Use of content and disclaimer

Use of notes and media: Please read this carefully before using the Nutritional Medicine Institute ("NMI") speaker ("speaker") presentation notes ("notes") audio and video ("media") at www.nmi.health ("website"). The notes and media provided on the website are the copyright and/ or intellectual property of the speaker. NMI has been granted a non-exclusive worldwide right to reproduce and distribute the presentation notes and media. You may not reuse, republish, or reprint such content without written consent.

Disclaimer: The contents of lectures such as this are for educational purposes and intended for health professionals. This information is not a substitution for standard medical care. Health professionals are solely responsible for the care and treatment provided to their own patients.

Nutritional Medicine Institute

1

4:45 - 5:30pm

Frailty and Physiological Dysregulation of Ageing:
From Assessment to Intervention



Benjamin Brown, ND

PRE-SUMMIT EVENT

Sponsored by pure encapsulations

2

Frailty and Physiological Dysregulation of Ageing: From Assessment to Intervention

3

Affiliations & Disclosures

Benjamin I. Brown, ND

Director, the Nutritional Medicine Institute

W: www.scientificwellness.com, www.nmi.health

E: ben@nmi.health

#BenBrownND

I would like to disclose that I have a professional relationship with with Pure Encapsulations. This presentation was developed independently, and Pure Encapsulations was not involved in its development.

I have no other relevant conflicts of interest to disclose.

4

Introduction

5

The challenge of frailty

"Frailty is without question one of the **most serious global public health challenges we will face this coming century.** The rapid expansion of the ageing population has brought a concomitant rise in the number of older adults with frailty, which in turn places an increased pressure non-health-care systems worldwide. Unfortunately, older people with frailty have an increased likelihood of unmet care needs, falls and fractures, hospitalisations, lowered quality of life, iatrogenic complications, and early mortality."

Lancet. 2019 Oct 12;394(10206):1376-1386.



Series

Frailty 2

Management of frailty: opportunities, challenges, and future directions

Elsa Dent, Finbarr C Martin, Howard Bergman, Jean Woo, Ramon Romero-Ortuno, Jeremy D Walston

Lancet 2019; 394: 1376–86

Frailty is a complex age-related clinical condition characterised by a decline in physiological capacity across several organ systems, with a resultant increased susceptibility to stressors. Because of the heterogeneity of frailty in clinical presentation, it is important to have effective strategies for the delivery of care that range across the continuum of frailty severity. In clinical practice, we should do what works, starting with frailty screening, case identification, and management of frailty. This process is unarguably difficult given the absence of an adequate evidence base for individual and health-system interventions to manage frailty. We advocate change towards individually tailored interventions that preserve an individual's independence, physical function, and cognition. This change can be addressed by promoting the recognition of frailty, furthering advancements in evidence-based treatment options, and identifying cost-effective care delivery strategies.

Introduction

Frailty is without question one of the most serious global public health challenges we will face this coming century. The rapid expansion of the ageing population has brought a concomitant rise in the number of older adults with frailty,[1,2] which in turn places an increased pressure on health-care systems worldwide.[3] Unfortunately, older people with frailty have an increased likelihood of unmet care needs, falls and fractures, hospitalisations, lowered quality of life, iatrogenic complications, and early mortality.[4,5] This increased risk of adverse outcomes can occur even without the presence of comorbidities.[1] Therefore, effective strategies that target the prevention and management of frailty in an ageing population will probably reduce the condition's burden at the level of both the individual and the health system.

In reflection of increased research interest, the term frailty was introduced as a PubMed Medline Search Heading (MeSH) in January, 2018. Frailty is recognised as an age-related clinical condition[6–8] that is typically observed by a deterioration in the physiological capacity of several organ systems,[4,9,10] and that causes an increased susceptibility to stressors.[4,5,9–11] When stressor events (such as acute illness) occur, a person with frailty rapidly deteriorates in functional capacity. Thus, interventions to prevent or slow the progression of frailty before it leads to substantial functional decline are key concerns for health-care policy and provision.

In general, frailty is recognised as the physical state that exists before occurrence of disability.[7,8] Although it is possible for frailty and disability to coexist,[8] frailty is also a dynamic entity that exists on a continuum from fit to frail,[4,9,10] wherein an individual's level of frailty is able to change in either direction over time.[1] Correspondingly, frailty is potentially reversible[8,9] and

Search strategy and selection criteria

We searched PubMed and the Cochrane Central Register of Controlled Trials for relevant publications using combinations of several search terms: "frailty", "frailty/therapy*", "patient care planning/standards*", "diet therapy", "physical therapy modalities", "drug therapy", "therapy", "aged", "frailty/complications", "frailty/diagnosis", "geriatric assessment", "frailty/metabolism", "frailty/rehabilitation", "micronutrients/administration and dosage" and "clinical trials". Searches were limited to work published in English. We sought additional publications from the reference lists of identified papers, and from the libraries of authors. To identify current and recently completed trials, we used the National Institute of Health's ClinicalTrials.gov database. Where possible, the research cited in this Series was from systematic reviews and clinical trials published in the previous 5 years, with the exception of key research publications. The literature search was done on Aug 27, 2018, and March 25, 2019.

Key messages

- Although presence of frailty might seem like an ideal way to identify people who need additional support services, there is a shortage of substantial research evidence to support this strategy and to identify the most effective instruments to detect frailty
- In clinical practice, the management of an older adult with frailty is complex because of the inadequate evidence base for individual and health-system interventions to manage the condition
- We need to accrue more knowledge about which intervention strategies are effective for frailty, and to determine whether they are feasible and cost-effective
- High quality clinical trials are needed that take into account the perspectives and needs of health-care providers, older people with frailty, and their carers
- In the absence of a firm evidence base for interventions, strategies to manage frailty in daily practice can be based on existing consensus guideline recommendations
- It is important that frailty does not become a new aspect of ageism that prevents access to interventions that could be appropriate

1376 www.thelancet.com Vol 394 October 12, 2019

6

Frailty is a major global health challenge

- Frailty affects **~24% of older adults**, rising to 51.5% among nursing home residents and people with chronic diseases.
- **In England** 3.9% of 8095 people **aged 50 to 65 years** were frail and **31.6% prefrail.**
- Prevalence is **higher in women** and increases with advancing age.
- Frailty is expected to become **increasingly common as the population ages.**
- Frailty is associated with a **1.8–2.3-fold increased risk of premature mortality.**
- It is also associated with **increased risk of falls and fractures** (1.2–2.8-fold), **hospitalisation** (1.2–1.8-fold), and **impairment in activities of daily living** (1.6–2.0-fold).
- Frailty imposes **significant quality-of-life reductions** for older adults while **creating substantial economic and caregiving burdens** for families and society.

Shi L, et al. Predicting the unseen: nutritional interventions as a key to combat frailty. Front Nutr. 2025 Jul 9;12:1575922.
Palmer KT, et al. Frailty, prefrailty and employment outcomes in Health and Employment After Fifty (HEAF) Study. Occup Environ Med. 2017 Jul;74(7):476-482.

pure encapsulations

7

Multidimensional and dynamic

"Frailty is a multidimensional and dynamic condition, theoretically defined as **"a state of increased vulnerability, resulting from age-associated declines in reserve and function across multiple physiologic systems, such that the ability to cope with every day or acute stressors is compromised."**

Gerontology. 2023;69(8):927-945.



Gerontology

Clinical Section: Review Article

Gerontology 2023;69:927–945
DOI: 10.1159/000528561

Received: May 5, 2022
Accepted: November 27, 2022
Published online: December 7, 2022

Frailty: Pathophysiology, Theoretical and Operational Definition(s), Impact, Prevalence, Management and Prevention, in an Increasingly Economically Developed and Ageing World

Paul Doody[a, b, c] Janet M. Lord[d, e] Carolyn A. Greig[a, d, e] Anna C. Whittaker[f]

[a]School of Sport, Exercise, and Rehabilitation Sciences, University of Birmingham, Birmingham, UK; [b]The Irish Longitudinal Study on Ageing, School of Medicine, Trinity College Dublin, Dublin, Ireland; [c]Nuffield Department of Primary Care Health Sciences, Medical Sciences Division, University of Oxford, Oxford, UK; [d]MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK; [e]NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham., Birmingham, UK; [f]Faculty of Health Sciences and Sport, University of Stirling, Stirling, UK

Keywords
Ageing · Demography · Exercise · Frailty · Rehabilitation

Abstract
The world's population is ageing, and most older adults experience a later life burdened with disease and disability. Frailty is a multidimensional and dynamic condition characterized by declines in reserve and function across multiple physiological systems, such that the ability to cope with every day or acute stressors becomes compromised. It is projected to become one of the most serious public health challenges economically developed societies will face in the coming century. This review provides a comprehensive overview of frailty, exploring its pathophysiology, theoretical and operational definition(s), impact, prevalence, management, and prevention, within the context of its emergence as a major public health challenge, in an increasingly economically developed and ageing world. Further, this review discusses the major limitations, deficiencies, and knowledge gaps presently within the field, and future research directions pertinent to the advancement of frailty research and the promotion of healthy longevity among the increasing global population of older adults.

© 2022 The Author(s).
Published by S. Karger AG, Basel

Introduction

The twentieth and presently twenty-first centuries have been characterized by accelerating medical, pharmacological, and technological advances [1–3]. In the context of population demographics, one of the most significant outcomes of these advances is the exponential increase in overall population, and the relatively rapid increase in life expectancy [4, 5]. These increases can be partially attributed to improvements in public health that have resulted in a profound reduction in global child mortality rates; with an increasing proportion of the population now living to sexual maturity [3, 6, 7]. However, increases in

Karger
OPEN ACCESS

Downloaded from S. Karger AG, Basel via [illegible] on 10.10.2022

pure encapsulations

8

Fried frailty phenotype criteria

Frailty criterion	Assessment / definition	Measurement / interpretation
Unintentional weight loss	Unintentional loss of >10 lb (≥4.5 kg) or ≥5% of body mass during the previous year	Obtained from the patient, caregiver, or medical records
Weakness	Reduced handgrip strength	Measured using a Kern digital dynamometer; interpreted according to sex and BMI
Exhaustion	Self-reported fatigue or exhaustion	Based on 2 questions from the CES-D scale. Scored 1 (rarely/not at all) to 4 (most of the time); scores of 3–4 indicate a positive criterion
Slow gait	Increased time required to walk 15 ft (4.57 m)	Walking time interpreted according to sex and height
Low physical activity	Low weekly energy expenditure	Calculated using the modified Minnesota Leisure Time Activity Questionnaire

0 points: Not frail.

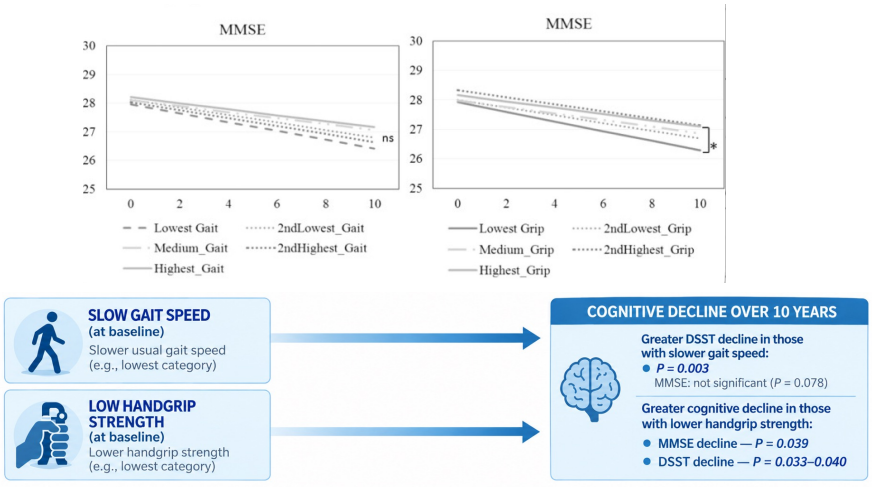
1 to 2 points: Pre-frail.

3 to 5 points: Frail.

Fried LP, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001 Mar;56(3):M146-56.

9

Slow gait or low handgrip are predictors of cognitive decline

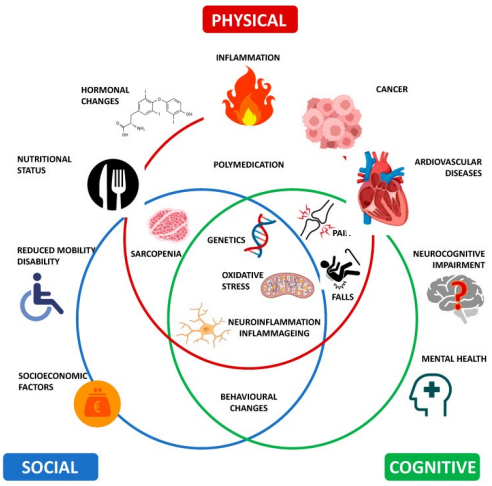


Key: Mini-Mental State Examination (MMSE), Digit symbol substitution test (DSST).

Adapted from: Chou MY, et al. Role of gait speed and grip strength in predicting 10-year cognitive decline among community-dwelling older people. BMC Geriatr. 2019 Jul 5;19(1):186.

10

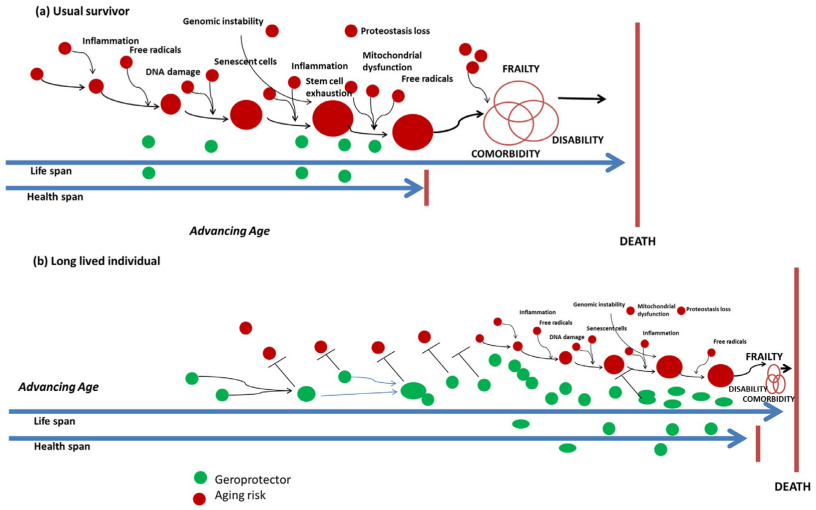
The complex network of frailty and the "frailty puzzle"



Sciacchitano et al. To Be Frail or Not to Be Frail: This Is the Question-A Critical Narrative Review of Frailty. J Clin Med. 2024 Jan 26;13(3):721.

11

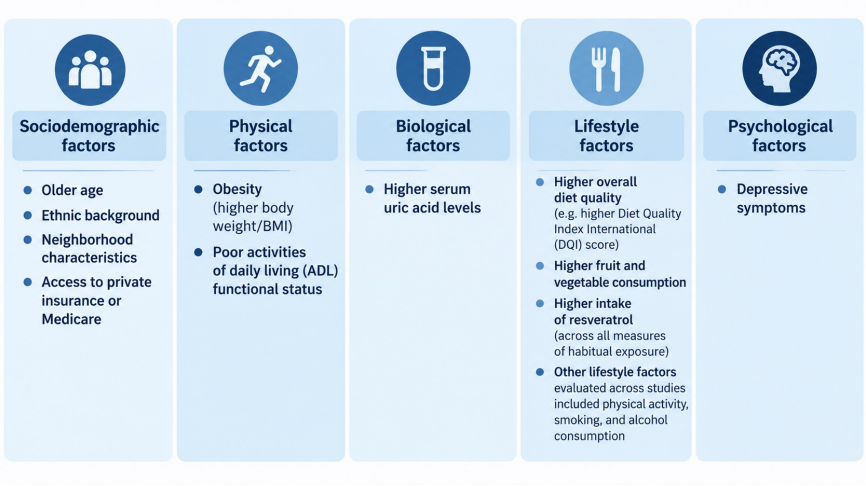
Models for interaction of longevity and frailty



Sathyan S, Verghese J. Genetics of frailty: A longevity perspective. Transl Res. 2020 Jul;221:83-96.

12

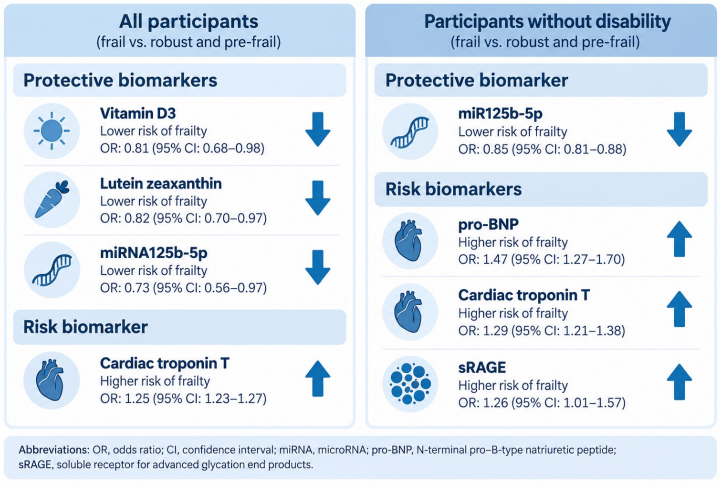
Risk factors and protective factors associated with frailty



Adapted from: Feng Z, et al. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: A systematic review of longitudinal studies. PLoS One. 2017 Jun 15;12(6):e0178383.

13

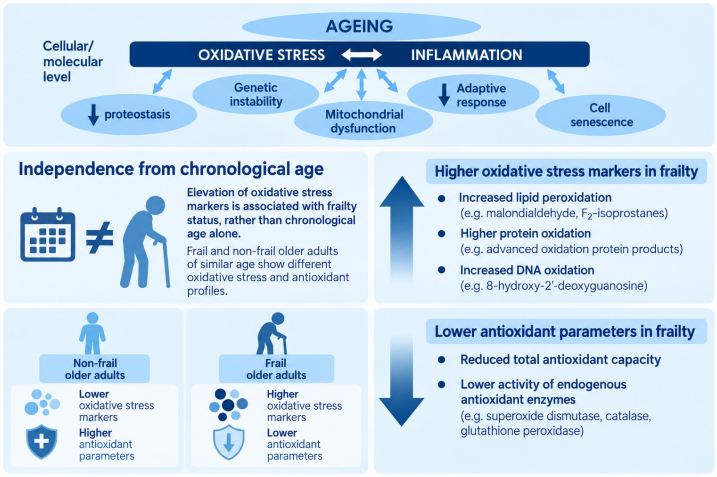
Phenotype-specific omic expression patterns in frailty



Adapted from: Gomez-Cabrero D, et al; FRAILOMIC initiative. A robust machine learning framework to identify signatures for frailty: a nested case-control study in four aging European cohorts. Geroscience. 2021 Jun;43(3):1317-1329.

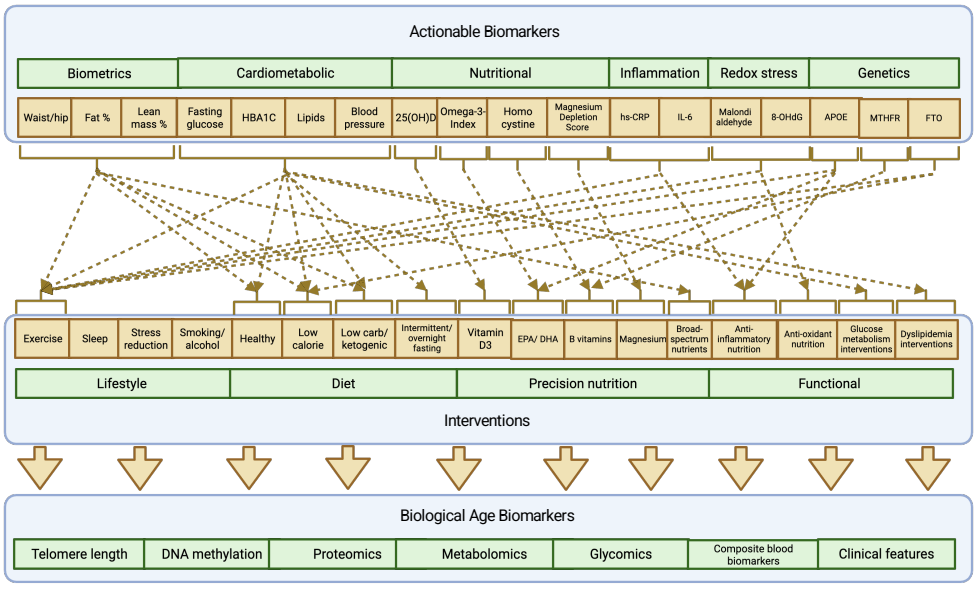
14

Redox, immunological and mitochondrial dysfunction



Adapted from: El Assar M, et al. Frailty as a phenotypic manifestation of underlying oxidative stress. Free Radic Biol Med. 2020 Mar;149:72-77.

15



Key: HbA1c; hemoglobin A1c, 25(OH)D; 25-hydroxy vitamin D, hs-CRP; high-sensitivity C-reactive protein, IL-6; interleukin-6, 8-OHdG; 8-hydroxy-2'-deoxyguanosine, APOE; apolipoprotein E, MTHFR; methylenetetrahydrofolate reductase, FTO; fat mass and obesity-associated gene region.

Image: Brown BI. Nutritional Medicine Institute. 2026.

16

Dietary associations

17

Associations between food and longevity, are complicated

"Assuming the meta-analyzed evidence from cohort studies represents life span–long causal associations, for a baseline life expectancy of 80 years;

- eating 12 hazelnuts daily (1 oz) would prolong life by 12 years (i.e., 1 year per hazelnut)
- drinking 3 cups of coffee daily would achieve a similar gain of 12 extra years,
- and eating a single mandarin orange daily (80 g) would add 5 years of life.
- Conversely, consuming 1 egg daily would reduce life expectancy by 6 years,
- and eating 2 slices of bacon (30 g) daily would shorten life by a decade, an effect worse than smoking.

Could these results possibly be true?"

A FOOD FOUNTAIN OF YOUTH?



Ioannidis JPA. The Challenge of Reforming Nutritional Epidemiologic Research. JAMA. 2018 Sep 11;320(10):969-970.

18

Healthy eating predicts risk

In a cross-sectional analysis of 14,300 U.S. adults from NHANES (2007–2018), **higher diet quality, measured by the Healthy Eating Index-2015 (HEI-2015), was significantly associated with lower frailty**, with participants in the highest HEI quintile having **31% lower adjusted odds of frailty** than those in the lowest quintile (OR 0.69; 95% CI 0.56–0.87), although the study design cannot establish causality.

BMC Public Health. 2025 Mar 19;25(1):1068.



He et al. BMC Public Health (2025) 25:1068
https://doi.org/10.1186/s12889-025-22245-x

BMC Public Health

RESEARCH Open Access

Association of dietary health indices with frailty

Ting He[†], Yifei Yan[†], Dongdong Wang*, Tingting Peng* and Liuyin Jin*

Abstract

Background The Healthy Eating Index (HEI-2015) assesses dietary quality, and lower scores may be associated with an increased risk of frailty. However, few epidemiological studies have examined the relationship between HEI-2015 and the Frailty Index (FI). This study explores the association between HEI-2015 and FI using data from the U.S. National Health and Nutrition Examination Survey (NHANES), analyzing how factors such as gender and age influence this relationship.

Methods NHANES data (2007–2018) were analyzed using logistic regression models to assess the HEI-2015-frailty association. Frailty diagnosis was based on physical activity, strength, fatigue, weight change, and gait speed, with FI scores ranging from 0 to 1. A threshold of 0.21 classified frailty. The R package "DALEX" was used for feature importance analysis to enhance the prediction of frailty. From this analysis, we selected 10 key factors to further improve the accuracy of frailty prediction.

Result Of 14,300 participants, 16.2% (2,322) were classified as frail. Frail participants had lower income, higher BMI, lower physical activity, and lower HEI-2015 scores. Higher HEI-2015 scores were associated with reduced frailty risk (adjusted OR: 0.69; 95% CI: 0.56–0.87, P < 0.01). The negative association was stronger in women, higher-income groups, and those with higher education (P < 0.01). Feature importance analysis showed HEI-2015 was the top predictor of frailty.

Conclusion Higher HEI-2015 scores are linked to lower frailty risk. Promoting healthy eating may prevent frailty, especially in high-risk groups, with education and demographic factors influencing this relationship.

Keywords NHANES, Hei, Frailty

Introduction

The Healthy Eating Index (HEI) is a widely used tool to quantitatively evaluate dietary patterns and quality [1]. The 2015 version of the Healthy Eating Index (HEI-2015) was developed based on the 2015–2020 Dietary Guidelines for Americans (DGA)2 to provide a comprehensive measure of diet quality. Previous studies have shown that healthy eating is associated with increased life expectancy and a reduced risk of adverse health outcomes. Higher HEI-2015 scores indicate better dietary quality and are positively correlated with improved mental health [2–4].However, these studies often fail to fully

© The Author(s) 2025. Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Nutrition-related parameters

In a large observational study of 9,030 adults, frailty was associated with multiple nutritional deficits—including **inadequate energy, protein and micronutrient intake, abnormal nutrient biomarkers, and body composition**—with the accumulation of nutritional deficits strongly associated with greater frailty and mortality risk.

BMC Med. 2018 Oct 26;16(1):188.



Jayanama et al. BMC Medicine (2018) 16:188
https://doi.org/10.1186/s12916-018-1176-6

BMC Medicine

RESEARCH ARTICLE Open Access

Frailty, nutrition-related parameters, and mortality across the adult age spectrum

Kulapong Jayanama[1,2], Olga Theou[2,3], Joanna M Blodgett[4], Leah Cahill[2,5] and Kenneth Rockwood[2,6*]

Abstract

Background: Nutritional status and individual nutrients have been associated with frailty in older adults. The extent to which these associations hold in younger people, by type of malnutrition or grades of frailty, is unclear. Our objectives were to (1) evaluate the relationship between individual nutrition-related parameters and frailty, (2) investigate the association between individual nutrition-related parameters and mortality across frailty levels, and (3) examine whether combining nutrition-related parameters in an index predicts mortality risk across frailty levels.

Methods: This observational study assembled 9030 participants aged ≥ 20 years from the 2003–2006 cohorts of the *National Health and Nutrition Examination Survey* who had complete frailty data. A 36-item frailty index (FI) was constructed excluding items related to nutritional status. We examined 62 nutrition-related parameters with established cut points: 34 nutrient intake items, 5 anthropometric measurements, and 23 relevant blood tests. The 41 nutrition-related parameters which were associated with frailty were combined into a nutrition index (NI). All-cause mortality data until 2011 were identified from death certificates.

Results: All 5 anthropometric measurements, 21/23 blood tests, and 19/34 nutrient intake items were significantly related to frailty. Although most nutrition-related parameters were directly related to frailty, high alcohol consumption and high levels of serum alpha-carotene, beta-carotene, beta-cryptoxanthin, total cholesterol, and LDL-c were associated with lower frailty scores. Only low vitamin D was associated with increased mortality risk across all frailty levels. Seventeen nutrition-related parameters were associated with mortality in the 0.1–0.2 FI group, 11 in the 0.2–0.3 group, and 16 in the > 0.3 group. Overall, 393 (5.8%) of the participants had an NI score less than 0.1 (abnormality in ≤ 4 of the 41 parameters examined). Higher levels of NI were associated with higher mortality risk after adjusting for frailty and other covariates (HR per 0.1: 1.19 (95%CI 1.133–1.257)).

Conclusions: Most nutrition-related parameters were correlated to frailty, but only low vitamin D was associated with higher risk for mortality across levels of frailty. As has been observed with other age-related phenomena, even though many nutrition-related parameters were not significantly associated with mortality individually, when combined in an index, they strongly predicted mortality risk.

Keywords: Nutrition, Dietary intake, Frailty, Frailty index, Mortality, NHANES

Background

Reflecting the increasing life expectancy of the global population [1], the number of adults aged 65 years or older is predicted to double by 2050 [2]. In parallel, the prevalence of age-related health deficits including cardiovascular, metabolic, cognitive, and musculoskeletal diseases is growing [3–6]. Frailty is a multiply determined, age-related state of vulnerability to adverse health outcomes compared with others of the same age [7, 8]. It is associated with a range of adverse outcomes, including morbidity, mortality, and increased healthcare costs [9, 10]. Frailty can be observed at all adult ages and is closely tied to ageing, suggesting that the prevalence of frailty is likely to increase as populations age [11]. Even so, two European cohorts have observed only very modest increases with age in the

© The Author(s). 2018, corrected publication December/2018. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Nutrition-related parameters

Category	Associated with greater frailty
Dietary intake	Low energy; low energy/kg; low protein; low protein/kg; low carbohydrate; high saturated fat; low vitamins A, C, B1, B2, B3 and B6; low folate; low phosphorus, copper, sodium and selenium; low fish-oil intake
Biochemical	Low lymphocytes, haemoglobin and albumin; abnormal MCV; low vitamins A, C, D and B6; low carotenoids; low iron; abnormal creatinine; high triglycerides; low HDL-C; abnormal glucose; high homocysteine
Anthropometric	Obesity; >10% weight loss; >10% weight gain; high waist circumference; high triceps skinfold; high subscapular skinfold

Jayanama K, et al. Frailty, nutrition-related parameters, and mortality across the adult age spectrum. BMC Med. 2018 Oct 26;16(1):188.

21

Diet and lifestyle interventions

22

Diet and lifestyle interventions

A systematic review of 11 randomised controlled trials found that **nutritional guidance may help prevent or improve frailty** in community-dwelling older adults, with the **most consistent benefits seen from long-term (≥6 months)**, individually tailored, professionally delivered interventions, **particularly when combined with structured physical activity**.

J Nutr Health Aging. 2026 Jan;30(1):100756.



The Journal of nutrition, health and aging 30 (2026) 100756

Contents lists available at ScienceDirect

The Journal of nutrition, health and aging

journal homepage: www.elsevier.com/locate/jnha

Review

Effects of nutritional guidance on frailty in older adults: A systematic review

Tatsuya Koyama [a,*], Junko Nohara [b], Mieko Nakamura [b]

[a] National Institutes of Biomedical Innovation, Health and Nutrition, National Institute of Health and Nutrition, Japan
[b] Eiii University, Japan

ARTICLE INFO

Keywords:
Frailty
Nutritional guidance
Dietary education
Older adults
Systematic review

ABSTRACT

Background: Frailty is a prevalent geriatric syndrome associated with risk of disability, hospitalization, and mortality. Despite nutrition and exercise playing central roles in maintaining muscle mass and function, the specific effects of nutritional guidance, distinct from supplementation, remain unclear.

Objective: This systematic review aimed to evaluate the effectiveness of nutritional guidance interventions on frailty in community-dwelling older adults.

Methods: A systematic search in MEDLINE (PubMed) identified relevant randomized controlled trials (RCTs) published up to April 2025. Eligible studies included those with participants aged ≥65 years who received nutritional guidance, defined as dietary counseling or education without supplementation, with frailty status as the primary outcome measure. The risk of bias was assessed using Cochrane RoB 2.0.

Results: From 211 initial records, 11 relevant RCTs were included in the analyses. The interventions varied in duration (12 weeks to 8 years), delivery (individual or group sessions), and implementers (dietitians, health professionals, or non-professionals). Short-term interventions produced mixed results, whereas long-term programs, particularly those combined with exercise, showed more consistent improvements in frailty measures. Individually tailored and professionally delivered interventions were generally more effective. However, substantial heterogeneity in intervention design, frailty definitions, and outcome measures limited comparability across studies. Few trials quantitatively assessed dietary intake, restricting mechanistic understanding.

Conclusion: Nutritional guidance can help prevent or improve frailty in older adults, especially when implemented as a long-term, individualized, and professionally delivered program, ideally combined with physical activity. Future research should adopt standardized frailty criteria, reliable dietary assessment methods, and multidisciplinary approaches to strengthen the evidence and inform sustainable strategies for healthy aging.

1. Introduction

Aging is a global health concern that affects all individuals. According to the World Health Organization, the number of people aged 60 years and older is projected to increase from 1 billion in 2019 to 1.4 billion by 2030, and more than 2.1 billion by 2050 [1]. Aging is associated with various physical, cognitive, and social changes affecting morbidity and mortality and accompanied by a progressive decline in muscle mass, strength, and physical performance. From approximately 50 years of age, individuals are estimated to lose 1–2% of leg muscle mass and 1.5–5% of leg strength per year [2]. These physiological changes contribute to an increased vulnerability to adverse health outcomes.

Frailty is a clinical syndrome characterized by a decline in physiological reserves across multiple organ systems. While sarcopenia—manifested as slowness, weakness, exhaustion, low activity, and weight loss—is an important feature, frailty extends beyond muscle loss to include cognitive, psychological, and social domains [3]. Frail individuals are at increased risk of adverse outcomes, including falls, fractures, disability, hospitalization, and mortality [4]. The prevalence of frailty among older adults varies widely, ranging from 4% to 59%, depending on the criteria and population studied [5]. Given its significant impact on health and quality of life, frailty prevention has become a major priority in geriatric care and public health.

Various interventions including physical activity, pharmacological treatment, and nutritional strategies have been explored to prevent or

* Corresponding author.
E-mail address: t-koyama@nibn.go.jp (T. Koyama).

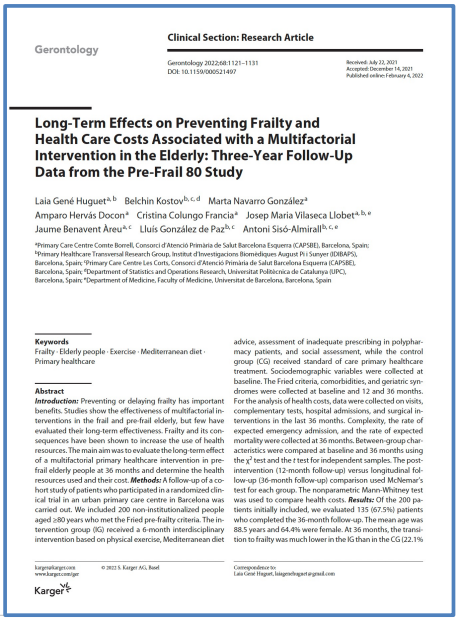
https://doi.org/10.1016/j.jnha.2025.100756
Received 19 September 2025; Received in revised form 1 December 2025; Accepted 3 December 2025
Available online 11 December 2025
1279-7707/© 2025 The Authors. Published by Elsevier Masson SAS on behalf of SERDI Publisher. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

23

The pre-frail 80 study

A randomised clinical trial in **200 community-dwelling pre-frail adults aged ≥80 years** found that a **6-month multifactorial intervention combining Mediterranean diet advice, aerobic and multicomponent exercise, medication review and social assessment** was associated with a significantly lower progression to frailty at **36 months** compared with usual primary care (**22.1% vs 32.8%; p = 0.013**), with lower but non-significantly different healthcare costs.

Gerontology. 2022;68(10):1121-1131.



Gerontology

Clinical Section: Research Article

Gerontology 2022;68:1121–1131
DOI: 10.1159/000521497

Received: July 23, 2021
Accepted: December 14, 2021
Published online: February 4, 2022

Long-Term Effects on Preventing Frailty and Health Care Costs Associated with a Multifactorial Intervention in the Elderly: Three-Year Follow-Up Data from the Pre-Frail 80 Study

Laia Gené Huguet[a, b] Belchin Kostov[b, c, d] Marta Navarro González[a]
Amparo Hervás Docon[a] Cristina Colungo Francia[a] Josep Maria Vilaseca Llobet[a, b, e]
Jaume Benavent Areu[a, c] Lluís González de Paz[b, c] Antoni Sisó-Almirall[b, c, e]

[a]Primary Care Centre Comte Borrell, Consorci d'Atenció Primària de Salut Barcelona Esquerra (CAPSBE), Barcelona, Spain; [b]Primary Healthcare Transversal Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [c]Primary Care Centre Les Corts, Consorci d'Atenció Primària de Salut Barcelona Esquerra (CAPSBE), Barcelona, Spain; [d]Department of Statistics and Operations Research, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain; [e]Department of Medicine, Faculty of Medicine, Universitat de Barcelona, Barcelona, Spain

Keywords
Frailty · Elderly people · Exercise · Mediterranean diet · Primary healthcare

Abstract
Introduction: Preventing or delaying frailty has important benefits. Studies show the effectiveness of multifactorial interventions in the frail and pre-frail elderly, but few have evaluated their long-term effectiveness. Frailty and its consequences have been shown to increase the use of health resources. The main aim was to evaluate the long-term effect of a multifactorial primary healthcare intervention in pre-frail elderly people at 36 months and determine the health resources used and their cost. ***Methods:*** A follow-up of a cohort study of patients who participated in a randomized clinical trial in an urban primary care centre in Barcelona was carried out. We included 200 non-institutionalized people aged ≥80 years who met the Fried pre-frailty criteria. The intervention group (IG) received a 6-month interdisciplinary intervention based on physical exercise, Mediterranean diet advice, assessment of inadequate prescribing in polypharmacy patients, and social assessment, while the control group (CG) received standard of care primary healthcare treatment. Sociodemographic variables were collected at baseline. The Fried criteria, comorbidities, and geriatric syndromes were collected at baseline and 12 and 36 months. For the analysis of health costs, data were collected on visits, complementary tests, hospital admissions, and surgical interventions in the last 36 months. Complexity, the rate of expected emergency admission, and the rate of expected mortality were collected at 36 months. Between-group characteristics were compared at baseline and 36 months using the χ^2 test and the *t* test for independent samples. The post-intervention (12-month follow-up) versus longitudinal follow-up (36-month follow-up) comparison used McNemar's test for each group. The nonparametric Mann-Whitney test was used to compare health costs. ***Results:*** Of the 200 patients initially included, we evaluated 135 (67.5%) patients who completed the 36-month follow-up. The mean age was 88.5 years and 64.4% were female. At 36 months, the transition to frailty was much lower in the IG than in the CG (22.1%

karger@karger.com
www.karger.com/ger

© 2022 S. Karger AG, Basel

Correspondence to:
Laia Gené Huguet, laiageneh@gmail.com

Karger

24

The pre-frail 80 study

Reference	Population & Study Design	Age Range	Intervention	Outcome Measures	Results
Gené Huguet et al. 2022	**n = 200** community-dwelling, pre-frail adults initially randomised (100 intervention; 100 control); **36-month follow-up of a randomised clinical trial**. At 36 months, **n = 135** remained (68 intervention; 67 control).	**≥80 years**; mean age of 36-month cohort **88.5 ± 3.3 years**	**6-month multifactorial intervention:** Mediterranean diet advice; aerobic exercise (walking 30–60 min/day ≥3 days/week) plus strength, resistance, balance and coordination exercises; medication review for inappropriate prescribing in patients with polypharmacy; and assessment of social needs/support. Control group received usual primary care. Participants were followed for **36 months**.	Primary long-term outcome: **frailty status according to Fried criteria** at 36 months. Secondary outcomes included comorbidities, geriatric syndromes, healthcare resource utilisation and healthcare costs.	At 36 months, **22.1%** of the intervention group had progressed to frailty versus **32.8%** of controls (**p = 0.013**); **14.7%** of the intervention group were robust versus **1.5%** of controls. Mean healthcare costs were lower in the intervention group (€2,679 vs €3,110), although the difference was **not statistically significant (p = 0.554)**.

25

Multi-component intervention

A randomised controlled trial in 246 community-dwelling prefrail or frail adults aged ≥65 years found that 24 weeks of **nutritional supplementation** (iron, folate, vitamin B6, vitamin B12, vitamin D and calcium)**, physical training, cognitive training, or a combination of all three significantly increased frailty reversal** compared with usual care, with benefits persisting at 12 months and **the greatest frailty reduction observed with the combined intervention** (47.8% vs 15.2% with control).

Am J Med. 2015 Nov;128(11):1225-1236.e1.



CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial

Tze Pin Ng, MD,[a] Liang Feng, PhD,[a] Ma Shwe Zin Nyunt, PhD,[a] Lei Feng, PhD,[a] Mathew Niti, PhD,[b] Boon Yeow Tan, MMED,[c] Gribson Chan, MSc,[c] Sue Anne Khoo, MPsych(Clin),[d] Sue Mei Chan, MHlthSc (Mgmt),[d] Philip Yap, MRCP,[d] Keng Bee Yap, FRCP(Edin)[e]

[a]Gerontology Research Programme, Department of Psychological Medicine, National University of Singapore, Singapore; [b]Performance and Technology Assessment, Ministry of Health, Singapore; [c]St Luke's Hospital, Singapore; [d]Khoo Teck Puat Hospital, Singapore; [e]Alexandra Hospital, Singapore.

ABSTRACT

BACKGROUND: It is important to establish whether frailty among older individuals is reversible with nutritional, physical, or cognitive interventions, singly or in combination. We compared the effects of 6-month-duration interventions with nutritional supplementation, physical training, cognitive training, and combination treatment vs control in reducing frailty among community-dwelling prefrail and frail older persons.

METHODS: We conducted a parallel group, randomized controlled trial in community-living prefrail and frail old adults in Singapore. The participants' mean age was 70.0 years, and 61.4% (n = 151) were female. Five different 6-month interventions included nutritional supplementation (n = 49), cognitive training (n = 50), physical training (n = 48), combination treatment (n = 49), and usual care control (n = 50). Frailty score, body mass index, knee extension strength, gait speed, energy/vitality, and physical activity levels and secondary outcomes (activities of daily living dependency, hospitalization, and falls) were assessed at 0 months, 3 months, 6 months, and 12 months.

RESULTS: Frailty score and status over 12 months were reduced in all groups, including control (15%), but were significantly higher (35.6% to 47.8%) in the nutritional (odds ratio [OR] 2.98), cognition (OR 2.89), and physical (OR 4.05) and combination (OR 5.00) intervention groups. Beneficial effects were observed at 3 months and 6 months, and persisted at 12 months. Improvements in physical frailty domains (associated with interventions) were most evident for knee strength (physical, cognitive, and combination treatment), physical activity (nutritional intervention), gait speed (physical intervention), and energy (combination intervention). There were no major differences with respect to the small numbers of secondary outcomes.

CONCLUSIONS: Physical, nutritional, and cognitive interventional approaches were effective in reversing frailty among community-living older persons.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). • The American Journal of Medicine (2015) 128, 1225-1236

KEYWORDS: Cognitive training; Frailty; Nutritional supplementation; Physical exercise

Trial Registration: clinicaltrials.gov; Identifier: NCT00973258.
Funding: See last page of article.
Conflict of Interest: See last page of article.
Authorship: See last page of article.

Requests for reprints should be addressed to Tze Pin Ng, MD, Gerontology Research Programme, National University of Singapore, Department of Psychological Medicine, NUHS Tower Block, 9th Floor, 1E Kent Ridge Road, Singapore 119228, Singapore.
E-mail address: pcmtpng@nus.edu.sg

0002-9343/© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.amjmed.2015.06.017

26

Multi-component intervention

Reference	Population & Study Design	Age Range	Intervention	Outcome Measures	Results
Ng et al. 2015	n = 246 community-dwelling prefrail or frail older adults in Singapore; parallel-group randomised controlled trial	≥65 years; mean 70.0 ± 4.7 years	**24 weeks:** nutritional supplementation (n=49); cognitive training (n=50); physical training (n=48); combined nutritional + cognitive + physical intervention (n=49); or usual-care control (n=50). Nutritional supplementation provided additional protein-energy and micronutrients; physical training comprised progressive strength and balance exercise; cognitive training targeted memory, attention, information processing, reasoning and problem solving.	Primary: CHS frailty score/status and frailty components including BMI, knee-extension strength, gait speed, exhaustion/energy and physical activity. Secondary: ADL/IADL dependency, hospitalisation and falls. Assessed at baseline, 3, 6 and 12 months.	At 12 months, frailty reduction occurred in **35.6%** of the nutritional group (OR 2.98), **35.6%** cognitive (OR 2.89), **41.3%** physical (OR 4.05) and **47.8%** combined (OR 5.00), compared with **15.2%** of controls. Benefits were evident during intervention and persisted at 12 months. Specific improvements included physical activity with nutrition, knee strength with cognitive/physical/combined interventions, gait speed with physical training, and energy with combined treatment. No significant differences were found for secondary clinical outcomes.

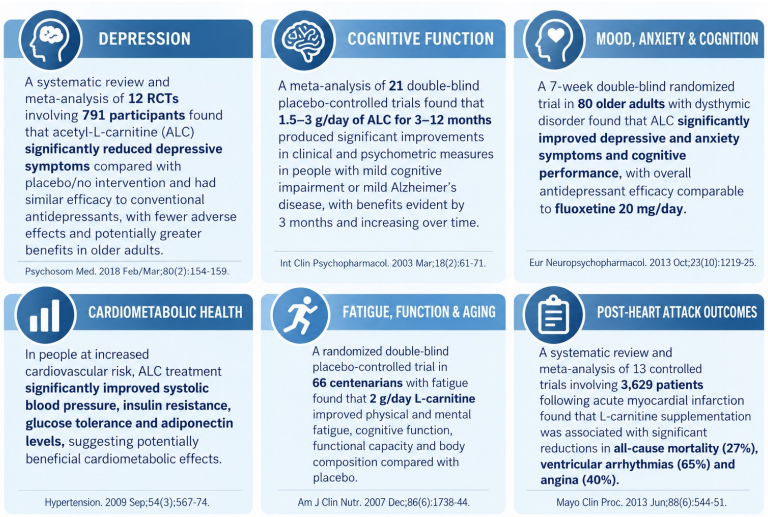
Am J Med. 2015 Nov;128(11):1225-1236.e1.

27

Carnitine

28

Clinical and meta-analysis data relevant to aging



29

Clinical and meta-analysis data relevant to aging

- Veronese N, Stubbs B, Solmi M, Ajnakina O, Carvalho AF, Maggi S. Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis. Psychosom Med. 2018 Feb/Mar;80(2):154-159.
- Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol. 2003 Mar;18(2):61-71.
- Bersani G, Meco G, Denaro A, Liberati D, Colletti C, Nicolai R, Bersani FS, Koverech A. L-Acetylcarnitine in dysthymic disorder in elderly patients: a double-blind, multicenter, controlled randomized study vs. fluoxetine. Eur Neuropsychopharmacol. 2013 Oct;23(10):1219-25.
- Ruggenenti P, Cattaneo D, Loriga G, Ledda F, Motterlini N, Gherardi G, Orisio S, Remuzzi G. Ameliorating hypertension and insulin resistance in subjects at increased cardiovascular risk: effects of acetyl-L-carnitine therapy. Hypertension. 2009 Sep;54(3):567-74.
- Malaguarnera M, Cammalleri L, Gargante MP, Vacante M, Colonna V, Motta M. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. Am J Clin Nutr. 2007 Dec;86(6):1738-44.

30

Not so rare?

"As we learn more about how metabolism is controlled by families of genes that work as a network rather than single genes working independently, we better understand that metabolic disorders exist on a continuum, ranging from the most extreme inborn error to that of more complex genotypic states that are not seen as a "rare disease" but rather as "functional" in origin."

Integr Med (Encinitas). 2016 Mar;15(1):14-6.



CREATING SYNTHESIS

When Is a Rare Disease Not so Rare? Implications for Medical Nutrition Therapy

Jeffrey Bland, PhD, Associate Editor

***Jeffrey Bland, PhD,** is the president and founder of the Personalized Lifestyle Medicine Institute in Seattle, Washington. He has been an internationally recognized leader in nutrition medicine for more than 25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book* The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life.

Recently, I had a conversation with a master clinician and teacher who is a living legend in the functional medicine world, Dr Sidney Baker. As we talked, he reminded me of another discussion we had had—one that took place more than 25 years ago.

That discussion related to a patient of Dr Baker's, an individual who had a chronic fat digestion problem that seemed intractable: All the traditional diagnostic tests had come back with no definitive diagnosis and the use of pancreatic enzyme supplements did not seem to alleviate the symptoms. Dr Baker reminded me that I suggested he read an article describing the role that taurine has in the synthesis of bile acids. This article described how defects in bile acid synthesis were found in some children to be a result of genetic alterations in the conjugation of taurine with bile salts, thereby resulting in a functional bile acid deficiency.[1,2] Following our conversation all those many years ago, Dr Baker tried taurine supplementation in his patient, and this individual's chronic digestive problem resolved permanently.

In our recent discussion of this long-ago case, both Dr Baker and I observed that taurine supplementation has continued to be studied for the past 2-plus decades, and in some individuals with fat maldigestion and steatorrhea, clinical trials using 1500 to 2000 mg of taurine have demonstrated resolution of fat intolerance.[3] It has recently been reported that a fat-modified enteral medical food that contains supplemental taurine and carnitine improves feeding tolerance in critically ill patients.[4] Response to taurine supplementation is related to genetic uniqueness among differing individuals in bile acid synthesis.

Not long after my conversation with Dr Baker, I ran into one of my former students—a woman who had taken the medical school biochemistry course I taught in the 1970s. She also mentioned a memory, and this one involved me discussing the relationship between zinc deficiency in infants and the skin disorder acrodermatitis enteropathica (AE). This former student, who had gone on to become a physician, saw an infant in her practice decades after my lecture who presented with an inflammation of the skin that resembled the slides I had shown—images of patients with AE treated by Dr Lucille Hurley at the University of California, Davis—so many years earlier. Dr Hurley had discovered that the cause of AE in these children resulted from feeding them cow's milk, which contains a zinc binding protein that prevents proper zinc absorption.[5] Some children have a genetic predisposition for this condition due to differences (compared with the population at large) in the way they absorb and metabolize zinc.

These conversations caused me to reflect. I recognized that both conditions are rare. They also are undoubtedly related to unique genetic differences between "normal" and "dysfunctional." But, I pondered: When does a condition go from being a more common functional disorder that varies from mild to moderate in its presentation to the more severe form of a "rare disease?"

This question started swirling around my mind like bees in a hive. For the next few weeks, I seemed to come back again and again to it: When is a rare disease not so rare? I began to explore the vitamin dependent genetic metabolism diseases of infancy, such as megaloblastic anemia, which results from an inborn error of vitamin B_{12} metabolism; with this condition, the amount of supplementation needed varies from individual to individual, ranging from several-fold to several hundred-fold the recommended intake of the vitamin to achieve adequate vitamin B_{12} status.[6] At what point in this spectrum of differing vitamin B_{12} needs does a functional disorder become a rare disease? When does medical nutrition therapy become pharmacology? I came to recognize that this concern could be applied to virtually all the essential nutrients for which there are recognized clinical biomarkers for defining inadequacies.[7]

This question—where is the line?—can even be applied to conditions traditionally considered monogenetic metabolic disorders, such as phenylketonuria (PKU). PKU is well known to be a result of a mutation in the gene that

14 Integrative Medicine • Vol. 15, No. 1 • February 2016 *Bland—Creating Synthesis*

31

Plasma acylcarnitines as metabolic signatures

Abnormal plasma acylcarnitines are biomarkers of mitochondrial dysfunction,[1-2] and have been observed in various metabolic and age-related conditions, including:

- Major depressive disorder[3]
- Type II diabetes mellitus[4]
- Alzheimer's disease[5,6]
- Frailty[7,8]
- Healthy aging[9]

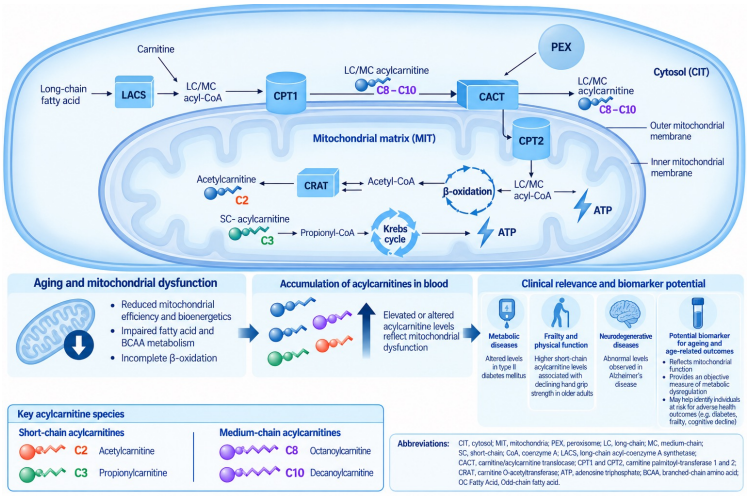
32

Plasma acylcarnitines as metabolic signatures

1. McGill MR, et al. Circulating acylcarnitines as biomarkers of mitochondrial dysfunction after acetaminophen overdose in mice and humans. Arch Toxicol. 2014;88(2):391–401.
2. Rinaldo P, Cowan TM, Matern D. Acylcarnitine profile analysis. Genet Med. 2008;10(2):151–156. doi:10.1097/gim.0b013e3181614289 15.
3. Nasca C, et al. Acetyl-l-carnitine deficiency in patients with major depressive disorder. Proc Natl Acad Sci U S A. 2018 Aug 21;115(34):8627-8632.
4. Schooneman MG, Vaz FM, Houten SM, Soeters MR. Acylcarnitines: reflecting or inflicting insulin resistance? Diabetes. 2013;62(1):1–8.
5. Ciavardelli D, et al. Medium-chain plasma acylcarnitines, ketone levels, cognition, and gray matter volumes in healthy elderly, mildly cognitively impaired, or Alzheimer's disease subjects. Neurobiol Aging. 2016;43:1–12.
6. Cristofano A, et al. Serum Levels of Acyl-Carnitines along the Continuum from Normal to Alzheimer's Dementia. PLoS One. 2016 May 19;11(5):e0155694.
7. Ng TKS, et al. Novel metabolomics markers are associated with pre-clinical decline in hand grip strength in community-dwelling older adults. Mech Ageing Dev. 2021;193:111405.
8. Malaguarnera G, et al. Carnitine Serum Levels in Frail Older Subjects. Nutrients. 2020 Dec 19;12(12):3887.
9. Jarrell ZR, et al. Plasma acylcarnitine levels increase with healthy aging. Aging (Albany NY). 2020 Jun 16;12(13):13555-13570.

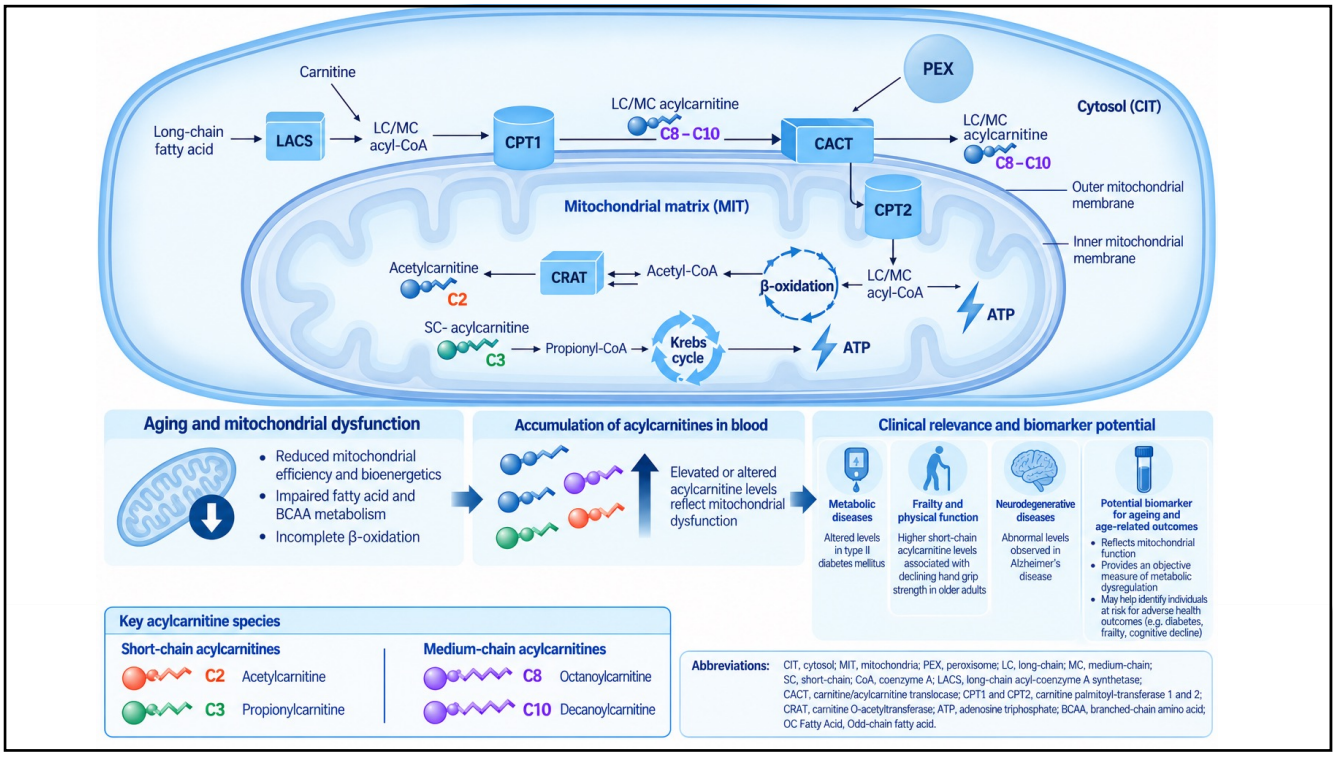
33

Plasma acylcarnitines as metabolic signatures



Adapted from: Ng TKS, et al. J Gerontol A Biol Sci Med Sci. 2024 Mar 1;79(3):glac114. Montanari S, et al. Transl Psychiatry. 2025 Feb 23;15(1):65.

34

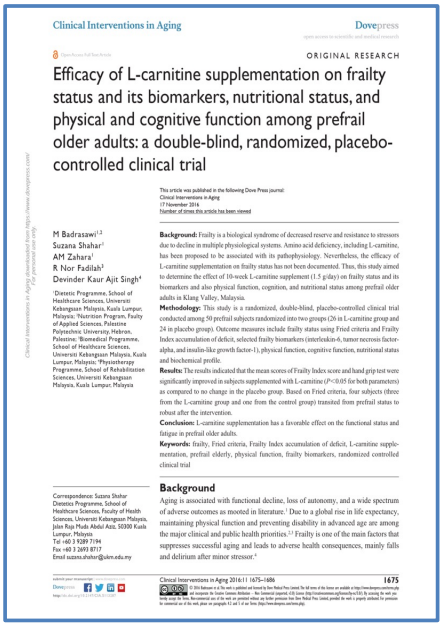


35

A potential biomarker?

In 120 community-dwelling older adults aged 54–91 years, **higher baseline plasma short-chain acylcarnitines** were identified as metabolic signatures predictive of declining health-related quality of life in older adults, potentially reflecting mitochondrial dysfunction detectable before clinically significant health decline.

J Gerontol A Biol Sci Med Sci. 2024 Mar 1;79(3):glac114.



Clinical Interventions in Aging — Dovepress

ORIGINAL RESEARCH

Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older adults: a double-blind, randomized, placebo-controlled clinical trial

M Badrasawi[1,2] Suzana Shahar[1] AM Zahara[1] R Nor Fadilah[3] Devinder Kaur Ajit Singh[4]

[1]Dietetic Programme, School of Healthcare Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [2]Nutrition Program, Faculty of Applied Sciences, Palestine Polytechnic University, Hebron, Palestine; [3]Biomedical Programme, School of Healthcare Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [4]Physiotherapy Programme, School of Rehabilitation Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Background

Aging is associated with functional decline, loss of autonomy, and a wide spectrum of adverse outcomes as mooted in literature.[1] Due to a global rise in life expectancy, maintaining physical function and preventing disability in advanced age are among the major clinical and public health priorities.[1,2] Frailty is one of the main factors that suppresses successful aging and leads to adverse health consequences, mainly falls and delirium after minor stressor.[3]

Clinical Interventions in Aging 2016:11 1675–1686 1675

pure encapsulations

36

A potential biomarker?

Reference	Population & Study Design	Age Range	Biomarkers	Outcome Measure	Results
Ng et al. 2024	**n = 120** community-dwelling older adults in Singapore; combined **cross-sectional and 18-month longitudinal observational pilot study**	**54–91 years**; mean 71.6 years	**Baseline fasting plasma short-chain acylcarnitines (ACs)** were quantified using targeted metabolomics and examined as predictors of health-related quality of life (HRQoL) over **18 months**.	**EQ-5D-5L index** and **EQ-VAS** at baseline and 18 months; clinically important EQ-5D decline (MCID ≥0.082).	Longitudinally, **higher baseline short-chain ACs were significantly associated with greater decline in EQ-5D**, including C2, C4, C4-OH, C3-DC/C5-OH, C4-DC/C6-OH, C5-DC and C6 after adjustment. Individual ACs explained approximately **4.6–8.5% of variance** in EQ-5D decline. Higher C4-DC/C6-OH was particularly strongly associated with clinically meaningful decline; a 1-unit increase was associated with approximately **14-fold greater odds** (OR 14.80; 95% CI 2.15–101.65). No significant adjusted longitudinal associations were found with EQ-VAS.

EuroQol-5 Dimension/EuroQol Visual Analogue Scale; EQ-5D/EQ-VAS.

J Gerontol A Biol Sci Med Sci. 2024 Mar 1;79(3):glac114.

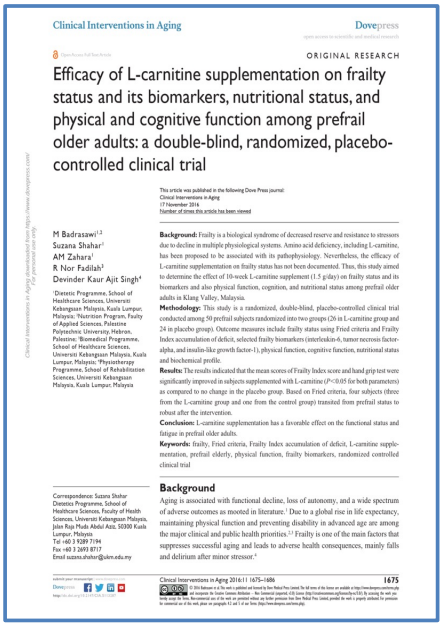
pure encapsulations

37

Improved frailty index scores

A 10-week double-blind, randomised, placebo-controlled trial in 50 prefrail community-dwelling older adults found that supplementation with **1.5 g/day L-carnitine** significantly improved **frailty index scores and hand-grip strength** compared with placebo, although no significant effects were observed on frailty biomarkers, cognition, nutritional status, body composition or most other measures of physical function.

Clin Interv Aging. 2016 Nov 17;11:1675-1686.



Clinical Interventions in Aging — Dovepress

ORIGINAL RESEARCH

Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older adults: a double-blind, randomized, placebo-controlled clinical trial

M Badrasawi[1,2] Suzana Shahar[1] AM Zahara[1] R Nor Fadilah[3] Devinder Kaur Ajit Singh[4]

[1]Dietetic Programme, School of Healthcare Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [2]Nutrition Program, Faculty of Applied Sciences, Palestine Polytechnic University, Hebron, Palestine; [3]Biomedical Programme, School of Healthcare Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [4]Physiotherapy Programme, School of Rehabilitation Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Background: Frailty is a biological syndrome of decreased reserve and resistance to stressors due to decline in multiple physiological systems. Amino acid deficiency, including L-carnitine, has been proposed to be associated with its pathophysiology. Nevertheless, the efficacy of L-carnitine supplementation on frailty status has not been documented. Thus, this study aimed to determine the effect of 10-week L-carnitine supplement (1.5 g/day) on frailty status and its biomarkers and also physical function, cognition, and nutritional status among prefrail older adults in Klang Valley, Malaysia.

Methodology: This study is a randomized, double-blind, placebo-controlled clinical trial conducted among 50 prefrail subjects randomized into two groups (26 in L-carnitine group and 24 in placebo group). Outcome measures include frailty status using Fried criteria and Frailty Index accumulation of deficit, selected frailty biomarkers (interleukin-6, tumor necrosis factor-alpha, and insulin-like growth factor-1), physical function, cognitive function, nutritional status and biochemical profile.

Results: The results indicated that the mean scores of Frailty Index score and hand grip test were significantly improved in subjects supplemented with L-carnitine ($P<0.05$ for both parameters) as compared to no change in the placebo group. Based on Fried criteria, four subjects (three from the L-carnitine group and one from the control group) transited from prefrail status to robust after the intervention.

Conclusion: L-carnitine supplementation has a favorable effect on the functional status and fatigue in prefrail older adults.

Keywords: frailty, Fried criteria, Frailty Index accumulation of deficit, L-carnitine supplementation, prefrail elderly, physical function, frailty biomarkers, randomized controlled clinical trial

Background

Aging is associated with functional decline, loss of autonomy, and a wide spectrum of adverse outcomes as mooted in literature.[1] Due to a global rise in life expectancy, maintaining physical function and preventing disability in advanced age are among the major clinical and public health priorities.[1,2] Frailty is one of the main factors that suppresses successful aging and leads to adverse health consequences, mainly falls and delirium after minor stressor.[3]

Correspondence: Suzana Shahar
Dietetics Programme, School of Healthcare Sciences, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia
Tel +60 3 9289 7194
Fax +60 3 2693 8717
Email suzana.shahar@ukm.edu.my

© 2016 Badrasawi et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (http://www.dovepress.com/terms.php).

pure encapsulations

38

Improved frailty index scores

Reference	Population & Study Design	Age Range	Intervention	Outcome Measures	Results
Badrasawi et al. 2016	**n = 50** community-dwelling prefrail older adults in Malaysia; double-blind, randomised, placebo-controlled clinical trial (L-carnitine n=26; placebo n=24 completing study)	≥60 years; mean age **68.2 ± 6.3 years** in L-carnitine group and **68.8 ± 6.5 years** in placebo group	**L-carnitine 1.5 g/day** (500 mg three times daily) or placebo for **10 weeks**	Frailty: Fried criteria and 40-item Frailty Index (FI); physical function including hand-grip strength, gait speed, chair stand, timed up-and-go, shoulder strength, 2-min step and PEFR; frailty biomarkers (IL-6, TNF-α, IGF-1); cognitive function; nutritional status/body composition; biochemical measures	L-carnitine significantly improved **FI score and hand-grip strength** compared with placebo. At 10 weeks, FI decreased **34.4% vs 2.1%** with placebo (P<0.001), while hand-grip strength increased **7.2% vs a 3.6% decrease** with placebo (P<0.05). Three L-carnitine participants (11.5%) transitioned from prefrail to robust/normal versus one (4.2%) receiving placebo. No significant between-group effects were found for frailty biomarkers, cognition, nutritional status, body composition or most other physical-function measures.

Clin Interv Aging. 2016 Nov 17;11:1675-1686.

39

Delaying prefrailty to frailty

In a randomized controlled trial, acetyl-L-carnitine (1,500 mg twice daily) was administered to pre-frail older patient over a 3-month intervention. Compared to placebo, **acetyl-L-carnitine treatment significantly reduced C reactive protein, increased serum-free carnitine and acetyl carnitine, improved cognitive function** (Mini-Mental State Examination) **and improved physical functional** (6-minute walk test).

Curr Pharm Des. 2022;28(38):3158-3166.


3158 Send Orders for Reprints to reprints@benthamscience.net

Current Pharmaceutical Design, 2022, 28, 3158-3166

RESEARCH ARTICLE

BENTHAM SCIENCE

Acetyl-L-carnitine Slows the Progression from Prefrailty to Frailty in Older Subjects: A Randomized Interventional Clinical Trial

Giulia Malaguarnera[1], Vito Emanuele Catania[2,*], Gaetano Bertino[3], Laura Maria Chisari[3], Maria Castorina[4], Claudia Bonfiglio[5], Omar Cauli[6,7] and Michele Malaguarnera[1,8]

[1]Department of Biomedical and Biotechnological Science, University of Catania, Catania, Italy; [2]Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania, Catania, Italy; [3]Hepatology Unit, A.O.U. Policlinico-San Marco, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [4]Azienda Sanitaria Provinciale di Siracusa, Italy; [5]Medical Centre INPS, Catania, Italy; [6]Department of Nursing, Faculty of Nursing and Podiatry, University of Valencia, c/Jaume Roig s/n, 46010 Valencia, Spain; [7]Frailty and Cognitive Impairment Organized Group (FROG), University of Valencia, 46010 Valencia, Spain; [8]Department of Psychobiology, Facultad de Psicología, Universidad de Valencia, Avda. Blasco Ibáñez, 21, 46010, Valencia, Spain

ARTICLE HISTORY

Received: February 08, 2022
Accepted: June 14, 2022

DOI: 10.2174/1381612828666220803093615

CrossMark

Abstract: Background: Ageing is characterized by a gradual decline in body function, representing the clinical situation called "frailty". Prefrailty is the intermediate stage between frailty and robust condition. L-carnitine (LC) plays an important role in energy production from long-chain fatty acids in mitochondria, and its serum level is lower in prefrail and frail subjects.

Objective: This study aims to evaluate the effect of Acetyl-L-carnitine (ALCAR) in pre-frail older patients.

Methods: We scheduled 3 months of treatment and then 3 months of follow-up. A total of 92 subjects were selected from May, 2009 to July, 2017, in a randomized, observational, double-blind, placebo-controlled study. We scheduled 3 months of treatment and then 3 months of follow-up. ALCAR (oral 1.5 g/bis in die - BID) or placebo groups were used.

Results: After the treatment, only the treated group displayed a decrease in C reactive protein (CRP) ($p < 0.001$ and an increase in serum-free carnitine and acetylcarnitine ($p < 0.05$) in Mini-Mental state (MMSE) ($p < 0.0001$ and 6-walking distance ($p < 0.0001$); ALCAR group vs. placebo group showed a decrease in HDL cholesterol and CRP ($p < 0.01$), an increase in MMSE score ($p < 0.001$) and in the 6-walking distance ($p < 0.001$).

Conclusions: ALCAR treatment delays the incidence and severity of onset of degenerative disorders of the elderly in prefrail subjects with improvement in memory and cognitive processes.

Keywords: Carnitine, cognitive impairment, motor impairment, elderly, aging, Acetyl-L-Carnitine, frailty, prefrailty.

1. INTRODUCTION

The frailty syndrome is characterized by the decline of physical, cognitive, psychological, and social skills that results in a progressive loss of autonomy and capacity to maintain optimal function [1, 2]. Frailty represents an independent risk factor for tolerating stressful events and has been associated with adverse outcomes, such as institutionalization, falls, delirium, incident disability, prolonged hospitalizations, and mortality, and is associated with higher health care use and corresponding costs [3-5].

The prevalence of frailty increases in older age [6]. Frailty is not a single homogeneous concept, and there is no single standard measure. In this study, we classified our patients on the Friend's frailty criteria. Five components were used: unintentional, weight loss, exhaustion, low grip strength, slow walking pace, and low physical activity. Prefrailty predicts future disability but might be modifiable, particularly at an early stage. The identification and planning of interventions may have an implication for prognosis and optimising care, particularly in individuals with multimorbidity [7, 8]. Prefrailty is the transitional state between robustness and frailty in which one or two of five of Fried's criteria are met [9]. Prefrailty has been reported to be associated with chronic comorbidity and functional decline [10-12]. Several systematic reviews have suggested a possible association between falls and prefrailty [13-15].

As prefrailty is prevalent in older people, the impact on this population would be rather large, and an intervention plan would be warranted [16, 17]. In a previous study, we observed carnitine deficiency in frail and prefrail patients [18]. Carnitine is a vitamin-like compound present in mammalian cells as free carnitine and acylcarnitine. L-carnitine plays an important role in energy production. In fact, it transports long-chain fatty acids into the mitochondrial matrix, allowing the fatty acids to be used during beta-oxidation [19-21]. This molecule may also have other roles in lipids, protein, and glucose metabolism.

ALCAR is able to cross the blood-brain barrier, and it is present in the brain in high concentrations, reaching the nervous areas where the linked acetyl group may be delivered. The possibility of providing acetyl groups makes ALCAR able to maintain the intramitochondrial salvage pathways to reactivate coenzyme A, reduce peroxidation and intracellular malonyl aldehyde levels, act as a scavenger, and contribute to neurotransmitter synthesis due to the

*Address correspondence to this author at the Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania, Catania, Italy; E-mail: vito.emania@policlinico.unict.it

1873-4286/22 $65.00+.00 © 2022 Bentham Science Publishers

Current Pharmaceutical Design

40

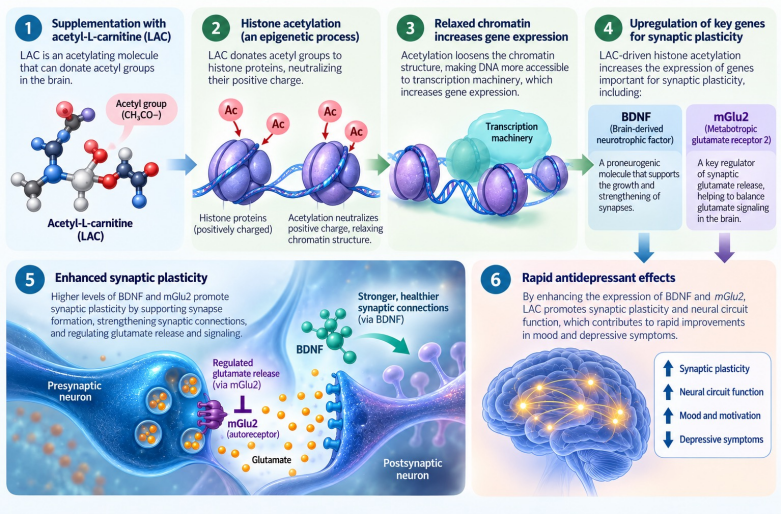
Delaying prefrailty to frailty

Reference	Population & Study Design	Age Range	Intervention	Outcome measures	Results
Malaguarnera et al. 2022	**n = 92** prefrail older adults; randomised, double-blind, placebo-controlled clinical trial; ALCAR n = 46, placebo n = 46	**66–81 years** in ALCAR group; **67–80 years** in placebo group	**Acetyl-L-carnitine (ALCAR), 1.5 g orally twice daily, for 3 months**, followed by 3 months of follow-up; compared with placebo	Frailty status using **Fried criteria**; cognitive function (MMSE); physical performance including 6-minute walking distance, handgrip strength and SPPB; ADL/IADL; serum/urinary carnitine; CRP and other biochemical markers	After 3 months, **15/46 (32.6%)** ALCAR-treated participants improved in frailty status versus **2/46 (4.4%)** with placebo (p = 0.0008), while **1/46 (2.2%)** versus **13/46 (28.3%)**, respectively, worsened (p = 0.0008). ALCAR significantly improved **MMSE** (20.4 → 23.9; p < 0.0001) and **6-minute walking distance** (10.5 → 13.7; p < 0.0001), and reduced **CRP** (4.80 → 3.20 mg/dL; p < 0.0001). Free carnitine and acylcarnitine also increased significantly. Benefits in frailty status persisted at the 3-month follow-up.

Curr Pharm Des. 2022;28(38):3158-3166.

41

Acetylating molecule acetyl-L-carnitine and the brain



Adapted from: Proc Natl Acad Sci U S A. 2018 Aug 21;115(34):8627-8632.

42

EPA/ DHA

43

Could EPA/ DHA status signal risk?

In a cross-sectional analysis of **18,802 UK Biobank adults aged ≥65 years**, higher plasma **n-3 PUFA levels** were associated with a lower prevalence of frailty, with frailty decreasing from **5.6% at <3.49% n-3 PUFA to 2.7% at >5.92%**, and the highest versus lowest quintile associated with **11% lower adjusted odds of frailty** (OR 0.89, 95% CI 0.84–0.95); higher DHA (>2.62% vs <1.56%) was similarly associated with lower frailty prevalence.

J Gerontol A Biol Sci Med Sci. 2024 May 1;79(5):glae085.



The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2024, 79(5), glae085
https://doi.org/10.1093/gerona/glae085
Advance access publication 22 March 2024
Research Article

GSA GERONTOLOGICAL SOCIETY OF AMERICA | OXFORD

Association of Plasma n-3 Polyunsaturated Fatty Acid Levels and the Prevalence of Frailty in Older Adults: A Cross-Sectional Analysis of UK Biobank

Junghyun Kim, BS,[1] Jason Westra, MS,[2] Nathan Tintle, PhD,[2,3] William S. Harris, PhD,[2,4] and Yongsoon Park, PhD[1,2,4,*]

[1]Department of Food and Nutrition, Hanyang University, Seoul, Republic of Korea.
[2]The Fatty Acid Research Institute, Sioux Falls, South Dakota, USA.
[3]Department of Population Health Nursing Science, College of Nursing, University of Illinois–Chicago, Chicago, Illinois, USA.
[4]Department of Internal Medicine, Sanford School of Medicine, University of South Dakota, Sioux Falls, South Dakota, USA.
*Address correspondence to: Yongsoon Park, PhD. E-mail: yongsoon@hanyang.ac.kr

Decision Editor: Roger A. Fielding, PhD, FGSA (Medical Sciences Section)

Abstract

Background: Circulating levels of n-3 polyunsaturated fatty acids (PUFAs) have been associated with frailty among Koreans (a population with a high intake of fish), but whether this association exists in Western populations with low fish intake is unknown. The present study examined the hypothesis that the prevalence of frailty was inversely associated with plasma levels of n-3 PUFAs, with the intake of oily fish, and with fish oil supplementation in older adults in the United Kingdom.

Methods: UK Biobank including 79 030 adults aged ≥65 years with dietary data, and 18 932 participants with plasma fatty acid data were used. Frailty was defined using the Cardiovascular Health Study index; plasma levels of n-3 PUFAs were measured by nuclear magnetic resonance, and intake of oily fish and/or fish oil supplements was collected via food frequency questionnaires.

Results: Frailty prevalence was inversely associated with n-3 PUFA levels (odds ratios (OR) per SD: 0.86, 95% confidence interval (CI) 0.79–0.94; $p < .001$), with oily fish intake (never vs ≥2 servings per week; OR 0.93, 95% CI 0.82–0.83, $p < .001$), and with the use of fish oil supplements (OR 0.72; 95% CI 0.68–0.78, $p < .001$) after adjusting for confounding factors. All 3 exposures were also associated with each frailty criterion, particularly low physical activity and walking pace.

Conclusions: Inverse associations between plasma n-3 PUFA levels and measures of frailty suggest that higher intakes of oily fish or the use of fish oil supplements may help prevent frailty in older adults in the United Kingdom.

Keywords: Biomarker of n-3 polyunsaturated fatty acids, Oily fish, Older

Frailty is a common geriatric syndrome characterized by unintentional weight loss, exhaustion, slow walking pace, low physical activity, and low grip strength, which results in adverse health outcomes including falls, fractures, hospitalization, disability, and death [1]. As populations age, the prevalence of frailty increases rapidly, ranging from 12% to 24% in 62 countries around the world [2].

Although the pathophysiological changes underlying and preceding frailty are unclear, chronic inflammation appears to be involved and the anti-inflammatory n-3 polyunsaturated fatty acids (PUFAs) can be related with frailty [3]. Previous epidemiological studies consistently showed that intake of fish was inversely associated with the prevalence of frailty in Korean older adults [4], Irish older adults [5], Japanese women [6], and Japanese women with rheumatoid arthritis [7]. Bruno et al. [8], reported that the intake of oily fish was inversely correlated with frailty score in the Ecuadorian older. Additionally, ENRICA cohort studies showed that intake of fish or seafood measured by frequency, as a component of the Mediterranean diet, was associated with reduced incidence of frailty among Spanish older individuals during 2–4 years follow-up [9,10].

Compared to nonfrail older adults, frail older adults had less use of fish oil supplementation in Taiwan [11]. Consumption of n-3 PUFAs including eicosapentaenoic acid (EPA; 20:5n3), docosapentaenoic acid (DPA; 22:5n3), and docosahexaenoic acid (DHA; 22:6n3) was lower in frail than nonfrail Spanish older adults, but was not associated with incidence of frailty during 3.5 years follow-up [12]. Jayanama et al. [13], reported that consumption of n-3 PUFAs including α-linolenic acid (ALA; 18:3n3), stearidonic acid (SDA; 18:4n3), EPA, DPA, and DHA was not associated with the prevalence of frailty among Americans aged ≥50 years old. Three previous clinical trials also found that supplementation of EPA and DHA had no significant effect on frailty scores among Americans aged ≥50 years old [14], or the incidence of frailty among European older adults [15,16]. Nevertheless, a meta-analysis of clinical trials showed that

Received: October 10 2023; Editorial Decision Date: March 19 2024.
© The Author(s) 2024. Published by Oxford University Press on behalf of The Gerontological Society of America. All rights reserved. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

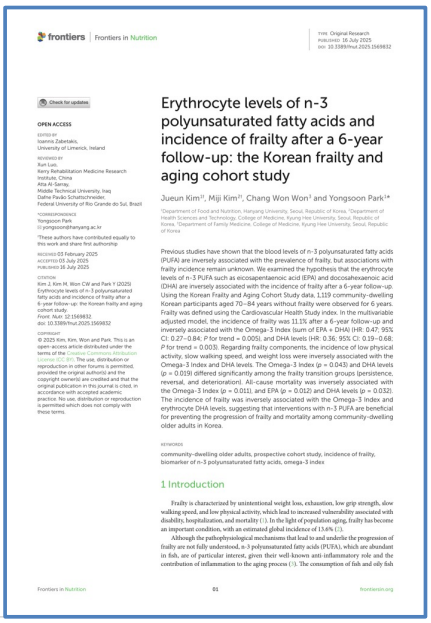
Downloaded from https://academic.oup.com/gerona/article/79/5/glae085/7632139 by guest on 21 October 2026

44

Omega-3 index predicts frailty

In a 6-year prospective cohort study of 1,119 community-dwelling Korean adults aged 70–84 years without frailty at baseline, a higher **Omega-3 Index (erythrocyte EPA + DHA)** was associated with a lower incidence of frailty, with those in the highest quintile (**>13.46%**) having a **53% lower risk** compared with those in the lowest quintile (**≤10.02%**; HR 0.47, 95% CI 0.27–0.84), while higher DHA levels were also independently associated with lower frailty risk.

Front Nutr. 2025 Jul 16;12:1569832.



frontiers | Frontiers in Nutrition

TYPE: Original Research
PUBLISHED: 16 July 2025
DOI: 10.3389/fnut.2025.1569832

Check for updates

OPEN ACCESS

EDITED BY
Ioannis Zabetakis,
University of Limerick, Ireland

REVIEWED BY
Run Luo,
Kerry Rehabilitation Medicine Research Institute, China
Ihsan Al-Saray,
Middle Technical University, Iraq
Dafne Pavão Schuttschneider,
Federal University of Rio Grande do Sul, Brazil

*CORRESPONDENCE
Yongsoon Park
yongsoon@hanyang.ac.kr

†These authors have contributed equally to this work and share first authorship

RECEIVED 05 February 2025
ACCEPTED 03 July 2025
PUBLISHED 16 July 2025

CITATION
Kim J, Kim M, Won CW and Park Y (2025) Erythrocyte levels of n-3 polyunsaturated fatty acids and incidence of frailty after a 6-year follow-up: the Korean frailty and aging cohort study.
Front. Nutr. 12:1569832.
doi: 10.3389/fnut.2025.1569832

COPYRIGHT
© 2025 Kim, Kim, Won and Park. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with those terms.

Erythrocyte levels of n-3 polyunsaturated fatty acids and incidence of frailty after a 6-year follow-up: the Korean frailty and aging cohort study

Jueun Kim[1†], Miji Kim[2†], Chang Won Won[3] and Yongsoon Park[1*]

[1]Department of Food and Nutrition, Hanyang University, Seoul, Republic of Korea, [2]Department of Health Sciences and Technology, College of Medicine, Kyung Hee University, Seoul, Republic of Korea, [3]Department of Family Medicine, College of Medicine, Kyung Hee University, Seoul, Republic of Korea

Previous studies have shown that the blood levels of n-3 polyunsaturated fatty acids (PUFA) are inversely associated with the prevalence of frailty, but associations with frailty incidence remain unknown. We examined the hypothesis that the erythrocyte levels of n-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are inversely associated with the incidence of frailty after a 6-year follow-up. Using the Korean Frailty and Aging Cohort Study data, 1,119 community-dwelling Korean participants aged 70–84 years without frailty were observed for 6 years. Frailty was defined using the Cardiovascular Health Study index. In the multivariable adjusted model, the incidence of frailty was 11.1% after a 6-year follow-up and inversely associated with the Omega-3 Index (sum of EPA + DHA) (HR: 0.47; 95% CI: 0.27–0.84; *P* for trend = 0.005), and DHA levels (HR: 0.36; 95% CI: 0.19–0.68; *P* for trend = 0.003). Regarding frailty components, the incidence of low physical activity, slow walking speed, and weight loss were inversely associated with the Omega-3 Index and DHA levels. The Omega-3 Index ($p = 0.043$) and DHA levels ($p = 0.019$) differed significantly among the frailty transition groups (persistence, reversal, and deterioration). All-cause mortality was inversely associated with the Omega-3 Index ($p = 0.011$), and EPA ($p = 0.012$) and DHA levels ($p = 0.032$). The incidence of frailty was inversely associated with the Omega-3 Index and erythrocyte DHA levels, suggesting that interventions with n-3 PUFA are beneficial for preventing the progression of frailty and mortality among community-dwelling older adults in Korea.

KEYWORDS
community-dwelling older adults, prospective cohort study, incidence of frailty, biomarker of n-3 polyunsaturated fatty acids, omega-3 index

1 Introduction

Frailty is characterized by unintentional weight loss, exhaustion, low grip strength, slow walking speed, and low physical activity, which lead to increased vulnerability associated with disability, hospitalization, and mortality (1). In the light of population aging, frailty has become an important condition, with an estimated global incidence of 13.6% (2).

Although the pathophysiological mechanisms that lead to and underlie the progression of frailty are not fully understood, n-3 polyunsaturated fatty acids (PUFA), which are abundant in fish, are of particular interest, given their well-known anti-inflammatory role and the contribution of inflammation to the aging process (3). The consumption of fish and oily fish

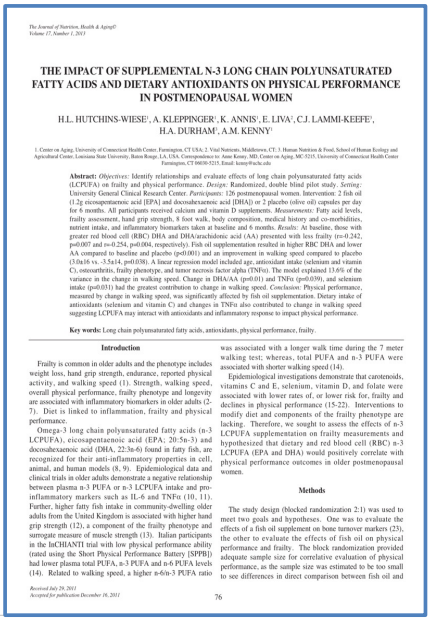
Frontiers in Nutrition 01 frontiersin.org

45

Improved physical performance

A randomised, double-blind, placebo-controlled trial in **126 older postmenopausal women** found that supplementation with **1.2 g/day EPA and DHA for six months significantly improved walking speed compared with placebo**, although no significant improvements were observed in overall frailty, hand-grip strength or chair-rise performance.

J Nutr Health Aging. 2013 Jan;17(1):76-80.



The Journal of Nutrition, Health & Aging©
Volume 17, Number 1, 2013

THE IMPACT OF SUPPLEMENTAL N-3 LONG CHAIN POLYUNSATURATED FATTY ACIDS AND DIETARY ANTIOXIDANTS ON PHYSICAL PERFORMANCE IN POSTMENOPAUSAL WOMEN

H.L. HUTCHINS-WIESE[1], A. KLEPPINGER[1], K. ANNIS[1], E. LIVA[1], C.J. LAMMI-KEEFE[2], H.A. DURHAM[1], A.M. KENNY[3]

1. Center on Aging, University of Connecticut Health Center, Farmington, CT USA; 2. Vital Nutrients, Middletown, CT; 3. Human Nutrition & Food, School of Human Ecology and Agricultural Center, Louisiana State University, Baton Rouge, LA, USA; Correspondence to: Anne Kenny, MD, Center on Aging, MC-5215, University of Connecticut Health Center Farmington, CT 06030-5215, Email: kenny@uchc.edu

Abstract: *Objectives:* Identify relationships and evaluate effects of long chain polyunsaturated fatty acids (LCPUFA) on frailty and physical performance. *Design:* Randomized, double blind pilot study. *Setting:* University General Clinical Research Center. *Participants:* 126 postmenopausal women. Intervention 2 fish oil (1.2g eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or 2 placebo (olive oil) capsules per day for 6 months. All participants received calcium and vitamin D supplements. *Measurements:* Fatty acid levels, frailty assessment, hand grip strength, 8 foot walk, body composition, medical history and co-morbidities, nutrient intake, and inflammatory biomarkers taken at baseline and 6 months. *Results:* At baseline, those with greater red blood cell (RBC) DHA and DHA/arachidonic acid (AA) presented with less frailty (r=-0.242, p=0.007 and r=-0.254, p=0.004, respectively). Fish oil supplementation resulted in higher RBC DHA and lower AA compared to baseline and placebo (p<0.001) and an improvement in walking speed compared to placebo (3.0±16 vs. -3.5±14, p=0.038). A linear regression model included age, antioxidant intake (selenium and vitamin C), osteoarthritis, frailty phenotype, and tumor necrosis factor alpha (TNFα). The model explained 13.6% of the variance in the change in walking speed. Change in DHA/AA (p<0.01) and TNFα (p=0.039), and selenium intake (p=0.031) had the greatest contribution to change in walking speed. *Conclusion:* Physical performance, measured by change in walking speed, was significantly affected by fish oil supplementation. Dietary intake of antioxidants (selenium and vitamin C) and changes in TNFα also contributed to change in walking speed suggesting LCPUFA may interact with antioxidants and inflammatory response to impact physical performance.

Key words: Long chain polyunsaturated fatty acids, antioxidants, physical performance, frailty.

Introduction

Frailty is common in older adults and the phenotype includes weight loss, hand grip strength, endurance, reported physical activity, and walking speed (1). Strength, walking speed, overall physical performance, frailty phenotype and longevity are associated with inflammatory biomarkers in older adults (2-7). Diet is linked to inflammation, frailty and physical performance.

Omega-3 long chain polyunsaturated fatty acids (n-3 LCPUFA), eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA, 22:3n-6) found in fatty fish, are recognized for their anti-inflammatory properties in cell, animal, and human models (8, 9). Epidemiological data and clinical trials in older adults demonstrate a negative relationship between plasma n-3 PUFA or n-3 LCPUFA intake and pro-inflammatory markers such as IL-6 and TNFα (10, 11). Further, higher fatty fish intake in community-dwelling older adults from the United Kingdom is associated with higher hand grip strength (12), a component of the frailty phenotype and surrogate measure of muscle strength (13). Italian participants in the InCHIANTI trial with low physical performance ability (rated using the Short Physical Performance Battery [SPPB]) had lower plasma total PUFA, n-3 PUFA and n-6 PUFA levels (14). Related to walking speed, a higher n-6/n-3 PUFA ratio was associated with a longer walk time during the 7 meter walking test; whereas, total PUFA and n-3 PUFA were associated with shorter walking speed (14).

Epidemiological investigations demonstrate that carotenoids, vitamins C and E, selenium, vitamin D, and folate were associated with lower rates of, or lower risk for, frailty and declines in physical performance (15-22). Interventions to modify diet and components of the frailty phenotype are lacking. Therefore, we sought to assess the effects of n-3 LCPUFA supplementation on frailty measurements and hypothesized that dietary and red blood cell (RBC) n-3 LCPUFA (EPA and DHA) would positively correlate with physical performance outcomes in older postmenopausal women.

Methods

The study design (blocked randomization 2:1) was used to meet two goals and hypotheses. One was to evaluate the effects of a fish oil supplement on bone turnover markers (23), the other to evaluate the effects of fish oil on physical performance and frailty. The block randomization provided adequate sample size for correlative evaluation of physical performance, as the sample size was estimated to be too small to see differences in direct comparison between fish oil and

Received July 29, 2011
Accepted for publication December 16, 2011

76

46

Improved physical performance

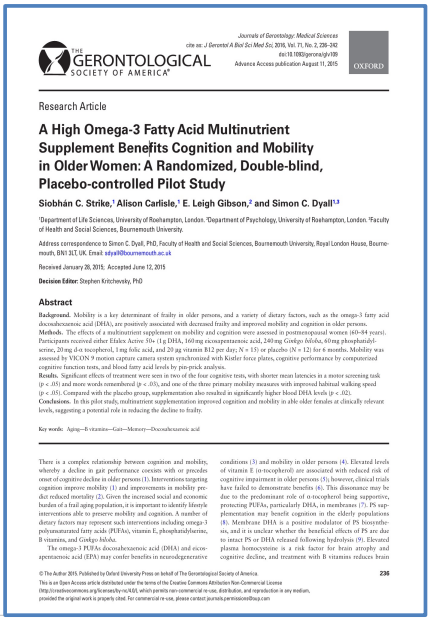
Reference	Population & Study Design	Age Range	Intervention	Outcome Measures	Results
Hutchins-Wiese et al. 2013	n = 126 postmenopausal women; randomised, double-blind, placebo-controlled pilot study; 118 completed the study.	64–95 years; mean 75 years	**1.2 g/day EPA + DHA** from fish oil (2 capsules/day; 720 mg EPA + 480 mg DHA) or olive oil placebo for **6 months**. All participants also received calcium and vitamin D supplementation.	Frailty phenotype; walking speed (8-foot walk); hand-grip strength; repeated chair rises; RBC fatty acids; inflammatory markers (IL-6, TNFα and hs-CRP); dietary nutrient intake	Fish oil significantly improved **walking speed compared with placebo** (+3.0% vs −3.5%; $p = 0.038$) and increased RBC DHA and DHA/AA ratio. No significant improvements occurred in overall frailty phenotype, hand-grip strength, chair-rise performance or inflammatory markers. Changes in DHA/AA and TNFα and dietary selenium intake significantly contributed to changes in walking speed.

47

Improved mobility

A **24-week randomised, double-blind, placebo-controlled pilot trial in 27 postmenopausal women aged 60–84 years** found that daily supplementation with a multinutrient formula containing **1 g DHA, 160 mg EPA, *Ginkgo biloba*, phosphatidylserine, vitamin E, folic acid and vitamin B12** significantly improved **psychomotor response speed, immediate verbal memory and habitual walking speed** compared with placebo.

J Gerontol A Biol Sci Med Sci. 2016 Feb;71(2):236-42



Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 2, 236–242
doi:10.1093/gerona/glv109
Advance Access publication August 11, 2015

THE GERONTOLOGICAL SOCIETY OF AMERICA®

OXFORD

Research Article

A High Omega-3 Fatty Acid Multinutrient Supplement Benefits Cognition and Mobility in Older Women: A Randomized, Double-blind, Placebo-controlled Pilot Study

Siobhán C. Strike,[1] Alison Carlisle,[1] E. Leigh Gibson,[2] and Simon C. Dyall[1,3]

[1]Department of Life Sciences, University of Roehampton, London. [2]Department of Psychology, University of Roehampton, London. [3]Faculty of Health and Social Sciences, Bournemouth University.

Address correspondence to Simon C. Dyall, PhD, Faculty of Health and Social Sciences, Bournemouth University, Royal London House, Bournemouth, BH1 3LT, UK. Email: sdyall@bournemouth.ac.uk

Received January 28, 2015; Accepted June 12, 2015

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background. Mobility is a key determinant of frailty in older persons, and a variety of dietary factors, such as the omega-3 fatty acid docosahexaenoic acid (DHA), are positively associated with decreased frailty and improved mobility and cognition in older persons.
Methods. The effects of a multinutrient supplement on mobility and cognition were assessed in postmenopausal women (60–84 years). Participants received either Efalex Active 50+ (1 g DHA, 160 mg eicosapentaenoic acid, 240 mg *Ginkgo biloba*, 40 mg phosphatidylserine, 20 mg d-α tocopherol, 1 mg folic acid, and 20 μg vitamin B12 per day; N = 15) or placebo (N = 12) for 6 months. Mobility was assessed by VICON 9 motion capture camera system synchronized with Kistler force plates, cognitive performance by computerized cognitive function tests, and blood fatty acid levels by pin-prick analysis.
Results. Significant effects of treatment were seen in two of the four cognitive tests, with shorter mean latencies in a motor screening task ($p < .05$) and more words remembered ($p < .03$), and one of the three primary mobility measures with improved habitual walking speed ($p < .05$). Compared with the placebo group, supplementation also resulted in significantly higher blood DHA levels ($p < .02$).
Conclusions. In this pilot study, multinutrient supplementation improved cognition and mobility in able older females at clinically relevant levels, suggesting a potential role in reducing the decline to frailty.

Key words: Aging—B vitamins—Gait—Memory—Docosahexaenoic acid

There is a complex relationship between cognition and mobility, whereby a decline in gait performance coexists with or precedes onset of cognitive decline in older persons (1). Interventions targeting cognition improve mobility (1) and improvements in mobility predict reduced mortality (2). Given the increased social and economic burden of a frail aging population, it is important to identify lifestyle interventions able to preserve mobility and cognition. A number of dietary factors may represent such interventions including omega-3 polyunsaturated fatty acids (PUFAs), vitamin E, phosphatidylserine, B vitamins, and Ginkgo biloba.

The omega-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may confer benefits in neurodegenerative conditions (3) and mobility in older persons (4). Elevated levels of vitamin E (α-tocopherol) are associated with reduced risk of cognitive impairment in older persons (5); however, clinical trials have failed to demonstrate benefits (6). This dissonance may be due to the predominant role of α-tocopherol being supportive, protecting PUFAs, particularly DHA, in membranes (7). PS supplementation may benefit cognition in the elderly populations (8). Membrane DHA is a positive modulator of PS biosynthesis, and it is unclear whether the beneficial effects of PS are due to intact PS or DHA released following hydrolysis (9). Elevated plasma homocysteine is a risk factor for brain atrophy and cognitive decline, and treatment with B vitamins reduces brain

© The Author 2015. Published by Oxford University Press on behalf of The Gerontological Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

48

Improved mobility

Reference	Population & Study Design	Age Range	Intervention	Outcome Measures	Results
Strike et al. 2016	**n = 27** community-dwelling postmenopausal women; randomised, double-blind, placebo-controlled pilot study (intervention n = 15; placebo n = 12 completing study)	**60–84 years**	**Efalex Active 50+** providing **1 g DHA, 160 mg EPA, 240 mg *Ginkgo biloba*, 60 mg phosphatidylserine, 20 mg d-α-tocopherol, 1 mg folic acid and 20 µg vitamin B12 daily**, compared with an isocaloric oil placebo, for **24 weeks (6 months)**.	**Cognition:** psychomotor response latency, verbal recognition memory (VRM), paired associate learning and executive function. **Mobility:** habitual and fast walking speed and vertical jump height. Blood fatty acids, including DHA and EPA, were also measured.	Compared with placebo, supplementation significantly **reduced psychomotor response latency** (p = .038), **improved immediate verbal recall** (+1.3 words adjusted difference; p = .029) and **improved habitual walking speed** (+0.07 m/s adjusted difference; p = .031). There were no significant effects on delayed word recognition, paired associate learning, executive function, fast walking speed or vertical jump height. Blood DHA increased by **17%** (p = .018) and EPA by **71%** (p < .002) versus placebo.

49

Vitamin D

50

Vitamin D? “No real benefit.”



Why you should bin your supplements, by Dr Xand van Tulleken

He's Britain's most famous TV doctor (along with his twin brother, Chris). Now, Xand van Tulleken is on a mission to expose our vitamin and wellness industry. He tells Janice Turner it's all a waste of money

Xand van Tulleken, 48. Vitamin D? "No real benefit." Collagen? "Don't believe the hype." Creatine? "Pointless"

ROBERT WILSON FOR THE TIMES MAGAZINE. STYLING: PRUE WHITE

“When I was at medical school, it was so exciting. We thought it [vitamin D] was going to cure everything.” But when he dug into two decades of trials, he found no benefits from vitamin D supplements, except for **a rare few people with a genuine deficiency.”**

Fact check: In the UK, 53% Asian, 34% black, 12% white participants had serum 25-hydroxyvitamin D level <25 nmol/L, and taking supplements was associated with a lower risk of vitamin D deficiency. BMJ Open. 2021 Jan 6;11(1):e038503.

Why you should bin your supplements, by Dr Xand van Tulleken. The Times. September 08 2026.

51

Low vitamin D status

Low vitamin D status is consistently associated with frailty and related musculoskeletal, immune, metabolic and cognitive vulnerabilities, but supplementation has generally shown little benefit in vitamin D–replete older adults, with **potential benefits largely confined to those with or at risk of deficiency**, supporting a personalised approach.

Metabolism. 2026 Oct;183:156697



Metabolism 103 (2026) 156697

Contents lists available at ScienceDirect

Metabolism

journal homepage: www.journals.elsevier.com/metabolism

Vitamin D and frailty: Clinical evidence, mechanistic insights, and translational challenges☆

Viola Viola [a,b,c], Flavia Tramontana [a,b], Giulia Leanza [a], Malak Faraj [a,b], Nicola Napoli [a,b,d,*]

[a] Department of Medicine and Surgery, Research Unit of Endocrinology and Diabetes, Università Campus Bio-Medico di Roma, Rome, Italy
[b] Operative Research Unit of Osteo-Metabolic and Thyroid Diseases, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[c] Department of Human Sciences and Promotion of the Quality of Life San Raffaele Roma Open University, Rome, Italy
[d] Division of Bone and Mineral Diseases, Washington University in St. Louis, St. Louis, MO, USA

ARTICLE INFO

Keywords:
Vitamin D
Frailty
Aging
25-hydroxyvitamin D

ABSTRACT

Vitamin D is increasingly recognized as a multisystem hormone whose actions converge on physiological domains central to frailty. Low circulating 25-hydroxyvitamin D [25(OH)D] concentrations are associated with sarcopenia, bone loss, immune and cognitive dysfunction, and excess mortality, while observational cohort studies link vitamin D deficiency to frailty onset and progression. Mechanistic evidence provides a biologically coherent framework for these associations. Vitamin D receptor (VDR) signaling regulates myogenic differentiation, neuromuscular junction integrity, osteoblast–osteoclast coupling, and osteocyte-mediated mechanotransduction. It also modulates innate and adaptive immune responses, restrains inflammasome activation, and preserves mitochondrial function and metabolic flexibility. Disruption of VDR signaling promotes muscle atrophy, skeletal fragility, immunosenescence, and impaired bioenergetic capacity, processes that mirror key biological features of frailty. Despite this strong mechanistic plausibility, randomized controlled trials have largely yielded neutral results in community-dwelling adults with adequate vitamin D status. Clinical benefits appear confined to individuals with deficiency or heightened vulnerability, whereas intermittent high-dose bolus regimens have been associated with increased risks of falls and fractures. These discordant findings reflect persistent methodological limitations, including heterogeneous frailty definitions, insufficient follow-up duration, interassay variability in 25(OH)D measurement, and uncertainty regarding thresholds relevant to non-skeletal outcomes. In this narrative review, we integrate clinical, epidemiological, and mechanistic evidence to position vitamin D as a biomarker and potential modulator of vulnerability within a broader prevalence framework.

1. Introduction

Few biological regulators embody the complexity of frailty as vividly as vitamin D. Once confined to the regulation of calcium–phosphate balance and bone integrity, vitamin D is now recognized as a hormone with pleiotropic actions extending to skeletal muscle, immunity, mitochondrial function, and cognition [1,2]. This pleiotropy is particularly relevant to frailty, since these systems overlap with the core domains of the syndrome [3]. This broad functional profile reflects a fundamental biological property of vitamin D signaling: the near-ubiquitous expression of the vitamin D receptor (VDR) across tissues and cell types, alongside widespread local regulation of vitamin D metabolism [4,5].

Within this framework, vitamin D can be conceptualized as a context-dependent regulator and fine-tuner of integrated biological processes, a perspective that is central to interpreting its role in frailty [6]. Vitamin D status is commonly assessed by circulating 25-hydroxyvitamin D (25(OH)D), with deficiency is generally defined as levels below 20 ng/mL (50 nmol/L), with severe deficiency below 10–12 ng/mL (25–30 nmol/L). These thresholds, derived from skeletal outcomes, may not reflect extra-skeletal or frailty-related requirements [7]. Low vitamin D status has been consistently associated with frailty-related traits, sarcopenia, bone loss, immune and cognitive decline, and with comorbidities such as type 2 diabetes (T2DM), obesity, and Alzheimer's disease [1,8–10]. These overlapping features support the view that vitamin D deficiency

☆ This article is part of a Special issue entitled: 'Vitamin D' published in Metabolism.
* Corresponding author at: Operative Research Unit of Osteo-Metabolic and Thyroid Diseases, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo, 200, 00128, Rome, Italy.
E-mail address: n.napoli@policlinicocampus.it (N. Napoli).

https://doi.org/10.1016/j.metabol.2026.156697
Received 31 December 2025; Received in revised form 30 June 2026; Accepted 12 July 2026
Available online 20 July 2026
0026-0495/© 2026 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

52

Observational epidemiological evidence linking vitamin D status to frailty-related domains.

First author, year	Study design / population	Vitamin D metric	Frailty-related domain	Key finding
Need et al., 2008 [29]	Observational study (patients with serum 25-hydroxyvitamin D ≤ 16 ng/mL (≤40 nmol/L))	Serum 25-hydroxyvitamin D categories (0–10, 11–20, 21–30, 31–40 nmol/L) (0–4, 4.4–8, 8.4–12, 12.4–16 ng/mL)	Skeletal integrity	Reduced calcium absorption and reduced 1,25-dihydroxyvitamin D observed only when 25-hydroxyvitamin D (≤4 ng/mL) ≤10 nmol/L
Marcos-Pérez et al., 2020 [21]	Meta-analysis of observational studies (older adults)	Serum 25-hydroxyvitamin D levels across frailty categories	Frailty phenotype	Lower 25-hydroxyvitamin D concentrations in frail and prefrail individuals compared with non-frail
Pan et al., 2024 [32]	Cross-sectional NHANES-based study (older adults)	Continuous serum 25-hydroxyvitamin D	Cognitive frailty	Higher 25-hydroxyvitamin D associated with lower cognitive frailty
Chai et al., 2019 [10]	Meta-analysis (prospective and cross-sectional studies; adults and older adults)	Serum 25-hydroxyvitamin D deficiency (moderate: 10–20 ng/mL (25–50 nmol/L); severe: <10 ng/mL (<25 nmol/L))	Cognitive decline / dementia	Vitamin D deficiency associated with increased risk of dementia and Alzheimer's disease
Zhang et al., 2024 [33]	Meta-analysis of prospective cohorts (adults and older adults)	Dose–response relationship with serum 25-hydroxyvitamin D	Cognitive decline / dementia	Nonlinear association, with higher dementia risk at low vitamin D levels
Çolak et al., 2021 [34]	Observational longitudinal cohort with Mendelian randomization analyses (adults aged 20–100 years)	Measured and genetically predicted serum 25-hydroxyvitamin D	Immune vulnerability	Lower 25-hydroxyvitamin D associated with increased risk of bacterial pneumonia
Ford et al., 2005 [35]	Cross-sectional study (adults ≥20 years)	Quintiles of serum 25-hydroxyvitamin D	Cardiometabolic vulnerability	Higher 25-hydroxyvitamin D associated with lower cardiometabolic risk
Martins et al., 2007 [36]	Cross-sectional NHANES III-based study (adults ≥20 years)	Quartiles of serum 25-hydroxyvitamin D	Cardiometabolic vulnerability	Low 25-hydroxyvitamin D associated with adverse cardiometabolic risk profile
Gaksch et al., 2017 [38]	Individual participant data meta-analysis of prospective cohorts (median age ~ 62 years)	Standardized serum 25-hydroxyvitamin D categories	Mortality	Lower 25-hydroxyvitamin D associated with increased all-cause mortality
Zhang et al., 2024 [23]	Longitudinal cohort study (UK Biobank; middle-aged and older adults)	Baseline and longitudinal changes in serum 25-hydroxyvitamin D	Frailty status and transitions	Low 25-hydroxyvitamin D predicts frailty; increasing levels associated with transitions toward lower frailty states
Buchebner et al., 2019 [41]	Prospective cohort study (community-dwelling women ≥75 years)	Serum 25-hydroxyvitamin D (insufficient <20 ng/mL (<50 nmol/L) vs sufficient ≥50 nmol/L)	Frailty and frailty progression	Low 25-hydroxyvitamin D associated with higher frailty and future frailty, except at very advanced age

Metabolism. 2026 Oct;183:156697.

53

Randomized and interventional evidence on vitamin D supplementation across frailty-related domains

First author, year	Study design / population	Vitamin D intervention	Frailty-related domain	Key finding
Chapuy et al., 1992	RCT (institutionalized women, mean age ~ 84 y)	D3 800 IU/day + Ca 1.2 g/day, 18 months	Skeletal fragility (fractures)	↓ hip and nonvertebral fractures
Chapuy et al., 2002	RCT (institutionalized women, mean age ~ 85 y)	D3 800 IU/day + Ca 1.2 g/day, 24 months	Skeletal fragility (fractures)	Trend toward ↓ hip fractures
Reid et al., 2014	Meta-analysis (RCTs)	Vitamin D (D3 or D2)	Skeletal health (BMD)	Minimal or no BMD benefit
Chakhtoura et al., 2022	Umbrella review (meta-analyses of RCTs)	Vitamin D ± calcium	Skeletal fragility (fractures)	Fracture benefit only with Ca + D
LeBoff et al., 2022	RCT (VITAL ancillary study; adults ≥50 y)	D3 2000 IU/day, ~5 years	Skeletal fragility (fractures)	No reduction in total, nonvertebral, or hip fractures
Waterhouse et al., 2021	RCT (community-dwelling adults 60–84 y)	D3 60,000 IU/month, ~5 years	Physical function (falls)	No fall reduction; ↑ falls in participants with BMI <25 kg/m^2

Metabolism. 2026 Oct;183:156697.

54

Randomized and interventional evidence on vitamin D supplementation across frailty-related domains

First author, year	Study design / population	Vitamin D intervention	Frailty-related domain	Key finding
Martineau et al., 2017	IPD meta-analysis (RCTs)	D2/D3 (daily/weekly vs bolus)	Immune resilience (ARI)	↓ ARI risk; strongest in deficient individuals and with non-bolus dosing
Jolliffe et al., 2021	Meta-analysis (RCTs)	D2/D3, various regimens	Immune resilience (ARI)	Modest ↓ ARI risk with daily dosing (400–1000 IU)
Pittas et al., 2020	Meta-analysis (RCTs)	Vitamin D3 (various doses)	Metabolic resilience / incident T2DM	Modest ↓ incident diabetes risk (≈10–13%) vs placebo in prediabetes
Kang et al., 2021	RCT (VITAL ancillary studies; adults ≥60 y)	D3 2000 IU/day, 2–3 years	Cognitive function	No overall effect on cognitive decline
Bischoff-Ferrari et al., 2020	RCT (DO-HEALTH; adults ≥70 y)	D3 2000 IU/day, 3 years	Physical & cognitive function; fractures; infections	No benefit across endpoints

"Collectively, interventional data support a targeted approach, focusing on deficient or high-risk groups rather than routine supplementation in replete populations."

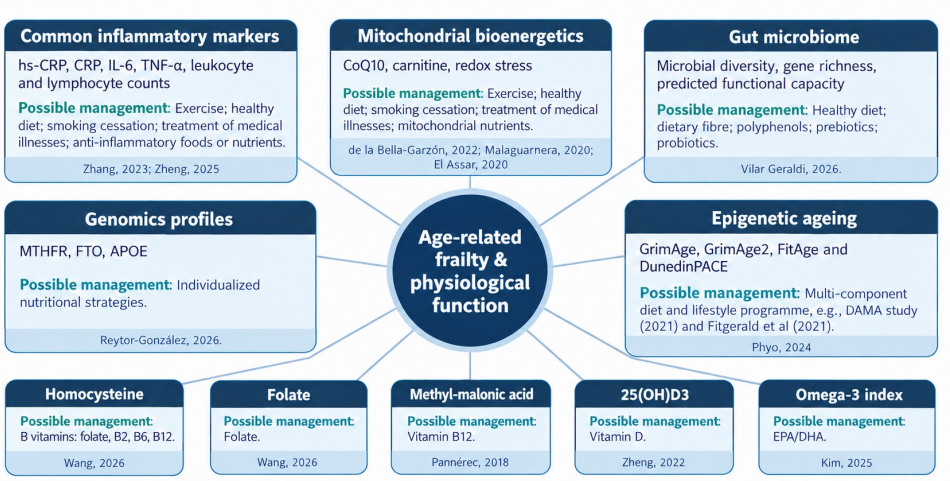
Metabolism. 2026 Oct;183:156697.

55

An opportunity for personalised nutrition and lifestyle medicine

56

Nutrition and lifestyle biomarkers associated with risk of frailty



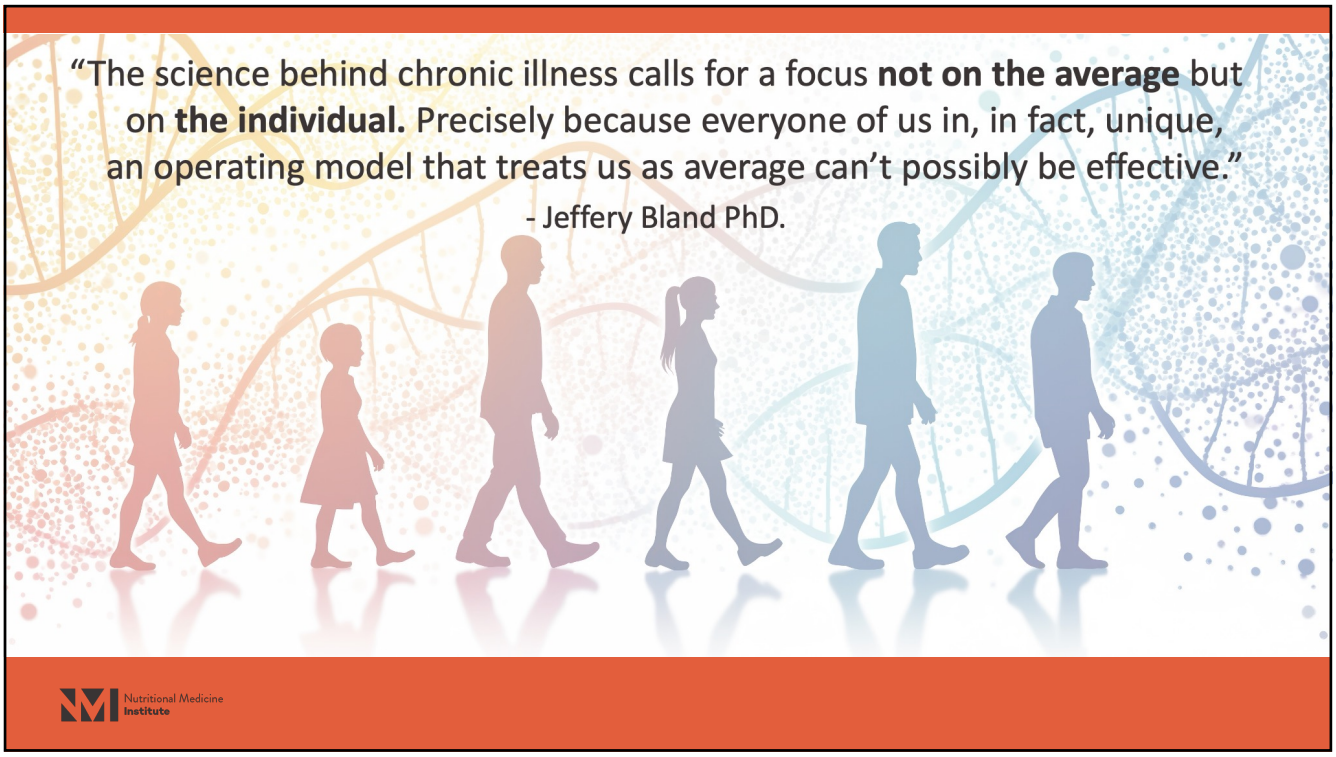
Key: High-sensitivity C-reactive protein; hs-CRP, serum 25-hydroxyvitamin D3; 25(OH)D3. EPA/DHA; eicosapentaenoic acid & docosahexaenoic acid, methylenetetrahydrofolate reductase; MTHFR, fat mass and obesity-associated; FTO, Apolipoprotein E; APOE

57

Nutrition and lifestyle biomarkers associated with risk of frailty

- Zhang L, Zeng X, He F, Huang X. Inflammatory biomarkers of frailty: A review. Exp Gerontol. 2023 Aug;179:112253.
- Zheng L, Ye J, Liao X, Li J, Wang Q, Wang F. Frailty, high-sensitivity C-reactive protein and cardiovascular disease: a nationwide prospective cohort study. Aging Clin Exp Res. 2025 Feb 28;37(1):58.
- de la Bella-Garzón R, et al. Levels of Plasma Coenzyme Q_{10} Are Associated with Physical Capacity and Cardiovascular Risk in the Elderly. Antioxidants (Basel). 2022 Jan 29;11(2):279.
- Malaguarnera G, Catania VE, Bonfiglio C, Bertino G, Vicari E, Malaguarnera M. Carnitine Serum Levels in Frail Older Subjects. Nutrients. 2020 Dec 19;12(12):3887.
- El Assar M, et al. Frailty as a phenotypic manifestation of underlying oxidative stress. Free Radic Biol Med. 2020 Mar;149:72-77
- Vilar Geraldi M, et al. Gut microbiota associates with frailty in older women. Nat Commun. 2026 Jul 8;17(1):5925. doi: 10.1038/s41467-026-75176-5. PMID: 42420265; PMCID: PMC13346421.
- Reytor-González C, et al. Personalized nutrition for healthy aging: precision diets based on genomic, metabolic, and microbiome profiles. Front Nutr. 2026 Aug 5;13:1844337.
- Phyo AZZ, et al. Epigenetic age acceleration and the risk of frailty, and persistent activities of daily living (ADL) disability. Age Ageing. 2024 Jun 1;53(6):afae127.
- Wang S, et al. Association between hyperhomocysteinemia and frailty in older adults with acute ischemic stroke: A cross-sectional study. Geriatr Nurs. 2026 Aug 25;73:104333.
- Wang T, Diao Z, Li J, Yan H, Xu Z, Huang W, Xu M, Niu Y, Zhong J, Li C, Chen L, Liang X, Liu D. Associations of Dietary, Serum, and Red Blood Cell Folate With Frailty: A Cross-Sectional Study. Mol Nutr Food Res. 2026 Jan;70(1):e70351.
- Pannérec A, et al. Vitamin B12 deficiency and impaired expression of amnionless during aging. J Cachexia Sarcopenia Muscle. 2018 Feb;9(1):41-52.
- Zheng Z, Xu W, Wang F, Qiu Y, Xue Q. Association between vitamin D3 levels and frailty in the elderly: A large sample cross-sectional study. Front Nutr. 2022 Sep 27;9:980908.
- Kim J, et al (2025) Erythrocyte levels of n-3 polyunsaturated fatty acids and incidence of frailty after a 6-year follow-up: the Korean frailty and aging cohort study. Front. Nutr. 12:1569832.

58



59

5:30 - 6:00pm

Ask the Expert

Healthy Ageing in Clinical Practice

Q&A

PRE-SUMMIT EVENT

Sponsored by pure encapsulations

60