

INPLASY PROTOCOL

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Effects of Whey Protein Supplementation on Sarcopenia Measures in Healthy Older Adults: A Systematic Review and Meta-analysis

Nasimi, N¹; Sohrabi, Z²; Nunes, E³; Jamshidi, S⁴; Gholami, Z⁵; Phillips, SM⁶.

Review question / Objective: Does a whey protein supplementation maintain or increase muscle mass, strength, and function in healthy older adults?

Condition being studied: Sarcopenia is a state of age-related progressive loss of muscle mass and function. This syndrome is considered an undesirable consequence of aging, contributing to various negative health outcomes including increased risk of chronic metabolic diseases, physical disabilities, falls and fractures, reduced independence, frailty, and hospitalization. Due to population ageing in recent decades, the prevalence of sarcopenia has been growing considerably worldwide. In this context, sarcopenia has globally affected more than 29% of community-dwelling and 14-33% of institutionalized older adult populations. Thus, sarcopenia has been considered to be an important health concern. Indeed, it has been estimated that 500 million older adults would suffer from sarcopenia by 2050.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 April 2022 and was last updated on 28 April 2022 (registration number INPLASY202240167).

INTRODUCTION

Review question / Objective: Does a whey protein supplementation maintain or increase muscle mass, strength, and function in healthy older adults?

Rationale: Sarcopenia has been defined as a geriatric syndrome characterized by

progressive loss of skeletal muscle mass, strength, and physical function. With a rapid rise in the elderly population and the high prevalence of sarcopenia, this syndrome has become a growing concern worldwide. Generally, modifiable risk factors in the progression of sarcopenia include physical inactivity and impaired nutritional status. In this regard, many

studies were conducted to define specific nutrition interventions and their effectiveness on sarcopenia. Dietary proteins such as whey protein have been often cited as a stimulator of muscle protein synthesis in older adults. Many studies assessed the effect of whey protein on muscle mass, strength and function; however, their results were controversial. Moreover, there is a gap in the knowledge about the efficacy of whey protein consumption on prevention or management of sarcopenia. Therefore, in this systematic review and meta-analysis, we aim to identify the effect of whey protein supplementation on three main criteria of sarcopenia in healthy older adults.

Condition being studied: Sarcopenia is a state of age-related progressive loss of muscle mass and function. This syndrome is considered an undesirable consequence of aging, contributing to various negative health outcomes including increased risk of chronic metabolic diseases, physical disabilities, falls and fractures, reduced independence, frailty, and hospitalization. Due to population ageing in recent decades, the prevalence of sarcopenia has been growing considerably worldwide. In this context, sarcopenia has globally affected more than 29% of community-dwelling and 14-33% of institutionalized older adult populations. Thus, sarcopenia has been considered to be an important health concern. Indeed, it has been estimated that 500 million older adults would suffer from sarcopenia by 2050.

METHODS

Search strategy: PubMed

#1 ("whey proteins"[MeSH Terms] OR "whey"[Title/Abstract] OR "whey proteins"[Title/Abstract] OR "whey protein"[Title/Abstract] OR "WP"[Title/Abstract] OR "whey supplementation"[Title/Abstract] OR "whey protein supplementation"[Title/Abstract] OR "whey intake"[Title/Abstract] OR "WPI"[Title/Abstract] OR "whey protein isolate"[Title/Abstract] OR "WPC"[Title/Abstract] OR "whey protein

concentrate"[Title/Abstract] OR "milk proteins"[Title/Abstract] OR "milk protein"[Title/Abstract] OR "dairy proteins"[Title/Abstract] OR "dairy protein"[Title/Abstract])

#2 ("skeletal muscle mass index"[Title/Abstract] OR "SMI"[Title/Abstract] OR "appendicular lean mass"[Title/Abstract] OR "ALM"[Title/Abstract] OR "lean mass"[Title/Abstract] OR "lean body mass"[Title/Abstract] OR "LBM"[Title/Abstract] OR "fat-free mass"[Title/Abstract] OR "fat free mass"[Title/Abstract] OR "FFM"[Title/Abstract] OR "muscle mass"[Title/Abstract] OR "skeletal muscle mass"[Title/Abstract] OR "skeletal muscle"[Title/Abstract] OR "whole mass"[Title/Abstract] OR "muscle"[Title/Abstract] OR "muscles"[Title/Abstract] OR "body composition"[Title/Abstract] OR "bioelectrical impedance analysis"[Title/Abstract] OR "BIA"[Title/Abstract] OR "dual X-ray absorptiometry"[Title/Abstract] OR "DXA"[Title/Abstract] OR "DEXA"[Title/Abstract] OR "Muscles"[MeSH Terms] OR "muscle, skeletal"[MeSH Terms] OR "strength"[Title/Abstract] OR "muscle strength"[Title/Abstract] OR "handgrip strength"[Title/Abstract] OR "handgrip"[Title/Abstract] OR "grip strength"[Title/Abstract] OR "dynamometer"[Title/Abstract] OR "knee extension"[Title/Abstract] OR "leg press"[Title/Abstract] OR "leg strength"[Title/Abstract] OR "muscle strength"[MeSH Terms] OR "physical performance"[Title/Abstract] OR "physical functional performance"[Title/Abstract] OR "function*"[Title/Abstract] OR "gait speed"[Title/Abstract] OR "walking speed"[Title/Abstract] OR "short physical performance battery"[Title/Abstract] OR "SPPB"[Title/Abstract] OR "activities of daily living"[Title/Abstract] OR "ADL"[Title/Abstract] OR "timed up and go test"[Title/Abstract] OR "timed up and timed go"[Title/Abstract] OR "TUG"[Title/Abstract] OR "TUTG"[Title/Abstract] OR "Physical Functional Performance"[MeSH Terms] OR "Walking Speed"[MeSH Terms] OR "Activities of Daily Living"[MeSH Terms])

#3 ("elder"[Title/Abstract] OR "elderly"[Title/Abstract] OR "aged"[Title/

Abstract] OR "aged"[MeSH Terms] OR "ageing"[Title/Abstract] OR "aging"[Title/Abstract] OR "old"[Title/Abstract] OR "older"[Title/Abstract] OR "geriatric"[Title/Abstract] OR "geriatric assessment"[Title/Abstract] OR "Geriatric Assessment"[MeSH Terms] OR "elderly people"[Title/Abstract] OR "older people"[Title/Abstract] OR "older adults"[Title/Abstract] OR "community-dwelling elderly"[Title/Abstract] OR "community-dwelling older adults"[Title/Abstract] OR "community-dwelling old"[Title/Abstract] OR "retired"[Title/Abstract])

#4 ("randomized clinical trial"[Title/Abstract] OR "RCT"[Title/Abstract] OR "randomized controlled clinical trial"[Title/Abstract] OR "randomized controlled trial"[Title/Abstract] OR "clinical trial"[Title/Abstract] OR "trial"[Title/Abstract] OR "controlled clinical trial"[Title/Abstract] OR "controlled trial"[Title/Abstract] OR "random*" [Title/Abstract] OR "randomized"[Title/Abstract] OR "double blind"[Title/Abstract] OR "double-blind"[Title/Abstract] OR "placebo"[Title/Abstract] OR "comparative study"[Title/Abstract] OR "cross over"[Title/Abstract] OR "crossover"[Title/Abstract] OR "cross-over" [Title/Abstract] OR "intervention"[Title/Abstract] OR "assignment"[Title/Abstract] OR "allocat*"[Title/Abstract])

#1 AND #2 AND #3 AND #4

ISI

#1 TS=("whey" OR "Whey proteins" OR "Whey protein" OR "WP" OR "Whey supplementation" OR "Whey protein supplementation" OR "Whey intake" OR "WPI" OR "Whey protein isolate" OR "WPC" OR "Whey protein concentrate" OR "Milk proteins" OR "Milk protein" OR "Dairy proteins" OR "Dairy protein")

#2 TS=("skeletal muscle mass index" OR "SMI" OR "appendicular lean mass" OR "ALM" OR "lean mass" OR "lean body mass" OR "LBM" OR "fat-free mass" OR "fat free mass" OR "FFM" OR "muscle mass" OR "skeletal muscle mass" OR "skeletal muscle" OR "whole mass" OR "Muscle" OR "Muscles" OR "body composition" OR "bioelectrical impedance analysis" OR "BIA" OR "dual X-ray

absorptiometry" OR "DXA" OR "DEXA" OR "muscle, skeletal" OR "Strength" OR "Muscle Strength" OR "handgrip strength" OR "Handgrip" OR "grip strength" OR "dynamometer" OR "knee extension" OR "leg press" OR "leg strength" OR "physical performance" OR "Physical Functional Performance" OR "function*" OR "gait speed" OR "Walking Speed" OR "Short Physical Performance Battery" OR "SPPB" OR "Activities of Daily Living" OR "ADL" OR "Timed Up and Go test" OR "timed up and timed go" OR "TUG" OR "TUTG")

#3 TS=("Elder" OR "Elderly" OR "Aged" OR "Ageing" OR "Aging" OR "Old" OR "Older" OR "Geriatric" OR "Geriatric Assessment" OR "Elderly people" OR "Older people" OR "Older adults" OR "Community-dwelling elderly" OR "Community-dwelling older adults" OR "Community-dwelling old" OR "Retired")

#4 TS=("Randomized clinical trial" OR "RCT" OR "Randomized controlled clinical trial" OR "Randomized controlled trial" OR "Clinical trial" OR "Trial" OR "Controlled clinical trial" OR "Controlled trial" OR "random*" OR "Randomized") OR "double blind" OR "double-blind" OR "Placebo" OR "Comparative study" OR "cross over" OR "Crossover" OR "cross-over" OR "Intervention" OR "Assignment" OR "allocat*")

#1 AND #2 AND #3 AND #4

SCOPUS

#1 TITLE-ABS-KEY ("whey" OR "Whey proteins" OR "Whey protein" OR "WP" OR "Whey supplementation" OR "Whey protein supplementation" OR "Whey intake" OR "WPI" OR "Whey protein isolate" OR "WPC" OR "Whey protein concentrate" OR "Milk proteins" OR "Milk protein" OR "Dairy proteins" OR "Dairy protein")

#2 TITLE-ABS-KEY ("skeletal muscle mass index" OR "SMI" OR "appendicular lean mass" OR "ALM" OR "lean mass" OR "lean body mass" OR "LBM" OR "fat-free mass" OR "fat free mass" OR "FFM" OR "muscle mass" OR "skeletal muscle mass" OR "skeletal muscle" OR "whole mass" OR "Muscle" OR "Muscles" OR "body composition" OR "bioelectrical impedance analysis" OR "BIA" OR "dual X-ray absorptiometry" OR "DXA" OR "DEXA" OR "muscle, skeletal" OR "Strength" OR

"Muscle Strength" OR "handgrip strength" OR "Handgrip" OR "grip strength" OR "dynamometer" OR "knee extension" OR "leg press" OR "leg strength" OR "physical performance" OR "Physical Functional Performance" OR "function*" OR "gait speed" OR "Walking Speed" OR "Short Physical Performance Battery" OR "SPPB" OR "Activities of Daily Living" OR "ADL" OR "Timed Up and Go test" OR "timed up and timed go" OR "TUG" OR "TUTG")
#3 TITLE-ABS-KEY ("Elder" OR "El.

Participant or population: Healthy older adults aged 60 years.

Intervention: Whey protein supplementation.

Comparator: Control or Placebo (protein or carbohydrate- based).

Study designs to be included: Randomized Controlled Trials.

Eligibility criteria: The inclusion criteria for the studies are (1) being published in English and (2) being a controlled clinical trial (either parallel or crossover design). However, (1) non-human studies (animal, in-vitro, and in-vivo studies), (2) cross-sectional studies, (3) reviews, (4) grey literature (book chapters, abstracts in conferences, editorials, letters, and seminars), (5) studies without any control groups, (6) studies with special diet such as low-caloric diet, and (7) studies lacking information for extracting mean and SD (or SE) are excluded. No restriction are considered on the type of whey protein, dose of whey protein supplementation, placebo source, intervention duration, measurement tools, and exercise training.

Information sources: Electronic Databases (PubMed, Web of Science, and Scopus) are searched from their inception.

Main outcome(s): Muscle mass (or its proxies) and/or muscle strength and/ or physical function.

Additional outcome(s): Fat mass.

Data management: The titles and abstracts are reviewed in duplicate by members of the review team and any marked for inclusion by either reviewer are reviewed at full text. Full-text inclusion is conducted independently by two people. All disagreements are resolved through discussions. Data will be extracted by one reviewer and independently verified by a second team member. Variables to be extracted include study characteristics, population details, intervention and control conditions and numerical data for the outcomes of muscle mass (total lean mass and appendicular lean mass), muscle strength (lower and upper), and physical function.

Quality assessment / Risk of bias analysis: The risk of bias will be assessed according to the Cochrane Collaboration risk-of-bias tool using RevMan5 by two team members.

Strategy of data synthesis: The mean difference and SD of the changes between baseline and post-intervention will be used for control and intervention groups to assess the pooled final effects. The Hedges random-effects models will be used to generate the summary measures of effect as standardized mean difference (SMD) for continuous outcomes. The Cochran's Q ($\alpha=0.05$) will be employed to detect statistical heterogeneity and I^2 statistic to quantify the magnitude of statistical heterogeneity between studies where I^2 30% to 60% represents moderate and I^2 60% to 90% represents substantial heterogeneity across studies. The quality of the evidence will be assessed by two team members using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Subgroup analysis: What is the impact of the dose of the whey protein supplement? What is the impact of study duration? What is the impact of the placebo source (protein or carbohydrate)? What is the impact of exercise training?

Sensitivity analysis: Sensitivity analyses will be conducted for all outcomes by the

'remove 1' technique to assess whether individual studies had a disproportionate effect on the meta-analyses results.

Language: Only randomized clinical trials published in English will be considered for inclusion.

Country(ies) involved: Canada and Iran.

Keywords: Whey protein; Aging; Muscle mass; Muscle strength; Physical function.

Dissemination plans: The results of this study will be published as a research article in a journal and possibly presented at a conference.

Contributions of each author:

Author 1 - Nasrin Nasimi - designing the review, data collection, data management, analysis of data, interpretation of data, and writing the final paper.

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Author 2 - Zahra Sohrabi - designing the review and coordinating the review, reviewing and editing the paper.

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Author 3 - Everson Nunes - analysis of data and interpretation of data, reviewing and editing the final paper.

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Author 5 - Zohreh Gholami - analysis of data, reviewing and editing the final paper.

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Author 6 - Stuart Phillips - designing the review, coordinating the review and interpretation of the data, reviewing and editing the final paper.

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Conflicts of interest: Dr. Phillips reports grants or contracts from US National Dairy Council, Dairy Farmers of Canada, Roquette Freres, Nestle Health Sciences, National Science and Engineering Research Council, Canadian Institutes for Health Research during the conduct of the study; personal fees from US National Dairy Council, non-financial support from Enhanced Recovery, outside the submitted

work; In addition, Dr. Phillips has a patent Canadian 3052324 issued to Exerkine, and a patent US 20200230197 pending to Exerkine but reports no financial gains from any patent or related work. No other authors report any real or perceived COI.