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FULL RESEARCH PAPER
Cardiac rehabilitation

Cardiac rehabilitation and frailty: a systematic review and meta-analysis

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Aims Frailty among cardiac rehabilitation (CR) participants is associated with worse health outcomes. However, no literature synthesis has quantified the relationship between frailty and CR outcomes. The purpose of this study was to examine frailty prevalence at CR admission, frailty changes during CR, and whether frailty is associated with adverse outcomes following CR.

Methods and results We searched CINAHL, EMBASE, and MEDLINE for studies published from 2000 to 2023. Eligible studies included a validated frailty measure, published in English. Two reviewers independently screened articles and abstracted data. Outcome measures included admission frailty prevalence, frailty and physical function changes, and post-CR hospitalization and mortality. Observational and randomized trials were meta-analysed separately using inverse variance random-effects models. In total, 34 peer reviewed articles (26 observational, 8 randomized trials; 19 360 participants) were included. Admission frailty prevalence was 46% [95% CI 29–62%] and 40% [95% CI 28–52%] as measured by Frailty Index and Kihon Checklist (14 studies) and Frailty Phenotype (11 studies), respectively. Frailty improved following CR participation (standardized mean difference (SMD): 0.68, 95% CI 0.37–0.99; $P < 0.0001$; six studies). Meta-analysis of observational studies revealed higher admission frailty and increased participants' risk of all-cause mortality (hazard ratio: 9.24, 95% CI 2.93–29.16; $P = 0.0001$; four studies). Frailer participants at admission had worse physical health outcomes, but improved over the course of CR.

Conclusion High variability in frailty tools and CR designs was observed, and randomized controlled trial contributions were limited. The prevalence of frailty is high in CR and is associated with greater mortality risk; however, CR improves frailty and physical health outcomes.

Registration PROSPERO: CRD42022311765.

Lay summary Frailty levels are high in cardiac rehabilitation and elevate the risk of adverse health outcomes; however, participating in cardiac rehabilitation may improve prognosis.

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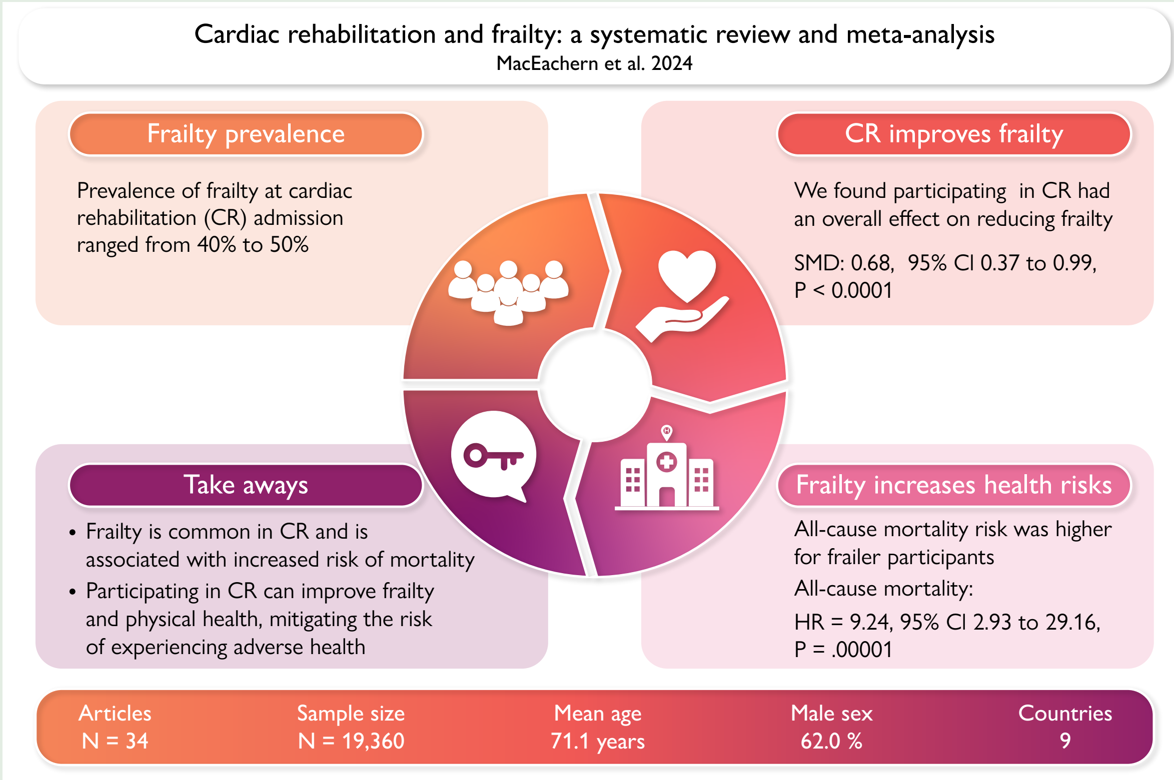
Graphical Abstract



Keywords Cardiac rehabilitation • Frailty • Cardiovascular • Systematic review • Meta-analysis

Key findings

- A large proportion of people in cardiac rehabilitation were frail. Frailty levels were improved by participating in cardiac rehabilitation, especially for those who were frailer at admission.
- Higher baseline frailty levels were associated with a greater risk of hospitalization and mortality and a reduced likelihood of completing the intervention.

Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and hospitalization.[1,2] Advancements in healthcare have seen a rise in longevity among people living with CVDs;[3,4] however, these individuals are also burdened with co-occurring health problems of aging.[5] The individual variability in health and age implies that certain people will live with more favourable CVD prognoses than others.[6] Frailty assessment is a robust method of quantifying health in aging, which characterizes the heterogeneity in the accumulation of health problems with age and decreased resiliency to physiological stress.[7,8] Frailty is characterized by the pace at which individuals will accumulate health problems over time—some rapidly, others gradually—allowing for comparison in health among age-matched peers.[9] Frailty is more prevalent among those living with CVD,[9] and the combination of CVD and frailty is associated with an elevated risk of morbidity[10,11] and mortality.[12] Accordingly, our aging global demographic suggests an urgent need for a care pathway that can manage CVD and frailty concurrently.

Cardiac rehabilitation (CR) is the standard of care to facilitate CVD recovery through exercise therapy, nutritional and medical management, risk factor modification, psychosocial support, and patient education.[13–15] Evidence suggests that the benefits of CR can extend beyond improvements in the secondary prevention of CVD to mitigate age-related health deficits.[16–19] Despite the growing volume of research examining frailty in CR,[11,12,16–18,20–22] a systematic analysis to examine the association of frailty and CR is lacking. Here, we conduct a systematic review and meta-analysis to better understand: (1) the prevalence of frailty at CR admission among the included studies where frailty was reported; (2) frailty changes during CR; and (3) whether frailty is associated with adverse outcomes (physical functioning, mortality, completion rate) following CR.

Materials and methods

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[23] and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[24] frameworks (see Supplementary material online, *Appendix A*). Our review was registered on PROSPERO (ID: CRD42022311765) and the Open Science Framework.

Data sources and searches

We searched EMBASE, CINAHL, and MEDLINE and developed a search strategy with a library scientist. Our search strategy can be found in Supplementary material online, Appendix A.1–3. We also searched PROSPERO and the Cochrane Reviews Library for relevant reviews. Final search results were exported to EndNote X9.3.3 (Bld:15659, Clarivate, Philadelphia, PA)[25] and Covidence (v2716, Veritas Health Innovation Ltd, Melbourne, Australia)[26] to remove duplicates.

Study selection

Reviewers E.M. and J.Q. performed a training exercise to ensure reviewer consistency. A random set of 100 titles and abstracts were used to identify articles meeting the eligibility criteria to ensure congruity of article selection. Reviewers E.M. and J.Q. then independently evaluated titles and abstracts and completed a full-text review of all eligible articles from the title and abstract screening process. Author E.M. identified grey literature by manually searching reference lists of articles which met eligibility criteria; including conference abstracts submitted to various journals generated by our search. All conflicts were resolved between reviewers and no third-party discussions were required. Results of grey literature are only reported in Supplementary material online, Appendix A.4. Eligible articles were observational studies or randomized controlled trials (RCTs) which included a validated measure of frailty in participants referred to CR. Eligible studies were published in English between 2000 and 2023. Articles were excluded if they did not capture frailty using a recognized assessment,[27] only reported on qualitative data, or were not written in English.

Data extraction and quality assessment

Reviewers E.M. and J.Q. developed a data extraction chart referring to the CONSORT data extraction checklist (2010) (see Supplementary material online, Appendix B). Reviewers E.M. and J.Q. independently extracted data on article characteristics, patient demographics, CR characteristics, frailty, physical function, and adverse events. Observational studies were evaluated for risk of bias using the RoBINS-E tool (Risk Of Bias In Non- randomized Studies of Exposures).[28] RCTs were evaluated for risk of bias using the RoB2 tool (Risk of Bias).[29] Results can be found in Supplementary material online, Appendix B.2., Supplementary material online, Appendix D.

Data synthesis and analysis

We meta-analysed prevalence rates of frailty across 25 studies ($n = 17$ 623). Prevalence estimates from each study were weighted based on the inverse variance method. We also meta-analysed frailty change in six studies ($n = 2546$). Proportional contributions of study weights were determined by sample sizes. Standardized mean differences (SMDs) were computed for each study, representing the effect size. Both models used the 'metafor' package in R software and employed a random-effects framework to account for potential heterogeneity among studies. Respective forest plots visually represent the estimated frailty prevalence, change, and 95% CIs for each analysis. The analyses were performed using R version 4.3.1 and RStudio 2023.06.0 + 421. We meta-analysed all-cause mortality by employing an inverse variance random-effects model for effect size combination. Pooled effect sizes were calculated with 95% CIs using RevMan 5.4. Following the Cochrane Handbook, observational studies and RCT were meta-analysed independently.[30] We qualitatively explored diverse study designs, without a formal meta-analysis, to synthesize the relationship between frailty and physical health outcomes (e.g. grip strength, walking tests) measured in CR, considering variations of admission, discharge, and post-discharge measurements (see Supplementary material online, Appendix C, Supplementary material online, Table S3).

Funding source

No financial support was provided for the conduct of this systematic review.

Equity, diversity, and inclusion statement

The systematic review and meta-analysis conducted herein did not explicitly consider equity, diversity, and inclusion factors pertaining to study participants. While these factors are recognized as crucial for comprehensive analysis and interpretation of research findings, they were not incorporated into the present study's methodology.

Results

In total, 1807 articles were identified from the search; 463 duplicates were removed (*Figure 1*). Of the remaining 1344 articles, 134 met the criteria for full-text review. After full-text review, 45 articles (26 observational studies, 8 RCTs, and 11 abstracts) were included in this review. Data from abstracts are reported in Supplementary material online, Appendix A.4 only.

Study characteristics

Thirty-four peer reviewed articles represented nine geographic locations: Japan ($n = 19$),[10–12,31–46] Canada ($n = 5$),[16,21,22,47,48] Lithuania ($n = 3$),[49–51] USA ($n = 2$),[20,52] Australia ($n = 1$),[17] China ($n = 1$),[53] Italy ($n = 1$),[54] Germany ($n = 1$),[55] and the UK ($n = 1$).[56] A total sample of 19 243 participants (mean age = 71.1, 64.8% male) were included; two studies did not report mean age,[17,47] one article did not report sex.[47] Articles evaluated frailty on CR participants with a history of mixed CVDs ($n = 15$),[11,12,16,20–22,33–35,43,45,46,48,52,54] heart failure (HF) ($n = 10$),[10,17,31,36,37,39–42,44] and cardiac surgery ($n = 8$).[32,47,49–51,53,55,56] Observational studies used retrospective ($n = 20$)[10–12,16,20–22,32,34–36,38,39,42,43,46–48,52,53] and prospective cohort designs ($n = 6$),[31,33,44,45,54,55] the eight remaining articles were RCTs.[17,37,40,41,49–51,56] CR programmes were described as Phase II outpatient care ($n = 20$, 58.8%),[11,16,17,20–22,31,33–36,38,40,43,45,47–49,52,56] Phase I inpatient care ($n = 5$, 14.7%),[12,32,37,46,55] or multi-phased (i.e. inpatient-to-outpatient care; $n = 6$, 17.6%);[10,39,41,50,51,53] three articles (8.8%) did not report the phase of CR (*Table 1*, Supplementary material online, *Table S1*).[42,44,54] CR programmes were generally supervised, provided aerobic or resistance type exercise at a moderate intensity, 60 min in duration, and occurred twice per week. CR duration ranged from a low of 6–10 days[37] to high of 24 weeks.[17,35] Further details on CR programme characteristics are provided in Supplementary material online, Appendix C.1. – Supplementary material online, *Table S1*.

Frailty assessment tools

Observational studies most often assessed frailty by the Frailty Phenotype[8] (or modified versions) ($n = 12$),[10,12,31–33,42,44–47,52,53] FI[7] ($n = 10$),[16,20–22,36,46–48,54,55] or Kihon Checklist ($n = 5$);[11,34,35,38,43] a 25-item frailty tool that is similar to the FI that was used in Japan-based cohorts.[57] RCTs used a combination of the Frailty Phenotype,[37,40,41,56] Kihon Checklist,[40] Clinical Frailty Scale,[41] Edmonton Frail Scale (EFS),[49–51,56] and FI.[17] Six studies assessed frailty using multiple tools (*Table 2*).[32,36,40,41,46,56] Frailty distinctions were

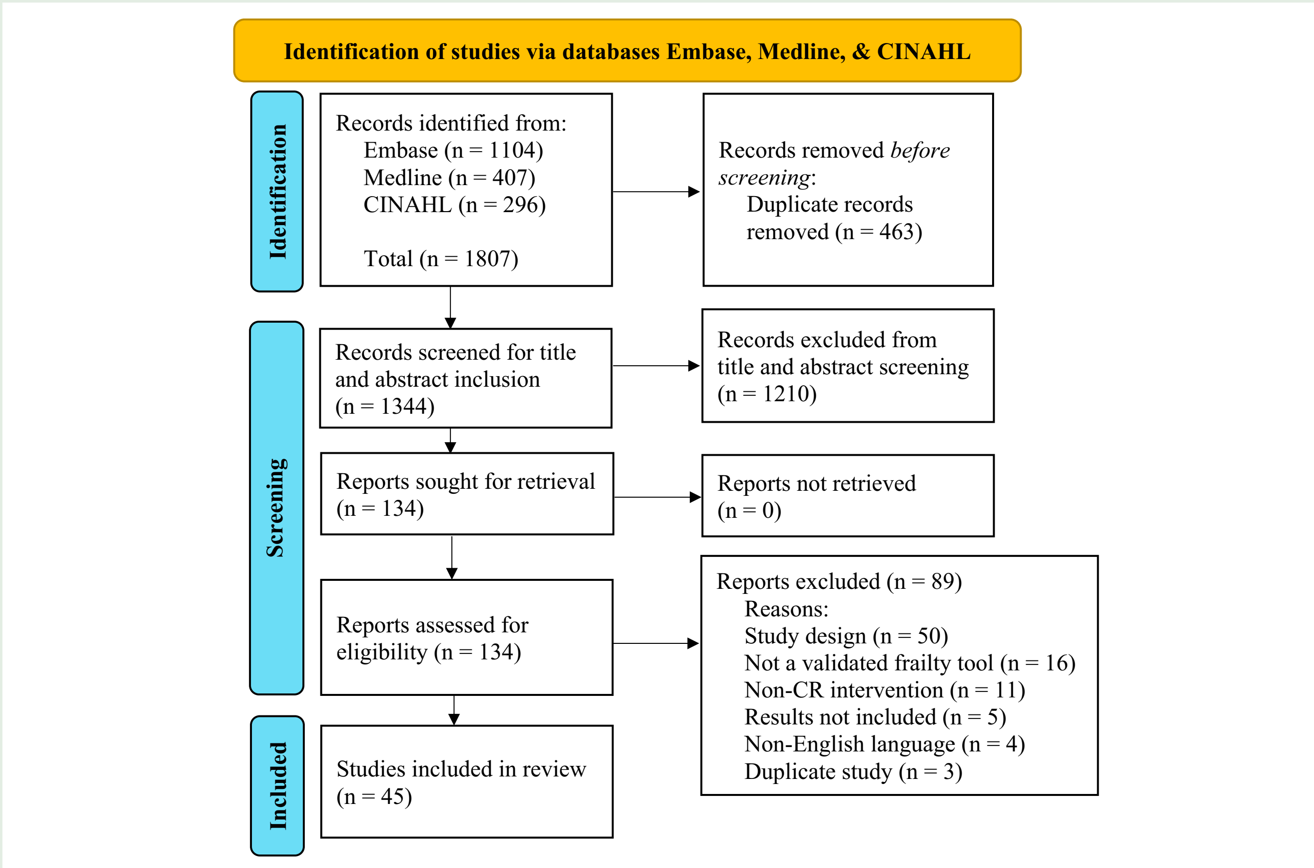


Figure 1 PRISMA flow diagram of systematic review search results.

often described as robust/non-frail, pre-frail, or frail and severely frail (*Table 2*). Frailty cut-offs or degrees of frailty varied among studies depending on the frailty tool. Unless indicated by study authors, we defined frailty as ≥0.20, pre-frailty as 0.10–0.19, and robust at <0.10 for studies using a FI for ease of comparisons with the Frailty Phenotype categorizations.

Prevalence of frailty at cardiac rehabilitation admission

Included articles assessed frailty prevalence at CR admission ($n = 30$),[11,12,16,17,20–22,32–37,39–46,48–56] CR discharge ($n = 10$),[10,21,31,40,42,44,50,53,55,56] or prior to CR admission ($n = 1$);[47] one article did not report the time of frailty assessment (*Table 2*).[38] Pooled prevalence of admission frailty within observational studies varied by tool. Frailty measured by both the FI[16,21,22,46,48,54,55] and Kihon Checklist[11,34,35,43] (*Figure 2A*), and with the Frailty Phenotype[10,12,31–33,42,44–47,53] (*Figure 2B*) were 46 and 43%, respectively. The pooled prevalence of frailty from all measures was 50% from RCTs; admission frailty prevalence was 40% with the frailty phenotype prevalence (*Figure 2B*). Seven articles discussed sex differences.[10,12,16,17,34,35,54] Five articles reported a significantly higher prevalence of frailty in females vs. males.[10,12,16,17,35] Honzawa and colleagues (2022) and Bencivenga et al. found no associations between sex and frailty.[34,54]

Frailty changes in cardiac rehabilitation

Nine observational articles[16,20,21,44,45,48,52,53,55] and three RCTs[17,40,56] explored frailty changes in CR. Overall, 10 articles found that completing CR was associated with lower frailty levels from admission to completion,[16,17,20,40,44,45,48,52,53,55] one article reported no overall effect of frailty change in CR ($P = 0.491$),[21] and one RCT reported an increase in frailty with the Frailty Phenotype, whereas, there was a reduction with the EFS three months post CR and then an increase in frailty 6 months post CR.[56] Other articles found frailty improvements could be sustained over periods of 4[52] and 6 month follow-up from CR admission.[17] We were able to meta-analyse frailty change from six observational studies, demonstrating an overall effect (SMD; 0.68, 95% CI 0.37–0.99; $P < 0.0001$) of frailty improvement in CR (*Figure 3*).[21,38,48,52,53,55] However, when removing the study by Quach et al.,[48] which contributed to over 80% of meta-analysis weight, sensitivity analysis revealed that there was no overall effect of CR on frailty change (SMD; 0.97, 95% CI −0.55 to 2.49; $P = 0.212$). CR provided clinically meaningful frailty improvements (FI change ≥0.03)[58] in three[16,17,48] of the four[16,17,21,48] articles that considered clinically meaningful changes. Two studies reported a small proportion (14.1%[16] and 6.1%[20]) of CR participants who had worsening frailty levels.[16,20] Four articles found frailty improvements were most pronounced among frailer participants at CR admission (Frailty Phenotype: five points;[52] FI range: 0.03[17] to >0.15[16])[16,17,21,52] Only one article reported on pedatric frailty levels in CR (≥5 years old, mean age = 16.8), where median

Table 1 Characteristics of articles

Author, year, and study design	Country of origin	Participant characteristics	Male sex (%)	Cardiac rehabilitation programme description	Assessment times	Primary outcomes
Observational Studies						
Adachi et al., 2023[31] Longitudinal study	Japan	2697 adults with HF Mean age = 76	60.4%	Outpatient CR—exercise training, patient education, and patient counselling	Baseline measures: Admission to CR Follow-up measures: CR discharge at 150 days, and every 4 months for 2 years	Rehospitalization and all-cause mortality, CR participation on HF prognosis
Aida et al., 2020[12] Longitudinal study	Japan	895 adults with various CVD Mean age = 76	60.4%	Inpatient CR—Programme not described	Baseline measures: Admission to CR Follow-up measures: All-cause mortality and unplanned readmission for CVD was measured up to hospital discharge (range 128–463 days)	All-cause mortality and unplanned CVD hospital readmission
Arai et al., 2019[32] Longitudinal study	Japan	78 adults having cardiac surgery Mean age = 71.7 ± 11.8	56.0%	Inpatient CR—Programme not described	Baseline measures: Prior to receiving cardiac surgery Follow-up measures: Upon post-operative hospital discharge (mean length 20.5 ± 10.2 days)	Time to 100 m walking mobility
Bencivenga et al., 2022[54] Longitudinal study	Italy	559 adults with various CVD Mean age = 72 (69–76)	69.2%	Phase of CR not described. CR described as a comprehensive, multidisciplinary intervention	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (duration not reported)	Frailty and 6MWD
Eichler et al., 2017[55] Longitudinal study	Germany	136 adults with elective TAVI Mean age = 80.6 ± 5	47.8%	Inpatient CR—standardised multicomponent CR	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (3 weeks)	Physical capacity, frailty, and quality of life
Hashimoto et al., 2022[33] Longitudinal study	Japan	52 adults with various CVD Mean age = 76.9 ± 6.8	53.8%	Outpatient CR—comprehensive programme with supplemental balance exercise assist robot	Baseline measures: Upon discharge from acute care Follow-up measures: 4 months post-CR discharge	Exercise on balance improvement
Hermsen et al., 2022[52] Longitudinal study	USA	120 pediatric-onset CVD patients Mean age = 16.8	51.7%	Outpatient CR—personalized exercise programme	Baseline measures: Admission to CR Follow-up measures: Every 30 days after discharging up to 120 days	Baseline frailty and frailty change
Hillier et al., 2023[22] Longitudinal study	Canada	3756 adults with various CVD Mean age = 61.5	72.8%	Outpatient CR—Group based exercise, education, nutrition, and medication reconciliation	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (12 weeks)	CR completion
Honzawa et al., 2020[35] Cross-sectional study	Japan	255 adults with various CVD Mean age = 74.9 ± 5.8	67.0%	Outpatient CR—medical evaluation, exercise therapy education on secondary prevention, and psychosocial support	Baseline measures: Admission to CR Follow-up measures: No follow-up	Frailty and anxiety

Continued

Table 1 *Continued*

Author, year, and study design	Country of origin	Participant characteristics	Male sex (%)	Cardiac rehabilitation programme description	Assessment times	Primary outcomes
Honzawa et al., 2022[34] Longitudinal study	Japan	137 adults with various CVD Mean age = 65.8 ± 13.0	71.0%	Outpatient CR—multicomponent intervention on risk stratification, exercise, education, and psychosocial support	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (5 months)	Physical function and anxiety by admission frailty
Kamiya et al., 2020[36] Longitudinal study	Japan	862 adults with HF Mean age = 66.9 ± 14.2	61.6%	Outpatient CR—Supervised and unsupervised portions of exercise training and multidisciplinary guidance on HF management	Baseline measures: Admission to CR Follow-up measures: Up to 5 years (median 2.4 years)	All-cause mortality and HF rehospitalization
Kato et al., 2021[38] Longitudinal study	Japan	29 patients attending CR prior to COVID-19 Mean age = 79.7 ± 6 Only 15 remained eligible following interruption of programme due to COVID-19	26.7%	Outpatient CR—Supervised and unsupervised exercise training. Programme interruptions due to COVID-19	Three assessment times: Baseline measures: Before nationwide state of emergency (COVID-19) in Japan (T1) Follow-up measures: post-state of emergency (T2) and 12 weeks after the resumption of outpatient CR (T3)	Frailty, physical function and activity (SPPB, hand grip strength, sit-to-stand, gait speed)
Kehler et al., 2020[16] Longitudinal study	Canada	2322 adults with various CVD Mean age = 62.26	75.3%	Outpatient CR—Group based exercise, education, nutrition, and medication reconciliation	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (12 weeks)	Frailty change
Kimber et al., 2018[47] Longitudinal study	Canada	235 CABG or valve surgery patients 188 in analysis 114 followed up in clinic		Outpatient CR—comprehensive, multidisciplinary lead with education and exercise training. Supplemented with optional additional education and voluntary exercise sessions	Baseline measures: Pre-operative cardiac surgery Follow-up measures: 1-year post-operatively	CR completion
Kunimoto et al., 2019[11] Cross-sectional study	Japan	845 adults with various CVD Mean age = 71	69.1%	Outpatient CR—Medical evaluation, exercise therapy, education, and support of psychosocial factors	Baseline measures: Admission to CR Follow-up measures: No follow-up	Frailty, clinical parameters, risk profiles, and physical function
Lutz et al., 2020[20] Longitudinal study	USA	243 adults with various CVD Mean age = 68	99.0%	Outpatient CR—Exercise and medication reconciliation	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (12 weeks)	Change in gait speed, TUG, tandem stand, hand grip strength, 6MWD
MacEachern et al., 2023[21] Longitudinal study	Canada	132 adults with various CVD Mean age = 64.5 ± 10.5	63.6%	Outpatient CR—comprehensive exercise and education centre- and virtual-based programmes	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (range 6–10 weeks)	Frailty change
Mori et al., 2023[39] Longitudinal study	Japan	183 adults with HF Mean age = 82.5 ± 8.1 years	48.6%	Inpatient and outpatient comprehensive CR programme—Exercise, medication management, nutrition guidance, counselling, risk factor evaluation	Baseline measures: Admission to hospital. Follow-up measures: One week prior to discharge	Dynamic balance and clinical characteristics

Continued

Table 1 *Continued*

Author, year, and study design	Country of origin	Participant characteristics	Male sex (%)	Cardiac rehabilitation programme description	Assessment times	Primary outcomes
Nishihira et al., 2022[42] Longitudinal study	Japan	185 adults with acute myocardial infarction exacerbated by HF Mean age = 85 [IQR: 82–88]	45.9%	Appears to be inpatient Phase I CR—programme not described	Baseline measures: Admission to hospital Follow-up measures: Upon hospital discharge (up to 2 years)	All-cause mortality
Nishitani-Yokoyama et al., 2021[43] Cross-sectional study	Japan	102 adults with various CVD Mean age = 62.7 ± 13.4	67.0%	Outpatient CR—Multicomponent intervention including exercise, education, nutrition, medication, lifestyle, smoking cessation, and psychosocial support	Baseline measures: As close to initiation of CR as possible Follow-up measures: No follow-up	Constipation and association between constipation and frailty
Nozaki et al., 2020[10] Longitudinal study	Japan	387 adults with HF aged >65 Mean age = 74.9 ± 6.1	63.6%	Inpatient and Outpatient CR—comprehensive supervised programme	Baseline measures: Admission to CR Follow-up measures: Upon CR discharge (duration not reported)	Rising time from bed
Quach et al., 2023[48] Longitudinal study	Canada	3371 adults with various CVD Mean age = 61.9 ± 10.7	74.2%	Outpatient CR—Group based exercise, education, nutrition, and medication reconciliation	Baseline measures: Admission to CR Follow-up measures: 5-year follow-up period	Admission frailty and frailty changes during CR with 5-year outcomes
Umehara et al., 2022[44] Longitudinal study	Japan	184 adults with HF Mean age = 81.8	60.8%	Appears to be inpatient CR—personalized for exercise and psychosocial support	Baseline measures: Admission to CR Follow-up measures: Upon CR discharge (duration not reported)	Prognosis of patients by pre-frailty and frailty
Ushijima et al., 2020[45] Longitudinal study	Japan	89 adults with various CVD aged >65 Mean age = 75 ± 6	76.0%	Outpatient CR—Group based exercise, education, nutrition, and medication reconciliation	Baseline measures: Admission to CR Follow-up measures: Upon CR discharge (12 weeks)	Physical function and exercise capacity (lower extremity strength, grip strength, upright posture, gait speed)
Yamato et al., 2022[46] Longitudinal study	Japan	707 adults with various CVD aged >65 Mean age = 76 ± 7	61.9%	Inpatient CR—programme not described	Baseline measures: Upon discharge from hospital Follow-up measures: Up to 2-years	Concordance of different frailty tools
Yu et al., 2021[53] Longitudinal study	China	90 post-procedure TAVI patients Mean age = 74.7 ± 8.1	60.0%	Three phase CR—Phase I: cardiopulmonary function, reduce infection Phase II: reduce complications and promote recovery Phase III: improve motor function and prognosis	Baseline measures: Before TAVI operation Follow-up measures: One month after hospital discharge	Change in self-care, cognition, nutrition, depression, frailty, and exercise capacity
Randomized Trials						
Beigiene et al., 2021[49]	Lithuania	97 adults post-heart surgery Mean age = 72.1 ± 5.3	73.2%	Control group received conventional outpatient CR Intervention group 1 received conventional CR + traditional resistance and balance training Intervention group 2 received conventional CR + resistance and balance training using mechanical devices	Baseline measures: Pre-admission to CR Follow-up measures: Upon CR completion (20 days)	Gait speed by TUG test

Continued

Table 1 *Continued*

Author, year, and study design	Country of origin	Participant characteristics	Male sex (%)	Cardiac rehabilitation programme description	Assessment times	Primary outcomes
Butkuviene et al., 2022[50]	Lithuania	100 adults post-heart surgery Mean age = 73.3	62.0%	Control group received inpatient CR—comprehensive programme, exercise, education, diet counselling, psychosocial support, risk factor management. Control group was asked to maintain usual physical activity regimen Intervention group received inpatient CR + 12 weeks of exercise at home according to individualized plan	Baseline measures: Admission to inpatient CR Follow-up measures: Upon completion of inpatient CR (mean duration 16.3 ± 2.9 days) and upon completion of home-based exercise training (12 weeks)	Functional capacity, 6MWD, and TUG tests
Kato et al., 2021[37]	Japan	28 adults with HF. 24 included in the final analysis Mean age = 72.9 ± 14.7	54.2%	The control group received inpatient CR—6 to 10 day exercise-based intervention The intervention group received a hybrid assisted limb (HAL) support exercise intervention	Baseline measures: Admission to inpatient CR Follow-up measures: Upon CR discharge (6–10 days)	Heart rate, blood pressure, RPE during exercise, days before walking independently, amount of therapy
Mudge et al., 2021[17]	Australia	256 adults with HF Mean age not reported	75.0%	The control group received 12 weeks of weekly one hour education sessions + home-based exercise programme The intervention group received outpatient CR—Supervised individualized exercise programme + education + a home-based exercise programme	Baseline measures: Admission to CR Follow-up measures: 3 months, 6 months, and 12 months for various outcomes	Attendance, 6MWD, physical activity participation, all-cause mortality, or hospital readmission
Nagatomi et al., 2022[40]	Japan	30 adults with HF Mean age = 63.7 ± 10.1	53.0%	The control group received standard care—pharmacological and non-pharmacological therapy but no home-based CR The intervention group received home-based CR—comprehensive education, exercise, and nutrition-based programme	Baseline measures: Admission to CR Follow-up measures: Upon completion of CR (12 weeks)	Change in 6MWD from admission to discharge
Nakaya et al., 2021[41]	Japan	75 adults with HF Mean age = 80.3	49.3%	The control group received inpatient CR—multi-phase programme (I–VI) The intervention group received the inpatient multi-phase CR programme + balance, resistance, and cycling training	Baseline measures: Admission to CR Follow-up measures: Upon CR completion (duration not reported)	SPPB improvement
Rogers et al., 2018[56]	United Kingdom	23 adults with TAVI Mean age = 82	55.0%	The control group received standard of care practices and outpatient clinic follow-up, medical management, and drug therapy The intervention group received outpatient CR—6 week exercise-based CR programme with medical management, drug therapy, and a biopsychosocial assessment	Baseline measures: 30 days post TAVI operation Follow-up measures: 3 months post randomization, 6 months post randomization	Recruitment rate, acceptability and uptake of CR, attrition rates 6MWD, ADLs, frailty, Hospital Anxiety and Depression Scores

Continued

Table 1 *Continued*

Author, year, and study design	Country of origin	Participant characteristics	Male sex (%)	Cardiac rehabilitation programme description	Assessment times	Primary outcomes
Sokas et al., 2023[51]	Lithuania	100 adults who had undergone open-heart surgery Mean age = 73	62.0%	Control group received inpatient CR—exercise-based programme Intervention group received inpatient CR + an additional 12 week home-based exercise programme	Baseline measures: Admission to inpatient CR Follow-up measures: Upon CR completion (Mean duration of 16.3 ± 2.9 days)	Cardiovascular function and heart rate response ADLs, 6MWD, stair climbing, and TUG

6MWD, 6-minute walk distance; ADL, activity of daily living; CABG, coronary artery bypass graft; CR, cardiac rehabilitation; CVD, cardiovascular disease; HF, heart failure; IQR, interquartile range; NR, not recorded; RPE, rate of perceived exertion; SPPB, short physical performance battery; TAVI, transcatheter aortic valve implantation, TUG, timed-up-and-go.

Table 2 **Prevalence rates of frailty at cardiac rehabilitation admission**

				Frailty prevalence			
Author and year	Sample size	Frailty assessment tool	Assessment time	Non-frail (%)	Pre-frail (%)	Frail (%)	Continuous frailty *(mean, SD) **(median, IQR)
Observational studies							
Mori et al., 2023[39]	188	Clinical Frailty Scale	Admission	68.1%	NR	31.9%	NR
Adachi et al., 2023[31]	2697	Frailty Phenotype (modified to FLAGSHIP study)	Discharge (5 months)	60.6%	NR	39.4%	NR
Aida et al., 2020[12]	895	Frailty Phenotype (J-CHS)	Admission	11.3%	45.5%	43.2%	NR
Arai et al., 2019[32]	78	Frailty Phenotype	Admission	57.7%	0.0%	25.6%	*1.7 ± 1.6
		Clinical Frailty Scale	Admission	NR	NR	NR	*3.5 ± 0.9
		SPPB	Admission	NR	NR	24.3%	NR
		Kaigo-Yobo Checklist	Admission	NR	NR	42.3%	*3.2 ± 2.4
Hashimoto et al., 2022[33]	52	Frailty Phenotype (J-CHS)	Admission	7.7%	63.5%	28.8%	NR

Continued

Table 2 Continued

Author and year	Sample size	Frailty assessment tool	Assessment time	Frailty prevalence: Non-frail (%)	Frailty prevalence: Pre-frail (%)	Frailty prevalence: Frail (%)	Continuous frailty *(mean, SD) **(median, IQR)
Hermsen et al., 2022[52]	120	Frailty Phenotype (Items scored 0–2)	Admission	NR	NR	NR	**4 (2–6)
Kimber et al., 2018[47]	186	Frailty Phenotype (7 variables. Added depression, cognition)	Pre-admission	50.5%	NR	49.5%	NR
		Frailty Index	Pre-admission	NR	NR	NR	NR
		Clinical Frailty Scale	Pre-admission	68.1%	NR	31.9%	NR
Nishihira et al., 2022[42]	185	Frailty Phenotype (Dodson)	Admission	59.5%	34.1%	6.5%	NR
			Discharge (NR)	30.3%	31.9%	11.9%	NR
Nozaki et al., 2020[10]	387	Frailty Phenotype (4 outcomes)	Discharge (NR)	46.5%	0.0%	53.5%	NR
Umehara et al., 2022[44]	184	Frailty Phenotype (J-CHS)	Admission	Excluded from study	15.2%	84.8%	NR
			Discharge (NR)	3.8%	42.4%	53.8%	NR
Ushijima et al., 2020[45]	89	Frailty Phenotype	Admission	11.2%	63.0%	25.8%	NR
Yamato et al., 2022[46]	707	Frailty Phenotype	Admission	11.3%	58.6%	30.1%	NR
		Frailty Screening Index	Admission	10.6%	63.1%	26.3%	NR
		FRAIL Scale	Admission	20.5%	53.6%	25.6%	NR
Yu et al., 2021[53]	90	Frailty Phenotype	Admission	NR	NR	83.0%	*3.82 ± 0.9
			30 days post discharge	NR	NR	26.0%	*1.7 ± 1.1
Bencivenga et al., 2022[54]	559	Frailty Index (40-items) Frailty cut off ≥0.25	Admission	47.6%	NR	52.4%	**0.25 (0.19–0.30)
Eichler et al., 2017[55]	122	Frailty Index (Scale 0–7) Frailty cut off ≥3	Admission	63.1%	0.0%	36.9%	*2.1 ± 1.5
			Discharge (3 weeks)	NR	NR	NR	*1.7 ± 1.5
Hillier et al., 2023[22]	3756	Frailty Index (25-items)	Admission	15.0%	0.0%	85.0%	NR
Kamiya et al., 2020[36]	862	Frailty Index (19-items)	Admission	NR	NR	NR	*0.28 ± 0.13
Kehler et al., 2020[16]	2322	Frailty Index (25-items)	Admission	17.8%	NR	82.2%	NR
Lutz et al., 2020[20]	188	Frailty Index	Admission	NR	NR	NR	NR
MacEachern et al., 2023[21]	132	Frailty Index (65-items)	Admission: Center-based CR	90.4%	6.7%	2.7%	*0.14 ± 0.003

Continued

Table 2 *Continued*

Author and year	Sample size	Frailty assessment tool	Assessment time	Frailty prevalence: Non-frail (%)	Pre-frail (%)	Frail (%)	Continuous frailty *(mean, SD) **(median, IQR)
			Discharge: Center-based CR (6 weeks)	NR	NR	NR	*0.14 (SD NR)
			Admission: Virtual CR	91.3%	6.8%	1.7%	*0.07 ± 0.003
			Discharge: Virtual CR (10 weeks)	NR	NR	NR	*0.083 (SD NR)
Quach et al., 2023[48]	3371	Frailty Index (25-items)	Admission	18.0%	NR	82.0%	*0.34 ± 0.13
Honzawa et al., 2020[35]	255	Kihon Checklist (25-items) Frailty cut off ≥8	Admission	29.4%	31.8%	38.8%	NR
Honzawa et al., 2022[34]	137	Kihon Checklist (25-items) Frailty cut off ≥8	Admission	46.0%	29.2%	24.8%	NR
Kato et al., 2021[38]	29	Kihon Checklist (25-items)	NR	NR	NR	NR	NR
Kunimoto et al., 2019[11]	845	Kihon Checklist (25-items)	Admission	33.9%	31.9%	34.2%	NR
Nishitani-Yokoyama et al., 2021[43]	102	Kihon Checklist (25-items)	Admission	31.3%	34.3%	34.3%	NR
Randomized Trials							
Kato et al., 2021[37]	24	Frailty Phenotype	Admission	0.0%	4.2%	95.8%	NR
Nagatomi et al., 2022[40]	30	Frailty Phenotype (J-CHS)	Admission	Excluded from study	67.0%	33.0%	NR
		Kihon Checklist	Admission	NR	NR	NR	*6.1 ± 4.1
			Discharge (12 weeks)	NR	NR	NR	*5.4 ± 2.9
Nakaya et al., 2021[41]	75	Frailty Phenotype	Admission	NR	NR	48.0%	NR
		Clinical Frailty Scale	Admission	NR	NR	22.6%	NR
Rogers et al., 2018[56]	23	Frailty Phenotype	Admission	12.0%	68.0%	20.0%	NR
			Discharge	12.0%	72.0%	16.0%	NR

Continued

Table 2 Continued

Author and year	Sample size	Frailty assessment tool	Assessment time	Frailty prevalence: Non-frail (%)	Pre-frail (%)	Frail (%)	Continuous frailty *(mean, SD) **(median, IQR)
		Edmonton Frail Scale	Admission	NR	NR	NR	*5.25 ± 1.8 (control) *5.08 ± 2.2 (intervention)
			Discharge	NR	NR	NR	*4.5 ± 2.0 (control) *4.4 ± 1.7 (intervention)
Beigjene et al., 2021[49]	97	Edmonton Frail Scale	Admission	20.6%	42.3%	37.1%	**5 (4–6)
Butkuviene et al., 2022[50]	100	Edmonton Frail Scale	Admission	NR	NR	NR	*6.1 ± 1.6
	90		Discharge (12 weeks)	20.0% *2.56 ± 0.62	44.4% *4.45 ± 0.50	35.5% *7.34 ± 1.18	NR
Sokas et al., 2023[51]	100	Edmonton Frail Scale	Admission	NR	NR	NR	*6.1 ± 1.6
Mudge et al., 2021[17]	256	Frailty Index (41-items)	Admission	43.0%	NR	57.0%	**0.22 (0.13–0.31)

J-CHS, Japanese version of Cardiovascular Health Study; NR, not recorded; SPPB, short physical performance battery.

Frailty Phenotype were scores significantly decreased from CR admission to completion.[52] Additional information on frailty changes with CR can be found in Supplementary material online, Appendix C, Supplementary material online, Table S2.

Frailty and health outcomes in cardiac rehabilitation

Frailty was examined in relation to number of hospitalizations,[12,17,31,36,48] hospitalization duration,[10] all-cause mortality (*Figure 4*),[12,17,31,36,42,46,48] and CR programme completion.[16,22,47] A collection of observational studies reported frailer participants at CR admission had a greater risk of rehospitalization[31,48] and all-cause mortality[31,42,46,48] both independently and as a composite outcome.[12,36] Overall, our meta-analysis shows CR participants who were defined as frail at admission had a significantly greater risk of all-cause mortality (*Figure 4*; HR: 9.24, 95% CI 2.93–29.16; $Z = 3.79$; $P = 0.0001$)[31,42,46,48] when compared with non-frail participants over an average follow-up of 2.5 years. Our sensitivity analysis for all-cause mortality removed Quach et al., 2023, which eliminated the heterogeneity (0%) while elevating the risk of all-cause mortality (HR: 13.91 95% CI 12.00–13.91; $Z = 34.88$; $P < 0.0001$). Participation in CR resulted in reduced HF-specific rehospitalization in both the admission frail and non-frail groups,[31] while RCT evidence found frailty levels were not associated with an elevated risk of all-cause mortality or hospitalization (composite outcome) at 12 months from CR admission (OR: 1.60, 95% CI 0.96–2.66, $P = 0.07$).[17] Finally, concordance of frailty diagnosis and all-cause mortality using the Frailty Phenotype, the Frailty Screening Index, and the FRAIL Scale was measured.[46] Analyses determined that there were similar associations between the frailty measures with all-cause mortality.[46]

Frailty and cardiac rehabilitation completion

Three observational studies examined the association of frailty with CR completion.[16,22,47] Two articles found CR non-completers were significantly frailer upon baseline assessment than CR completers,[16,47] and each report showed unit increases in frailty at baseline were significantly associated with CR non-completion.[16,47] The final article found that higher prevalence of frailty-related health deficits were associated with decreased odds of CR completion.[22]

Association of frailty with other outcomes

Higher admission frailty was associated with worse physical health outcomes, such as body mass index (BMI),[10,11,31,34,35,48,54] strength,[11,20,33–35,44,45] walking tests,[11,17,20,32–35,39,44–46,49,50,53,54] and SPPB scores.[33,44,46,54] Frailer CR participants at CR admission had significantly poorer admission BMI,[10,11,34,35,54] strength,[11,20,34,45,46] and were less likely to meet recommended physical activity guidelines.[17] Frailer participants at admission had lower admission 6MWD,[17,20,34,35,46,53] timed-up-and-go (TUG),[39] and 100 m walk[32] scores than non-frail peers. CR participants who were frail at admission had significantly lower SPPB scores at admission,[54] discharge,[10] and among those who did not improve frailty in CR.[44] See Supplementary material online, Appendix C—Supplementary material online, Table S3 for greater detail. Despite these reports, CR participants who were frail at admission could still observe significant improvements in grip[20,45] and lower extremity strength,[33,45] 6MWD,[20,34] gait speed,[20,33,45,49] TUG,[20,33] and SPPB.[33] In fact, TUG[20,33] and SPPB[33]

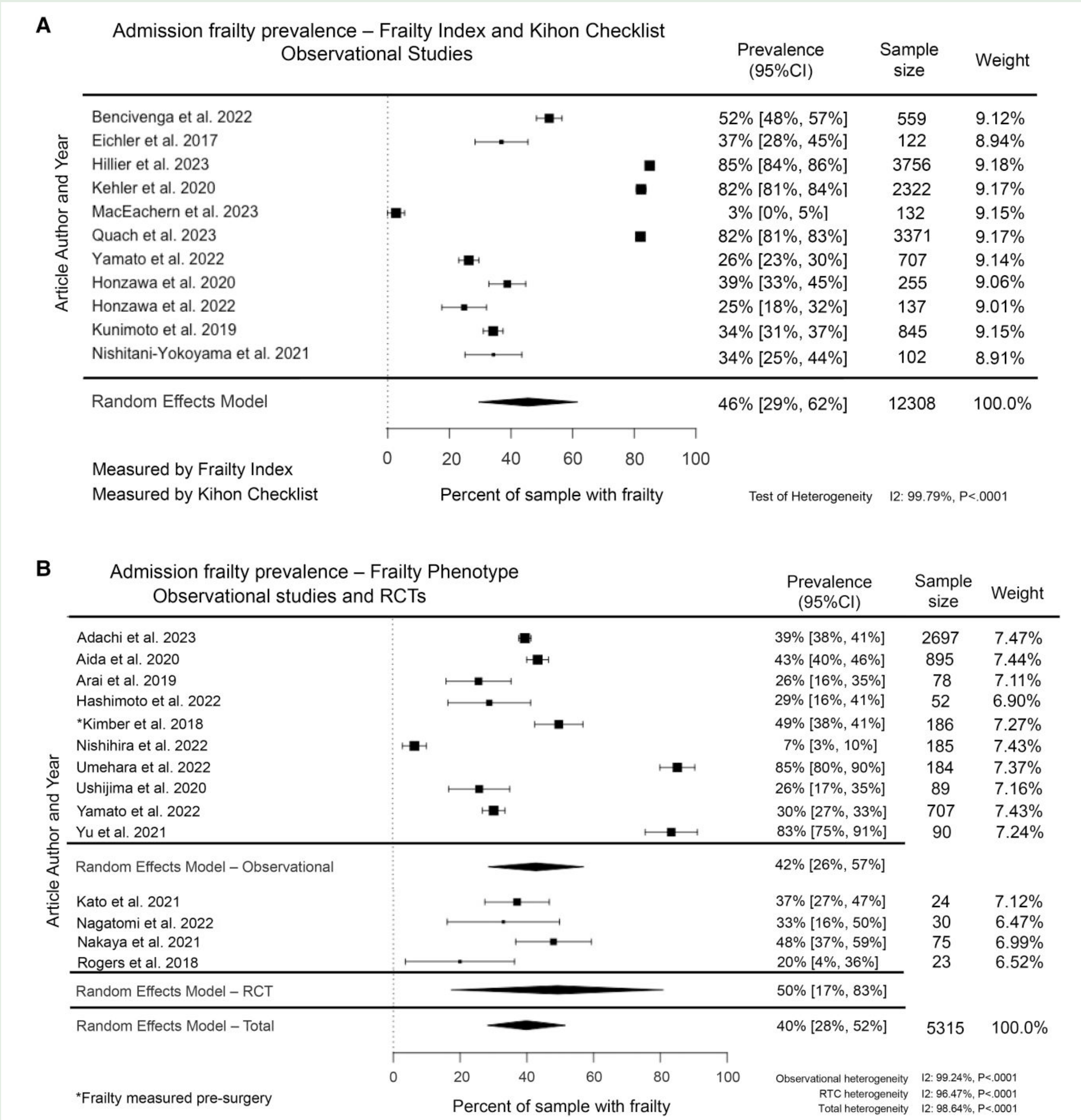


Figure 2 Admission frailty prevalence measured by (*A*) observational studies FI and Kihon checklist and (*B*) observational studies and RCTs frailty phenotype.

improvements were most pronouced in CR participants who were frailer at admission, indicating a greater intervention response.

Discussion

Our systematic review provides an extensive evaluation of the association of frailty with health outcomes in CR. From our investigation, four findings stand out: (1) admission frailty levels in CR are high; (2) CR participation had a moderate overall effect on reducing frailty levels; (3) frailer participants at admission gained the greatest response from CR interventions; and (4) higher admission frailty was associated with poor health outcomes following CR. Collectively, our review suggests that CR has far-reaching implications on the frailty status of CVD patients, extending beyond traditional cardiovascular health management.

We identified that several frailty assessments are used in CR ($n = 8$; *Table 2*), which is common in other analyses of clinical settings of people living with CVD.[59,60] The overall frailty prevalence range from 40 to

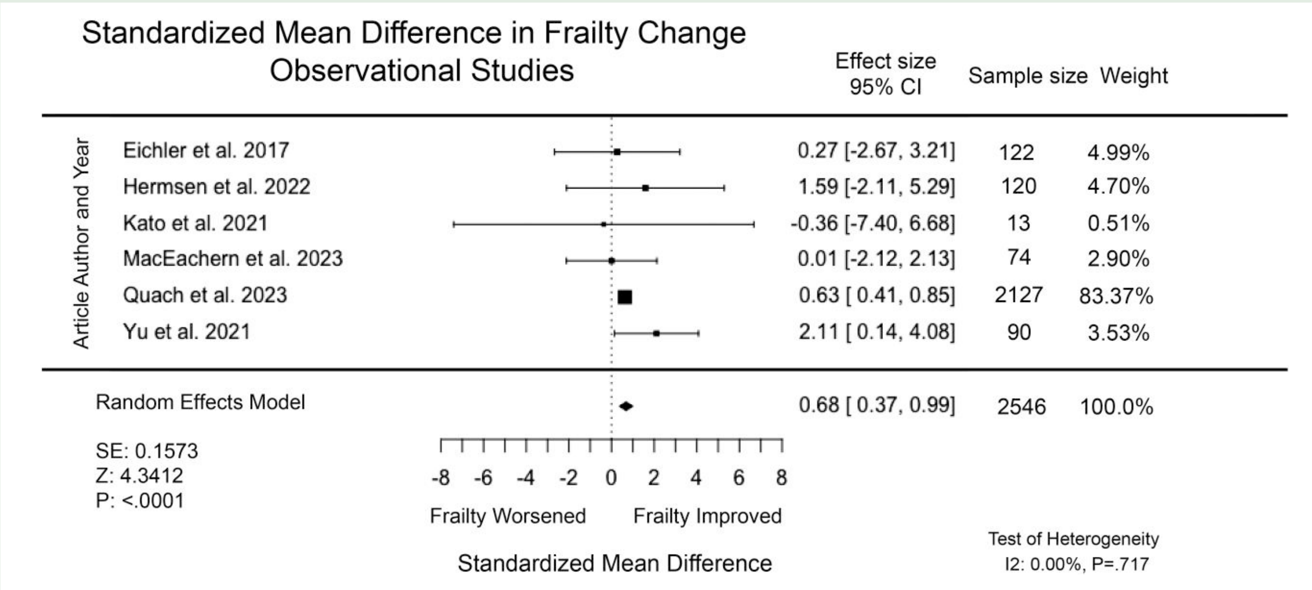


Figure 3 Standardized mean difference in frailty change—observational studies.

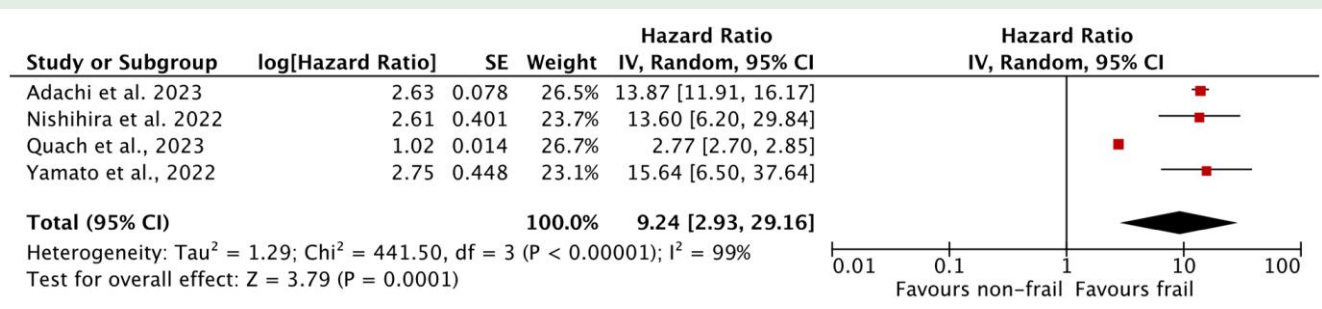


Figure 4 Observational studies meta-analysis of frail vs. non-frail participants' risk of all-cause mortality. Higher hazard or odds ratio represent greater risk of all-cause mortality for frail CR participants.

50% depending on the frailty tool used (*Figure 2*). This statistic aligns with previous estimates among general community dwelling adults,[61] CR participants,[62] and other CVD populations.[18,63] Studies using the FI to measure frailty had a slightly higher pooled prevalence of frail participants than those using the Frailty Phenotype (*Figure 2*), aligning with other work.[64] One caveat with the literature examined here is that it is difficult to ascertain the sensitivity level of competing frailty tools; that is, various frailty tools will quantify frailty using different metrics. The combination of an individual's high degree of frailty not being related to their CVD diagnosis highlights the need for the routine assessment of frailty to determine the expected prognosis and success within CR. Likewise, consistency in assessing frailty may provide generalizability for stakeholders to better manage frailty in CVDs.[65]

Our meta-analysis, and the supporting studies we were unable to meta-analyse,[17,40,44,56] suggest that individuals who complete CR can reduce their level of frailty (*Figure 3*). We recognize the studies included in our review held diverse samples featuring a range of CVD diagnoses, age groups, sex representations, and nationalities (*Table 1*). As a result, we believe our findings represent a high degree of generalizability to the CR demographic. Furthermore, we relate our findings to meaningful improvements among frail CVD patients with respect to frailty and cardiovascular health outcomes.[66] It is worth noting the REHAB-HF trial,[67] while categorized as a physical rehabilitation intervention, has several nuances of a standardized CR programme and was deemed especially important for the vulnerable frail CVD population.[66] The reviewed articles had a range of CR intensities which covered education, medication management, nutritional guidance, psychosocial support, and exercise training (see Supplementary material online, *Table S1*). The combination of CR's core components provides a robust and proven method of improving CR participant frailty; however, future research should investigate the specific impact of each CR component on changes in frailty. Others have recommended the adoption of routine frailty assessment for the management of CVD, suggesting frailer individuals should not be withheld from treatment due to pre-conceived notion of risk.[65] We concur with this stance, as described in the following section, frailer CVD patients may benefit more or as much as those without frailty.[65]

Our investigation highlights the frailest CR participants appear to benefit the most from completing their programmes.[16,17,21] Among CR participants falling into the category of very frail (FI ≥0.40)[17] to very severely frail (FI ≥0.50),[16] clinically meaningful improvements in frailty were reported, ranging from 0.03 to 0.08 and 0.03 to ≥0.15, respectively. The implications of reducing frailty are substantial, as evidenced by a study from our review[48] and others,[68] where even small increases in the FI, such as 0.01, can significantly increase an individual's mortality risk. Furthermore, the age range presented in our review suggests an independent relationship of CR and frailty, where frailty may be reported in pediatric-onset[52] and older adult CR participants alike (*Table 1*). However, we acknowledge the literature on frailty is generally associated with older age.[8,64] From our examination, no other studies identified a risk of CR participation based on the participants' level of frailty. We therefore concur with the former recommendation for health care providers to advocate and support frail CVD patients to enrol into CR programmes as a form of sustainable health management.[16]

Frailer CR participants were more likely to experience all-cause mortality (*Figure 4*) and contended with a greater proportion of adverse health outcomes than their robust peers. Frailty prevalence was also greater during periods of CR hospitalization,[42] aligning with other published work.[69,70] Understandably, frailer individuals were also less likely to complete CR.[16,47] However, our review demonstrates that frail individuals retain the ability to improve their health in CR, as frail participants generally saw significant improvements in physical performance (see Supplementary material online, *Table S3*).

By assessing frailty for patient risk stratification and operationalizing CR programmes accordingly, healthcare providers can help individuals with CVD improve prognosis and reduce the risk of future complications by managing their current level of frailty.[18,52,71] Implementation of routine frailty assessment at the point of care can assist healthcare providers in delivering CR programmes that are high-quality, person-centred, and tailored to individual needs.[72] Indeed, knowledge of participants' frailty through routine assessment may assist CR providers to detail the expected benefits of programme participation with their patients, which is in line with our findings which highlight that frail CR participants stand to gain benefit from participation. These strategies have the potential to enhance CR completion rates among frailer participants, an area that received limited investigation and formal analysis from this review. Finally, as our society shifts to greater uptake of electronic and remote delivery of information and care, we must also determine whether these methods are reliable for chronic disease patients. Indeed, digital health interventions have been previously explored in CR[73] and for frail adults,[74] however, further research in this area will assist traditional CR programmes adapt to the needs and accessibility of participants.

Our review has limitations. We chose to only include articles which used recognized frailty assessments; however, many articles made modifications to validated assessments to suit the needs of their intervention. Other research groups have used non-traditional frailty assessments such as the SPPB[75–78] or social frailty[79,80] to measure frailty among CR participants. We excluded such measures as they are limited to one domain of health (i.e. physical) or do not examine the breadth of health deficits other frailty tools capture in multiple domains. Future research may choose to explore SPPB or social frailty measures as they relate to CR participants' frailty upon further validation as a robust frailty assessment. We also excluded articles which examined frailty in CR through qualitative methods, leaving the opportunity for future research to yield a qualitative meta-synthesis on frailty and CR and build on our findings. Many articles examined a single cohort at a single centre, creating large variability in CR designs (i.e. length, frequency; Supplementary material online, Appendix *C*, Supplementary material online, *Table S1*). A limited number of RCTs were included, and few studies had similar outcome measures, limiting the extent of our meta-analyses. We explored risk of bias by providing quantitative heterogeneity I^2 statistics in *Figures 2*, *3*, and *4*, and visually provided supplementary figures of funnel plots in Supplementary material online, Appendix *C*.2., leading us to caution the findings of our results. The high heterogeneity of our analyses may be due to the large number of frailty assessments tools used, which is common in frailty research due to the number of tools in any knowledge synthesis. Finally, we limited our search to articles that were available in English, and therefore, may have missed relevant articles in other languages.

Conclusion

Frailty is a common and significant contributor to an individual's response to CR. Overall, we observed high but modifiable levels of admission frailty, which was associated with adverse health outcomes in patients attending CR. We found high variability in frailty assessment tools and CR designs. However, CR remained beneficial for participants with mild-to-severe admission frailty to improve frailty and physical health outcomes.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

S.K., E.M., O.T., and N.G. contributed to the conception or design of the work. E.M. and J.Q. contributed to the acquisition, analysis, or interpretation of data for the work. E.M. drafted the manuscript. E.M., S.K., O.T., I.A.A., M.G.L., and T.H. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

Materials may be provided upon request.

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