following the eligibility criteria for population and study design. Eligibility was independently and separately assessed by two authors (selected from FB, VN, UC, and EV), with disagreement resolved by a third author (FB). When abstracts did not provide sufficient information, they were selected for full-text evaluation. Full-text articles meeting criteria were retrieved and read independently by the reviewers and assessed for study inclusion.

2.2. Eligibility criteria

For the current review, we included prospective observational cohort studies assessing the association between muscle strength and/or CRF with mortality in patients with cancer. Primary outcomes were all-cause and cancer-specific mortality, defined as time between assessment and death for any cause (i.e., all-cause mortality) or for cancer (i.e., cancer-specific mortality), including any duration of the follow-up. The inclusion criteria were: (a) adult patients (i.e., ≥ 18 years of age) diagnosed with any type of cancer; (b) prospective studies assessing any form of muscle strength and/or CRF; and (c) studies investigating all-cause and cancer-specific mortality. Exclusion criteria were: (a) studies not reporting data regarding the variables of interest; (b) studies reporting data as odds ratio; and (c) studies written in a language other than English. Regarding physical fitness components, we included studies using: a) cut-off value approach to categorize participants into two distinct groups based on the variable of interest (patients categorized as either having high or low muscle strength or CRF based on a predefined cut-off point, e.g., muscle strength > 19.1 kg *vs.* those with muscle strength < 19 kg), allowing us to compare outcomes between these two groups (i.e., high *vs.* low); and b) changes per unit increment approach to measure the variable of interest based on the change in muscle strength

or CRF, without categorizing into distinct groups (e.g., we examined how each unit increment in physical fitness such as per 1-MET increment was associated with mortality).

2.3. Data extraction

Data extraction was independently and separately performed by two authors (selected from VN, LM, GQ, and EB), with disagreement resolved by a third author (FB). Study information, including sample size, age, BMI, cancer type, stage and treatment, study design, follow-up, physical fitness measured (i.e., muscle strength and/or CRF), method of assessment, and cut-off values were collected along with the outcomes of interest (i.e., all-cause and cancer-specific mortality). Hazard ratio (HR) for all-cause and cancer-specific mortality with their associated dispersion values such as 95% confidence intervals (CI) or standard errors (SE) from univariable and multivariable analyses, when available, and the number of covariates included in the multivariable models were extracted. Authors were contacted in case of missing data and, if no response was received, the respective studies were excluded from the analysis to ensure data integrity.

2.4. Study quality assessment

The quality of the study was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies [26]. The NOS evaluates studies based on three criteria: selection of cohort groups, comparability of cohorts, and the ascertainment of outcome of interest. The NOS assigns a star rating in each domain, with a maximum of nine stars indicating the highest quality [26]. The study quality assessment for all included studies was independently and separately performed by two authors (VN and GQ) with disagreements resolved by a third author (FB), if required.

2.5. Statistical analysis

The extracted HR from univariable and multivariable models on the association of muscle strength and CRF with all-cause and cancer-specific mortality were log-transformed as well as their 95% CI to be included in a random-effects model with inverse variance weighting. For cut-off analyses, muscle strength and CRF were dichotomized using predefined cut-off points reported in the original studies (e.g., muscle strength > 19.1 kg *vs.* < 19.0 kg, or CRF > 16.1 mL/kg/min *vs.* < 16.0 mL/kg/min). When data were stratified into tertiles or quartiles, the lowest and highest stratification levels were considered for analyses. In addition, for changes per unit increment analyses, we examined studies reporting changes in muscle strength or CRF per unit increment (e.g., per 1-MET increase in CRF or kg increase in muscle strength). A p-value ≤ 0.05 was considered statistically significant. Heterogeneity between studies was assessed by using the I^2 statistic and the p value from χ^2-based Cochran's Q test. High heterogeneity was defined by a threshold p-value of 0.1 or I^2 values greater than 50%. Outliers

were examined using sensitivity analysis by omitting one study at a time (leave-one-out method). To check for publication bias, contour-enhanced funnel plots of log HR against its SE were generated and explored using Egger's regression asymmetry test when more than 10 studies were available [27]. Subgroup analyses, when available, were provided for: 1) cancer stage, classified as proportion of early (i.e., stage 0 to 2) *vs*. advanced cancer (i.e., stage 3 to 4); 2) cancer type, classified as a single cancer type (e.g., lung) or group of cancers in the same system (i.e., digestive) [28, 29]. Analyses were conducted using the Review Manager (RevMan) software from the Cochrane Collaboration (version 5.4, Copenhagen: The Nordic Cochrane Centre) and the package 'metafor' from R (R Core Team, 2020) [30].

2.6. Equity, diversity and inclusion statement

Our research team was diverse in terms of gender and included researchers at various career stages. We stratified our results by cancer stage and type, which helped us recognize the need for greater diversity in this area of research. This stratification also enabled us to discuss the overall generalizability of our findings.

3. Results

A total of 2702 studies were retrieved from our search, with 1903 potential records retained for screening after duplicate removals. After excluding 1721 records due to their irrelevance to the research question, 182 were considered eligible for full-text assessment (Figure 1). A total of 42 articles investigating muscle strength and/or CRF on all-cause and cancer-specific mortality in adult patients with cancer were subsequently included in the meta-analyses [31-72].

*****Figure 1*****

3.1. Participants and intervention characteristics

A total of 46,694 adult patients with cancer participated in the included studies; median age was 64 years (interquartile range [IQR]: 58.8, 70.5 years) and median BMI was 24.8 kg/m^2 (IQR: 22.7, 26.6 kg/m^2). From the 42 studies, 26 were on multiple cancer types, nine related to lung cancer, two related to gastric cancer, and one each on pancreatic, breast, glioma, colon, and bladder cancer. Regarding physical fitness assessment, muscle strength was measured in 24 studies, whilst CRF in 16 studies, and only two studies examined both (Supplementary Table 1). Thirty-five studies adopted cut-off values, measuring high *vs.* low levels of muscle strength and/or CRF, whilst 12 studies examined changes as per unit increment. Overall, all-cause mortality was investigated in all studies, both all-cause and

cancer-specific mortality were assessed in two studies, and cancer-specific mortality only in one study [31-72].

For muscle strength, all studies adopted the HGS test [31-33, 35, 36, 41-43, 46, 48-60, 62, 64, 69, 70]. Cut-off values (i.e., high *vs.* low) were used in 19 studies [31-33, 35, 36, 42, 43, 46, 51-60, 62, 64, 69, 70], whilst analyses on changes per unit increment in muscle strength were used in seven studies [41, 42, 48-51, 54]. When examining cut-off values, low muscle strength was classified according to either: kg from < 13 to < 25.1 kg in women and from < 19.87 to < 40.2 kg in men, HGS test used in the Fried frailty phenotype index, age-dependent cut-offs, and percentile from ≤ 10^{th} to < 25^{th}; whilst kg was adopted for changes as per unit increment.

For CRF, 14 studies used the CPET [34, 37-40, 44, 45, 48, 61, 63, 65, 70, 72] and four utilized the 6MWT [47, 66-68]. Cut-off values (i.e., high *vs.* low) were used in 13 studies [34, 37, 39, 40, 44, 47, 61, 63, 65-68, 70, 72], whilst analyses on changes per unit increment in CRF were used in seven studies [34, 38, 39, 45, 48, 71, 72]. When analysing cut-off values from the CPET, low CRF was classified according to either: peak oxygen uptake (VO2peak) from < 13 to < 16 mL/kg/min, < 60 to < 80% VO2peak, based on a MET value, and minute ventilation (VE) to carbon dioxide output (VCO2) VE/VCO2 ≥ 31; whilst, low CRF from cut-off values derived from the 6MWT were set according to distance, from < 358.5 to < 400 meters. Changes as per unit increment was measured according to VO2peak, MET and distance increments, respectively.

Regarding quality assessment, the median total score was seven out of nine in the NOS, with scores ranging from four to nine points. The score of each study is shown in Supplementary Table 2.

3.2. Muscle strength – All-cause mortality

3.2.1. Main model and subgroup analyses for cut-off values

Main model. Twenty-two studies were undertaken for muscle strength on all-cause mortality (Figure 2) [31-33, 35, 36, 42, 43, 46, 51-60, 62, 64, 69, 70]. For the multivariable model, cancer patients with high muscle strength levels had a significant 31% reduced risk of all-cause mortality (HR = 0.69; 95%CI = 0.61 to 0.78; $p < 0.001$) compared to those with low muscle strength levels. Heterogeneity was I^2 = 67%, and no outliers were identified. Results were similar when data were derived from the univariable model (HR = 0.58; 95%CI = 0.51 to 0.56; $p < 0.001$). No publication bias was observed (t = -1.68 to -0.34; p = 0.12 to 0.74) (Supplementary Figure 7).

Cancer stage. Twenty-two studies were undertaken for muscle strength on all-cause mortality (Supplementary Figure 1) [31-33, 35, 36, 42, 43, 46, 51-60, 62, 64, 69, 70]. For the multivariable model in studies including a large proportion of patients with advanced cancer, those with high muscle

strength levels had a significant 23 to 46% reduced risk of all-cause mortality (50 to 75% of patients with advanced cancer: HR = 0.77; 95%CI = 0.71 to 0.84; p < 0.001; I^2 = 26% and > 75% of patients with advanced cancer: HR = 0.54; 95%CI = 0.38 to 0.75; p < 0.001; I^2 = 78%) compared to those with low muscle strength levels, while a non-significant association was observed for studies involving a large proportion of patients with early-stage cancer (< 50% of patients with advanced cancer: HR = 0.67; 95%CI = 0.41 to 1.09; p = 0.11; I^2 = 37%). Results were similar for studies including a large proportion of patients with advanced cancer (50 to 75% of patients with advanced cancer: HR = 0.64; 95%CI = 0.57 to 0.73; *p* < 0.001; I^2 = 65% and > 75% of patients with advanced cancer: HR = 0.50; 95%CI = 0.40 to 0.64; *p* < 0.001; I^2 = 83%), but not for early-stage cancer (< 50% of patients with advanced cancer: HR = 0.62; 95%CI = 0.50 to 0.77; *p* < 0.001; I^2 = 0%) derived from the univariable model.

Cancer type. Seven studies were undertaken for muscle strength on all-cause mortality (Supplementary Figure 2) [31, 43, 53, 55-57, 62]. For the multivariable model in digestive cancer (i.e., gastric [*n* = 4], colorectal [*n* = 3]), cancer patients with high muscle strength levels had a significant 41% reduced risk of all-cause mortality (HR = 0.59; 95%CI = 0.38 to 0.94; *p* = 0.03; I^2 = 0%) compared to those with low muscle strength levels. For lung cancer (*n* = 3), cancer patients with high muscle strength levels had a significant 19% reduced risk of all-cause mortality (HR = 0.81; 95%CI = 0.73 to 0.90; *p* < 0.001; I^2 = 0%) compared to those with low muscle strength levels. Results were similar when data were derived from the univariable model for digestive (HR = 0.62; 95%CI = 0.49 to 0.77; *p* < 0.001; I^2 = 0%) and lung cancer (HR = 0.74; 95%CI = 0.67 to 0.81; *p* < 0.001; I^2 = 0%).

Figure 2

3.2.2. Main model and subgroup analyses for changes per unit increment

Main model. Seven studies were undertaken for muscle strength on all-cause mortality (Figure 3) [41, 42, 48-51, 54]. For the multivariable model, unit increments in muscle strength in cancer patients were associated with a significant 11% reduction in the risk of all-cause mortality (HR = 0.89; 95%CI = 0.82 to 0.97; *p* = 0.005). Heterogeneity was I^2 = 94%, and no outliers were identified. Results were similar when data were derived from the univariable model (HR = 0.94; 95%CI = 0.88 to 0.99; *p* = 0.03).

Cancer stage. Five studies were undertaken for muscle strength on all-cause mortality (Supplementary Figure 3) [41, 42, 49, 51, 54]. For the multivariable model in studies including a large proportion of patients with advanced cancer, unit increments in muscle strength were associated with a significant 8 to 20% reduction in the risk of all-cause mortality (50 to 75% of patients with advanced cancer: HR = 0.80; 95%CI = 0.78 to 0.83; *p* < 0.001; I^2 = 0% and > 75% of patients with advanced cancer: HR = 0.92; 95%CI = 0.87 to 0.98; *p* = 0.009; I^2 = 85%). Results were similar for studies with 50 to 75% of patients with advanced cancer (HR = 0.90; 95%CI = 0.88 to 0.93; *p* < 0.001; I^2 = 0%), but not for > 75% of patients

with advanced cancer derived from the univariable model (HR = 0.92; 95%CI = 0.81 to 1.05; p = 0.21; I^2 = 92%).

Cancer type. There was an insufficient number of studies to examine changes per unit increment in muscle strength on all-cause mortality, when stratifying by cancer type.

Figure 3

3.3. Cardiorespiratory fitness – All-cause mortality

3.3.1. Main model and subgroup analyses for cut-off values

Main model. Thirteen studies were undertaken for CRF on all-cause mortality (Figure 4) [34, 37, 39, 40, 44, 47, 61, 63, 65-68, 70]. For the multivariable model, cancer patients with high CRF levels had a significant 46% reduced risk of all-cause mortality (HR = 0.54; 95%CI = 0.38 to 0.84; p = 0.005) compared to those with low CRF levels. Heterogeneity was I^2 = 90%, and no outliers were identified. Results were similar when data were derived from the univariable model (HR = 0.64; 95%CI = 0.53 to 0.79; p < 0.001; I^2 = 86%). An effect on publication bias was observed (t = -4.28; p < 0.05) (Supplementary Figure 8).

Cancer stage. Six studies were undertaken for CRF on all-cause mortality (Supplementary Figure 4) [39, 40, 44, 63, 65, 67]. For the multivariable model in studies including a large proportion of early-stage cancer, a non-significant association was observed for cancer patients with high CRF levels and the risk of all-cause mortality (< 50% of patients with advanced cancer: HR = 0.79; 95%CI = 0.53 to 1.19; p = 0.26; I^2 = 50%) compared to those with low CRF levels. Results differed when data were derived from the univariable model (< 50% of patients with advanced cancer: HR = 0.82; 95%CI = 0.69 to 0.98; p = 0.03, I^2 = 77%).

Cancer type. Ten studies were undertaken for CRF on all-cause mortality (Supplementary Figure 5) [37, 39, 44, 61, 63, 65-68, 70]. For the multivariable model in lung cancer (n = 5), cancer patients with high CRF levels had a significant 31% reduced risk of all-cause mortality (HR = 0.69; 95%CI = 0.50 to 0.96; p = 0.03; I^2 = 73%) compared to those with low CRF levels. Results were similar when data were derived from the univariable model for lung cancer (HR = 0.65; 95%CI = 0.47 to 0.91; p = 0.01; I^2 = 81%). For digestive and haematologic cancer only the univariable models were available and a non-significant association was observed for cancer patients with high CRF levels and the risk of all-cause mortality for digestive (HR = 0.86; 95%CI = 0.67 to 1.09; p = 0.20; I^2 = 67%) and haematologic cancer (HR = 0.28; 95%CI = 0.07 to 1.08; p = 0.06; I^2 = 62%) compared to those with low CRF levels.

Figure 4

3.3.2. Main model analyses for changes per unit increment

Main model. Six studies were undertaken for CRF on all-cause mortality (Figure 5) [34, 38, 39, 45, 48, 71]. For the multivariable model, a non-significant association was observed for unit increments in CRF in cancer patients and the risk of all-cause mortality (HR = 0.89; 95%CI = 0.76 to 1.04; p = 0.13). Heterogeneity was I^2 = 96%, and no outliers were identified. Results were similar when data were derived from the univariable model (HR = 0.88; 95%CI = 0.76 to 1.02; p = 0.09; I^2 = 95%).

Figure 5

Cancer stage and type. There was an insufficient number of studies to examine changes per unit increment in CRF on all-cause mortality, when stratifying by cancer stage and type.

3.4. Cardiorespiratory fitness – Cancer-specific mortality

3.4.1. Main model analyses for cut-off values

Main model. Three studies were undertaken for CRF on cancer-specific mortality (Supplementary Figure 6) [34, 63, 72]. For the multivariable model, a non-significant association was observed for cancer patients with high CRF levels and the risk of cancer-specific mortality (HR = 0.34; 95%CI = 0.08 to 1.38; p = 0.13) compared to those with low CRF levels. Heterogeneity was I^2 = 94%. Results were similar when data were derived from the univariable model (HR = 0.51; 95%CI = 0.13 to 1.93; p = 0.32; I^2 = 96%).

Cancer stage and type. There was an insufficient number of studies to examine changes per unit increment in CRF on cancer-specific mortality, when stratifying by cancer stage and type.

3.4.2. Main model analyses for changes per unit increment

Main model. Two studies were undertaken for CRF on cancer-specific mortality (Supplementary Figure 6) [34, 72]. For the multivariable model, unit increments in CRF in cancer patients were associated with a significant 18% reduction of the risk of cancer-specific mortality (HR = 0.82; 95%CI = 0.69 to 0.98; p = 0.03). Heterogeneity was I^2 = 90%.

Cancer stage and type. There was an insufficient number of studies to examine changes per unit increment in CRF on cancer-specific mortality, when stratifying by cancer stage and type.

4. Discussion

To the best of our knowledge, this is the first systematic review with meta-analysis examining the association between muscle strength and/or CRF, measured after cancer diagnosis, on all-cause and cancer-specific mortality in adults diagnosed with any form of cancer; and whether the association were affected by type and/or stage of cancer. There are two important findings. First, both muscle

strength and CRF were significantly associated with a lower risk of all-cause and cancer-specific mortality in patients with any form of cancer. Such findings were evident when analysing both the cut-off values (i.e., high *vs*. low) as well as change per unit increment in physical fitness components. Second, when considering cancer stage, muscle strength and CRF were significant predictors of all-cause mortality especially in patients with advanced cancer, and physical fitness components were also associated with a lower risk of mortality, specifically in lung and digestive system cancers. For cancer-specific mortality, considering the lack of studies, analyses by type and/or stage of cancer could not be performed. Collectively, such findings emphasize the importance of examining muscle strength and CRF in clinical practice to determine the mortality risk in patients with cancer, especially those with advanced cancer. Furthermore, implementing tailored exercise prescriptions to enhance muscle strength and CRF in patients with cancer may help to reduce cancer-related mortality [73].

a. Muscle strength

Our meta-analysis showed that higher muscle strength (i.e., cut-off values) as well as change per unit increment in muscle strength in patients with cancer resulted in a significant reduction in the risk of all-cause mortality by 11 to 31% (HR = 0.69 to 0.89). These findings are in line with previous reviews in apparently healthy subjects, observing that greater muscle strength is a significant predictor of all-cause mortality [5, 15]. In contrast, Garcia-Hermoso et al. [12] found a lower risk reduction (i.e., 2-3%) compared to our results (i.e., 11 to 31%), when examining cancer mortality risk. However, as mentioned above, in this previous work muscle strength assessment was measured in healthy adults before the diagnosis of cancer, whilst our meta-analysis included only studies which measured muscle strength after a cancer diagnosis. Similarly, Ezzatvar et al. [16] observed that both cut-off values as well as change per unit increment in muscle strength resulted in a significant reduction of the risk of all-cause mortality by 15 to 39% in patients with cancer. However, the study was limited to older patients with cancer (i.e., > 60 years), leaving other age ranges still to be investigated. Therefore, our study expands on the current knowledge pertaining to the significant role of muscle strength in predicting all-cause of mortality in any form and stage in adult patients with cancer. Unfortunately, we could not perform the meta-analysis on cancer-specific mortality, owing to the lack of studies investigating muscle strength and death related to cancer only. Our results were consistent in both the univariable and multivariable models and, although, moderate to high heterogeneity was observed (I^2 = 67 to 94%), no outliers were observed and there were no effects on publication bias as well as, increasing the confidence in our findings

In addition, we also observed that when sub-grouping by cancer stage, muscle strength was a strong predictor for all-cause mortality, especially in patients with advanced cancer (i.e., stage 3 to 4). Indeed, when the sample consisted of 50 to 75% or > 75% of patients with advanced cancer, cut-off values and change per unit increment in muscle strength resulted in a significant reduction of all-cause mortality by 8 to 46%. It is worth mentioning that such results were greater compared to the analyses performed in samples where early-stage cancer was predominant (i.e., < 50% of patients with advanced cancer), with a reduction in risk for all-cause mortality ranging from 10 to 33%. Our results are noteworthy especially when considering the detrimental effects of advanced cancer stages, where decreased muscle strength and mass, reduced CRF and heightened fatigue lead to poorer quality of life and increased risk of death [74]. Our findings highlight that muscle strength could potentially be used in clinical practice to determine mortality risk in cancer patients in advanced stages and, therefore, muscle strengthening activities could be employed to increase life expectancy. Lastly, when available, we also performed meta-analyses by cancer type. Only lung and digestive cancers were examined, showing that greater muscle strength in these specific cancer patients was associated with a significant reduction in all-cause mortality by 19 and 41%. Again, considering that lung, colorectal, liver and stomach cancer are among the leading causes of cancer death [75], our results underscore the relevance of muscle strength as a strong predictor of mortality in aggressive and highly prevalent forms of cancer and may be a priority target for exercise prescription.

b. Cardiorespiratory fitness

We observed that high CRF levels (i.e., cut-off values) were significantly associated with a lower risk of all-cause mortality by 46% (HR = 0.54) compared to low CRF levels, whilst no significant association was found when analysing change per unit increment in CRF. Our findings are in line with previous studies which observed that higher CRF was associated with lower risk of all-cause mortality [9, 20]; however, as with muscle strength, these studies were conducted in apparently healthy adults with CRF measured before cancer diagnosis. To the best of our knowledge, only Ezzatvar et al. [19] have investigated whether CRF was a predictor of mortality in patients already diagnosed with cancer. The authors examined both cut-off values as well as changes per unit increments in CRF, finding a significant decrease in mortality by 18 to 48%. However, some limitations should be considered. First, although the inclusion criteria were studies in adult patients with cancer, the authors included one study in children with cancer, who were assessed more than 26 years after their diagnosis [76], another potential study examining CRF and mortality in cancer patients was not included [68], and a study measuring cancer-specific mortality was included in the all-cause mortality analysis [72]. In addition, it is unclear whether the authors examined univariable or multivariable models in the statistical approach, leading to potential confounding factors in the analyses. Taken together, some bias may

have influenced the results that were provided by Ezzatvar et al. [19]. Therefore, our study expands on the current knowledge about CRF and mortality in cancer patients, highlighting how greater CRF is significantly associated with a reduction in all-cause mortality. Such results were confirmed in the univariable model. However, it should be noted that heterogeneity (i.e., I^2) was high, ranging from 86 to 96% and there was an effect on publication bias. Furthermore, our meta-analysis is the first to explore the association between CRF and cancer-specific mortality. Although very few studies were found, unit increments in CRF resulted in a significant decrease in cancer-specific mortality by 18%, whilst no significant associations were observed for cut-off values. However, more research is necessary to clearly elucidate the association between CRF and cancer-specific mortality.

When considering cancer stage, only the sample mainly comprising patients with early-stage cancer (i.e., < 50% of patients with advanced cancer) was available for sub-group analysis, showing no significant associations in the multivariable model, while in the univariable model, there was a significant reduction by 18% in all-cause mortality. The underlying reasons are not fully understood; however, it can be speculated that the multivariable model included only three studies and very few covariates (e.g., age, months since diagnosis, and physical performance status), whilst the univariable model included six studies. In line with this, a significant reduction in all-cause mortality was observed in lung cancer by 31 to 35%, after stratifying by cancer type in both models. This not only further highlights the importance of CRF in the deadliest form of cancer (i.e., lung cancer) [77], but from a practical standpoint, it also underscores the necessity to improve CRF to reduce the risk of mortality. In contrast, no significant associations were observed for haematologic and digestive system cancers. This may be related to the fact that lung cancer results in a greater deterioration in CRF than other forms of cancer and, therefore, preserving CRF levels is of utmost importance when dealing with lung cancer [78]; however, additional research is needed to explore the association between CRF and different cancer types.

c. Strength and limitations

The strengths of the current study are: 1) a large number of studies (n = 42) and cancer patients included (n = 46,694); 2) assessment of both univariable and multivariable models for all-cause and cancer-specific mortality; and 3) subgroup analyses based on cancer stage and type. However, some limitations should be considered. First, our study is limited by the inclusion of exclusively English language publications, potentially leading to language bias and the omission of pertinent research from non-English-speaking authors. In addition, only prospective cohort studies examining muscle strength and/or CRF were included in our review. This limits determining causality of physical fitness changes (e.g., decrease in muscle strength and/or CRF) after cancer-related treatment (e.g.,

chemotherapy) or side-effects (e.g., cancer-related fatigue, sarcopenia, change in body composition) on all-cause and cancer-specific mortality. Second, when examining physical fitness components different methods (e.g., CPET and 6MWT) and measures (e.g., kg force, Fried frailty phenotype index, age-dependent cut-offs, etc) were adopted. In addition, computing different cut-off values together (e.g., Fried frailty phenotype index and age-dependent cut-offs) may have somewhat reduced the internal validity of our findings. Although there is no consensus regarding the threshold for cut-off values, this should be considered when designing prospective studies examining the association between physical fitness and cancer mortality. Finally, most studies lacked reporting of follow-up and covariates for the multivariable models, which is a limitation that future empirical investigations should aim to address.

5. Conclusion

In this systematic review with meta-analysis, we examined the association between muscle strength and/or CRF on all-cause and cancer-specific mortality in patients diagnosed with cancer. We found that cancer patients with high muscle strength or CRF levels presented a significant reduction of the risk of all-cause mortality compared to those with low physical fitness levels. Similar results were also observed when examining change per unit increments in muscle strength or CRF. Furthermore, muscle strength and CRF were significant predictors of all-cause mortality, particularly of patients with advanced cancer; and physical fitness components were also associated with reduced mortality risk in lung and digestive system cancers. Lastly, unit increments in CRF were also associated with a significant reduced risk of cancer-specific mortality. This underscores the importance of assessing physical fitness in clinical practice for predicting mortality in cancer patients. Moreover, from a practical perspective, implementing tailored exercise prescriptions to enhance muscle strength and CRF throughout the cancer continuum may contribute to reducing cancer-related mortality.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contributors

FB is guarantor. FB conceived the study design, searched studies in the databases, extracted data, run statistical analysis, elaborated results, and drafted the manuscript; PL conceived the study design, run statistical analysis, and drafted the manuscript; VN conceived the study design, searched studies in the databases, extracted data, and drafted the manuscript; LM, GQ, EB extracted data and drafted the manuscript; UC, EV searched studies in the databases and drafted the manuscript; DAG, DRT, CB, and RUN conceived the study design, edited and revised the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

Competing interests

None declared.

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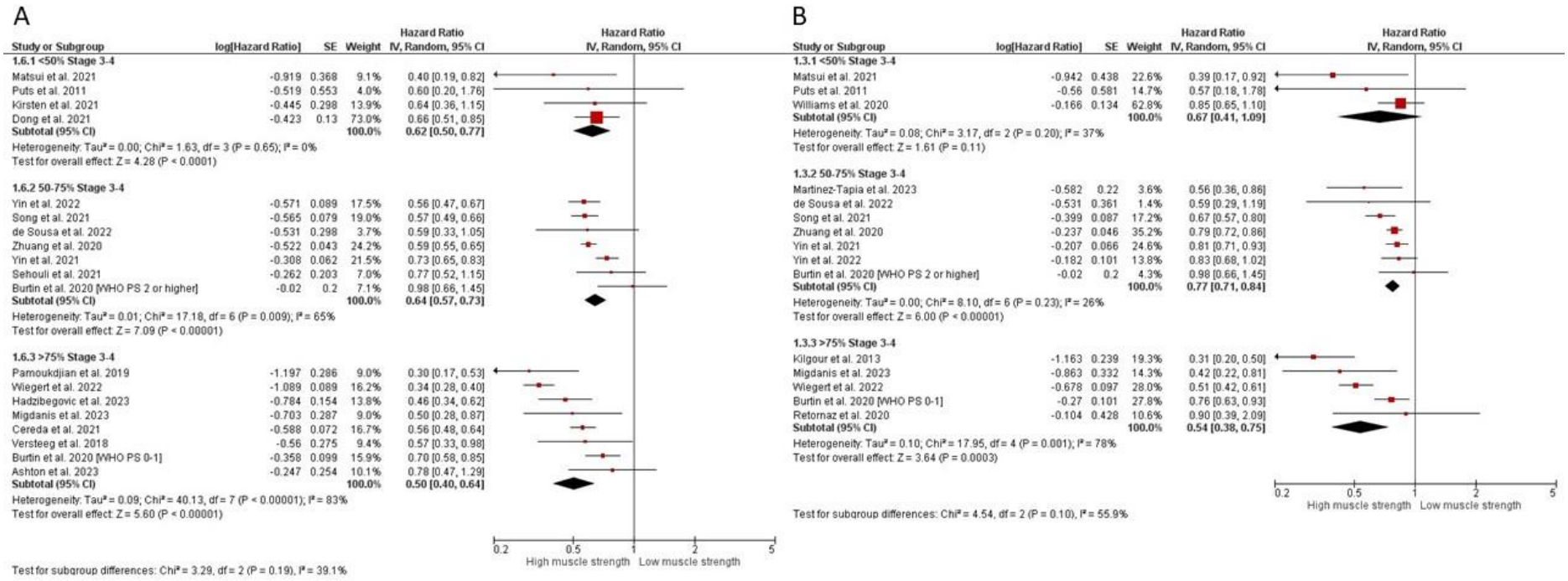

Figure 1. Association of high *vs.* low muscle strength levels (i.e., cut-off values) on all-cause mortality in patients with cancer according to cancer stage, univariable (A) and multivariable (B) models.

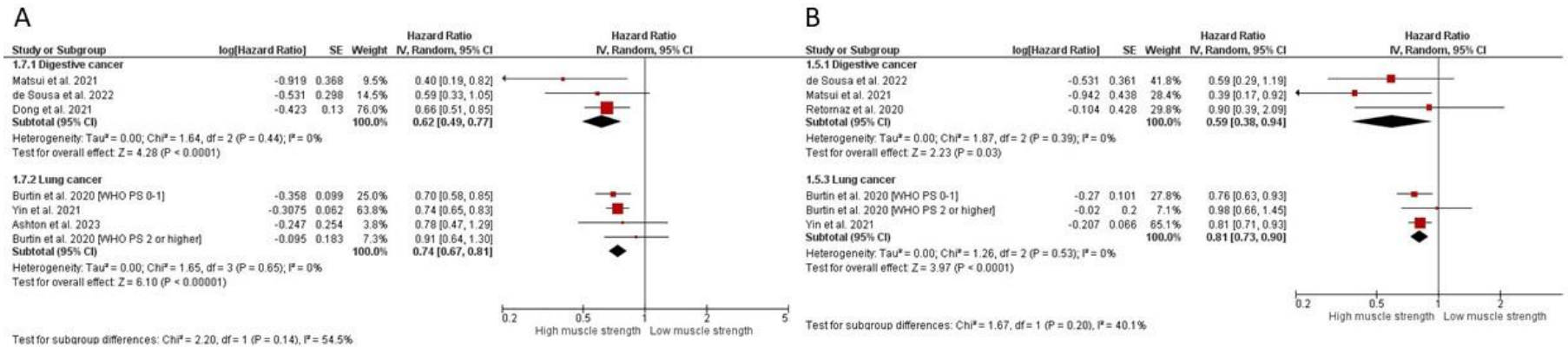

Figure 2. Association of high *vs.* low muscle strength levels (i.e., cut-off values) on all-cause mortality in patients with cancer according to cancer type, univariable (A) and multivariable (B) models.

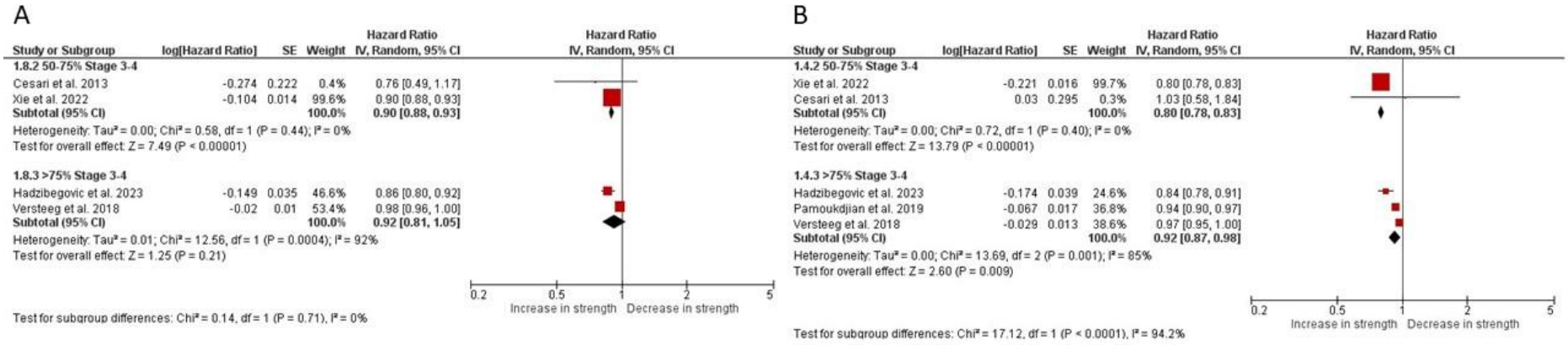

Figure 3. Association of changes per unit increments in muscle strength on all-cause mortality in patients with cancer according to cancer stage, univariable (A) and multivariable (B) models.

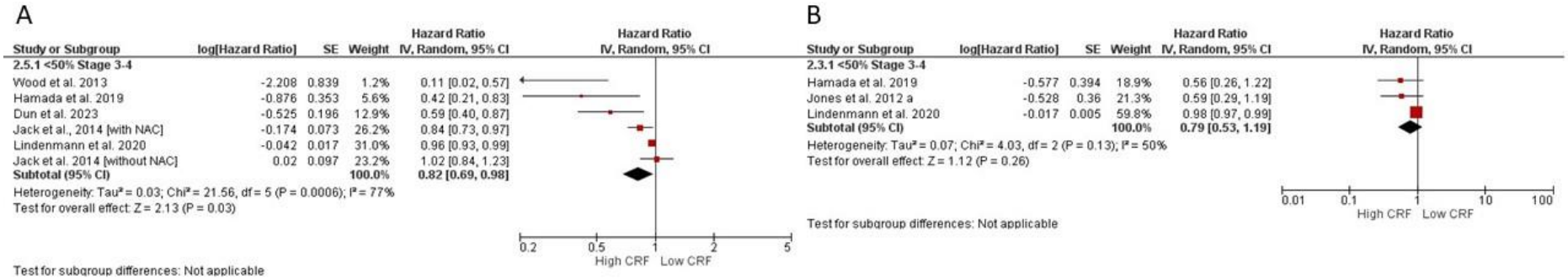

Figure 4. Association of high *vs.* low cardiorespiratory fitness levels (i.e., cut-off values) on all-cause mortality in patients with cancer according to cancer stage, univariable (A) and multivariable (B) models.

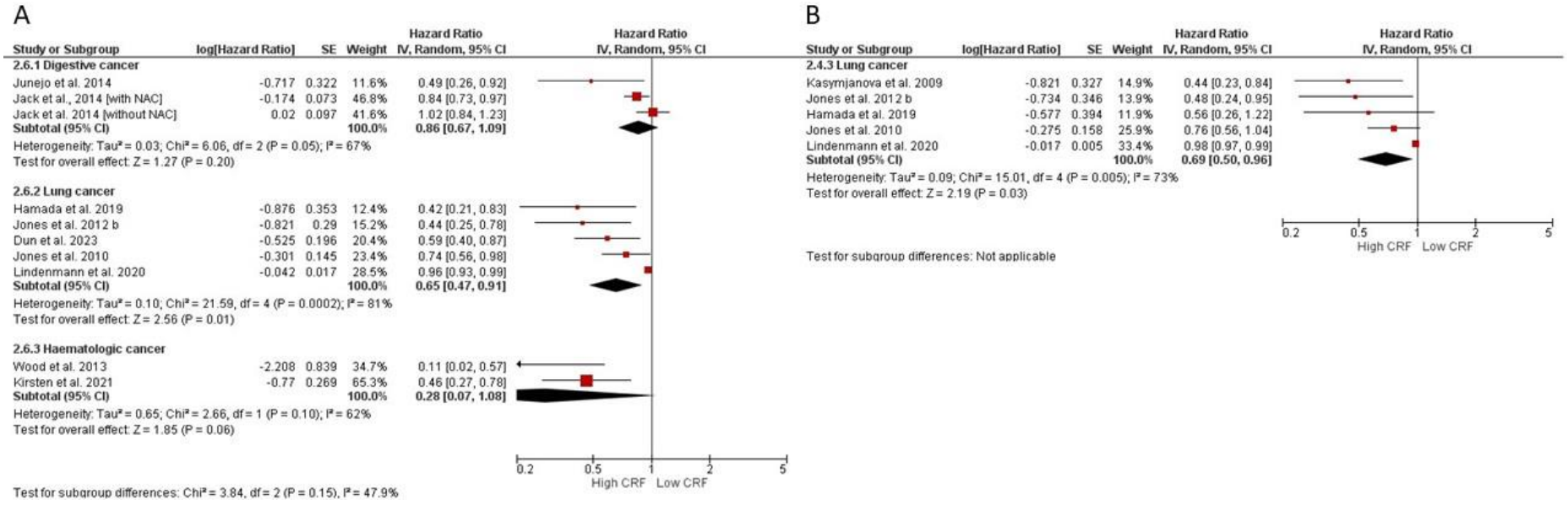

Figure 5. Association of high *vs.* low cardiorespiratory fitness levels (i.e., cut-off values) on all-cause mortality in patients with cancer according to cancer type, univariable (A) and multivariable (B) models.

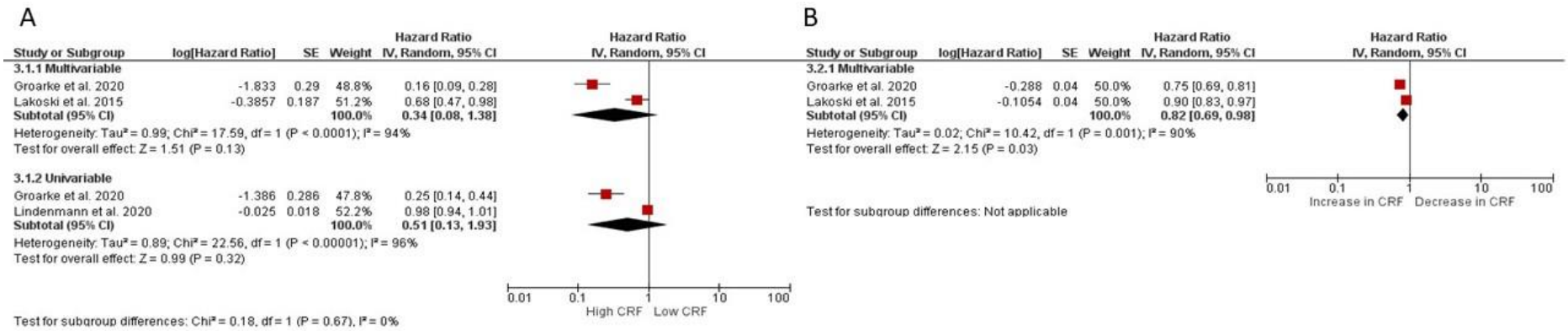

Figure 6. Association of high *vs.* low cardiorespiratory fitness levels (i.e., cut-off values - A) and changes per unit increments in CRF (B) on cancer-specific mortality in patients with cancer.