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Understanding the Mechanisms underlying the effects of Exercise on Cancer-Related Fatigue: A Systematic Review of Randomized Controlled Trials

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Cancer-related fatigue (CRF) affects the majority of patients during or after cancer treatment and can persist long after treatment completion. Although exercise is the most effective non-pharmacological strategy to reduce CRF, its underlying mechanisms remain unclear. This review synthesizes evidence from randomized controlled trials (RCTs) on biological, behavioural, psychological, social, and physiological mechanisms through which exercise may reduce CRF.

A systematic review was conducted following PRISMA guidelines and a PROSPERO-registered protocol. PubMed, Cochrane Library, and Embase were searched (March 27, 2025) for RCTs in adults with cancer comparing structured aerobic and/or resistance exercise with usual care, stretching, or waitlist controls. Two reviewers independently screened studies and extracted data on CRF outcomes and mechanisms. The mechanisms were categorized through a narrative synthesis.

Sixteen RCTs were included (N= 22-277), eight during cancer treatment and eight post-treatment. Most interventions involved supervised, 12-week resistance and/or aerobic exercise. Biological mediators were assessed in eleven studies (6 during and 5 post-treatment), of which three reported significant mediation effects for IL-6, IL-10, and inflammatory ratios (e.g., IL-6/IL-10, TNF- α /IL-10). Behavioural mechanisms, particularly physical activity outside the intervention, significantly mediated fatigue reductions in two post-treatment studies. Psychological mechanisms including general self-efficacy and sleep dysfunction were significant mediators in two studies post-treatment. One study examined social mechanisms (perceived exercise support and physical activity enjoyment) that reported mediation effects. Physiological mechanisms were examined in four post-treatment studies; two reported that increases in muscle strength mediated the effects of exercise on CRF, while two others reported mediating effects for improvements in cardiorespiratory fitness.

Exercise appears to reduce CRF through multiple mechanisms, including inflammatory ratios, behavioural changes, psychological improvements, and enhanced physical fitness. Findings were limited by small samples, heterogeneous measures, and temporal-order and confounding biases. Future trials should be prospectively designed for mediation testing with repeated measurements to clarify how these pathways interact.

Keywords

Exercise; Cancer-related fatigue; Mediation; Mechanisms

Conflict of Interest & Ethical Approval

yes

Abstract submitters declaration

yes

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