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Exercise During Chemotherapy in Colorectal Cancer: A Systematic Review

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ABSTRACT: This study investigates the effects of structured exercise on treatment tolerance, physical function, and frailty-related outcomes in adults with colorectal cancer (CRC) receiving chemotherapy, with separate appraisal for older patients to evaluate its potential to support safe and effective treatment delivery. Using a Systematic Review methodology, this study synthesized research published between January 2021 and March 2026 from PubMed, Taylor & Francis Online, and SAGE Journals searched (1 May–1 June 2026). Data were analyzed using a narrative synthesis approach, focusing on tolerance, function, fatigue, frailty, quality of life, adherence, and safety, with bias assessed via RoB 2 and ROBINS-I. The findings indicate that of 701 studies screened, 7 reports (5 cohorts) were eligible, with no serious exercise-related adverse events. A geriatric intervention with supervised physiotherapy showed higher chemotherapy completion than usual care (45% vs 28%, p=0.037), though not isolated from concurrent nutritional therapy and medication review. Unsupervised home-based resistance training did not improve relative dose intensity, while function improved most consistently with supervised or progressive resistance programs. Unlike previous review studies, this research integrates tolerance, function, frailty, and safety outcomes into a unified narrative framework specific to the CRC chemotherapy population. The study concludes that structured exercise appears feasible and may preserve physical function, though its independent contribution to treatment tolerance remains undetermined and frailty-specific evidence is limited to one geriatric cohort. Additionally, further research is required to compare exercise delivery models using adequately powered trials and standardized frailty/tolerance measures.

KEYWORDS: chemotherapy, colorectal cancer, exercise, frailty, geriatric, treatment tolerance

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer death worldwide, with approximately 1.93 million new cases and over 900,000 deaths in 2022, representing 10% of global cancer incidence and mortality.[1] Although incidence remains highest in high-income regions, CRC is rising rapidly across Asia and Latin America, with the global burden projected to exceed 3.2 million new cases annually by 2040.[2] This disease is strongly age-associated, with a median age at diagnosis of 66 years, which makes chemotherapy tolerance and functional status central concerns in supportive care.[3,4]

Systemic chemotherapy improves survival but carries substantial toxicity.[5] Among these treatment-related effects, cancer-related fatigue is one of the most frequently reported, affecting a majority of patients across published studies, although prevalence varies according to the definition, timing, and instrument used.[6] Acute, transient oxaliplatin-related neurosensory symptoms occur in most patients during infusion. In comparison, persistent and clinically meaningful chemotherapy-induced peripheral neuropathy (CIPN), which is relevant to long-term function, affects a smaller and less precisely defined proportion and should not be conflated with acute symptoms.[7] Furthermore, sarcopenia can compromise treatment tolerability and physical function, contributing to chemotherapy dose reductions and premature discontinuation.[8,9]

Due to the burden of treatment-related toxicity and functional decline, exercise has become a promising non-pharmacological supportive-care strategy during chemotherapy. Structured exercise may attenuate these toxicities and improve physical function, fatigue, and quality of life during chemotherapy, while counteracting the sarcopenia and functional decline that drive dose reduction.[10–12] The previous study supporting this method originated from the feasibility trial by Hatlevoll and colleagues, showing that a supervised multimodal program, incorporating aerobic, resistance, and balance, could be safely delivered alongside oxaliplatin-based adjuvant chemotherapy. This initial evidence provided a basis for further trials investigating the potential benefits of exercise during active chemotherapy.[13]

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Exercise is particularly relevant for patients with frailty, which is distinct from chronological age and increases the risk of severe toxicity, hospitalization, and inferior survival.[14] In a secondary analysis of GERICO trial, 66% of older CRC patients screened were classified as physically frail and qualified for referral to supervised exercise. Despite this high prevalence, most exercise-oncology trials have not specifically enrolled or analyzed patients with frailty.[15] Consequently, evidence on the role of exercise during active chemotherapy in older and vulnerable patients with CRC remains fragmented. A previous study has examined exercise and physical function in older patients with CRC receiving chemotherapy.[16] This review builds on the existing literature, while emphasizing treatment-tolerance outcomes, rather than considering older or vulnerable patients.

Based on the description above, this review aims to evaluate the effects of exercise on treatment tolerance, physical function, and frailty-related outcomes in adults with CRC receiving active chemotherapy. Due to the limited number of trials specifically enrolling frail older adults, evidence is synthesized across CRC patients with a separate and more cautious analysis of results applicable to older and vulnerable populations.

MATERIALS AND METHODS

This review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.

Protocol and Registration

This review was registered with PROSPERO-NIHR (International Prospective Register of Systematic Reviews National Institute for Health Research) under registration number CRD420261437488.

Eligibility criteria

Eligible studies enrolled adult patients with histologically confirmed CRC classified as stage II-IV according to AJCC/UICC TNM staging system. Participants were required to receive active systemic chemotherapy (adjuvant, neoadjuvant, or palliative) concurrent with structured exercise (aerobic, resistance, combined, or multimodal), compared to standard care. Eligible designs were randomized controlled trials and non-randomized studies published in English. However, non-human studies, grey literature, and non-English publications were excluded.

Based on the eligibility criteria, eligible outcomes were treatment tolerance (chemotherapy completion and relative dose intensity), cancer-related fatigue, physical function, frailty-related outcomes, quality of life, adherence, and exercise-related adverse events. Studies including participants receiving chemotherapy and immunotherapy were eligible only where data for chemotherapy-treated patients were reported separately or predominated the sample. The treatment composition of each study is presented in Table 1.

Frailty was not required as an eligibility criterion because preliminary scoping identified very few CRC chemotherapy trials specifically enrolling frail patients. Studies enrolling general adult CRC populations were eligible, while evidence relating to older and vulnerable patients was synthesized separately when a validated or study-defined frailty or vulnerability screen, such as G8, or a geriatric-specific population was reported.

This eligibility framework corresponded to the following PICO, namely Population, adults with histologically confirmed CRC (AJCC/UICC stage II-IV) receiving active chemotherapy, Intervention, structured exercise (aerobic, resistance, combined, or multimodal) during chemotherapy, Comparison, standard care, and Outcomes, treatment tolerance, relative dose intensity, chemotherapy completion, toxicity, fatigue, physical function, frailty-related outcomes, quality of life, adherence, and exercise-related adverse events.

Mixed-cancer studies were eligible for the main synthesis only where a CRC-specific subgroup analysis was available. Müller *et al.* enrolled a mixed-cancer population and did not report a CRC-specific subgroup.[17] Therefore, the study was retained only as indirect supportive evidence in a clearly separated section and was excluded from the main evidence synthesis and the summary tables of direct evidence.

Information sources and search strategy

The literature search was performed independently by two reviewers (RAVA and LH) from 1 May to 1 June 2026 across three databases, including PubMed, Taylor & Francis Online, and SAGE Journals. The search covered publications between January 2021 and March 2026 to update the previous systematic review in this field,[16] which explored the literature through 2020. Furthermore, the full search string, applied consistently across all three databases, alongside the search period, record counts per database, and

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the deduplication method and software used, was provided in Supplementary Data. The restriction to three databases and a five-year publication window was acknowledged as a limitation discussed in section 4.5. However, there was no trial-registry searching, citation searching, or contact with study authors.

Study selection

Screening was conducted in two stages following the review guidelines. First, titles and abstracts were screened to remove obviously non-relevant records. Second, full texts were assessed against the predetermined inclusion and exclusion criteria. RAVA and LH performed title/abstract and full-text screening independently and in duplicate, while a third reviewer (UK) acted as adjudicator to resolve discrepancies.

At the full-text stage, reasons for exclusion were recorded using five pre-specified categories. These included wrong population, not receiving active systemic treatment, non-structured exercise intervention, ineligible outcome, wrong study design, duplicate or secondary report without new eligible data, abstract only, and full text unavailable. Each excluded report was assigned to a single primary category. The number of reports excluded in each category is shown in Figure 1. The list of full-text reports excluded at the report level is not included in the review records.

Data extraction

Data extraction was performed independently in duplicate by two authors (RAVA and LH) using a standardized data collection form in Google Sheets. Extracted information included first author, year, country, study design, parent trial or cohort (to link multiple reports of the same trial), participant characteristics (age and frailty status where available), sample size, chemotherapy regimen, intervention characteristics (frequency, intensity, session-time structure, exercise type, duration, and supervision setting), comparator, outcome measures, adherence, attrition, and principal findings. Subsequently, exercise intensity was extracted according to the metric reported by each study, most commonly the percentage of one-repetition maximum or rating of perceived exertion in line with ACSM framework. However, none of the included studies reported intensity using a standardized MET framework, as presented in Table 1. Effect estimates were reported as given in the source publications. Outcomes for which the source publication did not report a usable effect estimate were recorded as not reported (NR) rather than estimated post hoc.

Risk of bias assessment

Methodological quality was assessed using the tool matched to each study's design rather than applying both tools to every report. The Cochrane RoB 2 tool was applied to the randomized comparisons (Müller 2021; FORCE [Caan 2024; Brown 2024]; Sánchez-González 2025; GERICO [Lund 2021]) across five domains, namely randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[18] ROBINS-I was applied only to the non-randomized comparisons (Hatlevoll 2021; Olsen 2023 [GERICO exercise sub-study]) across seven domains. These included confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.[19] The tool applied to each cohort is shown in Table 1.

Risk-of-bias was assessed for the primary outcome reported by each report rather than as a single generic label for the whole publication. Therefore, the two FORCE reports, showing different primary outcomes from one trial, were presented as two outcome-level assessments of a single parent cohort. Assessment was performed independently by two authors and verified by a third, with discrepancies resolved through discussion. Judgements reflect the assessed risk in each domain. A moderate or serious rating was not assigned only because participant blinding was infeasible, but where the lack of blinding plausibly caused deviations from the intended intervention or biased outcome measurement.

Data synthesis

Given major clinical and methodological heterogeneity across populations, interventions, comparators, and outcome definitions, statistical pooling (meta-analysis) was not performed. This decision was made a priori, in line with Cochrane guidance on when meta-analysis was inappropriate.[20] Therefore, results were synthesized narratively and organized by outcome domain, including treatment tolerance, physical function, fatigue, frailty-related outcomes, quality of life, and safety. In each domain, results were summarized according to the direction and magnitude of effect, with risk differences reported for dichotomous outcomes and mean variations or effect sizes for continuous outcomes when provided by the original publications. A formal certainty-of-evidence assessment (for example, GRADE) was not undertaken. Therefore, limitations and uncertainties in the available evidence were described narratively in section 4.5 rather than expressed as certainty ratings.

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RESULTS

Study selection and identification

A literature search across three databases, including PubMed, Taylor & Francis, and SAGE Journals, identified 771 studies, where 70 duplicates were removed, and 694 studies were excluded during screening. Figure 1 shows PRISMA flowchart. Thus, seven studies were included in this systematic review.

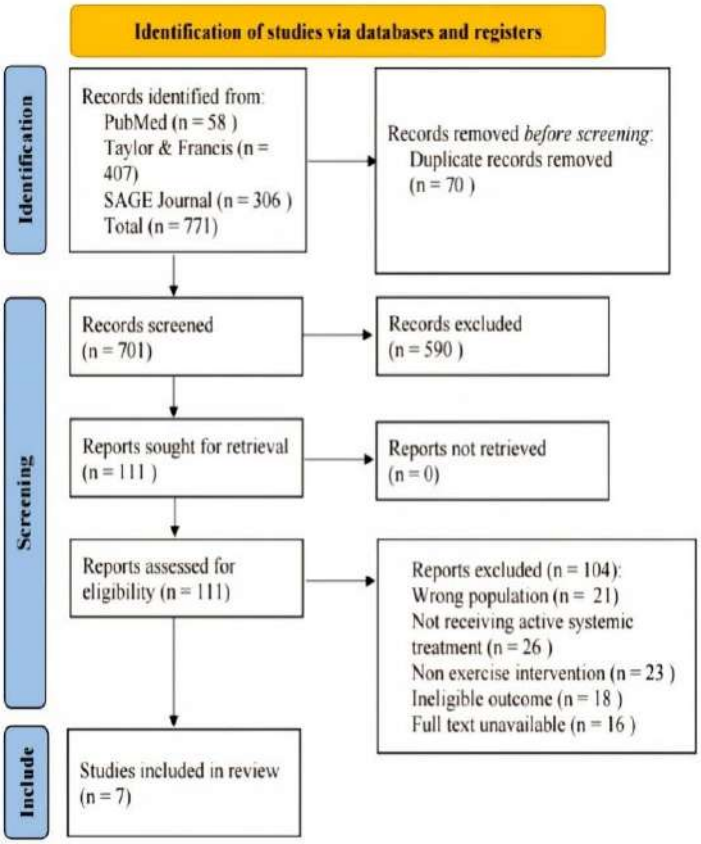

Figure 1. PRISMA Flowchart

Risk of bias

Methodological quality was evaluated using the design-appropriate tool for each cohort. Specifically, RoB 2 was used for the randomized comparisons (Müller 2021; FORCE [Caan 2024; Brown 2024]; Sánchez-González 2025; GERICO [Lund 2021]). ROBINS-I was used for the non-randomized comparisons (Hatlevoll 2021; GERICO exercise sub-study [Olsen 2023]).

Under RoB 2 (Figure 2), the assessments of Lund 2021, Müller 2021, Caan 2024, and Brown 2024 each raised some concerns. In all the assessments, these concerns were due to deviations from the intended intervention (D2), showing the impossibility of blinding participants to an exercise intervention and the reliance on per-protocol or adherence-defined analyses. Measurement of the outcome (D4) raised additional concerns in Caan 2024. Sánchez-González 2025 was judged at high risk overall due to deviations from the intended intervention (D2) and missing outcome data (D3). There are some concerns in the randomization process (D1) and measurement of the outcome (D4), consistent with the unblinded pilot design and 32.5% attrition. Selection of the reported result (D5) was at low risk in all five assessments.

Regarding ROBINS-I (Figure 3), both non-randomized cohorts were judged at serious risk overall. In each case, the judgement was driven by confounding (D1), which was inherent to a non-randomized design, where participation in exercise was not randomly allocated, and by missing data (D5). Classification of interventions (D3), deviations from intended interventions (D4), and selection of the reported result (D7) were at low risk in both cohorts. Furthermore, measurement of outcomes (D6) was judged at moderate risk in both cohorts, and selection of participants (D2) at moderate risk in Hatlevoll 2021.

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These judgements reflect the assessed risk of bias in each domain rather than poor conduct. The recurring limitations, particularly the infeasibility of participant blinding, attrition in older or vulnerable populations, and residual confounding in non-randomized designs, are structural features of exercise-oncology studies. However, these limitations constrain the strength of the interpretation that can be drawn from the results.

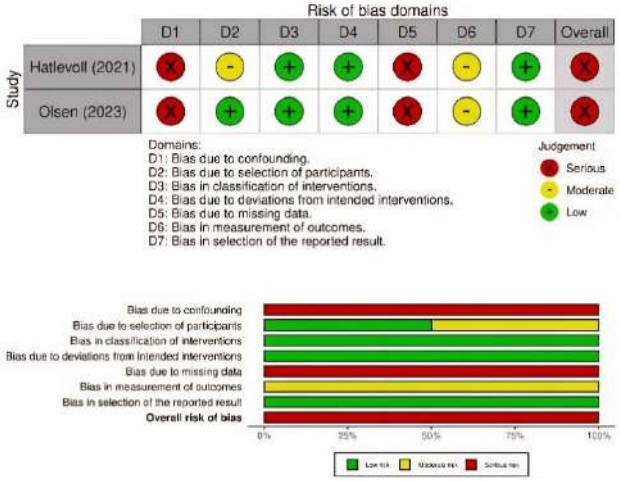

Figure 2. Risk of Bias Analysis Using ROBINS-I

Figure 3. Risk of Bias Analysis Using Cochrane RoB 2

Characteristics of included studies

A total of seven reports representing five unique cohorts were included. These comprised Hatlevoll 2021[13] and Müller 2021[17], which were retained as indirect evidence (sections 2.1 and 3.4), Caan 2024[21] and Brown 2024[22], reporting FORCE cohort, Lund 2021[14] and Olsen 2023[15] on GERICO program, and Sanchez-Gonzalez 2025.[23] Study characteristics are summarized in Table 1.

Among the included cohorts, only GERICO program specifically enrolled geriatric patients screened using the G8, with a score of 14 or below. This represented the only cohort explicitly targeting vulnerable older adults. The remaining cohorts recruited broader CRC populations receiving chemotherapy and did not formally assess frailty using a validated multidimensional instrument. G8 is a geriatric screening tool rather than a measure of frailty, while low SPPB scores or poor physical performance, as reported descriptively in FORCE, are not interchangeable with a validated frailty syndrome. Therefore, more precise terms are used throughout this review, namely "G8-screened vulnerable older adults" for GERICO, and "participants with low physical performance" for the post-hoc FORCE classification.[24]

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Table 1. Characteristics of included studies

No	Study (year)	Parent cohort	Country/ Setting	Design	Population	Intervention	Chemotherapy	FITT				
								Frequency	Intensity	Time	Type	Supervision
1	Müller et al. (2021) [17]	Müller (indirect evidence only)	Germany, single center	RCT, 3-arm	n = 170, mean age = 53 years, mixed cancer (CRC subset); TNM stage not reported by primary study; neurotoxic chemotherapy; no formal frailty	SMT vs. RT vs. UC (3arm); 3x/week, 105 min/w eek total; duration of neurotoxic chemotherapy (mean 20 weeks)	Neurotoxic regimens; oxaliplatin, paclitaxel, or vinca alkaloids	3x/ week	Moderate-vigorous, progressive (%1RM /RPE-based; ACSM classification)	35 min/ session (105 min/week total); warm-up/main/cool-down split NR	Resistance/sensorimotor	Supervised (cancer center)
2	Caan et al. (2024) [FORCE][21]	FORCE	USA, multicenter (3 sites)	RCT	n = 181, mean age = 55 years, colon cancer, stage II-III (TNM); a post-hoc SPPB-based frailty definition (SPPB ≤ 9 plus low appendicular lean mass per SPRINT criteria) was applied descriptively – 29/181 (16%) met this frailty threshold at baseline	Home-based resistance training (video-guided), progressive	Adjuvant CAPOX or FOLFOX	3x/week	Moderate, progressive (%1RM /RPE-based; ACSM classification)	30 min/session; warm-up/cool-down split NR	Resistance	Home-based, unsupervised
3	Brown et al. (2024) [FORCE][22]	FORCE (secondary report of	USA, multicenter	RCT (secondary	n = 181, mean age= 55 years, colon cancer,	Home-based resistance training (videogui	Adjuvant CAPOX or FOLFOX	3x/week	Moderate, progressive (%1RM	30 min/session; warm-up/cool	Resistance	Home-based, unsupervised

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		report)		FORCE)	stage II-III (TNM); frailty cohort same as Caan	ded) vs. usual care (same FORCE intervention as Caan 2024; secondary report assessing physical function)			/RPE-based; ACSM classification)	-down split NR		
4	Sánchez-González et al. (2025) [23]	Sánchez-González	Spain, single center	Pilot RCT, parallel-group	n = 40 randomized, 27 analyzed (15 hybrid/12 home); mean age Resistance Exercise Group (REG) = 65.7 ± 9.8 years, mean age Control Group (CG) = 64.7 ± 10.9 years, colon cancer stage II-IV (TNM); no formal frailty assessment tool – handgrip strength measured only as a functional/ strength outcome	Supervised resistance training added to home-based physical activity vs. home-based physical activity alone	Mixed regimens (primarily CAPOX and FOLFOX; some capecitabine monotherapy, with selected patients receiving concurrent chemoradiotherapy	2x/week	Individualized progressive resistance training (intensity tailored to each participant's functional capacity and progressively increased) (RPE-based; ACSM classification)	8-week program; per session duration and warm-up/cool-down split NR	Progressive resistance training + oral protein supplement post-session	Supervised (university/hospital) + home
5	Lund et al. (2021) [GERICO] [14]	GERICO	Denmark, multicenter	RCT, Phase 3	n = 142, median age = 75 years, colon cancer, stage II-III	Comprehensive Geriatric Assessment (CGA)-based interventi	Adjuvant (58%) + firstline palliative (42%); various regimens;	NR	Low-to-moderate intensity, individualized	NR	Individualized physiotherapy (including strength, balance, and	Supervised (hospital)

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					(TNM), G8 ≤ 14 = vulnerable /frail per screening cutoff; entire cohort met this threshold by eligibility design.	on: medication changes (62%), nutritional therapy (51%), physio therapy/resistance + mobility exercise (39%)	exact perpatient regimen distribution NR		according to each patient's functional capacity.		functional exercise)	
6	Olsen et al. (2023) [GERICO][15]	GERICO (exercise sub-study)	Denmark	Non-randomized, prospective secondary analysis (of GERICO RCT)	n = 47, median age = 75 years, colon cancer, stage II-IV (TNM), G8 ≤ 14 = vulnerable /frail) who were additionally screened for physical frailty using two physical-performance tests (handgrip strength and gait speed cut-offs); 47/71 (66%) of intervention-arm patients screened fell below cut-off on at least one test and were classified as physically frail	Progressive resistance training (PRT) + oral protein supplement	Adjuvant + palliative (various regimens)	2x/week	Low-moderate, RPE-individualized, progressive (ACSM classification)	60 min/session (warm-up + PRT + cool-down); 12 weeks, exact minute-by-minute split NR	Resistance	Supervised (hospital/rehabilitation center)

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7	Hatlevoll et al. (2021) [13]	Hatlevoll	Norway, single center	Non-randomized feasibility study	n = 19, median age = 66 years, CRC, stage II-III (TNM); no formal frailty assessment	Supervised aerobic + resistance + balance program	Adjuvant CAPOX or FOLFOX (oxaliplatin-based)	3x/week (2 supervised + 1 home-based session as an additional home component)	Moderate, progressive	60 min/session, structured as: 10 min warm-up + 20 min aerobic + 15 min resistance + 15 min balance /cool-down; 12-24 weeks	Multimodal	Supervised (hospital)+home

Abbreviations: RCT = Randomized Controlled Trial; CRC = Colorectal Cancer; CGA = Comprehensive Geriatric Assessment; G8 = Geriatric-8 screening tool; HGS = Handgrip Strength; CIPN = Chemotherapy-Induced Peripheral Neuropathy; RDI = Relative Dose Intensity; SPPB = Short Physical Performance Battery; SMT = Sensorimotor Training; RT = Resistance Training; UC = Usual Care; Adj. = Adjuvant, NR = Not Reported; PRT = Progressive Resistance Training.

Clinical outcomes

This review synthesized evidence from six reports representing four unique cohorts in the main database, while the Müller 2021 mixed-cancer trial was presented separately as indirect evidence. However, no serious exercise-related adverse events were reported in the included publications. Adverse-event ascertainment and reporting were heterogeneous and most studies depended on passive rather than active monitoring. Therefore, the absence of reported serious events should not be interpreted as definitive evidence of safety.

The results were organized by outcome domain. Table 2 reports treatment-tolerance outcomes, including chemotherapy completion or relative dose intensity, alongside the available effect estimates. Table 3 shows secondary outcomes, including physical function, fatigue, frailty-related outcomes, and symptom.

Treatment-tolerance results differed across cohorts and did not provide consistent evidence for an independent effect of exercise supervision. In GERICO, a multicomponent geriatric intervention comprising supervised physiotherapy, nutritional therapy, and medication review was associated with higher chemotherapy completion than usual care (45% vs 28%; risk difference approximately 17 percentage points; 95% CI not reported in the source publication; p = 0.037). Since exercise was delivered only as one component of this comprehensive intervention, the benefit could not be attributed to exercise or supervision alone.[14] Similarly, FORCE trial found no improvement in relative dose intensity with an unsupervised home-based resistance-training program in the intention-to-treat analysis.[21] In Müller 2021, a per-protocol analysis restricted to adherent exercisers showed higher relative dose intensity than usual care (96.6% vs 92.2%; risk difference approximately 4.4 percentage points; p = 0.032). This is indirect evidence for CRC because the trial enrolled a mixed-cancer population without a CRC-specific subgroup analysis, and per- protocol analyses are subject to adherence-related selection bias.[17] Due to the absence of a study that directly randomized participants to supervised versus unsupervised delivery, the independent effect of supervision on treatment tolerance remains uncertain.

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Table 2. Treatment-tolerance outcomes, with evidence type and cautious interpretation.

Study (cohort)	Evidence type	Delivery	Effect estimate	Cautious interpretation
GERICO (Lund 2021)[14]	Direct (frail older CRC)	Supervised, multicomponent geriatric intervention (physiotherapy + nutrition + medication review)	Chemotherapy completion: 45% vs 28%; RD ≈ 17 pp; p = 0.037; 95% CI NR	Benefit observed for the comprehensive geriatric intervention as a whole; the independent contribution of exercise/supervision cannot be isolated
FORCE (Caan 2024)[21]	Direct (CRC, ITT)	Home-based, unsupervised resistance training	RDI: no significant between-group difference (ITT)	Unsupervised home-based resistance training alone did not show an RDI benefit in this trial.
Müller 2021[17]	Indirect (mixed-cancer, per-protocol)	Supervised resistance/sensorimotor exercise	RDI: 96.6% vs 92.2% (adherent exercisers, per-protocol); RD ≈ 4.4 pp; p = 0.032; not significant in ITT; 95% CI NR	Hypothesis-generating only for CRC; per-protocol analysis is prone to adherence-related selection bias.

Table 3. Secondary outcomes: physical function, fatigue, frailty-related, and symptom outcomes.

Study (cohort)	Delivery	Key finding	Cautious interpretation
Sánchez-González 2025[23]	Supervised resistance training added to home-based activity	Significant reductions in fatigue and constipation (both > MCID); no significant effect on anxiety, depression, sleep, or CRP	Preliminary pilot-level finding (27/40 analyzed, unblinded, 32.5% attrition); requires replication in a larger, adequately powered trial.
Müller 2021[17]	Mixed delivery (supervised and home-based)	Muscle strength and EORTC QLQ-C30 improvements among adherent exercisers only	Indirect evidence for CRC (mixed-cancer trial, no CRC-specific subgroup).
FORCE / Brown 2024[22]	Home-based, unsupervised	No significant ITT improvement in SPPB/handgrip/sit-to-stand/SF-36; baseline SPPB (r=0.21) and handgrip (r=0.23) correlated with RDI	Baseline physical function appears prognostic; this trial did not show that unsupervised home-based training itself improves function.
GERICO exercise sub-study / Olsen 2023[15]	Supervised physiotherapy (G8-screened vulnerable older adults)	Improvements in lower-extremity strength and physical capacity among participants classified physically frail by performance testing (27/47)	Findings apply to G8-screened, physically frail older adults in this specific program, not to frailty in general.
Hatlevoll 2021[13]	Supervised, multimodal	Favorable trends in CIPN and fatigue scores (n=19); not powered for inference	Early feasibility signal only; complements but does not confirm GERICO's treatment-tolerance findings.

DISCUSSION

Principal findings

Across the cohorts providing direct evidence, structured exercise during chemotherapy for CRC appeared feasible, without serious exercise-related adverse events reported. A comprehensive geriatric intervention that included supervised physiotherapy (GERICO) was associated with higher chemotherapy completion than usual care, while an unsupervised home-based resistance-training trial (FORCE) showed no improvement. Physical function improved most consistently under supervised or progressive resistance programs. Frailty-specific evidence remained limited to the GERICO program. The evidence base is small, clinically heterogeneous, and subject to moderate serious risk of bias. Therefore, the results presented below are interpreted as provisional.

Treatment tolerance

The divergent treatment-tolerance results between GERICO and FORCE most reflect differences in intervention design (multicomponent geriatric care versus a single home-based modality), delivery setting, and adherence, rather than establishing that supervision is necessary or home-based exercise is generally ineffective. GERICO benefit was observed for a package of

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physiotherapy, nutritional therapy, and medication review. Therefore, the treatment-tolerance benefit cannot be attributed to exercise or supervision.[14] FORCE, the largest trial in this review (n = 181), tested a single unsupervised home-based modality, and its intention-to-treat analysis included low-adherence participants, which could have attenuated the observed effect.[21] The per-protocol result from Müller 2021 was directionally consistent but represented indirect evidence for CRC and remained susceptible to adherence-related selection bias.[17] Since no included study directly randomized participants to supervised versus unsupervised delivery, the independent effect of supervision on treatment tolerance remains uncertain. Therefore, the available evidence does not establish that supervision is essential or home-based resistance training alone is generally insufficient.

Physical function and symptoms

Physical function was the most consistently assessed outcome domain. In FORCE secondary analysis, home-based resistance training did not significantly prevent functional decline in the intention-to-treat analysis. However, baseline SPPB balance (r = 0.21) and handgrip strength (r = 0.23) correlated with relative dose intensity, indicating that physical function could be both an outcome and a baseline predictor of chemotherapy delivery.[22] In comparison, the supervised in-person training delivered within GERICO allowed fidelity monitoring and produced meaningful gains in strength and physical capacity among participants classified as physically frail who achieved adequate adherence.[15]

Based on the results, no included study reported a statistically significant between-group difference in fatigue as a primary outcome in a purely CRC population during active chemotherapy. The per-protocol improvement reported in Muller 2021 (+12.9 EORTC QLQ-C30 points; effect size approximately 0.64) was indirect evidence. The fatigue and constipation reductions reported by Sanchez-Gonzalez 2025 were also extracted from a small unblinded pilot trial that required replication before generalization.[23] Previous studies have explored the biologically plausible mechanisms connecting exercise to these outcomes, including preservation of muscle mass through IGF-1/Akt/mTOR signaling, improved cardiorespiratory fitness, and reduced systemic inflammation.[25,26] However, none of the mechanisms were evaluated in the included studies, with Figure 4 showing only a proposed conceptual pathway.

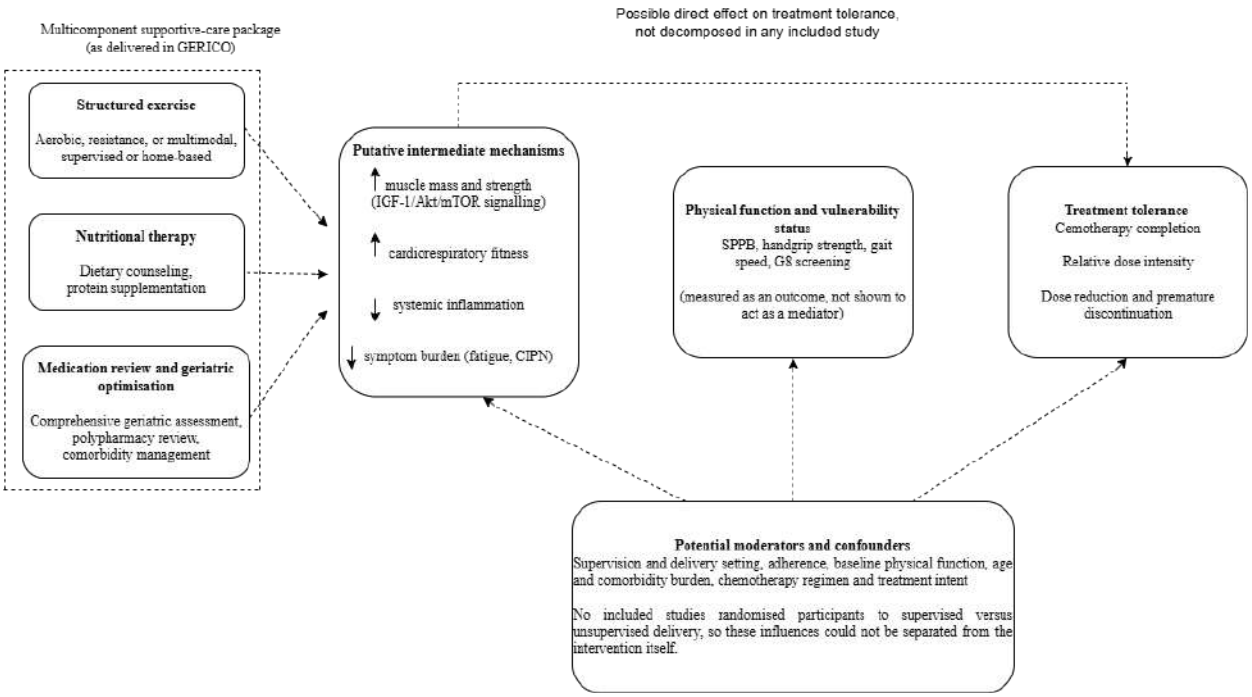

Figure 4. Conceptual pathway: Hypothesized (untested) relationship

Evidence in vulnerable older adults

Frailty-specific evidence was limited to GERICO program, whose two reports (Lund 2021 and Olsen 2023) represented one cohort rather than two independent frailty studies. This distinction played an important role because the G8 was used as an eligibility and

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vulnerability screen rather than a direct outcome measure of change in frailty. Similarly, low SPPB scores or handgrip weakness in the post-hoc FORCE classification are not interchangeable with a validated multidimensional frailty syndrome. Therefore, results from GERICO should be described using precise terms, namely "G8-screened vulnerable older adults", or "participants with low physical performance" for FORCE, rather than as evidence about "frailty" in general.

Despite these definitional limitations, GERICO remains the only prospective evidence specifically targeting G8-screened vulnerable older adults who are receiving chemotherapy. Among the older CRC patients screened in the GERICO program, 66% of participants met the study-defined physical-frailty criteria[15], highlighting the high level of vulnerability within this population. Despite this vulnerability, the comprehensive geriatric intervention was associated with a higher chemotherapy completion rate than usual care (45% vs. 28%).[14] Since high- and low-adherence participants were indistinguishable at baseline in GERICO exercise sub-study, benefit could not be predicted from baseline characteristics alone.[15] Therefore, the evidence is reported as a descriptive observation from one program rather than as a general recommendation.

Strengths and limitations

Strengths of this review are a current and focused synthesis restricted to CRC patients receiving active chemotherapy and explicit mapping of multiple reports to their parent trials to avoid double counting. Other identified strengths included the use of design-appropriate risk of bias tools, alongside a separate and appropriately cautious treatment of the evidence applicable to vulnerable older adults.

Despite the significant contribution of this review, several limitations must be acknowledged. First, the search was restricted to three databases, namely PubMed, Taylor & Francis Online, and SAGE Journals, and to reports published between January 2021 and March 2026, without trial-registry or citation searching. This method omitted relevant studies indexed only in Embase, CENTRAL, CINAHL, or SPORTDiscus, as well as reports published before 2021. The small number of included cohorts may reflect both the search strategy and genuine scarcity of evidence. Second, restricting the review to English-language publications may have introduced language bias. Third, only five unique cohorts contributed evidence, including the two FORCE reports, which originated from a single trial, while Müller 2021 enrolled a mixed-cancer population without a CRC-specific subgroup analysis and was treated as indirect evidence only. Fourth, evidence specifically relevant to vulnerable older adults derived predominantly from GERICO program, while FORCE contributed only a descriptive post-hoc classification based on physical performance. Fifth, Sánchez-González (2025), the most recently published study, was a small pilot RCT, with 27 of 40 randomized participants included in the analysis. The study also used an unblinded design, had an attrition rate of 32.5%, and included patients with colon cancer receiving chemotherapy and/or immunotherapy. Therefore, the results should be considered preliminary. Sixth, substantial clinical and methodological heterogeneity precluded meta-analysis. Seventh, no formal certainty-of-evidence assessment was undertaken, and limitations of the evidence base were described narratively rather than expressed as graded certainty ratings. Finally, adverse events were passively monitored in most included studies, limiting the conclusions that can be drawn regarding the safety of exercise during chemotherapy.

Novelty

This review updates the evidence published after a previous systematic review that examined exercise and physical function in older patients with CRC receiving chemotherapy.[16] The results provide a contribution to the existing evidence by incorporating more recent studies and shifting the focus toward treatment-tolerance outcomes, particularly chemotherapy completion and relative dose intensity. This review also provides a separate and more cautious description of the limited evidence applicable to vulnerable older adults. However, it is not presented as the first review to address older or frail patients.

Clinical implications

Since the evidence base is small and no study directly compared delivery models, this review offers cautious and non-mandatory implications rather than practice standards. A comprehensive geriatric assessment with consideration of exercise or physiotherapy referral may be a reasonable option for CRC patients aged 70 years or older who are starting chemotherapy, consistent with GERICO experience.[14] However, this observation should not be interpreted as evidence that exercise alone produced the observed benefit. Similarly, ASCO guidance positions exercise as a supportive-care option during treatment rather than as an intervention with established efficacy for improving treatment tolerance.[27] Pre-chemotherapy assessment of baseline physical function (SPPB, handgrip strength, gait speed) may help identify patients at higher risk of dose reduction, based on the correlations reported in

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FORCE.[22] The effectiveness of unsupervised home-based resistance training and the independent effect of supervision on treatment tolerance remain unresolved because no trial has directly compared supervised and unsupervised exercise delivery.[28]

Study priorities

Adequately powered trials that directly randomize CRC patients to supervised versus unsupervised delivery, or single-component versus multicomponent supportive care, are recommended to determine the independent contribution of supervision and exercise. These comparisons would help distinguish the effects of supervision and exercise from co-interventions, such as nutritional therapy and medication review.[29–31] Furthermore, trials specifically enrolling frail older adults with CRC during chemotherapy should incorporate validated, standardized frailty instruments, such as the Fried phenotype or Clinical Frailty Scale, as co-primary outcomes alongside relative dose intensity. Pre-specified subgroup analyses should examine differences by frailty status, age, and chemotherapy regimen.[32] Additional priorities include replicating the fatigue and constipation results from Sánchez-González (2025) in a larger blinded trial. Future studies should also provide a CRC-specific evaluation of the role of exercise in attenuating CIPN, as suggested but not established by Hatlevoll and Müller, and prospectively assess mediation along the pathway proposed in Figure 4.

CONCLUSION

In conclusion, this review shows that structured exercise during systemic treatment is feasible and can help preserve physical function and selected symptoms in patients with CRC. The results show that a multicomponent geriatric intervention that included supervised physiotherapy improves chemotherapy completion in vulnerable older adults, but the independent contribution of exercise cannot be determined. Evidence for frailty-specific outcomes remains limited to one geriatric cohort, while the overall evidence base is small, heterogeneous, and at moderate to serious risk of bias. These limitations show the need for adequately powered trials that directly compare delivery models and incorporate standardized frailty, adherence, safety, and treatment-tolerance outcomes.

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