frontiers | Research Topics

The role of nutrition in healthy aging

Edited by
Roberta Zupo, Rodolfo Sardone, Giovanni De Pergola, Fabio Castellana and Hélio José Coelho Júnior

Published in
Frontiers in Medicine
Frontiers in Endocrinology

ISSN 1664-8714
ISBN 978-2-8325-4155-5
DOI 10.3389/978-2-8325-4155-5

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

The role of nutrition in healthy aging

Topic editors

Roberta Zupo — University of Bari Aldo Moro, Italy
Rodolfo Sardone — Scientific Research Coordinator, Unit of Statistics and Epidemiology, Local Health Authority of Taranto, Italy
Giovanni De Pergola — University of Bari Aldo Moro, Italy
Fabio Castellana — National Institute of Gastroenterology S. de Bellis Research Hospital (IRCCS), Italy
Hélio José Coelho Júnior — Catholic University of the Sacred Heart, Rome, Italy

Citation

Zupo, R., Sardone, R., De Pergola, G., Castellana, F., Júnior, H. J. C., eds. (2023). *The role of nutrition in healthy aging*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-4155-5

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 04 December 2023
DOI 10.3389/fmed.2023.1335119

OPEN ACCESS

EDITED AND REVIEWED BY
Mario Ulises Pérez-Zepeda,
Instituto Nacional de Geriatría, Mexico

*CORRESPONDENCE
Roberta Zupo
✉ roberta.zupo@uniba.it;
✉ zuporoberta@gmail.com

RECEIVED 08 November 2023
ACCEPTED 23 November 2023
PUBLISHED 04 December 2023

CITATION
Zupo R, Castellana F, Coelho Júnior HJ, De Pergola G, Clodoveo ML and Sardone R (2023) Editorial: The role of nutrition in healthy aging. *Front. Med.* 10:1335119.
doi: 10.3389/fmed.2023.1335119

Editorial: The role of nutrition in healthy aging

Roberta Zupo[1]*, Fabio Castellana[1], Hélio José Coelho Júnior[2], Giovanni De Pergola[3], Maria Lisa Clodoveo[1] and Rodolfo Sardone[4]

[1]Department of Interdisciplinary Medicine (DIM), University of Bari Aldo Moro, Bari, Italy, [2]Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza University of Rome, Rome, Italy, [3]Department of Biomedical Science and Human Oncology, School of Medicine, University of Bari Aldo Moro, Bari, Italy, [4]Unit of Statistics and Epidemiology, Local Health Authority of Taranto, Taranto, Italy

KEYWORDS

aging, nutrition, public health, epidemiology, diet

Editorial on the Research Topic
The role of nutrition in healthy aging

All over the world, people are living longer. According to the World Health Organization (WHO), by 2050 people aged 65 and older will account for nearly 17 percent of the population (1). While health research in older people generally focuses on the occurrence of multiple chronic diseases, significant health conditions and geriatric syndromes are prevalent and have their own multifactorial biological phenotypes that do not necessarily conform to discrete disease categories. In fact, aging is usually associated with a series of physiological changes covering a wide range of functional domains, manifested in outcomes of sarcopenia (2), frailty (3), malnutrition by defect or excess, as well as reduced quality of life, and many other declines found in elders. Diet, energy balance, nutrient intake, and lifestyle (4, 5) are modifiable factors (6) for which research efforts have yet to shed light in order to promote healthy aging, improve the quality of life in old age, and reduce the health burden of the elderly population. This Research Topic aimed to address this current issue in order to provide additional evidence able to fill the still-existing research gap on the biological mechanisms underlying the link between nutrition and healthy aging.

The collection included nine articles, mostly original, with a minority of two systematic review reports. The original research focused on the relationship between nutritional status and multiple health outcomes, such as survival, quality of life, heart failure, kidney illness, and cognitive impairment. Here, Franz et al. examined prospective data from the multicenter EMAAge cohort to assess the nutritional status of elderly patients with hip fractures, factors associated with malnutrition risk, and the association between malnutrition and mortality at 6 months. Findings showed that the mean survival time was longer in those without malnutrition risk [171.9 (167.1–176.9) days vs. 153.1 (140.0–166.2) days]. In the adjusted Cox regression model, the risk of death was associated with the risk of malnutrition, older age, and a high burden of comorbidities. In light of these data, the authors concluded the importance of paying attention to malnutrition to initiate early interventions in this subset of the elderly population.

Zhou et al. conducted research to investigate the metabolic basis of the cognitive improvement driven by active B-vitamin supplementation by carrying out an extensive metabolomic analysis of 302 metabolites identified in serum samples at baseline and at 24 months of a cohort of 137 subjects randomly assigned to active supplementation or placebo. Pathway analysis showed increased gluconeogenesis and War-burg effects underlying cognitive improvement in non-aspirin-using subjects supplemented with active B vitamins. Furthermore, metabolomics revealed that aspirin use may interact with B vitamin supplementation by altering gut microbial metabolism, particularly in terms of propionate production. Finally, omics data showed that differing ability to assimilate B vitamins at baseline, perhaps mediated by differences in gut microbial composition, may underlie variations in interindividual responses to active B vitamin supplementation.

Liao et al. investigated the predictive validity of the geriatric nutritional risk index (GNRI) in critically ill elderly patients with acute kidney injury. In this research, 1-year mortality was considered the primary outcome, while in-hospital, intensive care unit (ICU), 28- and 90-day mortality, and prolonged ICU and hospital length of stay were selected as secondary outcomes. Multivariable regression analysis identified the independent prognostic ability of GNRI on research outcomes. The restricted cubic spline showed a linear correlation between GNRI and death at 1 year. The prognostic implication of GNRI on 1-year mortality was still significant in patients with most subgroups. The authors therefore concluded that in critically ill elderly patients with acute kidney injury, an elevated GNRI at admission was strongly correlated with a lower risk of adverse outcomes.

Among the noteworthy review articles published in this Research Topic, we must mention the investigations by Abedi et al. and Rondanelli et al. Here, Abedi et al. conducted an interesting updated systematic review and meta-analysis to evaluate the efficacy of saffron supplementation on a cluster of oxidative stress markers in randomized controlled trials (RCTs). Saffron consumption was found to cause a significant decrease in malondialdehyde and total oxidant status and a significant increase in total antioxidant capacity levels. Subgroup analysis showed a significant reduction in malondialdehyde levels in studies with saffron dosage >30 mg/day, age <50 years, and study duration <12 weeks. Although the majority of Iranian studies could have been a limitation of the study, the results showed that saffron has beneficial effects on oxidative stress markers. Instead, Rondanelli et al. research group conducted a review with the goal of evaluating the most recent research on the ideal dietary approach to prevent or promote the treatment of diabetic retinopathy, age-related macular degeneration, and cataracts, as well as constructing a food pyramid that would make it easy for people at risk of developing these diseases to decide what to eat. The food pyramid presented proposed what should be consumed every day: 3 servings of low glycemic index (GI) cereals (for fiber and zinc content), 5 servings (each serving: $\geq$200 g/day) of fruits and vegetables (spinach, broccoli, cooked zucchini, green leafy vegetables, oranges, kiwis, grapefruits are preferred for the content of folic acid, vitamin C and lutein/zeaxanthin, at least $\geq$42 μg/day), extra virgin olive oil (almost 20 mg/day for the content of vitamin E and polyphenols), nuts or oilseeds (20–30 g/day, for the content of zinc, at least $\geq$15.8 mg/day); weekly: fish (4 servings, for omega-3 content and eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) 0.35–1.4 g/day), white meat (3 servings, for vitamin B12 content), legumes (2 servings, for vegetable protein), eggs (2 servings, for lutein/zeaxanthin content), light cheeses (2 servings, for vitamin B6 content), and almost 3–4 times/week microgreens and spices (saffron and curcumin). At the top of the pyramid are two pennants: a green one, indicating the need for individualized supplementation (if daily requirements cannot be met by diet, supplementation of omega-3 and L-methylfolate), and a red one, indicating that certain foods are prohibited (salt and sugar). Finally, 30–40 minutes of aerobic and resistance exercise is required 3–4 times a week.

No less noteworthy, the present Collection included an analysis of the knowledge domain and emerging trends in nutrition research in sarcopenia (2, 7) and to provide implications for future research and strategies to prevent or manage sarcopenia in the context of an aging society. This research, conducted by Huang et al. was designed to provide health professionals and scholars with a comprehensive mapping of the knowledge base of nutrition and sarcopenia research over the past 30 years, as well as to help them quickly grasp research hot spots and choose future research projects.

Finally, Beasley et al. presented a randomized BRIDGE (BRInging the Diabetes prevention program to GEriatric Populations) study protocol aimed at comparing an in-person Diabetes Prevention Program (DPP) adapted for older adults (DPP-TOAT, i.e., Tailored for Older AdulTs) with a DPP-TOAT delivered via virtual group sessions (V-DPP-TOAT) in a randomized controlled trial design ($N = 230$). The primary efficacy outcome will be weight loss at 6 months and the primary implementation outcome will be participation in intervention sessions with a non-inferiority design. The results will inform best practices in the delivery of an evidence-based intervention.

In conclusion, when it comes to modifiable factors in the context of non-communicable diseases related to aging, nutrition remains critical. There remains ample room for research into the biological mechanisms underlying dietary strategies, individual foods, nutritional status, and dietary patterns that can shape the trajectories of chronic health outcomes, especially in the increasingly aging population.

Author contributions

RZ: Writing – original draft. FC: Data curation, Methodology, Software, Writing – original draft. HC: Visualization, Writing – review & editing. GD: Visualization, Writing – review & editing. MC: Methodology, Supervision, Writing – review & editing. RS: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. *Nature*. (2008) 451:716–9. doi: 10.1038/nature06516

2. Zupo R, Moroni A, Castellana F, Gasparri C, Catino F, Lampignano L, et al. A machine-learning approach to target clinical and biological features associated with sarcopenia: findings from northern and southern italian aging populations. *Metabolites*. (2023) 13:565. doi: 10.3390/metabo13040565

3. Zupo R, Castellana F, Guerra V, Donghia R, Bortone I, Griseta C, et al. Associations between nutritional frailty and 8-year all-cause mortality in older adults: the salus in apulia study. *J Intern Med*. (2021) 290:1071–82. doi: 10.1111/joim.13384

4. Bortone I, Sardone R, Lampignano L, Castellana F, Zupo R, Lozupone M, et al. How gait influences frailty models and health-related outcomes in clinical-based and population-based studies: a systematic review. *J Cachexia Sarcopenia Muscle*. (2021) 12:274–297. doi: 10.1002/jcsm.12667

5. Bortone I, Castellana F, Lampignano L, Zupo R, Moretti B, Giannelli G, et al. Activity energy expenditure predicts clinical average levels of physical activity in older population: results from salus in apulia study. *Sensors*. (2020) 20:4585. doi: 10.3390/s20164585

6. Zupo R, Castellana F, Bortone I, Griseta C, Sardone R, Lampignano L, et al. Nutritional domains in frailty tools: Working towards an operational definition of nutritional frailty. *Ageing Res Rev*. (2020) 64:101148. doi: 10.1016/j.arr.2020.101148

7. Lampignano L, Bortone I, Castellana F, Donghia R, Guerra V, Zupo R, et al. Impact of different operational definitions of sarcopenia on prevalence in a population-based sample: the salus in apulia study. *Int J Environ Res Public Health*. (2021) 18:12979. doi: 10.3390/ijerph182412979

frontiers | Frontiers in Medicine

ORIGINAL RESEARCH
published: 27 April 2022
doi: 10.3389/fmed.2022.864152

Metabolic Basis of Cognitive Improvement Associated With Active B Vitamin Supplementation in Cognitively Impaired Elderly Subjects – A Metabolomics Study

Haiming Zhou[1†], Yuanyuan Wu[2,3†], Binhua Jiang[1], Bowen Li[1], Martin Li[3], He Tian[4], Guanghou Shui[4], Sin Man Lam[1,4] and Timothy Kwok[3*]*

[1] LipidALL Technologies Company Limited, Changzhou, China, [2] Health Management Center, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3] Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China, [4] State Key Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Beijing, China

OPEN ACCESS

Edited by:
Marios Kyriazis,
National Gerontology Centre, Cyprus

Reviewed by:
Mathieu Maltais,
Université de Sherbrooke, Canada
Joshua Miller,
Rutgers, The State University of New Jersey, United States

***Correspondence:**
Sin Man Lam
smlam@genetics.ac.cn
Timothy Kwok
tkwok@cuhk.edu.hk

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

Specialty section:
This article was submitted to Geriatric Medicine, a section of the journal Frontiers in Medicine

Received: *28 January 2022*
Accepted: *05 April 2022*
Published: *27 April 2022*

Citation:
Zhou H, Wu Y, Jiang B, Li B, Li M, Tian H, Shui G, Lam SM and Kwok T (2022) Metabolic Basis of Cognitive Improvement Associated With Active B Vitamin Supplementation in Cognitively Impaired Elderly Subjects – A Metabolomics Study. Front. Med. 9:864152. doi: 10.3389/fmed.2022.864152

Intervention studies with active B vitamin supplementation in cognitively impaired individuals have yielded varying results in randomized controlled trials. In addition, a negative interaction of active B vitamin supplementation with aspirin usage on cognitive outcome was noted, but the molecular basis of the interaction has largely remained unknown. To investigate the metabolic basis of cognitive improvement brought about by active B vitamin supplementation, we conducted an extensive metabolomics analysis covering 302 identified metabolites on the baseline and 24-month serum samples from a cohort of 137 subjects randomly assigned to active supplementation or placebo. Pathway analysis uncovered enhanced gluconeogenesis and War-burg effects underlying cognitive improvement in non-aspirin users supplemented with active B vitamins. In addition, metabolomics revealed that aspirin usage may interact with B vitamin supplementation by altering gut microbial metabolism, particularly in terms of propionate production. Lastly, our omics data suggest that varying capacities to assimilate B vitamins at baseline, possibly mediated by differences in gut microbial composition, may underlie variations in inter-individual responses to active B vitamin supplementation.

Keywords: metabolomics, B vitamins, aspirin, cognitive impairment, dementia

INTRODUCTION

Approximately 50 million people across the globe live with dementia. The number is projected to increase to 152 million by the year 2050, especially in low-income and middle-income countries where close to two-thirds of the people afflicted with dementia reside (1). Dementia encumbers daily activities and financially strains the public health sector and the economy, with global costs estimated at USD one trillion annually (1). While the incidence of dementia is strongly correlated with age, dementia does not constitute normative aging and is a true disease instigated by exposure to genetic and environmental risk factors. Elevated homocysteine and lower-than-normal concentrations of B vitamins, which include folate, vitamin B12 and vitamin B6, denote candidate

risk factors for both Alzheimer's disease and vascular dementia (2). A plethora of cross-sectional and longitudinal studies comprising more than 36,000 subjects has demonstrated associations between cognitive impairment or dementia with homocysteine and/or B vitamins. Biologically plausible mechanisms for the beneficial action of B vitamins toward cognition have been proposed, but details await to be settled (2–4). Intervention studies with B vitamins in cognitively impaired individuals, however, have not yielded consistently positive results (5–9). Recent randomized trials uncovered a significant interaction between B vitamins and aspirin usage on cognitive function; and that B vitamin supplementation was associated with significantly favorable effects toward global cognitive functioning and whole brain atrophy rate in older people with mild cognitive impairment (MCI) who were not taking aspirin, but not in those who took aspirins concurrently (10, 11). Given these observations, it is imperative for research to delve into the molecular aspects of B vitamins and aspirin interaction that may underlie the clinical outcome of B vitamin supplementation in elderly subjects. High-coverage metabolomics offers an unbiased, inclusive approach to dissect molecular alterations in response to treatment intervention (12), and can unveil potential molecular pathways that underlie observed phenotypes (13).

Herein, we conduct an extensive metabolomics profiling that comprises 302 identified metabolites on pre-intervention (i.e., baseline) and post-intervention serum samples from 137 subjects randomly assigned to two main treatment interventions over a course of 24 months, which included active ingredient (folic acid and Vitamin B12) supplementation and placebo. Aspirin usage was monitored in these subjects, which further segregated the treatment groups into active + non-aspirin and active + aspirin, and their corresponding control groups being placebo + non-aspirin and placebo + aspirin, respectively. At the end of the two-year treatment intervention, cognitive outcome in these subjects were measured by the clinical dementia rating scale sum of boxes scores (CDR-SOB) (14). Differences in metabolomics profiles and dysregulated metabolic pathways between the treatment and control groups at the end of two-year intervention were examined in consideration of measured outcome i.e., CDR-SOB to uncover metabolic pathways implicated in the different treatment interventions and their associated cognitive outcomes.

MATERIALS AND METHODS

Study Participants

Patients aged ≥ 65 years were screened by the Montreal cognitive assessment (MoCA) test in the specialist medical outpatient clinics at the Prince of Wales Hospital (PWH) during April 2013 and July 2016. After obtaining written informed consent, subjects who had a MoCA score lower than 22, which suggested MCI, had fasting blood taken for serum homocysteine analysis. Those with homocysteine ≥ 10 μmol/L were further assessed of co-existing illnesses and a neurological examination, to exclude patients with dementia or clinical depression, or those with peripheral neuropathy, renal failure, anemia, disabling stroke and those who were receiving B vitamin supplementation or centrally acting medications. In total, 279 out of 975 outpatients were enrolled in this clinical trial (10). The trial was approved by the Medical Ethics Committee of Chinese University of Hong Kong and Hospital Authority of Hong Kong (CUHK_CCT00373).

Clinical Design

Subjects aged 65 years or more in the specialist medical outpatient clinics at the Prince of Wales hospital between April 2013 and July 2016 were screened for cognitive impairment. After obtaining written informed consent, fasting blood was taken from individuals with MCI for serum homocysteine analysis, and subjects with elevated serum homocysteine (more than 10 μmol/L) were recruited into the study (see section "Study Participants" for more details). Subjects were randomly assigned into active ingredient intervention (400 μg/d of folic acid and 500 μg/d of vitamin B12) and placebo (two placebo tablets per day) groups, and their aspirin usage was recorded. As the effects of B vitamin supplementation toward cognitive outcome have been conflicting based on past literature (7, 9), we included a greater number of subjects into the active + non-aspirin group of our study to allow a comparison of metabolome profiles based on two-year cognitive outcome. At the end of the 24-month intervention, changes in CDR-SOB were used to further delineate subjects under the active + non-aspirin group into sub-categories based on cognitive outcome, which included those with longitudinal decrease in CDR-SOB (positive outcome) i.e., responders, no significant changes (neutral), and longitudinal increase in CDR-SOB (negative outcome) i.e., decliners (**Figure 1** and **Table 1**).

Serum Collection

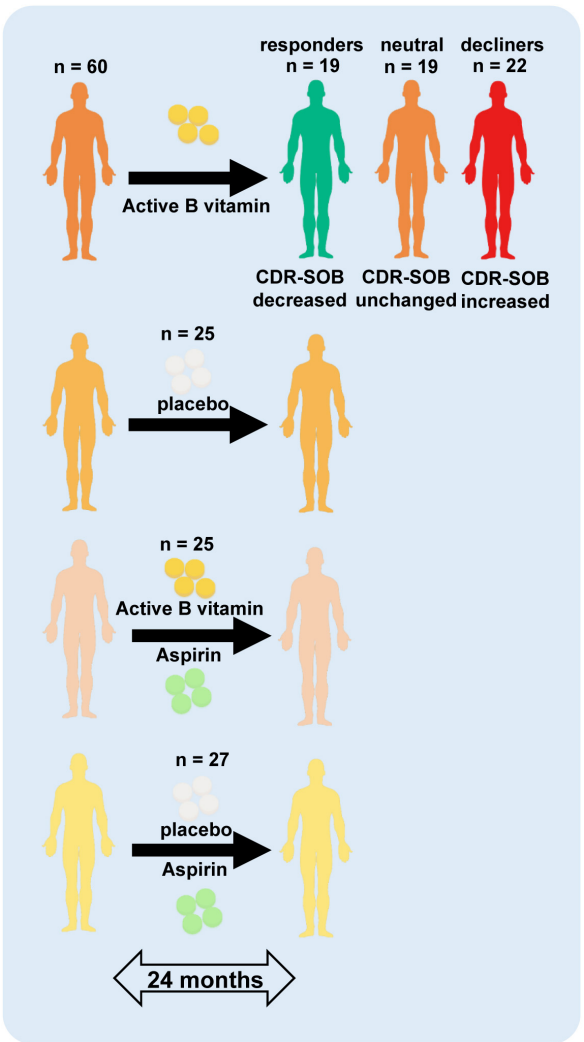
The blood samples were taken after an overnight fasting for serum folate, vitamin B_{12}, homocysteine and creatinine. The samples were temporarily stored in an icebox and transported within 2 h to the Department of Medicine and Therapeutics at PWH. The serum was then separated and kept under −80°C until further use.

Metabolite Extraction

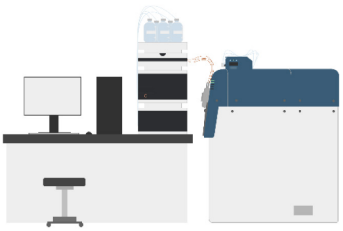
Polar metabolites were extracted from serum samples using a modified version of Bligh and Dyer's protocol as described previously (15). Serums samples were incubated for 30 min at 1500 rpm and 4°C in extraction solvent containing chloroform: methanol (1:2) (v/v); and water was added at the end of the incubation to induce phase separation. Samples were then centrifuged for 10 min at 12000 rpm and 4°C. The upper aqueous phase containing polar metabolites was transferred into a clean 1.5 ml centrifuge tube, and dried using SpeedVac under aqueous mode. Dried extracts were resuspended in 2% acetonitrile in water for LC-MS analysis.

Untargeted Metabolomics Analyses Based on UPLC-qTOF-MS

Metabolomics analysis was performed as previously described (12). The ACQUITY UPLC HSS T3 1.8 μm, 2.1 mm × 100 mm

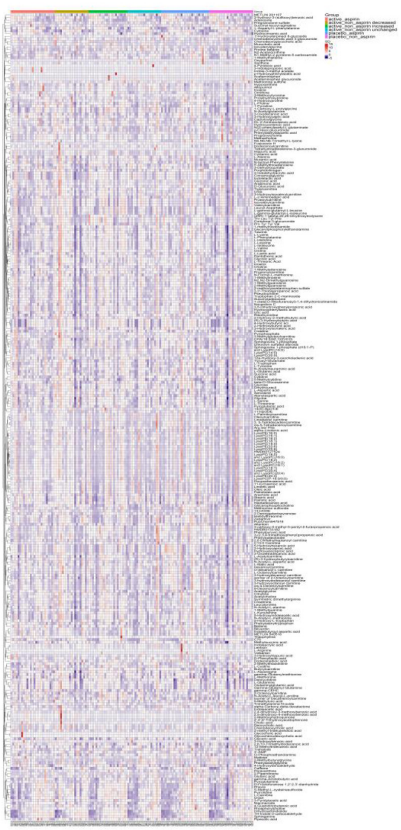


Serum collection
137 subjects
274 samples



Metabolomics based on
UPLC/TOF-MS

302 identified metabolites



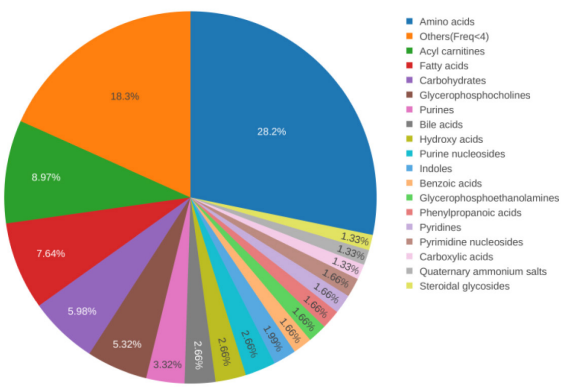


FIGURE 1 | Schematic diagram of clinical study design. Subjects were randomly assigned to active B vitamin supplementation or placebo. Aspirin usage was monitored, which further segregated the subjects into four clinical groups. To examine the molecular basis of differing responses to active B vitamin supplementation, subjects under active B vitamins, non-aspirin group were further segregated into three groups based on cognitive outcome measured by 24-month changes in CDR-SOB. Baseline and 24-month serum samples were analyzed using untargeted metabolomics covering more than 300 identified metabolites.

TABLE 1 | Clinical cohort summary.

	Active + aspirin	Active + non-aspirin, CDR-SOB increased	Active + non-aspirin, CDR-SOB unchanged	Active + non-aspirin, CDR-SOB decreased	Placebo + aspirin	Placebo + non-aspirin	*P*-value
n	**25**	**22**	**19**	**19**	**27**	**25**	
Age [mean (SD)]	76.5 (6.03)	76.9 (4.59)	75.0 (5.34)	76.8 (4.3)	77.96 (4.38)	78.0 (5.81)	0.4209
Change in CDR-SOB over 24 months [mean (SD)]	0.60 (1.46)	1.36 (1.15)*	0 (0)	−0.71 (0.35)*	−0.17 (0.67)	0.54 (0.095)*	*Indicates statistical significant changes compared to baseline
Sex							0.6676
Male	18 (72%)	16 (72.8%)	13 (68.4%)	11 (57%)	17 (63%)	16 (64%)	
Female	7 (28%)	6 (27.2%)	6 (31.6%%)	8 (42.1%)	10 (37%)	9 (36%)	

Differences in age across groups were compared using Welch's ANOVA. Changes in sex were compared using Chi-square's test. Longitudinal changes in CDR-SOB were compared using paired t-test.

column (Waters, Dublin, Ireland) was used for reverse-phase chromatographic analysis, while the ACQUITY UPLC BEH Amide 1.7 μm, 2.1 mm × 100 mm column (Waters, Dublin, Ireland) was utilized for normal-phase chromatographic analysis. An Agilent 1290 II Ultra-performance Liquid Chromatographer (Agilent Technologies) coupled to 5600 Plus Quadrupole-time-of-flight MS (5600 Triple TOF Plus, SCIEX) was used to acquire the metabolome data. The MS parameters for detection were as follows, ESI source voltage positive ion mode +5.5 k V, negative ion mode −4.5 kV; vaporizer temperature, 500°C; drying gas (N2) pressure, 50 psi; nebulizer gas (N2) pressure, 50 psi; curtain gas (N2) pressure, 35 psi; The scan range was m/z 60–900. Information-dependent acquisition mode was used for MS/MS analyses of the metabolites. The collision energy was set at (±) 35 ± 15 eV. Data acquisition and processing were performed using Analyst® TF 1.7.1 Software (Sciex, Concord, ON, Canada). All detected ions were extracted using MarkerView 1.3 (Sciex, Concord, ON, Canada) into Excel in the format of two dimensional matrix, including mass to charge ratio (m/z), retention time, and peak areas, and isotopic peaks were filtered. PeakView 2.2 (Sciex, Concord, ON, Canada) was applied to extract the MS/MS data, and spectral comparisons were performed with Metabolites database (Sciex, Concord, ON, Canada), HMDB, METLIN, and spectra acquired from standard reference compounds to annotate ion ID.

Statistical Analyses

Metabolite identity, corresponding HMDB ID and class were assigned using an internal library. Metabolite abundance was measured by peak area. Hierarchical clustering was performed based on centered and scaled data with Euclidean distance and complete linkage, and was visualized using R package "ComplexHeatmap." Average metabolite abundance was compared among all the groups using Kruskal–Wallis test, followed by *post hoc* Dunn's test for pair-wise comparison. *P*-value less than 0.05 was considered as statistically significant. Metabolite set enrichment analysis (MSEA) was performed based on the metabolites with $P < 0.05$ over the small molecules pathway database (SMPDB) using R package "MetaboAnalystR." The over-representation test for MSEA is hypergeometric test using all the annotated metabolites that can be mapped to HMDB IDs as the reference metabolome. The orthogonal partial least square discriminant analysis (OPLSDA) was performed using R package "ropls."

RESULTS

Differences in 24-Month Serum Metabolome Profiles Across Different Treatment Groups

Comparing 24-month serum metabolomes of responders from the active + non-aspirin group relative to placebo + non-aspirin control group, the levels of metabolites including alanyl-aspartic acid, creatine, glucose, hippuric acid, L-glutamine, and L-lactic acid were increased, while that of pregnenolone sulfate was decreased (**Figure 2A**). Similarly, when compared to active + non-aspirin group with neutral cognitive outcome, i.e., unchanged CDR-SOB, serum level of hippuric acid was consistently higher in non-aspirin users who responded positively to active B vitamins supplementation (**Figure 2B**). Comparing the 24-month serum metabolome profiles of the active + aspirin group to responders from the active + non-aspirin group, the level of tetrahydro-aldosterone-3-glucuronide (THA-G) was lower in aspirin users (**Figure 2C**). THA-G was also lower in the placebo + aspirin control group compared to active + aspirin group (**Figure 2D**). Thus, active B vitamin supplementation increases serum level of THA-G, but concurrent aspirin usage reduces its level. Next, we utilized metabolic pathway analysis (MSEA) (16) to systematically investigate altered metabolic pathways between the treatment and control groups.

Altered Metabolic Pathways Between Treatment and Control Groups

Relative to placebo + non-aspirin group, active B vitamin supplementation in non-aspirin users who responded positively (i.e., longitudinal reduction in CDR-SOB) resulted

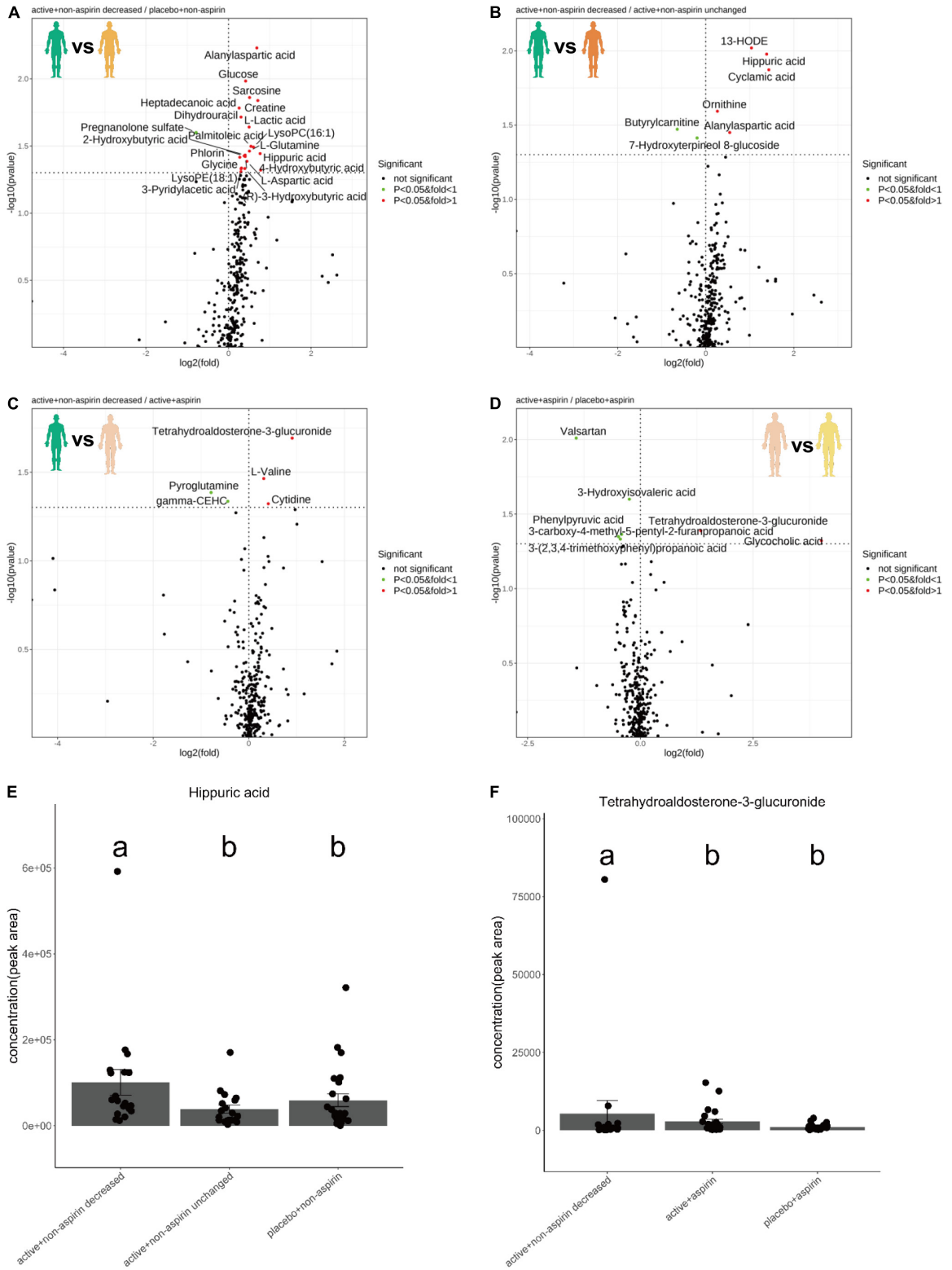


FIGURE 2 | Volcano plots illustrate serum metabolite changes at 24-month in selected pairwise comparisons of clinical groups, which included **(A)** active B vitamin supplementation in non-aspirin users with reduction in CDR-SOB relative to non-aspirin users on placebo; **(B)** active B vitamin supplementation in non-aspirin users with reduction in CDR-SOB relative to those without changes in CDR-SOB; **(C)** active B vitamin supplementation in non-aspirin users with reduction in CDR-SOB relative to active B vitamin supplementation in aspirin users; **(D)** active B vitamin supplementation in aspirin users relative to aspirin users on placebo. Dotplots illustrate changes in the levels in **(E)** hippuric acid and **(F)** tetrahydro-aldosterone-3-glucuronide at 24 months. *P*-values from two-sided Dunn's tests were displayed.

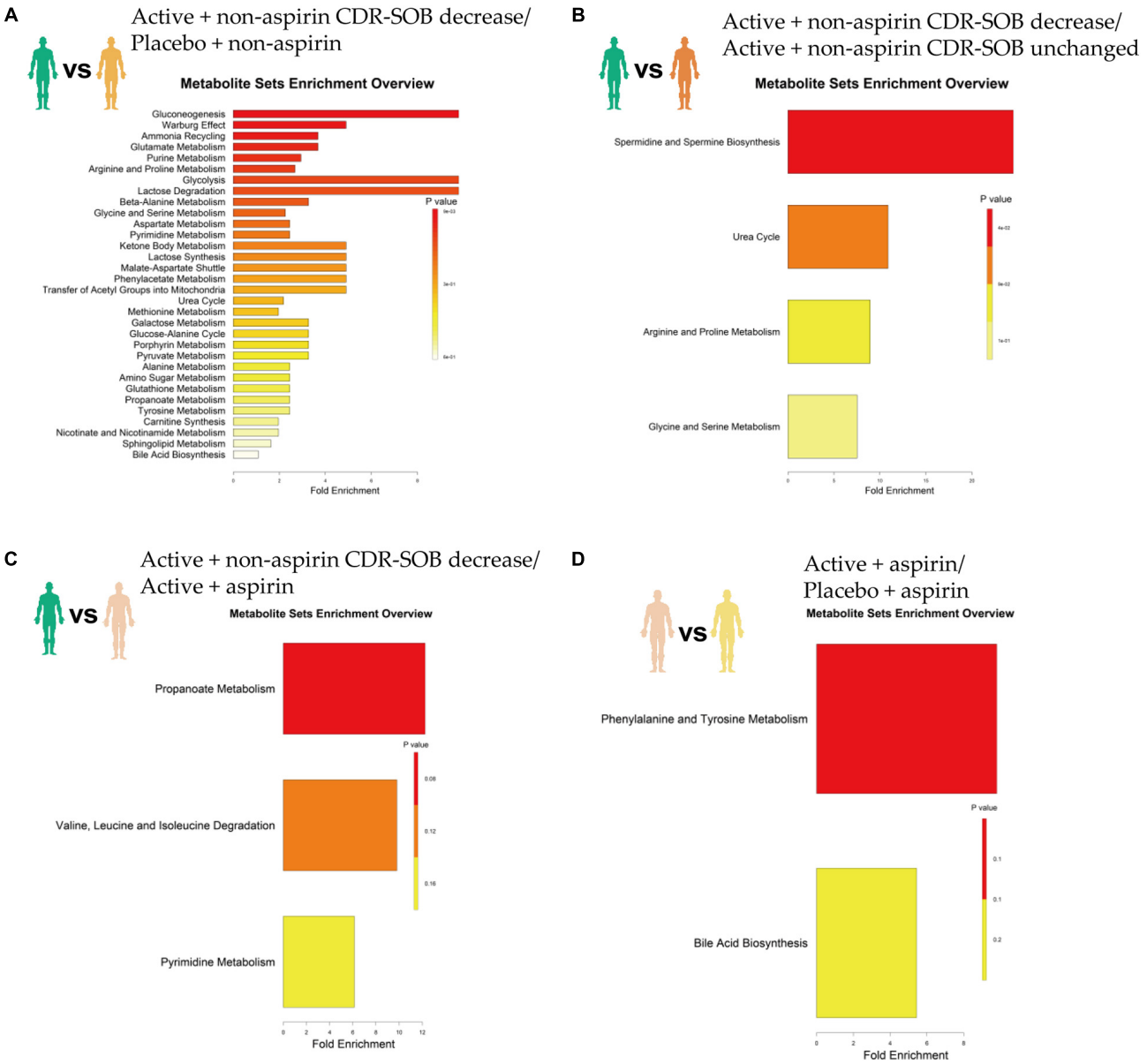


FIGURE 3 | Top altered metabolic pathways based on metabolome changes at 24-month in selected pairwise comparisons of clinical groups, which included **(A)** active B vitamin supplementation in non-aspirin users with reduction in CDR-SOB relative to non-aspirin users on placebo; **(B)** active B vitamin supplementation in non-aspirin users with reduction in CDR-SOB relative to those without changes in CDR-SOB; **(C)** active B vitamin supplementation in non-aspirin users with reduction in CDR-SOB relative to active B vitamin supplementation in aspirin users; **(D)** active B vitamin supplementation in aspirin users relative to aspirin users on placebo.

in significantly elevated gluconeogenesis, enhanced Warburg effect, as well as increased ammonia recycling, glutamate metabolism and purine metabolism (**Figure 3A** and **Table 2**). Relative to non-aspirin users that did not respond favorably to B vitamin supplementation, responders also displayed enhanced spermidine and spermine biogenesis (**Figure 3B**). Comparing with subjects on B vitamin supplementation with concurrent aspirin usage, subjects not on aspirins also exhibited marginally enhanced propanoate metabolism (**Figure 3C**). Concurrent aspirin usage largely abrogated the enhanced glucose metabolism brought about by B vitamin supplementation, and no metabolic pathways were significantly altered with respect to the placebo + aspirin control group (**Figure 3D**).

Metabolism Underlying Inter-Individual Variability to B Vitamin Supplementation

While it is clear from previous randomized trials that aspirin interacted with B vitamin supplementation to influence the

TABLE 2 | Summary of top altered pathways.

Comparisons	Metabolite set	Total	Expected	Hits	Fold	Raw *p*	Direction
Active non-aspirin CDR-SOB decreased/Placebo non-aspirin	Gluconeogenesis	2	0.204	2	9.8	0.00947	Upregulated
	Warburg effect	6	0.612	3	4.9	0.0133	Upregulated
	Ammonia recycling	8	0.816	3	3.68	0.0332	Upregulated
	Glutamate metabolism	8	0.816	3	3.68	0.0332	Upregulated
	Purine metabolism	10	1.02	3	2.94	0.0633	Upregulated
	Arginine and proline Metabolism	11	1.12	3	2.68	0.082	Upregulated
Active non-aspirin CDR-SOB decreased/active non-aspirin CDR-SOB unchanged	Spermidine and spermine biosynthesis	4	0.0408	1	24.51	0.0408	Upregulated
	Urea cycle	9	0.0918	1	10.89	0.0918	Upregulated
Active non-aspirin CDR-SOB decreased/active aspirin	Propanoate metabolism	4	0.0816	1	12.25	0.0804	Upregulated
	Valine, leucine and Isoleucine Degradation	5	0.102	1	9.8	0.0999	Upregulated
Active aspirin/placebo aspirin	Phenylalanine and tyrosine metabolism	5	0.102	1	9.8	0.0999	Downregulated

cognitive outcome of the intervention (10, 11), the effects of B vitamin supplementation toward cognitive outcome in non-aspirin users were also varied. To delve into the potential underlying metabolic differences that may have influenced the outcome, we then investigated the differences in baseline metabolome profiles of non-aspirin users who responded positively and negatively, respectively, to B vitamin supplementation over a course of 24-months. The baseline metabolome profiles between non-aspirin users on active B vitamin supplementation experiencing a drop in CDR-SOB were markedly different from those that exhibited increase in CDR-SOB. The baseline metabolome profiles were clearly segregated based on orthogonal projections to latent structures discriminant analysis (OPLS-DA) with an area under curve (AUC) at 0.981. Due to the relatively smaller cohort size, however, the OPLS-DA model exhibited overfitting (pR2Y = 0.05, pQ2 = 1) (**Figures 4A–D**). MSEA showed that baseline pyrimidine metabolism was marginally enhanced in individuals who responded positively to active B vitamin supplementation, relative to individuals who responded negatively (**Figure 4E**). The top metabolites contributing to the observed differences arranged based on VIP scores were illustrated in a heatmap (**Figure 4F**). Accordingly, deoxyuridine, which constitutes part of pyrimidine metabolism, was amongst the top three altered metabolites, and the baseline levels of deoxyuridines were lower in non-aspirin users who responded negatively to active B vitamin supplementation. Thus, this group of individuals who failed to respond favorably to active B vitamin supplementation exhibited abated pyrimidine metabolism and inherently less efficient folate cycle to effectively couple the conversion of homocysteine into methionine to begin with. They may require longer supplementation period at higher dosage, or may be endogenously incompetent in terms of incorporating and assimilating B vitamins due to deficiencies in specific enzymes. Indeed, a previous work had shown that B vitamin supplementation is effective only in individuals with intact dihydrofolate reductase (17).

DISCUSSION

Metabolomics analysis revealed a favorable serum metabolome profile in non-aspirin users who responded positively to active B vitamins supplementation, as illustrated by the increases in serum hippuric acid and creatine that contribute positively to cognitive outcome (18, 19). Hippuric acid is a frailty marker and diminished blood concentrations of hippuric acid were reported in elderly Japanese patients with mobility impairment (18). Plasma hippuric acid was also decreased in older patients at high-risk of sarcopenia (20), and dietary supplementation of hippuric acid in the form of blueberries led to cognitive enhancement and improved performance in verbal learning test (21). On another note, oral creatine supplementation promotes corticomotor excitability and cognitive performance during acute oxygen deprivation in adults (22), and is associated with improvements in short-term memory and reasoning of healthy individuals (19). In addition, while active B vitamin supplementation increased serum THA-G, while concurrent aspirin usage abrogated this increase. Aldosterone is metabolized to dihydro- and tetrahydro derivatives that subsequently undergo glucuronidation in the liver, with THA-G accounting for majority of daily aldosterone elimination *via* the urine (23). Given the role of aldosterone as a relevant factor in the evolution of arterial hypertension (24), impeded glucuronidation and the subsequent elimination of serum aldosterone in the form of THA-G may be detrimental toward vascular health. The current metabolomics profiles suggest that active B vitamin supplementation is associated with enhanced glucuronidation of aldosterone. Thus, the general serum metabolome profiles of active + non-aspirin group who responded positively was associated with enhanced levels of metabolites positively associated with cognitive improvement and vascular health. Concurrent aspirin usage largely abrogated these potentially beneficial metabolite changes associated with active B vitamin supplementation.

Enhanced gluconeogenesis and glycolysis revealed by MSEA analyses in non-aspirin responders are expected to contribute positively toward cognitive maintenance. Drastic reductions

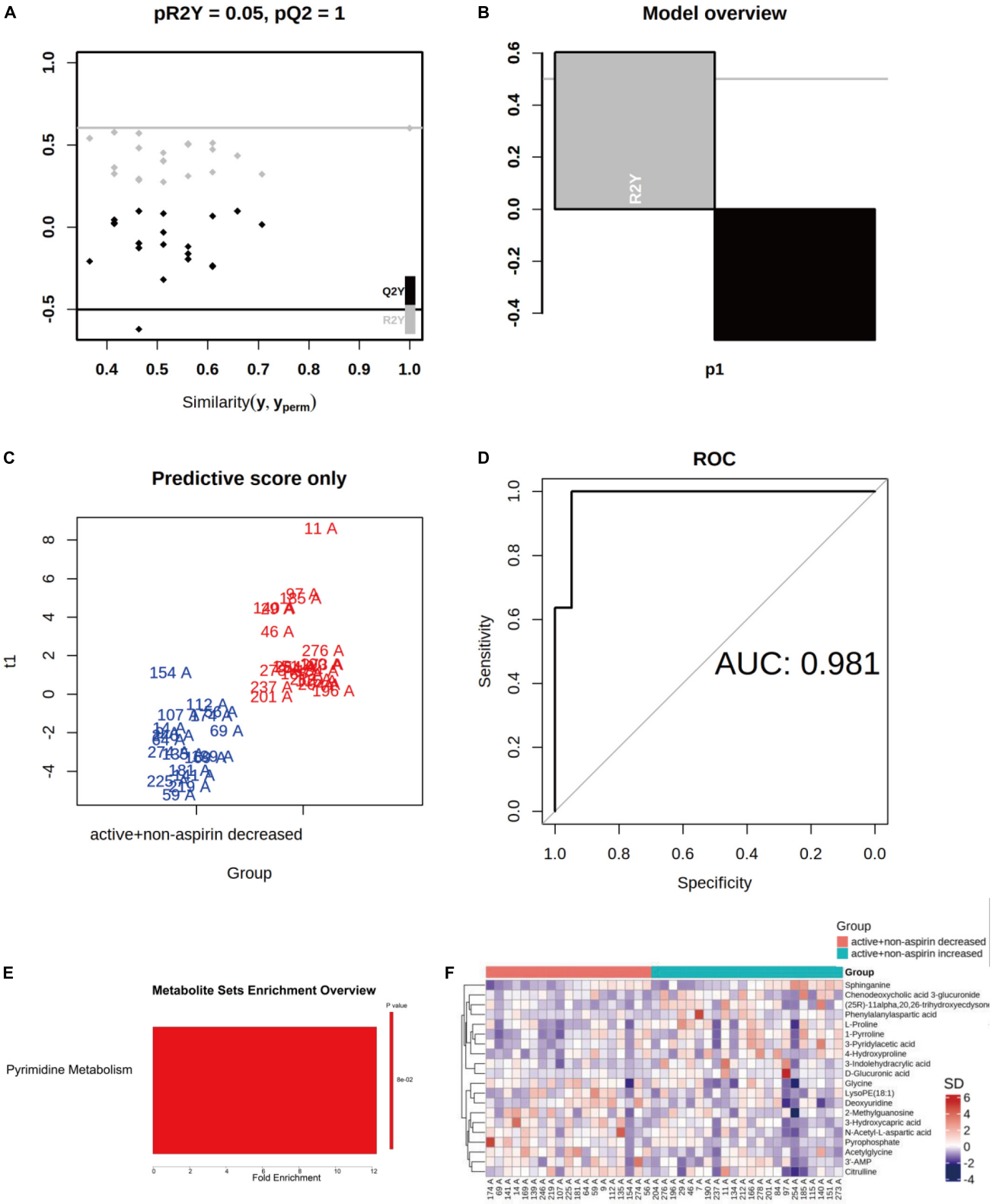


FIGURE 4 | Differences in baseline metabolome profiles between non-aspirin users on active B vitamin supplementation who responded positively (i.e., reduction in CDR-SOB) and negatively (i.e., increase in CDR-SOB) over the intervention period of 24 months. **(A–D)** OPLS-DA analysis of baseline serum metabolomes between the two groups; **(E)** Top altered metabolic pathway between the two groups; **(F)** Heatmap illustrates top altered metabolites based on VIP scores from OPLS-DA analysis.

in cerebral glucose metabolism and utilization are common patho-biochemical features of dementia of the Alzheimer type (25, 26). Restoration of glucose metabolism salvages amino acids and lipids that would otherwise be expended as fuel reserves when cerebral glucose metabolism falls below critical thresholds, thereby preserving critical lipid membranes and proteins crucial to maintaining normal brain function. Enhanced glucose metabolism also counteracts increases in glycated hemoglobin and attenuates the accumulation of advanced glycation end-products, which contributes to memory improvement in mice (27). Interestingly, enhanced Warburg effect was also observed in non-aspirin responders. Warburg effect, first observed by Otto Warburg in cancer cells, refers to the preferential dependency on glucose utilization, marked by elevated glycolysis and lactate production regardless of oxygen bioavailability. Biochemical measurement in port-mortem brain tissues of Alzheimer's disease (AD) patients, which denotes an assessment of the biochemical activities of viable beta-amyloid (Aβ)-resistant cells instead of susceptible, dying cells (28, 29), uncovered an elevation of glycolytic enzymes in the AD brains relative to that of age-matched controls. In addition, clonal nerve cell lines and primary cortical neuron resistant to Aβ toxicity exhibited elevated flux of glucose through the glycolytic pathway, attributed to the activation of the transcription factor hypoxia inducible factor 1 (HIF-1) (29). Furthermore, the existence of a specific group of asymptomatic individuals without pathological history of dementia but having high accumulation of Aβ plaques adds to the hypothesis that altered cellular metabolism, particularly enhanced glucose utilization *via* glycolysis, may offer resistance against the neurotoxic effects of Aβ (30). Based on these observations, it was proposed that neurons may acquire resistance to Aβ accumulation at the incipient stages of AD by skewing cellular metabolism toward enhanced glycolysis and lactate generation, which serves to silence mitochondrial oxidative phosphorylation, reducing the generation of reactive oxygen species that trigger apoptosis and neuronal death (31). These metabolic adaptations akin to Warburg effects preserve neuronal integrity and protect cognitive functions. Thus, active B vitamin supplementation in a specific group of non-aspirin users triggered enhanced Warburg effect that may contribute positively toward neuron survival in MCI individuals.

Non-aspirin users who responded favorably to active B vitamin supplementation also exhibited elevated purine metabolism, ammonia recycling and glutamate metabolism. Enhanced purine metabolism is likely attributed to the increased flow of metabolites through the folate cycle as a result of active B vitamin supplementation (32). Elevated ammonia recycling and glutamate metabolism may arise from the enhanced glutamine-glutamate cycle mediated by glutamine synthetase (GS). In the brain, GS serves to recover glutamate released by neurons by converting them to glutamine in astrocytes, which are then transported to neurons for subsequent conversion to glutamate again. This cycle replenishes the excitatory neurotransmitter glutamate essential for maintaining normal cognitive functions. Accordingly, GS expression was reduced in senile dementia of the Alzheimer type (33). The purine nucleotide cycle liberates ammonia (34), which the brain detoxifies by binding to alpha-ketoglutarate and glutamate to produce glutamine (35). Excess ammonia is detrimental to astrocytes and may lead to gliosis observed in early neurodegeneration in dementia (36). Indeed, AD brains were found to release a larger amount of ammonia (36). Enhanced ammonia recycling *via* glutamine formation and elevated purine metabolism in non-aspirin users who responded positively to active B vitamins thus serve to maintain astrocyte-neuron coupling pivotal to normal brain function.

The cognitively favorable changes were not observed in subjects who took aspirin concurrently, and a marginal difference in propanoate metabolism may partly explain the differing cognitive outcome. Compared to non-aspirin users, propanoate metabolism was downregulated in subjects on active B vitamin supplementation with concurrent aspirin usage. Propionate is a gut microbe-derived metabolite that positively modulates the peripheral and central nervous system. In particular, levels of fecal propionate were negatively correlated with Aβ-42 levels in MCI subjects (37). Based on our metabolomics analysis, aspirin may interact with active B vitamins in a manner that is mediated by gut microbial metabolism. Indeed, vitamin B12 modulates gut microbial ecology and influences host-microbe symbiosis in humans (38). The gut microbial metagenome displays considerable interpersonal variations, more so than that observed in host gene expressions, and may represent an important factor in determining inter-individual differences in disease predisposition and responses to treatment (38). Spermine and spermidine metabolism was enhanced in non-aspirin users who displayed improvement in CDR-SOB on active B vitamin supplementation compared to individuals who did not. The biosynthesis of major polyamines including spermidine and spermine from putrescine is coupled to the conversion of S-adenosylmethionine into decarboxylated S-adenosylmethionine (39), and is henceforth affected by the flux through the folate cycle (40). Gut microbiota is responsible for production of bulk polyamines in the lower part of the intestine (39), and spermines and spermidines were shown to delay brain ageing by promoting autophagy and improving mitochondria function (41). In non-aspirin users who did not respond well to active B vitamins supplementation, it is possible that their gut microbial configurations hindered effective vitamin B12 uptake. Indeed, subjects with high bacterial loads in their small intestines were found to possess low vitamin B12 (42), and specific gut microbe populations may compete with host for dietary vitamin B12 bioavailability in the small intestines (38).

This study has limitations. While our metabolomics analysis herein put forth enhanced Warburg effect and preferential glucose utilization as possible contributors to cognitive improvement brought about by active B vitamin supplementation in non-aspirin users, the current study design does not allow the interpretation of causality. We cannot conclude that these metabolic pathways alterations were resulted from active B vitamin supplementation alone, amidst other confounding factors such as dietary preferences that were not monitored; or that these pathway alterations actually lead to cognitive improvement reflected by the reduction in CDR-SOB.

Furthermore, our study makes the basic assumption that systems metabolic alterations in the serum are reflective of changes in neuro-metabolism. Further investigation in larger cohort of subjects from different ethnicities, and preferably based on cerebrospinal fluid samples, may allow a closer reflection of neuro-metabolic adaptations in response to active B vitamin supplementation. To determine causality between B vitamins supplementation and cognitive improvement mediated by enhanced Warburg effects and glucose utilization in brain cells, mechanistic studies using cell cultures and animal models are imperative. Finally, it may be worthy to examine the gut microbial compositional changes in fecal samples of future human cohorts subjected to active B vitamin supplementation, to determine if distinct microbial communities may underlie inter-individual differences in terms of their responses to B vitamin intervention observed in our study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The trial was approved by the Medical Ethics Committee of Chinese University of Hong Kong and Hospital Authority of Hong Kong (CUHK_CCT00373). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TK: conceptualization and project administration. HT and SL: methodology. BJ and BL: formal analysis and visualization. HZ, YW, and ML: investigation. SL: writing—original draft preparation. TK, YW, BL, GS, and HZ: writing—review and editing. SL and TK: supervision. TK and GS: funding acquisition. All authors have read and agreed to the published version of the manuscript.

FUNDING

This study was supported by the General Research Grant from the Hong Kong Research Grant Council (Ref No. 466612) and the National Key R&D Program of China (2018YFA0800901).

ACKNOWLEDGMENTS

We thank all participants in the clinical study, and Xiaojie Liu from LipidALL Technologies for artistic illustrations.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.864152/full#supplementary-material

Supplementary Table 1 | Clinical information.

Supplementary Table 2 | Metabolome dataset.

REFERENCES

1. Patterson C. *World Alzheimer Report 2018. The State of the Art of Dementia Research: New Frontiers. An Analysis of Prevalence, Incidence, Cost and Trends.* London: Alzheimer's Disease International (2018).
2. Smith AD. The worldwide challenge of the dementias: a role for B vitamins and homocysteine? *Food Nutr Bull.* (2008) 29:S143–72. doi: 10.1177/15648265080292S119
3. Smith AD, Refsum H. Homocysteine - from disease biomarker to disease prevention. *J Intern Med.* (2021) 290:826–54. doi: 10.1111/joim.13279
4. Smith AD, Refsum H. Homocysteine, B vitamins, and cognitive impairment. *Annu Rev Nutr.* (2016) 36:211–39. doi: 10.1146/annurev-nutr-071715-050947
5. Ma F, Wu TF, Zhao JG, Song AL, Liu H, Xu WL, et al. Folic acid supplementation improves cognitive function by reducing the levels of peripheral inflammatory cytokines in elderly Chinese subjects with MCI. *Sci Rep.* (2016) 6:37486. doi: 10.1038/srep37486
6. Jiang Y, Cheng D, Kong H, Pang W, Yang H, Sun S, et al. Supplementation B vitamins improves cognitive function in the middle-aged and elderly with hyperhomocysteinemia. *Ann Nutr Metab.* (2013) 63:713–713.
7. Cheng DM, Kong HY, Pang W, Yang HP, Lu H, Huang CY, et al. supplementation improves cognitive function in the middle aged and elderly with hyperhomocysteinemia. *Nutr Neurosci.* (2016) 19:461–6. doi: 10.1179/1476830514Y.0000000136
8. Zhang DM, Ye JX, Mu JS, Cui XP. Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases: a systematic review and meta-analysis. *J Geriatr Psych Neur.* (2017) 30:50–9. doi: 10.1177/0891988716673466
9. Moore E, Mander A, Ames D, Carne R, Sanders K, Watters D. Cognitive impairment and vitamin B12: a review. *Int Psychogeriatr.* (2012) 24:541–56. doi: 10.1017/S1041610211002511
10. Kwok T, Wu Y, Lee J, Lee R, Yung CY, Choi G, et al. A randomized placebo-controlled trial of using B vitamins to prevent cognitive decline in older mild cognitive impairment patients. *Clin Nutr.* (2020) 39:2399–405. doi: 10.1016/j.clnu.2019.11.005
11. Wu Y, Smith AD, Refsum H, Kwok T. Effectiveness of B vitamins and their interactions with aspirin in improving cognitive functioning in older people with mild cognitive impairment: pooled post-hoc analyses of two randomized trials. *J Nutr Health Aging.* (2021) 25:1154–60. doi: 10.1007/s12603-021-1708-1
12. Song JW, Lam SM, Fan X, Cao WJ, Wang SY, Tian H, et al. Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. *Cell Metab.* (2020) 32:188–202e5. doi: 10.1016/j.cmet.2020.06.016
13. Lam SM, Wang Z, Li B, Shui G. High-coverage lipidomics for functional lipid and pathway analyses. *Anal Chim Acta.* (2021) 1147:199–210. doi: 10.1016/j.aca.2020.11.024
14. O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, et al. Staging dementia using clinical dementia rating scale sum of boxes scores: a Texas alzheimer's research consortium study. *Arch Neurol.* (2008) 65:1091–5. doi: 10.1001/archneur.65.8.1091
15. Lam SM, Zhang C, Wang Z, Ni Z, Zhang S, Yang S, et al. A multi-omics investigation of the composition and function of extracellular vesicles along the temporal trajectory of COVID-19. *Nat Metab.* (2021) 3:909–22. doi: 10.1038/s42255-021-00425-4

16. Xia J, Wishart DS. MSEA: a web-based tool to identify biologically meaningful patterns in quantitative metabolomic data. *Nucleic Acids Res.* (2010) 38:W71–7. doi: 10.1093/nar/gkq329
17. Wu Y, Smith AD, Bastani NE, Refsum H, Kwok T. The dihydrofolate reductase 19-bp deletion modifies the beneficial effect of B-vitamin therapy in mild cognitive impairment: pooled study of two randomized placebo-controlled trials. *Hum Mol Genet*. (2021) 31:1151–8. doi: 10.1093/hmg/ddab246
18. Kameda M, Teruya T, Yanagida M, Kondoh H. Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility. *Proc Natl Acad Sci USA*. (2020) 117:9483–9. doi: 10.1073/pnas.1920795117
19. Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: a systematic review of randomized controlled trials. *Exp Gerontol.* (2018) 108:166–73. doi: 10.1016/j.exger.2018.04.013
20. Saoi M, Li A, McGlory C, Stokes T, von Allmen MT, Phillips SM, et al. Metabolic perturbations from step reduction in older persons at risk for sarcopenia: plasma biomarkers of abrupt changes in physical activity. *Metabolites.* (2019) 9:134. doi: 10.3390/metabo9070134
21. Rutledge GA, Sandhu AK, Miller MG, Edirisinghe I, Burton-Freeman BB, Shukitt-Hale B. Blueberry phenolics are associated with cognitive enhancement in supplemented healthy older adults. *Food Funct.* (2021) 12:107–18. doi: 10.1039/d0fo02125c
22. Turner CE, Byblow WD, Gant N. Creatine supplementation enhances corticomotor excitability and cognitive performance during oxygen deprivation. *J Neurosci.* (2015) 35:1773–80. doi: 10.1523/JNEUROSCI.3113-14.2015
23. Knights KM, Winner LK, Elliot DJ, Bowalgaha K, Miners JO. Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDP-glucuronosyltransferases: inhibition by NSAIDs. *Br J Clin Pharmacol.* (2009) 68:402–12. doi: 10.1111/j.1365-2125.2009.03469.x
24. Ruilope LM, Tamargo J. Aldosterone a relevant factor in the beginning and evolution of arterial hypertension. *Am J Hypertens.* (2017) 30:468–9. doi: 10.1093/ajh/hpx010
25. Gardener SL, Sohrabi HR, Shen KK, Rainey-Smith SR, Weinborn M, Bates KA, et al. Cerebral glucose metabolism is associated with verbal but not visual memory performance in community-dwelling older adults. *J Alzheimers Dis.* (2016) 52:661–72. doi: 10.3233/JAD-151084
26. Hoyer S. Possible role of ammonia in the brain in dementia of alzheimer type. *Adv Exp Med Biol.* (1994) 368:197–205. doi: 10.1007/978-1-4615-1989-8_21
27. Bonfili L, Cecarini V, Gogoi O, Berardi S, Scarpona S, Angeletti M, et al. Gut microbiota manipulation through probiotics oral administration restores glucose homeostasis in a mouse model of Alzheimer's disease. *Neurobiol Aging.* (2020) 87:35–43. doi: 10.1016/j.neurobiolaging.2019.11.004
28. Schubert D. Glucose metabolism and Alzheimer's disease. *Ageing Res Rev.* (2005) 4:240–57.
29. Soucek T, Cumming R, Dargusch R, Maher P, Schubert D. The regulation of glucose metabolism by HIF-1 mediates a neuroprotective response to amyloid beta peptide. *Neuron.* (2003) 39:43–56. doi: 10.1016/s0896-6273(03)00367-2
30. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol.* (1999) 45:358–68. doi: 10.1002/1531-8249(199903)45:3<358::aid-ana12>3.0.co;2-x
31. Atlante A, de Bari L, Bobba A, Amadoro G. A disease with a sweet tooth: exploring the Warburg effect in Alzheimer's disease. *Biogerontology.* (2017) 18:301–19. doi: 10.1007/s10522-017-9692-x
32. Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. with special references to cardiovascular disease and neural tube defects. *J Inherit Metab Dis.* (2011) 34:75–81. doi: 10.1007/s10545-010-9177-4
33. Le Prince G, Delaere P, Fages C, Lefrancois T, Touret M, Salanon M, et al. Glutamine synthetase (GS) expression is reduced in senile dementia of the Alzheimer type. *Neurochem Res.* (1995) 20:859–62. doi: 10.1007/BF00969698
34. Lowenstein JM. Ammonia production in muscle and other tissues: the purine nucleotide cycle. *Physiol Rev.* (1972) 52:382–414. doi: 10.1152/physrev.1972.52.2.382
35. Berl S, Takagaki G, Clarke DD, Waelsch H. Metabolic compartments in vivo. ammonia and glutamic acid metabolism in brain and liver. *J Biol Chem.* (1962) 237:2562–9.
36. Hoyer S, Nitsch R, Oesterreich K. Ammonia is endogenously generated in the brain in the presence of presumed and verified dementia of Alzheimer type. *Neurosci Lett.* (1990) 117:358–62. doi: 10.1016/0304-3940(90)90691-2
37. Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. *EBioMedicine.* (2019) 47:529–42. doi: 10.1016/j.ebiom.2019.08.032
38. Degnan PH, Taga ME, Goodman AL. Vitamin B12 as a modulator of gut microbial ecology. *Cell Metab.* (2014) 20:769–78. doi: 10.1016/j.cmet.2014.10.002
39. Tofalo R, Cocchi S, Suzzi G. Polyamines and gut microbiota. *Front Nutr.* (2019) 6:16. doi: 10.3389/fnut.2019.00016
40. Scott JM, Weir DG. Folic acid, homocysteine and one-carbon metabolism: a review of the essential biochemistry. *J Cardiovasc Risk.* (1998) 5:223–7. doi: 10.1097/00043798-199808000-00003
41. Xu TT, Li H, Dai Z, Lau GK, Li BY, Zhu WL, et al. Spermidine and spermine delay brain aging by inducing autophagy in SAMP8 mice. *Aging (Albany NY).* (2020) 12:6401–14. doi: 10.18632/aging.103035
42. Murphy MF, Sourial NA, Burman JF, Doyle DV, Tabaqchali S, Mollin DL. Megaloblastic anaemia due to vitamin B12 deficiency caused by small intestinal bacterial overgrowth: possible role of vitamin B12 analogues. *Br J Haematol.* (1986) 62:7–12. doi: 10.1111/j.1365-2141.1986.tb02894.x

Conflict of Interest: HZ BJ, BL, and SL are employees of LipidALL Technologies.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

,

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 October 2022
DOI 10.3389/fmed.2022.968814

OPEN ACCESS

EDITED BY
Roberta Zupo,
National Institute of Gastroenterology "S. de Bellis" Research Hospital (IRCCS), Italy

REVIEWED BY
Peter Kokol,
University of Maribor, Slovenia
Sousana Konstantinos Papadopoulou,
International Hellenic University, Greece

*CORRESPONDENCE
Huanhuan Huang
hxuehao@126.com
Qinghua Zhao
qh20063@163.com

SPECIALTY SECTION
This article was submitted to Geriatric Medicine, a section of the journal Frontiers in Medicine

RECEIVED 14 June 2022
ACCEPTED 03 October 2022
PUBLISHED 26 October 2022

CITATION
Huang H, Chen Z, Chen L, Cao S, Bai D, Xiao Q, Xiao M and Zhao Q (2022) Nutrition and sarcopenia: Current knowledge domain and emerging trends.
Front. Med. 9:968814.
doi: 10.3389/fmed.2022.968814

Nutrition and sarcopenia: Current knowledge domain and emerging trends

Huanhuan Huang[1]*, Zhiyu Chen[2], Lijuan Chen[1], Songmei Cao[1,3], Dingqun Bai[4], Qian Xiao[5], Mingzhao Xiao[6] and Qinghua Zhao[1]*

[1]Department of Nursing, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]Department of Orthopedic, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3]Department of Nursing, The Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, China, [4]Department of Rehabilitation Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [5]Department of Geriatric, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [6]Department of Urology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Objective: Non-pharmacological management like nutrient supplements has shown positive impacts on muscle mass and strength, which has burgeoned clinical and research interest internationally. The aim of this study was to analyze the current knowledge domain and emerging trends of nutrition-related research in sarcopenia and provide implications for future research and strategies to prevent or manage sarcopenia in the context of aging societies.

Materials and methods: Nutrition- and sarcopenia-related research were obtained from the Web of Science Core Collection (WoSCC) database from its inception to April 1, 2022. Performance analysis, science mapping, and thematic clustering were performed by using the software VOSviewer and R package "bibliometrix." Bibliometric analysis (BA) guideline was applied in this study.

Results: A total of 8,110 publications were extracted and only 7,510 (92.60%) were selected for final analysis. The production trend in nutrition and sarcopenia research was promising, and 1,357 journals, 107 countries, 6,668 institutions, and 31,289 authors were identified in this field till 2021. Stable cooperation networks have formed in the field, but they are mostly divided by region and research topics. Health and sarcopenia, metabolism and nutrition, nutrition and exercise, body compositions, and physical performance were the main search themes.

Conclusions: This study provides health providers and scholars mapped out a comprehensive basic knowledge structure in the research in the field of nutrition and sarcopenia over the past 30 years. This study could help them quickly grasp research hotspots and choose future research projects.

KEYWORDS

nutrition, sarcopenia, VOSviewer, co-words, bibliometric analysis

Introduction

People worldwide are living longer. According to World Health Organization (WHO), people aged 65 and over would nearly account for 17% of the population by 2050 (1). Aging is always along with a series of physiological and psychological changes, among them, the most conserved hallmarks are the decline of functional capabilities, which strew great challenges to health. Sarcopenia is an age-related disease that is defined as a decrease in muscle quantity and quality, as well as physical performance (2). Sarcopenia and frailty are closely related and there is a diagnostic overlap between sarcopenia and frailty (3, 4), especially in the concept of nutritional frailty (5). It is estimated that the global prevalence of sarcopenia is ranged from 3.3 to 17.5% depending on various diagnostic criteria and assessment tools (6, 7). Compared with the individuals without sarcopenia, those having low grip strength, lean mass, strength, power, or physical function have more grave physiological and clinical consequences (8) and have high risks of mobility, fall, and disability (9). Although some research suggests that hormonal changes (10), oxidative stress (11, 12), and mitochondrial dysfunction (13) may play a great role in the development of sarcopenia, the pathophysiology of the disease is complex and not yet fully elucidated (4). Accordingly, understanding more about sarcopenia's risk factors and its coping strategies is of great interest.

Non-pharmacological management like nutrient supplements has shown positive impacts on muscle mass and strength, which has burgeoned clinical and research interest internationally. Notably, due to the decline of physical exercise and a lower need for energy intake, as well as the difficulty in the assessment of nutritional status in frailty phenotype (3), community-dwelling older adults have a high risk of being at nutritional or becoming malnourished (14), and a large body of evidence has linked malnutrition with the negative health effects of the old on muscles (15, 16). Based on the International Clinical Practice Guidelines for Sarcopenia (ICFSR) (17), preserving or restoring adequate nutritional status is of great significance for the prevention and optimal management of sarcopenia. Studies have proved that prevent of general malnutrition or micronutrient deficiencies has some potential to promote the physical performance (18–20). Moreover, serval randomized controlled trials conducted in older adults with sarcopenia showed that nutrition intervention was not only feasible (21) but also safe (22). Given that nutrition may influence the development of sarcopenia, this topic deserves further discussion. However, despite the approximately 30-year history of sarcopenia research, a detailed quantitative analysis of the existing research has not been undertaken to elucidate the body of evidence on the nutrition research in the sarcopenia field. Thus, we aimed to analyze the current knowledge domain and emerging trends of the evidence that associates nutrition with muscle quality and quantity, and physical performance. Our study helps to bridge this gap and provide implications for future research and strategies to prevent or manage sarcopenia for clinical health providers, and attribute to gain a one-stop overview for the readers in the sarcopenia literature.

Materials and methods

Study design

As an important carrier of scientific research, academic publications could clearly reflect the basic knowledge domain and emerging trends of a certain discipline (23). Bibliometric analysis (BA) is a quantitative and comprehensive method associated with academic publications (24). This method could reveal the current knowledge domain through performance analysis with publication-related and citation-related metrics (25). In addition, mathematics, statistics, and philology methods are used to identify emerging trends through science mapping with citation, co-citation, or co-word analysis (26). To date, BA has been widely used to analyze the progress of research fields and to predict the development of disciplines due to its objectivity, quantitative, and macro characteristics compared to systematic or meta-analysis (27). Thus, BA and its guideline (28) were applied in this study, as shown in **Figure 1**. This study was not reviewed by the ethics committee for neither patients nor members of the public were involved.

Data source

Different databases (e.g., Scopus and Web of Science) have their own format of bibliometric data. BA guideline suggested that choose one appropriate database to mitigate the need of consolidation, as minimizing unnecessary action items can help to prevent potential human errors (28). The Web of Science Core Collection (WoSCC) of Clarivate Analytics including Science Citation Index Expanded, Social Sciences Index, and Arts & Humanities Citation Index, is regarded as one of the most complete and reliable databases for BA (29), which can retrieve the references of publications and track the latest citation (30). Therefore, all data used in this study were retrieved from the WoSCC.

Search strategy

On April 1, 2022, the WOSCC was searched using topic words and keywords plus. The search terms were "nutrition intake," "dietary supplements," "sarcopenia," "muscle strength," "muscle function," and "muscle mass." The strategy of Behnaz et al. (31) and Dongliang et al. (32) were mainly referenced during the process of string construction. After

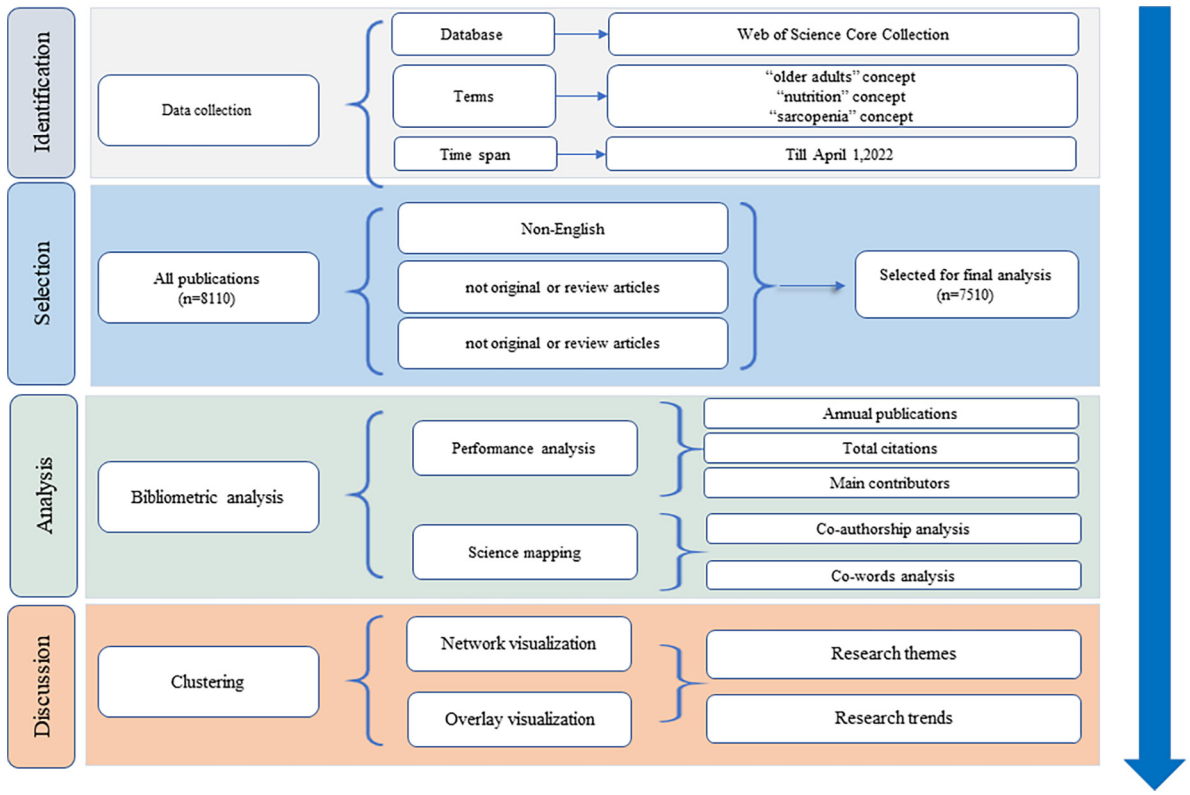


FIGURE 1
Flow chart of the research framework.

selecting all the relevant search terms and their combinations, Boolean operators and a general review were performed. English language, incorporated animal and human studies were acceptable, and no restrictions on the dates of publications.

Data collection

Two authors manually and independently evaluated the title and abstract of the selected publications. Publications without abstracts were full-text reviewed. The third author verified the consistency of the results. Finally, a total of 8,110 publications were identified from WoSCC and only 7,510 were selected for final analysis, 180 non-English documents, 110 were not original or review articles were excluded after general reviewing, and 310 were excluded for not associated with the topic of nutrition or sarcopenia after evaluated the title and abstract. **Figure 2** showed the flow chart of the data collection procedure.

Bibliometric analysis

Full records and cited references of the publications were downloaded in txt format, and then input to the VOSviewer version 1.6.15 (Leiden University, The Netherlands) and R package "bibliometrix" version 4.1.2, thesaurus file was used for data cleaning. The steps of analysis were as follows: (A) performance analysis was conducted to explore the current knowledge domain, which includes the annual publications, total citations, and main contributors, such as topics, journals, and core authors. Core authors was defined by Price's Law (33), that is, $m_p = 0.749\sqrt{n_{pmax}}$ in which $n_{p\,\max}$ is the output of the most prolific authors, m_p is the minimum number of output of core authors in the selected period. (B) Science mapping was conducted to analysis the emerging trends on science collaboration and research hotpots, which including co-authorship and co-words. (C) The thematic clustering was used to identify the research themes and evolution features according to Zipf's Law (34) by network and overlay visualizations.

Results

Annual publications and total citations

A total of 7,510 publications were selected for final analysis. As shown in **Figure 3**, though the publications have dropped slightly in some years, annual publications related to nutrition

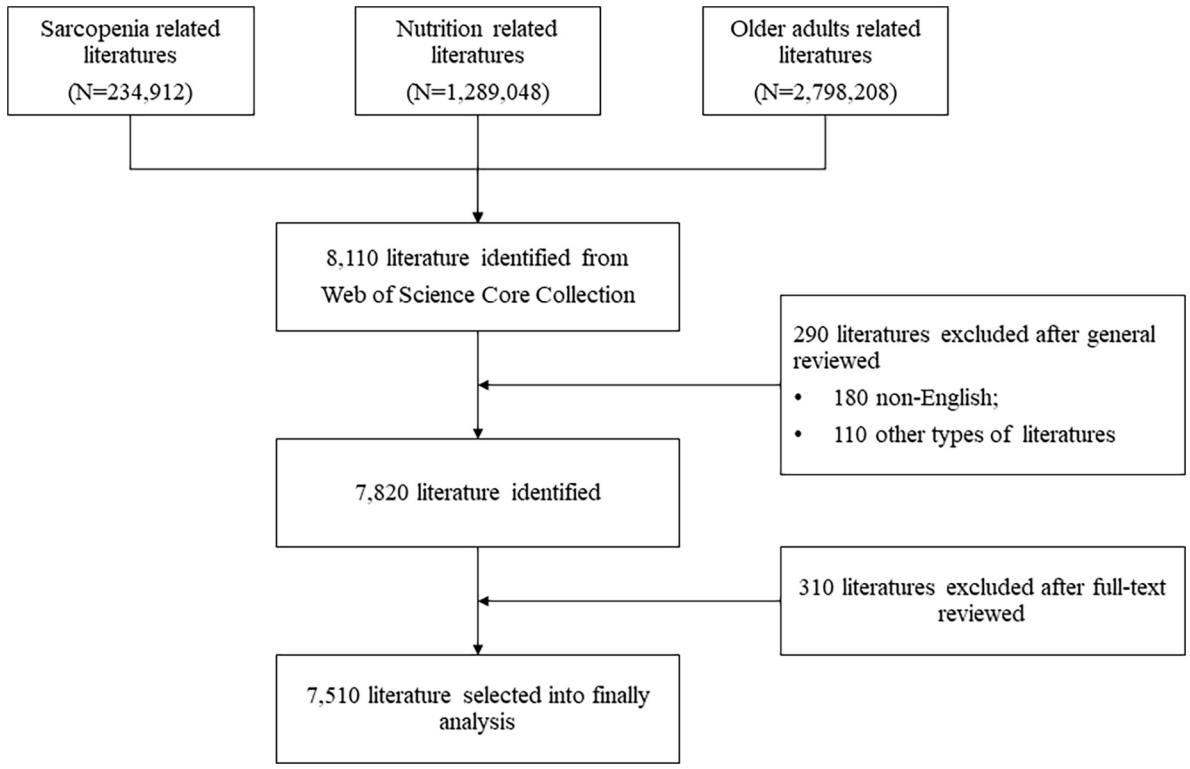


FIGURE 2
Flow chart of the data collection procedure.

in the sarcopenia field quickly increase from 58 in 1999 to 995 in 2021, showing a clear trend for growth. The correlation between the number of publications and the year was significant (R^2 = 0.9912). The total citations also showed a similar upward trend, with a correlation coefficient of 0.9703, the number jumped from 30 in 1999 to 44,585 in 2021. Convincingly, the publication and citation in the filed of nutrition- and sarcopenia-related research would reach a new milestone at 2022.

Main contributors

Topics and journals

Figure 4A showed the top 10 category in the nutrition- and sarcopenia-related research, among which the main topics were nutrition dietetics, followed by geriatrics gerontology, endocrinology metabolism, and sport science, covering a wide range of academic disciplines, indicating this filed was a multi-disciplinary work.

Journals are an important carrier of scientific research. Analyzing the source journals helps understand the research field it belongs to, and for other scholars to evaluate the development potential of this hotspot. Figure 4B showed the top 100 productive journals, in which color bubbles represent the number of publications in each journal, and lines indicate cooperation between two journals. Among which, *Nutrients* (406, 5.41%) from MDPI press ranked first in production, followed by *Clinical Nutrition* (319,4.25%), and *PLoS One* (174, 2.32%). Table 1 lists the ten journals with the largest number of nutrition-related research in sarcopenia field and their academic influence index. Almost all belonged to Q1 in JCR, and with an average influence factor of 5.92. Besides, *the Journal of Cachexia Sarcopenia and Muscle* have highest impact factor with 12.91.

Countries, institutions, and authors

After reviewing the contributors, a total of 107 countries, 6,668 institutions, and 31,289 authors were identified in the nutrition- and sarcopenia-related research field. Among those, the most productive country was the USA (2,284, 30.41%), followed by the United Kingdom (UK), Japan, Italy, and Canada, counting for 10.48, 8.08, 7.79, and 7.18% of the total publications, respectively. And Maastricht University (n = 138) and McMaster University (n = 104) were the leading institutions in terms of productivity.

Besides, Professor van Loon L.J.C. from Maastricht University Medical Centre was found to be the most productive with 96 publications. And according to Price's Law, core authors should publish at least 7.34 publications, that is, those who publish 8 articles or more could be identified as core authors.

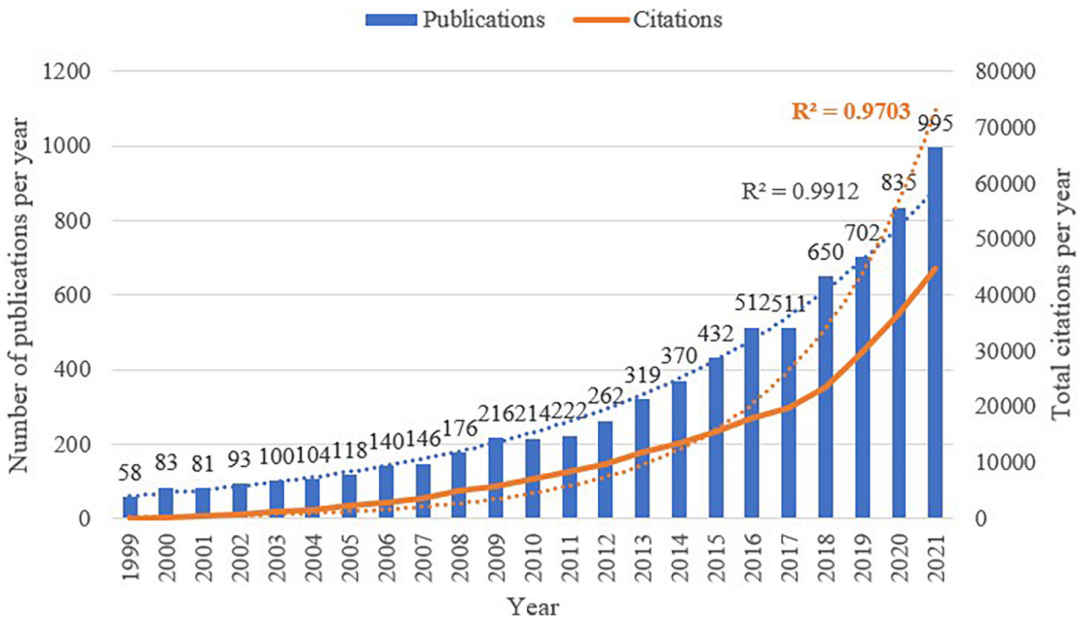


FIGURE 3
Annual publications and total citations number from 1999 to 2021.

In other words, there were 437 core authors in the field of nutrition-related research in sarcopenia. Figure 5 showed the top 20 most prolific authors and their academic impact, in which Professor van Loon L.J.C with the highest H index of 43 and most local citations as well.

Co-authorship analysis

Scientific cooperation occurs when scholars in relevant research fields work together to innovate scientific knowledge (35). Figure 6 showed the collaboration among countries among (A) productive countries, (B) countries, (C) authors, and (D) institutions on nutrition-related research in sarcopenia, in which each circle and label forms an element, the size of the element depends on the number of publications of the contributor, the strength of the element depends on the frequency of collaboration between two contributors, the color of the element represents the cluster of the research topic to which it belongs. In general, Figure 6 implied that compared with a country's collaboration, institutions and authors' collaboration provides a measure to examine interactions between agencies at a more granular level (36, 37).

Co-words analysis

One of the main functions of keywords is to provide core information about the article. At the same time, keywords are important for bibliometric analyses of the knowledge structure in an academic field, for similar articles are prone to adapt to neighbor keywords (38). Thus, research mapping was explored by investigating the co-occurrence of all keywords in the titles and abstracts of 7,510 documents, and clustering was applied to identify the emerging trend.

Figure 7 was a bubble chart of the co-words network of top 500 keywords. Figure 7A showed the network visualization, in which keywords were divided into four categories (red, blue, yellow, and green), indicating the four mainstream research topics in this filed: the first one in green centered on health and sarcopenia, associated with malnutrition, risk, and mortality; the second in red on metabolism and nutrition, associated with oxidative stress, insulin resistance, and obesity; the third in blue on nutrition and exercise, mainly associated with resistance exercise; and lastly in yellow, on body compositions and physical performance, associated with skeletal strength, vitamin D, calcium, magnesium (39, 40). Figure 7B showed the overlay visualization and colors represented the time of evolution, in which clusters of green and yellow were the hotpot and future research trends in the nutrition- and sarcopenia-related field.

Discussion

Bibliometric analysis method offers a one-stop overview to identify evolutionary nuances in different fields and capture emerging trends (41). In this study, we used BA quantitative method to analyze the development of nutrition-

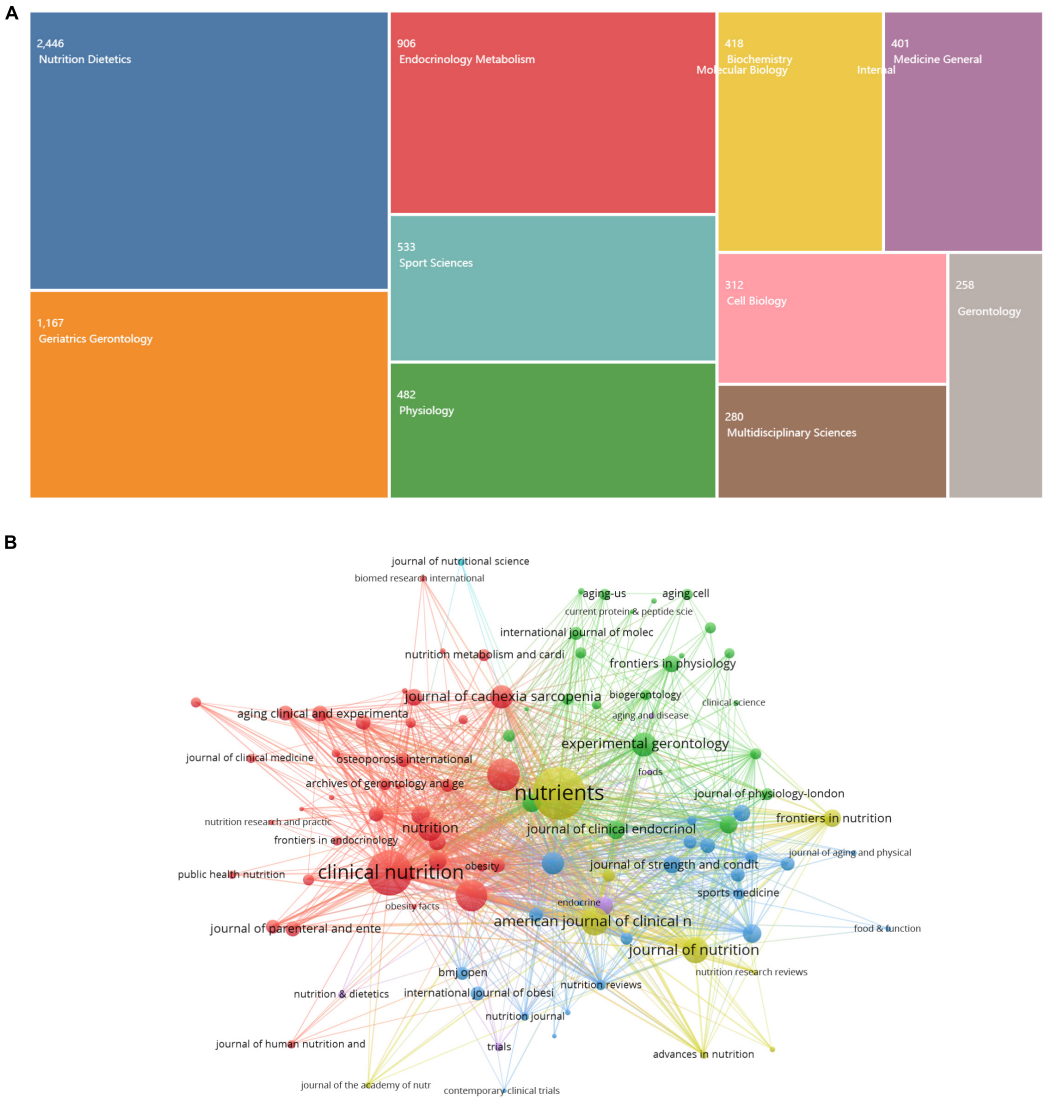


FIGURE 4
The main categories and journals in the nutrition-related sarcopenia research. **(A)** The top 10 journal citation reports (JCR) category of topic themes. **(B)** The top 100 most productive journals.

TABLE 1 Top 10 productive journals in the nutrition-related sarcopenia research.

Rank	Source	Documents	Counts	Citations	IF (2021)	JCR	Region
1	Nutrients	406	5.41%	5,869	5.719	Q1	Switzerland
2	Clinical nutrition	319	4.25%	14,651	7.325	Q1	Scotland
3	PLoS One	174	2.32%	4,260	3.24	Q2	USA
4	Journal of nutrition health and aging	171	2.28%	4,870	4.075	Q2	France
5	American journal of clinical nutrition	134	1.78%	12,980	7.047	Q1	USA
6	Journal of nutrition	117	1.56%	5,250	4.798	Q1	USA
7	Nutrition	104	1.38%	2,588	4.008	Q2	USA
8	Experimental gerontology	102	1.36%	2,630	4.032	Q2	England
9	Journal of cachexia sarcopenia and muscle	98	1.30%	2,683	12.91	Q1	Germany
10	Journals of gerontology series A-biological sciences and medical Science	92	1.23%	5,579	6.053	Q1	USA

IF, impact factor; JCR, journal citation reports; the US, The United States.

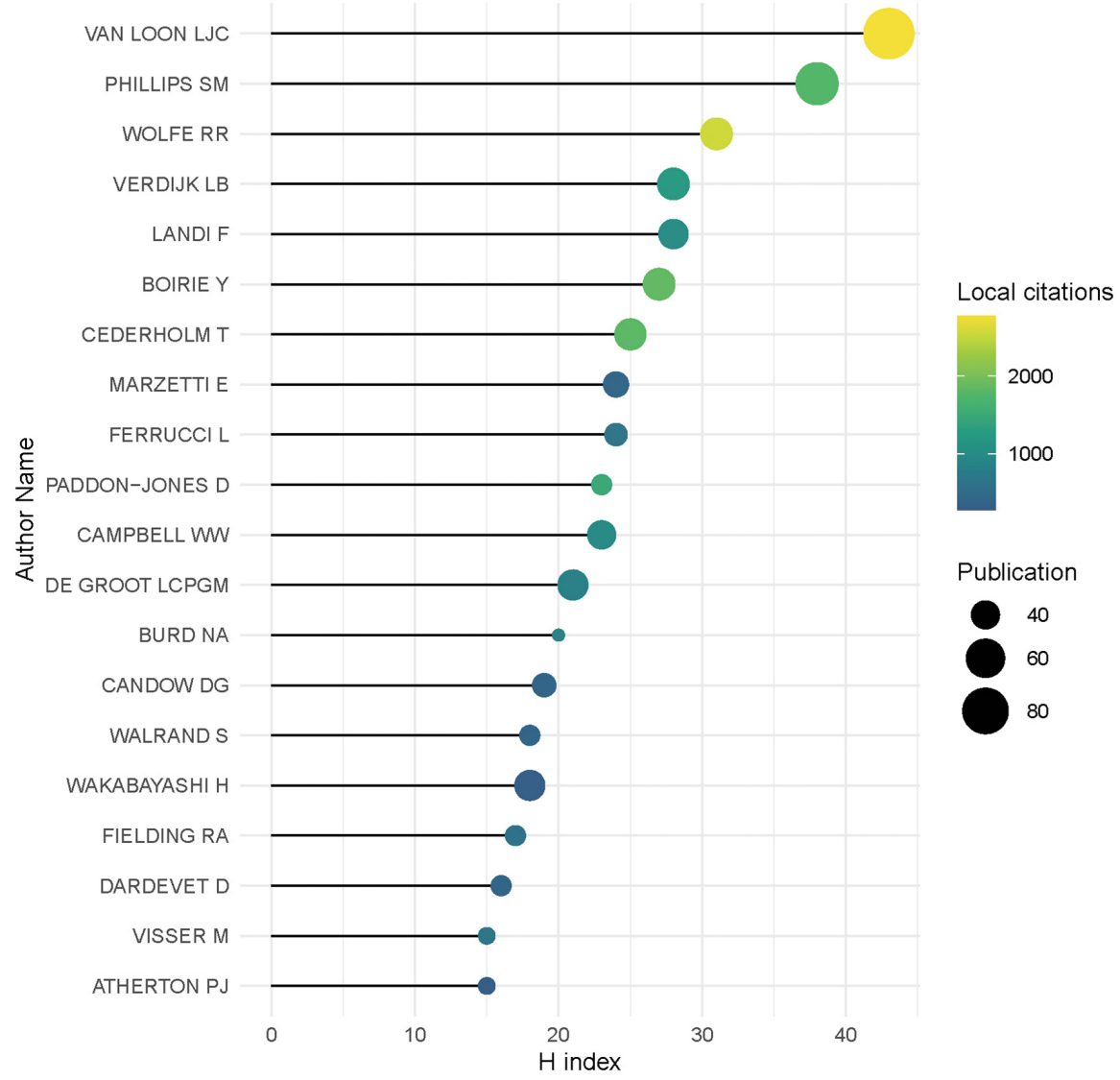


FIGURE 5
The top 20 most prolific authors and their academic impact.

and sarcopenia-related research at a global level, which would help sarcopenia and nutrition researchers gain a more comprehensive understanding of the current state of this topic and thus guide the direction of future research. Compared with other BA studies that only focus on single journals (42, 43) or are restricted to a specific time (32, 44), and unlike Meta-analysis or systematic literature review (45, 46) that aim to summarize and synthesize the findings of small literature on a specific research topic or field, our study provides scholars with a comprehensive basic knowledge structure and research trend.

We found that the nutrition- and sarcopenia-related field has shown a growing trend over the past 30 years. A similar trend was also observed in a few BA studies on sarcopenia along, which found the publication number rise dramatically between 2008 and 2010 (44, 47). One of the reasons is the incrassating recognition of the definition and diagnosis of sarcopenia. Actually, sarcopenia has a relatively short history, it was not until 1989 that Irwin Rosenberg proposed the term "sarcopenia" (48). The European Working Group on Sarcopenia in Older People (EWGSOP) was established in 2009 and developed the first practical clinical definition and consensus diagnostic criteria for this disease in 2010 (49) and, therefore, increased research interests in this field.

Our BA results also demonstrated that nutrition-related sarcopenia studies have become a research hotspot in not only nutrition dietetics and geriatrics gerontology but also multiple disciplines, like endocrinology metabolism and sports science. In fact, up to 108 Web of Science categories were

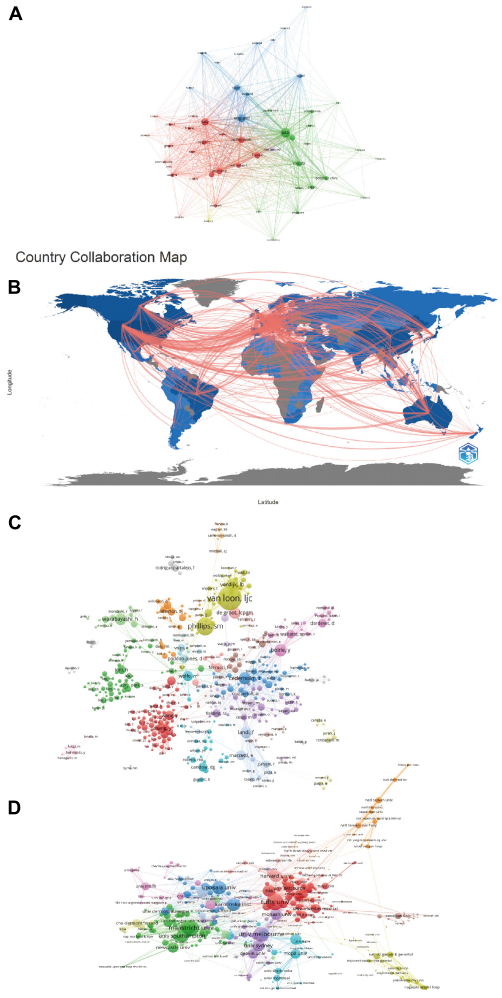


FIGURE 6
Co-authorship map among **(A)** productive countries, **(B)** countries, **(C)** authors, and **(D)** institutions on nutrition-related research in sarcopenia.

identified in this field. The potential explanation is that skeletal muscle is not only affecting the energy and protein metabolism throughout the body, but also plays an essential role in body movement and daily actions such as chewing, swallowing, and breathing (50). Overall, we emphasize the important role of close multidisciplinary collaboration in the prevention and treatment of sarcopenia. In addition, studies in this field are published in a wide range of journals covering many specialties, among which a large number of publications from *Nutrients* were impressive. Notably, *Nutrients* also own high citations in this field, which means the findings reported have been useful to other researchers for initiating, performing, or interpreting their own research.

We focused on the main contributors with productive performance in this field, the USA stands out from all countries as hegemony in the production of knowledge, followed by the UK, Japan, Italy, and Canada, and this may be due to those mentioned countries stepped into aging at the earliest. We also identified the most productive academic institutions in the relevant studies, and the result is similar to the finding on the contribution of countries. Interestingly, we recognized the core authors in the nutrition-related sarcopenia studies for the first time according to Price's Law, such as Loon L.J.C. We also ranked who with a comprehensive index, like total publications, local citations, and H index, which would provide more insights on the most influential author. It is important to note, however, that we only included the studies published in English, thus some individuals' productivity may be underestimated.

Moreover, from the perspective of macro-geographical distribution, the results of co-authorship analysis suggest that several relatively stable cooperation networks have been formed in the field of nutrition -related research in sarcopenia, but they are mostly divided by region and research topics. Therefore, cross-institutional and cross-border collaboration between main contributors needs to be further strengthened.

From a methodological standpoint, our study allows us to identify themes using co-word analysis. Compared with other publications, the results refreshed the ideas of some highly cited articles relating nutrition to sarcopenia (51–53). On the other hand, our study provided a larger database size for analysis, moreover, we not only analyzed the relationship between selected publications and clustered those with a quantitative method (54, 55), but also revealed the intellectual bases and research hotspots in this field.

Focusing on the current knowledge domain and emerging trends, nutrition-related sarcopenia studies would continue to conduct more in-depth large sample study and mechanism research in hotspots and fronts field. First, in terms of health and sarcopenia, it is expected more raw, longitudinal data and publicly available secondary data will be applied to explore the negative results and risk factors of malnutrition among the sarcopenia population. Second, is the discussion of the potential metabolism pathway of nutrition. As the major organ of insulin-induced glucose metabolism in the body, the loss of quantity and quality of skeletal muscle is associated with a complex of pathologies (56). Thus, those findings could provide an insight into the molecular pathogenesis of sarcopenia and a potential target for new nutrition interventions. Third, the combined intervention and mutual effect among nutrition and exercise, in which randomized controlled trial designs were overwhelming and promising. Last, is the research on body compositions and physical performance. It is relatively broad and has an obvious overlap with the other three clusters. However, the overlay visualization emphasizes its frontier, indicating that this theme is playing a vital role in the field, and the supplements and consumption of Vitamin D, and

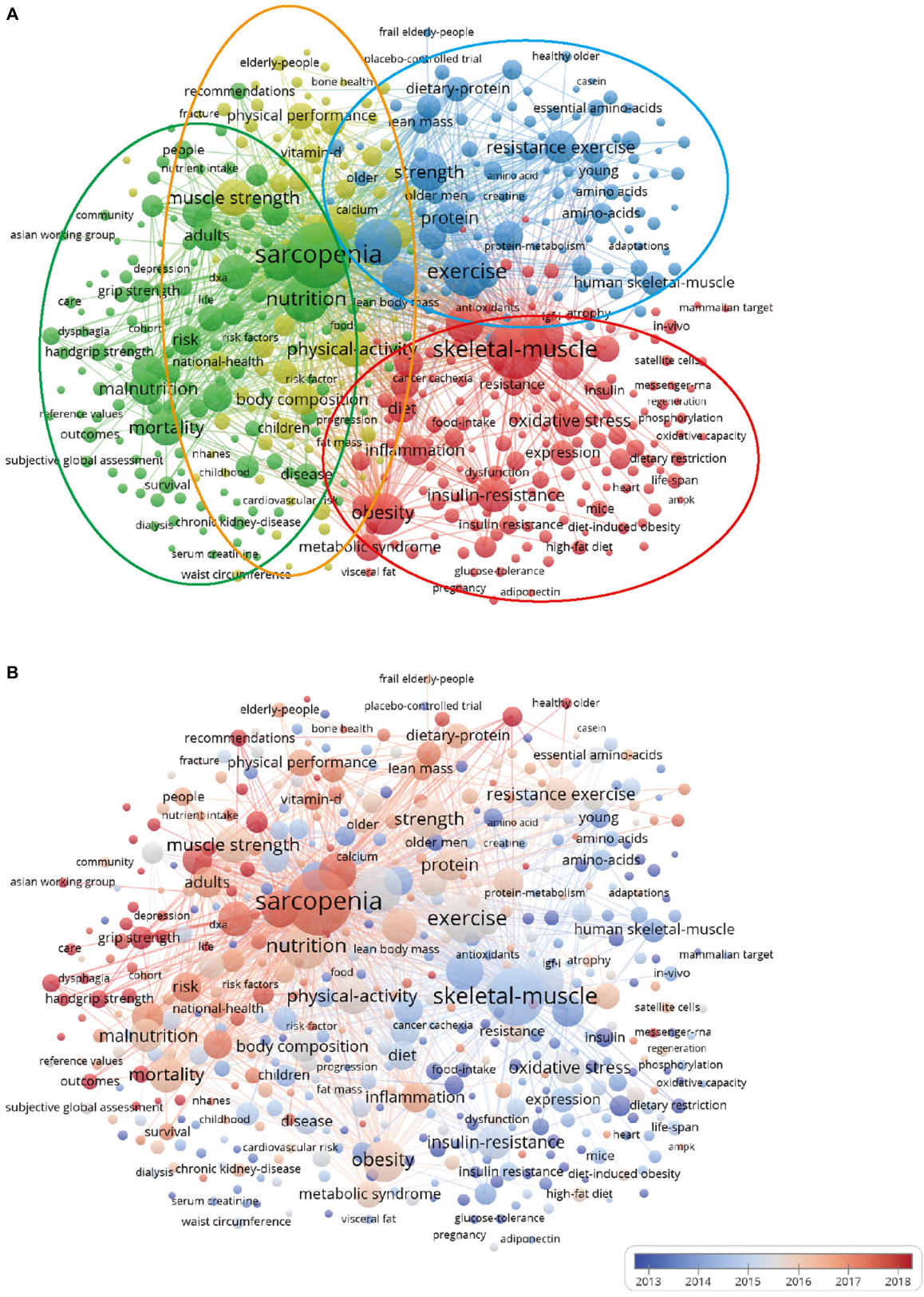


FIGURE 7
The co-words analysis of the top 500 keywords. **(A)** Network visualization; **(B)** overlay visualization.

minerals (57) (magnesium, selenium, iron, zinc et al.) are possible directions for breakthroughs in the future.

Limitations

Although efforts have been made to retrieve various publications relevant to nutrition-related sarcopenia studies, as a novel disease, the terms included in this study and the period may not be extensive enough. In addition, this study only searched in one database and restricted the language to English, which may limit the inclusion of relevant studies, especially those published in other languages. Last but not least, the practical implementation of citation analyses and co-words requires appreciable expertise. Thus, in subsequent studies, we will further optimize data sources and data filtering to improve the quality of overall data analysis and prediction, and synthetic knowledge synthesis would be applied to formally define themes, categories, and concepts.

Conclusion

In this study, a comprehensive BA of the nutrition-related sarcopenia study was performed using WoSCC data. Different visualization methods were used to interactively explore and understand specific data sets. Based on the above results and discussions, some valuable results for the nutrition and sarcopenia study were obtained, including the knowledge domain and emerging trends. In conclusion, the role of nutrition in sarcopenia has received growing research attention, with the USA having the largest number of publications. This study has also identified the main contributors involved in this research globally, and at the same time, it is reasonable to believe that the collaboration between different contributors will be strengthened when the core group is formally established among countries, institutions, and core authors. In addition, the themes of nutrition- and sarcopenia-related research currently could be divided into four categories, more in-depth large sample studies and mechanism research in hotspots and fronts field are needed.

Data availability statement

The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

HHH: conceptualization and writing – original draft. ZYC: formal analysis and review and editing. QHZ: funding acquisition. HHH and LJC: methodology. SMC and QHZ: project administration. DQB and QX: supervision. MZX and QHZ: validation. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by the Chongqing Science and Technology Bureau (CSTC2021jscx-gksb-N0021) and Chongqing Education Commission (yjg211006 and KJCX2020018).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. NIH-funded Census Bureau. *World's Older Population Grows Dramatically. National Institutes of Health (NIH).* (2016). Available online at: https://www.nih.gov/news-events/news-releases/worlds-older-population-grows-dramatically (accessed on June 6, 2022).

2. Chen L-K, Woo J, Assantachai P, Auyeung T-W, Chou M-Y, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc.* (2020) 21:300–7.e2. doi: 10.1016/j.jamda.2019.12.012

3. Zupo R, Castellana F, Bortone I, Griseta C, Sardone R, Lampignano L, et al. Nutritional domains in frailty tools: working towards an operational definition of nutritional frailty. *Ageing Res Rev.* (2020) 64:101148. doi: 10.1016/j.arr.2020.101148

4. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet.* (2019) 393:2636–46. doi: 10.1016/S0140-6736(19)31138-9

5. Zupo R, Castellana F, Guerra V, Donghia R, Bortone I, Griseta C, et al. Associations between nutritional frailty and 8-year all-cause mortality in older

adults: the Salus in Apulia study. *J Intern Med.* (2021) 290:1071–82. doi: 10.1111/joim.13384

6. Petermann-Rocha F, Balntzi V, Gray SR, Lara J, Ho FK, Pell JP, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle.* (2022) 13:86–99. doi: 10.1002/jcsm.12783

7. Chen Z, Li W-Y, Ho M, Chau P-H. The prevalence of sarcopenia in Chinese older adults: meta-analysis and meta-regression. *Nutrients.* (2021) 13:1441. doi: 10.3390/nu13051441

8. Suetta C, Haddock B, Alcazar J, Noerst T, Hansen OM, Ludvig H, et al. The Copenhagen sarcopenia study: lean mass, strength, power, and physical function in a Danish cohort aged 20-93 years. *J Cachexia Sarcopenia Muscle.* (2019) 10:1316–29. doi: 10.1002/jcsm.12477

9. Billot M, Calvani R, Urtamo A, Sánchez-Sánchez JL, Ciccolari-Micaldi C, Chang M, et al. Preserving mobility in older adults with physical frailty and sarcopenia: opportunities, challenges, and recommendations for physical activity interventions. *Clin Interv Aging.* (2020) 15:1675–90. doi: 10.2147/CIA.S253535

10. Gungor O, Ulu S, Hasbal NB, Anker SD, Kalantar-Zadeh K. Effects of hormonal changes on sarcopenia in chronic kidney disease: where are we now and what can we do? *J Cachexia Sarcopenia Muscle.* (2021) 12:1380–92. doi: 10.1002/jcsm.12839

11. Rosa CGS, Colares JR, da Fonseca SRB, Martins GDS, Miguel FM, Dias AS, et al. Sarcopenia, oxidative stress and inflammatory process in muscle of cirrhotic rats - Action of melatonin and physical exercise. *Exp Mol Pathol.* (2021) 121:104662. doi: 10.1016/j.yexmp.2021.104662

12. Zocchi M, Béchet D, Mazur A, Maier JA, Castiglioni S. Magnesium influences membrane fusion during myogenesis by modulating oxidative stress in C2C12 myoblasts. *Nutrients.* (2021) 13:1049. doi: 10.3390/nu13041049

13. Ferri E, Marzetti E, Calvani R, Picca A, Cesari M, Arosio B. Role of age-related mitochondrial dysfunction in sarcopenia. *Int J Mol Sci.* (2020) 21:5236. doi: 10.3390/ijms21155236

14. Norman K, Haß U, Pirlich M. Malnutrition in older adults-recent advances and remaining challenges. *Nutrients.* (2021) 13:2764. doi: 10.3390/nu13082764

15. Robinson S, Granic A, Sayer AA. Nutrition and muscle strength, as the key component of sarcopenia: an overview of current evidence. *Nutrients.* (2019) 11:2942. doi: 10.3390/nu11122942

16. Carbone JW, McClung JP, Pasiakos SM. Recent advances in the characterization of skeletal muscle and whole-body protein responses to dietary protein and exercise during negative energy balance. *Adv Nutr.* (2019) 10:70–9. doi: 10.1093/advances/nmy087

17. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. *J Nutr Health Aging.* (2018) 22:1148–61. doi: 10.1007/s12603-018-1139-9

18. Zupo R, Castellana F, De Nucci S, Sila A, Aresta S, Buscemi C, et al. Role of dietary carotenoids in frailty syndrome: a systematic review. *Biomedicines.* (2022) 10:632. doi: 10.3390/biomedicines10030632

19. Damanti S, de Souto Barreto P, Rolland Y, Astrone P, Cesari M. Malnutrition and physical performance in nursing home residents: results from the INCUR study. *Aging Clin Exp Res.* (2021) 33:2299–303. doi: 10.1007/s40520-021-01798-y

20. Ramsey KA, Meskers CGM, Trappenburg MC, Verlaan S, Reijnierse EM, Whittaker AC, et al. Malnutrition is associated with dynamic physical performance. *Aging Clin Exp Res.* (2020) 32:1085–92. doi: 10.1007/s40520-019-01295-3

21. Jyväkorpi SK, Ramel A, Strandberg TE, Piotrowicz K, Błaszczyk-Bębenek E, Urtamo A, et al. The sarcopenia and physical frailty in older people: multi-component treatment strategies (SPRINTT) project: description and feasibility of a nutrition intervention in community-dwelling older Europeans. *Eur Geriatr Med.* (2021) 12:303–12. doi: 10.1007/s41999-020-00438-4

22. Bauer JM, Mikušová L, Verlaan S, Bautmans I, Brandt K, Donini LM, et al. Safety and tolerability of 6-month supplementation with a vitamin D, calcium and leucine-enriched whey protein medical nutrition drink in sarcopenic older adults. *Aging Clin Exp Res.* (2020) 32:1501–14. doi: 10.1007/s40520-020-01519-x

23. Chen C. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inform Sci Technol.* (2006) 57:359–77. doi: 10.1002/asi.20317

24. Pritchard A. Statistical bibliography or bibliometrics? *J Doc.* (1969) 25:348–9.

25. Agarwal A, Durairajanayagam D, Tatagari S, Esteves SC, Harlev A, Henkel R, et al. Bibliometrics: tracking research impact by selecting the appropriate metrics. *Asian J Androl.* (2016) 18:296–309. doi: 10.4103/1008-682X.171582

26. Ding Y, Chowdhury GG, Foo S. Bibliometric cartography of information retrieval research by using co-word analysis. *Inform Process Manage.* (2001) 37:817–42. doi: 10.1016/S0306-4573(00)00051-0

27. Yu D, Xu Z, Pedrycz W, Wang W. Information sciences 1968–2016: a retrospective analysis with text mining and bibliometric. *Inform Sci.* (2017) 418:619–34.

28. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: an overview and guidelines. *J Bus Res.* (2021) 133:285–96. doi: 10.1016/j.jbusres.2021.04.070

29. Romanelli JP, Gonçalves MCP, de Abreu Pestana LF, Soares JAH, Boschi RS, Andrade DF. Four challenges when conducting bibliometric reviews and how to deal with them. *Environ Sci Pollut Res Int.* (2021) 28:60448–58. doi: 10.1007/s11356-021-16420-x

30. Kulkarni AV, Aziz B, Shams I, Busse JW. Comparisons of citations in web of science, scopus, and google scholar for articles published in general medical journals. *JAMA.* (2009) 302:1092–6. doi: 10.1001/jama.2009.1307

31. Abiri B, Vafa M. Nutrition and sarcopenia: a review of the evidence of nutritional influences. *Crit Rev Food Sci Nutr.* (2019) 59:1456–66. doi: 10.1080/10408398.2017.1412940

32. Yuan D, Jin H, Liu Q, Zhang J, Ma B, Xiao W, et al. Publication trends for sarcopenia in the world: a 20-year bibliometric analysis. *Front Med.* (2022) 9:802651. doi: 10.3389/fmed.2022.802651

33. Zhong W. Evaluation about the core authors based on price law and comprehensive index method——take journal of library development as an example. *Sci Technol Manage Res.* (2012) 32:57–60. doi: 10.3969/j.issn.1000-7695.2012.02.015

34. Contreras-Barraza N, Madrid-Casaca H, Salazar-Sepúlveda G, Garcia-Gordillo MÁ, Adsuar JC, Vega-Muñoz A. Bibliometric analysis of studies on coffee/caffeine and sport. *Nutrients.* (2021) 13:3234. doi: 10.3390/nu13093234

35. Katz JS, Martin BR. What is research collaboration? *Res Policy.* (1997) 26:1–18.

36. Yan E, Sugimoto CR. Institutional interactions: exploring social, cognitive, and geographic relationships between institutions as demonstrated through citation networks. *J Am Soc Inform Sci Technol.* (2011) 62:1498–514. doi: 10.1002/asi.21556

37. Harande YI. Author productivity and collaboration: an investigation of the relationship using the literature of technology. *Libri.* (2001) 51:124–7. doi: 10.1515/LIBR.2001.124

38. Romero L, Portillo-Salido E. Trends in sigma-1 receptor research: a 25-year bibliometric analysis. *Front Pharmacol.* (2019) 10:564. doi: 10.3389/fphar.2019.00564

39. Ratajczak AE, Rychter AM, Zawada A, Dobrowolska A, Krela-Kaźmierczak I. Do only calcium and vitamin D matter? micronutrients in the diet of inflammatory bowel diseases patients and the risk of osteoporosis. *Nutrients.* (2021) 13:525. doi: 10.3390/nu13020525

40. Bayle D, Coudy-Gandilhon C, Gueugneau M, Castiglioni S, Zocchi M, Maj-Zurawska M, et al. Magnesium deficiency alters expression of genes critical for muscle magnesium homeostasis and physiology in mice. *Nutrients.* (2021) 13:2169. doi: 10.3390/nu13072169

41. Mukherjee D, Lim WM, Kumar S, Donthu N. Guidelines for advancing theory and practice through bibliometric research. *J Bus Res.* (2022) 148:101–15. doi: 10.1016/j.jbusres.2022.04.042

42. Anker MS, Anker SD, Coats AJS, von Haehling S. The journal of cachexia, sarcopenia and muscle stays the front-runner in geriatrics and gerontology. *J Cachexia Sarcopenia Muscle.* (2019) 10:1151–64. doi: 10.1002/jcsm.12518

43. von Haehling S, Ebner N, Anker SD. Oodles of opportunities: the journal of cachexia, sarcopenia and muscle in 2017. *J Cachexia Sarcopenia Muscle.* (2017) 8:675–80. doi: 10.1002/jcsm.12247

44. Yang M, Tan L, Li W. Landscape of sarcopenia research (1989–2018): a bibliometric analysis. *J Am Med Dir Assoc.* (2020) 21:436–7. doi: 10.1016/j.jamda.2019.11.029

45. Hsu K-J, Liao C-D, Tsai M-W, Chen C-N. Effects of exercise and nutritional intervention on body composition, metabolic health, and physical performance in adults with sarcopenic obesity: a meta-analysis. *Nutrients.* (2019) 11:2163. doi: 10.3390/nu11092163

46. Hanach NI, McCullough F, Avery A. The impact of dairy protein intake on muscle mass, muscle strength, and physical performance in middle-aged to older adults with or without existing sarcopenia: a systematic review and meta-analysis. *Adv Nutr.* (2019) 10:59–69. doi: 10.1093/advances/nmy065

47. Suzan V, Suzan AA. A bibliometric analysis of sarcopenia: top 100 articles. *Eur Geriatr Med.* (2021) 12:185–91. doi: 10.1007/s41999-020-00395-y

48. Rosenberg IH, Roubenoff R. Stalking sarcopenia. *Ann Intern Med.* (1995) 123:727–8. doi: 10.7326/0003-4819-123-9-199511010-00014

49. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. *Age Ageing.* (2010) 39:412–23. doi: 10.1093/ageing/afq034

50. Argilés JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Mañas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. *J Am Med Direct Assoc.* (2016) 17:789–96. doi: 10.1016/j.jamda.2016.04.019

51. Ganapathy A, Nieves JW. Nutrition and sarcopenia-what do we know? *Nutrients.* (2020) 12:1755. doi: 10.3390/nu12061755

52. Bloom I, Shand C, Cooper C, Robinson S, Baird J. Diet quality and sarcopenia in older adults: a systematic review. *Nutrients.* (2018) 10:308. doi: 10.3390/nu10030308

53. Robinson SM, Reginster JY, Rizzoli R, Shaw SC, Kanis JA, Bautmans I, et al. Does nutrition play a role in the prevention and management of sarcopenia? *Clin Nutr.* (2018) 37:1121–32. doi: 10.1016/j.clnu.2017.08.016

54. Liu, Y, Li X, Ma L, Wang Y. Mapping theme trends and knowledge structures of dignity in nursing: a quantitative and co-word biclustering analysis. *J Adv Nurs.* (2022) 78:1980–89. doi: 10.1111/jan.15097

55. Pourhatami A, Kaviyani-Charati M, Kargar B, Baziyad H, Kargar M, Olmeda-Gómez C. Mapping the intellectual structure of the coronavirus field (2000-2020): a co-word analysis. *Scientometrics.* (2021) 126:6625–57. doi: 10.1007/s11192-021-04038-2

56. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. *Nutrients.* (2021) 13:3519. doi: 10.3390/nu13103519

57. van Dronkelaar C, van Velzen A, Abdelrazek M, van der Steen A, Weijs PJM, Tieland M. Minerals and sarcopenia; the role of calcium, iron, magnesium, phosphorus, potassium, selenium, sodium, and zinc on muscle mass, muscle strength, and physical performance in older adults: a systematic review. *J Am Med Dir Assoc.* (2018) 19:6–11.e3. doi: 10.1016/j.jamda.2017.05.026

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 01 February 2023
DOI 10.3389/fmed.2023.1071514

OPEN ACCESS

EDITED BY
Silvia Bisti,
University of L'Aquila, Italy

REVIEWED BY
Mahnaz Talebi,
Tabriz University of Medical Sciences, Iran
Karolina Skonieczna-Żydecka,
Pomeranian Medical University, Poland

*CORRESPONDENCE
Mohammad Reza Aslani
✉ mraslani105@yahoo.com;
✉ mr.aslani@arums.ac.ir

SPECIALTY SECTION
This article was submitted to Geriatric Medicine, a section of the journal Frontiers in Medicine

RECEIVED 16 October 2022
ACCEPTED 17 January 2023
PUBLISHED 01 February 2023

CITATION
Abedi A, Ghobadi H, Sharghi A, Iranpour S, Fazlzadeh M and Aslani MR (2023) Effect of saffron supplementation on oxidative stress markers (MDA, TAC, TOS, GPx, SOD, and pro-oxidant/antioxidant balance): An updated systematic review and meta-analysis of randomized placebo-controlled trials. *Front. Med.* 10:1071514. doi: 10.3389/fmed.2023.1071514

Effect of saffron supplementation on oxidative stress markers (MDA, TAC, TOS, GPx, SOD, and pro-oxidant/antioxidant balance): An updated systematic review and meta-analysis of randomized placebo-controlled trials

Ali Abedi [1], Hassan Ghobadi [2,3], Afshan Sharghi [4], Sohrab Iranpour [4], Mehdi Fazlzadeh [5] and Mohammad Reza Aslani [2,6]*

[1]Department of Physiology, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [2]Lung Diseases Research Center, Ardabil University of Medical Sciences, Ardabil, Iran, [3]Department of Internal Medicine, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [4]Department of Community Medicine, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [5]Social Determinants of Health Research Center, Ardabil University of Medical Sciences, Ardabil, Iran, [6]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction: This study aimed to perform an updated systematic review and meta-analysis to evaluate the effectiveness of saffron supplementation on oxidative stress markers [malondialdehyde (MDA), total antioxidant capacity (TAC), total oxidant status (TOS), glutathione peroxidase (GPx), superoxide dismutase (SOD), and prooxidant/antioxidant balance (PAB)] in randomized controlled trials (RCTs).

Methods: We searched PubMed/Medline, Web of Science, Scopus, Cochrane CENTRAL, and Google Scholar until December 2022. Trial studies investigating the effects of oral saffron supplements on MDA, TAC, TOS, GPx, SOD, and PAB concentrations were included in the study. To analyze the results, mean differences (SMD) and 95% confidence intervals (CI) were pooled using a random effects model. Heterogeneity was assessed using the Cochrane Q and I^2 values. Sixteen cases were included in the meta-analysis (468 and 466 subjects in the saffron and control groups, respectively).

Results: It was found that saffron consumption caused a significant decrease in MDA (SMD: −0.322; 95% CI: −0.53, −0.16; I^2 = 32.58%) and TOS (SMD: −0.654; 95% CI: −1.08, −0.23; I^2 = 68%) levels as well as a significant increase in TAC (SMD: 0.302; 95% CI: 0.13, 0.47; I^2 = 10.12%) and GPx (SMD: 0.447; 95% CI: 0.10, 0.80; I^2 = 35%). Subgroup analysis demonstrated a significant reduction in MDA levels in studies with a saffron dosage of >30 mg/day, age of <50 years, and study duration of <12 weeks. Among the limitations of the study, we can point out that the studies were from

Iran, the different nature of the diseases included, and were not considered of some potential confounders such as smoking, physical activity, and diet in the studies.

Discussion: In summary, the results showed that saffron has beneficial effects on oxidative stress markers.

KEYWORDS

Crocus sativus, oxidative stress, meta-analysis, saffron, malondialdehyde, total antioxidant capacity

Introduction

Oxidative stress is caused by an imbalance between the production of free radicals and peroxidants as well as the antioxidant defense system (1). Under mild oxidative stress, tissues counteract the effects of oxidative stress by antioxidant defense, while under severe oxidative stress conditions, biological damage and even cell death may occur (2). The sources of reactive oxygen species (ROS) are both environmental and cellular. Environmental ROS sources include industrial pollution, smoking, exhaust fumes, and occupational exposure to dust, and cellular sources of ROS include activation of xanthine oxidase (XO), nicotine adenine disphosphonucleotide (NADPH) oxidase, superoxide dismutase-1 (SOD-1), and nitric oxide synthase (NOS) (3). On the other hand, important antioxidant factors include glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (3). Increased ROS production inhibits various intracellular antioxidant mechanisms. It leads to oxidative damage to nucleic acids, DNA, proteins, and membrane lipids and disrupts cellular processes, including cellular metabolism, gene expression, and cell proliferation (4).

Oxidative stress is involved in a wide range of pathological conditions. In general, it is divided into two categories based on the role of oxidative stress in the etiology of diseases. Oxidative stress is the main pathological factor in various diseases (including atherosclerosis, radiation toxicity, and paraquat toxicity). Oxidative stress is a secondary factor in disease progression [idiopathic pulmonary fibrosis, asthma, type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), hypertension, neurodegenerative disorders, cancer, ischemia-reperfusion injury, systemic inflammatory response syndrome, and aging] (4–8).

Many recent studies have shown the effectiveness of medicinal plants for inflammatory and oxidative stress markers (9–12). Saffron (*Crocus sativus* L.) is a Mediterranean plant with nutritional and therapeutic uses. Animal and human studies have reported the beneficial therapeutic effects of saffron and its biologically active compounds (crocin, crocetin, picrocrocin, and safranal) in a variety of disorders, such as COPD, asthma, polycystic ovary syndrome (PCOS), diabetes, cardiovascular disease, metabolic syndrome, obesity, and cancer (13–19). One of the important properties of saffron is its antioxidant and anti-inflammatory effects. Recently, trial studies have examined the effects of saffron and crocin on inflammatory and oxidative stress markers in some diseases with contradictory results (17, 20). In a systematic review and meta-analysis, Morvaridzadeh et al. (21) showed the beneficial effects of saffron on oxidative stress markers [malondialdehyde (MDA) and total antioxidant capacity (TAC)]. The present study aimed to conduct an updated systematic review and meta-analysis of randomized controlled trials (RCTs) that examined the effects of saffron on oxidative stress factors, including MDA, TAC, total oxidant status (TOS), GPx, SOD, and the pro-oxidant/antioxidant balance (PAB) in various diseases.

Materials and methods

The present systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategies (22).

Search strategy

Electronic databases PubMed/Medline, Web of Science, Scopus, Cochrane CENTRAL, and Google Scholar from inception until December 2022 were searched to find studies evaluating the effects of saffron on serum oxidant/antioxidant levels. The mesh and non-mesh terms used in the search are presented in the Supplementary Appendix. No time restrictions were applied to the search strategy. Considering that most of the trial studies on saffron have been conducted in Iran, the original research published in languages other than English and Persian were excluded from the study. Additionally, we conducted a manual search of all relevant article reference lists to identify potentially relevant trials.

Selection criteria

The criteria of population, intervention, comparison, and outcome (PICOS) used for the present updated meta-analysis are presented in **Table 1**. In addition, time restrictions were not included in the study. Considering that most of the trial studies on saffron have been conducted in Iran, the original research published in languages other than English and Persian were excluded from the study.

Synthesis methods

Since crocin is one of the active ingredients of saffron, and recent clinical trial studies have focused on its effects, the present study decided that it should include both crocin and saffron trials. However, subgroup analysis of crocin and saffron was performed to evaluate the effects of each on oxidant/antioxidant markers alone. In addition to

10.3389/fmed.2023.1071514

TABLE 1 The population, intervention, comparison, outcome, study design (PICOS) criteria.

Criteria	Selection criteria
Population	Adults (aged ≥18 years)
Intervention	Saffron/Crocin supplement
Comparison	Placebo or no intervention
Outcome	Clinical changes in serum concentrations of oxidative stress biomarkers including TAC, TOS, CAT, MDA, NO, GSH, PAB, SOD, GPx, and isoprostanes
Study design	Randomized controlled trials

CAT, catalase activity; GPx, glutathione peroxidase activity; GSH, glutathione; MDA, malondialdehyde; NO, nitric oxide; PAB, pro-oxidant/antioxidant balance; SOD, superoxide dismutase; TAC, total antioxidant capacity; TOS, total oxidant status.

this analysis, subgroups were also performed for age, study duration, and dosage of supplementation.

Data extraction

The data were extracted by two researchers (AA and SI), and a chief reviewer (MA) made a final decision if there was disagreement between the two researchers. The data collected from each trial were as follows: author details, mean age of participants, sex of participants, dose of saffron, number of participants in each group, study location, length of follow-up, the year the article was published, and primary outcomes. The results are reported as the mean and standard deviation for the serum levels of TAC, TOS, MDA, GPx, SOD, and PAB in the intervention and placebo groups at the beginning and end of the study.

Statistical analysis

Results were extracted as mean ± standard deviation (SD). To calculate the standard mean difference (SMD), converted the reported results as a confidence interval, standard error (SE), minimum and maximum values, and quadratic range (IQR) to SD. Used comprehensive Meta-Analysis software version 2 and the random-effects model to analyze the results and defined statistical significance at $p < 0.05$.

Heterogeneity was evaluated using the Q-test and the I^2 index with a significant heterogeneity level at $p < 0.10$. Subgroup analysis and sensitivity analysis to assess the impact of each study on the pooled effect size were performed. Publication bias was analyzed using the funnel plot examination and Egger's regression test.

Results

Search results

In the initial search, 1753 studies were extracted. We removed 922 duplicate articles and 831 articles remained for further assessment. After screening the titles and abstracts, 795 articles were removed from the study because they did not meet the inclusion criteria, such as animal studies, unrelated, and review articles. The full-text screening revealed that 18 articles could not be included in the study due to the failure to report the variables (23–40). In addition, we removed one article because the level of oxidative markers measured were saliva and urine (41). A study that had a short duration of intervention was also excluded from the study (42). It has been shown that the short duration of the intervention with saffron did not have a significant effect (43). Therefore, 16 trials were selected based on the criteria of this systematic review and meta-analysis (**Figure 1**). Compared to the Morvaridzadeh et al. meta-analysis, six more recent studies have been included in this meta-analysis. In the present study as well as in Marvaridzadeh, three studies were not included in the meta-analysis because they measured markers (ox-LDL, F2-isoprostanes, and DPPH) that were not reported in other studies (20, 44, 45). Finally, the current meta-analysis was performed with 13 studies (**Figure 1**). The selected studies were all published in English.

Characteristics of the included studies

The characteristics of the included trials are listed in **Table 2**. A total of 934 subjects were recruited from the included RCTs (468 and 466 subjects in the saffron and control groups, respectively). All articles were published between 2015 and 2022, and the RCTs were performed in Iran. The duration of the intervention with saffron ranged from 4 to 12 weeks. The mean age range of the participants in the included studies was 29–55 years. Nine studies used saffron supplementation and seven used crocin supplementation for intervention. The dosage used for saffron intervention was between 30 and 1,000 mg/day, and that for crocin was between 15 and 30 mg/day. The selected trials included participants with coronary artery disease (44), type 2 diabetes (45–49), COPD (17), multiple sclerosis (50), ulcerative sclerosis (51), non-alcoholic fatty liver (52), overweight/obese prediabetic patients (20, 53, 54), rheumatoid arthritis (55), Alzheimer's Disease (56), and methadone maintenance treatment patients (57).

Quality assessment

The risk of bias in eligible studies was evaluated using the Cochrane's risk-of-bias tool for randomized trials (58). **Figure 2** shows the criteria evaluated by the two researchers independently (AA and SI) for each paper included in the study.

Qualitative results

Several oxidative stress markers were investigated in the trials but were not included in the meta-analysis due to the small number of studies. Abedimenesh et al. (44) investigated the effect of saffron supplementation on the serum levels of oxidized low-density cholesterol (ox-LDL), an indicator of oxidative stress. Their results revealed that 8 weeks of intervention with saffron (30 mg/day) significantly reduced ox-LDL levels in patients with coronary artery disease.

Another study evaluated the effect of saffron supplementation on F2-isoprostanes levels and reported that receiving saffron

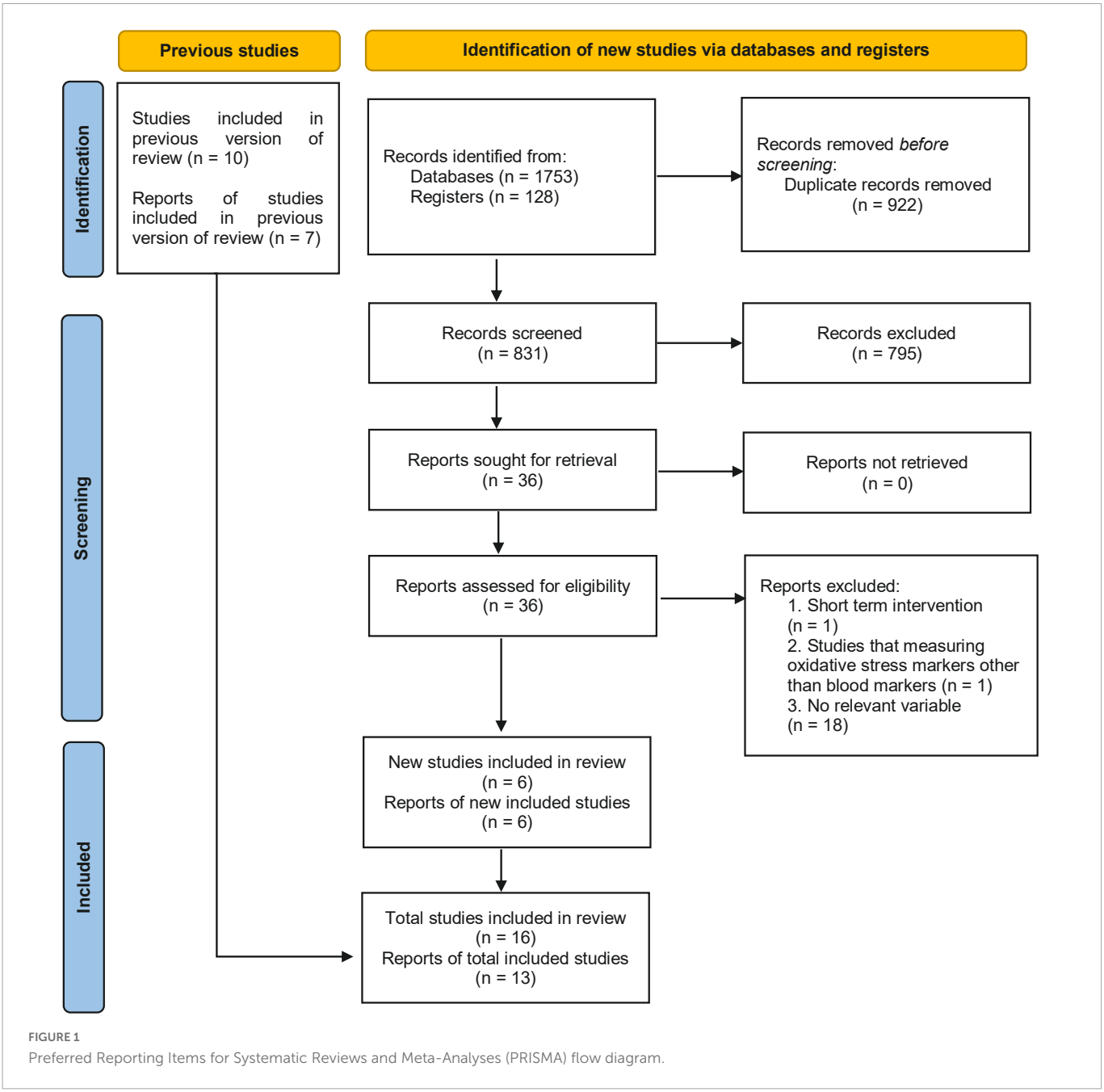


FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

had no significant impact on the F2-isoprostanes concentration (45). F2-isoprostanes are considered one of the oxidative stress markers derived from arachidonic acid, the primary substance involved in lipid peroxidation. Karimi et al. (20) showed the effect of saffron supplementation on increasing the activity of diphenyl pycryl hydrazyl (DPPH) radical scavenging. Saffron exerts antioxidant effects by donating a hydrogen atom to the DPPH radical anion.

In methadone maintenance treatment patients that 8 weeks of intervention with crocin led to an increase in GSH levels (antioxidant marker) and a decrease in total nitrite (oxidant marker) levels (57). In addition, in patients with multiple sclerosis, it has been shown that treatment with crocin for 4 weeks significantly increased total thiol group (TTG) levels (50).

Effect of saffron on MDA levels

The effects of saffron and crocin supplementation on MDA levels were investigated in 9 studies (6 and 3, respectively). MDA levels were measured in 551 patients (278 patients and 273 controls). Using a random-effects model, a significant decrease in MDA levels was observed after treatment with saffron (SMD: −0.322; 95% CI: −0.53, −0.16; I^2 = 32.58%, Figure 3). Decreased heterogeneity occurred when subgroup analysis was performed for study duration (I^2 = 0.0%, p = 0.69), age (I^2 = 0.0%, p = 0.66), type of supplementation (I^2 = 0.0%, p = 0.98), and saffron dosage (I^2 = 0.0%, p = 0.98).

Subgroup analysis revealed that serum MDA levels were significantly reduced following saffron supplementation in trials participants involving the following: the dosage of supplementation >30 mg/day (SMD: −0.34 mg/L; 95% CI: −0.56 to −0.11; p = 0.004),

10.3389/fmed.2023.1071514

TABLE 2 Characteristics of included studies investigating the effects of saffron supplementation on serum concentrations of oxidative stress biomarkers.

References	Country	Condition	Duration (weeks)	Group	*n*	Dose	Age, years, mean ± SD	Outcomes (change of mean ± SD)
Abedimanesh et al. (44)	Iran	Coronary artery disease	8	Saffron	22	30 mg/once daily	54.83 ± 5.99	Ox-LDL: −2.54 ± 3.30
				Placebo	20		56.00 ± 5.67	Ox-LDL: −0.24 ± 4.79
Azimi et al. (45)	Iran	Type 2 diabetes mellitus	8	Saffron	42	1,000 mg/once daily	57.02 ± 1.0	F2-isoprostan: −0.62 ± 4.00
				Placebo	39		53.64 ± 1.3	F2-isoprostan: −0.23 ± 7.15
Behrouz et al. (49)	Iran	Type 2 diabetes mellitus	12	Crocin	22	15 mg/twice daily	57.08 ± 7.41	MDA: 1.48 ± 4.98
				Placebo	22	–	59.86 ± 9.46	MDA: 1.86 ± 4.45
Dastkhosh et al. (48)	Iran	Type 2 diabetes mellitus	12	Crocin	22	15 mg/twice daily	57.08 ± 7.41	TOS: −0.82 ± 1.43
								TAC: 0.24 ± 0.39
				Placebo	22	–	59.86 ± 9.46	TOS: 0.55 ± 1.09
								TAC: −0.05 ± 0.40
Ebrahimi et al. (46)	Iran	Type 2 diabetes mellitus	12	Saffron	40	100 mg/twice daily	55.2 ± 7.3	MDA: −1.10 ± 3.41
								TAC: −0.06 ± 0.65
				Placebo	40	–	53 ± 10.6	MDA: 0.1 ± 2.7
								TAC: −0.01 ± 0.6
Ghaderi et al. (57)	Iran	Methadone maintenance treatment	8	Crocin	26	15 mg/twice daily	44.5 ± 9.4	MDA: −0.4 ± 1
								TAC: 52.30 ± 97.14
								GSH: 73.2 ± 119
								Total nitrite: 0.3 ± 5.05
				Placebo	27	–	45.6 ± 9.9	MDA: 0.1 ± 1.25
								TAC: −14.6 ± 141.75
								GSH: 21.4 ± 293.38
								Total nitrite: 1.4 ± 5.12
Ghiasian et al. (50)	Iran	Multiple sclerosis	4	Crocin	20	15 mg/twice daily	29 ± 4.99	MDA: −46.32 ± 16.75
								TAC: 24.42 ± 40.68
								TTG: 20.83 ± 15.27
				Placebo	20	–	31.47 ± 5.31	MDA: −17.94 ± 25.73
								TAC: 9.44 ± 42.69
								TTG: 4.37 ± 16.88
Ghobadi et al. (17)	Iran	COPD	12	Crocin	23	30 mg/once daily	62.04 ± 8.83	TOS: −0.14 ± 1.01
								TAC: 0.27 ± 0.51
				Placebo	23	–	61.72 ± 8.54	TOS: 0.30 ± 1.81
								TAC: −0.05 ± 0.61
Hamidi et al. (55)	Iran	Rheumatoid arthritis	12	Saffron	33	100 mg/once daily	51.55 ± 8.26	MDA: −0.54 ± 9.37
								TAC: 0.23 ± 0.94
				Placebo	32	–	51.80 ± 9.62	MDA: 2.57 ± 7.71
								TAC: 0.04 ± 1.10
Karimi-Nazari et al. (20)	Iran	Prediabetes obese individuals	8	Saffron	26	15 mg/once daily	57.95 ± 8.12	DPPH: 2.40 ± 2.02
				Placebo	30	–	57.90 ± 8.70	DPPH: −0.85 ± 2.11
Kavianipour et al. (52)	Iran	Non-alcoholic fatty liver disease	12	Saffron	38	100 mg/once daily	43.42 ± 10.62	MDA: −1.9 ± 3.51
								TAC: 0.43 ± 0.70
				Placebo	38	–	42.05 ± 8.27	MDA: −1.09 ± 2.71
								TAC: 0.08 ± 0.60

(Continued)

10.3389/fmed.2023.1071514

TABLE 2 (Continued)

References	Country	Condition	Duration (weeks)	Group	*n*	Dose	Age, years, mean ± SD	Outcomes (change of mean ± SD)
Kermani et al. (54)	Iran	Metabolic syndrome	12	Saffron	26	50 mg/twice daily	42.19 ± 11.52	PAB: −13.36 ± 26.71
				Placebo	30	–	43.60 ± 9.05	PAB: −4.19 ± 28.71
Rasi Marzabadi et al. (56)	Iran	Alzheimer disease	12	Saffron	27	15 mg/twice daily	76.70 ± 6.10	TAC: 0.18 ± 0.43
								MD: −0.15 ± 0.44
								GPx: 12.01 ± 14.97
								SOD: 124.4 ± 207.84
				Placebo	27	–	75.33 ± 5.06	TAC: 0.11 ± 0.53
								MD: −0.11 ± 0.37
								GPx: 8.99 ± 16.71
								SOD: 142.52 ± 207.11
Nikbakht-Jam et al. (53)	Iran	Metabolic syndrome	8	Crocin	29	15 mg/twice daily	38.97 ± 13.33	PAB: −16.12 ± 48.75
				Placebo	29	–	43.46 ± 12.77	PAB: −0.88 ± 36.53
Shahbazian et al. (47)	Iran	Type 2 diabetes mellitus	12	Saffron	32	15 mg/twice daily	53.5 ± 9.9	MDA: −8.94 ± 66.42
								TAC: 0.11 ± 0.43
								H-Cys: −0.12 ± 5.48
				Placebo	32	–	52.4 ± 13	MDA: −4.37 ± 63.78
								TAC: 0.1 ± 0.51
								H-Cys: −4.11 ± 6.14
Tahvilian et al. (51)	Iran	Ulcerative colitis	8	Saffron	40	100 mg/once daily	40.55 ± 12.71	MDA: −4.07 ± 12.03
								TAC: 0.11 0.88
								SOD: 5.61 ± 9.68
								GPx: 7.61 ± 15.23
				Placebo	35	–	40.97 ± 11.34	MDA: −0.11 ± 11.82
								TAC: −0.1 ± 0.90
								SOD: 0.65 ± 6.52
								GPx: −1.63 ± 10.40

DPPH, 2,2-Diphenyl-1-picrylhydrazyl; GPx, glutathione peroxidase; GSH, total glutathione; H-cys, homocysteine; MDA, malondialdehyde; Ox-LDL, oxidized LDL; PAB, proxidant/antioxidant balance; SD, standard deviation; SOD, superoxide dismutase; TAC, total antioxidant capacity; TTG, total thiol group.

age of <50 years old (SMD: −0.53 mg/L; 95% CI: −0.93 to −0.13; $p = 0.010$), study duration <12 weeks (SMD: −0.50 mg/L; 95% CI: −0.95 to −0.05; $p = 0.028$), non-diabetic patients (SMD: −0.415 mg/L; 95% CI: −0.69 to 0.14; $p = 0.003$), and trials that used saffron (SMD: −0.26 mg/L; 95% CI: −0.46 to −0.07; $p = 0.008$) (Table 3).

Effect of saffron on TAC levels

The effects of saffron and crocin supplementation on TAC levels were investigated in 10 studies (6 and 4, respectively). A total of 597 patients had TAC levels (301 cases and 296 controls). Using a random-effects model, a significant increase in serum TAC levels was found after treatment with saffron (SMD: 0.288; 95% CI: 0.12, 0.45; $I^2 = 2.62\%$, Figure 4). Decreased heterogeneity occurred when subgroup analysis was performed for the study duration ($I^2 = 0.0\%$, $p = 0.74$), age ($I^2 = 0.0\%$, $p = 0.77$), type of supplementation ($I^2 = 0.0\%$, $p = 0.53$), and saffron dosage ($I^2 = 0.0\%$, $p = 0.44$).

Subgroup analysis revealed that serum TAC levels were significantly increased following saffron supplementation in trials participants involving the following: the dosage of supplementation <30 mg/day (SMD: 0.36 mg/L; 95% CI: 0.13 to 0.60; $p = 0.002$), age of <50 years old (SMD: 0.42 mg/L; 95% CI: 0.16 to 0.67; $p = 0.001$), non-diabetic patients (SMD: 0.358 mg/L; 95% CI: 0.16 to 0.55; $p = 0.000$), and trials that used crocin (SMD: 0.55 mg/L; 95% CI: 0.26 to 0.85; $p = 0.000$) (Table 3).

Effect of saffron on TOS serum levels

The effects of crocin supplementation on serum TOS levels were investigated in 2 studies. A total of 90 patients had serum TOS levels (45 cases and 45 controls). Using a fixed-effects model, a significant

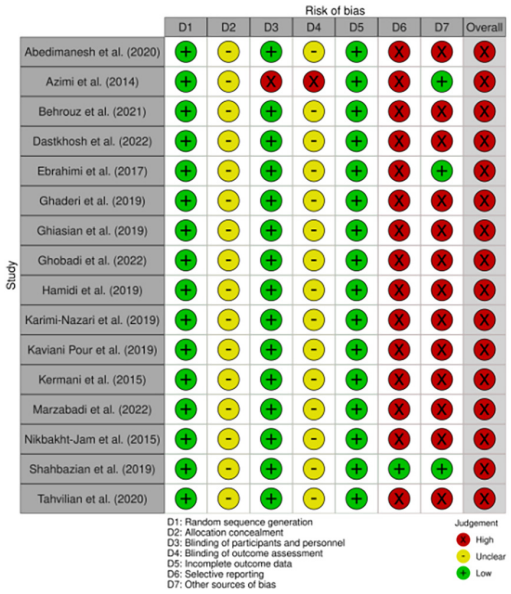


FIGURE 2
Study quality and risk of bias assessment of included studies according to the Cochrane Collaboration's tool.

decrease in serum TOS levels was found after treatment with crocin (SMD: −0.654; 95% CI: −1.08, −0.23; I^2 = 68%, Figure 5).

Effect of saffron on PAB

The effects of saffron supplementation on PAB levels were investigated in 2 studies. A total of 106 patients had PAB levels (55 cases and 51 controls). Using a fixed-effects model, there was not a significant change in PAB levels after treatment with saffron (SMD: −0.342; 95% CI: −0.71, 0.03; I^2 = 00%, Figure 5).

Effect of saffron on GPx serum levels

The effects of saffron supplementation on serum GPx levels were investigated in 2 studies. A total of 129 patients had serum GPx levels (67 cases and 62 controls). Using a fixed-effects model, a significant increase in serum GPx levels was found after treatment with saffron (SMD: 0.447; 95% CI: 0.10, 0.80; I^2 = 35%, Figure 6).

Effect of saffron on SOD serum levels

The effects of saffron supplementation on serum SOD levels were investigated in 2 studies. A total of 129 patients had serum SOD levels (67 cases and 62 controls). Using a fixed-effects model, there was not a significant change in SOD levels after treatment with saffron (SMD: 0.316; 95% CI: −0.03, 0.67; I^2 = 18%, Figure 6).

Publication bias

Visual inspection of the funnel plots did not reveal any evidence of asymmetry. Formal assessments of publication bias using Egger's regression tests also demonstrated a lack of publication bias for both MDA (p = 0.23) and TAC (p = 0.07).

Meta-regression

Since MDA and TAC levels were significant, meta-regression analysis was performed to determine the relationship between saffron supplement dose, saffron duration of intervention, and the age of subjects included in the study with oxidant/antioxidant markers.

Meta-regression analysis showed that there was no significant direct relationship between saffron dosage with MDA (z = −0.37, p = 0.71) and TAC (z = −1.58, p = 0.11) as well as the age with MDA (z = 0.88, p = 0.40) and TAC (z = −1.73, p = 0.08). Although there was no significant relationship between the duration of intervention with saffron and TAC (z = −0.52, p = 0.60), there was a significant direct relationship with MDA (z = 2.66, p = 0.007) (Supplementary Figure 1).

Discussion

This study is an updated systematic review and meta-analysis of the effects of saffron on oxidative stress markers (MDA, TAC, TOS, GPx, SOD, and PAB). A combination of 16 eligible trials showed that saffron supplementation significantly reduced MDA and TOS levels, as well as increased TAC and GPx levels. In addition, subgroup analysis revealed that in trials in which the duration of administration was <12 weeks, the supplement dosage was <30 mg/day, the age of participants was under 50 years old, and used the crocin supplement, reduced MDA and increased TAC were significant events.

Saffron has long been used not only as a food source but also as a medicinal plant. In various human and animal studies, the effects of saffron are anti-inflammatory, antioxidant, anticancer, antidepressant, anti-genotoxic, analgesic, antibacterial, and respiratory relaxant (13, 23, 59). The effects mentioned above of saffron have been observed in various chronic inflammatory diseases such as asthma, COPD, cardiovascular disease, sexual dysfunction, cancer, and diabetes mellitus (14, 17, 60–62). The active ingredients of saffron with high biological activity are crocin, safranal, crocetin, and picrocrocin.

In several *in vivo* and *in vitro* studies, the anti-inflammatory effects of saffron have been attributed to its potent antioxidant and radical scavenging properties (59). Oxidative stress is caused by an imbalance in oxidant/antioxidant markers, disruption of endogenous antioxidant defense, and an increase in oxidative factors (3). Among the highly oxidative products of oxidative stress are MDA and TOS. Instead, the depletion of antioxidant markers, such as TAC, GSH, catalase, and SOD, occurs under oxidative stress conditions (3). In addition, the PAB ratio has been investigated as an indicator of oxidative stress (53). Although most preclinical studies have shown the antioxidant effects of saffron and crocin, clinical trials are essential to determine their effectiveness in human studies.

The current updated meta-analysis of RCTs showed that intervention with saffron had beneficial effects on MDA, TOS, GPx, and TAC levels. Subgroup analysis revealed that a supplement dosage of >30 significantly reduced MDA levels in the trials. Interestingly, regarding TAC levels, it was found that in the trials prescribed, a dosage of <30 supplements was beneficial. In addition, contradictory

10.3389/fmed.2023.1071514

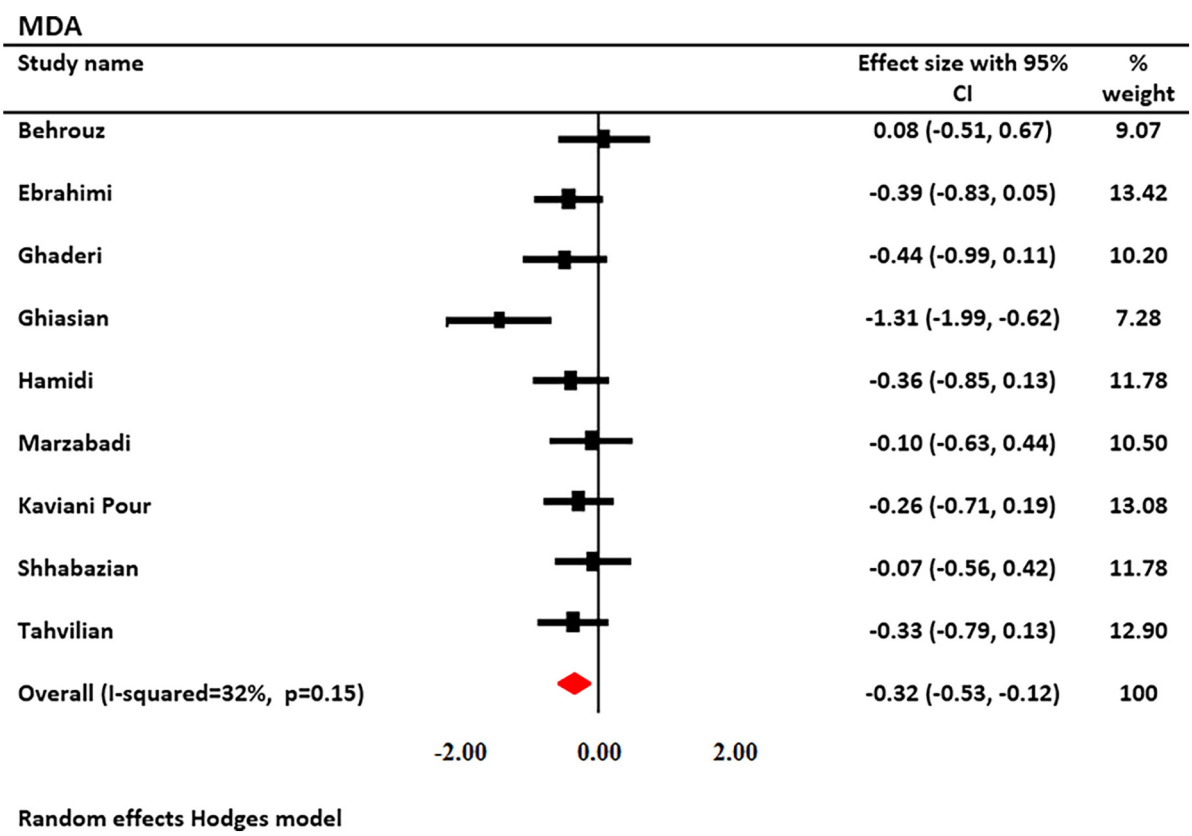


FIGURE 3
Forest plot showing the summary effect size for malondialdehyde (MDA) levels between saffron and placebo groups.

TABLE 3 Subgroup analysis assessing the effect of saffron intake on MDA and TAC.

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
MDA	Duration	≥12ωεεκσ	5	−0.228	−0.45, −0.01	0	0.68
		<12ωεεκσ	4	−0.5	−0.95, −0.05	62.6	0.045
	Saffron dosage	>30μγ/δαψ	4	−0.335	−0.56, −0.11	0	0.981
		≤30μγ/δαψ	5	−0.335	−0.77, 0.09	65.5	0.02
	Age	<50	4	−0.526	−0.93, −0.13	57	0.073
		50≤	5	−0.196	−0.42, 0.03	0	0.66
	Supplementation type	Saffron	6	−0.262	−0.46, −0.07	0	0.908
		Crocin	3	−0.537	−1.28, 0.21	78	0.011
	Disease type	Diabetic	3	−0.169	−0.46, 0.19	0	0.408
		Non-diabetic	6	−0.415	−0.69, −0.14	41.5	0.128
TAC	Duration	≥12ωεεκσ	6	0.292	0.03, 0.55	37.1	0.159
		<12ωεεκσ	4	0.308	0.04, 0.57	0	0.746
	Saffron dosage	>30μγ/δαψ	4	0.214	−0.04, 0.47	16.9	0.306
		≤30μγ/δαψ	6	0.362	0.13, 0.60	0	0.443
	Age	<50	4	0.415	0.16, 0.67	0	0.774
		50≤	6	0.213	−0.03, 0.45	22.6	0.263
	Supplementation type	Saffron	6	0.174	−0.02, 0.37	0	0.534
		Crocin	4	0.552	0.26, 0.85	0	0.875
	Disease type	Diabetic	3	0.183	−0.27, 0.64	58	0.092
		Non-diabetic	6	0.358	0.16, 0.55	0	0.825

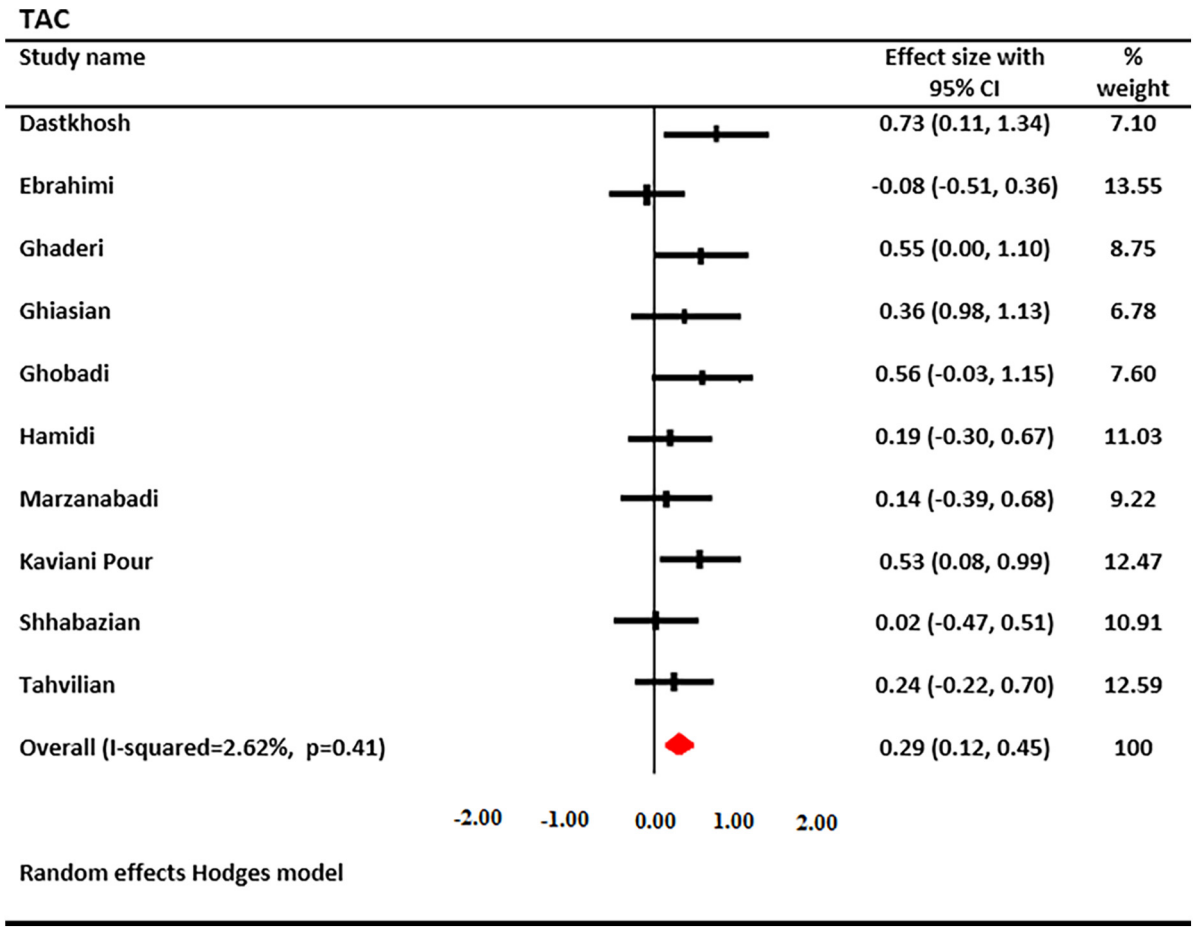


FIGURE 4
Forest plot showing the summary effect size for total antioxidant capacity (TAC) levels between saffron and placebo groups.

results were observed regarding the effect of saffron supplementation duration on MDA and TAC levels in the subgroup analysis. Decreased levels of MDA were significantly evident in the administration duration of saffron <12 weeks, whereas increased levels of TAC were significant in the intervention for more than 12 weeks. Perhaps the reason for these contradictory results is the ambiguity of the findings due to the small sample size included in the subgroup analysis.

On the other hand, subgroup analysis of the results showed that the effect of age on oxidative stress markers was similar; therefore, under 50 years old, decreased MDA and increased TAC levels were significant compared to those above 50 years old. Severe oxidant/antioxidant imbalance in old age may have been an essential factor in the effects of saffron in seniors over 50 old. The results of the subgroup analysis also showed that crocin administration significantly reduced MDA and increased TAC levels compared with saffron administration. The results of the current meta-analysis are consistent with preclinical studies of the effectiveness of active saffron components such as crocin, crocetin, and safranal (63). Beneficial effects of crocin have been reported in various disorders such as asthma, COPD, PCOS, gastritis, and hepatitis (16, 17, 64). By upregulating the expression of mitochondrial antioxidant genes, crocin reduced ROS formation, decreased lipid peroxidation levels and MDA levels, increased TAC, and modified TOS (65).

The results of trial studies evaluating serum levels of TOS also showed the protective effects of crocin on serum levels. Two trials included in this study revealed that intervention with crocin reduced the serum TOS levels. No significant effect of saffron on the amount of PAB was observed. In fact, in two trial studies that examined the effect of saffron on PAB levels, it was not significant despite the decrease in serum PAB levels. The probable reason for the lack of significance in the results was the small sample size used in the current meta-analysis.

Various mechanisms have been proposed to explain the beneficial effects of saffron and its biologically active components in improving oxidative stress. In inflammatory diseases, ROS formation increases the production of intracellular advanced glycation end products, and activation of protein kinase C pathways occurs, leading to the activation of inflammatory signals, such as the NF-κB pathway, p38 mitogen-activated protein kinase (p38MAPK), Jun N-terminal kinases (JNK), and ER stress. The activation of inflammatory signaling cascades increases the synthesis and secretion of inflammatory cytokines, growth factors, eicosanoids, and chemokines. The antioxidant and anti-inflammatory effects of saffron are probably mediated by modulation of the following signaling pathways: NF-κB p65, protein kinase C (PKC), mitogen-activated protein kinases (MAPK/ERK), signal transducer and transcription activator 6 (STAT6), inducible nitric oxide synthase (iNOS), Ca2 + /calmodulin-dependent protein kinase 4 (CAMK4), ER stress markers, phosphoinositide-3-kinase (PI3K)/Akt, Nrf2,

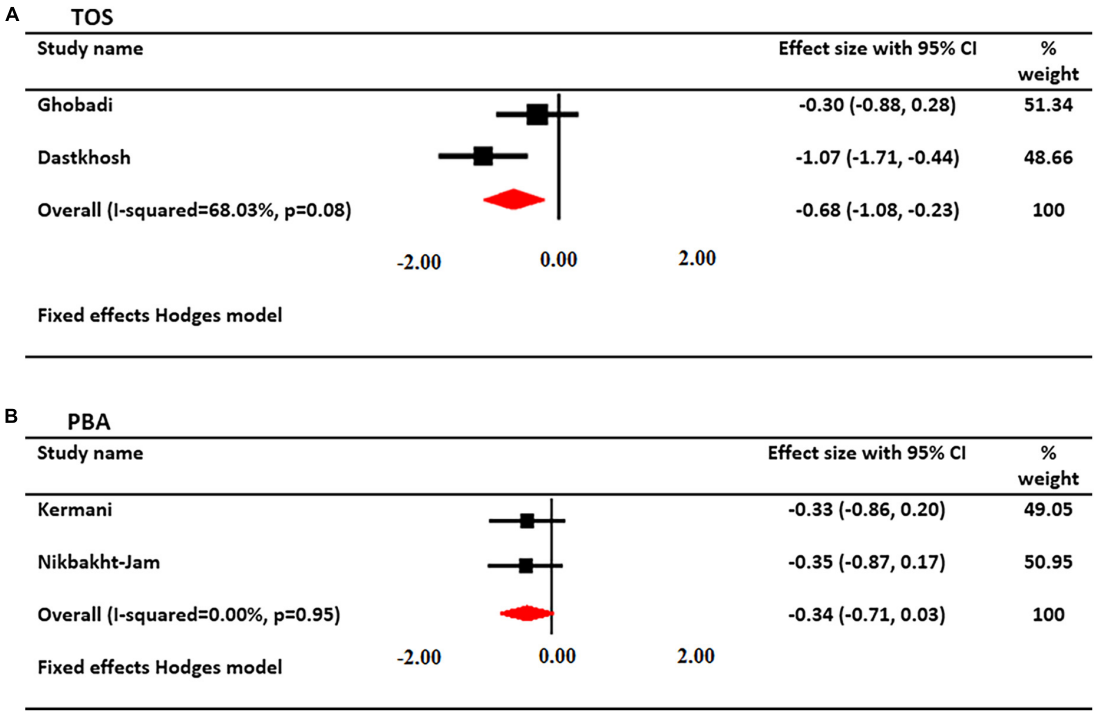


FIGURE 5
Forest plot showing the summary effect size for **(A)** total oxidant status (TOS) and **(B)** pro-oxidant/antioxidant balance (PAB) levels between saffron and placebo groups.

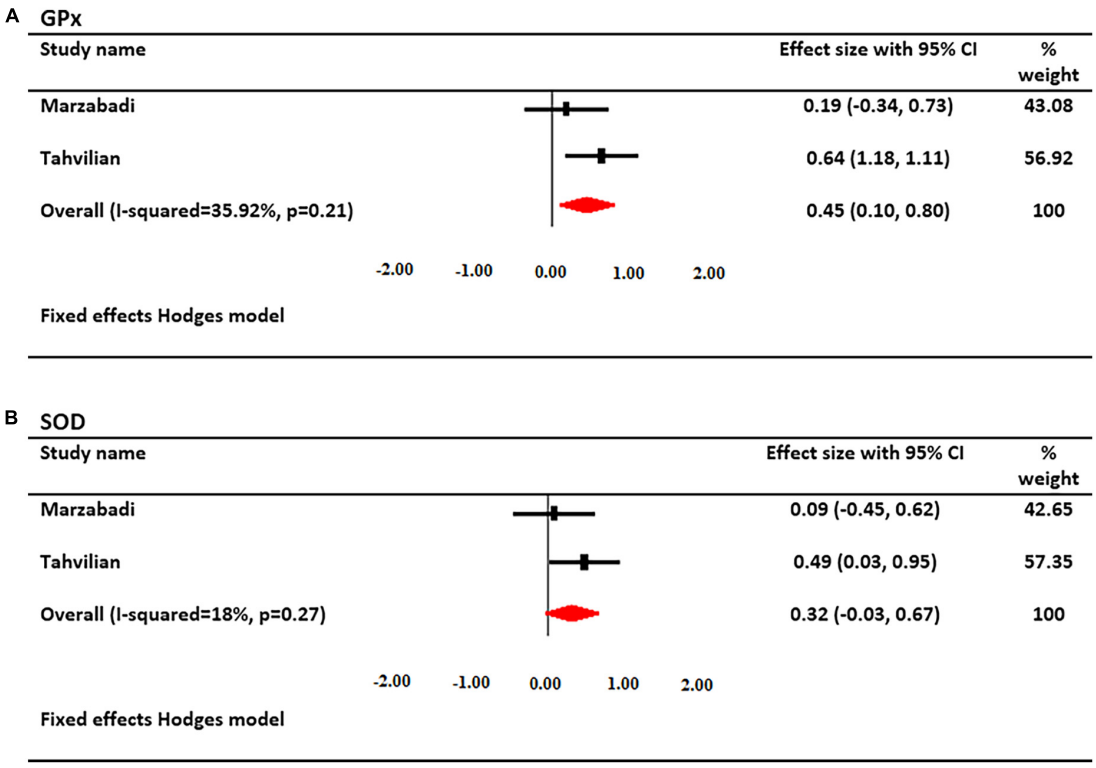


FIGURE 6
Forest plot showing the summary effect size for **(A)** glutathione peroxidase (GPx) and **(B)** superoxide dismutase (SOD) levels between saffron and placebo groups.

c-JNK, and high-mobility group box 1 (HMGB-1) pathways (15, 17, 59).

Although the current meta-analysis revealed the beneficial effects of saffron and crocin in clinical trial studies on oxidative stress markers such as TAC, MDA, and TOS, some limitations must be considered. First, the number of studies included in the current study, although higher than the previous study, was small for a more detailed analysis. Second, all the studies included in the meta-analysis were from Iran and could not be generalized to other nationalities. Third, some potential confounders that may have influenced the study results were not considered in the analysis of the trial studies, such as smoking, physical activity, and diet. Fourth, the nature of the diseases included in the trial study was different, which may have affected the study results. Finally, the lack of protocol registration was another limitation of the study.

In summary, the results of the current study showed that saffron and its active ingredients were able to establish a balance of oxidants/antioxidants in various disease conditions in trial studies. However, additional trial studies are necessary to reveal the effectiveness of saffron and its active ingredients on inflammatory and oxidative stress markers.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

This study was conducted after approved by the Ethics Committee of the Ardabil University of Medical Sciences (IR.ARUMS.MEDICINE.REC.1401.078).

Author contributions

MA: conceptualization, methodology, data analysis, manuscript preparation, and revising the manuscript. AA and SI: data extraction and writing—original draft preparation. HG, AS, and MF: writing—original draft preparation, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1071514/full#supplementary-material

References

1. Flohé L. Looking back at the early stages of redox biology. *Antioxidants.* (2020) 9:1254. doi: 10.3390/antiox9121254

2. Halliwell B. Oxidative stress and neurodegeneration: where are we now? *J Neurochem.* (2006) 97:1634–58.

3. Sies H, Berndt C, Jones D. Oxidative stress. *Annu Rev Biochem.* (2017) 86:715–48.

4. Forman H, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. *Nat Rev Drug Discov.* (2021) 20:689–709.

5. Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. *World J Gastroenterol.* (2014) 20:8082–91.

6. Chen A, Chen D, Daiber A, Faraci F, Li H, Rembold C, et al. Free radical biology of the cardiovascular system. *Clin Sci.* (2012) 123:73–91.

7. Brennan L, McGreal R, Kantorow M. Oxidative stress defense and repair systems of the ocular lens. *Front Biosci.* (2012) 4:141–55. doi: 10.2741/365

8. Ozbek E. Induction of oxidative stress in kidney. *Int J Nephrol.* (2012) 2012:465897.

9. Boskabadi M, Aslani M, Mansouri F, Ameri S. Relaxant effect of *Satureja hortensis* on guinea pig tracheal chains and its possible mechanism(s). *DARU J Pharm Sci.* (2007) 15:199–204.

10. Saadat S, Aslani M, Ghorani V, Keyhanmanesh R, Boskabady M. The effects of *Nigella sativa* on respiratory, allergic and immunologic disorders, evidence from experimental and clinical studies, a comprehensive and updated review. *Phytother Res.* (2021) 35:2968–96. doi: 10.1002/ptr.7003

11. Khazdair M, Saadat S, Aslani M, Shakeri F, Boskabady M. Experimental and clinical studies on the effects of *Portulaca oleracea* L. and its constituents on respiratory, allergic, and immunologic disorders, a review. *Phytother Res.* (2021) 35:6813–42. doi: 10.1002/ptr.7268

12. Ghasemi Z, Rezaee R, Aslani M, Boskabady M. Anti-inflammatory, anti-oxidant, and immunomodulatory activities of the genus Ferula and their constituents: a review. *Iran J Basic Med Sci.* (2021) 24:1613–23. doi: 10.22038/IJBMS.2021.59473.13204

13. Boskabady M, Aslani M. Relaxant effect of *Crocus sativus* (saffron) on guinea-pig tracheal chains and its possible mechanisms. *J Pharm Pharmacol.* (2006) 58:1385–90. doi: 10.1211/jpp.58.10.0012

14. Saeideh S, Yasavoli M, Gholamnezhad Z, Aslani M, Boskabady M. The relaxant effect of crocin on rat tracheal smooth muscle and its possible mechanisms. *Iran J Pharm Res.* (2019) 18:1358–70. doi: 10.22037/ijpr.2019.1100713

15. Aslani M, Amani M, Masrori N, Boskabady M, Ebrahimi H, Chodari L. Crocin attenuates inflammation of lung tissue in ovalbumin-sensitized mice by altering the expression of endoplasmic reticulum stress markers. *Biofactors.* (2022) 48:204–15. doi: 10.1002/biof.1809

16. Rahimi G, Shams S, Aslani M. Effects of crocin supplementation on inflammatory markers, lipid profiles, insulin and cardioprotective indices in women with PCOS: a randomized, double-blind, placebo-controlled trial. *Phytother Res.* (2022) 36:2605–15. doi: 10.1002/ptr.7474

17. Ghobadi H, Abdollahi N, Madani H, Aslani M. Effect of crocin from saffron (*Crocus sativus* L.) supplementation on oxidant/antioxidant markers, exercise capacity, and pulmonary function tests in COPD patients: a randomized, double-blind, placebo-controlled trial. *Front Pharmacol.* (2022) 13:884710. doi: 10.3389/fphar.2022.884710

18. Hosseini S, Zilaee M, Shoushtari M, Ghasemi Dehcheshmeh M. An evaluation of the effect of saffron supplementation on the antibody titer to heat-shock protein (HSP) 70, hsCRP and spirometry test in patients with mild and moderate persistent allergic asthma: a triple-blind, randomized placebo-controlled trial. *Respir Med.* (2018) 145:28–34. doi: 10.1016/j.rmed.2018.10.016

19. Aslani M, Jafari Z, Rahbarghazi R, Rezaie J, Delkhosh A, Ahmadi M. Effects of crocin on T-bet/GATA-3 ratio, and miR-146a and miR-106a expression levels in lung tissue of ovalbumin-sensitized mice. *Iran J Basic Med Sci.* (2022) 25:1267–74. doi: 10.22038/IJBMS.2022.65622.14433

20. Karimi-Nazari E, Nadjarzadeh A, Masoumi R, Marzban A, Mohajeri S, Ramezani-Jolfaie N, et al. Effect of saffron (*Crocus sativus* L.) on lipid profile, glycemic indices and antioxidant status among overweight/obese prediabetic individuals: a double-blinded, randomized controlled trial. *Clin Nutr ESPEN.* (2019) 34:130–6. doi: 10.1016/j.clnesp.2019.07.012

21. Morvaridzadeh M, Agah S, Dulce Estêvão M, Hosseini A, Heydari H, Toupchian O, et al. Effect of saffron supplementation on oxidative stress parameters: a systematic review and meta-analysis of randomized placebo-controlled trials. *Food Sci Nutr.* (2021) 9:5809–19. doi: 10.1002/fsn3.2463

22. Page M, McKenzie J, Bossuyt P, Boutron I, Hoffmann T, Mulrow C, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71.

23. Akhondzadeh S, Tahmacebi-Pour N, Noorbala A, Amini H, Fallah-Pour H, Jamshidi A, et al. *Crocus sativus* L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytother Res.* (2005) 19:148–51.

24. Ahmadikhatir S, Ostadrahimi A, Safaiyan A, Ahmadikhatir S, Farrin N. Saffron (*Crocus sativus* L.) supplements improve quality of life and appetite in atherosclerosis patients: a randomized clinical trial. *J Res Med Sci.* (2022) 27:30. doi: 10.4103/jrms.JRMS_1253_20

25. Moravej Aleali A, Amani R, Shahbazian H, Namjooyan F, Latifi S, Cheraghian B. The effect of hydroalcoholic Saffron (*Crocus sativus* L.) extract on fasting plasma glucose, HbA1c, lipid profile, liver, and renal function tests in patients with type 2 diabetes mellitus: a randomized double-blind clinical trial. *Phytother Res.* (2019) 33:1648–57. doi: 10.1002/ptr.6351

26. Behrouz V, Dastkhosh A, Hedayati M, Sedaghat M, Sharafkhah M, Sohrab G. The effect of crocin supplementation on glycemic control, insulin resistance and active AMPK levels in patients with type 2 diabetes: a pilot study. *Diabetol Metab Syndr.* (2020) 12:59. doi: 10.1186/s13098-020-00568-6

27. Bozorgi H, Ghahremanfard F, Motaghi E, Zamaemifard M, Zamani M, Izadi A. Effectiveness of crocin of saffron (*Crocus sativus* L.) against chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled clinical trial. *J Ethnopharmacol.* (2021) 281:114511. doi: 10.1016/j.jep.2021.114511

28. Broadhead G, Grigg J, McCluskey P, Hong T, Schlub T, Chang A. Saffron therapy for the treatment of mild/moderate age-related macular degeneration: a randomised clinical trial. *Graefes Arch Clin Exp Ophthalmol.* (2019) 257:31–40. doi: 10.1007/s00417-018-4163-x

29. Fadai F, Mousavi B, Ashtari Z, Ali beigi N, Farhang S, Hashempour S, et al. Saffron aqueous extract prevents metabolic syndrome in patients with schizophrenia on olanzapine treatment: a randomized triple blind placebo controlled study. *Pharmacopsychiatry.* (2014) 47:156–61. doi: 10.1055/s-0034-1382001

30. Falsini B, Piccardi M, Minnella A, Savastano C, Capoluongo E, Fadda A, et al. Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration. *Invest Ophthalmol Vis Sci.* (2010) 51:6118–24. doi: 10.1167/iovs.09-4995

31. Farokhnia M, Shafiee Sabet M, Iranpour N, Gougol A, Yekehtaz H, Alimardani R, et al. Comparing the efficacy and safety of *Crocus sativus* L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. *Hum Psychopharmacol.* (2014) 29:351–9. doi: 10.1002/hup.2412

32. Gout B, Bourges C, Paineau-Dubreuil S. Satiereal, a *Crocus sativus* L extract, reduces snacking and increases satiety in a randomized placebo-controlled study of mildly overweight, healthy women. *Nutr Res.* (2010) 30:305–13. doi: 10.1016/j.nutres.2010.04.008

33. Heidary M, Vahhabi S, Reza Nejadi J, Delfan B, Birjandi M, Kaviani H, et al. Effect of saffron on semen parameters of infertile men. *Urol J.* (2008) 5:255–9.

34. Kermani T, Kazemi T, Molki S, Ilkhani K, Sharifzadeh G, Rajabi O. The efficacy of crocin of saffron (*Crocus sativus* L.) on the components of metabolic syndrome: a randomized controlled clinical trial. *J Res Pharm Pract.* (2017) 6:228–32. doi: 10.4103/jrpp.JRPP_17_26

35. Khalatbari-Mohseni A, Banafshe H, Mirhosseini N, Asemi Z, Ghaderi A, Omidi A. The effects of crocin on psychological parameters in patients under methadone maintenance treatment: a randomized clinical trial. *Subst Abuse Treat Prev Policy.* (2019) 14:9. doi: 10.1186/s13011-019-0198-1

36. Hooshmand-Moghadam B, Eskandari M, Shabkhiz F, Mojtahedi S, Mahmoudi N. Saffron (*Crocus sativus* L.) in combination with resistance training reduced blood pressure in the elderly hypertensive men: a randomized controlled trial. *Br J Clin Pharmacol.* (2021) 87:3255–67. doi: 10.1111/bcp.14746

37. Hosseini A, Mousavi S, Ghanbari A, Shandiz F, Raziee H, Rad M, et al. Effect of saffron on liver metastases in patients suffering from cancers with liver metastases: a randomized, double blind, placebo-controlled clinical trial. *Avicenna J Phytomed.* (2015) 5:434–40.

38. Kazemi F, Vosough I, Sepahi S, Mohajeri S. Effect of crocin versus fluoxetine in treatment of mild to moderate obsessive-compulsive disorder: a double blind randomized clinical trial. *Hum Psychopharmacol.* (2021) 36:e2780. doi: 10.1002/hup.2780

39. Khatir, S, Bayatian A, Barzegari A, Roshanravan N, Safaiyan A, Pavon-Djavid G, et al. Saffron (*Crocus sativus* L.) supplements modulate circulating MicroRNA (miR-21) in atherosclerosis patients; a randomized, double-blind, placebo-controlled trial. *Iran Red Crescent Med J.* (2018) 20:e80260. doi: 10.5812/ircmj.80260

40. Rajabi F, Rahimi M, Sharbafchizadeh M, Tarrahi M. Saffron for the management of premenstrual dysphoric disorder: a randomized controlled trial. *Adv Biomed Res.* (2020) 9:60. doi: 10.4103/abr.abr_49_20

41. Ami Ahmadi S, Kazemi A, Sabahi M, Razipour S, Salehipour A, Ghiasian M, et al. Probable antioxidant therapy of Saffron Crocin in patients with multiple sclerosis: a randomized controlled trial. *Biomedicine.* (2021) 40:516–21.

42. Gudarzi S, Jafari M, Pirzad Jahromi G, Eshrati R, Asadollahi M, Nikdokht P. Evaluation of modulatory effects of saffron (*Crocus sativus* L.) aqueous extract on oxidative stress in ischemic stroke patients: a randomized clinical trial. *Nutr Neurosci.* (2022) 25:1137–46. doi: 10.1080/1028415X.2020.1840118

43. Setayesh L, Ashtary-Larky D, Clark C, Rezaei Kelishadi M, Khalili P, Bagheri R, et al. The effect of saffron supplementation on blood pressure in adults: a systematic review and dose-response meta-analysis of randomized controlled trials. *Nutrients.* (2021) 13:2736.

44. Abedimanesh N, Motlagh B, Abedimanesh S, Bathaie S, Separham A, Ostadrahimi A. Effects of crocin and saffron aqueous extract on gene expression of SIRT1, AMPK, LOX1, NF-κB, and MCP-1 in patients with coronary artery disease: a randomized placebo-controlled clinical trial. *Phytother Res.* (2020) 34:1114–22. doi: 10.1002/ptr.6580

45. Azimi P, Ghiasvand R, Feizi A, Hariri M, Abbasi B. Effects of cinnamon, cardamom, saffron, and ginger consumption on markers of glycemic control, lipid profile, oxidative stress, and inflammation in type 2 diabetes patients. *Rev Diabet Stud.* (2014) 11:258–66. doi: 10.1900/RDS.2014.11.258

46. Ebrahimi F, Sahebkar A, Aryaeian N, Pahlavani N, Fallah S, Moradi N, et al. Effects of saffron supplementation on inflammation and metabolic responses in type 2 diabetic patients: a randomized, double-blind, placebo-controlled trial. *Diabetes Metab Syndr Obes.* (2019) 12:2107–15. doi: 10.2147/DMSO.S216666

47. Shahbazian H, Moravej Aleali A, Amani R, Namjooyan F, Cheraghian B, Latifi S, et al. Effects of saffron on homocysteine, and antioxidant and inflammatory biomarkers levels in patients with type 2 diabetes mellitus: a randomized double-blind clinical trial. *Avicenna J Phytomed.* (2019) 9:436–45.

48. Dastkhosh A, Behrouz V, Sohrab G, Sedaghat M. *Effects of crocin supplementation on lipid profile and oxidative stress in patients with type 2 diabetes: a randomized clinical trial*. Durham, NC: Research Square (2022).

49. Behrouz V, Sohrab G, Hedayati M, Sedaghat M. Inflammatory markers response to crocin supplementation in patients with type 2 diabetes mellitus: a randomized controlled trial. *Phytother Res.* (2021) 35:4022–31. doi: 10.1002/ptr.7124

50. Ghiasian M, Khamisabadi F, Kheiripour N, Karami M, Haddadi R, Ghaleiha A, et al. Effects of crocin in reducing DNA damage, inflammation, and oxidative stress in multiple sclerosis patients: a double-blind, randomized, and placebo-controlled trial. *J Biochem Mol Toxicol.* (2019) 33:e22410. doi: 10.1002/jbt.22410

51. Tahvilian N, Masoodi M, Faghihi Kashani A, Vafa M, Aryaeian N, Heydarian A, et al. Effects of saffron supplementation on oxidative/antioxidant status and severity of disease in ulcerative colitis patients: a randomized, double-blind, placebo-controlled study. *Phytother Res.* (2021) 35:946–53. doi: 10.1002/ptr.6848

52. Kavianipour F, Aryaeian N, Mokhtare M, Mirnasrollahiparsa R, Jannani L, Agah S, et al. The effect of saffron supplementation on some inflammatory and oxidative markers, leptin, adiponectin, and body composition in patients with nonalcoholic fatty liver disease: a double-blind randomized clinical trial. *Phytother Res.* (2020) 34:3367–78. doi: 10.1002/ptr.6791

53. Nikbakht-Jam I, Khademi M, Nosrati M, Eslami S, F'oroutan-Tanha M, Sahebkar A, et al. Effect of crocin extracted from saffron on pro-oxidant–anti-oxidant balance in subjects with metabolic syndrome: a randomized, placebo-controlled clinical trial. *Eur J Integr Med.* (2016) 8:307–12.

54. Kermani T, Mousavi S, Shemshian M, Norouzy A, Mazidi M, Moezzi A, et al. Saffron supplements modulate serum pro-oxidant-antioxidant balance in patients with metabolic syndrome: a randomized, placebo-controlled clinical trial. *Avicenna J Phytomed.* (2015) 5:427–33.

55. Hamidi Z, Aryaeian N, Abolghasemi J, Shirani F, Hadidi M, Fallah S, et al. The effect of saffron supplement on clinical outcomes and metabolic profiles in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled clinical trial. *Phytother Res.* (2020) 34:1650–8. doi: 10.1002/ptr.6633

56. Rasi Marzabadi L, Fazljou S, Araj-Khodaei M, Sadigh-Eteghad S, Naseri A, Talebi M. Saffron reduces some inflammation and oxidative stress markers in donepezil-treated mild-to-moderate Alzheimer's disease patients: a randomized double-blind placebo-control trial. *J Herb Med.* (2022) 34:100574.

57. Ghaderi A, Rasouli-Azad M, Vahed N, Banafshe H, Soleimani A, Omidi A, et al. Clinical and metabolic responses to crocin in patients under methadone maintenance treatment: a randomized clinical trial. *Phytother Res.* (2019) 33:2714–25. doi: 10.1002/ptr.6445

58. Rosenblad A. Introduction to meta-analysis by Michael Borenstein, Larry V. Hedges, Julian P.T. Higgins, Hannah R. Rothstein. *Int Stat Rev.* (2009) 77:478–9.

59. Boskabady M, Farkhondeh T. Antiinflammatory, antioxidant, and immunomodulatory effects of *Crocus sativus* L. and its main constituents. *Phytother Res.* (2016) 30:1072–94. doi: 10.1002/ptr.5622

60. Shakeri M, Hashemi Tayer A, Shakeri H, Sotoodeh Jahromi A, Moradzadeh M, Hojjat-Farsangi M. Toxicity of saffron extracts on cancer and normal cells: a review article. *Asian Pac J Cancer Prev.* (2020) 21:1867–75. doi: 10.31557/APJCP.2020.21.7.1867

61. Razavi B, Hosseinzadeh H. Saffron: a promising natural medicine in the treatment of metabolic syndrome. *J Sci Food Agric.* (2017) 97:1679–85. doi: 10.1002/jsfa.8134

62. Leone S, Recinella L, Chiavaroli A, Orlando G, Ferrante C, Leporini L, et al. Phytotherapic use of the *Crocus sativus* L. (Saffron) and its potential applications: a brief overview. *Phytother Res.* (2018) 32:2364–75. doi: 10.1002/ptr.6181

63. Asbaghi O, Sadeghian M, Sadeghi O, Rigi S, Tan S, Shokri A, et al. Effects of saffron (*Crocus sativus* L.) supplementation on inflammatory biomarkers: a systematic review and meta-analysis. *Phytother Res.* (2021) 35:20–32. doi: 10.1002/ptr.6748

64. Ashktorab H, Soleimani A, Singh G, Amin A, Tabtabaei S, Latella G, et al. Saffron: the golden spice with therapeutic properties on digestive diseases. *Nutrients.* (2019) 11:943. doi: 10.3390/nu11050943

65. Rahiman N, Akaberi M, Sahebkar A, Emami S, Tayarani-Najaran Z. Protective effects of saffron and its active components against oxidative stress and apoptosis in endothelial cells. *Microvasc Res.* (2018) 118:82–9. doi: 10.1016/j.mvr.2018.03.003

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 20 April 2023
DOI 10.3389/fmed.2023.1173528

OPEN ACCESS

EDITED BY
Roberta Zupo,
National Institute of Gastroenterology S. de Bellis Research Hospital (IRCCS), Italy

REVIEWED BY
Simona Aresta,
National Institute of Gastroenterology S. de Bellis Research Hospital (IRCCS), Italy
Lorenzo Pradelli,
AdRes srl, Italy

*CORRESPONDENCE
Kristina Franz
✉ kristina.franz@charite.de

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

SPECIALTY SECTION
This article was submitted to Geriatric Medicine, a section of the journal Frontiers in Medicine

RECEIVED 24 February 2023
ACCEPTED 30 March 2023
PUBLISHED 20 April 2023

CITATION
Franz K, Deutschbein J, Riedlinger D, Pigorsch M, Schenk L, Lindner T, Möckel M, Norman K and Müller-Werdan U (2023) Malnutrition is associated with six-month mortality in older patients admitted to the emergency department with hip fracture. *Front. Med.* 10:1173528. doi: 10.3389/fmed.2023.1173528

Malnutrition is associated with six-month mortality in older patients admitted to the emergency department with hip fracture

Kristina Franz[1*†], Johannes Deutschbein[2†], Dorothee Riedlinger[3], Mareen Pigorsch[4], Liane Schenk[2], Tobias Lindner[3], Martin Möckel[3], Kristina Norman[1] and Ursula Müller-Werdan[1]

[1]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Geriatrics and Medical Gerontology, Geriatrics Research Group, Berlin, Germany, [2]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Medical Sociology and Rehabilitation Science, Berlin, Germany, [3]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Division of Emergency Medicine Campus Mitte and Virchow, Berlin, Germany, [4]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Biometry and Clinical Epidemiology, Berlin, Germany

Background: Hip fractures in older people are a common health problem often associated with malnutrition that might affect outcomes. Screening for malnutrition is not a routine examination in emergency departments (ED). This analysis of the EMAAge study, a prospective, multicenter cohort study, aimed to evaluate the nutritional status of older patients (≥ 50years) with hip fracture, factors associated with malnutrition risk, and the association between malnutrition and the six-months mortality.

Methods: Risk of malnutrition was evaluated using the Short Nutritional Assessment Questionnaire. Clinical data as well as data on depression and physical activity were determined. Mortality was captured for the first six months after the event. To assess factors associated with malnutrition risk we used a binary logistic regression. A Cox proportional hazards model was used to assess the association of malnutrition risk with six-month survival adjusted for other relevant risk factors.

Results: The sample consisted of *N*=318 hip fracture patients aged 50 to 98 (68% women). The prevalence of malnutrition risk was 25.3% (*n*=76) at the time of injury. There were no differences in triage categories or routine parameters measured in the ED that could point to malnutrition. 89% of the patients (*n*=267) survived for six months. The mean survival time was longer in those without malnutrition risk (171.9 (167.1–176.9) days vs. 153.1 (140.0–166.2) days). The Kaplan Meier curves and the unadjusted Cox regression (Hazard Ratio (HR) 3.08 (1.61–5.91)) showed differences between patients with and patients without malnutrition risk. In the adjusted Cox regression model, risk of death was associated with malnutrition risk (HR 2.61, 1.34–5.06), older age (70–76years: HR 2.5 (0.52–11.99); 77–82years: HR 4.25 (1.15–15.62); 83–99years: HR 3.82 (1.05–13.88)) and a high burden of comorbidities (Charlson Comorbidity Index ≥3: HR 5.4 (1.53–19.12)).

Conclusion: Risk of malnutrition was associated with higher mortality after hip fracture. ED parameters did not differentiate between patients with nutritional deficiencies and those without. Therefore, it is particularly important to pay

attention to malnutrition in EDs to detect patients at risk of adverse outcomes and to initiate early interventions.

KEYWORDS

hip fracture, malnutrition, acute medicine, emergency department, geriatrics, short nutritional assessment questionnaire, health services research

Introduction

Hip fractures are a common musculoskeletal injury in older people with a serious impact on the patient's daily life. Consequences are reduced mobility, loss of independence, impaired quality of life, and increased morbidity (1). Patients with hip fracture make up a significant proportion of the growing number of older and multimorbid adults with complex medical and psychosocial problems, posing a challenge to healthcare providers, including emergency departments (2). Malnutrition is a particularly pronounced health problem in old age and is associated with a higher risk of hip fracture in older adults (3).

Old adults are particularly prone to nutritional deficiencies due to their age-associated physiological changes and decreasing physiological reserves (4), thus they are of high risk to develop malnutrition (5). Causes of malnutrition in older adults are multifactorial and associated with physiological, pathological, social, and mental problems in old age (6). A systematic review of the literature based on longitudinal data revealed significant risk factors for malnutrition in older adults such as age, polypharmacy, impairments in physical function, cognitive impairment, dementia, loss of appetite and poor nutritional status, depressive symptoms as well as institutionalization (7). Patients with hip fracture have a considerably lower intake of calories and protein during the first 10 days of hospitalization than recommended (8). Furthermore, the increase in energy demand due to inflammation results in a catabolic status that persists for up to 4 months after the fracture (9, 10). Following weight loss, older adults are less able to regain body weight, particularly lean mass, compared to younger adults (11). This is attributed to a lack of adaptation in energy metabolism as well as reduced postprandial muscle protein synthesis (12, 13). Malnutrition has a significant negative impact on functional status and leads to reduced rehabilitation rates in hip fracture patients (14). The health economic importance of malnutrition in patients with hip fracture results from longer inpatient stays increased rehospitalization rates, and increased resource consumption and treatment costs (15, 16). This emphasizes the need for nutritional support in clinical (17) as well as in community and long-term care settings (18).

Few studies have addressed malnutrition in older patients in emergency departments (ED), and especially in Germany there is too little data on the prevalence of malnutrition in ED patients with hip fractures and its correlation with mortality. Previous studies have reported a prevalence of malnutrition in older ED patients up to 29% (19–22) which was associated with a higher mortality (20, 23).

The aim of this study was to determine the prevalence of self-reported signs of malnutrition in a cohort of older ED patients with hip fracture (≥ 50 years), to explore factors associated with risk of malnutrition, and to analyze the association between risk of malnutrition and six-month mortality.

Materials and methods

Study design and study population

Analyzes are based on data from the EMAAge study. EMAAge is a multicenter, prospective cohort study in the context of EMANet, a regional network of health services research in emergency and acute medicine in Berlin-Mitte, Germany (24, 25). The study included $N = 318$ patients aged 50 years and older ($M = 76.6$, SD = 11.0) with a hip fracture admitted to the EDs of six hospitals between June 2017 and June 2019 (24). Patients with dementia were included *via* their relatives or legal guardians. Participants or their proxies were interviewed by study nurses during the first days after initial treatment of the fracture by using a standardized questionnaire. Follow-up interviews were conducted *via* telephone or postal questionnaires six months later. Patient-reported data were complemented by clinical data on the ED and in-hospital care from hospital information systems. More details on the study design and data collection have been reported previously (26).

The study was approved by the ethics committee of Charité – Universitätsmedizin Berlin (EA1/362/16) and was registered in the German Clinical Trials Register (DRKS-ID: DRKS00014273). Written informed consent was obtained from all study participants. The authors confirm that all methods were carried out in accordance with good clinical practice.

Data and variables

The following clinical parameters were extracted from the hospital information systems using an electronic clinical report form: Manchester Triage System category (MTS, categorized in high acuity: MTS levels 1 to 3 and low acuity: MTS levels 4 and 5), vital signs (systolic blood pressure, heart rate, respiratory rate and numerical pain scale), Glasgow Coma Scale (GCS) (27), ICD diagnoses, type of surgery, ICU stay, complications (yes/no), and length of hospital stay (LOS). Documented comorbidities were used to calculate the Charlson Cormorbidity Index(CCI) (28). Polypharmacy was defined as five or more medications per day. Pre-fracture care dependency

Abbreviations: BMI, Body mass index; CCI, Charlson Cormorbidity Index; ED, Emergency department; GCS, Glasgow Coma Scale; GLIM, Global Leadership Initiative on Malnutrition; LOS, Length of hospital stay; MTS, Manchester Triage System; MNA-SF, Mini Nutritional Assessment Short-Form; PHQ-4, Patient Health Questionnaire 4; ONS, Oral nutritional supplements; SNAQ, Short Nutritional Assessment Questionnaire.

was determined according to the German long-term care insurance which classifies the level of dependency in patients' activities of daily living.

The following variables were constructed by using self-reported patient data: The standardized questionnaire the *Short Nutritional Assessment Questionnaire* (SNAQ) was used to screen for the risk of malnutrition (29). It includes the following questions: *"(1.) Did you lose weight unintentionally? More than 6 kg in the last 6 months (3 points) or More than 3 kg in the last month (2 points)? (2.) Did you experience a decreased appetite over the last month? (1 point) (3.) Did you use supplemental drinks or tube feeding over the last month? (1 point)."* The SNAQ instrument classifies patients into three groups: normal nutritional status (0–1 points), moderate risk of malnutrition (2 points) and severe risk of malnutrition (≥ 3 points).

Self-reported weight and height were used to calculate the body mass index (BMI, kg / m^2) by using the formula BMI = body weight / $height^2$. Physical activity before the fracture was assessed with the question: *"How often do you do things that are slightly or moderately strenuous?"* (≥ 1x / week, 1x / week, 1x -3x / month or never). Furthermore, participants were asked to report the frequency of previous falls (six months before the fracture). The Patient Health Questionnaire 4 (PHQ-4) was used to screen for symptoms of depression and anxiety (30). The PHQ-4 ranges from 0–12 points, increased PHQ-4 scores (cut-off ≥6) indicate depressive disorder. Cognitive impairment was assessed according to the 6-CIT screening instrument (31). Signs of moderate and severe impairment were interpreted as cognitive impairment. Patients participating *via* proxies were classified as cognitively impaired as well.

At six months, a follow-up interview was conducted. Additionally, mortality was determined through inquiries with registration offices.

Data analysis

Descriptive parameters are given as absolute and relative frequencies (*n*, %). For continuous variables, with means and standard deviations (SD) or median and interquartile range (IQR) are reported. Effect sizes of group differences are given as standardized mean differences.

To assess factors associated with the risk of malnutrition, binary logistic regression analysis was performed. Based on a systematic review on risk factors for malnutrition (7), we included age, gender, BMI, cognitive impairment (binary category), PHQ-4 depression (binary category), the burden of comorbidities (CCI), and reduced physical activity in the binary logistic regression model as independent variables. Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

The influence of malnutrition risk on the risk of mortality within the first six months after hip fracture was determined by using a Cox proportional hazards model calculating hazard ratios (HR) with 95% CI. The model was adjusted for age, gender and CCI score. In addition, Kaplan–Meier survival curves were created for patients with and without the risk of malnutrition. Survival time was calculated as the number of days from initial hospital stay to six-months follow up.

For all analyses, risk of malnutrition was used as a binary variable combining moderate and severe risk. For the multiple models, age was categorized into four groups: 50–69 years; 70–76 years; 77–82 years and 83–99 years.

To handle missing values within the regression models, we used multiple imputation (32). The imputation models consisted of the variables in the corresponding analysis model. In the imputation model for the logistic regression, we added further variables from the EMAAge study with the potential to improve the estimation of imputed data: we used items from the health-related quality of life questionnaire *EQ-5D-5L* (mobility, usual activities and anxiety (33), educational status, dependency in ADLs), the presence of a wheelchair or walker, and the usage of insoles due to urinary incontinence. For the imputation of the malnutrition variable, we first imputed the three SNAQ-variables and did a passive imputation when only single malnutrition items were missing (32). Sensitivity analyses were done for different modifications of the imputation models. For both regression models we used the R package "mice for multiple imputation" with $m = 20$ imputations (34).

The analyses of this paper are explorative and are not designed to draw confirmatory conclusions, therefore we did not correct for multiple testing. Descriptive statistics were performed using the statistics program IBM SPSS statistic (version 27). The models were done using *R* version 4.1.1.

Results

Characteristics of the study population

The characteristics of the study population are shown in Table 1. The analysis included $N = 318$ hip fracture patients aged 50 to 98 years ($M = 76.6$, SD = 11.0), 68% were women. For $n = 300$ participants, complete information on their risk of malnutrition could be obtained according to the SNAQ instrument. An involuntary weight loss of more than 6 kg within six months or more than 3 kg in the previous month was found in 18% ($n = 54$) and 6.7% ($n = 20$) of the patients, respectively. A quarter of the patients reported a loss of appetite in the previous month. Oral nutritional supplements were used by 6.3% ($n = 19$) of the patients. According to the SNAQ score, 22.3% ($n = 67$) of the study cohort showed a severe risk of malnutrition, followed by 3% ($n = 9$) with a moderate malnutrition risk. Compared to well-nourished patients, patients with risk of malnourishment were older and had a lower BMI (Table 1): 7.1% ($n = 19$) showed a BMI below 20 kg / m^2 (≤ 70 years) and 20.8% ($n = 56$) below 22 kg / m^2 (> 70 years).

At ED admission, almost nine in 10 patients had a high acuity (1–3) in the Manchester Triage System (MTS) rating. There was no difference between patients with and without malnutrition. The vital signs at admission, namely systolic blood pressure, pain score, and GCS did not differ between patients with and without malnutrition risk. During their hospital stay, patients with malnutrition risk experienced more often complications (69.9% vs. 53.2%) and were admitted to the ICU more frequently (43.4% vs. 31.8%). Patients at risk received a higher number of medications per day (6.7 ± 4.1 vs. 5.0 ± 4.1) and were more frequently cognitively impaired (54.1% vs. 30.2%). Participants at risk of malnutrition reported more often previous falls in the last six months (36.8% vs. 28.1%). Symptoms of depression were reported by 23.1% of the patients at risk of malnutrition compared to 10.6% in the normal group. Patients at risk of malnutrition were more frequently dependent on long-term care at admission (52.1% vs. 34.2%) and had a lower physical activity level (no activity: 46.3% vs. 19.9%). During the initial hospital stay, 1.7% of

TABLE 1 Characteristics of ED patients with hip fracture screened for malnutrition.

Characteristics	All (*n*=300)	Risk of malnutrition (*n*=76)	No risk of malnutrition (*n*=224)	Standardized mean difference between groups
Gender (male) *n* (%)	96 (32.0)	22 (28.9)	74 (33.0)	0.097
Age (years) mean (SD)	76.6 (11.0)	79.2 (10.5)	75.7 (11.1)	0.306
Age categories n (%)				
50–69 years	84 (28.0)	13 (17.1)	71 (31.7)	0.376
70–76 years	37 (12.3)	10 (13.2)	27 (12.1)	
77–82 years	83 (27.7)	20 (26.3)	63 (28.1)	
83–99 years	96 (32.0)	33 (43.4)	63 (28.1)	
MTS Triage level[a] *n* (%)				0.312
High acuity (MTS level 1–3)	212 (86.9)	62 (92.5)	150 (84.7)	
Low acuity (MTS level 4 and 5)	32 (13.1)	5 (7.5)	27 (15.3)	
Type of fracture *n* (%)				0.364
Femoral neck fractures (ICD-10 S72.0)	137 (45.7)	26 (34.2)	111 (49.6)	
Pertrochanteric fractures (ICD-10 S72.1)	138 (46.0)	44 (57.9)	94 (42.0)	
Subtrochanteric fractures (ICD-10 S72.2)	20 (6.7)	4 (5.3)	16 (7.1)	
Periprosthetic hip fractures	5 (1.7)	2 (2.6)	3 (1.3)	
BMI (kg/m^2)[b] mean (SD)	24.1 ± 13.9	22.5 ± 4.6	25.1 ± 5.5	0.468
Dimensions of Malnutrition (SNAQ)				
Involuntary weight loss *n* (%) > 6 kg within six months	54 (18.0)	54 (71.1)	–	
> 3 kg in the last month	20 (6.7)	20 (26.3)		
Loss of appetite *n* (%)	75 (25)	44 (57.9)	31 (13.8)	1.034
Intake of ONS in last three month (yes) *n* (%)	19 (6.3)	14 (18.4)	5 (2.2)	0.552
Vital signs at ED admission median (IQR)				
GCS (points)[c]	15 (15;15)	15 (15;15)	15 (15;15)	0.165
Systolic blood pressure (mmHg)[d]	150 (131; 161)	142 (120;157)	150 (134;163)	0.461
Heart rate (Bpm)[e]	81 (70; 90)	81 (65;89)	82 (71;90)	0.099
Respiratory rate (Breaths/min)[f]	15 (14; 17)	16 (14;17)	15 (14;17)	0.020
Numerical pain scale (points)[g]	5 (4; 6)	5 (4;7)	5 (4;6)	0.217
Polypharmacy (yes) *n* (%)	161 (53.7)	45 (59.2)	116 (51.8)	0.161
Long-term care dependency at admission (yes)[h] *n* (%)	113 (38.7)	38 (52.1)	75 (34.2)	0.366
Admitted to ICU (yes) *n* (%)	104 (34.8)	33 (43.4)	71 (31.8)	0.229
Complications (yes) *n* (%)	167 (57.4)	51 (69.9)	116 (53.2)	0.342
LOS (length of stay in days)[i] mean (SD)	11.7 (10.0)	13.2 (13.2)	11.0 (8.3)	0.198
Burden of comorbidity (CCI) n (%)				
0	87 (29.0)	15 (19.7)	72 (32.1)	0.306
1–2	118 (39.3)	32 (42.1)	86 (38.4)	
3–4	64 (21.3)	19 (25.0)	45 (20.1)	
>5	31 (10.3)	10 (13.2)	21 (9.4)	
Cognitive impairment[j] n (%)				
No cognitive impairment	189 (63.9)	34 (45.9)	155 (69.8)	0.483
Moderate and severe cognitive impairment	107 (36.1)	40 (54.1)	67 (30.2)	
Depression (PHQ-4 category)[k] n (%)				
Depression (≥ 6 points)	32 (13.3)	12 (23.1)	20 (10.6)	0.327
No depression (< 6 points)	208 (86.7)	40 (76.9)	168 (89.4)	
Physical activity level [l] n (%)				
≥ 1x / week	155 (62.0)	20 (37.0)	135 (68.9)	0.706
1x / week	21 (8.4)	5 (9.3)	16 (8.2)	
1x - 3x / month	10 (4.0)	4 (7.4)	6 (3.1)	
Never	64 (25.6)	25 (46.3)	39 (19.9)	
Number of falls in six months prior to hip fracture[m] n (%)				
1	42 (46.2)	11 (39.3)	31 (49.2)	0.294
2–3	31 (34.1)	10 (35.7)	21 (33.3)	
≥ 3	18 (19.8)	7 (25.0)	11 (17.5)	
Mortality n (%)				
Initial hospital stay	5 (1.7)	1 (1.3)	4 (1.8)	0.040
Six-month follow up	33 (11.2)	18 (24.0)	15 (6.8)	0.431

BMI, Body Mass Index; ONS: oral nutritional supplements. ED, Emergency Department. GCS, Glasgow Coma Scale. MTS, Manchester Triage System. ICU, Intensive care unit. CCI: Charlson Comorbidity Index. Sample size of the cohort regarding each parameter: [a]*n* = 243; [b]*n* = 269; [c]*n* = 257; [d]*n* = 245; [e]*n* = 229; [f]*n* = 179; [g]*n* = 166; [h]*n* = 292; [i]*n* = 291; [j]*n* = 294; [k]*n* = 240; [l]*n* = 250; [m]*n* = 286. [k,l]: all proxy cases are missing by design, because these questions could only be answered by the participants themselves.

TABLE 2 Binary logistic regression model for malnutrition among ED patients with hip fracture.

	OR	Lower 95% CI	Upper 95% CI	value of *p*
Intercept	5,79	0,78	42,80	0,087
Age (70–76 y)[a]	1,99	0,74	5,40	0,175
Age (77–82 y)	1,08	0,45	2,57	0,868
Age (83–99 y)	1,78	0,77	4,11	0,179
Gender (men)[b]	1,02	0,53	1,96	0,946
BMI (kg/m²)	0,89	0,83	0,96	0,001
Cognitive impairment (moderate and severe)[c]	1,34	0,67	2,67	0,409
CCI (= 1)[d]	0,98	0,40	2,42	0,963
CCI (= 2)	1,51	0,59	3,86	0,387
CCI (≥ 3)	1,39	0,61	3,18	0,440
Reduced physical activity (1x/months or less)[e]	0,28	0,14	0,58	0,001
Depression (PHQ-4 ≥ 6)[f]	1,20	0,49	2,97	0,695

Reference categories: [a] 50–69 y, [b] women, [c] no cognitive impairment, [d] CCI = 0, [e] physical activity 1x / week or more, [f] PHQ-4 score < 6 (no depressive symptoms).
ED, Emergency Department. CI, Confidence Interval. OR, Odds Ratio. BMI, body mass index. CCI, Charlson Comorbidity Index. PHQ-4, Patient Health Questionnaire-4.

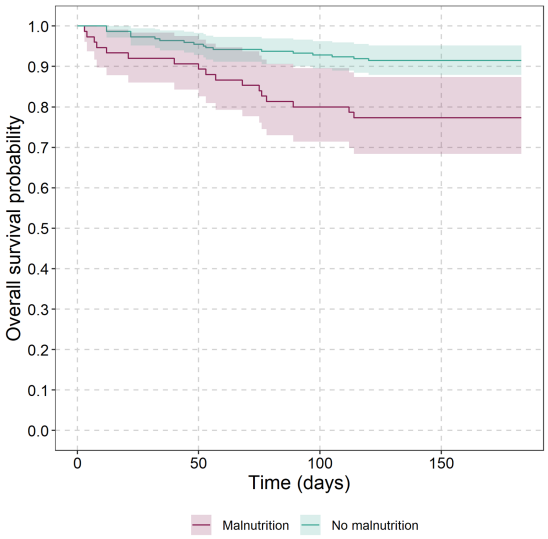


FIGURE 1
Kaplan-Meier curves for older ED patients with and without malnutrition from the beginning of the initial hospital stay after ED until the follow up at six months without adjustment. Number of patients at risk and patients who died at selected time points for malnutrition: 0 days (75 vs. 0), 50 days (68 vs. 8), 100 days (60 vs. 15) and 150 days (58 vs. 17); no malnutrition: 0 days (223 vs. 0), 50 days (213 vs. 10), 100 days (207 vs. 16) and 150 days (204 vs. 19).

all participants died, overall mortality after six months was 11.2% (Table 1).

Parameters associated with risk of malnutrition in hip fracture patients and six-month mortality

Table 2 shows the results of the binary logistic regression for risk of malnutrition in ED patients with hip fracture. Higher BMI was associated with lower risk of malnutrition in ED patients (OR: 0.89, 0.83–0.96). There was a negative association between reduced physical activities and risk of malnutrition (OR: 0.28, 0.14–0.58). Risk of mortality was higher in patients with malnutrition risk (unadjusted Cox regression HR: 3.08, 1.61–5.91). Figure 1 shows the Kaplan–Meier curves indicating differences between patients with and without malnutrition risk during the first six months after hip fracture. The mean survival time was longer in patients without malnutrition risk (171.9 days; 95% CI: 167.1–176.9 days vs. 153.1 days; 95% CI: 140.0–166.2 days). In Table 3, the results of the Cox regression model for mortality in the first six months after hip fracture is shown: malnutrition (HR: 2.61, 1.34–5.06), older age (70–76 years: HR: 2.5, 0.52–11.99; 77–82 years: HR: 4.25, 1.15–15.62; 83–99 years: HR: 3.82, 1.05–13.88) and a higher CCI score ≥ 3 (HR: 5.4, 1.53–19.12) were associated with higher risk of mortality.

Discussion

In this study of ED patients with hip fracture over 50 years of age, the risk of malnutrition was observed in every fourth patient. Malnutrition was associated with a higher risk of mortality during the first six months after adjusting for age, gender, and the burden of comorbidities. Several studies have shown an association of the mortality risk in patients with hip fractures with various patient and health system factors. However, few studies have investigated the underlying mechanisms that influence mortality in patients with hip fracture (35). A systematic review by Xu and colleagues identified the following predictors for mortality in patients with hip fracture: medical factors (presence of concomitant diseases, sarcopenia), surgical factors (including delay of surgery, e.g., > 48 h), type of fracture, socioeconomic factors (age, gender and ethnicity), and system factors (centers with lower case volume) (35). Malnutrition in old patients with hip fracture has at least three different dimensions: Malnutrition is a risk factor for hip fracture (36), it is associated with reduced functional capacity and worse recovery after hospital discharge (37), and, as shown in our study, it is associated with a higher mortality rate.

TABLE 3 Cox proportional hazards model of six-month mortality among patients with hip fracture.

	HR	Lower 95% CI	Upper 95% CI	value of *p*
Unadjusted Model				
Malnutrition[a]	3.08	1.61	5.91	0.001
Adjusted Model				
Malnutrition[a]	2.61	1.34	5.06	0.006
Age (70–76 y)[b]	2.50	0.52	11.99	0.242
Age (77–82 y)	4.25	1.15	15.62	0.031
Age (83–99 y)	3.82	1.05	13.88	0.042
Gender (men)[c]	0.93	0.46	1.91	0.846
CCI (= 1)[d]	2.48	0.62	9.95	0.193
CCI (= 2)	1.91	0.42	8.56	0.388
CCI (≥ 3)	5.40	1.53	19.12	0.011

Reference categories: [a] normal nutritional status, [b] 50–69 y, [c] women, [d] CCI = 0.
ED, Emergency Department. CI, Confidence Interval. HR, Hazard Ratio. CCI, Charlson Comorbidity Index.

The 25.3% prevalence of malnutrition risk is within the range of prevalence rates found in studies with similar patient populations and clinical settings (4). Previous studies reported that the prevalence of malnourished patients with hip fracture has increased and ranges from about 7 to 26% (1). Compared to our study, the recently published Irish OPTI-MEND study showed in secondary analyses a lower prevalence of malnutrition (7.6%) in older ED patients, using the validated Mini Nutritional Assessment Short-Form (MNA-SF) screening tool. However, they found a higher number of ED patients with ED patients with malnutrition had lower MTS triage levels and had a lower risk of adverse health outcomes (38). This may partly be explained by our cohort, since hip fractures are associated with malnutrition, and these patients are typically more vulnerable or frail compared to older ED patients overall. The OPTI-MEND data revealed that at 30 days after ED, malnourished patients had a higher readmission rate, increased functional limitations and lower quality of life (38).

Differences in prevalence of malnutrition in studies can also be explained by the usage of different tools for the assessment of malnutrition. A recent secondary data analysis including 11 European and one New Zealand study with over 5,000 older adults showed higher malnutrition rates in adults >80 years of age, in women, and in people with one or more morbidities, with varying prevalence rates depending on geographic location and the tools used (39). Despite numerous publications and international discussions, there was no generally accepted definition of malnutrition until 2019, the time our study was conducted. Today, the concept of the Global Leadership Initiative on Malnutrition (GLIM) defines diagnostic criteria of malnutrition in all clinical settings, initiated by four world-leading clinical nutrition societies: the American Society for Parenteral and Enteral Nutrition, the European Society of Clinical Nutrition and Metabolism, Federación Latinoamericana de Terapia Nutritional, Nutrición Clínica y Metabolismo, and The Parenteral and Enteral Nutrition Society of Asia (40). The GLIM concept includes phenotypic parameters such as weight loss (> 5% in the last six months or > 10% beyond six months), low BMI (< 70 years: < 20 kg/m^2; > 70 years: < 22 kg/m^2), and reduced muscle mass as well as etiologic parameters such as reduced food intake, food reduction for more than 2 weeks, or any chronic gastrointestinal diseases and inflammation (40). In our study, one of the phenotypic criteria (involuntary weight loss) and one of the etiologic criteria (reduced food intake) were considered through the validated SNAQ instrument. Our study showed no difference between patients with and without malnutrition when assessing important ED routine parameters such as vital signs and triage levels, so malnourished patients may remain unnoticed without targeted screening.

Causes of malnutrition are diseases, aging processes, and lifestyle factors; the interaction between these factors is known. Patients screened for the risk of malnutrition in our study were older, had a reduced BMI, a higher number of medications per day, and more often experienced complications during their hospital stay. These malnourished patients were also more likely to be reduced in their physical activity status before hip fracture. Furthermore, patients with malnutrition risk were more likely to have a higher depression score. The regression analysis revealed lower BMI and self-reported lower physical activity as relevant factors associated with malnutrition risk in older ED patients with hip fracture. However, malnutrition in obese patients with higher BMIs is rarely recognized or completely missed since their fat mass masks the underlying muscle breakdown, and weight loss due to malnutrition is not detected (41). Although malnutrition was predominantly associated with a low BMI in our study, 12.1% of the cohort were obese (BMI ≥ 30.0 kg/m^2). A higher BMI was recently found to be a nutritional risk factor for malnutrition in older adults (42) and the geriatric syndrome sarcopenic obesity is equally important in this context (43).

Data conflicting with our results have been published concerning comorbidity risk factors for negative nutritional outcomes (7), whereas in our study these parameters were not associated with malnutrition risk. We suspect that these differences to previous studies can be explained by the heterogeneity of older adults and their health conditions (44). Identifying the determinants of malnutrition is critical to effectively tackling the issue, but the complex etiology of malnutrition is still not completely understood. However, predicting nutritional deficiencies in older ED patients with hip fracture could reduce the negative impact on the patient's functional status and quality of life (1) as well as reduce the health costs and rate of adverse events (45).

The study has clear strengths. First, as a health services research study, it aimed to be inclusive and patient-centered: we tried to include all patients affected by a hip fracture including cognitively impaired

patients that were unable to participate in the interview themselves as well as hard to reach patients such as people from community shelters, nursing homes, and patients with a migration background. Second, the use of the short SNAQ questionnaire can be seen as another strength. With its three question units it can elicit malnutrition in times of high clinical workload through a quick and concrete evaluation. The study has a few limitations. The integrative real-life approach leads to a comparatively heterogeneous sample. Our results cannot be generalized to other population groups since the data come from an inner-city neighborhood of a major German city with specific living and healthcare conditions. Furthermore, body weight and height were self-reported resulting in a potential recall bias. The anthropometric data from our EMAAge cohort cannot easily be compared with other studies using medical measurement instruments.

Conclusion

Malnutrition is an important risk factor for death after hip fracture. However, to date, a systematic screening for malnutrition is not performed in all patients with hip fractures or other geriatric indications. Identification of particularly vulnerable, older, malnourished patients in the ED or the subsequent in-patient stay could prevent negative outcomes and lead to the initiation of a patient-centered care approach including nutritional therapy. A recently implemented national guideline for the treatment of hip fracture patients defines new standards of care (46). This includes a systematic screening for geriatric syndromes and the involvement of geriatricians which has been recommended and evaluated internationally (47). The potential of this approach to meet the risks of malnutrition needs to be analyzed in future studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation for scientific reasons.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of Charité –Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM is initiator of the EMANet research network, principal investigator, and speaker. LS is a co-speaker of EMANet. LS and JD designed the EMAAge study. JD processed the data and performed basic analyses. KF designed the research question and drafted the first version of the manuscript. KF, JD, and MP created the statistical plan. MP did the multiple imputations and the corresponding analyses. KF and JD gave the interpretation of the data. DR, MM, TL, KN, and UM-W gave critical advice. All authors contributed to the article and approved the submitted version.

Funding

The EMANet project is supported by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung -BMBF, grant number: 01GY1604). The sponsor is not involved in the design and conduct of the study, data collection, analysis, and interpretation of data or in writing this manuscript. We acknowledge financial support from the Open Access Publication Fund of Charité – Universitätsmedizin Berlin and the German Research Foundation (DFG).

Acknowledgments

The authors would like to thank the participating hospitals in the EMANet research network, namely Charité –Universitätsmedizin Berlin (Campus Charité Mitte and Campus Virchow-Klinikum), St. Hedwig Hospital (Alexianer St. Hedwig-Krankenhaus Berlin), Elisabeth Hospital (Evangelische Elisabeth Klinik der Paul-Gerhardt Diakonie), Franziskus Hospital (Franziskus-Krankenhaus Berlin), German Armed Forces Hospital Berlin (Bundeswehr Krankenhaus Berlin), German Red Cross Hospital Berlin-Mitte (DRK Kliniken Berlin-Mitte), and the Berlin Jewish Hospital (Jüdisches Krankenhaus Berlin). The authors would like to thank all study participants as well as all EMANet researchers and study personnel responsible for study planning, patient recruitment, and data management. Furthermore, we would like to acknowledge Bridget Schäfer for language proofreading to improve the clarity of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Inoue T, Maeda K, Nagano A, Shimizu A, Ueshima J, Murotani K, et al. Undernutrition, sarcopenia, and frailty in fragility hip fracture: advanced strategies for improving clinical outcomes. *Nutrients*. (2020) 12:3743. doi: 10.3390/nu12123743

2. Dufour I, Chouinard MC, Dubuc N, Beaudin J, Lafontaine S, Hudon C. Factors associated with frequent use of emergency-department services in a geriatric population: a systematic review. *BMC Geriatr*. (2019) 19:185. doi: 10.1186/s12877-019-1197-9

3. Wiklund R, Toots A, Conradsson M, Olofsson B, Holmberg H, Rosendahl E, et al. Risk factors for hip fracture in very old people: a population-based study. *Osteoporos Int*. (2016) 27:923–31. doi: 10.1007/s00198-015-3390-9

4. Norman K, Hass U, Pirlich M. Malnutrition in older adults-recent advances and remaining challenges. *Nutrients*. (2021) 13:2764. doi: 10.3390/nu13082764

5. Moriguti JC, Moriguti EK, Ferriolli E, de Castilho CJ, Iucif N Jr, Marchini JS. Involuntary weight loss in elderly individuals: assessment and treatment. *Sao Paulo Med J*. (2001) 119:72–7. doi: 10.1590/S1516-31802001000200007

6. Evans C. Malnutrition in the elderly: a multifactorial failure to thrive. *Perm J*. (2005) 9:38–41. doi: 10.7812/TPP/05-056

7. Favaro-Moreira NC, Krausch-Hofmann S, Matthys C, Vereecken C, Vanhauwaert E, Declercq A, et al. Risk factors for malnutrition in older adults: a systematic review of the literature based on longitudinal data. *Adv Nutr*. (2016) 7:507–22. doi: 10.3945/an.115.011254

8. Eneroth M, Olsson UB, Thorngren KG. Insufficient fluid and energy intake in hospitalised patients with hip fracture. A prospective randomised study of 80 patients. *Clin Nutr*. (2005) 24:297–303. doi: 10.1016/j.clnu.2004.12.003

9. Anbar R, Beloosesky Y, Cohen J, Madar Z, Weiss A, Theilla M, et al. Tight calorie control in geriatric patients following hip fracture decreases complications: a randomized, controlled study. *Clin Nutr*. (2014) 33:23–8. doi: 10.1016/j.clnu.2013.03.005

10. Koren-Hakim T, Weiss A, Hershkovitz A, Otzrateni I, Grosman B, Frishman S, et al. The relationship between nutritional status of hip fracture operated elderly patients and their functioning, comorbidity and outcome. *Clin Nutr*. (2012) 31:917–21. doi: 10.1016/j.clnu.2012.03.010

11. Moriguti JC, Das SK, Saltzman E, Corrales A, McCrory MA, Greenberg AS, et al. Effects of a 6-week hypocaloric diet on changes in body composition, hunger, and subsequent weight regain in healthy young and older adults. *J Gerontol A Biol Sci Med Sci*. (2000) 55:B580–7. doi: 10.1093/gerona/55.12.B580

12. Roberts SB, Rosenberg I. Nutrition and aging: changes in the regulation of energy metabolism with aging. *Physiol Rev*. (2006) 86:651–67. doi: 10.1152/physrev.00019.2005

13. Grevendonk L, Connell NJ, McCrum C, Fealy CE, Bilet L, Bruls YMH, et al. Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. *Nat Commun*. (2021) 12:4773. doi: 10.1038/s41467-021-24956-2

14. Wong AM, Xu BY, Low LL, Allen JC Jr, Low SG. Impact of malnutrition in surgically repaired hip fracture patients admitted for rehabilitation in a community hospital: a cohort prospective study. *Clin Nutr ESPEN*. (2021) 44:188–93. doi: 10.1016/j.clnesp.2021.06.024

15. Braunschweig C, Gomez S, Sheean PM. Impact of declines in nutritional status on outcomes in adult patients hospitalized for more than 7 days. *J Am Diet Assoc*. (2000) 100:1316–22; quiz 23-4–22. doi: 10.1016/S0002-8223(00)00373-4

16. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr*. (2003) 22:235–9. doi: 10.1016/S0261-5614(02)00215-7

17. Elia M, Normand C, Norman K, Laviano A. A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in the hospital setting. *Clin Nutr*. (2016) 35:370–80. doi: 10.1016/j.clnu.2015.05.010

18. Elia M, Normand C, Laviano A, Norman K. A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in community and care home settings. *Clin Nutr*. (2016) 35:125–37. doi: 10.1016/j.clnu.2015.07.012

19. Vivanti A, Isenring E, Baumann S, Powrie D, O'Neill M, Clark D, et al. Emergency department malnutrition screening and support model improves outcomes in a pilot randomised controlled trial. *Emerg Med J*. (2015) 32:180–3. doi: 10.1136/emermed-2013-202965

20. Gentile S, Lacroix O, Durand AC, Cretel E, Alazia M, Sambuc R, et al. Malnutrition: a highly predictive risk factor of short-term mortality in elderly presenting to the emergency department. *J Nutr Health Aging*. (2013) 17:290–4. doi: 10.1007/s12603-012-0398-0

21. Pereira GF, Bulik CM, Weaver MA, Holland WC, Platts-Mills TF. Malnutrition among cognitively intact, noncritically ill older adults in the emergency department. *Ann Emerg Med*. (2015) 65:85–91. doi: 10.1016/j.annemergmed.2014.07.018

22. Burks CE, Jones CW, Braz VA, Swor RA, Richmond NL, Hwang KS, et al. Risk factors for malnutrition among older adults in the emergency department: a multicenter study. *J Am Geriatr Soc*. (2017) 65:1741–7. doi: 10.1111/jgs.14862

23. Drame M, Jovenin N, Novella JL, Lang PO, Somme D, Laniece I, et al. Predicting early mortality among elderly patients hospitalised in medical wards via emergency department: the SAFES cohort study. *J Nutr Health Aging*. (2008) 12:599–604. doi: 10.1007/BF02983207

24. Schmiedhofer M, Inhoff T, Krobisch V, Schenk L, Rose M, Holzinger F, et al. EMANet: a regional network for health services research in emergency and acute medicine. *Z Evid Fortbild Qual Gesundhwes*. (2018) 135-136:81–8:81-8. doi: 10.1016/j.zefq.2018.07.009

25. Schneider A, Riedlinger D, Pigorsch M, Holzinger F, Deutschbein J, Keil T, et al. Self-reported health and life satisfaction in older emergency department patients: sociodemographic, disease-related and care-specific associated factors. *BMC Public Health*. (2021) 21:1440. doi: 10.1186/s12889-021-11439-8

26. Deutschbein J, Lindner T, Möckel M, Pigorsch M, Gille G, Stöckle U, et al. Quality of life and associated factors after hip fracture. Results from a six-months prospective cohort study. *Peerj*. (2023) 11:e14671. doi: 10.7717/peerj.14671

27. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. (1974) 2:81–4. doi: 10.1016/S0140-6736(74)91639-0

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8

29. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst–de van der Schueren MAE. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). *Clin Nutr*. (2005) 24:75–82. doi: 10.1016/j.clnu.2004.07.015

30. Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics*. (2009) 50:613–21. doi: 10.1176/appi.psy.50.6.613

31. Connon P, Larner AJ. Six-item cognitive impairment test (6CIT): diagnostic test accuracy study in primary care referrals. *Int J Geriatr Psychiatry*. (2017) 32:583–4. doi: 10.1002/gps.4692

32. van Buuren S. *Flexible Imputation of Missing Data. 2nd* ed. Boca Raton, FL: CRC Press (2018).

33. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. (2011) 20:1727–36. doi: 10.1007/s11136-011-9903-x

34. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. (2011) 45:1–67. doi: 10.18637/jss.v045.i03

35. Xu BY, Yan S, Low LL, Vasanwala FF, Low SG. Predictors of poor functional outcomes and mortality in patients with hip fracture: a systematic review. *BMC Musculoskelet Disord*. (2019) 20:568. doi: 10.1186/s12891-019-2950-0

36. Goisser S, Schrader E, Singler K, Bertsch T, Gefeller O, Biber R, et al. Malnutrition according to mini nutritional assessment is associated with severe functional impairment in geriatric patients before and up to 6 months after hip fracture. *J Am Med Dir Assoc*. (2015) 16:661–7. doi: 10.1016/j.jamda.2015.03.002

37. Nuotio M, Tuominen P, Luukkaala T. Association of nutritional status as measured by the mini-nutritional assessment short form with changes in mobility, institutionalization and death after hip fracture. *Eur J Clin Nutr*. (2016) 70:393–8. doi: 10.1038/ejcn.2015.174

38. Griffin A, O'Neill A, O'Connor M, Ryan D, Tierney A, Galvin R. The prevalence of malnutrition and impact on patient outcomes among older adults presenting at an Irish emergency department: a secondary analysis of the OPTI-MEND trial. *BMC Geriatr*. (2020) 20:455. doi: 10.1186/s12877-020-01852-w

39. Wolters M, Volkert D, Streicher M, Kiesswetter E, Torbahn G, O'Connor EM, et al. Prevalence of malnutrition using harmonized definitions in older adults from different settings -a MaNuEL study. *Clin Nutr*. (2019) 38:2389–98. doi: 10.1016/j.clnu.2018.10.020

40. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition -a consensus report from the global clinical nutrition community. *Clin Nutr*. (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

41. Sharma K, Mogensen KM, Robinson MK. Under-recognizing malnutrition in hospitalized obese populations: the real paradox. *Curr Nutr Rep*. (2019) 8:317–22. doi: 10.1007/s13668-019-00288-y

42. Katsas K, Mamalaki E, Kontogianni MD, Anastasiou CA, Kosmidis MH, Varlamis I, et al. Malnutrition in older adults: correlations with social, diet-related, and neuropsychological factors. *Nutrition*. (2020) 71:110640. doi: 10.1016/j.nut.2019.110640

43. von Berens A, Obling SR, Nydahl M, Koochek A, Lissner L, Skoog I, et al. Sarcopenic obesity and associations with mortality in older women and men -a prospective observational study. *BMC Geriatr*. (2020) 20:199. doi: 10.1186/s12877-020-01578-9

44. Lowsky DJ, Olshansky SJ, Bhattacharya J, Goldman DP. Heterogeneity in healthy aging. *J Gerontol A Biol Sci Med Sci*. (2014) 69:640–9. doi: 10.1093/gerona/glt162

45. Haentjens P, Lamraski G, Boonen S. Costs and consequences of hip fracture occurrence in old age: an economic perspective. *Disabil Rehabil*. (2005) 27:1129–41. doi: 10.1080/09638280500055529

46. G-BA. Richtlinie zur Versorgung der hüftgelenknahen Femurfraktur/QSFFx-RL [Guideline for the treatment of hip fractures]. (2019). Available at: https://www.g-ba.de/downloads/62-492-3035/QSFFx-RL_2022-12-07_iK-2023-01-01.pdf (Accessed April 6, 2020).

47. Ranhoff AH, Saltvedt I, Frihagen F, Raeder J, Maini S, Sletvold O. Interdisciplinary care of hip fractures.: Orthogeriatric models, alternative models, interdisciplinary teamwork. *Best Pract Res Clin Rheumatol*. (2019) 33:205–26. doi: 10.1016/j.berh.2019.03.015

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 11 May 2023
DOI 10.3389/fmed.2023.1165428

OPEN ACCESS

EDITED BY
Roberta Zupo,
University of Bari Aldo Moro, Italy

REVIEWED BY
Takahiro Yajima,
Matsunami General Hospital, Japan
Tommaso Martino,
Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia, Italy

*CORRESPONDENCE
Dan Liao
✉ danliaomych@126.com

†These authors have contributed equally to this work

RECEIVED 14 February 2023
ACCEPTED 12 April 2023
PUBLISHED 11 May 2023

CITATION
Liao D, Deng Y, Li X, Huang J, Li J, Pu M, Zhang F and Wang L (2023) The prognostic effects of the geriatric nutritional risk index on elderly acute kidney injury patients in intensive care units. *Front. Med.* 10:1165428. doi: 10.3389/fmed.2023.1165428

The prognostic effects of the geriatric nutritional risk index on elderly acute kidney injury patients in intensive care units

Dan Liao[1*†], Yonghua Deng[2†], Xinchun Li[3], Ju Huang[4], Jiayue Li[5], Ming Pu[5], Fenglian Zhang[1] and Lijun Wang[1]

[1]Department of Nephrology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China, [2]Department of Nephrology, Chengdu Second People's Hospital, Chengdu, China, [3]North Sichuan Medical College, Nanchong, China, [4]Department of Nephrology, Mianyang People's Hospital, Mianyang, China, [5]Chengdu Medical College, Chengdu, China

Introduction: The geriatric nutritional risk index (GNRI), a nutritional screening tool specifically for the aging population, has been proven to be associated with worse outcomes in chronic kidney disease patients, especially in the hemodialysis population. However, the predictive validity of GNRI in critically ill elderly patients with acute kidney injury (AKI) is yet to be determined. This analysis sought to examine the prognostic effects of GNRI on elderly AKI patients in intensive care units (ICUs).

Methods: We collected elderly AKI patient-relevant data from the Medical Information Mart for Intensive Care III database. AKI was diagnosed and staged according to the "Kidney Disease Improving Global Outcomes" criteria. In the study, 1-year mortality was considered the primary outcome, whereas in-hospital, ICU, 28-day and 90-day mortality, and prolonged length of stay in ICU and hospital were selected as the secondary outcomes.

Results: In all, 3,501 elderly patients with AKI were selected for this study, with a 1-year mortality rate of 36.4%. We classified the study population into low (≤98) and high (>98) GNRI groups based on the best cutoff value. The incidence of endpoints was remarkably lower in patients with elevated GNRI ($p < 0.001$). When stratified by the AKI stage, patients with high GNRI at AKI stages 1, 2, and 3 had markedly lower 1-year mortality than those with low GNRI (all $p < 0.05$). The multivariable regression analysis identified the independent prognostic ability of GNRI on the research outcomes (all $p < 0.05$). Restricted cubic spline exhibited a linear correlation between GNRI and 1-year death (p for non-linearity = 0.434). The prognostic implication of GNRI on 1-year mortality was still significant in patients with the most subgroups.

Conclusion: In critically ill elderly patients with AKI, elevated GNRI upon admission was strongly correlated with a lower risk of unfavorable outcomes.

KEYWORDS

geriatric nutritional risk index, acute kidney injury, intensive care unit, elderly, prognosis

1. Introduction

Acute kidney injury (AKI) is a frequent complication in intensive care units (ICUs) and contributes to important nutritional problems (1, 2). A previous study has reported that the caloric intake of severe AKI patients receiving renal replacement therapy is very low (3). The European Society for Parenteral and Enteral Nutrition (ESPEN) guideline strongly recommends providing nutritional support for hospitalized AKI patients (4), and some medical nutrients may facilitate the recovery of renal function in AKI patients (5). However, malnutrition remains under-recognized and underdiagnosed, particularly in older patients with frailty. It has been reported that ∼ 9% of inpatients are diagnosed with malnutrition, and in fact, the incidence of malnutrition among inpatients is ∼ 40% (6–8). Thus, an accurate assessment of the nutritional status is pivotal to improving malnutrition.

The geriatric nutritional risk index (GNRI), a simple and useful nutritional screening tool specifically for the aging population, has been widely used in multiple clinical scenarios, including patients with cancer, heart failure, cardio-cerebrovascular disease, and acute respiratory failure (9–14). Furthermore, a previous study revealed the prognostic implication of GNRI in critically ill patients (15). An increasing body of evidence has established the correlation between GNRI and worse outcomes in patients with chronic kidney disease (CKD) and hemodialysis (16, 17). Taken together, it is reasonable to speculate that GNRI might be correlated with the poor prognosis in AKI patients. No studies have hitherto assessed the predictive validity of GNRI in critically ill elderly patients with AKI. Accordingly, this research sought to evaluate the ability of GNRI to predict the prognosis in elderly AKI patients in the ICU.

2. Materials and methods

2.1. Data sources

This research was based on the Medical Information Mart for Intensive Care III (MIMIC-III), a freely accessible large critical-care database covering many critically ill patients at the Beth Israel Deaconess Medical Center from 2001 to 2012 (https://mimic.mit.edu/). The researcher (Yonghua Deng) received the seniority to extract data from this database after completing the required training course.

2.2. Population selection

Patients aged over 65 years old and diagnosed with AKI were involved in this analysis. We excluded patients who lacked serum albumin or weight or height, had repeat admissions, and stayed in the ICU for <2 days, as well as patients with pre-existing CKD.

2.3. Data extraction and definitions

The extracted variables contained demographic data (age, gender, weight, and height), vital signs (heart rate and blood pressure), comorbidities [such as coronary heart disease (CHD), sepsis, and liver cirrhosis], laboratory parameters at admission [such as albumin, blood urea nitrogen (BUN), and serum creatinine (SCr)], sequential organ failure assessment (SOFA), Charlson comorbidity index (CCI), treatment information [continuous renal replacement therapy (CRRT), vasopressors, and mechanical ventilation], and types of intensive care unit (ICU). The laboratory indicators were taken from the first measurement recorded after admission. BMI was defined as weight in kilograms/(height in meters)^2. GNRI was calculated as follows: 14.89 × serum albumin (g/dl) + 41.7 × BMI/22 (18). AKI was diagnosed and staged according to the "Kidney Disease Improving Global Outcomes" criteria (19). In the study, 1-year mortality was considered the primary outcome, whereas in-hospital, ICU, 28-day and 90-day mortality, and prolonged length of stay (LOS) in the ICU and hospital were selected as the secondary outcomes. Excessive LOS was determined as the length of stay above the 75th percentile. Thus, the prolonged ICU and hospitalization LOS were more than 10 and 19 days, respectively.

2.4. Statistical analysis

A Kolmogorov–Smirnov test was used with continuous variables to determine whether their distributions were normal. Continuous variables were summarized as median (interquartile range) and examined by the Mann–Whitney U-test because of the skewed distribution of these variables. Categorical data were characterized as numbers with proportions, and comparisons between groups were employed using the chi-square test. We built a receiver operating characteristic (ROC) curve to determine the optimal cutoff value of GNRI for predicting 1-year death. The cutoff point was applied to divide patients into two groups. A multivariable linear regression analysis was employed to confirm the relationship between GNRI and relevant clinical variables. Furthermore, the 365-day cumulative survival between the two groups was compared using the Kaplan–Meier (KM) curve with the log-rank test. We carried out multivariable logistic and Cox proportional hazards regression analyses to verify the impact of GNRI on the adverse outcomes, adjusting for the potential confounding factors. These covariates were related to the 1-year mortality in the univariable Cox regression analyses. Meanwhile, GNRI was examined as both a continuous and a categorical variable. Restricted cubic spline (RCS) with four knots was applied to explore the curve relationship between GNRI and 365-day death. We also carried out a stratification analysis to figure out whether the predictive significance of GNRI for 1-year mortality was sustained across the different subgroups classified by gender, age, AKI stage, comorbidities, sofa score, CCI, ICU types, CRRT, vasopressors, and mechanical ventilation. We employed all statistical analyses with the R software (version 3.6.3) and MedCalc (version 19.1). A P-value < 0.05 was regarded as statistically significant.

TABLE 1 Baseline characteristics of participants according to the GNRI category.

Variables	Total	High GNRI (>98)	Low GNRI (≤98)	*P*
	N = 3,501	*N* = 1,941	*N* = 1,560	
Age, years	76.7 (71.1, 82.4)	75.7 (70.3, 81.2)	78.1 (72.6, 83.6)	<0.001
Male, *n* (%)	1,880 (53.7)	1,076 (55.4)	804 (51.5)	0.022
SBP, mmHg	120 (104, 138)	119 (105, 137)	120 (103, 139)	0.937
DBP, mmHg	59.0 (50.0, 70.0)	60.0 (51.0, 70.0)	59.0 (50.0, 69.0)	0.283
Heart rate, bpm	86.0 (75.0, 98.0)	85.0 (75.0, 94.2)	88.0 (76.0, 102.0)	<0.001
Hypertension, *n* (%)	2,078 (59.4)	1,284 (66.2)	794 (50.9)	<0.001
Diabetes, *n* (%)	995 (28.4)	670 (34.5)	325 (20.8)	<0.001
CHD, *n* (%)	1,607 (45.9)	1,074 (55.3)	533 (34.2)	<0.001
Heart failure, *n* (%)	1,450 (41.4)	822 (42.3)	628 (40.3)	0.211
Liver cirrhosis, *n* (%)	123 (3.5)	70 (3.6)	53 (3.4)	0.739
Malignancy, *n* (%)	786 (22.5)	381 (19.6)	405 (26.0)	<0.001
Sepsis, *n* (%)	462 (13.2)	186 (9.6)	276 (17.7)	<0.001
WBC, k/ul	9.9 (7.2, 13.8)	9.2 (6.9, 12.9)	10.8 (7.8, 14.9)	<0.001
Hemoglobin, g/dl	11.9 (10.5, 13.2)	12.3 (10.9, 13.6)	11.4 (10.1, 12.7)	<0.001
BUN, mg/dl	22.0 (16.0, 31.0)	22.0 (16.0, 30.0)	23.0 (16.0, 33.0)	0.046
SCr, mg/dl	1.0 (0.8, 1.4)	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	0.036
Sodium, mEq/l	139 (136, 141)	139 (136, 141)	138 (135, 141)	<0.001
Potassium, mEq/l	4.1 (3.8, 4.5)	4.1 (3.8, 4.5)	4.1 (3.8, 4.6)	0.485
Anion gap, mEq/L	14.0 (13.0, 17.0)	15.0 (13.0, 17.0)	14.0 (12.0, 17.0)	0.884
Bicarbonate, mEq/L	25.0 (22.0, 27.0)	25.0 (23.0, 28.0)	24.0 (21.0, 27.0)	<0.001
ALT, u/l	23.0 (15.0, 41.0)	23.0 (16.0, 37.0)	24.0 (14.0, 45.0)	0.293
AST, u/l	31.0 (21.0, 57.0)	29.0 (20.0, 50.0)	35.0 (21.0, 66.0)	<0.001
SOFA score	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	5.0 (3.0, 8.0)	0.006
CCI	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)	<0.001
ICU types				<0.001
CSRU	1,271 (36.3)	869 (44.8)	402 (25.8)	
CCU	617 (17.6)	346 (17.8)	271 (17.4)	
MICU	850 (24.3)	384 (19.8)	466 (29.9)	
SICU	492 (14.1)	225 (11.6)	267 (17.1)	
TSICU	271 (7.7)	117 (6.0)	154 (9.9)	
CRRT, *n* (%)	198 (5.7)	96 (4.9)	102 (6.5)	0.043
Vasopressors, *n* (%)	2,445 (69.8)	1,376 (70.9)	1,069 (68.5)	0.130
Ventilation, *n* (%)	1,375 (39.3)	651 (33.5)	724 (46.4)	<0.001
Length of ICU stay	5.2 (3.2, 9.9)	4.7 (3.0, 8.0)	6.2 (3.6, 12.5)	<0.001
Length of hospital stay	11.9 (7.9, 18.8)	10.9 (7.8, 16.6)	13.3 (8.2, 22.0)	<0.001
In-hospital mortality	678 (19.4)	256 (13.2)	422 (27.1)	<0.001
ICU-mortality	540 (15.4)	213 (11.0)	327 (21.0)	<0.001
28-days mortality	848 (24.2)	329 (17.0)	519 (33.3)	<0.001
90-days mortality	1,005 (28.7)	391 (20.1)	614 (39.4)	<0.001
1-year mortality	1,276 (36.4)	519 (26.7)	757 (48.5)	<0.001

GNRI, geriatric nutritional risk index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; WBC, white blood cell count; BUN, blood urea nitrogen; SCr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOFA, sequential organ failure assessment; CCI, Charlson comorbidity index; ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiothoracic surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma and surgical intensive care unit; CRRT, continuous renal replacement therapy.

TABLE 2 Linear regression analysis for GNRI.

	Univariable analysis		Multivariable analysis	
	β (95%CI)	P	β (95%CI)	P
Age	−0.48 (−0.56, −0.41)	<0.001	−0.37 (−0.44, −0.29)	<0.001
Male	0.71 (−0.36, 1.79)	0.195		
Hypertension	5.01 (3.93, 6.09)	<0.001	3.92 (2.89, 4.94)	<0.001
Diabetes	7.01 (5.84, 8.17)	<0.001	6.07 (4.89, 7.25)	<0.001
CHD	6.51 (5.45, 7.56)	<0.001	3.55 (2.50, 4.60)	<0.001
Heart failure	1.55 (0.46, 2.64)	0.005	3.14 (2.06, 4.23)	<0.001
Liver cirrhosis	1.19 (−1.73, 4.10)	0.425		
Malignancy	−3.01 (−4.29, −1.73)	<0.001	−0.03 (−1.36, 1.29)	0.962
Sepsis	−5.98 (−7.55, −4.41)	<0.001	−3.55 (−5.08, −2.02)	<0.001
Hemoglobin	1.57 (1.32, 1.82)	<0.001	1.24 (1.00, 1.48)	<0.001
SOFA score	−0.27 (−0.44, −0.10)	0.002	−0.04 (-0.20, 0.12)	0.651
CCI	−1.01 (−1.29, −0.73)	<0.001	−0.86 (−1.19, −0.52)	<0.001
CRRT	−0.41 (−2.73, 1.91)	0.729		
Ventilation	−3.73 (−4.83, −2.64)	<0.001	−1.61 (−2.69, −0.54)	0.003
Vasopressors	0.78 (−0.39, 1.95)	0.191		

95% CI, 95% confidence interval; other abbreviations as in Table 1.

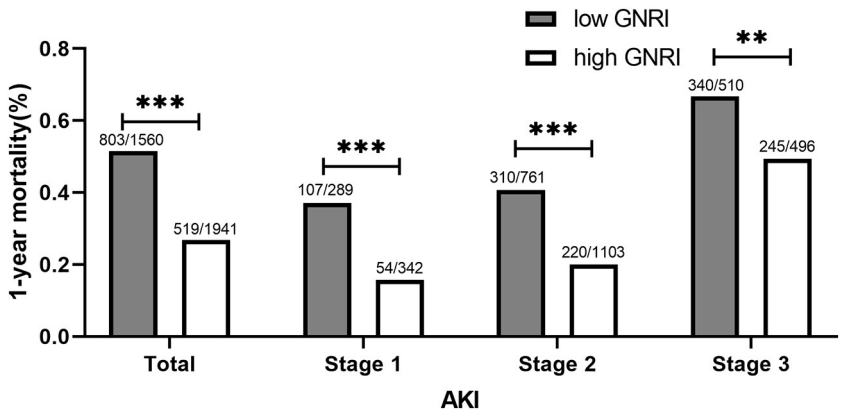


FIGURE 1
1-year mortality at different AKI stages between high and low GNRI groups. GNRI, geriatric nutritional risk index; AKI, acute kidney injury. $^{**}P < 0.01$; $^{***}P < 0.001$.

3. Results

3.1. Patient characteristics

In total, 3,501 elderly patients with AKI were selected for this analysis, with a 1-year mortality rate of 36.4% (Supplementary Figure 1). Patients were categorized into low (≤98) and high (>98) GNRI groups based on the optimum cutoff score determined by ROC curve analysis (the area under the curve was 0.655, and the sensitivity and specificity were 0.618 and 0.623, respectively; Supplementary Figure 2). The baseline characteristics by categories of GNRI (high and low GNRI groups) are summarized in Table 1. The two groups presented a statistically significant difference in terms of age, gender, heart rate, hypertension, diabetes, CHD, malignancy, sepsis, white blood cell count (WBC), hemoglobin, BUN, SCr, sodium, bicarbonate, aspartate aminotransferase (AST), SOFA score, CCI, ICU types, and CRRT. The low GNRI group had worse in-hospital mortality, ICU mortality, 28-day mortality, 90-day mortality, 1-year mortality, and longer ICU and hospital stay length than the high GNRI group (all $p < 0.001$, Table 1). A multivariable linear regression analysis was carried out to examine the relationship between GNRI and the relevant clinical variables. In the univariable analysis, elevated GNRI was associated with decreased age, the prevalence of malignancy and sepsis, sofa score, CCI, the use of mechanical ventilation, and increased prevalence of hypertension, diabetes, CHD, heart failure, and a higher level of hemoglobin (Table 2). The multivariable analysis confirmed that

GNRI was positively related to diabetes, hypertension, CHD, heart failure, and hemoglobin and negatively related to age, sepsis, CCI, and ventilation (Table 2).

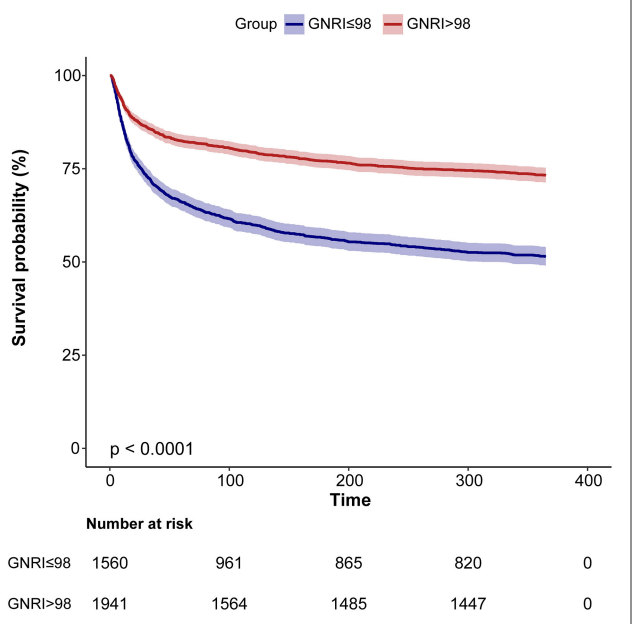


FIGURE 2
Kaplan–Meier curves for 1-year accumulative survival rates grouped by high and low GNRI. GNRI, geriatric nutritional risk index.

3.2. Clinical outcomes

When stratified by the AKI stage, patients with high GNRI at AKI stages 1, 2, and 3 had markedly lower 1-year mortality than those with low GNRI (all $p < 0.05$, Figure 1). The KM curves for 365-day cumulative survival are presented in Figure 2, showing the significant survival advantage for patients with increased GNRI compared with those with decreased GNRI (log-rank $p < 0.001$).

Next, the multivariable regression analysis was conducted to confirm the independent relationship between GNRI and the worse outcomes. A one-unit increment of GNRI was remarkably associated with a lower risk of clinical outcomes after potential confounding factor adjustment (all $p \leq 0.001$, Table 3), and these covariates (including age, gender, systolic blood pressure, heart rate, hypertension, diabetes, CHD, heart failure, liver cirrhosis, malignancy, sepsis, WBC, hemoglobin, BUN, SCr, sodium, potassium, anion gap, bicarbonate, alanine aminotransferase, AST, SOFA score, CCI, ICU types, CRRT, and ventilation) were significant in the univariable Cox regression analyses (Supplementary Table 1). Patients with elevated GNRI also had markedly reduced risk of adverse outcomes even after the potential confounding factors were controlled [OR (95% CI): 0.63 (0.51–0.77) for in-hospital mortality; OR (95% CI): 0.70 (0.56–0.87) for ICU mortality; OR (95% CI): 0.60 (0.50–0.73) for 28-day death; OR (95% CI): 0.59 (0.49–0.71) for 90-day death; OR (95% CI): 0.66 (0.54–0.79) for hospital stay ≥ 19 days; OR (95% CI): 0.62 (0.51–0.76) for ICU stay ≥ 10 days; and HR (95% CI): 0.68 (0.60–0.77) for 1-year mortality, Table 3]. RCS verified a linear association between GNRI and 1-year mortality (p for non-linearity = 0.434, Figure 3).

TABLE 3 Adjusted OR/HR of GNRI for adverse outcomes.

	Univariable analysis		Multivariable analysis	
	OR/HR (95%CI)	*P*	OR/HR(95%CI)	*P*
GNRI as continuous variable				
In-hospital death	0.97 (0.96–0.97)	<0.001	0.98 (0.97–0.99)	<0.001
ICU death	0.97 (0.97–0.98)	<0.001	0.99 (0.98–0.99)	<0.001
28-days death	0.97 (0.96–0.97)	<0.001	0.98 (0.97–0.99)	<0.001
90-days death	0.97 (0.96–0.97)	<0.001	0.98 (0.97–0.99)	<0.001
Hospital stay ≥19 days	0.98 (0.97–0.98)	<0.001	0.98 (0.98–0.99)	<0.001
ICU stay ≥10 days	0.98 (0.97–0.98)	<0.001	0.98 (0.98–0.99)	<0.001
1-year death	0.97 (0.97–0.98)	<0.001	0.98 (0.98–0.99)	<0.001
GNRI as categorical variable				
In-hospital death	0.41 (0.34–0.49)	<0.001	0.63 (0.51–0.77)	<0.001
ICU death	0.46 (0.39–0.56)	<0.001	0.70 (0.56–0.87)	0.002
28-days death	0.41 (0.35–0.48)	<0.001	0.60 (0.50–0.73)	<0.001
90-days death	0.39 (0.33–0.45)	<0.001	0.59 (0.49–0.71)	<0.001
Hospital stay ≥19 days	0.51 (0.44–0.60)	<0.001	0.66 (0.54–0.79)	<0.001
ICU stay ≥10 days	0.49 (0.42–0.58)	<0.001	0.62 (0.51–0.76)	<0.001
1-year death	0.47 (0.42–0.52)	<0.001	0.68 (0.60–0.77)	<0.001

Multivariable analysis adjusted for age, gender, systolic blood pressure, heart rate, hypertension, diabetes, CHD, heart failure, liver cirrhosis, malignancy, sepsis, WBC, hemoglobin, BUN, SCr, sodium, potassium, anion gap, bicarbonate, alanine aminotransferase, AST, SOFA score, CCI, ICU types, CRRT, and ventilation.
OR, odds ratio; HR, hazard ratio; other abbreviations as in Table 1.

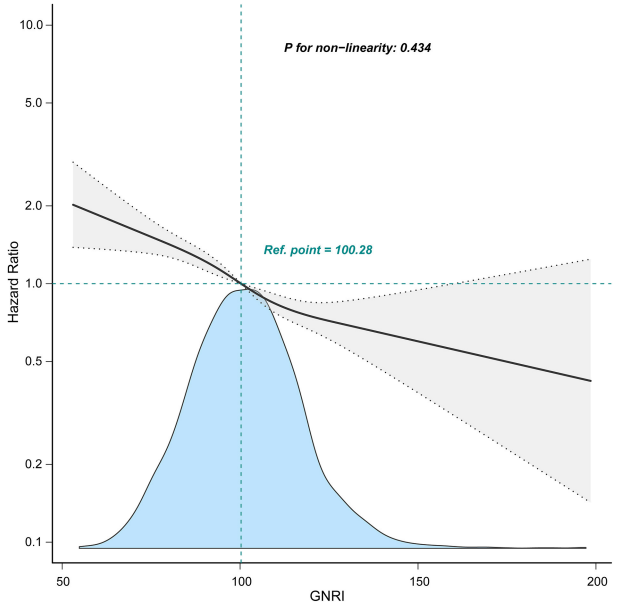


FIGURE 3
Relationship between GNRI and 1-year mortality using restricted cubic spline analysis. A linear relationship between GNRI and 1-year mortality was observed after adjusting for age, gender, heart rate, hypertension, diabetes, CHD, heart failure, CKD, liver cirrhosis, malignancy, sepsis, WBC, hemoglobin, BUN, SCr, sodium, potassium, anion gap, bicarbonate, ALT, AST, SOFA score, CRRT, and ventilation. GNRI, geriatric nutritional risk index.

3.3. Subgroup analyses

We further carried out subgroup analyses to figure out whether the correlation between GNRI and 1-year death was constant in various subclasses (Figure 4). GNRI still independently predicted 1-year death in patients with the most subgroups. Notably, the predictive implication of GNRI appeared to be more pronounced in patients with AKI stages 1 and 2 ($P_{interaction} = 0.022$), diabetes ($P_{interaction} = 0.012$), and CHD ($P_{interaction} = 0.005$) and also patients who did not receive mechanical ventilation ($P_{interaction} = 0.035$).

4. Discussion

Our study confirmed a negative linear correlation between GNRI and 1-year death in elderly AKI patients in the ICU, and upon an increase in GNRI, the mortality rate gradually decreased. GNRI at admission was remarkably related to a lower risk of research outcomes even after the covariates were controlled. Moreover, the relationship between GNRI and long-term mortality remained significant irrespective of the AKI stages.

At present, the common nutritional screening tools recommended for the older population include the Mini-Nutritional Assessment (MNA), Subjective Global Assessment (SGA), and Nutritional Risk Screening 2002 (NRS-2002) (20). Research studies have verified that SGA and NRS-2002 were vital markers for predicting poor prognosis in AKI patients (21, 22). No studies were found on MNA and AKI prognosis. These nutritional scoring tools are easily influenced by a subjective evaluation by trained professionals, particularly for questions regarding weight loss and dietary intake changes. These questions are too complex and cumbersome for critically ill older patients, which results in an inaccurate assessment of the patient's nutritional status. GNRI is a straightforward, objective, and well-established nutritional screening tool specially developed for the hospitalized elderly (18). Our analysis exhibited that decreased GNRI was remarkably associated with elevated mortality risk and prolonged stay length. This was in agreement with the results of the previously published studies: Malnourished AKI patients revealed lower survival rates (21–23). The BMI and ALB, components of GNRI, demonstrated a strong correlation with the mortality of critically ill AKI patients (24, 25). The present study extends the population to the elderly. More importantly, GNRI was consistently significantly related to long-term mortality irrespective of the AKI stage. Therefore, we recommend using GNRI to accurately assess the nutritional status of elderly patients with severe AKI, to identify high-risk malnutrition patients and provide nutritional guidance.

It has been well-established that comorbidities, such as sepsis, malignancy, heart failure, and liver cirrhosis, can further aggravate the nutritional status of patients in multiple ways (26). Nutritional status becomes worse with advancing age (27). Interventions, including CRRT, vasopressors, and mechanical ventilation, have been independently related to the mortality of severe AKI patients (28). Our results exhibited that the prognostic implication of GNRI remained significant in most of the subgroups, which indicated that the correlation between GNRI and long-term mortality could be generalized to different clinical settings. However, we could not explain why the predictive implication of GNRI was not significant in patients with CKD.

A higher GNRI indicates a lower nutritional risk. There was a negative linear relationship between GNRI and the research outcomes in the present analysis. High GNRI is caused by elevated albumin and BMI. The main pathological mechanisms of malnutrition in AKI patients are the reduced intake of nutrients and the loss of protein and energy related to metabolic disorders (4, 29), which lead to a decrease in BMI and albumin. Patients with high BMI tend to have better outcomes. This theory is called the obesity paradox, which has been proved in patients with AKI (25), CHD (30, 31), and heart failure (32) and in those receiving hemodialysis (33). Another mechanism that explains the association between albumin and malnutrition in patients with kidney disease is that albumin possesses anti-inflammatory and antioxidant properties (34, 35). It has been documented that inflammatory cascades and oxidative stress play an essential role in the progression of malnutrition (29, 36).

Our analysis still existed certain limitations. Although the data in this study were obtained from large public databases, no external verification was conducted to verify the predictive significance of GNRI. Second, GNRI was assessed only at admission. Further research should be conducted to explore the prognostic implication of the dynamic change of GNRI. Third, since MIMIC III is based on data from 2001 to 2012, our research

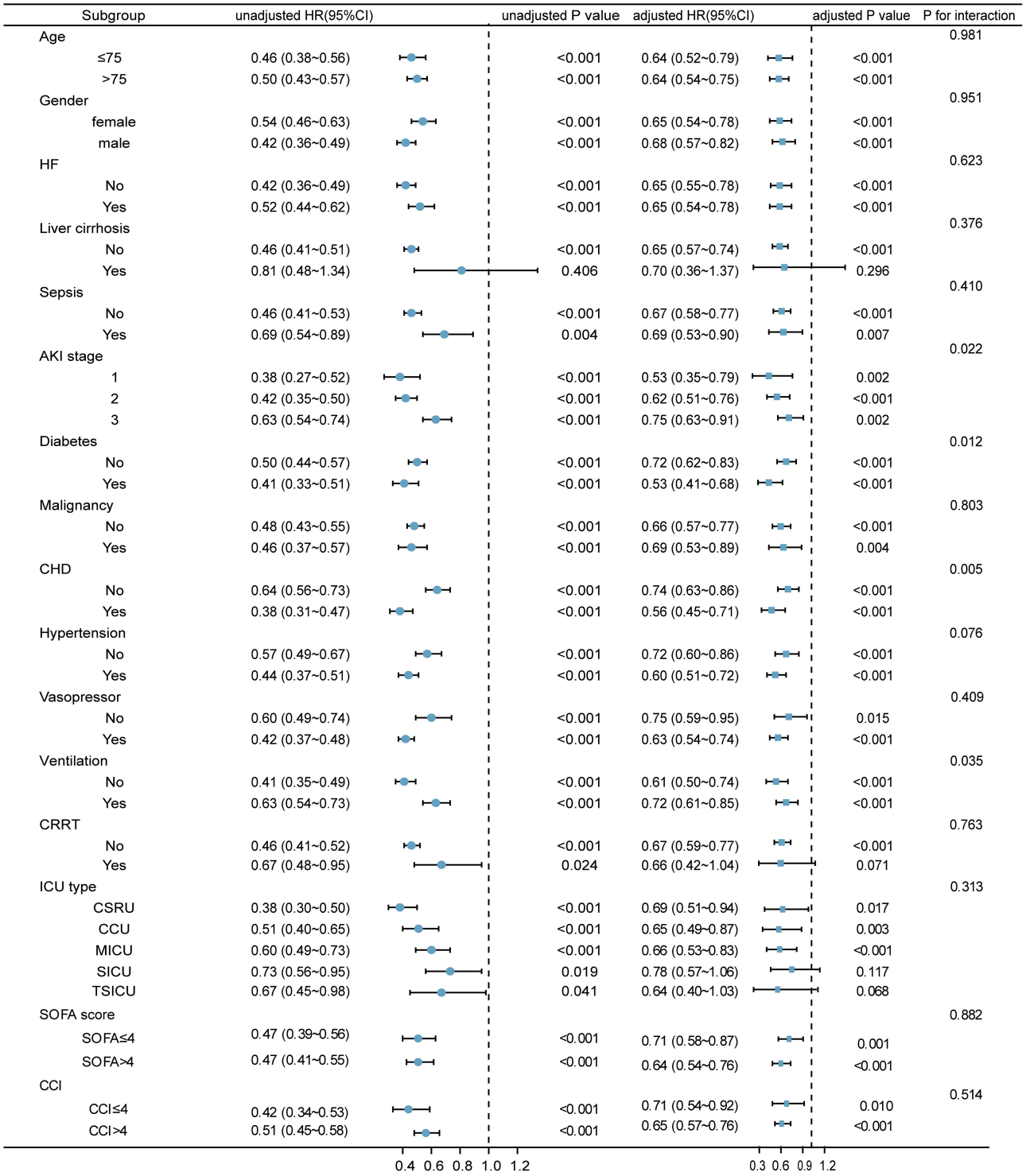


FIGURE 4
Relationship between GNRI and 1-year mortality in various subgroups. The HR was examined regarding the low GNRI as reference. HF, heart failure; AKI, acute kidney injury; CKD, chronic kidney disease; CHD, coronary heart disease; CRRT, continuous renal replacement therapy; GNRI, geriatric nutritional risk index; HR, hazard ratio; 95% CI, 95% confidence interval.

may not be fully generalizable to current medical conditions. Next, because of the limitations of the MIMIC database, we could not collect information on diet and physical activity, which was correlated with the nutritional status of patients. Finally, we cannot clarify the reason for AKI due to the limitations of the MIMIC database.

5. Conclusion

On-admission GNRI is a pivotal predictor of the adverse endpoints of elderly AKI patients in the ICU. Our results suggested that GNRI helped to identify elderly AKI patients at a high risk of malnutrition to ensure timely and effective nutritional support.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://mimic-iv.mit.edu.

Author contributions

DL was responsible for designing the protocol, conducting the search and analyzing data from MIMIC-III, interpreting results, and creating summary of findings tables. YD, XL, JH, and JL were responsible for designing the review protocol and extracting data. YD, XL, and MP contributed to updating reference lists and provided feedback on the report. FZ and LW contributed to analyzing data, interpreting results, as well as creating tables and figures, and writing the paper. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1165428/full#supplementary-material

References

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med.* (2015) 41:1411–23. doi: 10.1007/s00134-015-3934-7

2. Meyer D, Mohan A, Subev E, Sarav M, Sturgill D. Acute kidney injury incidence in hospitalized patients and implications for nutrition support. *Nutr Clin Pract.* (2020) 35:987–1000. doi: 10.1002/ncp.10595

3. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al. Calorie intake and patient outcomes in severe acute kidney injury: findings from the randomized evaluation of normal vs. augmented level of replacement therapy (RENAL) study trial. *Crit Care.* (2014) 18:R45. doi: 10.1186/cc13767

4. Fiaccadori E, Sabatino A, Barazzoni R, Carrero JJ, Cupisti A, De Waele E, et al. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. *Clin Nutr.* (2021) 40:1644–68. doi: 10.1016/j.clnu.2021.01.028

5. Fiaccadori E, Regolisti G, Maggiore U. Specialized nutritional support interventions in critically ill patients on renal replacement therapy. *Curr Opin Clin Nutr Metab Care.* (2013) 16:217–24. doi: 10.1097/MCO.0b013e32835c20b0

6. Guenter P, Abdelhadi R, Anthony P, Blackmer A, Malone A, Mirtallo JM, et al. Malnutrition diagnoses and associated outcomes in hospitalized patients: United States, 2018. *Nutr Clin Pract.* (2021) 36:957–69. doi: 10.1002/ncp.10771

7. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. *Int J Environ Res Public Health.* (2011) 8:514–27. doi: 10.3390/ijerph8020514

8. Agarwal E, Ferguson M, Banks M, Bauer J, Capra S, Isenring E. Nutritional status and dietary intake of acute care patients: results from the Nutrition Care Day Survey 2010. *Clin Nutr.* (2012) 31:41–7. doi: 10.1016/j.clnu.2011.08.002

9. Xie H, Tang S, Wei L, Gan J. Geriatric nutritional risk index as a predictor of complications and long-term outcomes in patients with gastrointestinal malignancy: a systematic review and meta-analysis. *Cancer Cell Int.* (2020) 20:530. doi: 10.1186/s12935-020-01628-7

10. Ruan GT, Zhang Q, Zhang X, Tang M, Song MM, Zhang XW, et al. Geriatric Nutrition Risk Index: Prognostic factor related to inflammation in elderly patients with cancer cachexia. *J Cachexia Sarcopenia Muscle.* (2021) 12:1969–82. doi: 10.1002/jcsm.12800

11. Nishi I, Seo Y, Hamada-Harimura Y, Yamamoto M, Ishizu T, Sugano A, et al. Geriatric nutritional risk index predicts all-cause deaths in heart failure with preserved ejection fraction. *ESC Heart Fail.* (2019) 6:396–405. doi: 10.1002/ehf2.12405

12. Fan Y, He L, Zhou Y, Man C. Predictive value of geriatric nutritional risk index in patients with coronary artery disease: a meta-analysis. *Front Nutr.* (2021) 8:736884. doi: 10.3389/fnut.2021.736884

13. Yuan K, Zhu S, Wang H, Chen J, Zhang X, Xu P, et al. Association between malnutrition and long-term mortality in older adults with ischemic stroke. *Clin Nutr.* (2021) 40:2535–42. doi: 10.1016/j.clnu.2021.04.018

14. Shi X, Shen Y, Yang J, Du W, Yang J. The relationship of the geriatric nutritional risk index to mortality and length of stay in elderly patients with acute respiratory failure: a retrospective cohort study. *Heart Lung.* (2021) 50:898–905. doi: 10.1016/j.hrtlng.2021.07.012

15. Shao Y, Lai QC, Duan Q, Ge P, Ye L. Nutritional indices at admission are associated with mortality rates of patients in the intensive care unit. *Eur J Clin Nutr.* (2022) 76:557–63. doi: 10.1038/s41430-021-00994-3

16. Nakagawa N, Maruyama K, Hasebe N. Utility of geriatric nutritional risk index in patients with chronic kidney disease: a mini-review. *Nutrients.* (2021) 13:3688. doi: 10.3390/nu13113688

17. Panichi V, Cupisti A, Rosati A, Di Giorgio A, Scatena A, Menconi O, et al. Geriatric nutritional risk index is a strong predictor of mortality in hemodialysis patients: data from the Riscavid cohort. *J Nephrol.* (2014) 27:193–201. doi: 10.1007/s40620-013-0033-0

18. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr.* (2005) 82:777–83. doi: 10.1093/ajcn/82.4.777

19. Ad-hoc working group of E, Fliser D, Laville M, Covic A, Fouque D, Vanholder R, et al. A European renal best practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant.* (2012) 27:4263–72. doi: 10.1093/ndt/gfs375

20. Abd Aziz NAS, Teng N, Abdul Hamid MR, Ismail NH. Assessing the nutritional status of hospitalized elderly. *Clin Interv Aging.* (2017) 12:1615–25. doi: 10.2147/CIA.S140859

21. Khor BH, Tiong HC, Tan SC, Abdul Rahman R, Abdul Gafor AH. Protein-energy wasting assessment and clinical outcomes in patients with acute kidney injury: a systematic review with meta-analysis. *Nutrients*. (2020) 12:2809. doi: 10.3390/nu12092809

22. Li C, Xu L, Guan C, Zhao L, Luo C, Zhou B, et al. Malnutrition screening and acute kidney injury in hospitalised patients: a retrospective study over a 5-year period from China. *Br J Nutr*. (2020) 123:337–46. doi: 10.1017/S000711451900271X

23. Wang N, Wang P, Li W, Jiang L, Wang M, Zhu B, et al. Prognostic significance of malnutrition risk in elderly patients with acute kidney injury in the intensive care unit. *BMC Nephrol*. (2022) 23:335. doi: 10.1186/s12882-022-02949-7

24. Lv J, Wang H, Sun B, Gao Y, Zhang Z, Pei H. Serum albumin Before CRRT was associated with the 28- and 90-day mortality of critically ill patients with acute kidney injury and treated with continuous renal replacement therapy. *Front Nutr*. (2021) 8:717918. doi: 10.3389/fnut.2021.717918

25. Wang B, Li D, Gong Y, Ying B, Cheng B, Sun L. Body mass index is associated with the severity and all-cause mortality of acute kidney injury in critically ill patients: an analysis of a large critical care database. *Biomed Res Int*. (2021) 2021:6616120. doi: 10.1155/2021/6616120

26. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nutr*. (2008) 27:5–15. doi: 10.1016/j.clnu.2007.10.007

27. Hickson M. Malnutrition and ageing. *Postgrad Med J*. (2006) 82:2–8. doi: 10.1136/pgmj.2005.037564

28. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. (2005) 294:813–8. doi: 10.1001/jama.294.7.813

29. Sabatino A, Regolisti G, Karupaiah T, Sahathevan S, Sadu Singh BK, Khor BH, et al. Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. *Clin Nutr*. (2017) 36:663–71. doi: 10.1016/j.clnu.2016.06.007

30. Lavie CJ, Milani RV, Artham SM, Patel DA, Ventura HO. The obesity paradox, weight loss, and coronary disease. *Am J Med*. (2009) 122:1106–14. doi: 10.1016/j.amjmed.2009.06.006

31. Niedziela J, Hudzik B, Niedziela N, Gasior M, Gierlotka M, Wasilewski J, et al. The obesity paradox in acute coronary syndrome: a meta-analysis. *Eur J Epidemiol*. (2014) 29:801–12. doi: 10.1007/s10654-014-9961-9

32. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J*. (2008) 156:13–22. doi: 10.1016/j.ahj.2008.02.014

33. Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. *Mayo Clin Proc*. (2010) 85:991–1001. doi: 10.4065/mcp.2010.0336

34. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. *FEBS Lett*. (2008) 582:1783–7. doi: 10.1016/j.febslet.2008.04.057

35. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial*. (2004) 17:432–7. doi: 10.1111/j.0894-0959.2004.17603.x

36. Saha SK, Lee SB, Won J, Choi HY, Kim K, Yang GM, et al. Correlation between oxidative stress, nutrition, and cancer initiation. *Int J Mol Sci*. (2017) 18:1544. doi: 10.3390/ijms18071544

frontiers | Frontiers in Medicine

TYPE Study Protocol
PUBLISHED 18 May 2023
DOI 10.3389/fmed.2023.1144156

OPEN ACCESS

EDITED BY
Roberta Zupo,
University of Bari Aldo Moro, Italy

REVIEWED BY
Sathish Thirunavukkarasu,
Emory University, United States
Amutha Ramadas,
Monash University Malaysia, Malaysia

*CORRESPONDENCE
Jeannette M. Beasley
✉ jbeasley@nyu.edu

RECEIVED 13 January 2023
ACCEPTED 24 April 2023
PUBLISHED 18 May 2023

CITATION
Beasley JM, Johnston EA, Sevick MA, Jay M, Rogers ES, Zhong H, Zabar S, Goldberg E and Chodosh J (2023) Study protocol: BRInging the Diabetes prevention program to GEriatric Populations.
Front. Med. 10:1144156.
doi: 10.3389/fmed.2023.1144156

Study protocol: BRInging the Diabetes prevention program to GEriatric Populations

Jeannette M. Beasley[1,2]*, Emily A. Johnston[2], Mary Ann Sevick[2,3], Melanie Jay[2,3,4], Erin S. Rogers[3], Hua Zhong[3], Sondra Zabar[2], Eric Goldberg[2] and Joshua Chodosh[2,3,4]

[1]Department of Nutrition and Food Studies, New York University, New York, NY, United States, [2]Department of Medicine, New York University Grossman School of Medicine, New York, NY, United States, [3]Department of Population Health, Institute for Excellence in Health Equity, New York University, New York, NY, United States, [4]VA New York Harbor Healthcare System, Medicine Service, New York, NY, United States

In the Diabetes Prevention Program (DPP) randomized, controlled clinical trial, participants who were ≥60years of age in the intensive lifestyle (diet and physical activity) intervention had a 71% reduction in incident diabetes over the 3-year trial. However, few of the 26.4 million American adults age ≥65years with prediabetes are participating in the National DPP. The BRInging the Diabetes prevention program to GEriatric Populations (BRIDGE) randomized trial compares an in-person DPP program Tailored for Older AdulTs (DPP-TOAT) to a DPP-TOAT delivered via group virtual sessions (V-DPP-TOAT) in a randomized, controlled trial design (*N*=230). Eligible patients are recruited through electronic health records (EHRs) and randomized to the DPP-TOAT or V-DPP-TOAT arm. The primary effectiveness outcome is 6-month weight loss and the primary implementation outcome is intervention session attendance with a non-inferiority design. Findings will inform best practices in the delivery of an evidence-based intervention.

KEYWORDS

diabetes prevention, older adults, nutrition, physical activity, lifestyle change, virtual, social support, implementation science

1. Introduction

Over one-quarter (29.2%) of US adults aged 65 and older have Type 2 diabetes (i.e., 15.9 million people), and the Centers for Disease Control and Prevention (CDC) estimated that an additional 26.4 million older adults had prediabetes, defined as fasting plasma glucose values of 100 to 125 mg/dl or hemoglobin A1C values of 5.7 to 6.4%, in 2019 (1). Evidence-based diabetes prevention strategies, such as the National Diabetes Prevention Program (DPP), reduce the risk of developing diabetes but remain underutilized. In the original Diabetes Prevention Program (DPP) study, the diet and physical activity intervention conferred a 71% reduction in risk of type 2 diabetes for the participants who were ≥60 years of age (n = 648) after 3 years of follow-up (2). Since the seminal DPP was established as efficacious (2), the intervention has been implemented in hospital, community, work, and other settings.

Despite this, just 14.6% of rural counties and 48.4% of urban counties in the nation have a DPP site. Barriers to DPP participation exist for both individuals and healthcare systems. Individuals face barriers to access, including travel to 22 in-person sessions, as well as cost if they elect to utilize a commercial online program. Older adults, in particular, face barriers to

care, including transportation, costs, time burden, and limited physical function/reserve. Healthcare systems face significant cost burdens for training DPP facilitators and hosting the program (3). In the few studies that have reported on costs of administering the DPP, there was a 5-fold difference in cost per participant across studies, with a virtual program costing less than on-site delivery (4, 5). In the BRInging the Diabetes prevention program to GEriatric Populations (BRIDGE) trial, we will address these barriers by generating a DPP Tailored for Older Adults (DPP-TOAT) and delivered via Virtual sessions (V-DPP-TOAT).

Technology use among older adults is increasing. Almost two-thirds (63%) of adults aged 66–75 years use the Internet to access health information, including 49% of adults aged 75 and older (6). Furthermore, 69% of adults ≥65 have a mobile phone, including 56% of adults ≥75 years of age. Web-based interventions have effectively increased health knowledge (7) and physical activity among older adults (8–10). The proportion of older adults enrolling in internet-based programs will grow with the aging of younger cohorts who are more accustomed to depending on technology to meet their health care and other needs.

Delivering a DPP through a videoconferencing platform may extend the program's reach into the older adult community that may otherwise lack access (11). The NYU Langone Health catchment area includes more than 7.2 million people, of whom nearly 1 million individuals are aged 65 and older. An intervention using technology to provide remote training and individualized feedback increases the likelihood of reproducibility outside of the NYU Langone Health network and sustainability over time (12). Virtual interventions do not require brick-and-mortar facilities or centralized staff; these highly scalable interventions can be delivered from any location. However, a recent behavioral weight loss trial reported that in-clinic group visits, but not telephone group visits, resulted in statistically significant greater weight loss at 24 months compared with traditional in-clinic individual visits (13). Lessons learned from the implementation evaluation of the BRIDGE DPP will provide the opportunity for other healthcare systems to offer the program to eligible patients. The study aims are to compare the effectiveness and implementation of V-DPP-TOAT versus DPP-TOAT within a large healthcare system.

2. Methods

2.1. Study design and overview

We will conduct a type 1 hybrid (14), randomized, controlled trial of the BRInging the Diabetes prevention program to GEriatric Populations (BRIDGE) study, which will compare an in-person DPP Tailored for Older AdulTs (DPP-TOAT) to a DPP-TOAT delivered via group virtual sessions (V-DPP-TOAT; Figure 1). All randomized individuals ($N = 230$; 1:1 randomization) will receive 22 intervention sessions over the course of a year facilitated by a certified DPP lifestyle coach, but the delivery method will vary (virtual versus in-person).

Outcome assessments will be conducted at 0, 6, and 12 months at the clinic where we will assess weight, hemoglobin A1c, diet, and physical activity in both groups. At baseline, we will assess height, weight, waist circumference, and administer questionnaires to all participants. The trial design will adhere to the CONSORT checklist (see Appendix A), including an intention-to-treat analysis (15). Meticulous adherence to the study protocol and fidelity monitoring will ensure robust and unbiased results.

2.2. Recruitment

The NYU Langone Health patient population includes over 15,000 patients aged 65 or older with a diagnosis of prediabetes who meet the basic inclusion criteria. NYU Langone Health clinical providers utilize Epic, one of the country's largest electronic health record platforms, and its patient portal (*MyChart*), which allows for direct outreach and bi-directional communication with patients. Using Epic, we will continuously identify eligible older adults with prediabetes. As in our prior work (16–19), patients will be recruited through both physician referral and proactive outreach to patients. For proactive outreach, we use Epic-generated lists of eligible patients based on our eligibility criteria. A research team member will send lists to patients' primary care provider (PCP), who will subsequently identify any contraindications to participating. Potential participants will be sent a message through the patient portal (*MyChart*) and/or mailed a letter signed by the principal investigators (JB and JC) and medical director (EG) that describes the study and gives them the opportunity to opt out (i.e., request not to be contacted). We will then call potential participants to recruit, screen for eligibility, and schedule a baseline visit. Table 1 outlines eligibility criteria for study participation.

2.2.1. Randomization into Intervention Arms

The study statistician (HZ), will generate randomized treatment allocation in a blinded environment using a Research Electronic Data Capture (REDCap, https://projectredcap.org/) randomization tool.

2.2.2. Retention

We will use the following strategies to encourage retention of participants in both arms of the study: (1) reminder of study visits and intervention sessions via email and phone call, (2) financial incentives following successful completion of study visits ($50 gift card for each baseline, 6, 12 month visits), (3) birthday cards, (4) certificates of completion and milestone emails.

2.2.3. Masking

As with most behavioral trials, it is difficult to mask participants to the intervention arm. To reduce bias, all outcome assessors will be masked to the intervention arm and participants will be asked not to disclose treatment allocation. To detect potential unmasking, we will ask outcome assessors about participant allocation after each post-randomization measurement visit.

2.3. Intervention arms

2.3.1. Common components to both interventions: V-DPP-TOAT and DPP-TOAT

Both programs will be composed of sixteen 60-min weekly/bi-weekly sessions followed by six 60-min monthly support sessions (see Appendix B) with a group size of 8–15 facilitated by a certified DPP lifestyle coach. The DPP intervention is based on Social Cognitive Theory (20), which focuses on the role played by

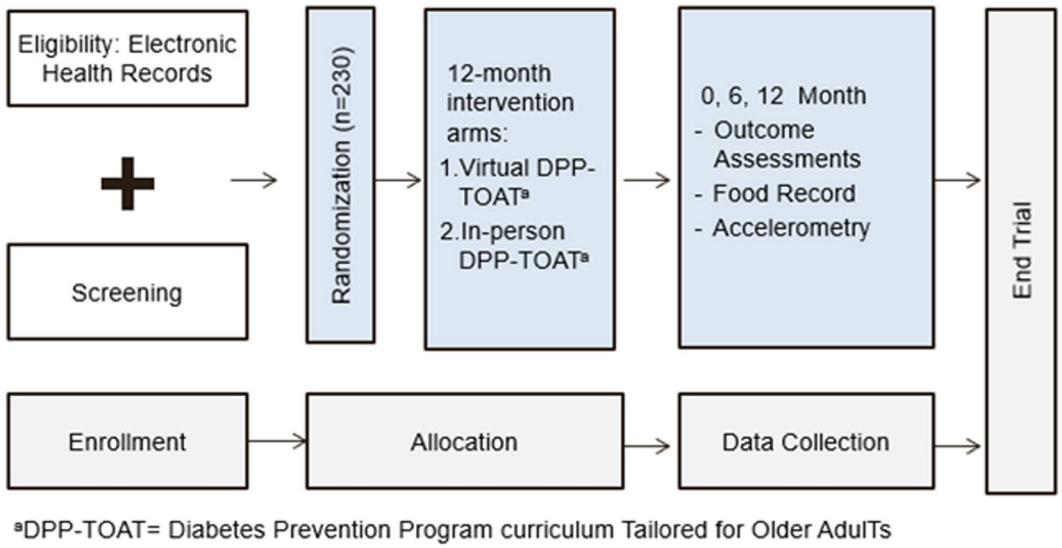


FIGURE 1
Study flow diagram.

TABLE 1 Eligibility criteria.

Inclusion Criteria
• Aged ≥65 years*
• Prediabetes (A1C 5.7–6.4%, fasting glucose 100–125 mg/dl, or oral glucose tolerance test of 140–199 mg/dl within 12 mo) *
• BMI of ≥25 kg/m^2, ≥ 23 kg/m^2 if Asian American*
• English speaking*
• Under the care of PCP in the NYU Langone Health system*
• Able to travel to NYU medical center for in-person evaluations *
Exclusion Criteria
• Prevalent diabetes or End-Stage Renal Disease (> = CKD stage 3)*±
• Prior participation in Diabetes Prevention Program±
• A documented history of active psychosis or other cognitive issues via ICD-10 codes*
• Taking FDA-approved weight loss medications*±
• PCP stating that patient should not participate
• Inability to communicate due to severe, uncorrectable hearing loss or speech disorder±
• Severe visual impairment (if it precludes completion of assessments and/or intervention)±

*if assessed through EPIC, ±if assessed during screening. A1c, hemoglobin A1c; BMI, body mass index; mo, months; PCP, primary care provider; FDA, Food and Drug Administration.

self-referent thought in the maintenance of behavior change. The following describes the theoretical concepts threaded throughout the intervention sessions. Self-efficacy (e.g., the participant's confidence in their ability to engage in healthier behavior) is derived from four major sources of information: (1) mastery experiences; (2) social modeling; (3) verbal persuasion; and (4) physiological states. Mastery experiences emphasize past successes; setting incremental, easily achievable goals; identifying modifiable barriers to healthy behavior; receiving positive feedback on goal achievement; and practicing problem solving skills around barriers to adherence. Social modeling enhances mastery when participants share their successes and help each other problem-solve around barriers they encounter. Verbal persuasion emphasizes the participant's previous successes to demonstrate their capability (e.g., "As a result of your effort, you lost a pound last week. You can do it again.") We will assist participants in recognizing physiologic benefits they experience from lifestyle change (e.g., more energy, better sleep, or BP control). Intervention materials, which are based on the 2021 PreventT2 lifestyle change program (21), will include:

- *Participant Manual*: An evidence-based manual describing detailed program content and personalized calorie and macronutrient recommendations to achieve the desired weight. Written at the sixth-grade reading level in a large (14 point) sans serif font, self-assessments and goal setting procedures will be included along with approaches to self-monitor food intake, physical activity, and cooking and meal pattern guides. To enhance self-identification with the program and for ongoing visual cues for program affiliation, we will provide tote bags inscribed with the institutional logo.
- *Tailoring of content for aging*: Based on our prior work (22), we have adapted group sessions to the unique needs of older adults. Resources include healthful eating strategies for dentition issues, changes in taste, and special attention to interactions between food and medications. Physical activity sessions provide adaptations for physical limitations, including chair exercises and strength training.
- *Food Guide*: Resources developed by the United States Department of Agriculture (23) providing tailored advice for older adults will be provided, along with instructions and tips for using programs such as Healthwatch 360 (24) to track calorie and nutrient intake compared to recommendations.
- *Hearing Assistance*: For participants in the in-person arm, we will offer a personal amplifier (PA; PockeTalker™) to all participants

to address any self-reported or suspected hearing loss. A simple PA consists of an amplifier and microphone with the amplifier feeding a speaker's voice directly into the wearer's ears via headphones or ear buds. These devices reduce the difficulty with hearing in "difficult listening situations" by feeding the speaker's amplified voice directly into the patient's ear, while headphones or ear buds muffle external sounds (i.e., signal is louder than background noise level). These devices require no professional customization; simple volume and tuning controls allow for use directly out of the box. PAs enhance communication for those who have hearing loss in a variety of clinical settings (25–27). PAs were equivalent in performance to hearing aids in one randomized controlled trial (28), sound quality of PAs was preferred over hearing aids, improved physician-patient communication for elderly hospitalized patients (29) and understanding discharge information in an Emergency Department setting (30). Participants in the virtual arm will be offered ear buds to address any self-reported or suspected hearing loss.

- *Videos*: Each intervention session will also feature educational and behavioral coaching videos developed by our team or reputable organizations such as the National Institutes Health and VA MOVE (Weight Management Program, supported by VA's National Center for Health Promotion and Disease Prevention) (31). The videos last 3–5 min, and will be used to anchor the discussion. Videos will also be available on the study website for participants to review as they desire.
- *Smart Scales*: We will provide participants with a Renpho® (Joicom Corporation, Eastvale, CA) Smart Scale for Body Weight, Digital Bathroom Scale for self-monitoring purposes and to monitor weight given the possibility of disruptions in in-person study visits due to COVID-19 pandemic restrictions. Renpho® Scales will transmit weights to researchers automatically using BlueTooth technology and have been used in other weight management studies. A research assistant will instruct each participant during the baseline visit on using the scale to report weekly weights, providing written instructions as well as a phone number and email address to obtain technical support as needed.

2.3.1.1. V-DPP-TOAT Arm specific information

Intervention sessions will take place via videoconference rather than in-person, and we will encourage participants to use their preferred device to connect with the group (e.g., tablet, computer, and smartphone). Participants will be offered a tablet computer if they do not have an electronic device they'd like to use to connect. A research assistant will orient each participant to the tablet during the baseline visit, providing written instructions, a phone number and email address to obtain technical support as needed. Before or after the intervention session, participants will be assigned to breakout rooms where they will have a 1-on-1 visit with the lifestyle coach, report their weight, physical activity minutes and discuss action plan and goal achievement.

2.3.1.2. DPP-TOAT Arm specific information

All interactions will be in-person and weights will be measured immediately before or after intervention sessions using a Renpho® scale.

2.4. Data collection

In-person data collection will occur during study visits for both arms. Assessments will occur at: baseline (first in-person encounter), six, and 12 months (Tables 2, 3). Participants will meet with a research assistant masked to treatment assignment to complete surveys and to measure glycemia, weight, height, and waist circumference (baseline, six, and 12 months). Research staff will administer all surveys, entering data directly into a REDCap database. The DPP facilitator will record DPP attendance data.

2.4.1. Aim 1: to evaluate the effectiveness of the V-DPP-TOAT compared to the DPP-TOAT

Core measures for Aim 1 are displayed in Table 2.

2.4.2. Aim 1: quantitative data analysis

We will compare the effect of the V-DPP-TOAT versus the DPP-TOAT interventions on weight and glycemia, which are both continuous outcomes. First, we will report means and standard deviations by randomization assignment and assess the assumption of normality in the outcomes. We will estimate the model using ordinary least squares regression

$$Y6_i = \beta_0 + \alpha_0 Y0_i + \alpha_1 P_i + e_i$$

TABLE 2 Aim 1 BRIDGE measures.

Measures	Month		
	0	6	12
Demographics, health-related characteristics[1,2,3]	X		
Anthropometrics (height, weight, waist circumference)[4]	X	X	X
Hemoglobin A1c[5]	X	X	X
Social support[6]	X	X	X
Self-efficacy[7]	X	X	X
Dietary intake including alcohol, Food records (4 days including weekend day)	X	X	X
Physical activity record	X	X	X
Physical activity/sleep, accelerometry	X	X	X
Smoking[8]	X	X	X
Quality of life[9,10]	X	X	X
Physical function, walking limitations[11]	X	X	X

[1]Prediabetes Risk Test (32).
[2]Health literacy (33, 34).
[3]Technology use (35).
[4]Anthropometric measures (36).
[5]Blood draw per standard HbA1c protocol.
[6]NIH adult toolbox social relationship scales (37).
[7]Weight efficacy lifestyle questionnaire (38).
[8]Smoking (39).
[9]Emotional wellbeing (40).
[10]Summary score (40).
[11]Physical functioning (40).

TABLE 3 Aim 2 BRIDGE measures.

		Month		
Component		0	6	12
R	Recruitment[1,2,3]	X		
E	Weight and HbA1c outcomes[4]	X	X	X
A	Adoption by the healthcare system[5]		X	X
	Fidelity to CDC DPP curriculum[6]		X	X
I	Participant attendance at group sessions[7]		X	X
	Participant and DPP facilitator acceptability[8]		X	X
	Cost analysis[9]			X
M	Weight and HbA1c outcomes[4]			X
	Program maintenance and growth[5]			X

RE-AIM, reach, efficacy, adoption, implementation, maintenance; HbA1c, hemoglobin A1c; CDC, Centers for Disease Control and Prevention; DPP, diabetes prevention program.

[1]Use EPIC to evaluate the number (proportion) of individuals who are:

[a]Eligible for the study based on EHR data.

[b]Invited to participate through MyChart and/or via study recruitment mailings.

[c]Responsive to study invitation.

[d]Enrolled in study.

[2]Evaluate factors associated with participation by comparing the demographic and clinical characteristics of patients reached by the intervention vs. those not reached.

[3]Evaluate reasons for not participating (one multiple choice question at end of screening).

[4]Outcomes assessment per standardized procedures (see aim 1 measures table).

[5]Intervention process data and key informant interviews.

[6]Training Period – Monitor skill acquisition and quality of counseling.

- Lifestyle coaches completed CDC training via New York City Department of Health.
- Curriculum certification requirements are built into data collection (e.g., attendance, weekly weigh-ins, physical activity minute tracking).
- Intervention Period – Record group sessions throughout the intervention period, and a study team member will monitor 10% of the sessions.
  - o Fidelity Checklist.
  - o Will provide refresher training if fidelity checklist ratings average < 80%.

[7]Measure attendance, outcomes assessment completion, and diet and physical activity monitoring completion.

[8]Acceptability and Feasibility.

[9]Costs associated with staffing, supplies, and participant time for each arm.

where $Y6_i$ is the 6-month weight or Hemoglobin A1c for participant i. $Y0_i$ is the baseline weight or A1c for participant i. P_i is an indicator variable, where $P_i = 1$ if the participant i has been randomized to V-DPP-TOAT, and $P_i = 0$ for the DPP-TOAT. e_i is an error term. The parameters to be estimated are as follows: β_0 is the average for those in the DPP-TOAT group; α_0 represents the relationship between the baseline and follow-up outcome (weight or A1c) measurement; if the relationship is strong, the inclusion of the baseline measurement can increase statistical power; and α_1 represents the effect of the V-DPP-TOAT intervention. Specifically, the hypothesis test will compare $H_0 : \alpha_1 < \Delta$ vs. $H_A : \alpha_1 \geq -\Delta$ with the noninferiority margin Δ set as 5% for each of the outcomes. We will calculate the 95% confidence interval of α_1. If the lower bound is above the margin -Δ, the V-DPP-TOAT is deemed non-inferior and the trial is a "success." Further, if the lower bound of that same CI is also above zero, then superiority of V-DPP-TOAT can also be declared (41). Interaction terms between $Y0_i$ and P_i will be tested to see if there is effect modification by any of the baseline covariates.

We will assess heterogeneity in outcomes among healthcare settings/clinics by estimating an intraclass correlation coefficient (ICC). If the heterogeneity cannot be ignored, we will use a multi-level model with nested random effects in the above equation to accommodate the correlations caused by healthcare settings/centers. Outcomes analysis will use an intention-to-treat principle, with a per-protocol analysis as a sensitivity analysis (41) employing R software (version 1.2.5019, R Foundation for Statistical Computing) for all analyses.

2.4.2.1. Sensitivity analysis for missing data

We will compare demographic and clinical covariates in participants with and without missing data to identify factors potentially contributing to missingness. We will use 10 multiple imputations from the original dataset using the predictive mean matching method substituting missing values within each impute.

2.4.2.2. Power: aim 1

To achieve 80% power to detect non-inferiority using a one-sided, two-sample *t*-test (lower bound), we will need 85 participants per group. The margin of non-inferiority is 5% of weight loss in the DPP-TOAT arm. The true efficacy difference between the 6-month weight loss is assumed to be 1.6 kg (weight loss of 5 kg in the V-DPP-TOAT arm and 6.6 kg in the in-person DPP-TOAT arm with standard deviation of 5 kg in each arm (42)). The significance level (alpha) of the test is 0.05. A total of 230 participants are needed, assuming 25% attrition at 6 months based on data from our work and others (22, 42, 43).

2.4.3. Aim 2: to evaluate the implementation of DPP-TOAT

To determine the feasibility of generalizing the DPP-TOAT intervention to other clinics within the NYU Langone Health system in New York and, ultimately, to other states, we will evaluate the implementation of the program during the RCT. Based on previous work, we hypothesize that adherence to the V-DPP-TOAT will be greater than the DPP-TOAT, as measured by the number of group sessions completed by each participant (42). We will use the RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework (44) to assess quantitative implementation outcomes during the Aim 1 effectiveness trial (Table 3). We will use the Consolidated Framework for Implementation Research (CFIR) (45) to examine barriers/facilitators to implementation within five main domains (intervention characteristics, inner setting, outer setting, participant/stakeholder characteristics, and implementation process), ensuring that this intervention can be generalized and readily disseminated and implemented elsewhere.

- Reach: We define the reach of the intervention as the number (proportion) of individuals who are (a) eligible for the study based on electronic health record data, (b) exposed to recruitment, (c) who initially responded, and (d) who decided to participate. We will survey those who decline participation to evaluate reasons for not participating. We will evaluate factors associated with participation by comparing the demographic and clinical characteristics of patients reached by the intervention vs. those not reached.

- Effectiveness: We will explore potential outcome differences in subgroups (e.g., sex, BMI category). We will conduct descriptive exploratory data analyses to explore which components may contribute most to the improvement of the outcomes.
- Adoption: We will assess willingness to adopt the intervention if it is found to be effective among key settings serving older adults with prediabetes, including other healthcare systems (e.g., a public hospital setting, senior centers, and rural settings, identifying barriers/facilitators toward future adoption.
- Implementation: We will evaluate implementation fidelity and resource requirements. We will also evaluate the acceptability and feasibility of the intervention among participants and facilitators, as well as barriers to implementing the program during the trial and to inform future implementation efforts. We will collect data on time spent delivering the intervention by lifestyle coaches including number of sessions, cost of materials, and other program costs.
- Maintenance: We will assess long-term maintenance of primary clinical outcomes (weight maintenance and glycemia at 12 months post-baseline visit).

2.4.3.1. Aim 2 data collection

Research assistants keep detailed recruitment records using standardized forms to capture variables related to intervention *reach* described above (e.g., percent eligible, percent who enroll). Recordings of each session provide rich data related to *implementation fidelity* described above (e.g., number of group sessions completed, session length, topics covered during each session). Core measures for Aim 2 are listed in Table 3.

2.4.3.2. Quantitative data analysis

Aim 2 uses the RE-AIM framework to evaluate implementation of the V-DPP-TOAT and in-person DPP-TOAT interventions. We will compare the number of group sessions completed by each participant in the two arms using generalized linear models with count outcomes, because DPP session attendance is positively associated with weight loss (42, 46), and is a CDC recognition status benchmark (47). The proportion of participants who complete at least eight intervention sessions will be compared by logistic regression between the two arms to make our findings comparable to other DPP implementation studies (42, 46). However, our primary implementation outcome of attendance is independent of any threshold chosen in the number of sessions. We will test interaction terms between baseline covariates and treatment assignment to determine if there is effect modification by any of the baseline covariates.

If there are imbalances at baseline for any important participant health, demographic or other factors, we will adjust the models to take these imbalances into consideration. For the remaining analyses, we will conduct similar types of analyses, using logistic regression for categorical outcomes and linear regression models for continuous outcomes.

We will use mediation analysis to dissect the indirect effects of the treatment acting through the intermediate variables (social support, self-efficacy, and self-monitoring) on the primary outcome (attendance), and the direct effects of treatment on the outcome (attendance) not mediated through the mediators. For each of the three mediators, an overall score and subscale scores will be computed by summing relevant items. This analysis will help understand the underlying treatment mechanisms of behavior change. Specifically, we will use the principal stratification and structural mean models. We will assess the assumptions necessary for attaining identifiability of key parameters of the basic causal model and perform a series of sensitivity analyses. We will also investigate the interactions between baseline covariates and the mediation effects to determine whether any baseline factors modify the mediation effects (48, 49).

In order to inform cost for future implementations and policy makers (4), we will compare the sum of variable (e.g., operating costs, supply costs, percent time of intervention and staff) and fixed costs (e.g., space, equipment) between intervention arms (50).

2.4.3.3. Aim 2 power

Based on data from Lee 2018, we expect a higher proportion of V-DPP-TOAT participants will complete at least eight intervention sessions compared to DPP-TOAT participants (89 vs. 63%, respectively) (42). With 90 samples in each arm at 6 months, we achieve 98% power to detect the difference in session completion proportions of 26% at alpha = 0.05 (89 vs. 63% respectively) and 80% power to detect smaller difference of 19% (82 vs. 63% respectively).

2.4.3.4. Aim 2 qualitative data

All interviews will be recorded using Zoom (in-person sessions will use Zoom via conference room video and audio system) with transcripts saved. Data analysis from transcriptions will follow techniques of narrative analysis (51, 52) and a "constant comparison" analytic approach (53). To code transcripts, the research team will develop an initial set of codes, informed by the open-ended questions and the interviews' guiding conceptual framework. For each core code, we will ultimately develop one or more "secondary codes" that represent either more specific or restricted aspects of the phenomenon for contextualization or to suggest underlying personal meanings. The secondary codes will vary in specificity or subtlety depending on the judged substantive value of additional refinements. The coding schema is a strategy for organizing and assimilating the large amount of data that the interviews will yield. To ensure that the coding is both valid (i.e., well grounded in the data) and reliable (consistent in meaning), the criteria for assigning a specific code to a block of text will be systematically developed and well documented. The resulting codebook will be refined and expanded upon to reflect and incorporate emerging insights throughout the coding process. All transcripts will be double-coded, and discrepancies will be resolved by consensus discussion.

The coded transcripts will be analyzed with *Atlas.ti* (Version 8, Berlin, Germany), a software package for qualitative data analysis. With *Atlas.ti*, concepts (constructs, themes), contextual factors, participant characteristics, behaviors and attitudes can be related to one another. This will be particularly important to examine, for example, how themes vary or are consistent across different participant subgroups. Frequency counts will be generated for core or secondary codes by identified subgroups, and the total data file.

2.4.3.5. Intervention fidelity

We will use a fidelity checklist to monitor skill acquisition and quality of counseling. A study team member will monitor 10% of the recorded intervention sessions using a fidelity checklist. We will provide refresher training if fidelity checklist ratings average <80%. We will measure attendance, outcomes assessment completion, and diet and physical activity monitoring completion.

Dissemination. The RE-AIM and CFIR frameworks analyses will address generalizability and transportability to facilitate future dissemination.

3. Discussion

Previous DPP studies have shown great benefit for older adult participants with reductions in incidence of diabetes of up to 71% (2). Barriers to attendance in older adults limit participation and barriers to engagement may include reduced hearing acuity in a group setting, reduced visual acuity and ability to read DPP materials, and reduced applicability of diet and physical activity recommendations. These barriers may be attenuated by adaptations made in the BRIDGE study.

This work will contribute to the growing body of implementation studies that at present, consist largely of commercial online DPP programs that engaged older adults (Table 4) (42, 46, 54, 55). Most recently, Omada's randomized, controlled trial recruiting from primary care centers in Nebraska demonstrated meaningful reductions in weight and HbA1c (42, 46, 54, 56–58). However, none of the commercial programs provide facilitated theory-based group sessions. Data from our work and others suggests the social support provided by these sessions is critical for engagement and retention of older adults (22, 43, 59). Furthermore, existing programs do not offer adaptations for older adults for nutrition, physical activity, hearing impairment, and/or low vision. Due to the COVID-19 pandemic, Medicare allowed for virtual delivery of the DPP (60), and it is likely that demand for convenient, online programs will continue (61, 62). The goal of this project is to test the effectiveness of a

TABLE 4 Healthcare system implementations of online diabetes prevention programs (DPP) engaging older adults.

Lead Author/ Year	Study design	N	Population	Program	Program delivery	Results
Block, 2015 (54, 55)	Randomized, controlled trial	339	Recruited from Palo Alto Medical Foundation; Mean age 55.0 (8.9)	Alive PD-1-year program of regular contact and goal setting, weekly in the first 6 months and biweekly thereafter, plus midweek automated email and mobile phone	Automated online platform with interactive voice response phone calls and a mobile app.	Alive-PD participants achieved significantly greater reductions than controls in fasting glucose (mean −7.36 vs. −2.19 mg/dl, $p < 0.001$), HbA1c (mean −0.26%vs. mean −0.18% $p < 0.001$), and body w eight (mean −3.3 vs. −1.3 kg, $p < 0.001$).
Castro Sweet, 2018 (46)	Single-arm, retrospective	501	Humana Medicare Advantage beneficiaries with evidence of prediabetes/ metabolic syndrome	Prevent – a DPP-based group lifestyle intervention that integrates a private online social network, weekly lessons, health coaching, and a w ireless scale and pedometer. Consists of a core 16-w eek intensive lifestyle change intervention and post-core lifestyle change maintenance intervention	Online platform, mobile app	92% completed at least 9 of 16 core lessons. At 12 months, average weight loss was 7.5% (7.8). Among participants with clinical data, average HbA1c decrease was 0.14% ($p = 0.001$) and average total cholesterol decrease was 7.08 mg/dl ($p = 0.008$). Self-reported w ell-being, depression, and self-care improved ($p < 0.0001$).
Lee, 2018 (42)	*Post hoc* analysis of two prospective, pragmatic, nonrandomized studies	≥65 years: 120 <65 years: 258	Veterans with prediabetes	VA-DPP – DPP Group Lifestyle Balance curriculum's 16 core sessions over 6 months followed by 6 monthly maintenance sessions Online-DPP – Prevent curriculum, weekly online modules over 12 months	VA-DPP: In-person Online-DPP: Online platform, mobile app	A higher proportion completed eight or more sessions in the Online-DPP intervention than in the VA-DPP intervention ($p < 0.05$). Veterans ≥65 years achieved similar participation and weight loss as younger adults, whether DPP was delivered in person or online. Both age groups lost a clinically and statistically significant amount of weight (5 kg or 5% weight at 6 and 12 months; $p < 0.05$) and had similar w eight loss trajectories over the 12 months ($p < 0.05$).
Almeida, 2020/ Katula, 2020 (56, 57)	Randomized, controlled trial	599	Nebraska Medicine primary care clinics	Omada Health Program – 16-week intensive curriculum focusing on w eight loss follow ed. by 36-week curriculum focusing on weight maintenance	Online platform, mobile app versus one two hour group diabetes prevention class	Omada produced significantly greater reductions in HbA1c (−0.23 vs. −0.15%, $p < 0.01$) and reduction in percent change of body w eight from initial w eight (−5.4 vs. −2.0%, $p < 0.01$) relative to control at 12 months.
Fitzpatrick 2021 (55)	Mixed-methods natural experiment	7,123	Kaiser Permanente Northwest patients	In-person DPP Digital DPP versus Omada Health Program compared	In-person versus online platform	In progress

DPP, diabetes prevention program; HbA1c, hemoglobin A1c; VA, veterans administration.

virtual adaptation that will: (1) be accessible to those who cannot afford to pay for commercial programs; (2) provide social support by the facilitated group sessions; (3) reduce the barriers associated with in-person DPP programs; and (4) serve the unique needs of older adults.

Our study has several strengths. The results of our trial can directly inform policy recommendations to Medicare that will have broad implications for older adults with prediabetes (63). Another major strength is our ability to recruit a diverse study population from broad socioeconomic backgrounds, which will help us to better understand how implementation may need to be tailored for different populations and settings. Our team has the breadth and depth of experience in conducting behavioral intervention trials and implementation to analyze results and interpret them for stakeholders to inform potential future adoption of the DPP by a large healthcare system. We have also identified several challenges and discussed ways to address these. First, trials often have challenges recruiting people from underrepresented groups. Our experience recruiting underserved populations from health care systems enhances our ability to meet recruitment targets. Second, there is inherent measurement error associated with self-reported dietary intake, but we do not expect the measurement error to differ between randomized groups, allowing for a valid, randomized comparison. Third, though using technology to engage participants can be challenging, technology use among older adults is increasing (64), and our prior and ongoing work suggests it is feasible and increases opportunities for broader dissemination of successful interventions.

This work will generate a high fidelity, easily implemented adaptation of a theory-based DPP for older adults in a virtual setting. This will increase access to an evidence-based prediabetes intervention tailored to older adults, providing opportunities to address multiple potential barriers for care (e.g., travel, need for care partners, social distancing due to COVID-19). We anticipate that including virtual social support will increase adherence and maintain effectiveness of the intervention. The information gained will inform best practices for other virtual health interventions both for the general population as well as for older adults.

Online/remote learning is rapidly becoming a critical piece of the new normal going forward for DPP programs. Findings will inform policy decisions regarding the use of virtual DPP programs to prevent diabetes among the Medicare population to improve best practices in the delivery of an evidence-based intervention, having the potential to help over 26.4 million people with prediabetes (1).

Author contributions

JB wrote the protocol, secured funding, and drafted the manuscript. EJ is a co-facilitator of the intervention sessions and contributed substantively to the development of the manuscript. MS provided expertise related to recruitment, retention, and group facilitation. MJ provided clinical insight to sample characteristics and interpretation of survey data. ER provided oversight of aim 2 measures and interpretation of pilot data to inform updating of implementation measures. HZ provided statistical guidance including power analyses and analytic plan. SZ and EG served as physician champions, recruited other physicians, and provided resources for intervention delivery. JC provided oversight of recruitment and retention and provided edits to the manuscript. All authors contributed to the article and approved the submitted version.

Funding

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number R01 DK127916.

Acknowledgments

We thank BRIDGE study participants for their time and feedback.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1144156/full#supplementary-material

References

1. Centers for Disease Control and Prevention (2022). https://www.cdc.gov/diabetes/data/statistics-report/index.html. [Accessed May 8, 2023].

2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. (2002) 346:393–403. doi: 10.1056/NEJMoa012512

3. Smith KJ, Kuo S, Zgibor JC, McTigue KM, Hess R, Bhargava T, et al. Cost effectiveness of an internet-delivered lifestyle intervention in primary care patients with high cardiovascular risk. *Prev Med*. (2016) 87:103–9. doi: 10.1016/j.ypmed.2016.02.036

4. Sun Y, You W, Almeida F, Estabrooks P, Davy B. The effectiveness and cost of lifestyle interventions including nutrition education for diabetes prevention: a systematic review and meta-analysi. *J Acad Nutr Diet*. (2017) 117:404–421.e36. doi: 10.1016/j.jand.2016.11.016

5. Vadheim LM, Brewer KA, Kassner DR, Vanderwood KK, Hall TOButcher MK, et al. Effectiveness of a lifestyle intervention program among persons at high risk for cardiovascular disease and diabetes in a rural community. *J Rural Health*. (2010) 26:266–72. doi: 10.1111/j.1748-0361.2010.00288.x

6. Hall AK, Bernhardt JM, Dodd V, Vollrath MW. The digital health divide: evaluating online health information access and use among older adults. *Health Educ Behav*. (2015) 42:202–9. doi: 10.1177/1090198114547815

7. Freund O, Reychav I, McHaney R, Goland E, Azuri J. The ability of older adults to use customized online medical databases to improve their health-related knowledge. *Int J Med Inform*. (2017) 102:1–11. doi: 10.1016/j.ijmedinf.2017.02.012

8. Peels DA, Hoogenveen RR, Feenstra TL, Golsteijn RH, Bolman C, Mudde AN, et al. Long-term health outcomes and cost-effectiveness of a computer-tailored physical activity intervention among people aged over fifty: modelling the results of a randomized controlled trial. *BMC Public Health*. (2014) 14:1099. doi: 10.1186/1471-2458-14-1099

9. Peels DA, Bolman C, Golsteijn RH, de Vries H, Mudde AN, van Stralen MM, et al. Long-term efficacy of a printed or a web-based tailored physical activity intervention among older adults. *Int J Behav Nutr Phys Act*. (2013) 10:104. doi: 10.1186/1479-5868-10-104

10. Peels D, Mudde A, Bolman C, Golsteijn R, de Vries H, Lechner L. Correlates of the intention to implement a tailored physical activity intervention: perceptions of intermediaries. *Int J Environ Res Public Health*. (2014) 11:1885–903. doi: 10.3390/ijerph110201885

11. Madigan E, Schmotzer BJ, Struk CJ, DiCarlo CM, Kikano G, Pina IL, et al. Home health care with telemonitoring improves health status for older adults with heart failure. *Home Health Care Serv Q*. (2013) 32:57–74. doi: 10.1080/01621424.2012.755144

12. Singer JP, Soong A, Bruun A, Bracha A, Chin G, Hays SR, et al. A mobile health technology enabled home-based intervention to treat frailty in adult lung transplant candidates: a pilot study. *Clin Transpl*. (2018) 32:e13274. doi: 10.1111/ctr.13274

13. Befort CA, VanWormer JJ, Desouza C, Ellerbeck EF, Gajewski B, Kimminau KS, et al. Effect of behavioral therapy with in-clinic or telephone group visits vs in-clinic individual visits on weight loss among patients with obesity in rural clinical practice: a randomized clinical trial. *JAMA*. (2021) 325:363–72. doi: 10.1001/jama.2020.25855

14. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. (2012) 50:217–26. doi: 10.1097/MLR.0b013e3182408812

15. Schulz KF, Altman DG, Moher DGroup C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. (2010) 8:18. doi: 10.1186/1741-7015-8-18

16. Viglione C, Bouwman D, Rahman N, Fang Y, Beasley JM, Sherman S, et al. A technology-assisted health coaching intervention vs. enhanced usual care for primary care-based obesity treatment: a randomized controlled trial. *BMC Obes*. (2019) 6:4. doi: 10.1186/s40608-018-0226-0

17. Wittleder S, Ajenikoko A, Bouwman D, Fang Y, McKee MD, Meissner P, et al. Protocol for a cluster-randomized controlled trial of a technology-assisted health coaching intervention for weight management in primary care: the GEM (goals for eating and moving) study. *Contemp Clin Trials*. (2019) 83:37–45. doi: 10.1016/j.cct.2019.06.005

18. Sevick MA, Woolf K, Mattoo A, Katz SD, Li H, St-Jules DE, et al. The healthy hearts and kidneys (HHK) study: design of a 2x2 RCT of technology-supported self-monitoring and social cognitive theory-based counseling to engage overweight people with diabetes and chronic kidney disease in multiple lifestyle changes. *Contemp Clin Trials*. (2018) 64:265–73. doi: 10.1016/j.cct.2017.08.020

19. Popp CJ, St-Jules DE, Hu L, Ganguzza L, Illiano P, Curran M, et al. The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2 diabetes. *Contemp Clin Trials*. (2019) 79:80–8. doi: 10.1016/j.cct.2019.03.001

20. Bandura A. Human agency in social cognitive theory. *Am Psychol*. (1989) 44:1175–84. doi: 10.1037/0003-066X.44.9.1175

21. Centers for Disease Control and Prevention (2018). National DPP PreventT2 curricula and handouts. Available At: https://nationaldppcsc.cdc.gov/s/article/National-DPP-PreventT2-Curricula-and-Handouts [Accessed April 3, 2020].

22. Beasley JM, Kirshner L, Wylie-Rosett J, Sevick MA, DeLuca L, Chodosh J. BRInging the diabetes prevention program to GEriatric populations (BRIDGE): a feasibility study. *Pilot Feasibility Stud*. (2019) 5:129. doi: 10.1186/s40814-019-0513-7

23. Build a Healthy Eating Routine as You Get Older (2021). Dietary Guidelines [Internet]. Available at: https://www.dietaryguidelines.gov/sites/default/files/2021-12/DGA_OlderAdults_FactSheet-508c.pdf [Accessed November 7, 2022].

24. HealthWatch360 (n.d.). Available at: https://healthwatch360.gbhealthwatch.com/ [Accessed November 7, 2022].

25. Wallhagen MI, Pettengill E, Whiteside M. Sensory impairment in older adults: part 1: hearing loss. *Am J Nurs*. (2006) 106:40–8. doi: 10.1097/00000446-200610000-00030

26. Palumbo MV. Hearing access 2000. Increasing awareness of the hearing impaired. *J Gerontol Nurs*. (1990) 16:26–31. doi: 10.3928/0098-9134-19900901-09

27. Smith AK, Jain N, Wallhagen ML. Hearing loss in palliative care. *J Palliat Med*. (2015) 18:559–62. doi: 10.1089/jpm.2014.0367

28. Jerger J, Chmiel R, Florin E, Pirozzolo F, Wilson N. Comparison of conventional amplification and an assistive listening device in elderly persons. *Ear Hear*. (1996) 17:490–504. doi: 10.1097/00003446-199612000-00005

29. Fook L, Morgan R, Sharma P, Adekoke A, Turnbull CJ. The impact of hearing on communication. *Postgrad Med J*. (2000) 76:92–5. doi: 10.1136/pmj.76.892.92

30. Chodosh J, Goldfeld K, Weinstein BE, Radcliffe K, Burlingame M, Dickson V, et al. The HEAR-VA pilot study: hearing assistance provided to older adults in the emergency department. *J Am Geriatr Soc*. (2021) 69:1071–8. doi: 10.1111/jgs.17037

31. MOVE! (n.d.). Weight management program Available at: https://www.move.va.gov/ [Accessed November 7, 2022].

32. Bang H, Edwards AM, Bomback AS, Ballantyne CM, Brillon D, Callahan MA, et al. Development and validation of a patient self-assessment score for diabetes risk. *Ann Intern Med*. (2009) 151:775–83. doi: 10.7326/0003-4819-151-11-200912010-00005

33. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med*. (2004) 36:588–94.

34. Wallace LS, Rogers ES, Roskos SE, Holiday DB, Weiss BD. Brief report: screening items to identify patients with limited health literacy skills. *J Gen Intern Med*. (2006) 21:874–7. doi: 10.1111/j.1525-1497.2006.00532.x

35. American Community Health Survey (2017-2021). United states census bureau. Available at: https://www.census.gov/acs/www/about/why-we-ask-each-question/computer/ [Accessed May 8, 2023].

36. Wittleder S, Smith S, Wang B, Beasley JM, Orstad SL, Sweat V, et al. Peer-assisted lifestyle (PAL) intervention: a protocol of a cluster-randomised controlled trial of a health-coaching intervention delivered by veteran peers to improve obesity treatment in primary care. *BMJ Open*. (2021) 11:e043013. doi: 10.1136/bmjopen-2020-043013

37. Cyranowski JM, Zill N, Bode R, Butt Z, Kelly MA, Pilkonis PA, et al. Assessing social support, companionship, and distress: National Institute of health (NIH) toolbox adult social relationship scales. *Health Psychol*. (2013) 32:293–301. doi: 10.1037/a0028586

38. Clark MM, Abrams DB, Niaura RS, Eaton CA, Rossi JS. Self-efficacy in weight management. *J Consult Clin Psychol*. (1991) 59:739–44. doi: 10.1037/0022-006X.59.5.739

39. Centers for Disease Control and Prevention (2021). Behavioral risk factor surveillance system. Available at: https://www.cdc.gov/brfss/index.html [Accessed May 8, 2023].

40. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item health survey 1.0. *Health Econ*. (1993) 2:217–27. doi: 10.1002/hec.4730020305

41. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. *Trials*. (2011) 12:106. doi: 10.1186/1745-6215-12-106

42. Lee PG, Damschroder LJ, Holleman R, Moin T, Richardson CR. Older adults and diabetes prevention programs in the veterans health administration. *Diabetes Care*. (2018) 41:2644–7. doi: 10.2337/dc18-1141

43. Kramer MK, Vanderwood KK, Arena VC, Miller RG, Meehan R, Eaglehouse YL, et al. Evaluation of a diabetes prevention program lifestyle intervention in older adults: a randomized controlled study in three senior/community centers of varying socioeconomic status. *Diabetes Educ*. (2018) 44:118–29. doi: 10.1177/0145721718759982

44. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health*. (1999) 89:1322–7. doi: 10.2105/AJPH.89.9.1322

45. Damschroder LJ, Reardon CM, Widerquist MAO, Lowery J. The updated consolidated framework for implementation research based on user feedback. *Implement Sci*. (2022) 17:75. doi: 10.1186/s13012-022-01245-0

46. Castro Sweet CM, Chiguluri V, Gumpina R, Abbott P, Madero EN, Payne M, et al. Outcomes of a digital health program with human coaching for diabetes risk reduction in a Medicare population. *J Aging Health*. (2017) 30:692–710. doi: 10.1177/0898264316688791

47. Centers for Disease Control and Prevention (2021). Diabetes prevention recognition: program standards and operating procedures. Available at: https://www.cdc.gov/diabetes/prevention/pdf/dprp-standards.pdf. [Accessed May 8, 2023].

48. Maracy M, Dunn G. Estimating dose-response effects in psychological treatment trials: the role of instrumental variables. *Stat Methods Med Res*. (2011) 20:191–215. doi: 10.1177/0962280208097243

49. Landau S, Emsley R, Dunn G. Beyond total treatment effects in randomised controlled trials: baseline measurement of intermediate outcomes needed to reduce confounding in mediation investigations. *Clin Trials*. (2018) 15:247–56. doi: 10.1177/1740774518760300

50. Saldana L, Chamberlain P, Bradford WD, Campbell M, Landsverk J. The cost of implementing new strategies (COINS): a method for mapping implementation resources using the stages of implementation completion. *Child Youth Serv Rev*. (2014) 39:177–82. doi: 10.1016/j.childyouth.2013.10.006

51. Mishler E. *Research interviewing: Context and narrative*. Cambridge, MA: Harvard University Press (1986).

52. Riessman C. *Narrative analysis*. Newbury Park, CA: Sage (1993).

53. Blumer H. *Symbolic interactions: Perspective and method*. Englewood Cliffs, NJ: Prentice Hall (1969).

54. Block G, Azar KM, Romanelli RJ, Block TJ, Hopkins D, Carpenter HA, et al. Diabetes prevention and weight loss with a fully automated behavioral intervention by email, web, and Mobile phone: a randomized controlled trial among persons with prediabetes. *J Med Internet Res*. (2015) 17:e240. doi: 10.2196/jmir.4897

55. Fitzpatrick SL, Mayhew M, Catlin CL, Firemark A, Gruss I, Nyongesa DB, et al. Evaluating the implementation of digital and in-person diabetes prevention program in a large, integrated health system: natural experiment study design. *Perm J*. (2021) 26:21–31. doi: 10.7812/TPP/21.056

56. Block G, Azar KM, Block TJ, Romanelli RJ, Carpenter H, Hopkins D, et al. A fully automated diabetes prevention program, alive-PD: program design and randomized controlled trial protocol. *JMIR Res Protoc*. (2015) 4:e3. doi: 10.2196/resprot.4046

57. Almeida FA, Michaud TL, Wilson KE, Schwab RJ, Goessl C, Porter GC, et al. Preventing diabetes with digital health and coaching for translation and scalability (PREDICTS): a type 1 hybrid effectiveness-implementation trial protocol. *Contemp Clin Trials*. (2020) 88:105877. doi: 10.1016/j.cct.2019.105877

58. Katula J, Dressler E, Kittle C, Almeida F, Wilson K, Michaud T, et al., editors. (2020). Effects of a digital diabetes prevention program on HbA1c and body weight in prediabetes. Obesity week.

59. Venditti EM, Wylie-Rosett J, Delahanty LM, Mele L, Hoskin MA, Edelstein SL, et al. Short and long-term lifestyle coaching approaches used to address diverse participant barriers to weight loss and physical activity adherence. *Int J Behav Nutr Phys Act*. (2014) 11:16. doi: 10.1186/1479-5868-11-16

60. CMS (2020). Participants in the Medicare diabetes prevention program: CMS flexibilities to fight COVID-19. Available at: https://www.cms.gov/files/document/covid-medicare-diabetes-prevention-program.pdf [Accessed November 4, 2020].

61. Mann DM, Chen J, Chunara R, Testa PA, Nov O. COVID-19 transforms health care through telemedicine: evidence from the field. *J Am Med Inform Assoc*. (2020) 27:1132–5. doi: 10.1093/jamia/ocaa072

62. Chunara R, Zhao Y, Chen J, Lawrence K, Testa PA, Nov O, et al. Telemedicine and healthcare disparities: a cohort study in a large healthcare system in new York City during COVID-19. *J Am Med Inform Assoc*. (2021) 28:33–41. doi: 10.1093/jamia/ocaa217

63. Kalyani RR, Golden SH, Cefalu WT. Diabetes and aging: unique considerations and goals of care. *Diabetes Care*. (2017) 40:440–3. doi: 10.2337/dci17-0005

64. Anderson M, Perrin A. (2017). Technology use among seniors: Pew Research Center Internet & Technology; Available at: http://www.pewinternet.org/2017/05/17/technology-use-among-seniors/. [Accessed May 8, 2023].

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 30 May 2023
DOI 10.3389/fmed.2023.1168560

OPEN ACCESS

EDITED BY
Roberta Zupo,
University of Bari Aldo Moro, Italy

REVIEWED BY
Giacosa Attilio,
University of Pavia, Italy
Emanuele Cereda,
San Matteo Hospital Foundation (IRCCS), Italy
Alfredo Caturano,
University of Campania Luigi Vanvitelli, Italy

*CORRESPONDENCE
Clara Gasparri
✉ clara.gasparri01@universitadipavia.it

RECEIVED 17 February 2023
ACCEPTED 09 May 2023
PUBLISHED 30 May 2023

CITATION
Rondanelli M, Gasparri C, Riva A, Petrangolini G, Barrile GC, Cavioni A, Razza C, Tartara A and Perna S (2023) Diet and ideal food pyramid to prevent or support the treatment of diabetic retinopathy, age-related macular degeneration, and cataracts. *Front. Med.* 10:1168560. doi: 10.3389/fmed.2023.1168560

Diet and ideal food pyramid to prevent or support the treatment of diabetic retinopathy, age-related macular degeneration, and cataracts

Mariangela Rondanelli[1,2], Clara Gasparri[3]*, Antonella Riva[4], Giovanna Petrangolini[4], Gaetan Claude Barrile[3], Alessandro Cavioni[3], Claudia Razza[3], Alice Tartara[3] and Simone Perna[5]

[1]Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation, Pavia, Italy, [2]Unit of Human and Clinical Nutrition, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy, [3]Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona "Istituto Santa Margherita", University of Pavia, Pavia, Italy, [4]R&D Department, Indena SpA, Milan, Italy, [5]Department of Biology, College of Science, University of Bahrain, Zallaq, Bahrain

Many eye diseases, such as diabetic retinopathy (DR), age-related macular degeneration (AMD), and cataracts are preventable and treatable with lifestyle. The objective of this review is to assess the most recent research on the ideal dietary approach to prevent or support the treatment of DR, AMD, and cataracts, as well as to construct a food pyramid that makes it simple for people who are at risk of developing these pathologies to decide what to eat. The food pyramid presented here proposes what should be consumed every day: 3 portions of low glycemic index (GI) grains (for fiber and zinc content), 5 portions (each portion: ≥200 g/day) of fruits and vegetables (spinach, broccoli, zucchini cooked, green leafy vegetables, orange, kiwi, grapefruit for folic acid, vitamin C, and lutein/zeaxanthin content, at least ≥42 μg/day, are to be preferred), extra virgin olive (EVO) oil (almost 20 mg/day for vitamin E and polyphenols content), nuts or oil seeds (20–30 g/day, for zinc content, at least ≥15.8 mg/day); weekly: fish (4 portions, for omega-3 content and eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) 0.35–1.4 g/day), white meat (3 portions for vitamin B12 content), legumes (2 portions for vegetal proteins), eggs (2 portions for lutein/zeaxanthin content), light cheeses (2 portions for vitamin B6 content), and almost 3–4 times/week microgreen and spices (saffron and curcumin). At the top of the pyramid, there are two pennants: one green, which indicates the need for personalized supplementation (if daily requirements cannot be met through diet, omega-3, and L-methylfolate supplementation), and one red, which indicates that certain foods are prohibited (salt and sugar). Finally, 3–4 times per week, 30–40 min of aerobic and resistance exercises are required.

KEYWORDS

diet, food pyramid, diabetic retinopathy, age-related macular degeneration, cataract, phytoextracts

1. Introduction

The 2019 WHO World Report on Vision confirms that more than a billion people worldwide suffer from vision disorders, which can be prevented or treated to avoid blindness. Furthermore, the number of people suffering from partial or severe blindness is increasing alarmingly. Cataracts and refractive defects make up half of the cases of blindness or severe vision impairment; diabetic retinopathy (DR) is the major cause among persons of working age, whereas age-related macular degeneration (AMD) is the major cause in the elderly (1). While there is a surgical treatment for cataracts, there is still no cure for many eye conditions that cause blindness. Among these is AMD. This is why it is very important to study mechanisms that lead to disease and to slow down the progression through prevention. Diet and lifestyle are two of the most important thoroughly studied factors, but are still little known by patients. Both seem to significantly influence the onset of the disease and rate of progression. Many eye diseases are treatable and preventable, especially in the first phase in which they occur and lifestyle, understood as nutrition and physical activity (PA), plays an essential role. The growth of studies in the literature on the subject suggests that various eye diseases, including glaucoma, AMD, and DR are associated with lower levels of physical activity. Similarly, physical activity levels are lower in people with lower vision (2). The relationship between PA and three of the most common vision diseases has abundant evidence supporting a possible protective role of PA against vision loss. A very recent narrative review (3) analyzed evidence in the literature between dietary styles and common eye diseases: specifically, the authors conclude that there is enough evidence in the literature to suggest that the Mediterranean diet and the "Asian diet" are linked with a reduced incidence of AMD, whereas the Western diet is associated with a greater incidence. Moreover, there seems to be evidence of a positive correlation between the Western diet and the development of cataracts, while there are not enough data to identify a correct dietary style that prevents this pathology. The data currently available come mainly from observational studies and some randomized clinical studies related to nutritional epidemiology. Among these, the most important to-date remain the Age-Related Eye Disease Study (AREDS) and AREDS2 studies (4, 5).

1.1. Antioxidants

1.1.1. Carotenoids

Only zeaxanthin and meso-zeaxanthin (a lutein metabolite formed in the macula through metabolic transformation) are present in significant amounts in the macula of human plasma (6). Together, these two carotenoids form the pigment of the macula, an essential component for maintaining vision at optimal levels, and this pigment can be used as a marker to assess the risk of AMD. Diet and supplements can alter the concentration of lutein and zeaxanthin, and thus their potential biological function. In 1997, the study by Hammon showed that the modification of one's diet can modify retinal receptor density: the addition of 60 mg of spinach (10.8 mg of lutein, 0.3 mg of zeaxanthin, and 5 mg of b-carotene) and/or 150 g of corn (0.4 mg of lutein and 0.3 of zeaxanthin) for 15 weeks to one's daily diet affected retinal receptor density (+19%) in 8 out of 12 subjects studied (7). In 2007, Schalch administered lutein (10 mg), zeaxanthin (10 mg), or a combination of the two (10+10 mg) to 126 male subjects for 1 year to assess their ability to influence macular pigment optical density (MPOD), by measuring monthly retinal parameters. It was found that the administration of one of the two components alone or the combined administration of both can improve MPOD up to 15% of the initial value. Furthermore, it was found that lutein tends to act mainly on the fovea, while zeaxanthin acts on the entire surface of the retina (8). Johnson (2008) investigated the effect of lutein (12 mg) and docosahexaenoic acid (DHA) (800 mg) supplementation for 4 months in preventing AMD in a sample of 49 women (aged 60–80 years): the subjects were randomized into four treatment groups (placebo, DHA, lutein, and DHA+lutein) and were evaluated before and after treatment for blood parameters and MPOD. The study showed that both lutein and DHA can significantly increase MPOD individually and in combination ($p < 0.01$) at 2 and 4 months after administration (9). Another feature of lutein is that it can be retained in the human retina for an extended period. In the study carried out by Landrum, two healthy subjects were supplemented with lutein esters equivalent to 30 mg of free lutein for 140 days, and during the intake period, it was possible to highlight a significant increase (+20–40% depending on the eye and the subject analyzed) of the MPOD, and this parameter continued to increase up to 50 days after the suspension of the supplementation and then progressively decreased (10). The articles by Eisenhauer and Perry report the content of lutein and zeaxanthin in foods; foods rich in lutein (lutein>900 mg/100 g) are in descending order of content: cooked spinach, cooked kale, cilantro, raw spinach, parsley, green leafy vegetables (lettuce and romaine), pistachios, zucchini cooked with skin, cooked asparagus. Foods rich in zeaxanthin (zeaxanthin>500 mg/100 g) are in descending order of content: scallions cooked in oil, oranges, raw egg yolk, and cooked egg yolk (11, 12).

The behavior of carotenoids in cooking has been investigated in the literature, but mainly for lutein, while studies on zeaxanthin are lacking. From a review by Palermo (13) regarding the effects of cooking on phytochemicals, several studies have analyzed lutein content in various vegetables before and after different types of cooking. Lutein tends to increase with steam cooking, probably due to the degradation of cellulose which allows for greater release and tends to be reduced with frying in proportion to the temperatures and surfaces exposed to cooking (cutting into smaller pieces tends to increase the surface in contact with the oil and therefore the loss of lutein). Evidence is conflicting for microwave cooking. A new frontier in the food sector is the use of "microgreens" or young seedlings (harvested 7–21 days after sowing) of various species of vegetables, wild plants, and aromatic herbs. These foods are richer in vitamins, micronutrients, and antioxidant compounds more than matured vegetables and plants. Xiao analyzed the content of lutein, zeaxanthin, tocopherol, beta carotene, and violaxanthin of these "young" vegetables (14): the microgreens richest in beta carotene (beta carotene:>10 mg/100 g fresh weight) are: cilantro, peppercress, red cabbage, and red sorrel, while

the microgreens richest in lutein/zeaxanthin (lutein/zeaxanthin>8 mg/100 g fresh weight) include cilantro, garnet amaranth, and red cabbage. In consideration of these high contents of compounds useful for eye health, microgreens can be an excellent addition to a diet aimed at the prevention of eye diseases. Egg yolk is the finest non-vegetarian food source of lutein and zeaxanthin because eggs' high-fat content boosts the absorption of carotenoids (15), even though their level mostly depends on the hen's diet, which includes lutein and zeaxanthin in its esterified forms along with trace amounts of lycopene and β-carotene (16). In-depth knowledge of release into the circulation and before that of the absorption, transport, and accumulation of carotenoids in the eye is essential to evaluate their beneficial aspects. Carotenoids are generally lipophilic, however, lutein and zeaxanthin are more polar substances than hydrocarbon carotenoids like beta-carotene and lycopene because of the presence of the hydroxyl group. Lutein and zeaxanthin absorption from meals determines their bioavailability in ocular tissue (17), and intestinal absorption is in turn influenced by several factors: the type of the food matrix (natural food or supplement), the amount and type of fats consumed, which let carotenoids circulate, the potential existence of phospholipids, and the availability of dietary fiber. The characteristics of the food matrices have a significant impact on the bioavailability of carotenoids (18). Lutein, zeaxanthin, and beta-cryptoxanthin have been found to release almost completely from fruits (orange, kiwi, grapefruit, and sweet potato), but only 19–38% from green vegetables (spinach and broccoli) (19). Human tissues do not all contain the same amounts of lutein, with the macula having the highest concentration (20).

1.1.2. Vitamin A

Unsaturated isoprenoid chain structure distinguishes the group of fat-soluble, vegetal, and animal-derived chemicals known as vitamin A and, in general, they are defined "retinoids." All vitamin A types have the same physiological effects on an organism and a comparable structural makeup and they could be either from a natural or synthetic source. Unlike water-soluble vitamins, all of these substances are liposoluble and can easily accumulate in the body, particularly in the liver and adipose tissue (21). In this instance, 11-cis-retinol is the active vitamin A derivate; it is connected to the G-coupled protein receptor in the retina known as opsin. The complex is referred to as rhodopsin, and it is the essential pigment for seeing in the dark (22). Vitamin A deficiency, common in the presence of generalized malnutrition, is associated with night blindness, conjunctival xerosis, and corneal ulceration, particularly with concomitant measles infection (23, 24). Two recent reviews have shown significant effects of vitamin A in preventing ocular diseases such as cataracts: data from the meta-analysis presented by Wang A et al. showed that ingesting enough vitamin A decreased the risk of cataracts by 17% (95% CI, 0.757–0.913) (25) and the review of Jiang H et al. showed a significant reduced risk of cataract by the consumption of carotenoids [relative risk (RR), 0.81; 95% CI, 0.71–0.92] (26). Although data from the National Health and Nutrition Examination Survey (NHANES I) initially showed a protective effect of a diet based on the high amount of fruit and vegetables rich in vitamin A on developing AMD (27), the following epidemiological studies did not found any significative evidence on the association between dietary intake of vitamin A and reduced risk of AMD (28), so further investigations are needed.

In light of this background, the objective of this review is to assess the most recent information regarding the ideal dietary approach to prevent or support the treatment of DR, AMD, and cataracts, and to construct a food pyramid that enables subjects who are at risk of developing these pathologies or subjects who have these pathologies to easily figure out what to eat.

Figure 1 summarizes the main risk factors common to the three eye diseases discussed in the review.

2. Methods

The procedures used to carry out this narrative review are as follows (29): (1) Three clinical nutrition-trained operators compose the working group (one acting as a methodological operator and two participating as clinical operators); (2) Formulation of the revision question based on the abstract's points: "the most recent information on the optimal dietary approach to prevent or support the treatment of DR, AMD, and cataracts"; (3) Identification of pertinent studies: The following research method was planned on PubMed [Public MEDLINE, operated by the National Center for Biotechnology Information (NCBI) of the National Library of Medicine of Bethesda (Bethesda, MD, USA)]: (a) the definition of the keywords (DR, foods, nutrients, and diet), which can be used singly or in combination, (b) the use of the Boolean operator, which enables the establishment of logical relationships between concepts, (c) advanced search as a research modality, (d) Limitations: human subjects; English; articles published within the last 30 years; and (e) manual search by senior researchers skilled in clinical nutrition through the revision of reviews and particular patient dietary therapy publications published in journals qualified in the Index Medicus; (4) analysis and presentation of outcomes: the data extrapolated from the "revised studies" were allocated in tables; in particular, for each study, the authors, year of publication, and study characteristics were reported; (5) A narrative review of the reports was used to carry out the analysis. Each section's introduction includes a list of the studies that were considered as well as the type of study and keywords. We reviewed studies of any design that took account of the importance of diet, foods, nutrients, and dietary patterns (DPs) to prevent or support the treatment of DR, AMD, and cataracts.

Figure 2 shows the eligible studies and Figure 3 represents proper nutrition and lifestyle to prevent or support the treatment of DR, AMD, and cataracts, specifying the quality and amount of food needed to provide ideal dietary management and to construct a food pyramid.

3. Results

3.1. DR

3.1.1. Dietary and food patterns

The following keywords served as the basis for this research: "diet" OR "Mediterranean diet" OR "natural food "OR "Fruits

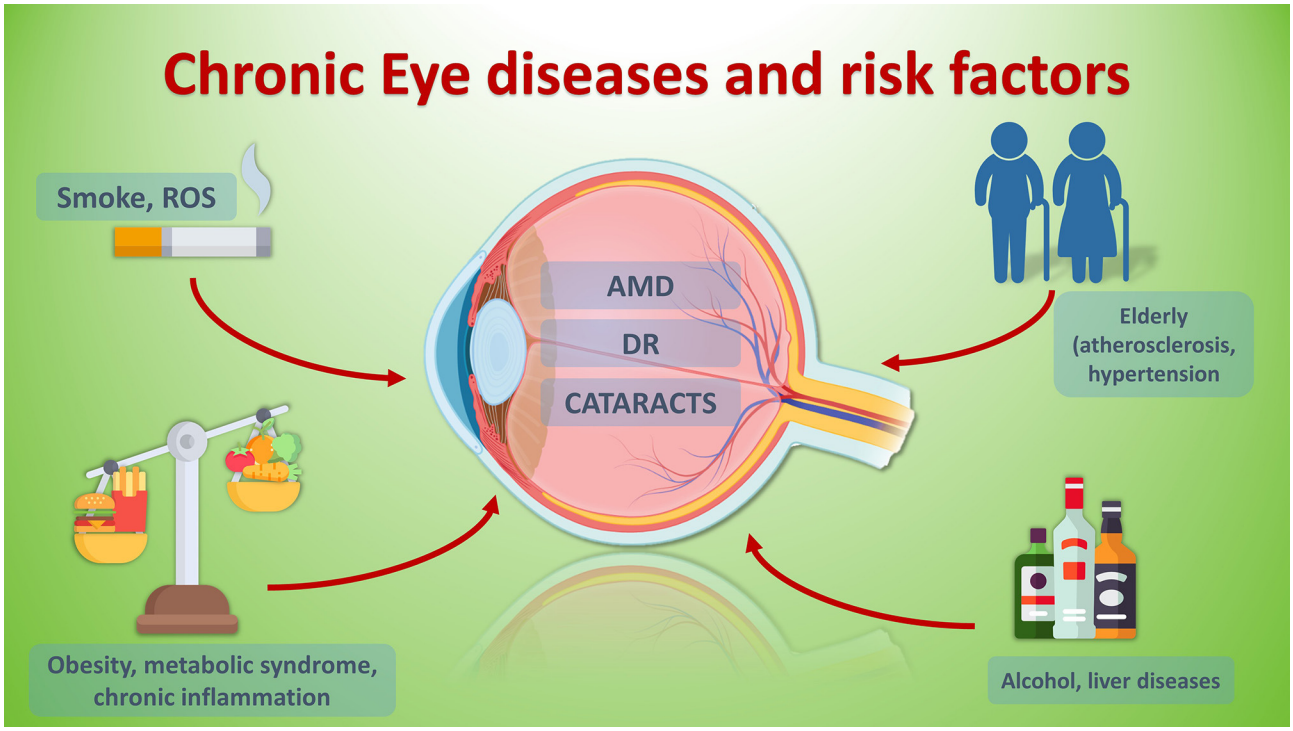


FIGURE 1
Chronic eye disease and risk factors.

and vegetables" OR "nuts" OR "saffron" OR "curcumin" OR "Tea and coffee" AND "diabetic retinopathy" OR "eye diseases" OR "diabetes." Thirty-one articles were consulted, including five narrative reviews, four systematic reviews, one systematic review & meta-analysis, a review of *in vitro* studies, 11 clinical trials (two *post hoc* analyses of randomized trials, one cross-sectional study, one retrospective study, two cohort studies, one randomized controlled trial, two case–control studies, and one prospective trial), six *in vitro* studies, and three studies on animal models.

Table 1 shows the studies that evaluated the relationship between DPs and food and diabetic retinopathy with their strength of evidence.

3.1.2. Nutrients, vitamins, and antioxidants and DR

This research was conducted based on the keywords: "nutrients" OR "Vitamins" OR "antioxidants" OR "Vitamin A and carotenoids "OR "vitamin E" OR "vitamin D and 25-hydroxyvitamin D" OR "Polyphenols" OR "vitamin C" OR "B vitamins" OR "Fatty acids" OR "zinc" AND "diabetic retinopathy" OR "eye diseases" OR "diabetes." Forty-one studies have been referenced, including nine narrative reviews, one systematic review, 19 clinical trials (two cross-sectional studies, five retrospective studies, three cohort studies, five randomized controlled trials, two case–control studies, one prospective study, and one longitudinal study), seven *in vitro* studies, three animal model studies, one book, and one Health Professional Fact Sheet.

Table 2 shows the studies that evaluated the relationship between Nutrients, Vitamins, and antioxidants and diabetic retinopathy with their strength of evidence.

3.1.3. Fiber and hydratation, and DR

The keywords used in this research were: "fiber" OR "hydration status" OR "water intake" AND "DR" OR "eye diseases" OR "diabetes." Six articles were sourced: one narrative review, one systematic review, two cross-sectional studies, one randomized controlled trial, and one *post-hoc* analysis of a randomized trial.

Table 3 includes studies that assessed the connection between fiber and hydration, and DR alongside the strength of evidence.

3.1.4. Gut microbiota and DR

These keywords were used as the basis for the research: "Gut microbiota" OR "dysbiosis;" AND "diabetic retinopathy" OR "eye diseases" OR "diabetes." Four articles were sourced: one narrative review, two studies on animal models, and one comment on a study based on animal models.

3.1.5. PA and DR

This study was done based on the following keywords: "physical activity" OR "sedentary behavior" OR "lifestyle" OR "resistance training" OR "aerobic exercise" AND "diabetic retinopathy" OR "eye diseases" OR "diabetes." Twenty-four articles were sourced: four narrative reviews, three systematic reviews and meta-analysis, one review of *in vitro* studies, one mini review, nine clinical trials (one cross-sectional study, one retrospective study, one cohort study, three prospective trials, and three observational studies), five studies on animal models, and one Clinician's Guide.

The studies that assessed the connection between PA and DR are listed in Table 4 along with their strength of evidence.

Table 5 shows the reviews about DR and DPs.

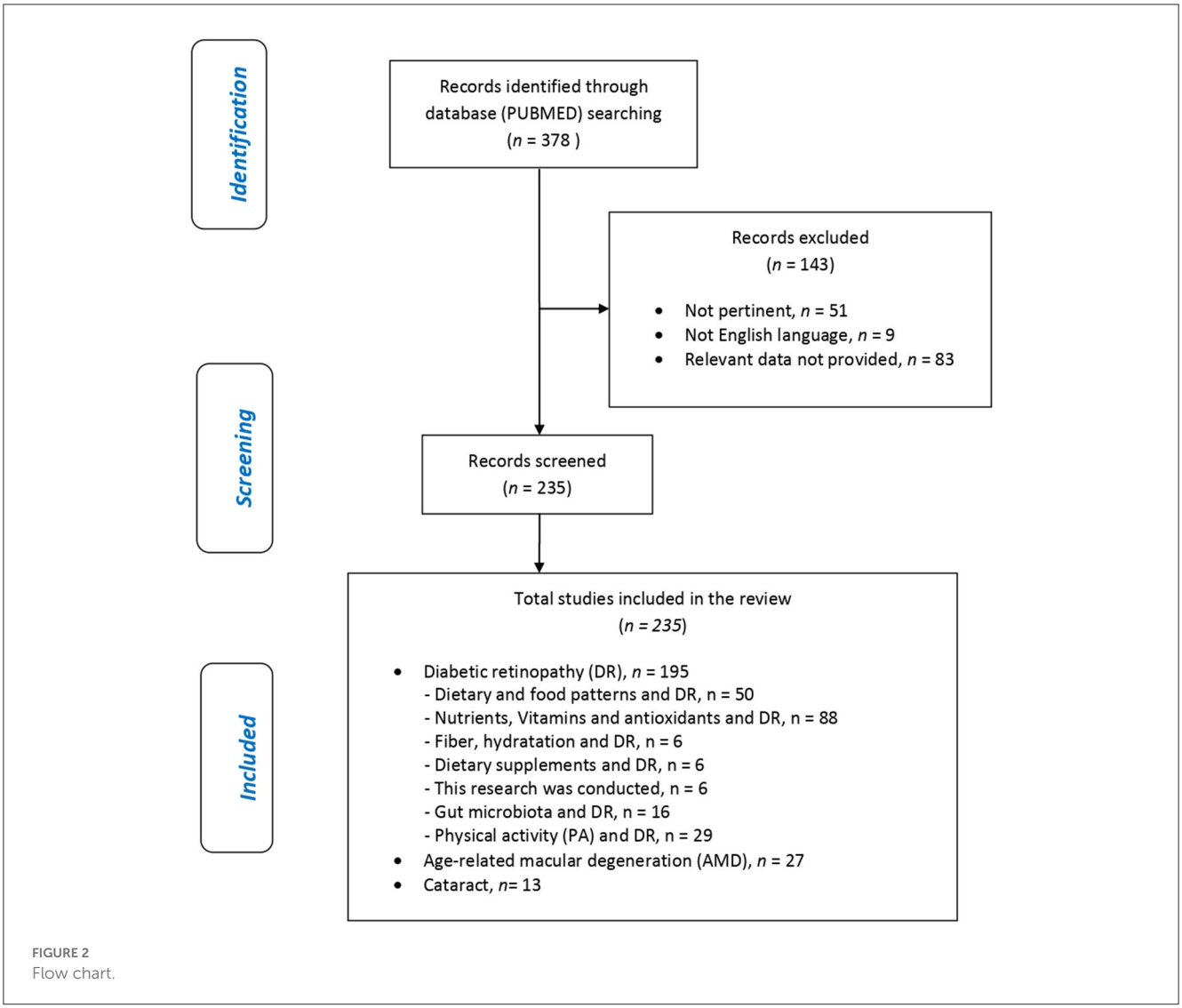


FIGURE 2
Flow chart.

3.2. AMD

This research was conducted based on the keywords: "AMD" OR "AMD" AND "diet" OR "nutrients" OR "nutrition" OR "food" OR "supplements" OR "supplementation." Nineteen articles were sourced: one randomized controlled trial, one cross-sectional trial, seven cohort studies, two multi-center studies, four population-based prospective studies, three case–control studies, and one clinical trial.

Table 6 includes the research that assessed the connection between AMD nutrition, including supplement use, and their level of evidence.

3.3. Cataracts

These keywords served as the basis for the research: "cataract" OR "lens opacities" AND "nutrition" OR "supplementation" OR "supplementation" OR "physical activity" OR "hydration." Eleven articles were sourced: Four observational studies, four case–control studies, one narrative review, one systematic review, and one meta-analysis.

Tables 7, 8 include the research that evaluated the relationship between PA and bone along with the strength of the evidence.

4. Discussion

4.1. DR

DR is a major microvascular complication of diabetic disease and is a major cause of vision loss in working-age populations globally (106–108). In a meta-analysis of 35 studies conducted worldwide between 1980 and 2008, an overall prevalence of DR of 34.6% (95% CI 34.5–34.8), proliferative DR (PDR) of 6.96% (6.87–7.04), and diabetic macular edema (DME) of 6.81% (6.74–6.89) was recorded; it has also been estimated that 10.2% (10.1–10.3) of diabetic patients are at risk of visual impairment from retinopathy (107). Complex microvascular, neurodegenerative, immunological, genetic/epigenetic, and inflammatory interactions

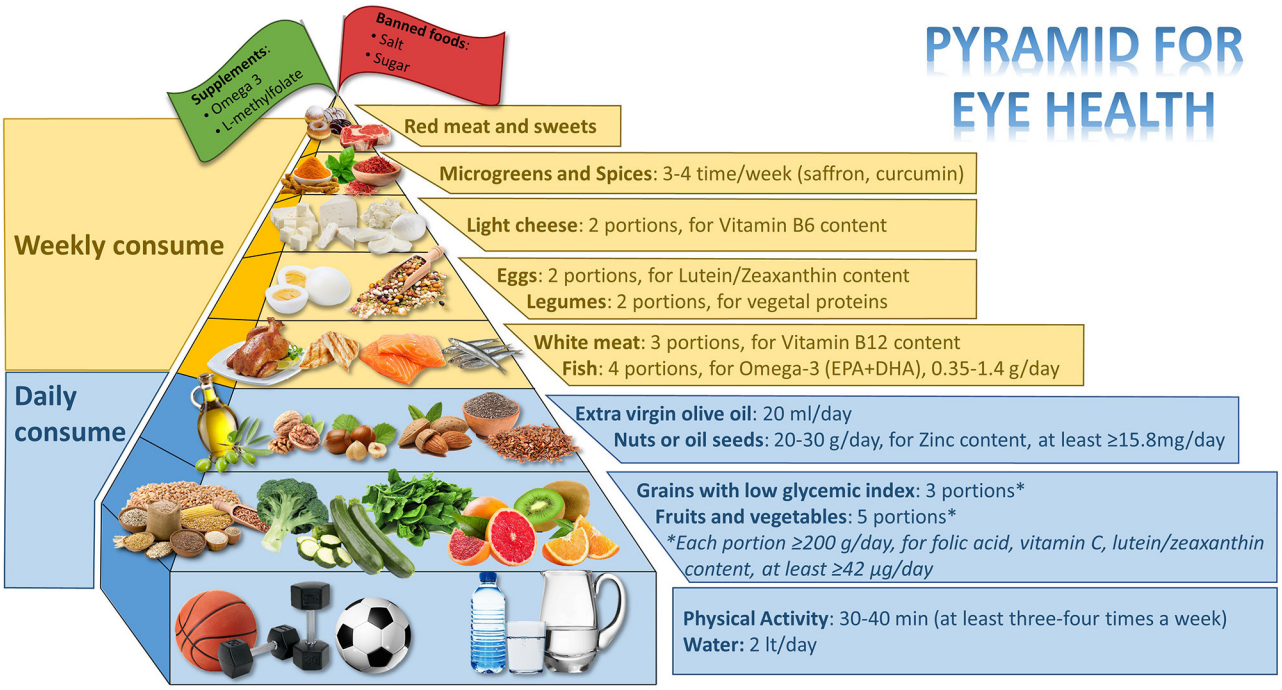


FIGURE 3
Food pyramid for eye health.

contribute to the development of DR (109). Among the various factors involved, there are both modifiable and non-modifiable risk factors. Modifiable risk factors include hyperglycemia, arterial hypertension, dyslipidemia, obesity and inadequate nutritional status, hyperhomocysteinemia, chronic kidney disease, alcohol consumption, and smoking. Those that cannot be modified are represented by gender, age, myopia, duration of the diabetic disease, type of diabetes, and family history of DR (110, 111).

This broad range of pathogenic pathways explains how hyperglycemia is etiologically related to aging and other pathologies, including DR and AMD. Therefore, in this context, these pathologies can be considered metabolic diseases of the retina in all aspects (112).

Obesity is frequently linked to DM and cardiovascular disease as a risk factor. It can be defined by waist-to-hip ratio, waist circumference, and body mass index (BMI). Both higher waist-to-hip ratio and waist circumference are risk factors for DR (113–115). The OR of DR is 1.28 per 5 cm increase in waist circumference (OR = 1.28; 95% CI, 1.05–1.56; $P = 0.014$) (115). Also, malnutrition is a potential risk factor for the development of DR (116).

4.1.1. Hyperhomocysteinemia

The enzyme methylenetetrahydrofolate reductase (MTHFR) is essential for adding the methyl group to folates. Polymorphisms in the MTHFR gene that reduce its activity, impairing the enzyme's ability to generate L-methylfolate, are common (117). These mutations are associated with hyperhomocysteinemia and other diseases, including DR (118, 119). At the cellular level, it has been demonstrated that a high level of homocysteine is harmful to the hemo-retinal barrier and has a pro-inflammatory effect on the epithelial cells of the retinal pigment, with the risk of increasing apoptosis phenomena (120). Elevated homocysteine levels increase the risk of hypertension, hypertensive retinopathy, diabetes, and DR (121) and are also associated with increased incidence and progression of DR (118, 119).

Supplementation with L-methylfolate [the bioactive form of folic acid (118)] can lead to the conversion of homocysteine into methionine, restoring its stocks, regardless of dietary deficiencies or genetic polymorphisms (122, 123). Optimal combinations of vitamins B1, B2, B6, L-methylfolate, methylcobalamin (B12), C, D, natural vitamin E complex, lutein, zeaxanthin, and alpha-lipoic acid are identified for protecting the retina and choroid. Nutritional interventions can support conventional therapies for DR to reduce the disease risk and severity of DR (122).

As far as alcohol is concerned, two important publications in literature have dealt with the relationship between DR and the consumption of alcoholic beverages (124, 125). Both concluded that there was no statistically significant association between alcohol consumption and DR risk. A first meta-analysis was conducted by Zhu in 2017 and included a total of 15 studies. Interestingly, in the statistical analysis analyzing different types of alcoholic beverages, wine or sherry intake was associated with a reduced risk of DR. In the publication, however, it was not possible to establish the dose responsible for this reduction, since there were no statistically significant differences between the various quantities taken (124, 125). The authors attributed this result to the potential protective effects of consuming low-to-moderate alcohol levels on the risk of diabetes mellitus (DM) and cardiovascular disease (126). However, the inflammatory response and oxidative stress could be influenced by alcohol, and are significantly associated with the risk of DR (127, 128). The stratified analyses of this

TABLE 1 Dietary and food patterns and DR.

References	Study design	Study period	Endpoint	Subjects (age, sex, number...)	Method	Results	Strength of evidence
Diaz-Lopez et al. (30)	*Post-hoc* analysis of a randomized trial	6 years (from 2003 to 2009)	To determine the effect of the three dietary interventions on the incidence of diabetes complications.	Type 2 diabetes participating in the "PREvencion con DIeta MEDiterranea (PREDIMED)" randomized clinical trial, who were free of microvascular complications at enrolment (n = 3,614, aged 55–80 years)	Patients were randomly assigned to one of three dietary interventions: MedDiet supplemented with extravirgin olive oil (MedDiet+EVOO), MedDiet supplemented with mixed nuts (MedDiet+Nuts), or a low-fat control diet. Two independent outcomes were considered: new onset of diabetic retinopathy and nephropathy. Hazard ratios (HRs) were calculated using multivariable-adjusted Cox regression.	Compared with the control diet, multivariable-adjusted HRs for diabetic retinopathy were 0.56 (95% CI 0.32–0.97) for the MedDiet+EVOO and 0.63 (0.35–1.11) for the MedDiet+Nuts. No between-group differences were found for nephropathy.	Moderate
Salas-Salvadó et al. (31)	*Post-hoc* analysis of a randomized trial	8 years (2003 to 2011)	To assess the efficacy of Mediterranean diets for the primary prevention of diabetes in the Prevención con Dieta Mediterránea trial.	7447 partecipants at high cardiovascular risk, aged between 55 and 80 years (57% were female)	Participants were randomly assigned and stratified by site, sex, and age but not diabetes status to receive 1 of 3 diets: Mediterranean diet supplemented with extra-virgin olive oil (EVOO), Mediterranean diet supplemented with nuts, or a control diet (advice on a low-fat diet). No intervention to increase physical activity or lose weight was included.	A Mediterranean diet enriched with EVOO but without energy restrictions reduced diabetes risk among persons with high cardiovascular risk.	Moderate
Sala-Vila et al. (32)	Prospective randomized trial	6 years (From 2003 to 2009)	To determine whether LCω3PUFA intake relates to a decreased incidence of sight-threatening DR in individuals with type 2 diabetes older than 55 years	3,614 individuals aged 55 to 80 years with a previous diagnosis of type 2 diabetes, participating in the "PREvencion con DIeta MEDiterranea (PREDIMED)" randomized clinical trial, considering only subjects with type 2 diabetes at baseline.	Dietary intake was assessed at baseline and yearly during follow-up up by using a 137-item semiquantitative food-frequency questionnaire validated for the PREDIMED study. Information on seafood products was collected in 8 items of the questionnaire (uncanned oily fish; lean fish; smoked/salted fish; mollusks; shrimp, prawn, and crayfish; octopus, baby squid and squid; oily fish canned in oil; and oily fish canned in salted water).	In middle-aged and older individuals with type 2 diabetes, intake of at least 500 mg/d of dietary LCω3PUFA, easily achievable with 2 weekly servings of oily fish (as recommended in the Mediterranean diet), is associated with a decreased risk of sight-threatening DR.	Moderate
El Bilbeisi et al. (33)	Cross sectional study	2 years (from 2015 to 2016)	To identify major dietary patterns among DM2 pt and its association with diabetes complications	1,200 T2DM patients, selected by a cluster random sampling method, aged 20–64 years receiving care in the primary healthcare centers (PHCs) in Gaza Strip, Palestine, (59.8% females, 40.2% males)	Data about dietary patterns were collected by an expert nutritionist, using a validated semi-quantitative food frequency questionnaire (FFQ). Dietary patterns were obtained using factor analysis after the classification of food items into 25 groups.	The Asian-like dietary pattern (high intake of whole grains, potatoes, beans, legumes, vegetables, tomatoes and fruit) is associated with a lower prevalence of diabetes complications among DM2 patients rather than sweet-soft drinks-snacks pattern	Low
Tanaka et al. (34)	Cohort	8 years (from 1995 to 2003)	To establish the effect of fruit & vegetables (Vitamin C, Vitamin E, Carotenoids, fiber) intake on DR incidence	This study is part of the Japan Diabetes Complications Study, an open-labeled randomized trial originally designed evaluate the efficacy of a long-term therapeutic intervention focused on lifestyle education. It included 978 patients aged 40–70 years.	Baseline dietary intake was assessed by a food frequency questionnaire based on food groups and 24-h dietary records. Primary outcome was incident diabetic retinopathy determined using international severity scales.	Adequate fruit consumption of 173.2 g per day was associated with a 50% reduced risk of DR incidence, compared with consumption of 53.2 g of fruit per day or less	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 1 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number...)	Method	Results	Strength of evidence
Bazzano et al. (35)	Retrospective	4 years (from 1971 to 1975)	To examine the association of fruit and vegetable intake with the risk of cardiovascular disease	9608 adults aged 25–74 years participating in the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study and free of cardiovascular disease at the time of their baseline examination.	Fruit and vegetable intake at baseline was measured with a food-frequency questionnaire.	The frequency of fruit and vegetable intake is inversely associated with stroke incidence and mortality, ischemic heart disease mortality, cardiovascular disease mortality, and all-cause mortality in the general US population. fruit and vegetables should be consumed in each meal in adequate quantities equal to at least 400 g per day. Each additional serving of fruit and vegetables reduces the risk of cardiovascular events by 4% and stroke by 5%	Low
Sala-Vila et al. (36)	Randomized controlled trial	2 years	To examinate the cognitive effects of a 2-years walnut intervention in cognitively healthy elders	636 participants (63–79 yeras old, 68% women) of the Walnuts And Healthy Aging (WAHA) study (Barcelona, Spain; Loma Linda, CA)	The participants were randomly allocated to a diet enriched with walnuts at ∼15% energy (30–60 g/d) or a control diet (abstention from walnuts). a comprehensive neurocognitive test battery was administered at baseline and 2 years.	Walnut supplementation for 2 y had no effect on cognition in healthy elders. However, brain fMRI and *post-hoc* analyses by site suggest that walnuts might delay cognitive decline in subgroups at higher risk.	Moderate
Nunes et al. (37)	Case-control study	/	To characterize the association of lifestyle and nutritional risk profiles with age-related macular degeneration (AMD) in two subpopulations with differing AMD prevalence.	1,992 participants included 768 patients with AMD and 1,224 age- and sex-matched participants without AMD	Enrolled participants completed a validated lifestyle and food frequency questionnaire. A score to measure adherence to the Mediterranean diet (mediSCORE; Range, 0–9) was constructed from individual food intakes, which were further analyzed by conversion to nutrient consumption	High adherence to a Mediterranean diet and regular physical activity seem to be protective factors for AMD in a Portuguese population. The effect of the diet is likely driven by the increased consumption of vegetables, fruits, and nut.	Low
Ma et al. (38)	Case-control study	1 year (2013)	To determine the association between regular Chinese green tea consumption and the risk of DR in diabetic patients in China.	200 patients: 100 DR patients and 100 age-sex-matched diabetic controls without retinopathy, including 68 men and 132 women aged 35–85 years	DR was defined from retinal photographs and detailed information on Chinese green tea consumption of the participants was collected through a face-to-face interview.	Diabetic patients who had regularly drunk Chinese green tea every week for at least 1 year in their lives had a DR risk reduction of about 50% compared with those who had not.	Low
Hjellvik et al. (39)	Cohort	4 years (from 2004 to 2008)	To study the association between consumption of filtered boiled coffee consumption and incident of type 2 diabetes.	3,62,045 Norwegians (1,71,414 Men and 1,90,631 Women) aged 40–45 years old at the time of health survey administration.	Information on self-reported coffee consumption was available from health surveys conducted from 1985 to 1999 in Norway. Type 2 diabetes incidences were extimated from redeemed prescriptions of oral antidiabetic drugs in the period 1 January 2004 to 1 January 2008 from the Norwegian Prescription Database.	A moderate inverse association was found between consumption of both boiled and other types of coffee at the age of 40–45 years and the risk of being prescribed oral antidiabetic drugs 5–20 years later.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 1 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Tuomilehto et al. (40)	Prospective study	mean follow-up of 12 years	To determine the relationship between coffee consumption and the incidence of type 2 DM among Finnish individuals, who have the highest coffee consumption in the world.	6,974 Finnish men and 7,655 women aged 35 m to 64 years without history of stroke, coronary heart disease, or DM at baseline	Information on self-reported coffee consumption was obtained from combined surveys conducted in 1982, 1987, and 1992. Mean follow-up of 12 years. Main Outcome Measures Hazard ratios for the incidence of type 2DM were estimated for different levels of daily coffee consumption	Coffee drinking has a graded inverse association with the risk of type 2 DM. In both sexes combined, the multivariate-adjusted inverse association was significant (P for trend 0.001) and persisted when stratified by younger and older than 50 years; smokers and never smokers; healthy weight, overweight, and obese participants; alcohol drinker and non-drinker; and participants drinking filtered and non-filtered coffee.	Low

meta-analysis were mixed due to the presence of various types of included studies; therefore, the results of these analyses are unreliable. A second meta-analysis in 2020 by Chen undertaken to correct the previous one and to implement the analysis with the new works that had been published in the meantime, confirmed the results of the previous one, not finding any significant association between alcohol intake and risk of DR of alcoholic beverages (125). However, even in this case, most of the studies considered reported inconsistent results. The Casteldaccia study showed that the duration of alcohol intake between 1 and 19 years was not associated with a risk of DR, but conversely, there was a reduction in the risk of DR with alcohol intake for a greater or equal number of years at 20 (129). According to Beulens' study, people with type 1 diabetes who drink moderate amounts of alcohol had a lower risk of microvascular problems (130). Fenwick showed that people with type 2 diabetes who occasionally consumed white wine had a lower risk of developing diabetic complications (131). This cross-sectional study was conducted in 2015 in patients with type 2DM, who were given a questionnaire that evaluated alcohol consumption and lifestyle. Patients included in the study then underwent retinography, and DR was staged as absent, present without, and at risk of vision loss. The relationship of DR intensity to alcohol consumption was adjusted for clinical-demographic, socioeconomic, and lifestyle factors. After adjusting for traditional risk factors and those for which they varied in univariate analysis, it was discovered that moderate drinkers (1–14 units/week) had a decreased risk of developing DR than non-drinkers. Therefore, the study concludes that in type 2 diabetics, the moderate consumption of alcoholic beverages is independently associated with a reduced risk of DR.

4.1.2. Dietary and food patterns

Regarding DPs, there is evidence for the protective effect of the Mediterranean diet on the onset of DR. Diaz-López conducted a nutritional intervention study in type 2 DM patients who did not have microvascular complications at baseline. Three different dietary models were analyzed: the Mediterranean diet supplemented with extra virgin olive (EVO) oil, the Mediterranean diet supplemented with nuts, and a low-fat control diet. After a 6-year follow-up, it was observed that the Mediterranean diet supplemented with EVO oil had a protective effect on the development of DR (30). A 2018 review by Dow examined the association among individual foods, macro- or micronutrients, dietary supplements, DPs, and DR or DME. In particular, the following were taken into consideration: fruit, vegetables, fish, milk, carbohydrates, fibers, fats, proteins, salt, potassium, vitamins C, D, and E, carotenoids, food supplements, green tea, and alcohol. Studies suggest that adherence to the Mediterranean diet and a high intake of fruit, vegetables, and fish may protect against the development of DR, although evidence is limited (70). Another review, also published in 2018, systematically searched the literature for studies on diet and DR published between 1967 and 2017 using standardized criteria for diet and DR. The review concluded that higher dietary intake of fiber and fish and higher adherence to the Mediterranean diet were protective against DR. Conversely, high total caloric intake was associated with increased risk of DR. No

TABLE 2 Vitamins and antioxidants and DR.

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Brazionis et al. (41)	Cross-sectional study	/	To evaluate the relationship between plasma carotenoids and diabetic retinopathy.	111 individuals with type 2 diabetes aged 44–77 years	Data for clinical and demographic variables and risk factors for diabetic retinopathy were obtained from 24 h urine and fasting blood samples, and an interviewer-assisted lifestyle questionnaire.	The study suggests synergies between carotenoids and DR, regardless of established risk factors. The results indicate that dietary modulation of retinopathy risk may be possible by increasing intakes of lutein- and lycopene-rich foods (higher plasma levels of lutein and zeaxanthin were associated with a lower risk of DR).	Low
Garcia-Medina et al. (42)	Randomized clinical trial	5 years	To evaluate the effect of antioxidant supplementation on DR over a 5-year follow-up period.	105 type 2 diabetic patients with nonproliferative DR, aged 41–68 years (53 males, 52 femakes).	A complete ophthalmic checkup and a plasma determination of oxidative [malonyldialdehyde (MDA)] and antioxidant parameters [total antioxidant status (TAS)] were obtained as the baseline. Patients were randomly assigned to the oral antioxidant supplementation group at nutritional doses (OASG) ($n = 62$) or to the absence of supplementation group (ASG) ($n = 43$). The best-corrected visual acuity, DR score, MDA, and TAS values were compared at the beginning and after 5 years (the end of the follow-up).	Best-corrected visual acuity did not change during the follow-up, irrespective of supplementation. However, the retinopathy stage showed a retardation of progression in the subgroup with supplementation, but worsened in the subgroup with no antioxidant supplementation. Furthermore, the antioxidant supplementation group maintained its antioxidant plasma status levels, which was related to decreased oxidative plasma activity.	Moderate
Zhang et al. (43)	Randomized, double-blind, placebo-controlled trial	9 months	To determine whether supplementation with lutein improved visual function in patients with non-proliferative diabetic retinopathy.	31 patients (8 females, 23 males) aged 40–85 years with type 2 diabetes and NPDR	The participants were assigned randomly to 10 mg/d of lutein or identical placebo for 36 weeks. Visual performance indices, including visual acuity (VA), contrast sensitivity (CS) and glare sensitivity (GS) at four different spatial frequencies, were measured at baseline, week 18 and 36.	In patients with NPDR, supplementation with lutein resulted in potential improvements in CS at low spatial frequency. Further studies are required to determine the possibility that such intervention could be used as an adjunct therapy to prevent vision loss in diabetic patients.	High
Moschos et al. (44)	Retrospective study	2 years	To investigate the effects of a carotenoid supplementation on retinal thickness and macular function of patients with diabetes using optical coherence tomography (OCT) and multifocal electroretinography (mfERG).	120 eyes of 60 patients age between 40 and 60 years with non-insulin dependent type 2 diabetes mellitus without diabetic retinopathy	Patients underwent OCT and mfERG and took vitamin supplements for a period of 2 years. Patients received a carotenoid supplement containing lutein (10 mg), zeaxanthin (2 mg) and meso-zeaxanthin (10 mg) once a day for 2 years. The thickness of the fovea was evaluated using OCT and the macular function was tested by mfERG.	OCT showed an increase in the central foveal thickness and mfERG revealed increased retinal response density within the central 13° surrounding the fovea (rings 1 to 3) at 2 years after the onset of carotenoids supplement intake. The use of carotenoid supplements may be of benefit for improving visual function of type 2 diabetes patients.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 2 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Millen et al. (45)	Cohort study	From 1987 to 1998	To study the association between prevalent DR and intake of vitamins C and E in participants of the Atherosclerosis Risk in Communities Study.	A total of 1353 subjects, aged 45–64 years, with type 2 diabetes diagnosed between 1993 and 1995 or before were included. The subjects were extracted from the Atherosclerosis Risk in Communities Study (ARIC Study), who is a prospective study designed to investigate the etiology of atherosclerosis.	Participants were recruited to return 3 additional times after visit 1: visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998). Dietary data were collected from participants at visits 1 and 3. Eye photographs of the participants were taken only at visit 3. Nutrient intake was assessed with a food-frequency and supplement questionnaire administered between 1987–1989 and 1993–1995. Prevalent retinopathy ($n = 224$) was determined in 1993–1995 from graded fundus photographs.	No association of DR with intake of vitamin C or E from food alone or from food and supplements combined was observed. A decreased odds of DR was found among users (reported use > or =3 y before 1993–1995) of vitamin C or E supplements or multisupplements compared with reported use of no supplements: 0.5 (0.3, 0.8), 0.5 (0.2, 0.8), and 0.4 (0.2, 0.9), respectively. Therefore, supplement use may reflect non-dietary factors or a possible benefit of supplementation.	Low
Mayer-Davis et al. (46)	Longitudinal study	/	to examine the relation between dietary and supplement intakes of vitamins C, E, and beta-carotene and the risk of DR.	A total of 387 participants with type 2 diabetes, from the San Luis Valley Diabetes Study, including non-Hispanic white and Hispanic adults in southern Colorado.	Ordinal logistic regression analysis was used, taking advantage of multiple clinic visits by individual participants and observations from both eyes, to assess the risk for increased DR severity over time as a function of changes in intake of vitamin C, vitamin E, and beta-carotene. Inteake of vitamina C, E and beta-carotene was obtained from a 24-h dietary recall (including vitamin supplement use). Six categories of intake for each nutrient (first to fourth quintiles and ninth and tenth deciles) were considered to ascertain any potential threshold effect. Analyses accounted for age, duration of diabetes, insulin use, ethnicity, glycated hemoglobin, hypertension, gender, and caloric intake.	No protective effect was observed between antioxidant nutrients and DR. Depending on insulin use, there appeared to be a potential for deleterious effects of nutrient antioxidants	Low
Millen et al. (47)	Cohort study	8 years (1987–1995)	To examine the association between vitamin D status and prevalent DR in participants with diabetes from a population-based cohort.	1339 participants (710 females and 629 males, aged 45–65 years) were included from the ARIC Study, recruited participants from different areas of USA. This study sample consists of Caucasian and African American participants with T2DM.	The study steps include 3 visit: at visit 1 (1987–1989) dietary intake of vitamin D was assessed, at visit 2 (1989–1992) the participants had serum 25-hydroxyvitamin (25[OH]D) concentrations assessed and at visit 3 (1993–1995) and non-mydriatic retinal photographs were taken. Logistic regression was used to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) for diabetic retinopathy by categories of season-adjusted 25(OH)D (<30 [referent], 30–<50, 50–<75 and ≥75 nmol/L), by quartile of vitamin D intake (IU/day), and use of vitamin D or fish oil supplements (yes/no). P for trend was estimated using continuous 25(OH)D or vitamin D intake. ORs were adjusted for race, and duration of diabetes. A further adjustement was for HBA1c and hypertension to examine if 25(OH)D influenced diabetic retinopathy via its effects on either glycemic control or blood pressure.	ORs (95 % CIs) for retinopathy, adjusted for race and duration, were 0.77 (0.45–1.32), 0.64 (0.37–1.10), and 0.39 (0.20–0.75), p for trend = 0.001, for participants with 25(OH)D of 30–<50, 50–<75, and ≥75 nmol/L, respectively. No statistically significant association was observed between vitamin D intake from foods or supplements and retinopathy. Therefore, 25(OH)D concentrations ≥75 nmol/L were associated with lower odds of any retinopathy assessed 3 years later. The aauthors suggest this may be due in part to vitamin D's influence on blood glucose control.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 2 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Long et al. (48)	Retrospective, population-based, cross-sectional study	3 years (2005–2008)	To evaluate the association between vitamin D deficiency and retinopathy severity in diabetic patients with poorly or well-controlled glycaemia.	The National Health and Nutrition Examination Survey (NHANES) 2005–2008 data were used for the study. The population included 842 adults (52.8% women) with mean age of 61.2 years.	Outcomes assessed included retinopathy severity, HbA1c levels, socioeconomic, behavioral, and biological factors. Univariate and multivariate regression analysis was used to evaluate association of different parameters with retinopathy severity. The interaction among HbA1c control, vitamin D deficiency, and retinopathy severity were also explored.	Multivariate ordinal regression analysis found being male (odds ratio (OR): 1.602, $P = 0.001$), increased duration of diabetes (OR: 1.072, $P = 3.77E-7$) and poorly controlled HbA1c (OR: 3.522, $P = 2.00E-5$) were associated with greater retinopathy severity. The association between vitamin D deficiency and DR severity only found in diabetic patients with well-controlled glycaemia.	Low
Mahoney et al. (49)	Retrospective, population-based, cross-sectional study	3 years (2003–2006)	To determine the relationship between dietary flavonoid-rich fruit and vegetable consumption on diabetes-related biomarkers (e.g., HgbA1c) and DR.	381 participants with diabetes from the NHANES study 2003–2006, mean age 61.4 years, 53.8% female.	Blood samples were taken to measure C-reactive protein (CRP), HgbA1C, and fasting glucose and insulin. Diabetic retinopathy was assessed from a retinal imaging exam. A high-flavonoid fruit and vegetable consumption (HFVC) index variable was created from a food frequency questionnaire (FFQ).	Greater HFVC was associated (p b 0.05) with lower levels of CRP ($\beta = -0.005$), HgbA1C ($\beta = -0.005$) and glucose ($\beta = -0.59$), with greater HFVC reducing the odds of having DR by 30%. Therefore, adults with diabetes consuming more flavonoid-rich fruits and vegetables had lower degrees of inflammation, better glycemic control, and reduced odds of DR.	Low
Park et al. (50)	Case-control prospective study	/	To determine whether vitreous level of vitamin C is compromised in patients with PDR and to investigate the association of diabetic macular ischemia and vitamin C.	40 patients (13 males, 27 females) who underwent pars plana vitrectomy for the treatment of PDR (PDR group, $n = 20$) and non-diabetic patients with idiopathic epiretinal membrane (control group, $n = 20$). PDR patients (60.4 ± 2.1 y) were younger than non-diabetic control patients (67.4 ± 1.2 y).	Serum, aqueous humor, and the vitreous were collected for the analysis of vitamin C level by HPLC. Diabetic macular ischemia (DMI) in PDR group was evaluated with fluorescein angiography (FA).	Vitreous level of vitamin C in PDR patients showed a 10 fold decrease, which was associated with the degree of macular ischemia. This suggests that vitreous vitamin C depletion may cause macula ischemia in PDR patients.	Low
Gurreri et al. (51)	Retrospective study	/	to demonstrate that statins and vitamin C (alone or in combination with statins) as complementary therapy could have an impact on the non-proliferative NPDR complication rate.	479 patients with NPDR	Statins and vitamin C intake were analyzed, along with the rate of diabetic macular edema (DME), vitreous hemorrhage (VH), circinate maculopathy (CM), and proliferative DR (PDR).	Statins, alone or with vitamin C, appear to reduce the complication rate of NPDR.	Low
Thosar et al. (52)	Randomized Controlled Trial	/	To test the hypothesis that antioxidant Vitamin C prevents the impairment of endothelial function during prolonged sitting.	Eleven men (24.2 ± 4.4 yrs)	Participants are randomized in 2 groups: the sitting without vitamin C (SIT) and the sitting with vitamin C (VIT). Participants were seated for 3 h without moving their legs. Additionally, in the VIT trial, participants ingested 2 vitamin C tablets (1 g and 500 mg) at 30 min and 1 h 30 min, respectively. Superficial femoral artery (SFA) flow-mediated dilation (FMD) was measured hourly for 3 h.	Three hours of sitting resulted in impaired SFA FMD. Antioxidant Vitamin C prevented the decline in SFA FMD, suggesting that oxidative stress may contribute to the impairment in endothelial function during sitting.	Moderate

(Continued)

10.3389/fmed.2023.1168560

TABLE 2 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Memisogullari et al. (53)	Case-control study	/	To assess the relationship between serum homocysteine, a potential parameter for atherosclerosis, and the ocular blood flow velocity and the resistivity index in highway toll collectors.	22 toll collectors (mean age 39,7 ±7,1) and 24 control subjects (mean age 38 ±6,7). All subjects are male.	The peak systolic and end diastolic flow velocities and the resistivity index were measured in 22 toll collectors and 24 control subjects by color Doppler ultrasonography. The resistivity index, which is an indirect measure of the atherosclerotic process, was calculated: resistivity index = (peak systolic velocity – end diastolic velocity)/peak systolic velocity. Serum homocysteine levels were determined by fluorometric high-performance liquid chromatography	There were significant correlations between the serum homocysteine level and ophthalmic artery resistivity index in both highway toll collectors ($p < 0.001$) and controls ($p < 0.005$). Exposure to exhaust particles might increase the serum homocysteine level, which in turn could lead to the decreased ocular blood flow and the increased resistivity index.	Low
Horikawa et al. (54)	Case-control study	/	To investigate the relationship between vitamin B6 intake and the incidence of diabetic retinopathy in Japanese patients with type 2 diabetes.	978 particiapnts from an examination of a nationwide cohort of patients with type 2 diabetes aged 40–70 years with HbA1c ≥ 48 mmol/mol, 47% female.	Cox regression analyses estimated hazard ratios (HRs) for retinopathy according to vitamin B6 intake adjusted for age, gender, body mass index, HbA1c, smoking, energy intake, and other confounders.	HRs for diabetic retinopathy in the 2nd, 3rd, and 4th quartile groups of vitamin B6 intake compared with the 1st quartile group were 1.17 (95% confidence interval 0.81–1.69, $p = 0.403$), 0.88 (0.58–1.34, $p = 0.550$), and 0.50 (0.30–0.85, $p = 0.010$), respectively. Findings suggested that high vitamin B6 intake was associated with a lower incidence of DR in Japanese with type 2 diabetes.	Low
Gopinath et al. (55)	Cohort study	/	To investigate associations between intakes and serum concentrations of folate and vitamin B-12 or serum tHcy and 10-y age-related macular degeneration (AMD) incidence.	1,390 participants, aged 59–78 years from the Blue Mountains Eye Study (BMES, a population-based cohort study of common eye diseases and other health outcomes in a suburban Australian population located west of Sydney. Steps of data collection: Baseline (1992–1994, BMES-1), after 5 y (1997–1999; BMES-2), 10 y (2002–2004; BMES-3), and 15 y (2007–2009; BMES-4).	Serum folate, vitamin B-12, and tHcy were determined from blood samples drawn in 1997–1999 from cohort members aged ≥55 y. AMD was assessed in 1,760 survivors from retinal photographs taken in 2002–2004 and 2007–2009. Total intakes of folate and vitamin B-12 were assessed by using a food-frequency questionnaire.	Elevated serum tHcy and folate and vitamin B-12 deficiencies predicted increased risk of incident AMD, which suggests a potential role for vitamin B-12 and folate in reducing AMD risk.	Low
Sasaki et al. (56)	Cross-sectional study	/	To assess the associations between dietary intake of polyunsaturated fatty acids (PUFAs) and DR.	379 patients (median age: 66.0 years, 66% male) with diabetes attending a diabetes eye clinic	Daily fatty acid intake was assessed by using a validated Food Frequency Questionnaire and adjusted for energy intake. Diabetic retinopathy was graded from fundus photographs as no DR, non-proliferative DR, or proliferative DR. Patients were categorized as "well-controlled diabetes" ($n = 123$) and "poorly controlled diabetes" ($n = 256$), defined as glycated hemoglobin (HbA1c) level < 7.0% or ≥ 7.0%, respectively.	Increasing PUFA intake was associated with a reduced likelihood of the presence and severity of DR in well-controlled diabetes, whereas increasing saturated fatty acid intake was associated with an increased likelihood of the presence and severity of DR.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 2 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Ansar et al. (57)	Randomized Controlled Trial	8 weeks	To examine the effects of alpha-lipoic acid (ALA) treatment over a period of 2 months on fasting blood glucose (FBG), insulin resistance (IR), and glutathione peroxidase (GH-Px) activity in type 2 diabetes (T2DM) patients.	57 type 2 DM patients (n = 57)	Patients were divided into 2 groups to receive either ALA (300 mg daily) or placebo by systematic randomization, and were followed-up for 8 weeks. After an overnight fasting and 2 h after breakfast, patients' blood samples were drawn and tested for FBG, 2 h PPG, serum insulin level, and GH-Px activity.	The study showed a significant decrease in FBG and PPG levels, IR-Homeostasis Model Assessment (IR-HOMA index) and GH-Px level in the ALA group. The comparison of differences between FBG and IR at the beginning and at the end of study in the ALA treated group and the placebo group were also significant. Therefore, this study supports the use of ALA as an antioxidant in the care of diabetic patients.	Moderate
Xiang et al. (58)	Randomized controlled trial	/	To examine endothelial dysfunction (ED) in the fasting state and after a glucose challenge as well as after administration of an antioxidant agent.	The study subjects included 42 with Impaired glucose tolerance (IGT) and 26 healthy individuals (control group).	The IGT patients were randomly divided into two groups, 21 in each group (the alpha-lipoic acid group and the placebo group). In the alpha-lipoic acid group, 300 mg of alpha-lipoic acid was administrated before an oral glucose tolerance test (OGTT); in the placebo group, 250 ml of 0.9% sodium chloride was administrated before the OGTT. In addition, 250 ml of 0.9% sodium chloride was also administrated to the control subjects before the OGTT (control group), and then vascular function was examined in the fasting state and repeated 1 and 2 h after the glucose load. High-resolution ultrasound was used to measure flow-mediated endothelium-dependent arterial dilation (FMD) and glyceryltrinitrate (GTN)-induced endothelium-independent arterial dilation.	In subjects with IGT, FMD was impaired both in the fasting state and after a glucose challenge, probably through increased production of oxygen-derived free radicals. The Endothelial dysfunction observed after a glucose challenge is related to the extent of hyperglycaemia and thiobarbituric acid reactive substances, and an antioxidant agent can improve the impairment of endothelial function induced by acute hyperglycaemia.	Moderate
Luo et al. (59)	Retrospective	1 years	To analyze the relationship between zinc level and each diabetic microvascular complication and identify the features related to low serum zinc level.	412 hospitalized T2D patients (233 males, 179 females, aged 41–71 years) In Department of Endocrinology, Peking University People's Hospital, Beijing, China, from May 30, 2013 to March 31, 2014.	The authors initially compared the serum zinc levels between patients with specific microvascular complications and those without. They then analyzed the association between zinc level and each microvascular complication. Furthermore, they identified the unique features of patients with high and low serum zinc levels and analyzed the risk factors related to low zinc level.	Lower serum zinc level in T2D patients was related to higher prevalence of diabetic microvascular complications, and represented as an independent risk factor for DN. Patients with lower zinc level were more likely to have a longer duration of diabetes, poorer glucose control, and worse β-cell function.	Low

10.3389/fmed.2023.1168560

TABLE 3 Fiber, hydratation, and DR.

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Diaz- Lopez et al. (30)	*Post-hoc* analysis of a randomized trial	6 years (from 2003 to 2009)	To determine the effect of the three dietary interventions on the incidence of diabetes complications.	Type 2 diabetes participating in the "PREvencion con DIeta MEDiterranea (PREDIMED)" randomized clinical trial, who were free of microvascular complications at enrolment (n = 3,614, aged 55–80 years)	Patients were randomly assigned to one of three dietary interventions: MedDiet supplemented with extravirgin olive oil (MedDiet+EVOO), MedDiet supplemented with mixed nuts (MedDiet+Nuts), or a low-fat control diet. Two independent outcomes were considered: new onset of diabetic retinopathy and nephropathy. Hazard ratios (HRs) were calculated using multivariable-adjusted Cox regression.	Compared with the control diet, multivariable-adjusted HRs for diabetic retinopathy were 0.56 (95% CI 0.32–0.97) for the MedDiet + EVOO and 0.63 (0.35–1.11) for the MedDiet+Nuts. No between-group differences were found for nephropathy.	Moderate
Salas-Salvadó et al. (31)	Randomized controlled trial	4 years	To test the effects of two Mediterranean diet (MedDiet) interventions vs. a low-fat diet on incidence of diabetes.	418 non-diabetic subjects aged 55–80 years recruited in one center of the Prevención con Dieta Mediterránea [PREDIMED] study, a large nutrition intervention trial for primary cardiovascular prevention in individuals at high cardiovascular risk.	Participants were randomly assigned to education on a low-fat diet (control group) or to one of two MedDiets, supplemented with either free virgin olive oil (1 liter/week) or nuts (30 g/day). Diets were *ad libitum*, and no advice on physical activity was given. The main outcome was diabetes incidence diagnosed by the 2009 American Diabetes Association criteria.	The Mediterranean diet, in fact, rich in food sources of fiber, such as fruit, vegetables and unrefined carbohydrates, has been associated with a reduced incidence of DR.	High
Zhang et al. (60)	Cross-sectional study	3 years	To explore the association between hydration status and DR.	5,220 US adults 40 years of age and older (2005–2008 NHANES study)	Serum osmolality was used to assess hydration status for all participants and calculated osmolality was evaluated for only older people.	Adults with lower hydration status had higher risk of DR, moderate/severe non-proliferative retinopathy, and proliferative diabetic retinopathy. Dehydration in older adults, classified by calculated osmolality, is associated with a higher rate of DR.	Low

10.3389/fmed.2023.1168560

TABLE 4 Physical activity (PA) and DR.

References	Study design	Study period	Endpoint	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Praidou et al. (61)	Cross-sectional, non-interventional study	1 years	to investigate potential correlation between physical activity and diabetic retinopathy	320 patients were included in the study: 240 patients with diabetes type 2 (80 patients with mild to moderate NPDR, 80 patients with severe to very severe NPDR and 80 ones with PDR) were compared with 80 non-diabetic patients (control group).	Physical activity of patients was assessed by the international physical activity questionnaire. HbA1c and BMI were also measured in diabetic patients. Group comparisons were attempted for levels of physical activity and sedentary behavior.	Increased physical activity is associated with less severe levels of diabetic retinopathy, independent of the effects of HbA1c and BMI.	Low
Yan et al. (62)	Cohort study	10 years	To examine the association of physical activities (PA) with diabetic retinopathy (DR) progression based on a 10-year follow-up of a large cohort of working-aged diabetic populations in Australia.	Nine thousand and eighteen working-aged diabetic patients were enrolled from the baseline of the 45 and Up Study from New South Wales, Australia.	Self-reported PA collected by questionnaire at baseline in 2006 was graded into low (<5 sessions/week), medium (≥5 to 14), and high (≥14) levels. Retinal photocoagulation (RPC) treatment during the follow-up period was used as a surrogate for DR progression and was tracked through the Medicare Benefits Schedule, which was available from 2004 to 2016. Cox regression was used to estimate the association between PA and RPC incidence.	Higher PA level was independently associated with a lower risk of DR progression among working-aged diabetic populations in this large cohort study.	Low
Kuwata et al. (63)	Prospective observational study	2 years	To assess the association between baseline levels of physical activity (PA) and the incidence of newly developed diabetic retinopathy (DR) in patients with type 2 diabetes.	1,814 patients (mean age 65.5 years) with type 2 diabetes without DR were obtained from a Japanese diabetes registry at Tenri Hospital, Nara, Japan.	The participants were divided into five categories based on their PA levels. A Cox proportional hazards model with time-varying exposure information was used and adjusted for potential confounders to assess the independent correlations.	higher PA was independently associated with a lower incidence of DR in patients with type 2 diabetes.	Low
Al-Othman et al. (64)	Observational study	/	To determine whether the prevalence of vitamin D deficiency is related to degree of physical activity and sun exposure among apparently healthy Saudi children and adolescents.	331 Saudi children aged 6–17 years (153 boys and 178 girls)	Levels of physical activity and sun exposure were determined using a standard questionnaire. Anthropometry, serum calcium and 25-(OH) vitamin D were analyzed.	Vitamin D deficiency is common among Saudi children and adolescents, and is influenced by both sun exposure and physical activity. Promotion of an active outdoor lifestyle among Saudi children in both homes and schools may counteract the vitamin D deficiency epidemic in this vulnerable population.	Low
Scott et al. (65)	Prospective study	mean follow-up of 2.6 ± 0.4 years	To verify prospective associations between 25OHD, muscle parameters, and PA in community-dwelling older adults.	Six hundred and eighty-six community-dwelling older adults (49% women; mean ± SD 62 ± 7 years old).	Appendicular lean mass percentage (%ALM) and body fat assessed by Dual-energy X-ray Absorptiometry, leg strength by dynamometer, leg muscle quality (LMQ), PA assessed by pedometer, self-reported sun exposure by questionnaire, and serum 25OHD measured by radioimmunoassay.	25OHD may be important for the maintenance of muscle function, and higher skeletal muscle mass and function as well as general PA levels may also be beneficial for 25OHD status, in community-dwelling older adults.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 4 (Continued)

References	Study design	Study period	Endpoint	Subjects (age, sex, number...)	Method	Results	Strength of evidence
Klenk et al. (66)	Observational study	1 week	To analyse the seasonal relationship of objectively measured physical activity with vitamin D status in older persons from Southern Germany (latitude: 48.4°N).	1,193 community-dwelling individuals aged ≥65 years (58% men)	Physical activity was assessed in participants over 1 week using a thigh-worn accelerometer. Furthermore, the 25-hydroxyvitamin D (25(OH)D) level was measured. Least-square means of 25(OH)D serum levels were calculated for quartiles of average daily walking duration stratified by season and adjusted for gender, age and body mass index.	Although a positive dose-response relationship was seen between walking duration and the 25(OH)D serum level for most seasons, vitamin D insufficiency was still very prevalent even in high-active persons during all seasons.	Low
Black et al. (67)	Prospective study	6 years	To investigate vitamin D status and predictors of serum 25-hydroxyvitamin D (25(OH)D) concentrations in adolescents.	1,045 Australian adolescents	Serum 25(OH)D concentrations were measured in the same participants at 14 and 17 years (*n* 1,045 at both time points). The authors examined the predictors of serum 25(OH)D concentrations, including sex, race, month of blood collection, physical activity, BMI, family income, and Ca and vitamin D intakes (*n* 919 at 14 years; n 570 at 17 years), using a general linear mixed model.	The authors identified physical activity as a significant predictor of serum 25(OH)D concentrations in 258 adolescents	Low
Herrmann et al. (68)	Observational study	5 years	To investigate the relationship between blood 25-hydroxyvitamin D (25OH-D) concentration and vascular disease risk in type 2 diabetes.	9,795 participants aged 50–75 years with type 2 diabetes from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial	The relationships between blood 25OH-D concentration at baseline and the incidence of macrovascular (including myocardial infarction and stroke) and microvascular (retinopathy, nephropathy, neuropathy, and amputation) disease were analyzed with Cox proportional hazards models and logistic regression.	Low blood 25OH-D concentrations are associated with an increased risk of macrovascular and microvascular disease events in type 2 diabetes.	Low
Schneider et al. (69)	Retrospective study	10 years	To examine the effects of a program of diet and exercise on various metabolic and hemodynamic parameters, and to assess the ability of patients to perform physical training safely.	255 previously sedentary diabetic patients and 58 control subjects	A group of individuals with diabetes attempted to use regular exercise as part of their therapeutic management. The patients were followed for varying times, up to 1 yr after entry into the physical training component of a diabetes lifestyle modification program. Metabolic and hemodynamic parameters were collected.	Study suggests a program of regular aerobic training can be safely and effectively used in an outpatient population with diabetes mellitus for up to 3 mo.	Low

10.3389/fmed.2023.1168560

TABLE 5 Dietary and food patterns and DR.

References	Study design	Purpose	Main findings
Dow et al. (70)	Systematic review	To identify, summarize and interpret the literature on the association between the diet and dietary intakes of specific foods, nutrients, and food groups, and the risk of diabetic retinopathy.	Adherence to the Mediterranean diet and high fruit, vegetable and fish intake may protect against the development of diabetic retinopathy, although the evidence is limited. Studies concerning other aspects of the diet are not in agreement. The role of the diet in the development of diabetic retinopathy is an area that warrants more attention.
Wong et al. (71)	Systematic review	To study the associations between dietary intake and DR, with the primary goal of providing a comprehensive assessment of the existing knowledge on the topic.	No significant associations of carbohydrate, vitamin D, and sodium intake with DR were found. Associations of antioxidants, fatty acids, proteins and alcohol with DR remain equivocal. Dietary fiber, oily fish, a Mediterranean diet and a reduced caloric intake are associated with lower risk of DR.
Francisco et al. (3)	Narrative review	To discuss the impact of dietary patterns on the incidence and progression of age-related eye diseases, namely age-related macular degeneration (AMD), cataracts, diabetic retinopathy, and glaucoma.	The authors found strong evidence about dietary patterns in regard to AMD and some in cataract, but there is surprisingly little conclusive evidence linking specific dietary patters with DR and glaucoma. Across studies looking at AMD progression, there are consensus findings that adherence to a prudent dietary pattern, the Mediterranean diet, and the healthy eating index all protect against AMD and that the western dietary pattern can accelerate AMD progression.
Ros et al. (72)	Narrative review	To focused on the latest findings concerning health effects of walnuts and ALA and relevant micronutrients.	Walnuts have a high content of fiber, polyphenols, phytosterols, gamma-tocopherol, and mainly linolenic acid (ALA), as well as various minerals, which confer antioxidant, anti-inflammatory, cardio- and neuro-protective, antithrombotic, antiarrhythmic, hypocholesterolemic properties and regulation of the intestinal microbiota
Poulose et al. (73)	Narrative review	To review evidences for the beneficial effects of consuming a walnut-rich diet.	Polyphenolic compounds found in walnuts not only reduce the oxidant and inflammatory load on brain cells but also improve interneuronal signaling, increase neurogenesis, and enhance sequestration of insoluble toxic protein aggregates.
Valero-Vello et al. (74)	Systematic review	To identify he role of diet and nutrition in the eyes and vision, and the potential antioxidant, anti-inflammatory and neuroprotective effects of natural food (broccoli, saffron, tigernuts and walnuts), the MD and nutraceutic for patients at risk of vision loss.	Nut-enriched diet bring benefits in ocular diseases, such as glaucoma, DR and degenerative maculopathy, chronic pathologies of a degenerative nature for the ocular structures, which have common pathophysiological mechanisms, related precisely to oxidative stress and inflammation
Meng et al. (75)	Systematic review	To summarize and discusses the effects of tea against diabetes mellitus and its complications based on the findings from epidemiological, experimental, and clinical studies, with the special attention paid to the mechanisms of action.	Epidemiological studies found that drinking tea could reduce the risk of diabetes mellitus and diabetic complications. In addition, experimental studies have shown that tea could protect against diabetes mellitus and diabetic complications by improving insulin resistance, activating the insulin signaling pathway, playing an insulin-like role, improving oxidative stress, and alleviating inflammatory response. Further, tea has synergistic effects with certain antidiabetic drugs. Tea has been observed to act as a potent neuroprotector in the retina.
Natella et al. (76)	Narrative review	To examine the possibility that the pattern of coffee consumption could influence risk of type 2 diabetes, and to evaluate the possible relationship between coffee consumption and other risk factors associated with diabetes.	The studies conducted thus far provide a clear indication that healthy, habitual coffee drinkers are more protected from the risk of contracting diabetes than individuals who do not drink coffee. Long-term consumption of coffee is able to reduce oxidative stress. This could be due to the caffeine itself, which is considered an antioxidant, but also to other coffee components,
Akash et al. (77)	Narrative review	To explore and summarize the scientific literature on the potential effects of coffee consumption on T2DM.	Coffee may directly affect different mechanistic factors that are involved in the pathogenesis of T2DM. Several components of coffee may ameliorate the symptoms of T2DM by affecting glucose regulation. These may include the effects of CGA on glucose-6-phosphatase, the antioxidant activity of polyphenols on α-glucosidase, and the effects of caffeine on insulin secretion.
Carlström et al. (78)	Meta-analyses of observational studies	To cover current knowledge regarding the effects of coffee consumption on development of T2D or modulation of adverse complications. Moreover, bioactive components in coffee, polymorphisms, and potential underlying mechanisms in relation to T2D and adverse complications are discussed.	Available evidence indicates that coffee consumption is inversely associated with risk of T2D. Possible mechanisms behind this association include thermogenic, antioxidative, and anti-inflammatory effects; modulation of adenosine receptor signaling; and microbiome content and diversity.

TABLE 6 Nutrition and AMD.

References	Study design	Study period	End point	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Gopinath et al. (55)	Cohort study	2 years	Association between intakes and serum concentrations of folate and vit B12 or serum tHcy and 10-y AMD incidence	1,760 subjects aged ≥ 55 years	Serum folate, vit B12, and tHcy determined from blood samples drawn	Elevated serum tHcy and folate and vit B12 deficiencies predicted increased risk of incident AMD, suggesting a potential role for vit B12 and folate in reducing AMD risk	Low
Seddon et al. (79)	Cross-sectional study	/	Modifiable risk and protective factors for AMD among elderly twins	681 twins (222 with intermediate or advanced stage AMD and 459 without AMD or with initial signs of the disease)	Eye examination, fundus photography, food frequency and risk factor questionnaires. Risk for AMD according to cigarette smoking and dietary fat intake estimated using logistic regression analyses.	Cigarette smoking increases risk while fish consumption and omega-3 fatty acid intake reduce risk of AMD	Low
Chua et al. (80)	Cohort study	5 years	Associations between dietary fat and incident age-related maculopathy (ARM)	2,335 subjects aged ≥ 49 years	Semiquantitative food frequency questionnaire	Participants in the top quintile of omega-3 fatty acid intake had a lower risk of early AMD onset than the lowest quintile, with a 40% reduction in incidence when consuming fish at least once a week. No association between incident ARM and butter, margarine, or nut consumption.	Low
Tan et al. (81)	Cohort study	5 and/or 10 years	Relationship between baseline dietary fatty acids and 10-year incident AMD	3,654 participants examined at baseline and 2,454 examined 5 and/or 10 years later	Evaluation of AMD from retinal photographs; semiquantitative food frequency questionnaire	Evidence of protection against early AMD from regularly eating fish, greater consumption of omega-3 polyunsaturated fatty acids, and low intakes of foods rich in linoleic acid. Association between consumption of 1–2 portions of nuts per week (compared to less than one portion per week) and a reduction in the risk of early AMD.	Low
SanGiovanni et al. (82)	Case-control study (AREDS study)	/	Association of lipid and vit C intake with baseline severity of AMD	4,519 subjects (60–80 years of age at enrolment)	Stereoscopic color fundus photographs; estimates of habitual nutrient intake through self-administered semi-quantitative food frequency questionnaires	Top quintile of total long-chain omega-3 intake and DHA associated with a lower risk of neovascular AMD (NV AMD) than the bottom quintile. Higher consumption of fish inversely related to NV AMD; arachidonic acid taken with food directly associated with the incidence of this pathology. Reduced probability of developing neovascular AMD in subjects with the highest vitamin C intake (not confirmed following addition of covariates).	Low
Robman et al. (83)	Cohort study	7 years	Effects of dietary intake of lutein, zeaxanthin and fats on the progression of AMD	252 subjects (134 F—118 M) diagnosed with early AMD	Food frequency questionnaires to estimate the intakes of lutein, zeaxanthin and fatty acids	Association of increased intakes of dietary lutein, zeaxanthin and omega-3 fatty acids with progression of AMD, suggesting that too much of a good thing might be harmful.	Low/Moderate

(Continued)

10.3389/fmed.2023.1168560

TABLE 6 (Continued)

References	Study design	Study period	End point	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Delcourt et al. (84)	Population-based study	1 year	Correlation between fats and increased risk of age-related maculopathy	832 subjects ≥70 years	Dietitian-administered food-frequency questionnaire	Association of high total, saturated and monounsaturated fat intake with increased risk for ARM. Total polyunsaturated fatty acid not significantly associated with ARM. Total and white fish intake not significantly associated with ARM; association of fatty fish intake (more than once a month vs. less than once a month) with a 60% reduction in risk for ARM	Low
Seddon et al. (85)	Multicenter case-control study	1 year	Relationship between intake of total and specific types of fat and risk for AMD	349 cases (age 55–80 years), affected by advanced neovascular AMD, and 504 controls without AMD but with other ocular diseases	Standardized interview, physical examination, ophthalmic examination, laboratory analysis of blood specimens, semi-quantitative food-frequency questionnaire (a modification of an extensively validated questionnaire, containing a list of food items selected as the major sources of a variety of nutrients and adapted for use among elderly subjects with eye disease)	Higher intake of specific types of fat (including vegetable, monounsaturated, and polyunsaturated fats and linoleic acid) rather than total fat intake associated with greater risk for advanced AMD. Inverse association between diets high in omega-3 fatty acids and fish and risk for AMD if low intake of linoleic acid.	Low
Chiu et al. (86)	Clinical trial	8 years	Effects of AREDS supplement, intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and dietary glycaemic index (dGI) on AMD	2,924 subjects, mean age 69.3 years, 1,698 F−1,226 M	Validated 90-item modified Block FFQ; stereoscopic fundus photographs of the macula.	Association of higher intakes of DHA, EPA and lower dGI with a lower risk for progression to advanced AMD.	Moderate
Seddon et al. (87)	US multicentre study EDCCS (Eye Disease Case-Control Study)	/	Association of blood levels of carotenoids and dietary carotenoids and vitamins C, A and E intake with risk of AMD.	421 patients with neovascular AMD and 615 controls	Blood analysis; surveys.	Markedly reduced risk (equal to one-half and one-third, respectively) in subjects with intermediate and high blood levels of carotenoids compared to participants with low levels; subjects in the top quintile of dietary carotenoid intake with a risk of AMD 43% lower than subjects in the bottom quintile (lutein and zeaxanthin associated with the strongest reduction of AMD risk). No statistically significant association between consumption of vitamin C and risk of AMD.	Low
Snellen et al. (88)	Case-control study	/	Association of low antioxidant intake with the occurrence of AMD	72 cases and 66 control patients	Interview on antioxidant intake (i.e., in fruit and vegetables), cigarette smoking, sunlight exposure and familial predisposition. Antioxidant intake calculated according to the method described in the Framingham Eye Study.	Prevalence rate of AMD in patients with low antioxidant intake and low lutein intake (dichotomized at the median value) about twice as high as that in patients with high intake, with a clear dose–response relationship.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 6 (Continued)

References	Study design	Study period	End point	Subjects (age, sex, number...)	Method	Results	Strength of evidence
Goldberg et al. (27)	NHANES study	2 years	Determination of factors associated with the prevalence of AMD.	Subjects aged ≥45 years at the time of the ophthalmology examination	Ophthalmology examination; FFQ.	Negative association of the frequency of consumption of fruits and vegetables rich in vitamins A and C with the prevalence of AMD after stratified adjustment for age.	Low
Simonelli et al. (89)	Case-control study	/	Determination of the weight of oxidative status as risk factor in the early stage of AMD.	Forty-eight ARM patients (19 early and 29 late form) and 46 normal subjects	Determination of serum/plasma antioxidants (vitamins C, E, A, total and individual carotenoids, zinc, total plasma antioxidant capacity— TRAP) and oxidative parameters (reactive oxygen metabolites—ROM, oxidized-low-density lipoprotein antibodies—anti-Ox- LDL).	Association of a deficit of antioxidants (vitamins C, E and carotenoids) with AMD in Italian patients, particularly the advanced form (in AMD patients macular susceptibility to oxidative damage not related with age).	Low
Kassoff et al. (90)	11- center, randomized, placebo-controlled, double-masked clinical trial (AREDS)	Average follow-up of 6.3 years	Photographic assessment of progression to or treatment for advanced AMD and at least moderate visual acuity loss from baseline.	3,640 participants, aged 55–80 years (3416 M−224 F)	Participants randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide, and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.	Statistically significant reduction fof the development of advanced AMD with antioxidants plus zinc. Association of both zinc and antioxidants plus zinc with significantly reduced odds of developing advanced AMD. No statistically significant serious adverse effect associated with any of the formulations.	High
Klein et al. (91)	Population-based prospective study (Beaver Dam Eye Study)	15 years	Incidence of age-related cataracts, AMD, and high IOP for one set of analyses and incidence of supplement use for the second set of analyses.	Participants in the Beaver Dam Eye Study contributing data in 1988 to 1990 (n = 4,926), 1993 to 1995 (n = 3,722), 1998 to 2,000 (n = 2,962), and 2003 to 2005 (n = 2,375).	Data about use of all medications and supplements collected from participants at each of 4 examinations; intraocular pressure (IOP) measurement and fundus and lens photography at each visit; visual field data available only from baseline; photographs of the lenses, retina, and discs graded using standard protocols by trained graders.	Little evidence of any significant associations between supplement use and incident ocular outcomes except for a small protective effect for cortical cataracts by vitamins A and D, zinc, and multivitamins and increased odds of late AMD. Association of late AMD with incident use of vitamins A, C, and E and zinc.	Low
Merle et al. (92)	Prospective cohort study	13 years of follow-up	Association of adherence to the Mediterranean diet and genetic susceptibility with progression to advanced AMD	2,525 subjects (1,124 M−1401 F)	Demographic questionnaires; FFQ; the alternate Mediterranean diet (aMeDi) score; examination of ten genetic loci in 7 genes.	Association of a higher adherence to a Mediterranean diet with reduced risk of progression to advanced AMD, modifiable by genetic susceptibility.	Low
de Koning-Backus et al. (93)	Prospective population-based cohort study	9.1 ± 5.8 years of follow-up	Association of the intake of vegetables, fruit, and fish with incident AMD.	4202 participants from the Rotterdam Study (≥55 years of age)	Fundus photographs; validated 170-item FFQ (food intakes categorized into food patterns based on guidelines from Health Council).	Association of a diet of 200 grams per day of vegetables, fruit two times per day, and fish two times per week with a significantly reduced risk of AMD.	Low

(Continued)

10.3389/fmed.2023.1168560

TABLE 6 (Continued)

References	Study design	Study period	End point	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Chiu et al. (94)	/	/	Relationship of predominant dietary patterns with AMD	A total of 8,103 eyes from 4,088 participants	Using principle component analysis, characterization of major and minor dietary patterns; logistic regression.	Association of the two major patterns (Oriental and Western) with both early and advanced AMD; no association of minor patterns with early AMD; only four of these significantly associated with advanced AMD, including Steak pattern, Breakfast pattern, Caribbean pattern and Peanut pattern.	Low
Amirul Islam et al. (95)	Cohort study	9–17 years of follow-up	Odds ratios for early stages and advanced AMD in association with dietary patterns	21,132 participants, aged 40 to 70 years	Retinal photographs; FFQ; principal component analysis used to identify dietary patterns; logistic regression.	Association of a dietary pattern high in fruits, vegetables, chicken, and nuts and a pattern low in red meat with a lower prevalence of advanced AMD; no association of a particular food pattern with the prevalence of the earliest stages of AMD.	Low

significant association was found among carbohydrates, vitamin D, sodium, and DR; however, the association between DR and antioxidants, fatty acid (FA), proteins, and alcohol remained in doubt (71). In a more recent review, released in 2020, the effect of DPs on the occurrence and development of age-related eye illnesses such as DR, degenerative maculopathy, cataracts, and glaucoma was reviewed. Treatments for diabetes should slow the growth of DR. However, only a small number of research have confirmed if following particular DPs or eating a more or less healthy diet affects the prevalence of DR (3). For example, the randomized clinical trial PREDIMED (Prevention with Mediterranean Diet) (132) demonstrated how adherence to the Mediterranean diet could prevent diabetes. To see if DR might be avoided similarly, it seemed sense to do so. According to Dáz-post-hoc López's *post-hoc* analysis of the PREDIMED research, consuming 500 mg/day of omega-3 fatty acids (a readily feasible intake with strong adherence to the Mediterranean DP) considerably lowers the chance of getting DR (30).

Eating fish (an omega-3-rich dietary source) does, in fact, assist to delay the onset of DR. Eating oily fish at least two times weekly (rather than less frequently) has been related to a roughly 60% lower incidence of retinopathy (32). According to a 2017 cross-sectional study carried out in Palestine, a healthy eating pattern known as "Asian," which is characterized by a high intake of whole grains, potatoes, legumes, vegetables, and fruit, can be linked to a lower prevalence of diabetes problems. This was contrasted with the "sweet-soft drinks-snacks pattern," which was described as a harmful eating behavior characterized by high consumption of refined cereals, sugar, sweets, desserts, snacks, and soft drinks (33).

4.1.3. Fruits and vegetables

In a Japanese cohort study that considered type 2 DM patients, a high fruit intake was linked to a decreased risk of DR. It was discovered that daily fruit eating of at least 173.0 g was related to a 50% lower risk of retinopathy incidence than daily fruit consumption of 53.2 g or less (34). Fruits and vegetables are generally good sources of flavonoids, fiber, minerals, and vitamins. They should be consumed in sufficient amounts, or at least 400 g per day, at each meal. The risk of cardiovascular events is decreased by 4% and the risk of stroke is decreased by 5% with each additional serving of fruit and vegetables (35).

4.1.4. Nuts

Gamma-tocopherol, phytosterols, polyphenols, fiber, and linolenic acid (ALA) are all abundant in walnuts, as well as various minerals, which confer antioxidant, anti-inflammatory, cardio- and neuro-protective, antithrombotic, antiarrhythmic, hypocholesterolemic properties, and regulation of the intestinal microbiota (72). Nut consumption has been linked in human clinical trials to enhance cognitive function, with favorable effects on memory, learning, motor coordination, anxiety, and locomotor activity (36, 73). These researches also concluded that a diet high in nuts is beneficial for treating brain disorders and other chronic conditions linked to inflammation and oxidative stress (36, 37, 73). These health benefits also occur at the ocular level in various diseases, such as glaucoma, DR and degenerative maculopathy,

TABLE 7 Nutrition and cataract (observational studies and case-control studies).

References	Study design	Endpoint	Study period	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Christen et al. (96)	Observational study	to examine whether higher fruit and vegetable intake reduces the risk of cataract and cataract extraction in a large, prospective cohort of women.	8 years of medium follow up	39,876 apparently healthy female health professionals aged ≥45 y	Fruit and vegetable intake was assessed at baseline with the use of a validated, semiquantitative food-frequency questionnaire. A total of 35 724 of these women were free of a diagnosis of cataract at baseline and were followed for incident cataract and cataract extraction.	During an average of 10 y of follow-up, 2,067 cataracts and 1,315 cataract extractions were confirmed. Compared with women in the lowest quintile of fruit and vegetable intake, women with higher intakes had modest 10–15% reduced risks of cataract (P for trend < 0.05).	Moderate
Jacques et al. (97)	Observational study	To assess the relation between usual nutrient intake and subsequently diagnosed age-related nuclear lens opacities	15 years	Four 478 non-diabetic women aged 53–73 years without previously diagnosed cataracts sampled from the Nurses' Health Study cohort	Usual nutrient intake was calculated as the average intake from 5 food frequency questionnaires that were collected during a 13- to 15-year period before the evaluation of lens opacities. The duration of vitamin supplement use was determined from 7 questionnaires collected during this same period	vitamin C intake remained significantly associated ($P = 0.003$ for trend) with the prevalence of nuclear opacities. The prevalence of nuclear opacities was significantly lower ($P < 0.001$) in the highest vitamin C intake quintile category relative to the lowest quintile category (odds ratio, 0.31; 95% confidence interval, 0.16–0.58). There were also statistically significant trends of decreasing prevalence of nuclear opacities with increasing duration of use of vitamin C ($P = 0.004$ for trend).	MODERATE
Delcourt et al. (84)	Observational study	To assess the associations of plasma lutein and zeaxanthin and other carotenoids with the risk of age-related maculopathy (ARM) and cataract in the population-based Pathologies Oculaires Liées à l'Age (POLA) Study	–	2,584 participants, age over 60 years	Cataract classification was based on a direct standardized lens examination at the slit lamp, according to Lens Opacities Classification System III. Plasma carotenoids were measured by high-performance liquid chromatography (HPLC), in 899 subjects of the cohort.	After multivariate adjustment, the highest quintile of plasma zeaxanthin was significantly associated with reduced risk of nuclear cataract (OR = 0.23; 95% CI: 0.08–0.68; P for trend = 0.003) and any cataract (OR = 0.53; 95% CI: 0.31–0.89; P for trend = 0.01). Among other carotenoids, only β-carotene showed a significant negative association with nuclear cataract.	Moderate
Moeller et al. (98)	Observational study	to evaluate associations between nuclear cataract (determined from slitlamp photographs between May 2001 and January 2004) and lutein and zeaxanthin in the diet and serum	–	total of 1,802 women aged 50 to 79 years with intakes of lutein and zeaxanthin above the 78th (high) and below the 28th (low) percentiles in the Women's Health Initiative Observational Study (1994–1998) were recruited 4 to 7 years later (2001–2004) into the Carotenoids in Age-Related Eye Disease Study.	Serum samples were obtained from participants at WHI baseline examinations (1994–1998) after a ≥ 10-h fast and were stored at −80 degrees centigrade 0.29 Serum levels of lutein, zeaxanthin, and tocopherols were determined at Tufts University (2004–2005) by a reverse phase HPLC analysis. Measurements were made using a standardized protocol by the psychophysical method of heterochromatic flicker photometry (HFP) during CAREDS study visits conducted from 2001 to 2004. This protocol, described in detail previously, 20, 33 had high test-retest reliability ($r = 0.9$) and participant response. T-tests, ANCOVA, and Chi-Square tests were performed to assess the statistical significance of potential covariates	Women in the group with high dietary levels of lutein and zeaxanthin had a 23% lower prevalence of nuclear cataract (age-adjusted odds ratio, 0.77; 95% confidence interval, 0.62–0.96) compared with those with low levels.). Women in the highest quintile category of diet or serum levels of lutein and zeaxanthin as compared with those in the lowest quintile category were 32% less likely to have nuclear cataract (multivariable-adjusted odds ratio, 0.68; 95% confidence interval, 0.48–0.97; P for trend = 0.04; and multivariable-adjusted odds ratio, 0.68; 95% confidence interval, 0.47–0.98; P for trend = 0.01, respectively).	Moderate

(Continued)

10.3389/fmed.2023.1168560

TABLE 7 (Continued)

References	Study design	Endpoint	Study period	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Pastor-Valero et al. (99)	Case-control study	To Investigate the association of antioxidant vitamins and minerals and risk of cataract in a Mediterranean population	-	Cases with cataract (343) and 334 age/sex frequency-matched controls aged 55 to 74 y were selected from an ophthalmic outreach clinic	Participants were interviewed about their diet using a Food Frequency Questionnaire, and other information on potential confounders, such as smoking, alcohol, and education. Blood samples were analyzed by a colorimetric method for vitamin C and by reversed-phase HLPC for other blood antioxidants	Blood levels of vitamin C above 49 micromol/L were associated with a 64% reduced odds for cataract ($P < 0.0001$). Dietary intake of vitamins C, E and selenium were marginally associated with decreased odds ($P = 0.09$, $P = 0.09$, $P = 0.07$, respectively), whereas moderately high levels of blood lycopene (>0.30 micromol/L) were associated with a 46% increased odds of cataract ($P = 0.04$). results strengthen the evidence for a protective role for vitamin C on the aging lens as this effect was seen in a population characterized by high vitamin C intakes	Moderate
Ghanavati et al. (100)	case-control study	To evaluate and compare healthy eating index among the patients with cataract and healthy individual	–	97 patients with cataract and 198 healthy people (as a control group)	Individuals were selected by the convenience sampling method and the food frequency questionnaire (FFQ) was completed for them. At first, HEI was calculated and then the HEI scores were compared in cataract patients and healthy individuals.	The analysis of FFQ showed that the scores of vegetables (7.81 vs. 10), nutritional variation (5.5 vs. 7) and sodium (2 vs. 6) groups ($P < 0.001$) were significantly lower among the patients with cataract than the healthy individuals. Also this significant difference was observed in the scores of total HEI and fruits (respectively 73.26 vs.79.30 and 7.1 vs. 9.8) ($P < 0.01$). On the other hand, the scores of saturated fatty acids (10 vs. 9; $P = 0.02$), total fat (8 vs. 7; $P = 0.004$) and cereals (10 vs. 10; $P < 0.001$) were higher among the patients with cataract than the healthy individuals. In addition, after adjusting the confounding factors the results showed that the HEI high score was associated with reducing the risk of coming down with cataract (OR = 0.18, CI: 95%, $P < 0.001$, 0.08–0.41).	Moderate

(Continued)

10.3389/fmed.2023.1168560

TABLE 7 (Continued)

References	Study design	Endpoint	Study period	Subjects (age, sex, number…)	Method	Results	Strength of evidence
Sedaghat et al. (101)	case-control study	To assess the relation between nutrient patterns and cataract risk	–	97 cataract patients and 198 matched controls.	Dietary consumption was collected through a valid food frequency questionnaire (FFQ). Nutrient patterns were detected by applying factor analysis. Unconditional logistic regression models were used to estimate odds ratio (ORs) and 95%Cis. They identified 5 main nutrient patterns: -Pattern 1: included niacin, thiamin, carbohydrates, protein, zinc, vitamin B6 and sodium (sodium pattern) -Pattern 2: characterized by oleic acid, monounsaturated fats, polyunsaturated fats, linoleic acid, trans fatty acid, linolenic acid, vitamin E and saturated fats (fatty acid pattern). -Pattern 3: factor represented high intake of vitamin B12, vitamin D, cholesterol and calcium (mixed pattern) -Pattern 4: high in intake of beta and alpha carotene, vitamin A and vitamin C (antioxidant pattern). - Pattern 5: pattern loaded heavily on docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (omega-3 pattern)	In crude and multivariate analysis, the sodium pattern was associated with increased risk of cataract (OR = 1.97, 95%CI: 1.09–3.96). The fatty acid pattern elevated the risk of cataract (OR = 1.94, 95%CI: 1.1–3.86). Antioxidant pattern was associated with a significant 79% reduced risk (2nd category compared with the 1st). Omega-3 pattern was significantly negatively associated with risk of cataract ($P = 0.04$).	Moderate
Minassian et al. (102)	case-control study	To investigate the association between cataract and clinical manifestations concearning hydratation	24 months	1,364 patients, 881 males, 483 females. Divided in cataract and non-cataract group depending on ophthalmic diagnosis	All patients aged 30 to 69 attending the eye unit during the study period were systematically tested and examined to assess visual acuity and central lens opacities. Generalities and antropometry were assessed. All patient underwent an interview about past risk factor and past diseases concearning hydratation.	The results strongly confirm the findings from the first study and indicate thatan estimated 38% of blinding cataract may be attributable to repeated de-hydrational crises resulting from severe life threatening diarrhoeal disease and/or heatstroke. The risk of blinding cataract was strongly related to level of exposure to de-hydrational crises in a consistent and dose-dependent manner, thus indicating a causal association.	Moderate

10.3389/fmed.2023.1168560

TABLE 8 Nutrition and cataract (reviews).

References	Study design	Purpose	Main findings	Strength of evidence
Chong and Wong (103)	Narrative review	To examine literature evidences about cataract and nutrition	Dietary modifications that can retard cataract formation, if found, can have pro- found implications by reducing the personal, community, and financial burden caused by this common condition. However, based on the literature available currently, definitive recommendations on the use of a multivitamin supplement in preventing age-related cataract are premature	Low
Jiang et al. (104)	Meta-analysis	To summarize quantitatively the prospective association between physical activity and age-related cataract (ARC) risk	The findings from this Meta-analysis provide additional evidence that increased physical activity is inversely associated with age-related cataract risk dose-responsively	High
Sherwin et al. (105)	Systematic review	To investigate current evidence implicating changes in hydration and their association with ocular physiology and morphological characteristics and to asses relevant clinical correlations of changes in hydration and major common eye diseases	systemic hydration status broadly affects a variety of ocular pathophysiologic processes and disease states and the assessment of hydration status may be an important consideration in the management of patients with chronic eye diseases.	High

and chronic pathologies of a degenerative nature for the ocular structures, which have common pathophysiological mechanisms related precisely to oxidative stress and inflammation (74).

4.1.5. Saffron

In DR, saffron may reduce insulin resistance in patients with "prediabetes" (74). It has been shown *in vitro* that saffron can control the activation of microglia. Moreover, crocin (the carotenoid that gives saffron its distinctive color) supplementation reduces retinal thickness and enhances visual acuity in patients with diabetic macular edema, perhaps as a result of its anti-inflammatory effects (120).

This was observed in a double-blind, placebo-controlled, randomized phase 2 clinical trial. Sixty patients with diabetic maculopathy refractory to conventional therapy [including macular photocoagulation and intravitreal injection of an endothelial growth factor inhibitor (bevacizumab) with or without steroids (triamcinolone)] were considered. Patients were divided into three groups: patients in the crocin group were given 5 mg or 15 mg crocin tablets daily for 3 months, while patients in the placebo group received one placebo tablet daily during the study. Best corrected visual acuity (BCVA) and central macular thickness (CMT) were measured at baseline, and then monthly for a total of 3 months post-operatively. Blood chemistry tests were also evaluated at baseline and at the end of the study. BCVA and CMT were evaluated as primary outcomes, while glycated hemoglobin (HbA1c) and fasting blood glucose (FBS) were investigated as secondary outcomes in this study. The results showed that administering crocin tablets 15 mg daily could significantly reduce HbA1cg and CMT and improve BCVA compared to the placebo group. Although administering crocin tablets 5 mg daily can improve HbA1c, FBS, CMT, and BCVA, the difference was not significant compared with the placebo group. Thus, this study highlighted how crocin may act as a potent antioxidant and neuroprotective in short-term refractory DME; however, the clinical significance has yet to be demonstrated in a longer study with a larger sample size that includes treatment-naïve patients (120).

4.1.6. Curcumin

Literature has shown that turmeric has an interesting activity on the retina; *in vitro*, treatment of high-glucose-induced human retinal endothelial cells (HRECs) with curcumin significantly reduced the intracellular production of reactive oxygen species (ROS), as well as the release of tumor necrosis factor-α (TNFα) (133).

Similar results were also obtained when curcumin was added to particular cell lines of the retinal pigment epithelium, called ARPE-19 (a spontaneous human retinal pigment epithelium cell line with normal karyotype that forms polarized epithelial monolayers on porous filter media) (134, 135).

Curcumin reduced the production of ROS and increased the expression of heme oxygenase-1 (HO-1), a type of redox-sensitive protein, whose activation protects cells from various types of stress. These findings imply that curcumin exhibits indirect antioxidant activity in addition to direct antioxidant activity by enhancing the activity of HO-1 and other antioxidant enzymes (134, 136).

Similarly, Maugeri argued that curcumin treatment can largely prevent the changes of DNA methyltransferase activity in high glucose-related stress ARPE-19 cells by downregulation of ROS production (137).

Given this background, although the studies are currently conducted exclusively *in vitro* and in the animal model, the results of the same encourage the routine intake of curcumin at least weekly.

4.1.7. Tea and coffee

Tea has been found to act as a strong neuroprotector in the retina (75), inhibiting neovascularization and protecting

pericytes preventing neovascularization (138). By lowering the production of ROS, boosting the expression of the glutamate transporter, reestablishing intercellular connections, and promoting glutamine/glutamate recycling, green tea can preserve retinal neurons in diabetes patients and control the retinal microenvironment (139). Furthermore, a low dose of green tea improves antioxidant defenses, reduces markers of inflammation, and prevents retinal basement membrane thickening (140). In a Chinese case–control study, including diabetic patients without DR, regular consumption of Chinese green tea every week for at least 1 year was associated with a reduced likelihood of DR in female subjects, but not in male subjects (38). In an animal model study, black tea was shown to lower blood sugar and slow the development of cataracts (141). Green and black tea (in 1.25% water) were administered to streptozotocin-induced diabetic rats for 3 months. Normal and diabetic control groups were also studied. As expected, the tested diabetic animals showed a significant increase in lens and plasma glucose. Red blood cell lens and sorbitol were significantly increased due to activation of the aldose reductase pathway. The thiobarbituric acid reactive substances of plasma, lens lipids, and protein glycation were also significantly elevated. Both teas significantly inhibited diabetic cataracts and caused significant reductions in the biochemical pathway implicated in the development of the disease. After corrections for glucose, teas have been found to delay the development of diabetic cataracts due to a hypoglycemic effect, which in turn inhibits biomarkers of the disease. Significant correlations were found among glucose level, cataract severity, and these indicators. Green tea, but not black tea, caused a significant drop in triglycerides in diabetic animals. The study concludes that tea may be a simple and cost-effective means of preventing or delaying diabetes in humans and resulting complications. Therefore, tea should also be studied as a therapeutic adjuvant in the treatment of diabetes. As for coffee, its long-term consumption can reduce oxidative stress (76). This could be due to the caffeine itself, which is considered an antioxidant, but also due to other coffee components, such as some trace elements (zinc, copper, and iron) and other substances, including chlorogenic acid (CGA), cafestol, trigonelline, and caffeic and ferulic acids (77). By modifying adenosine signaling, inhibiting glucose-6-phosphatase, inhibiting glucose-6-phosphate translocase 1, inhibiting intestinal glucose absorption, decreasing glucose production in the liver, increasing insulin secretion from pancreatic islets, and improving peripheral insulin sensitivity and glucose uptake, caffeine and CGA affect insulin and glucose homeostasis (by stimulation of the glucose transporter type 4 (GLUT4) and modulation of the activation of the intracellular signaling pathway that includes Akt, AMPK, and MAPK) (78). In healthy, obese, and 2DM adults, regular coffee consumption can reduce levels of pro-inflammatory biomarkers. The anti-inflammatory adiponectin, interleukin 4, and interleukin 10 can all be increased by it (76, 77). A Norwegian study found that high compared with low coffee consumption reduced the risk of type 2 DM by about 35% (39). This study looked at more than 360,000 subjects between 40 and 45 years of age, over 20 years, who were divided according to coffee consumption into four groups: <1 cup of coffee per day, 1 to 4 cups/day, 5 to 8, or more than 9 cups of coffee per day. The group that drank less than one cup of coffee per day was used as a reference. Compared to this, the other groups had relative risks of developing type 2 DM (0.87 for the 1–4 cups/day group, and 0.65 for both the 5–8 cups/day and > 9 cups/day groups). This regards the consumption of "boiled" coffee, while for other types of coffee, mainly filtered, the relative risks were as follows: 0.84 (1–4 cups/day), 0.67 (5–8 cups/day), and 0.62 (>9 cups/day). Similar results were obtained in a Finnish cohort study, in which coffee consumption was inversely correlated with type 2 DM (40).

4.1.8. Nutrients

4.1.8.1. Vitamins and antioxidants

It has been demonstrated that vitamins and antioxidants (such as vitamins C, E, and carotenoids) may play a role in the pathogenesis of DR as they lead to a reduction of retinal neovascularization, with the restoration of blood flow and have a protective role against free radicals (142). Furthermore, vitamins C and E appear to suppress vascular endothelial growth factor (VEGF) production in animal models and decrease advanced glycation end-products (AGEs) accumulation. Vitamin C can decrease protein kinase C activation (143), prevent glucose-induced pericyte apoptosis (144), and reduce oxidative stress in human retinal pigment epithelium (145). Given these premises, several studies have attempted to establish whether there was a relationship between DR and dietary antioxidant intake.

4.1.8.2. Vitamin A and carotenoids

According to Brazionis, greater plasma levels of lutein and zeaxanthin were linked to a decreased risk of DR, just like they were for AMD (41). Taking lutein supplements at a level of 6 mg per day for 20 days per month (considered a "nutritional" intake, meaning typically ingested with a healthy and diverse diet) can stop the progression of DR within 5 years, according to a randomized trial on certain antioxidants (42). Patients with non-proliferative DR (NPDR) who take 10 mg of lutein daily report improved contrast sensitivity, glare, and visual acuity (43). In a 2-year study, diabetic individuals without DR who received 10 mg of lutein and 12 mg of zeaxanthin/day showed improved retinal density on multifocal electroretinography and a modest increase in non-edematous foveal thickness (44).

4.1.8.3. Vitamin D

It was observed that plasma concentrations of 25-hydroxyvitamin D ≥75 nmol/L were associated with a reduced probability of developing retinopathy at 3 years (47). Subsequently, in a 2017 retrospective cross-sectional study on over 800 adults emerged that an optimal level of vitamin D is fundamental for reducing the risk and severity of DR (48).

4.1.8.4. Polyphenols

A cross-sectional study by Mayoney examined the effect of flavonoids in diabetic patients who were divided into groups based on the frequency of consumption of fruits and vegetables with high flavonoid contents. It was observed that there was a significant association between a high intake of these foods and lower levels of c-reactive protein (CRP), HgbA1C, and glucose. In addition to

lower levels of inflammation and better glycemic control, these patients also had a 30% reduction in the likelihood of DR (49).

4.1.8.5. Vitamin C

It was observed that patients with PDR had a 10-fold lower level of ascorbate in the vitreous humor and a greater tendency to DME (50), and that vitamin C taken with statins decreased NPDR, in a dose-dependent manner, more than statins alone (51). However, regarding the vitamin C–DR relationship, not all studies agree: a Japanese cohort study found that high vitamin C intake (4th quartile) was associated with a 40% reduction in retinopathy risk (34), while two cross-sectional studies showed no association between vitamin C consumption and retinopathy (45, 46), except for an increased likelihood of retinopathy in the 9th decile of vitamin C intake in the study by Mayer-Davis (46). In diabetic subjects, oral supplementation with 1,500 mg of vitamin C reduces capillary endothelial dysfunction (52) and therefore can be a useful support in microvascular pathologies such as RD.

4.1.8.6. B vitamins

Vitamin B1 (thiamine). In addition to controlling intracellular glucose and preventing the activation of the polyol pathway, which is brought on by increased intracellular glucose levels, thiamine is a powerful free radical scavenger (146). This pathway represents one of the mechanisms in the pathogenesis of DR (147). Furthermore, elevated serum thiamine levels protect the vascular endothelium from injury by advanced glycation end products (146, 148, 149). As reported in a 2020 review published in "Eye and Vision" by Shi, for the treatment and prevention of vascular end-organ damage, such as that seen in DR and diabetic nephropathy, high-dose thiamin supplementation (50–100 mg/day) is safe and effective for neuroprotection. Because of the low toxicity, no upper limits (UL) have been recorded (150).

Vitamin B2 (riboflavin). Riboflavin supplementation in humans likely guards against damage caused by oxidative stress, hyperglycemia, and homocysteine (53, 151, 152). Supplementing with vitamins B6 and B12 may also be advantageous since these nutrients lower homocysteine levels (150).

Vitamin B6. A cohort of Japanese 2DM patients was followed for 8 years, monitoring vitamin B6 intake and DR onset. It was noted that low vitamin B6 intake (particularly the lowest quartile of vitamin B6 intake) was correlated with a higher incidence of DR (54). There are various forms of B6, and the naturally occurring active form pyridoxal-5-phosphate (P5P) is the safest and most efficient form for lowering homocysteine levels (153). P5P supplementation may lower the chance of developing DR and diabetes. Vitamin B6 therapy alone, at a dosage of 50–200 mg per day, was associated with a decreased long-term incidence of DR in a small cohort trial of a few participants (150).

Vitamin B9 (folate). The use of supplements with L-methylfolate, B2, B6 (in the form of P5P), and B12 can reduce homocysteine levels, the incidence of DR, and other diabetes-related diseases (150).

Vitamin B12 (Cobalamin). Increased homocysteine levels, as already stated, are linked to decreased cerebral and retinal blood flow, as well as decreased central retinal artery caliber, VEGF expression, and DR (53, 55, 154). Supplementation with vitamin B12 increases the release of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (155) and allows for the reduction of DR-associated long-term complications (140). The active transport necessary for gastrointestinal absorption of vitamin B12 from food requires the presence of an intrinsic factor, an acidic environment, and an intact intestinal mucosa (156).

4.1.8.7. FA

FA can influence retinopathy through several pathways. First, the accumulation of long-chain FA can lead to activation of the protein kinase C pathway, just as occurs with excess glucose (112, 157). Second, since the retina is an extremely oxidizing and polyunsaturated fatty acids (PUFA)-rich environment, an accumulation of lipids can more easily undergo peroxidation and accumulation of advanced lipoxidation end products (ALEs) (158). Both ALEs and AGEs activate a pro-inflammatory response via the AGE receptor, which activates the proinflammatory transcription factor NF-kB and decreases the antioxidant response (159). Concerning the PUFA and DR relationship in Sazaki's study, an increase in PUFA intake was linked to a lower likelihood of DR occurrence and severity in individuals with well-controlled diabetes, whereas an increase in short-chain fatty acid intake (SFA) was linked to a higher probability of DR occurrence and severity (56). A 500 mg/day consumption of omega-3 FA can greatly lower the possibility of developing DR, as was highlighted in a *post-hoc* analysis of the PREDIMED study by Diáz-López (32). Alpha lipoic acid, an important cofactor of mitochondrial metabolism, has an antioxidant action by counteracting ROS and enhancing the effects of endogenous antioxidants such as glutathione and vitamins C and E (160). The administration of alpha lipoic acid shields the retina's ganglion cells and pigment epithelial cells, in particular, from ischemic damage and apoptosis (161). Furthermore, alpha lipoic acid reduces hyperglycemia and hyperglycemia-induced endothelial dysfunction in type 2 DM patients (57, 58). Daily supplementation with 600 mg of alpha lipoic acid is safe and well-tolerated (150).

4.1.8.8. Zinc

Several chronic disorders, including metabolic syndrome, diabetes-related complications, such as DR, and metabolic syndrome, are known to advance more quickly when there is zinc deficiency. Low serum zinc levels correlate with DM duration, elevated HbA1c levels, hypertension, and microvascular complications. Blood zinc levels gradually decline with DR duration and severity (59).

4.1.8.9. Fiber

A higher risk of getting DR is linked to lower dietary fiber consumption (162). Furthermore, once this complication occurs, intensive glycemic control can slow the rate of development (163). The Mediterranean diet is rich in food sources of fiber, such as fruits, vegetables, and unrefined carbohydrates, and has been associated with a lower incidence of DR (30, 31).

4.1.8.10. Hydratation

Results emerging from the review by Sherwin et al. showed that chronic activation of the renin-angiotensin-aldosterone system (RAAS) may be implicated in the pathogenesis of DR and glaucoma, thus suggesting a possible new therapeutic target on

which to base new studies' intervention (105). The cross-sectional population analysis of the 2005–2008 NHANES study (5220 US adults 40 years of age and older) also found that low levels of hydration, as assessed by measured (or calculated) formulas based on blood levels of glucose, sodium, potassium, and urea (limited to subjects aged ≥65 years), were associated with an increased risk of DR (60). So, the intake of adequate quantities of water, equal to 1.5–2 liters per day, is a fundamental objective to achieve.

4.1.8.11. Gut microbiota

Beli (164) first described the link between the gut microbiome and DR in differently fed rodents. The intermittently fasting mice exhibited retinal histology that was comparable to that of non-diabetic controls, while the *ad libitum* diet animals displayed ocular symptoms of DR. Intermittently fasted rodents showed increased Firmicutes to Bacteroidetes ratio and changes in bacterial metabolites, with increased levels of taurochenodeoxycholate (TUDCA) derived from bile acids and known to have anti-inflammatory effects. TUDCA enters the bloodstream and activates GPBAR1, even referred to as TGR5, the TUDCA receptor in the retina. The results imply that intermittent fasting may protect against DR by increasing TUDCA levels and, in addition, TGR5 could represent a novel therapeutic target for the diabetic retina (165). Regarding the role of prebiotics, oligofructose, used alone or in combination with metformin, is effective in preventing the development of DM and its microvascular complications, opening the door for new treatment approaches and research ideas (166). These results suggest that the growth of beneficial bacteria in patients with healthy diets, either through pre- and probiotics, or even through intermittent fasting, could protect against the development of T2DM (167).

4.1.8.12. Physical activity

Increased PA reduced the risk of its onset (61, 62). Higher levels of PA were shown to be independently linked to a decreased incidence of DR in type 2 DM patients (63). A minimum of 30 min of PA, 5 days a week, might minimize the risk of DR advancement by 40% (168). Conversely, it has been revealed that diabetic subjects who lead a sedentary lifestyle have a higher risk of developing DR than those who live actively (169). The results of a meta-analysis also revealed a possible mechanism of impact of PA on DR due to improved glycemic control (170). An alteration in 25-hydroxyvitamin D levels could be another probable mechanism. Supporting evidence is the finding in subjects of all ages that 25-hydroxyvitamin D levels improve with increased PA (64–67, 171). Low levels of 25-hydroxyvitamin D in the blood have been linked to an increased risk of macrovascular and microvascular events, including DR (68). Furthermore, exercise has been shown to modulate oxidative stress (172). Research on animal models has shown that exercise reduces oxidative stress in the retinas of DR mice (173–176). It should be remembered, however, that high-intensity resistance and aerobic exercise should be avoided in diabetic patients with DR to lower the risk of vitreous hemorrhage or retinal detachment (69, 177). Moreover, the risk of vitreous hemorrhage is increased by any exercise which can lead to a rise in systolic blood pressure (178, 179). In animal model studies of diabetic disease, resistance exercise has been shown to lead to increased muscle mass (180). Skeletal muscle is an essential reservoir of glucose in the body, and exercise is a powerful stimulator of glucose uptake, which in part is stored within skeletal muscles (181). Resistance exercise has a direct impact on skeletal muscle and may be used to manage individuals with DM2 (182).

4.2. AMD

In the transversal AREDA study conducted on 4,088 participants (whose eyes were divided into three groups: controls, early AMD, and advanced AMD), two major DPs were identified: the Western pattern and the Oriental pattern by using a food frequency questionnaire (FFQ) with subsequent factorial analysis. The first pattern had a higher prevalence of progressive AMD, while an "oriental" dietary style appears to be protective against this pathology (183). Furthermore, according to a recent review, for both early and late AMD, abdominal obesity would be a risk factor (184). In a 2013 cohort study that enrolled 1,760 subjects aged ≥55 years, the authors tried to provide epidemiological evidence for the possible relationship among serum levels of homocysteine, vitamin B12, and folate, and the risk of AMD, finding that high homocysteine levels, as well as a vitamin B12 or folate deficiency, were linked to a higher incidence of AMD at age 10 years; this risk was decreased by 47% with vitamin B12 supplementation (55). Moreover, the effects of several dietary sources, including omega-3 and omega-6 fatty acids, mono-, polyunsaturated, and saturated fats, total fats, trans fats, and cholesterol, on the risk of AMD have been investigated. In particular, omega-3 has anti-inflammatory properties and, when transformed into neuroprotectin, can help prevent oxidation-induced apoptosis in retinal cells and support the fluidity of the photoreceptor membrane (185). The polyunsaturated fatty acids EPA and DHA are linked to a lower incidence of AMD and play a preventive role in the course of the illness, according to a 2018 review of epidemiological, clinical, and experimental data. Indeed, in humans, the retina has a lipid profile that is especially high in long and very long-chain polyunsaturated FA, which is crucial for maintaining retinal structure and function (184). In the US Twin Study of AMD, a cross-sectional study performed on 681 twins, of which 222 subjects had intermediate or advanced stage AMD and 459 did not or just exhibited initial signs of the disease, it was demonstrated that a higher omega-3 FA level (upper quartile, corresponding to a mean daily intake of 0.35 g of omega-3, vs. lower quartile, corresponding to 0.06 g/day) was inversely related to AMD, with a significant risk reduction observed primarily in subjects with a lower than average intake of linoleic acid (an omega-6 FA) (1.8 g/day) (79). In the Blue Mountains Eye Study, 2,335 participants aged 49 years and older underwent reevaluation at 5 years for the development of AMD. Results showed that those in the highest quintile of omega-3 fatty acid intake (0.52–2.11%, expressed as a percentage of total energy intake) had a lower risk of early AMD onset than those in the lowest quintile (0.05–0.26%), with a 40% reduction in incidence when consuming fish at least once a week (80). Consumption of 1–2 portions of nuts per week (compared to less than one portion per week) was also related to a lower risk of early AMD onset, with a protective impact in comparisons of retinal pigment

abnormalities reported in non-smokers, subjects with a lower-than-average total cholesterol-to-HDL-cholesterol blood ratio, and those with higher-than-average beta-carotene intake (6836 g/day) (81). Within the Age-Related Eye Disease Study (AREDS), 4,519 subjects (60–80 years) provided an estimate of habitual nutrient intake through self-administered, semi-quantitative FFQ, from which the study showed that those in the top quintile of total long-chain-omega-3 intake (0.110% of total energy intake) and DHA (0.061%) had a lower risk of neovascular (NV) AMD (NV AMD) than bottom quintile (0.013% for total omega-3 and 0.010% for DHA). In general, higher consumption of fish was inversely related to NV AMD, while arachidonic acid taken with food was directly associated with the incidence of this pathology (82). Several other studies have looked into the connection between lipid intake and the risk of AMD, including a cohort study with 6,734 people (aged 58 to 69) who completed the FFQ and also reported using supplements (ascorbic acid, vitamin E, cod liver oil, and fish oil). A greater trans-fat intake was linked to a higher prevalence of late AMD, whereas higher omega-3 FA and olive oil intake would lessen the incidence of both early and late AMD, respectively (upper quartile, 1.4 g/d vs. lower quartile, 1.0 g/d; OR, 0.85; 95% confidence range, 0.71–1.02; $P = 0.03$). However, neither monounsaturated FA nor oleic acid, of which olive oil is particularly rich, were associated with late AMD; presumably, therefore, other non-FA contained in this oil could be responsible for its protective effect. Conversely, conflicting results emerged from an Australian study on 254 subjects diagnosed with early AMD, in which the possible progression of the disease at 7 years was evaluated: these findings contribute to a relationship between omega-3 intake (as measured by FFQ) and the development of AMD, potentially demonstrating how excessive consumption of a drug having therapeutic effects can be hazardous (83). Furthermore, high consumption of total, saturated, and monounsaturated fats was linked to an elevated risk of age-related maculopathy in the POLANUT trial, which involved a sample of 832 people from southern France. While no significant correlation emerged with polyunsaturated FA intake, a 60% decrease in the risk of maculopathy was associated with fatty fish consumption frequency (more than once per month vs. less than once per month) (84). The multi-center, case–control study by Seddo examined 504 controls without AMD but with other ocular pathologies, as well as 349 patients (55–80 years) with advanced neovascular AMD. It concluded that higher consumption of certain types of fats, especially mono- and polyunsaturated-FA of vegetable origin, may be linked to an increased risk of advanced AMD, while diets high in omega-3s and fish (two or more servings/week vs. less than one serving/week) seemed to be inversely associated with this risk, but limited to subjects with low linoleic acid intake ($\leq$5.5 g vs. $\geq$5.6 g) (85). Given that the GI of foods appears to play a role in the pathogenesis of AMD, a significant group of studies have looked into the potential involvement of carbs in AMD. Low dietary GI values (dGI75.2 vs. 81.5, computed as the average of GI of specific items weighed by the presence of carbs) were linked to a lower chance of developing advanced forms of AMD, according to an analysis of the data from the AREDS study: More specifically, it was discovered that a dGI reduction of 6 units (roughly equivalent to substituting 5 slices of white bread with 5 slices of whole grain bread in a subject's daily diet who consumes 250 g/day of total available carbohydrates) could prevent 8% of advanced AMD cases for 5 years. The production of advanced glycosylation products, the aggregation and precipitation of glycosylated protein aggregates, and the ensuing inflammatory and angiogenic responses have all been linked to higher post-prandial glycoxidative stress caused by high GI foods. Furthermore, the compensatory hyperlipidemia that occurs in the late post-prandial phase following the intake of high GI foods could also play a role in the pathogenesis of AMD (86). A higher mean dietary GI (lower quartile vs. upper quartile) is associated with a higher 10-year risk of developing early AMD, according to the Australian Blue Mountain Eye Study (3,654 participants, 49 years and older, examined at baseline in 1992–1994, of whom 2,335 were re-examined after 5 years, and 1952 after 10 years). This is after adjusting data for potential confounders and diet constituents. On the contrary, a greater consumption of whole-meal bread and cereals (in particular, those with a lower GI) was related to a reduction in this risk. In 1993, the Eye Disease Case-Control Study Group found that participants with intermediate and high blood levels of carotenoids had a much lower chance of developing neovascular AMD than those with low levels—equivalent to half and one-third, respectively. Within the same study, surveys performed on a sample of 356 patients with advanced-stage AMD (55–80 years) and 520 controls showed that subjects in the top quintile of dietary carotenoid intake had a risk of AMD 43% lower than subjects in the bottom quintile, and how, among the specific carotenoids, lutein and zeaxanthin (mainly found in green leafy vegetables) had the strongest association with a reduced risk of AMD (consuming spinach and collard greens more frequently was linked to a significantly decreased incidence of AMD) (87). A case–control study on the intake of antioxidants (72 patients and 66 controls) revealed that AMD was almost two times as common in patients who consumed fewer antioxidants and lutein than the typical person compared to those who consumed more, indicating a clear dose–response relationship (88). Vitamin A, which the body stores as retinol, is the source of several carotenoids. Even after adjusting for variables, demographics, and specialists, the National Health and Nutrition Examination Survey (NHANES) study found a negative correlation between the frequency of consumption of vitamin A-rich fruits and vegetables and the prevalence of macular degeneration in subjects under the age of 45 years (27). These observational studies collectively imply that lutein and zeaxanthin are the carotenoids that benefit the retina the most out of all those under investigation. These effects seem to be exclusive to certain types or stages of macular degeneration, with advanced disease benefiting most from a lower risk of damage. It is reasonable to speculate that vitamin C's potent antioxidant activities may be crucial in the onset and progression of the illness given the significance of oxidative stress on the etiopathogenesis of AMD. Most of the early studies were case–control studies. In 2002, Simonelli et al. analyzed the oxidative status of the serum/plasma in 48 Italian patients with macular degeneration (19 with the early form and 29 with the late form) and 46 healthy subjects, showing that subjects with late pathology had plasma levels of vitamin C, vitamin E, total carotenoids, and beta-cryptoxanthin compared to patients with early AMD, but with no differences in plasma levels of vitamin C between patients with ocular disease and healthy controls (89).

Other observational studies have confirmed a small effect of vitamin C on the risk of macular degeneration. Data obtained from 4,519 participants in the AREDS study, which suggested a reduced probability of developing neovascular AMD in subjects with the highest vitamin C intake, were then not confirmed following the addition of covariates (82). Even the multicenter Eye Disease Case–Control Study (EDCCS), which included 520 controls with other eye diseases and 356 patients with advanced-stage AMD (55–80 years), failed to detect any statistically significant link between vitamin C consumption and risk of AMD, even though the data appeared to point to a lower risk among those with the highest intake of vitamin C (particularly that contained in food) (87). Following multivariate adjustment, the examination of NHANES data from 1971 to 1972 revealed that there was no correlation between vitamin C intake and the prevalence of AMD at any stage (27). In addition to serving as a catalyst for more than 50 different enzymes, zinc also controls the expression of genes and contributes to the structure of proteins, making it a vital component of many physiological processes (186). Furthermore, zinc, together with copper, is an essential microelement for the retina, particularly concentrated in photoreceptors and pigmented epithelium of the human eye. Zinc and copper also act as cofactors for numerous ocular enzymes, including superoxide dismutase, a component of the main antioxidant system that modulates oxidative stress in the body. Oxidative stress and a reduced antioxidant capacity have been included among the possible pathogenetic factors implicated in the genesis of AMD, as the retina, and in particular the RPE, are particularly susceptible to oxidative stress due to high oxygen tension, high content of polyunsaturated fats, and intense exposure to light. These factors have led some researchers to hypothesize that taking zinc supplements may benefit retinal health (187). Zinc was a component of the antioxidant mixture given to the intervention group in the AREDS study. Participants were first randomized into four groups at random and given one of the following treatments per day: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta-carotene, 15 mg); (2) zinc, 80 mg; and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; and (4) placebos. Data on subjects who took zinc (thus including both those who took zinc alone and those who took zinc plus antioxidants) proved to be suggestive of a reduction in the risk of developing advanced forms of AMD, while no significant effect emerged in subjects taking antioxidants (including both the antioxidants-only group and the antioxidants-plus-zinc group). A statistically significant risk reduction was seen for antioxidants + zinc and suggestive for zinc alone, but not for antioxidants alone, when individual intervention groups were compared with placebo. Additionally, considering only individuals with the most severe forms of AMD, the size of the risk decrease increased (90). The Beaver Dam Eye Study, a prospective population-based study that initially enrolled 4,926 participants in 1990 and then reexamined 3,722, 2,962, and 2,375 participants in 1993–1995, 1998–2000, and 2003–2005, respectively, has revealed a higher risk of late AMD in users of supplements based on vitamins A, C, E, and zinc (91). In more recent times, attempts have been made to analyze the associations between illness and diet not so much understood as a single nutrient or food, but as a food style, comparing healthy styles and not starting from the large studies done in the past. The first and most important investigation of the Mediterranean diet and AMD was the French prospective cohort study by Merle et al. from 2015, conducted on 2,525 participants of the AREDS study (in which 1,028 eyes were found to have progressed to an advanced form of AMD for 13 years). The alternate Mediterranean Diet score (aMeDi, range: 0–9, from non-adherent to fully adherent) was calculated for each subject using a validated, self-administered, semi-quantitative FFQ. This score is widely used to assess adherence to the Mediterranean Diet in the US population based on the individual intake of nine components: vegetables, fruit, legumes, whole grains, nuts, fish, red and processed meats, alcohol, and the ratio of monounsaturated and saturated fats. In addition, 10 genetic loci associated with AMD located in seven different genes were determined and analyzed as covariates (for inherited predisposition). A high aMeDi score (6–9) was significantly associated with a 26% reduced risk of progression to advanced disease after adjusting for demographic, behavioral, ocular, and genetic covariates (HR: 0.74; 95% CI: 0.61–0.91; *P*-trend = 0.007). Furthermore, the aMeDi score appeared to be associated with a lower risk of incidence of advanced disease among subjects carrying non-at-risk alleles, while no association with AMD emerged among subjects homozygous for the risk allele. Greater adherence to the Mediterranean diet, therefore, appears to be associated with a reduced risk of progression to advanced disease, a risk that can be modified by genetic susceptibility. Finally, the data collected demonstrated that two components of the aMeDi score, in particular, the consumption of fish and that of vegetables, were associated with a lower risk of progression (92). Surveys conducted on 4,202 participants in the Rotterdam Study, through the administration of a validated FFQ comprising 170 items and classifying the data obtained on dietary intakes in nine food patterns according to the Health Councils guidelines, showed an association of fish with 24% reduced risk of AMD occurrence (mean follow-up of 9.1 ± 5.8 years), while no other association with single food categories reached statistical significance. Furthermore, the authors highlighted that only one DP, the one characterized by the intake of ≥200 g/day of vegetables, ≥200 g/day (two servings a day) of fruit, and ≥32 g/day (equivalent to two servings per week) of fish, was significantly associated with a lower risk of developing AMD (hazard ratio 0.58 [95% confidence interval 0.36–0.93]) (93). An additional survey conducted on 4,088 subjects participating in the AREDS study identified, based on the data obtained through FFQ, two major DPs (Oriental and Western) and eight minor DPs (subgroups or extensions of one of the two main patterns, generally including a smaller number of characterizing foods). The two major patterns were significantly associated with both early (OR Oriental pattern: 0.74; OR Western pattern:1.56) and advanced AMD (OR Oriental pattern:0.38; OR Western pattern:3.70), while no minor pattern showed a correlation with early AMD, and only four of these were found to be significantly associated with advanced AMD, including Steak pattern [similar to the Western DP; OR comparing the highest to the lowest quintile of the pattern score = 1.73 (95% confidence interval: 1.24–2.41; *P* trend = 0.02)], Breakfast pattern [cereals, fruit, and fruit juices; 0.60 (0.44–0.82); *P* trend = 0.004], Caribbean pattern [white meat, fish, rice, low-fat dairy, and offal; 0.64 (0.47–0.89; *P* trend = 0.009)], and Peanut pattern [peanuts, snacks, high-fat dairy, and sweets;

0.64 (0.46–0.89; *P* trend = 0.03)]. The data collected suggested that specific foods may harbor potentially beneficial effects (peanuts, pizza, coffee, and tea) or harmful effects (salad dressing) against the development of AMD (94). Amirul Islam discovered six food patterns (or factors) that are characterized by a preponderance of consumption of fruit (Factor 1), vegetables (Factor 2), grains, fish, steamed or boiled chicken, vegetables, nuts (Factor 3), red meat (Factor 4), processed foods, such as cakes, cookies, pastries, and desserts (Factor 5), and salads (Factor 6). Patterns from factors 1–3 were associated with a lower prevalence of AMD, while factors 4 and 6 were associated with a higher prevalence of advanced AMD. Notably, factor 4, which also included processed fish, eggs, and a low intake of whole grain foods (wheat or rye bread) was associated with an increased risk of late AMD, but not early AMD (OR = 1.46; 95% CI:1.0–2.17). The typical Western DP containing mostly processed foods (Factor 5) was found to have no significant association with AMD. In contrast, the latter pattern also included foods such as dairy, tea, and peanuts, which are known to protect against AMD, demonstrating that the impacts of potentially harmful foods featured in the DP may be mitigated by the consumption of beneficial foods (95).

4.2.1. Physical activity

An active lifestyle, defined by at least 3 h of daily low-to-moderate intensity physical activity, is related to a decreased risk of AMD, according to a recent meta-analysis of nine cross-sectional studies that assessed the effects of PA on AMD in 15 research, with a protective association against both early AMD [8 studies, n = 38,112, odds ratio (OR) 0.92, 95% confidence interval (CI) 0.86–0.98] and late AMD [7 studies, N=28,854, OR 0.59, 95% CI 0.49–0.72] (188).

4.3. Cataracts

The Women's Health Study (WHS) is the largest prospective cataract study that also correlates total fruit and vegetable consumption (96). The study boasts an average of 10 years of follow-up, in which there were 2,067 cases of cataract onset and 1,315 cases of lens replacement due to cataracts. Compared with women in the lowest fruit and vegetable consumption quintile, women in quintiles 2–5 (≥3.4 servings/day) had a moderate (10–15%) reduction in the risk of cataracts (P = 0.05). In the 2013 study by M. Pator-Valero, an inverse association between increasing quartiles of fruit and vegetable intake and the prevalence of cataracts was demonstrated. The study's stated consumption was much higher than what other studies had described. The WHO recommendation of five or more servings of fruit and/or vegetables per day (>400 g/day), with a median of 440 g/day, was actually met by 50% of the Spanish study population (IQR 226). The Alicante diet (study population) is a Mediterranean diet abundant in fruits and vegetables, particularly citrus fruits, and offers high levels of antioxidant vitamins (99) compared to the best American diets of other studies examined. Among the antioxidants examined in the Spanish study, dietary vitamin C has a more consistent effect on cataract prevalence. The results show that daily intake of vitamin C in the diet >107 mg/day are inversely linked with a decreased risk of developing cataracts (P trend between the four quartiles = 0.047). Compared with the lowest quartiles, with vitamin C intakes between 13 mg/day and 83 mg/day, vitamin C intakes between 83 and 107 mg/day were discovered to be 38 times less likely to be related to cataract prevalence and intakes between 107 and 143 mg/day were associated with a 51% lower probability of cataract development. Arrives at 54% with intakes between 143 and 408 mg/day. These data are consistent with previous studies that demonstrated that human eye tissues become saturated with vitamin C with dietary intakes between 200 and 300 mg/day (189). An analysis of the Nutrition and Vision Project (97) also obtained similar results observing a significant 48% reduction in the likelihood of nuclear opacity for vitamin C intakes between 140 and 180 mg/day, a reduction of 53% for intakes between 180 and 240 mg/day, and of 66% for intakes between 240 and 360 mg/day compared to the intakes of the highest quintiles (<140 mg/day). The French study POLA (84) instead found an inverse association between nuclear cataracts and plasmatic zeaxanthin [OR = 0.23 (0.08–0.68)], thus concluding that xanthophylls are important for the prevention of ocular compared to individuals who had low plasma zeaxanthin levels (0.04 mol/L). Nuclear cataract risk was reduced by 75% in people with high plasma zeaxanthin levels (>0.08 mol/L), but not for other types of cataracts. The authors found no association between lutein and cataracts of any type. The CAREDES study (98), composed of women previously enrolled in an observational study and who were above and below the 78th and 28th percentiles, respectively, for consumption of lutein and zeaxanthin, demonstrated that women whose overall scores for HEI-95 (Healthy Eating Index-95) were in the highest vs. lowest quintiles had diets that were less rich in fat, saturated fat, in particular, and contained less sodium. The prevalence of cataracts was related to low values for most of the subscale scores (vegetables, fruit, milk, cereals, total saturated fat, and food variety in general). Furthermore, this study shows that meat consumption is directly related to cataracts (p = 0.07). The analysis of sodium and cholesterol consumption did not lead to any specific results. Two studies on the same population in Iran (100, 101) highlighted how DPs rich in sodium and trans-fats were linked to a higher prevalence of cataracts. Ghanavati used a case–control study evaluating the association of cataracts with a healthy eating style, the Healthy Eating Index (HEI). The analysis of FFQ led to dividing the population into three sub-groups with respect to the diet followed. The two categories of HEI were found to be protective against cataracts, while the population in the lowest quartile [OR = 0.19 (95% CI: 0.09–0.4); P < 0.01] had the greatest prevalence. Factor analysis was used on dietary data (101) to extract nutritional patterns and identified two particularly inadequate nutritional patterns, defined as sodium regimen and fatty acid regimen. Sedaghat has redivided the nutritional models into five models based on nutrients. The regimens are as follows: (1) sodium regimen: included niacin, thiamine, high amounts of carbohydrates and proteins, zinc, vitamin B6, and sodium; (2) fatty acid regimen featuring oleic acid, monounsaturated fatty acids (MUFA), PUFA, linoleic acid, trans FA, vitamin E, and saturated fat; (3) mixed regimen represented a high intake of vitamin B12, vitamin D, cholesterol, and calcium; (4) the antioxidant regimen

had high intakes of beta and alpha carotene, vitamin A, and vitamin C; and (5) omega-3 regimen contained a high intake of DHA and EPA. In the crude, multivariate analysis, the sodium model was associated with an increased risk of cataracts (OR = 1.97, 95% CI: 1.09–3.96). The FA pattern (this model represents a surrogate for meats and processed foods) was associated with high risk (OR = 1.94, 95%CI: 1.1–3.86), while the antioxidant regimen was associated with 79% reduced risk compared to the sodium regimen. Finally, the omega-3 model was negatively associated with cataract risk ($P = 0.04$). The narrative review by Chong in 2008 suggests that the risk of cataracts can be reduced by adhering to diets high in vitamin C, xanthophylls (lutein and zeaxanthin, present not only in the macula but also in the lens), omega-3 FA, and avoiding frequent and abundant intakes of simple carbohydrates with a high GI (103).

4.3.1. Hydration

The high-water content in the eye, as well as the peculiar fluid regulation system in its context, suggest that the state of hydration may also play an important role in determining the health or disease state of the eye itself (105). A 2015 review suggested that dehydration correlates with the onset of some eye diseases, such as dry eye syndrome, cataracts, retinal vascular diseases, and refractive defects (105). In particular, the cornea, the main refractive medium of the eye, is made up of ∼80% water, and its transparency mainly depends on its state of hydration. Indeed, changes in the state of hydration of the cornea can result in a change in its central thickness and the ability to recover from such changes decreases with age (190, 191). This could also affect the outcome of cataract surgery (105). Indeed, diabetes has also been observed to increase the risk of developing cataracts, as well as in diabetic patients suffering from cataracts, the total water content of the eye's lens system is reduced (192, 193). In a case–control study conducted in India in 1989 on 434 cases and 930 controls (30–69 years), 38% of the cases suggested that the cause could be attributed to episodes of severe dehydration, in a dose-dependent manner (102). Given this background, water must therefore be taken in a quantity of 1.5–2 liters per day, as per the indications of all international guidelines for a healthy diet.

4.3.2. Physical activity

A recent review (104) evaluated the outcome of PA on cataracts, finding that regular activity decreases the rate of progression and risk of incidence. Results from prospective cohort studies accessible and examined in this review revealed that greater PA was inversely related to cataract risk and that the association was significant in studies that measured the metabolic equivalent of task (MET) PA as opposed to studies that measured it as a weekly activity. According to a dose–response analysis, each increase of 6 METs/day resulted in a 2% reduction in the chance of developing cataracts. The ocular lens is highly susceptible to oxidative damage as it is rich in polyunsaturated FA and the presence of greater quantities of ROS has great toxicity on the components of the lens itself, such as the crystalline proteins, whose damage leads to the development of opacities (194, 195). From this point of view, PA could reduce the levels of oxidative stress by increasing the activity of antioxidant enzymes and thus favoring the prevention of cataracts.

5. Conclusion

Many common eye diseases, in particular DR, AMD, and cataracts, are treatable and preventable, especially in the first phase in which they occur. Lifestyle, especially nutrition and physical activity, plays an essential role. To create a food pyramid that makes it simple for people who are at risk of developing DR, AMD, and cataracts to decide what to eat, this narrative review analyzed the most recent research on the best dietary strategy needed to avoid the development of these pathologies. In preventive terms, the subjects who can benefit most from following the indications given in the pyramid are the following: diabetic and hypertensive subjects as they are at greater risk of diabetic retinopathy since both pathologies tend to damage the retina; subjects who are hypertensive and smokers as they are at increased risk of age-related macular degeneration; subjects suffering from other eye diseases such as glaucoma or uveitis, diabetics, and who have undergone prolonged therapies with cortisone as they are at greater risk of diabetic retinopathy. The pyramid illustrates the recommended daily diet: three portions of grains with low GI (for high fiber and zinc content), five portions (≥200 g/die) of fruits and vegetables, especially spinach and broccoli and cooked zucchini and green leafy vegetables, orange, kiwi, grapefruit (for luteina/zeaxantina at least ≥942 μg/die content, are to be preferred), light yogurt (125 ml), skim milk (200 ml), EVO oil (almost 20 mg/day for high vitamin E and polyphenols content), and nuts or oilseeds (20–30 g/day, for zinc content, at least ≥15.8 mg/die); and weekly: fish (4 portions, for omega-3 content, EPA+DHA at least 0.35 as far as 1.4 g/day), white meat (3 portions for vitamin B12 and folic acid content), legumes (2 portions for vegetal proteins), eggs (2 portions for lutein/zeaxanthin content), fresh and low-fat cheeses for the content of vitamins of group B), and red or processed meats (once/week) and microgreen (at least once a week). There are two pennants at the top of the pyramid: one green indicates the need for individualized supplementation (if daily requirements cannot be met through diet, omega-3 supplementation and L-metilfolate may be a useful strategy with a great benefit-to-cost ratio) and one red indicates the presence of certain foods that are prohibited) (salt and sugar). Finally, 30 to 40 min of aerobic and resistance workouts must be done three to four times per week, and the intake of adequate quantities of water, equal to 1.5–2 liters/day, is a fundamental objective to achieve. Another important topic on which most of the literature agrees is the importance of maintaining a BMI between 19 and 25 kg/m^2. Finally, in these conclusions, it is necessary to remember a topic that will be the subject of many studies in the near future: the relationship between intestinal microbiota and eye diseases because the microbiota can influence several metabolic pathways involved in the regulation of ocular health. Inflammation and hyperglycemia can lead to intestinal permeability of microbial products, which can in turn bind to ocular receptors and transmit inflammatory signals. The gut microbiota influences bacterial and host-derived metabolites,

which signal distally to the brain and eye and influences systemic lipid metabolism, and has been shown to influence the lipid composition of the retina.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MR, SP, and AR contributed to the conception and design of the study. AC, CR, and AT wrote the first draft of the manuscript. CG, GB, and GP wrote sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

AR and GP are employed by Indena Spa.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GA declared a shared affiliation with the authors MR, CG, GB, AC, CR, and AT to the handling editor at time of review.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. WHO. *World Report on Vision* (2019).

2. Ong SR, Crowston JG, Loprinzi PD, Ramulu PY. Physical activity, visual impairment, and eye disease. *Eye.* (2018) 32:1296–303. doi: 10.1038/s41433-018-0081-8

3. Francisco SG, Smith KM, Aragonès G, Whitcomb EA, Weinberg J, Wang X, et al. Dietary patterns, carbohydrates, and age-related eye diseases. *Nutrients.* (2020) 12:2862. doi: 10.3390/nu12092862

4. The age-related eye disease study (AREDS). *Control Clin Trials.* (1999) 20:573–600. doi: 10.1016/S0197-2456(99)00031-8

5. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration. *JAMA.* (2013) 309:2005. doi: 10.1001/jama.2013.4997

6. Bernstein PS, Li B, Vachali PP, Gorusupudi A, Shyam R, Henriksen BS, et al. Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Prog Retin Eye Res.* (2016) 50:34–66. doi: 10.1016/j.preteyeres.2015.10.003

7. Hammond BR, Johnson EJ, Russell RM, Krinsky NI, Yeum KJ, Edwards RB, et al. Dietary modification of human macular pigment density. *Invest Ophthalmol Vis Sci.* (1997) 38:1795–801.

8. Schalch W, Cohn W, Barker FM, Köpcke W, Mellerio J, Bird AC, et al. Xanthophyll accumulation in the human retina during supplementation with lutein or zeaxanthin – the LUXEA (LUtein Xanthophyll Eye Accumulation) study. *Arch Biochem Biophys.* (2007) 458:128–35. doi: 10.1016/j.abb.2006.09.032

9. Johnson EJ, Chung H-Y, Caldarella SM, Snodderly DM. The influence of supplemental lutein and docosahexaenoic acid on serum, lipoproteins, and macular pigmentation. *Am J Clin Nutr.* (2008) 87:1521–9. doi: 10.1093/ajcn/87.5.1521

10. Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE. A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res.* (1997) 65:57–62. doi: 10.1006/exer.1997.0309

11. Eisenhauer B, Natoli S, Liew G, Flood V. Lutein and zeaxanthin—food sources, bioavailability and dietary variety in age-related macular degeneration protection. *Nutrients.* (2017) 9:120. doi: 10.3390/nu9020120

12. Perry A, Rasmussen H, Johnson EJ. Xanthophyll (lutein, zeaxanthin) content in fruits, vegetables and corn and egg products. *J Food Compos Anal.* (2009) 22:9–15. doi: 10.1016/j.jfca.2008.07.006

13. Palermo M, Pellegrini N, Fogliano V. The effect of cooking on the phytochemical content of vegetables. *J Sci Food Agric.* (2014) 94:1057–70. doi: 10.1002/jsfa.6478

14. Xiao Z, Lester GE, Luo Y, Wang Q. Assessment of vitamin and carotenoid concentrations of emerging food products: edible microgreens. *J Agric Food Chem.* (2012) 60:7644–51. doi: 10.1021/jf300459b

15. Mangels AR, Holden JM, Beecher GR, Forman MR, Lanza E. Carotenoid content of fruits and vegetables: an evaluation of analytic data. *J Am Diet Assoc.* (1993) 93:284–96. doi: 10.1016/0002-8223(93)91553-3

16. Schaeffer JL, Tyczkowski JK, Parkhurst CR, Hamilton PB. Carotenoid composition of serum and egg yolks of hens fed diets varying in carotenoid composition. *Poult Sci.* (1988) 67:608–14. doi: 10.3382/ps.0670608

17. Bohn T. Bioavailability of non-provitamin A carotenoids. *Curr Nutr Food Sci.* (2008) 4:240–58. doi: 10.2174/157340108786263685

18. van het Hof KH, West CE, Weststrate JA, Hautvast JGAJ. dietary factors that affect the bioavailability of carotenoids. *J Nutr.* (2000) 130:503–6. doi: 10.1093/jn/130.3.503

19. O'Connell OF, Ryan L, O'Brien NM. Xanthophyll carotenoids are more bioaccessible from fruits than dark green vegetables. *Nutr Res.* (2007) 27:258–64. doi: 10.1016/j.nutres.2007.04.002

20. Castenmiller JJM, West CE, Linssen JPH, van het Hof KH, Voragen AGJ. The food matrix of spinach is a limiting factor in determining the bioavailability of β-carotene and to a lesser extent of lutein in humans. *J Nutr.* (1999) 129:349–55. doi: 10.1093/jn/129.2.349

21. Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladěnka P. Vitamin a update: forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. *Nutrients.* (2021) 13:1703. doi: 10.3390/nu13051703

22. Zhong M, Kawaguchi R, Kassai M, Sun H. Retina, retinol, retinal and the natural history of vitamin A as a light sensor. *Nutrients.* (2012) 4:2069–96. doi: 10.3390/nu4122069

23. Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, Bhutta ZA. Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis. *BMJ.* (2011) 343:d5094. doi: 10.1136/bmj.d5094

24. Wolf G. The discovery of the visual function of vitamin A. *J Nutr.* (2001) 131:1647–50. doi: 10.1093/jn/131.6.1647

25. Wang A, Han J, Jiang Y, Zhang D. Association of vitamin A and β-carotene with risk for age-related cataract: a meta-analysis. *Nutrition.* (2014) 30:1113–21. doi: 10.1016/j.nut.2014.02.025

26. Jiang H, Yin Y, Wu CR, Liu Y, Guo F, Li M, et al. Dietary vitamin and carotenoid intake and risk of age-related cataract. *Am J Clin Nutr.* (2019) 109:43–54. doi: 10.1093/ajcn/nqy270

27. Goldberg J, Flowerdew G, Smith E, Brody JA, Tso MOM. Factors associated with age-related macular degeneration. An analysis of data from the first National Health and Nutrition Examination Survey. *Am J Epidemiol.* (1988) 128:700–10. doi: 10.1093/oxfordjournals.aje.a115023

28. Delcourt C, Cristol JP, Tessier F, Léger CL, Descomps B, Papoz L. Age-related macular degeneration and antioxidant status in the POLA study. POLA Study Group. Pathologies Oculaires Liées à l'Age. *Arch Ophthalmol.* (1999) 117:1384–90. doi: 10.1001/archopht.117.10.1384

29. Egger Matthias, Smith GDavey, Altman DG. *Systematic Reviews in Health Care : Meta-Analysis in Context*. BMJ Books (2001). p. 487. doi: 10.1002/9780470693926

30. Diaz-Lopez A, Babio N, Martinez-González MA, Corella D, Amor AJ, Fitó M, et al. Mediterranean diet, retinopathy, nephropathy, and microvascular diabetes complications: a *post hoc* analysis of a randomized trial. *Diabetes Care.* (2015) 38:2134–41. doi: 10.2337/dc15-1117

31. Salas-Salvadó J, Bulló M, Babio N, Martínez-González MÁ, Ibarrola-Jurado N, Basora J, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean DietResults of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care.* (2011) 34:14–9. doi: 10.2337/dc10-1288

32. Sala-Vila A, Díaz-López A, Valls-Pedret C, Cofán M, García-Layana A, Lamuela-Raventós RM, et al. Dietary marine ω-3 fatty acids and incident sight-threatening retinopathy in middle-aged and older individuals with type 2 diabetes: prospective investigation from the PREDIMED trial. *JAMA Ophthalmol.* (2016) 134:1142–49. doi: 10.1001/jamaophthalmol.2016.2906

33. el Bilbeisi AH, Hosseini S, Djafarian K. Association of dietary patterns with diabetes complications among type 2 diabetes patients in Gaza Strip, Palestine: a cross sectional study. *J Health Popul Nutr.* (2017) 36:1–11. doi: 10.1186/s41043-017-0115-z

34. Tanaka S, Yoshimura Y, Kawasaki R. *Fruit intake and incident diabetic retinopathy with type 2 diabetes.* JSTOR (2013). Available online at: https://www.jstor.org/stable/23487820?casa_token=ED906ID4cTAAAAAA:6ZWHvgjkJQi77Nzc8DKO5HAv4cMoCEQqWLuNbS7yIfk7-4YdQT8XX6ADyKBvqGnaTIJ_ozfiU9edjnPLIuxTPqFdT0b3dt2DsQoV0daS_4XOJ8ybs5w0 (accessed June 30, 2022).

35. Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Am J Clin Nutr.* (2002) 76:93–9. doi: 10.1093/ajcn/76.1.93

36. Sala-Vila A, Valls-Pedret C, Rajaram S, Coll-Padrós N, Cofán M, Serra-Mir M, et al. Effect of a 2-year diet intervention with walnuts on cognitive decline. The Walnuts And Healthy Aging (WAHA) study: a randomized controlled trial. *Am J Clin Nutr.* (2020) 111:590–600. doi: 10.1093/ajcn/nqz328

37. Nunes S, Alves D, Barreto P, Raimundo M, da Luz Cachulo M, Farinha C, et al. Adherence to a Mediterranean diet and its association with age-related macular degeneration. The Coimbra Eye Study–Report 4. *Nutrition.* (2018) 51–2:6–12. doi: 10.1016/j.nut.2017.12.010

38. Ma Q, Chen D, Sun HP, Yan N, Xu Y, Pan CW. Regular Chinese green tea consumption is protective for diabetic retinopathy: a clinic-based case-control study. *J Diabetes Res.* (2015) 2015:231570. doi: 10.1155/2015/231570

39. Hjellvik V, Tverdal A, Strøm H. Boiled coffee intake and subsequent risk for type 2 diabetes. *Epidemiology.* (2011) 22:418–21. doi: 10.1097/EDE.0b013e31821083e3

40. Tuomilehto J, Hu G, Bidel S, Lindström J. *Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women*. jamanetwork.com. Available online at: https://jamanetwork.com/journals/jama/article-abstract/198353 (accessed July 18, 2022). doi: 10.1001/jama.291.10.1213

41. Brazionis L, Rowley K, Itsiopoulos C, O'dea K. Plasma carotenoids and diabetic retinopathy. *Br J Nutr.* (2008) 101:270–7. doi: 10.1017/S0007114508006545

42. Garcia-Medina JJ, Pinazo-Duran MD, Garcia-Medina M, Zanon-Moreno V, Pons-Vazquez S. A 5-year follow-up of antioxidant supplementation in type 2 diabetic retinopathy. *Eur J Ophthalmol.* (2011) 21:637–43. doi: 10.5301/EJO.2010.6212

43. Zhang PC, Wu CR, Wang ZL, Wang LY, Han Y, Sun SL, et al. Effect of lutein supplementation on visual function in nonproliferative diabetic retinopathy. *Asia Pac J Clin Nutr.* (2017) 26:406–11. doi: 10.6133/APJCN.032016.13

44. Moschos MM, Dettoraki M, Tsatsos M, Kitsos G, Kalogeropoulos C. Effect of carotenoids dietary supplementation on macular function in diabetic patients. *Eye Vis.* (2017) 4:23. doi: 10.1186/s40662-017-0088-4

45. Millen AE, Klein R, Folsom AR, Stevens J, Palta M, Mares JA. Relation between intake of vitamins C and E and risk of diabetic retinopathy in the Atherosclerosis Risk in Communities Study. *Am J Clin Nutr.* (2004) 79:865–73. doi: 10.1093/ajcn/79.5.865

46. Mayer-Davis E, Bell R, Reboussin B. Antioxidant nutrient intake and diabetic retinopathy: the San Luis Valley Diabetes Study. *Ophthalmology*. 105:2264–70. doi: 10.1016/S0161-6420(98)91227-1

47. Millen AE, Sahli MW, Nie J, LaMonte MJ, Lutsey PL, Klein BEK, et al. Adequate vitamin D status is associated with the reduced odds of prevalent diabetic retinopathy in African Americans and Caucasians. *Cardiovasc Diabetol.* (2016) 15:1–11. doi: 10.1186/s12933-016-0434-1

48. Long M, Wang C, Liu D. Glycated hemoglobin A1C and vitamin D and their association with diabetic retinopathy severity. *Nutr Diab.* (2017) 7:e281. doi: 10.1038/nutd.2017.30

49. Mahoney SE, Loprinzi PD. Influence of flavonoid-rich fruit and vegetable intake on diabetic retinopathy and diabetes-related biomarkers. *J Diabetes Complic.* (2014) 28:767–71. doi: 10.1016/j.jdiacomp.2014.06.011

50. Park SW, Ghim W, Oh S, Kim Y, Park UC, Kang J, et al. Association of vitreous vitamin C depletion with diabetic macular ischemia in proliferative diabetic retinopathy. *PLoS ONE.* (2019) 14:e0218433. doi: 10.1371/journal.pone.0218433

51. Gurreri A, Pazzaglia A, Schiavi C. Role of statins and ascorbic acid in the natural history of diabetic retinopathy: a new, affordable therapy? *Ophthalmic Surg Lasers Imaging Retina.* (2019) 50:S23–7. doi: 10.3928/23258160-20190108-06

52. Thosar SS, Bielko SL, Wiggins CS, Klaunig JE, Mather KJ, Wallace JP. Antioxidant vitamin C prevents decline in endothelial function during sitting. *Med Sci Monitor.* (2015) 21:1015–21. doi: 10.12659/MSM.893192

53. Memisogullari R, Yüksel H, Coskun A, Yüksel HK, Yazgan Ö, Bilgin C. High serum homocysteine levels correlate with a decrease in the blood flow velocity of the ophthalmic artery in highway toll collectors. *Tohoku J Exp Med.* (2007) 212:247–52. doi: 10.1620/tjem.212.247

54. Horikawa C, Aida R, Kamada C, Fujihara K, Tanaka S, Tanaka S, et al. Vitamin B6 intake and incidence of diabetic retinopathy in Japanese patients with type 2 diabetes: analysis of data from the Japan Diabetes Complications Study (JDCS). *Eur J Nutr.* (2020) 59:1585–94. doi: 10.1007/s00394-019-02014-4

55. Gopinath B, Flood VM, Rochtchina E, Wang JJ, Mitchell P. Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration. *Am J Clin Nutr.* (2013) 98:129–35. doi: 10.3945/ajcn.112.057091

56. Sasaki M, Kawasaki R, Rogers S, Man REK, Itakura K, Xie J, et al. The associations of dietary intake of polyunsaturated fatty acids with diabetic retinopathy in well-controlled diabetes. *Invest Ophthalmol Vis Sci.* (2015) 56:7473–9. doi: 10.1167/iovs.15-17485

57. Ansar H, Mazloom Z, Kazemi F, Hejazi N. Effect of alpha-lipoic acid on blood glucose, insulin resistance and glutathione peroxidase of type 2 diabetic patients. *Saudi Med J.* (2011) 32:584–8.

58. Xiang G-D, Sun H-L, Zhao L-S, Hou J, Yue L, Xu L. The antioxidant alpha-lipoic acid improves endothelial dysfunction induced by acute hyperglycaemia during OGTT in impaired glucose tolerance. *Wiley Online Library.* (2008) 68:716–23. doi: 10.1111/j.1365-2265.2007.03099.x

59. Luo YY, Zhao J, Han XY, Zhou XH, Wu J, Ji LN. Relationship between serum zinc level and microvascular complications in patients with type 2 diabetes. *Chin Med J.* (2015) 128:3276–82. doi: 10.4103/0366-6999.171357

60. Zhang J, Ren Z, Zhang Q, Zhang R, Zhang C, Liu J. Lower hydration status increased diabetic retinopathy among middle-aged adults and older adults: results from NHANES 2005-2008. *Front Public Health.* (2022) 10:1023747. doi: 10.3389/fpubh.2022.1023747

61. Praidou A, Harris M, Niakas D, Labiris G. Physical activity and its correlation to diabetic retinopathy. *J Diabetes Complic.* (2017) 31:456–61. doi: 10.1016/j.jdiacomp.2016.06.027

62. Yan X, Han X, Wu C, Shang X, Zhang L, He M. Effect of physical activity on reducing the risk of diabetic retinopathy progression: 10-year prospective findings from the 45 and Up Study. *PLoS ONE.* (2021) 16:e0239214. doi: 10.1371/journal.pone.0239214

63. Kuwata H, Okamura S, Hayashino Y, Tsujii S, Ishii H. Higher levels of physical activity are independently associated with a lower incidence of diabetic retinopathy in Japanese patients with type 2 diabetes: a prospective cohort study, Diabetes Distress and Care Registry at Tenri (DDCRT15). *PLoS ONE.* (2017) 12:e0172890. doi: 10.1371/journal.pone.0172890

64. Al-Othman A, Al-Musharaf S, Al-Daghri NM, Krishnaswamy S, Yusuf DS, Alkharfy KM, et al. Effect of physical activity and sun exposure on vitamin D status of Saudi children and adolescents. *BMC Pediatr.* (2012) 12:92. doi: 10.1186/1471-2431-12-92

65. Scott D, Blizzard L, Fell J, Ding C, Winzenberg T, Jones G. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. *Clin Endocrinol.* (2010) 73:581–7. doi: 10.1111/j.1365-2265.2010.03858.x

66. Klenk J, Rapp K, Denkinger M, Nagel G, Nikolaus T, Peter R, et al. Objectively measured physical activity and vitamin D status in older people from Germany. *J Epidemiol Community Health.* (2015) 69:388–92. doi: 10.1136/jech-2014-204632

67. Black LJ, Burrows SA, Jacoby P, Oddy WH, Beilin LJ, Ping-Delfos WCS, et al. Vitamin D status and predictors of serum 25-hydroxyvitamin D concentrations in Western Australian adolescents. *Br J Nutr.* (2014) 112:1154–62. doi: 10.1017/S000711451400186X

68. Herrmann M, Sullivan DR, Veillard A-S, McCorquodale T, Straub IR, Scott R, et al. Serum 25-hydroxyvitamin d: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. *Diabetes Care.* (2015) 38:521–8. doi: 10.2337/dc14-0180

69. Schneider SH, Khachadurian AK, Amorosa LF, Clemow L, Ruderman NB. Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. *Diabetes Care.* (1992) 15:1800–10. doi: 10.2337/diacare.15.11.1800

70. Dow C, Mancini F, Rajaobelina K, Boutron-Ruault MC, Balkau B, Bonnet F, et al. Diet and risk of diabetic retinopathy: a systematic review. *Eur J Epidemiol.* (2018) 33:141–56. doi: 10.1007/s10654-017-0338-8

71. Wong MYZ, Man REK, Fenwick EK, Gupta P, Li LJ, van Dam RM, et al. Dietary intake and diabetic retinopathy: a systematic review. *PLoS ONE.* (2018) 13:e0186582. doi: 10.1371/journal.pone.0186582

72. Ros E, Izquierdo-Pulido M, Sala-Vila A. Beneficial effects of walnut consumption on human health: role of micronutrients. *Curr Opin Clin Nutr Metab Care.* (2018) 21:498–504. doi: 10.1097/MCO.0000000000000508

73. Poulose SM, Miller MG, Shukitt-Hale B. Role of walnuts in maintaining brain health with age. *J Nutr.* (2014) 144:561S–66. doi: 10.3945/jn.113.184838

74. Valero-Vello M, Peris-Martínez C, García-Medina JJ, Sanz-González SM, Ramírez AI, Fernández-Albarral JA, et al. Searching for the antioxidant, anti-inflammatory, and neuroprotective potential of natural food and nutritional supplements for ocular health in the mediterranean. *Foods.* (2021) 10:1231. doi: 10.3390/foods10061231

75. Meng J-M, Cao S-Y, Wei X-L, Gan R-Y, Wang Y-F, Cai S-X, et al. Effects and mechanisms of tea for the prevention and management of diabetes mellitus and diabetic complications: an updated review. *Antioxidants.* (2019) 8:170. doi: 10.3390/antiox8060170

76. Natella F, Scaccini C. Role of coffee in modulation of diabetes risk. *Nutr Rev.* (2012) 70:207–17. doi: 10.1111/j.1753-4887.2012.00470.x

77. Akash MSH, Rehman K, Chen S. Effects of coffee on type 2 diabetes mellitus. *Nutrition.* (2014) 30:755–63. doi: 10.1016/j.nut.2013.11.020

78. Carlström M, Larsson SC. Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. *Nutr Rev.* (2018) 76:395–417. doi: 10.1093/nutrit/nuy014

79. Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. *Arch Ophthalmol.* (2006) 124:995–1001. doi: 10.1001/archopht.124.7.995

80. Chua B, Flood V, Rochtchina E, Wang JJ, Smith W, Mitchell P. Dietary fatty acids and the 5-year incidence of age-related maculopathy. *Arch Ophthalmol.* (2006) 124:981–6. doi: 10.1001/archopht.124.7.981

81. Tan JSL, Wang JJ, Flood V, Mitchell P. Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol.* (2009) 127:656–65. doi: 10.1001/archophthalmol.2009.76

82. SanGiovanni JP, Chew EY, Clemons TE, Ferris FL, Gensler G, Lindblad AS, et al. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report No. 22. *Arch Ophthalmol.* (2007) 125:1225–32. doi: 10.1001/archopht.125.9.1225

83. Robman L, Vu H, Hodge A, Tikellis G, Dimitrov P, McCarty C, et al. Dietary lutein, zeaxanthin, and fats and the progression of age-related macular degeneration. *Can J Ophthalmol.* (2007) 42:720–6. doi: 10.3129/i07-116

84. Delcourt C, Carrière I, Cristol JP, Lacroux A, Gerber M. Dietary fat and the risk of age-related maculopathy: the POLANUT study. *Eur J Clin Nutr.* (2007) 61:1341–4. doi: 10.1038/sj.ejcn.1602685

85. Seddon JM, Rosner B, Sperduto RD, Yannuzzi L, Haller JA, Blair NP, Willett W. Dietary fat and risk for advanced age-related macular degeneration. *Arch Ophthalmol.* (2001) 119:1191–9. doi: 10.1001/archopht.119.8.1191

86. Chiu CJ, Klein R, Milton RC, Gensler G, Taylor A. Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements? *Br J Ophthalmol.* (2009) 93:1241. doi: 10.1136/bjo.2008.143412

87. Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *JAMA.* (1994) 272:1413–20. doi: 10.1001/jama.272.18.1413

88. Snellen ELM, Verbeek ALM, Van Den Hoogen GWP, Cruysberg JRM, Hoyng CB. Neovascular age-related macular degeneration and its relationship to antioxidant intake. *Acta Ophthalmol Scand.* (2002) 80:368–71. doi: 10.1034/j.1600-0420.2002.800404.x

89. Simonelli F, Zarrilli F, Mazzeo S, Verde V, Romano N, Savoia M, et al. Serum oxidative and antioxidant parameters in a group of Italian patients with age-related maculopathy. *Clinica Chimica Acta.* (2002) 320:111–5. doi: 10.1016/S0009-8981(02)00056-6

90. Kassoff A, Kassoff J, Buehler J, Eglow M, Kaufman F, Mehu M, et al. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* (2001) 119:1417–36. doi: 10.1001/archopht.119.10.1417

91. Klein BEK, Knudtson MD, Lee KE, Reinke JO, Danforth LG, Wealti AM, et al. Supplements and age-related eye conditions the beaver dam eye study. *Ophthalmology.* (2008) 115:1203–8. doi: 10.1016/j.ophtha.2007.09.011

92. Merle BM, Silver RE, Rosner B, Seddon JM. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study 1-3. *Am J Clin Nutr.* (2015) 102:1196–206. doi: 10.3945/ajcn.115.111047

93. de Koning-Backus APM, Buitendijk GHS, Kiefte-de Jong JC, Colijn JM, Hofman A, Vingerling JR, et al. Intake of vegetables, fruit, and fish is beneficial for age-related macular degeneration. *Am J Ophthalmol.* (2019) 198:70–9. doi: 10.1016/j.ajo.2018.09.036

94. Chiu CJ, Chang ML, Li T, Gensler G, Taylor A. Visualization of dietary patterns and their associations with age-related macular degeneration. *Invest Ophthalmol Vis Sci.* (2017) 58:1404. doi: 10.1167/iovs.16-20454

95. Amirul Islam FM, Chong EW, Hodge AM, Guymer RH, Aung KZ, Makeyeva GA, et al. Dietary patterns and their associations with age-related macular degeneration: the Melbourne collaborative cohort study. *Ophthalmology.* (2014) 121:1428–34.e2. doi: 10.1016/j.ophtha.2014.01.002

96. Christen WG, Liu S, Schaumberg DA, Buring JE. Fruit and vegetable intake and the risk of cataract in women. *Am J Clin Nutr.* (2005) 81:1417–22. doi: 10.1093/ajcn/81.6.1417

97. Jacques PF, Chylack LT, Hankinson SE, Khu PM, Rogers G, Friend J, et al. Long-term nutrient intake and early age-related nuclear lens opacities. *Arch Ophthalmol.* (2001) 119:1009–19. doi: 10.1001/archopht.119.7.1009

98. Moeller SM, Taylor A, Tucker KL, McCullough ML, Chylack LT, Hankinson SE, et al. Overall adherence to the dietary guidelines for Americans is associated with reduced prevalence of early age-related nuclear lens opacities in women. *J Nutr.* (2004) 134:1812–9. doi: 10.1093/jn/134.7.1812

99. Pastor-Valero M, Fletcher AE, De Stavola BL, Vioque J, Alepuz VC. Vitamin C is associated with reduced risk of cataract in a Mediterranean population. *J Nutr.* (2002) 132:1299–306. doi: 10.1093/jn/132.6.1299

100. Ghanavati M, Behrooz M, Rashidkhani B, Ashtray-Larky D, Zameni SD, Alipour M. Healthy eating index in patients with cataract: a case-control study. *Iran Red Crescent Med J.* (2015) 17:e22490. doi: 10.5812/ircmj.22490

101. Sedaghat F, Ghanavati M, Hajian PN, Hajishirazi S, Ehteshami M, Rashidkhani B. Nutrient patterns and risk of cataract: a case-control study. *Int J Ophthalmol.* (2017) 10:586–92. doi: 10.18240/ijo.2017.04.14

102. Minassian DC, Mehra V, Verrey JD. Dehydrational crises: a major risk factor in blinding cataract. *Br J Ophthalmol.* (1989) 73:100–5. doi: 10.1136/bjo.73.2.100

103. Chong EW, Wong TY. Multivitamin Supplements and cataract prevention. *Ophthalmology.* (2008) 115:597–8. doi: 10.1016/j.ophtha.2008.01.033

104. Jiang H, Wang LN, Liu Y, Li M, Wu M, Yin Y, et al. Physical activity and risk of age-related cataract. *Int J Ophthalmol.* (2020) 13:643–9. doi: 10.18240/ijo.2020.04.18

105. Sherwin JC, Kokavec J, Thornton SN. Hydration, fluid regulation and the eye: in health and disease. *Clin Exp Ophthalmol.* (2015) 43:749–64. doi: 10.1111/ceo.12546

106. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet.* (2010) 376:124–36. doi: 10.1016/S0140-6736(09)62124-3

107. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care.* (2012) 35:556–64. doi: 10.2337/dc11-1909

108. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Curr Diab Rep.* (2012) 12:346–54. doi: 10.1007/s11892-012-0283-6

109. Grzybowski A, Brona P, Kim SJ. Microbial flora and resistance in ophthalmology: a review. *Graefe's Arch Clin Exp Ophthalmol.* (2017) 255:851–62. doi: 10.1007/s00417-017-3608-y

110. Raman R, Rani PK, Gnanamoorthy P, Sudhir RR, Kumaramanikavel G, Sharma T. Association of obesity with diabetic retinopathy: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS Report no. 8). *Acta Diabetol.* (2010) 47:209–15. doi: 10.1007/s00592-009-0113-8

111. Scanlon PH, Aldington SJ, Stratton IM. Epidemiological issues in diabetic retinopathy. *Middle East Afr J Ophthalmol.* (2013) 20:293–300. doi: 10.4103/0974-9233.120007

112. Chiu CJ, Taylor A. Dietary hyperglycemia, glycemic index and metabolic retinal diseases. *Prog Retin Eye Res.* (2011) 30:18–53. doi: 10.1016/j.preteyeres.2010.09.001

113. Wong TY, Klein R, Islam FMA, Cotch MF, Folsom AR, Klein BEK, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol.* (2006) 141:446–55. doi: 10.1016/j.ajo.2005.08.063

114. Van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, et al. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study. *Arch Ophthalmol.* (2003) 121:245–51. doi: 10.1001/archopht.121.2.245

115. Rajalakshmi R, Amutha A, Ranjani H, Ali MK, Unnikrishnan R, Anjana RM, et al. Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. *J Diabetes Complic.* (2014) 28:291–7. doi: 10.1016/j.jdiacomp.2013.12.008

116. Sharma Y, Saxena S, Mishra A, Saxena A, Natu SM. Nutrition for diabetic retinopathy: plummeting the inevitable threat of diabetic vision loss. *Eur J Nutr.* (2017) 56:2013–27. doi: 10.1007/s00394-017-1406-2

117. Van der Put N, Gabreëls FES-TAJ of 1998 undefined. *A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects?* Elsevier. Available online at: https://www.sciencedirect.com/science/article/pii/S0002929707615249 (accessed July 18, 2022).

118. McNulty H, Strain JJ, Hughes CF, Ward M. Riboflavin, MTHFR genotype and blood pressure: a personalized approach to prevention and treatment of hypertension. *Mol Aspects Med.* (2017) 53:2–9. doi: 10.1016/j.mam.2016.10.002

119. Yigit S, Karakus N, vision AI-M. *Association of MTHFR gene C677T mutation with diabetic peripheral neuropathy and diabetic retinopathy.* (2013).

Available online at: ncbi.nlm.nih.gov; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3724957/ (accessed July 18, 2022).

120. Yaribeygi H, Atkin SL, Sahebkar A. A review of the molecular mechanisms of hyperglycemia-induced free radical generation leading to oxidative stress. *J Cell Physiol.* (2019) 234:1300–12. doi: 10.1002/jcp.27164

121. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, et al. Impaired tissue perfusion. *Circulation.* (2008) 118:968–76. doi: 10.1161/CIRCULATIONAHA.107.763730

122. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N, et al. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham offspring study. *Am Diabetes Assoc.* 24:1403–10. doi: 10.2337/diacare.24.8.1403

123. Scaglione F, Xenobiotica GP. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. *Xenobiotica.* (2014) 44:480–8. doi: 10.3109/00498254.2013.845705

124. Zhu W, Meng YF, Wu Y, Xu M, Lu J. Association of alcohol intake with risk of diabetic retinopathy: a meta-analysis of observational studies. *Sci Rep.* (2017) 7:1–9. doi: 10.1038/s41598-017-00034-w

125. Chen C, Sun Z, Xu W, Tan J, Li D, Wu Y, Zheng T, Peng D. Associations between alcohol intake and diabetic retinopathy risk: a systematic review and meta-analysis. *BMC Endocr Disord.* (2020) 20:106. doi: 10.1186/s12902-020-00588-3

126. Raum P, Lamparter J, Ponto KA, Peto T, Hoehn R, Schulz A, et al. Prevalence and cardiovascular associations of diabetic retinopathy and maculopathy: results from the Gutenberg health study. *PLoS ONE.* (2015) 10:e0139527. doi: 10.1371/journal.pone.0139527

127. Yu W, Fu YC, Wang W. Cellular and molecular effects of resveratrol in health and disease. *J Cell Biochem.* (2012) 113:752–9. doi: 10.1002/jcb.23431

128. Srikanta AH, Kumar A, Sukhdeo SV, Peddha MS, Govindaswamy V. The antioxidant effect of mulberry and jamun fruit wines by ameliorating oxidative stress in streptozotocin-induced diabetic Wistar rats. *Food Funct.* (2016) 7:4422–31. doi: 10.1039/C6FO00372A

129. Giuffrè G, Lodato G, Dardanoni G. Prevalence and risk factors of diabetic retinopathy in adult and elderly subjects: the Casteldaccia Eye Study. *Graefe's Arch Clin Exp Ophthalmol.* (2004) 242:535–40. doi: 10.1007/s00417-004-0880-4

130. Beulens JWJ, Kruidhof JS, Grobbee DE, Chaturvedi N, Fuller JH, Soedamah-Muthu SS. Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: the EURODIAB Prospective Complications Study. *Diabetologia.* (2008) 51:1631–8. doi: 10.1007/s00125-008-1091-z

131. Fenwick EK, Xie J, Man REK, Lim LL, Flood VM, Finger RP, et al. Moderate consumption of white and fortified wine is associated with reduced odds of diabetic retinopathy. *J Diabetes Complic.* (2015) 29:1009–14. doi: 10.1016/j.jdiacomp.2015.09.001

132. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas M-I, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med.* (2014) 160:1–10. doi: 10.7326/M13-1725

133. Premanand C, Rema M, Sameer MZ, Sujatha M, Balasubramanyam M. Effect of curcumin on proliferation of human retinal endothelial cells under *in vitro* conditions. *Invest Opthalmol Visual Sci.* (2006) 47:2179. doi: 10.1167/iovs.05-0580

134. Bucolo C, Drago F, Maisto R, Romano GL, D'Agata V, Maugeri G, Giunta S. Curcumin prevents high glucose damage in retinal pigment epithelial cells through ERK1/2-mediated activation of the Nrf2/HO-1 pathway. *J Cell Physiol.* (2019) 234:17295–304. doi: 10.1002/jcp.28347

135. Platania CBM, Fidilio A, Lazzara F, Piazza C, Geraci F, Giurdanella G, et al. Retinal protection and distribution of curcumin *in vitro* and *in vivo*. *Front Pharmacol.* (2018) 9:670. doi: 10.3389/fphar.2018.00670

136. Woo JM, Shin D-Y, Lee SJ, Joe Y, Zheng M, Yim JH, et al. Curcumin protects retinal pigment epithelial cells against oxidative stress via induction of heme oxygenase-1 expression and reduction of reactive oxygen. *Mol Vis.* (2012) 18:901–8.

137. Maugeri A, Mazzone MG, Giuliano F, Vinciguerra M, Basile G, Barchitta M, et al. Curcumin modulates dna methyltransferase functions in a cellular model of diabetic retinopathy. *Oxid Med Cell Longev.* (2018) 2018:1–12. doi: 10.1155/2018/5407482

138. Mustata GT, Rosca M, Biemel KM, Reihl O, Smith MA, Viswanathan A, et al. Paradoxical effects of green tea (*Camellia sinensis*) and antioxidant vitamins in diabetic rats improved retinopathy and renal mitochondrial defects but deterioration of collagen matrix glycoxidation and cross-linking. *Diabetes.* (2005) 54:517–26. doi: 10.2337/diabetes.54.2.517

139. Silva KC, Rosales MAB, Hamassaki DE, Saito KC, Faria AM, Ribeiro PAO, et al. Green tea is neuroprotective in diabetic retinopathy. *Invest Ophthalmol Vis Sci.* (2013) 54:1325–36. doi: 10.1167/iovs.12-10647

140. Kumar B, Gupta SK, Nag TC, Srivastava S, Saxena R. Green tea prevents hyperglycemia-induced retinal oxidative stress and inflammation in streptozotocin-induced diabetic rats. *Ophthalmic Res.* (2012) 47:103–8. doi: 10.1159/000330051

141. Vinson JA, Zhang J. Black and green teas equally inhibit diabetic cataracts in a streptozotocin-induced rat model of diabetes. *J Agric Food Chem.* (2005) 53:3710–3. doi: 10.1021/jf048052l

142. Silva S Da, Costa J, Pintado M, Ferreira D. Antioxidants in the prevention and treatment of diabetic retinopathy a review. *J Diabet Metabol.* (2010) 1:111. doi: 10.4172/2155-6156.1000111

143. Lee Chong T, Ahearn EL, Cimmino L. Reprogramming the epigenome with vitamin C. *Front Cell Dev Biol.* (2019) 7:128. doi: 10.3389/fcell.2019.00128

144. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxid Redox Signal.* (2013) 19:2068–83. doi: 10.1089/ars.2013.5205

145. Yin J, Thomas F, Lang JC, and Chaum E. Modulation of oxidative stress responses in the human retinal pigment epithelium following treatment with vitamin C. *Wiley Online Library.* (2011) 226:2025–32. doi: 10.1002/jcp.22532

146. Berrone E, Beltramo E, Solimine C, Ape AU, Porta M. Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultured in high glucose. *J Biol Chem.* (2006) 281:9307–13. doi: 10.1074/jbc.M600418200

147. Dagher Z, Park YS, Asnaghi V, Hoehn T, Gerhardinger C, Lorenzi M. Studies of rat and human retinas predict a role for the polyol pathway in human diabetic retinopathy. *Am Diabetes Assoc.* 53:2404–11. doi: 10.2337/diabetes.53.9.2404

148. Pácal L, Kuricová K, diabetes KK. Evidence for altered thiamine metabolism in diabetes: is there a potential to oppose gluco-and lipotoxicity by rational supplementation? *World J Diabetes.* 5:288–95. doi: 10.4239/wjd.v5.i3.288

149. Booth AA, Khalifah RG, Hudson BG. Thiamine pyrophosphate and pyridoxamine inhibit the formation of antigenic advanced glycation end-products: comparison with aminoguanidine 1. *Biochem Biophys Res Commun.* (1996) 220:113–9. doi: 10.1006/bbrc.1996.0366

150. Shi C, Wang P, Airen S, Brown C, Liu Z, Townsend JH, et al. Nutritional and medical food therapies for diabetic retinopathy. *Eye Vis.* (2020) 7:1–16. doi: 10.1186/s40662-020-00199-y

151. Xu C, Wu Y, Liu G, Liu X, Wang F, Yu J. Relationship between homocysteine level and diabetic retinopathy: a systematic review and meta-analysis. *Diagn Pathol.* (2014) 9:167. doi: 10.1186/s13000-014-0167-y

152. Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov S, et al. Müller cells in the healthy and diseased retina. *Prog Retin Eye Res.* (2006) 25:397–424. doi: 10.1016/j.preteyeres.2006.05.003

153. Vrolijk MF, Opperhuizen A, Jansen EHJM, Hageman GJ, Bast A, Haenen GRMM. The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. *Toxicol in Vitro.* (2017) 44:206–12. doi: 10.1016/j.tiv.2017.07.009

154. Braun DJ, Abner E, Bakshi V, Goulding DS, Grau EM, Lin AL, et al. Blood flow deficits and cerebrovascular changes in a dietary model of hyperhomocysteinemia. *ASN Neuro.* (2019) 11:1759091419865788. doi: 10.1177/1759091419865788

155. Rathod RS, Khaire AA, Kale AA, Joshi SR. Effect of vitamin B12 and omega-3 fatty acid supplementation on brain neurotrophins and cognition in rats: a multigeneration study. *Biochimie.* (2016) 128–9:201–8. doi: 10.1016/j.biochi.2016.08.009

156. Vitamin B12-Health Professional Fact Sheet. *National Institutes of Health.* (2020). Available online at: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/. - Cerca con Google. https://www.google.com/search?q=Vitamin$+$B12-Health$+$Professional$+$Fact$+$Sheet.$+$National$+$Institutes$+$of$+$Health.$+$2020.$+$https%3A%2F%2Fods.od.nih.gov%2Ffactsheets%2FVitaminB12-HealthProfessional%2F.&rlz=1C1AVFC_enIT851IT852&oq=Vitamin$+$B12-Health$+$Professional$+$Fact$+$Sheet.$+$National$+$Institutes$+$of$+$Health.$+$2020.$+$https%3A%2F%2Fods.od.nih.gov%2Ffactsheets%2FVitaminB12-HealthProfessional%2F.&aqs=chrome.0.69i57.404j0j7&sourceid=chrome&ie=UTF-8 (accessed July 14, 2022).

157. Tarr JM, Kaul K, Wolanska K, Kohner EM, Chibber R. Retinopathy in diabetes. *Adv Exp Med Biol.* (2013) 771:88–106. doi: 10.1007/978-1-4614-5441-0_10

158. Augustine J, Troendle EP, Barabas P, McAleese CA, Friedel T, Stitt AW, et al. The role of lipoxidation in the pathogenesis of diabetic retinopathy. *Front Endocrinol.* (2021) 11:1146. doi: 10.3389/fendo.2020.621938

159. Bengmark S. Advanced glycation and lipoxidation end products–amplifiers of inflammation: the role of food. *J Parenteral Enteral Nutr.* (2007) 31:430–40. doi: 10.1177/0148607107031005430

160. Park S, Karunakaran U, Jeoung N, Jeon J-H, Lee I-K. Physiological effect and therapeutic application of alpha lipoic acid. *Curr Med Chem.* (2014) 21:3636–45. doi: 10.2174/0929867321666140706141806

161. Volobouева LA, Liu J, Suh JH, Ames BN, Miller SS. (R)-alpha-lipoic acid protects retinal pigment epithelial cells from oxidative damage. *Invest Ophthalmol Vis Sci.* (2005) 46:4302–10. doi: 10.1167/iovs.04-1098

162. Diabetes Control and Complications Trial Research Group, DMNathan, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* (1993) 329:977–986. doi: 10.1056/NEJM199309303291401

163. Linee guida per la pratica clinica : gestione delle complicanze oculari del diabete. Retinopatia diabetica ed edema maculare. *Rodríguez, F Cabrera*

Available online at: https://scielo.isciii.es/scielo.php?pid=S0365-66912009000900003&script=sci_arttext&tlng=en (accessed July 20, 2022).

164. Beli E, Yan Y, Moldovan L, Vieira CP, Gao R, Duan Y, et al. Restructuring of the Gut microbiome by intermittent fasting prevents retinopathy and prolongs survival in db/db mice. *Diabetes.* (2018) 67:1867–79. doi: 10.2337/db18-0158

165. Haluzík M, Mráz M. Intermittent fasting and prevention of diabetic retinopathy: where do we go from here? *Diabetes.* (2018) 67:1745–7. doi: 10.2337/dbi18-0022

166. Li Q, He R, Zhang F, Zhang J, Lian S, Liu H. Combination of oligofructose and metformin alters the gut microbiota and improves metabolic profiles, contributing to the potentiated therapeutic effects on diet-induced obese animals. *Front Endocrinol.* (2020) 10:939. doi: 10.3389/fendo.2019.00939

167. Maria Tanase D, Maria Gosav E, Neculae E, Florida Costea C, Ciocoiu M, Liliana Hurjui L, et al. Role of gut microbiota on onset and progression of microvascular complications of type 2 diabetes (T2DM). *Nutrients.* (2020) 12:3719. doi: 10.3390/nu12123719

168. Dirani M, Crowston JG, van Wijngaarden P. Physical inactivity as a risk factor for diabetic retinopathy? A review. *Clin Exp Ophthalmol.* (2014) 42:574–81. doi: 10.1111/ceo.12306

169. Ren C, Liu W, Li J, Cao Y, Xu J, Lu P. Physical activity and risk of diabetic retinopathy: a systematic review and meta-analysis. *Acta Diabetol.* (2019) 56:823–37. doi: 10.1007/s00592-019-01319-4

170. Boniol M, Dragomir M, Autier P, Boyle P. Physical activity and change in fasting glucose and HbA1c: a quantitative meta-analysis of randomized trials. *Acta Diabetol.* (2017) 54:983–91. doi: 10.1007/s00592-017-1037-3

171. Makanae Y, Ogasawara R, Sato K, Takamura Y, Matsutani K, Kido K, et al. Acute bout of resistance exercise increases vitamin D receptor protein expression in rat skeletal muscle. *Exp Physiol.* (2015) 100:1168–76. doi: 10.1113/EP085207

172. Sallam N, Laher I. Exercise modulates oxidative stress and inflammation in aging and cardiovascular diseases. *Oxid Med Cell Longev.* (2016) 2016:7239639. doi: 10.1155/2016/7239639

173. Kim CS, Park S, Chun Y, Song W, Kim HJ, Kim J. Treadmill exercise attenuates retinal oxidative stress in naturally-aged mice: an immunohistochemical study. *Int J Mol Sci.* (2015) 16:21008–20. doi: 10.3390/ijms160921008

174. Kruk J, Kubasik-Kladna K, Aboul-Enein YH. The role oxidative stress in the pathogenesis of eye diseases: currnt status and a dual role of physical activity. *Mini Rev Med Chem.* (2016) 16:241–57. doi: 10.2174/1389557516666151120114605

175. Allen RS, Hanif AM, Gogniat MA, Prall BC, Haider R, Aung MH, et al. TrkB signalling pathway mediates the protective effects of exercise in the diabetic rat retina. *Eur J Neurosci.* (2018) 47:1254–65. doi: 10.1111/ejn.13909

176. Cui JZ, Wong M, Wang A, Laher I, Matsubara JA. Exercise inhibits progression of diabetic retinopathy by reducing inflammatory, oxidative stress, and ER stress gene expression in the retina of db/db mice. *Invest Ophthalmol Vis Sci.* (2016) 57:5434–4.

177. Colberg SR. Exercise and diabetes: a clinician's guide to prescribing physical activity. *Am Diabetes Assoc.* (2013). doi: 10.2337/9781580404853

178. Graham C, Lasko-m P. Exercise options for persons with diabetic complications. *Diabetes Educ.* (1990) 16:212–20. doi: 10.1177/014572179001600312

179. Hamdy O, Goodyear LJ, Horton ES. Diet and exercise in type 2 diabetes mellitus. *Endocrinol Metab Clin North Am.* (2001) 30:883–907. doi: 10.1016/S0889-8529(05)70220-6

180. Farrell PA, Fedele MJ, Hernandez J, Fluckey JD, Miller JL, Lang CH, et al. Hypertrophy of skeletal muscle in diabetic rats in response to chronic resistance exercise. *J Appl Physiol.* (1999) 87:1075–82. doi: 10.1152/jappl.1999.87.3.1075

181. Liew G, Klein R, Wong TY. The role of genetics in susceptibility to diabetic retinopathy. *Int Ophthalmol Clin.* (2009) 49:35–52. doi: 10.1097/IIO.0b013e31819fd5d7

182. Irvine C, Taylor NF. Progressive resistance exercise improves glycaemic control in people with type 2 diabetes mellitus: a systematic review. *Austral J Physiother.* (2009) 55:237–46. doi: 10.1016/S0004-9514(09)70003-0

183. Chiu CJ, Chang ML, Zhang FF, Li T, Gensler G, Schleicher M, et al. The relationship of major American dietary patterns to age-related macular degeneration. *Am J Ophthalmol.* (2014) 158:118–27.e1. doi: 10.1016/j.ajo.2014.04.016

184. Rinninella E, Mele MC, Merendino N, Cintoni M, Anselmi G, Caporossi A, et al. The role of diet, micronutrients and the gut microbiota in age-related macular degeneration: new perspectives from the gut¯retina axis. *Nutrients.* (2018) 10. doi: 10.20944/preprints201810.0369.v1

185. Schweigert FJ, Reimann J. Mikronährstoffe und ihre Bedeutung für das Auge Wirkungsweise von Lutein/Zeaxanthin und Omega-3-Fettsäuren. *Klin Monbl Augenheilkd.* (2011) 228:537–43. doi: 10.1055/s-0029-1245527

186. King JC. Zinc: an essential but elusive nutrient. *Am J Clin Nutr.* (2011) 94: 679S—84. doi: 10.3945/ajcn.110.005744

187. Erie JC, Good JA, Butz JA, Pulido JS. Reduced zinc and copper in the retinal pigment epithelium and choroid in age-related macular degeneration. *Am J Ophthalmol.* (2009) 147**:**276–82.e1. doi: 10.1016/j.ajo.2008.08.014

188. McGuinness MB, Le J, Mitchell P, Gopinath B, Cerin E, Saksens NTM, et al. Physical activity and age-related macular degeneration: a systematic literature review and meta-analysis. *Am J Ophthalmol.* (2017) 180:29–38. doi: 10.1016/j.ajo.2017.05.016

189. Taylor A, Jacques PF, Nowell T, Perrone G, Blumberg J, Handelman G, et al. Vitamin C in human and guinea pig aqueous, lens and plasma in relation to intake. *Curr Eye Res.* (1997) 16:857–64. doi: 10.1076/ceyr.16.9.857.5039

190. Polse KA, Brand R, Mandell R, Vastine D, Demartini D, Flom R. Age differences in corneal hydration control. *Invest Ophthalmol Vis Sci.* (1989) 30:392–9.

191. Sabetti L, Renzetti A, D'Alessandri L, Balestrazzi E. Eventual error caused by dehydration with pachometry. *Ophthalmologica.* (2001) 215:97–101. doi: 10.1159/000050837

192. Heys KR, Friedrich MG, Truscott RJW. Free and bound water in normal and cataractous human lenses. *Invest Ophthalmol Vis Sci.* (2008) 49:1991–7. doi: 10.1167/iovs.07-1151

193. Obrosova IG, Chung SSM, Kador PF. Diabetic cataracts: mechanisms and management. *Diabetes Metab Res Rev.* (2010) 26:172–80. doi: 10.1002/dmrr.1075

194. Kisic B, Miric D, Zoric L, Ilic A, Dragojevic I. Antioxidant capacity of lenses with age-related cataract. *Oxid Med Cell Longev.* (2012) 2012:467130. doi: 10.1155/2012/467130

195. Njie-Mbye YF, Kulkarni-Chitnis M, Opere CA, Barrett A, Ohia SE. Lipid peroxidation: pathophysiological and pharmacological implications in the eye. *Front Physiol.* (2013) 4:366. doi: 10.3389/fphys.2013.00366

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 12 September 2023
DOI 10.3389/fmed.2023.1225689

OPEN ACCESS

EDITED BY
Roberta Zupo,
University of Bari Aldo Moro, Italy

REVIEWED BY
Michał Czapla,
Wroclaw Medical University, Poland
Sergio Perez-Burillo,
Public University of Navarre, Spain

*CORRESPONDENCE
Mary Beth Arensberg
✉ mary.arensberg@abbott.com

RECEIVED 19 May 2023
ACCEPTED 25 August 2023
PUBLISHED 12 September 2023

CITATION
Arensberg MB, Gahche J, Clapes R, Kerr KW, Merkel J and Dwyer JT (2023) Research is still limited on nutrition and quality of life among older adults.
Front. Med. 10:1225689.
doi: 10.3389/fmed.2023.1225689

Research is still limited on nutrition and quality of life among older adults

Mary Beth Arensberg[1]*, Jaime Gahche[2], Raquel Clapes[3], Kirk W. Kerr[1], Joyce Merkel[2] and Johanna T. Dwyer[2,4]

[1]Abbott Nutrition Division of Abbott, Columbus, OH, United States, [2]Office of Dietary Supplements, National Institutes of Health, Bethesda, MD, United States, [3]Abbott Nutrition Division of Abbott, Granada University Science Park, Granada, Spain, [4]School of Medicine and Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA, United States

Introduction: Globally, the number of older adults is growing exponentially. Yet, while living longer, people are not necessarily healthier. Nutrition can positively impact healthy aging and quality of life (QoL). Two decades ago, nutrition and diet were rarely viewed as key QoL domains, were not part of QoL screening, and QoL studies frequently used unvalidated tools. It is unclear how the nutrition and QoL research area may have since evolved.

Methods: A scoping review was conducted in Pubmed of research with community-living older adults (aged ≥65) from developed economies that included 1 of 29 common, valid QoL instruments, nutrition indices, and was published between 1/2000–12/2022. The review followed published methodology guidance and used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram to document identified studies and record number of included/excluded studies (based on scoping review's pre-specified criteria).

Results: Of 258 studies identified initially, 37 fully met scoping review inclusion criteria; only 2 were QoL studies, 30 focused on nutrition, 3 on measurement tool validation/testing, and 2 were other study types. Most studies (n = 32) were among populations outside of North America; majority were conducted in Europe (n = 22) where the EuroQol 5 Dimension (Eq5D) was used in >1/2 the studies. Of 5 North American studies, the 36-Item Short Form Survey (SF-36) was most frequently used (n = 4). Myriad nutrition indices described various aspects of eating, dietary intake, and nutrition status, making comparability between studies difficult. Studies included several different nutrition questionnaires; Mini Nutritional Assessment (MNA) (n = 8) or Mini Nutritional Assessment Short Form (MNA-SF) (n = 5) were used most frequently. The most frequent anthropometric measure reported was Body Mass Index (BMI) (n = 28). Nutrition-related biochemical indices were reported infrequently (n = 8).

Discussion: The paucity of studies over the last two decades suggests research on nutrition and QoL among community-living older adults remains underdeveloped. Valid QoL instruments and nutrition indices are now available. To ensure greater comparability among studies it is important to develop consensus on core indices of QoL and particularly nutrition. Greater agreement on these indices will advance further research to support healthy aging and improve QoL for community-dwelling older adults.

KEYWORDS

nutrition, quality of life, healthy aging, older adults, community-living

1. Introduction

Globally the number of older adults is growing exponentially, spurred by increasing longevity and decreasing fertility rates (1). Indeed, in the year 2020, for the first time in history, the number of people aged 60 and older outnumbered children younger than five years of age in the world. By 2030, one in six people will be aged 60 or older, and by 2050, those aged 60 plus will be double in number compared to today, reaching an estimated 2.1 billion. At the same time, the number of oldest old (those aged 80 or older) will triple to reach 426 million by 2050 (2).

The aging of a population is more economically sustainable when older adults are healthy and continue to remain actively engaged in society (3). Older individuals' contributions to society depend heavily on their health, and so healthy aging has become a priority for health systems throughout the world (4). However, while many people are living longer, their lives are not necessarily healthier, even in higher-income countries such as the United States (US). All countries face major challenges in dealing with current demographic shifts, although the shifts are particularly pronounced in the US. Americans aged 65 and older represented 16% of the population in 2019, and by 2040 this segment is expected to grow to 22%. During the same timeframe, the number of Americans aged 85 or older is projected to more than double, from 6.6 million to 14.4 million (a 118% increase) (5).

Most older Americans, particularly those who are 75 years and older, are afflicted with multiple chronic conditions and other health-related problems (6). Those with major noncommunicable diseases have earlier and steeper rates of functional decline than their healthier peers (7). Healthy aging involves developing and maintaining the functional abilities that enable well-being and a high quality of life (QoL) in older age, including physical, as well as mental and social functional domains (2). This healthy aging goal is recognized in the US *Healthy People 2030* national health goals that include "reducing health problems and improving quality of life for older adults" (8).

Nutrition is fundamental to helping achieve such national health goals. The 2022 US White House Conference on Hunger, Nutrition, and Health described the vital and often unrecognized role that nutrition plays in helping older adults remain healthy and independent (9). In addition, food and eating are part of the pleasures of life (10) that contribute to physical, mental, and social QoL domains. Older adults themselves regard maintaining functional independence and QoL as of primary importance (11). Yet difficulties with eating, poor diet, and other nutrition issues including malnutrition often remain unidentified, although they are potent contributors to frailty, functional impairments, and poor QoL, especially among the very old. Further, age-associated changes in diet and nutrition status are also frequently involved in the development, severity, and/or exacerbation of many chronic degenerative diseases that have an impact on QoL (12).

There is evidence of a link between nutrition and QoL but there is a dearth of research on this important area of healthy aging (13). Four decades ago, the 1979 US *Surgeon General's Report on Health Promotion and Disease Prevention* proclaimed that the main goal for older adults was to improve their health and QoL, and recognized nutrition as a factor that could help increase older adults' independence, self-sufficiency, and QoL (14). Over 20 years later a review of nutrition and QoL in older adults found that nutrition and diet were still not part of mainstream research on QoL and were seldom included among key QoL domains (15). The absence of both nutrition in QoL research and QoL considerations in nutrition research after all those years is puzzling since the connection between the two is so relevant to both health policy and older adults themselves.

In their nutrition and QoL review, Amarantos et al. found that the diversity of QoL screening tools was limited and that unvalidated QoL screening tools were frequently used in studies (15). Siette et al. recently summarized existing research on the validity and reliability of 29 commonly used, self-reported instruments for assessing QoL among older adults (16). However, Siette et al. (16) did not consider whether any of these QoL instruments included nutrition.

To guide the development of further research and inform healthy aging policy, we sought to identify how the intersection between nutrition and QoL studies in community-living older adults has evolved in the last 20 years. Specifically, we conducted a scoping review to determine: (1) how much QoL research in community-living older adults included nutrition indices and used one or more of 29 common, validated QoL instruments and (2) how much research on nutrition in community-living older adults included one or more of the same 29 QoL instruments.

2. Methods

We performed a scoping review with the assistance of a scientific and health communications expert (JM) to examine the research literature, focusing on studies with community-living older adults that assessed both nutrition and QoL and used one or more of the 29 common, validated QoL instruments identified in Siette et al. (16). The review followed published guidance on methodology (17). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram was used to document the studies we identified and record the number of studies included and excluded based on our pre-specified criteria as detailed below.

2.1. Search strategy

Studies were included if they had: (1) one or more of the 29 common, validated general QoL instruments used in their entirety, (2) a measure of nutrition status and/or a nutrition intervention, (3) a research population of older adults aged 65 and over who were living in the community or independently, and (5) a study population in a country that has a developed economy. Search terms were a combination of nutrition terms (i.e., nutrition, nutritional, food, diet, hunger, food insecurity) AND independent or community living AND the QoL instruments specified in the paper by Siette et al. AND older adults (complete research search string available in the Supplementary Figure). Articles were retrieved from Pubmed and included those published between January 1, 2000, and December 31, 2022.

Studies were also identified through citations from relevant literature reviews that were initially included in the Pubmed retrieval. Specifically, all systematic reviews, meta-analyses and umbrella reviews were ultimately excluded from our final list of studies but were first screened to identify any studies in the reviews that met our pre-specified inclusion criteria but were not found in the Pubmed search.

2.2. Study selection and data extraction

2.2.1. Pre-specified inclusions

At least one of the 29 general QoL instruments that Siette et al. recently reviewed for validity and reliability (16) had to be used in included studies. These instruments were: Alzheimer's Disease-Related Quality of Life (ADRQOL), Assessment of Quality of Life instrument (including AQoL-8, AQoL-4D, AQoL-6D, AQoL-7D AQoL-8D versions), Adult Social Care Outcomes Toolkit (ASCOT), Comfort Around Dying-End of Life in Dementia (CAD-EOLD), Comprehensive Quality of Life Scale (COMQOL), 15-Dimensional instrument (15-D), Dementia Quality of Life measure (DEMQOL), Dementia Quality of Life Instrument (DQOL), Duke Health Profile (DUKE), EuroQoL-5 Dimensions (EQ-5D), Health Utility Index (HUI), ICEpop CAPability measure for Older people (ICECAP-O), inter Resident Assessment Instrument Long Term Care Facility (inteRAI (LTCF)), Joy-of-Life Scale (JoLS), Long Term Care Quality Of Life assessment scale (LTC-QOL), Manchester Short Assessment of quality of life (MANSA), Nottingham Health Profile (NHP), Nursing Home Vision-Targeted Health-related QoL (NHVQOL), Oral Health Impact Profile (OHIP), Older Peoples Quality Of Life (OPQOL), Philadelphia Geriatric Centre Moral Scale (PGCMS), Quality of Life in Alzheimer's Disease (QoL-AD), Quality of Life In Late-Stage Dementia (QUALID), Dementia Specific Quality of Life Instrument (QUALIDEM), Short Form-8 Health Survey (SF-8)/12-Item Short Form Survey (SF-12)/36-Item Short Form Survey (SF-36), Satisfaction With Life Scale (SWLS), World Health Organization Quality of Life Scale – AGE (WHOQOL-AGE), WHO Quality of Life-Bref (WHOQOL-BREF), World Health Organization Quality of Life Scale–OLD (WHOQOL-OLD). Note that all of these instruments were described as more general QoL instruments and *not* chronic-disease or nutrition-specific instruments. We also searched for additional well-validated and reliable QoL instruments that might have been developed after the publication of the Siette et al. paper (16); none were identified through our further search.

2.2.2. Pre-specified exclusions

Studies were excluded if the research was: (1) only an abstract, poster, study protocol/design (i.e., no published paper with results), (2) targeted toward a palliative care population, (3) focused on QoL for families/caregivers vs. older adults themselves, (4) using only a portion of a validated QoL instrument vs. the complete instrument, (5) conducted with older adults in assisted living or hospitalized older adults but had no follow-up of these subjects in a community-living setting, (6) published before the year 2000, (7) published in languages other than English, and/or (8) not conducted in a country identified by the United Nations as a "developed economy" (18).

2.2.3. Study selection

Five independent researchers (MBA, JG, RC, KWK, JTD) initially screened the titles and corresponding abstracts identified during the search. Twenty percent of the titles and corresponding abstracts were screened by two researchers. All discrepancies involving whether studies would advance to the next step in the review process were discussed as a group and adjudicated accordingly. Next, the full-text articles were reviewed to confirm that the studies fully met the defined inclusion criteria. All five researchers screened the full-text articles, with 32% of the articles screened by two researchers. Again, all discrepancies regarding whether to include studies in the final review were discussed among the group and adjudicated.

2.2.4. Data extraction

Once the final group of studies was identified, all five researchers were assigned full-text articles to review and more detailed study specifics were extracted. Thirty-two percent of the articles were reviewed by two researchers and all discrepancies in the study specifics extracted were adjudicated as a group. Study-specific details extracted included (1) study focus (nutrition intervention, nutrition status, validation or test of an instrument, quality of life, other), (2) objective of the study, (3) validated QoL instrument used, (4) category of nutrition indices used (i.e., questionnaire, anthropometric, biochemical), (5) description of nutrition indices used, (6) country where the study was conducted, and (7) study title and year published. All data were extracted and entered in a Microsoft Excel worksheet.

3. Results

Figure 1 illustrates the PRISMA diagram summarizing the number of articles retrieved and screened as well as reasons for exclusions. The Pubmed database search identified 248 articles. An additional 10 articles were identified by screening articles included in systematic reviews, meta-analyses, and umbrella reviews. After all exclusions, 37 articles were included in the final review to identify articles exhibiting the integration of nutrition and QoL research over the last 20 years.

The Supplementary material Table contains study-specific data extracted from the research articles. Of the 37 studies included, the most frequently used QoL instruments were the EQ-5D ($n = 14$), SF-36 ($n = 13$), and SF-12 ($n = 5$) (Figure 2). The WHOQOL-BREF ($n = 3$) was among the QoL instruments that were used less frequently. The 15-D, SWLS, OHIP, and the AQol-6D were each used in only a single study. Most of the studies included in the final review were conducted in Europe ($n = 22$) or Oceania ($n = 7$). The QoL tools they used most frequently also varied by country. Studies conducted in Europe tended to use the EQ-5D, while most studies in North America used the SF-36 (Figure 3). However, it should be noted that North America was represented in only five of the 37 studies included in the final review.

Figure 4 shows that two of the 37 studies included in the final review were focused specifically on QoL. Thirty of the 37 studies were nutrition-focused research studies (describing either nutrition interventions ($n = 22$) or nutrition status ($n = 8$)). The remaining categories of studies were validation and/or testing studies of questionnaires ($n = 3$) and an "other" group ($n = 2$) in which one study concerned healthcare resource use and another involved factors related to frailty.

Various nutrition indices were used to evaluate dietary or nutrition status (supplementary material Table). Twenty studies reported collecting some type of dietary intake information. Most of the studies measured nutrition status by questionnaires rather than by biochemical examination (Figure 5). The most commonly used nutrition questionnaire to measure nutrition status was the Mini Nutritional Assessment or MNA ($n = 8$) or its shorter version, the Mini Nutritional Assessment Short-Form or MNA-SF ($n = 5$) (Supplementary Table).

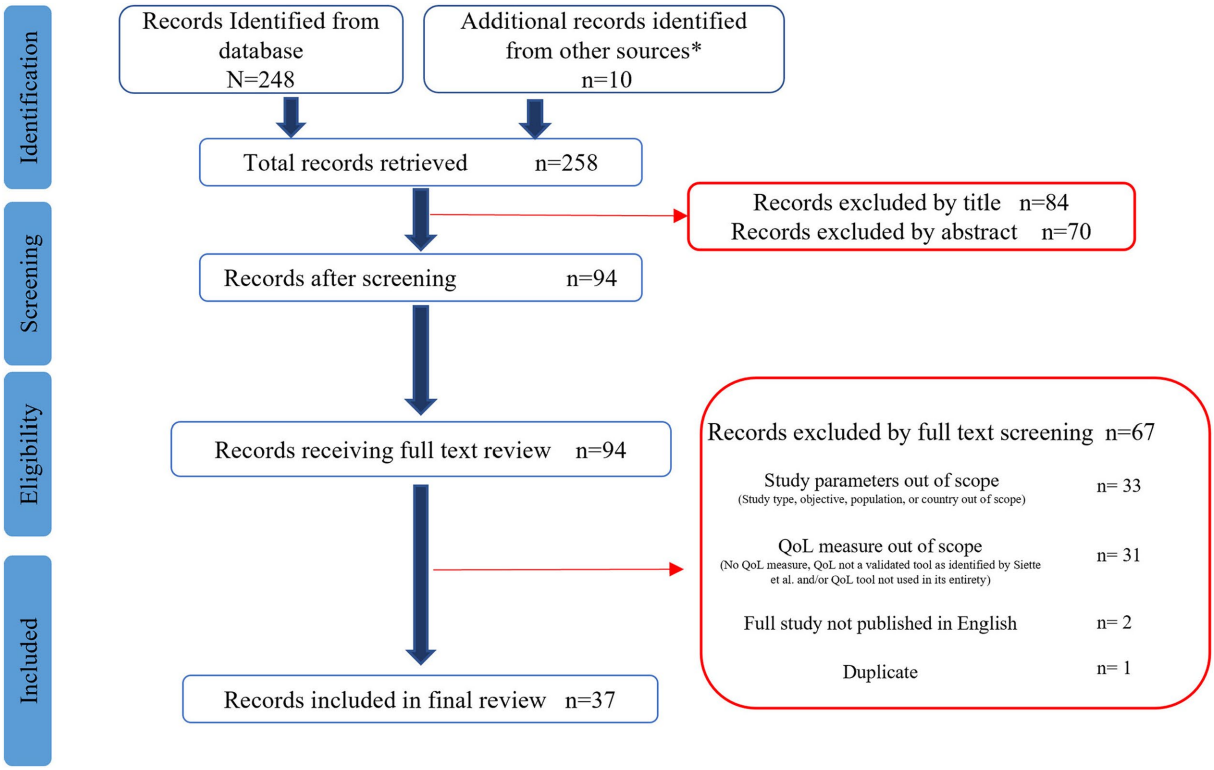


FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for nutrition and quality of life scoping review. *Additional articles identified from systematic reviews (19).

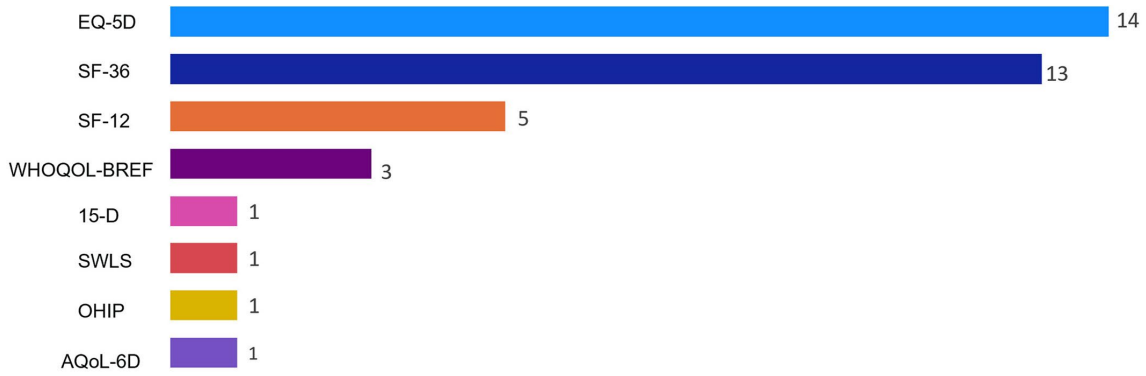


FIGURE 2
Frequency of quality of life instruments used for studies included in nutrition and quality of life scoping review ($N = 37$). Reported frequencies >37 because some studies used multiple quality of life instruments. 15-D, 15-Dimensional instrument; AQoL-6D, Assessment of Quality of Life instrument-6D Version; EQ-5D, EuroQoL 5-Dimensions; OHIP, Oral Health Impact Profile; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey; SWLS, Satisfaction With Life Scale; WHOQOL-BREF, World Health Organization Quality of Life-Bref.

Anthropometric measures (i.e., body mass index (BMI), muscle circumference) were reported in nearly all the nutrition intervention studies but less frequently in studies focused on nutrition status, QoL, or validation/test development studies (Figure 5). BMI was the most collected anthropometric measure and was specifically reported in 28 studies and handgrip strength was the most-commonly reported measure of muscle status (supplementary material Table). Regardless of the type of study, biochemical measures were infrequently reported. Biochemical measures were only collected in 8 of the studies, with albumin being the most commonly reported assay ($n = 6$) (Supplementary Table).

4. Discussion

This scoping review identified nutrition and QoL research published during the last two decades that both focused on

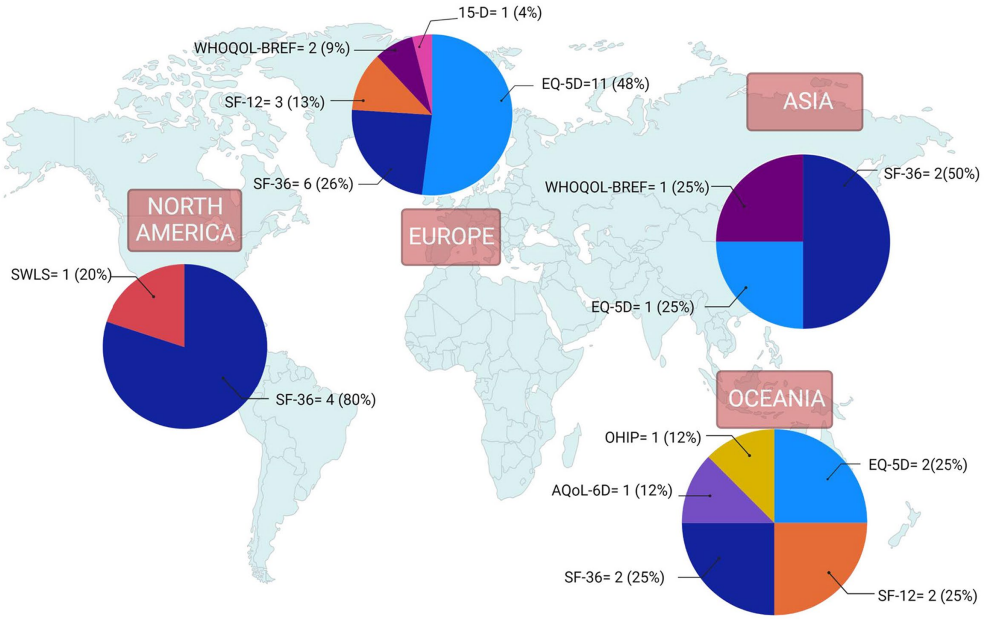


FIGURE 3
Quality of life instruments by world region for studies included in nutrition and quality of life scoping review (*N* = 37). Reported frequencies >37 because some studies used multiple quality of life instruments and one study included countries from 2 regions. 15-D, 15-Dimensional instrument; AQoL-6D, Assessment of Quality of Life instrument-6D Version; EQ-5D, EuroQoL 5-Dimensions; OHIP, Oral Health Impact Profile; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey; SWLS, Satisfaction With Life Scale; WHOQOL-BREF, World Health Organization Quality of Life-Bref.

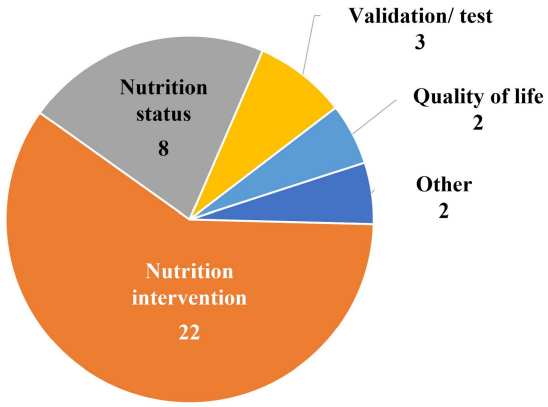


FIGURE 4
Focus of studies included in nutrition and quality of life scoping review (*N* = 37).

community-living older adults and included nutrition parameters as well as one or more of 29 common, validated QoL instruments. The number of studies found was limited ($n = 37$). The majority were nutrition intervention ($n = 22$) or nutrition status studies ($n = 8$), while only two were QoL studies. The remainder were either focused on validation/test development ($n = 3$) or other types of studies ($n = 2$).

Across the studies identified, the most-used QoL instruments were the EQ-5D and SF-36, although there were some regional differences; European studies most frequently used the Eq-5D and North American studies mostly used the SF-36. This is not surprising given the origins of these instruments. The EQ-5D is a widely used generic instrument for describing and valuing health, developed by the EuroQol Group. It is a preference-based instrument, with one question for each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (20). The individual questions have a range of three or five responses, depending on the instrument version (3 L or 5 L).

The SF-36 is an older, longer instrument first developed in the US at the Rand Corporation. It assesses eight health concepts: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions (21). The standard form of the instrument asks for participants to reply to questions according to how they have felt over the previous week and uses Likert-type scales, some with five or six points and others with two or three points. The SF-36 has also been widely used, has excellent psychometrics, (22, 23) and has shorter versions such as the SF-12 (24).

Most of the QoL instruments are self-report questionnaires designed for administration in surveys. Self-report is generally preferred for QoL because there can be significant differences between self-reports and proxy reports, even for people with disabilities (25). Most of the studies that included nutrition indices also used nutrition questionnaires, as might be expected since questionnaires are likely the most feasible tools for use in community settings.

In contrast to the finding that a few common, validated QoL instruments were used in many studies, the studies used myriad nutrition indices that considered different dimensions of the term, including eating and swallowing, food intake, anthropometric, and

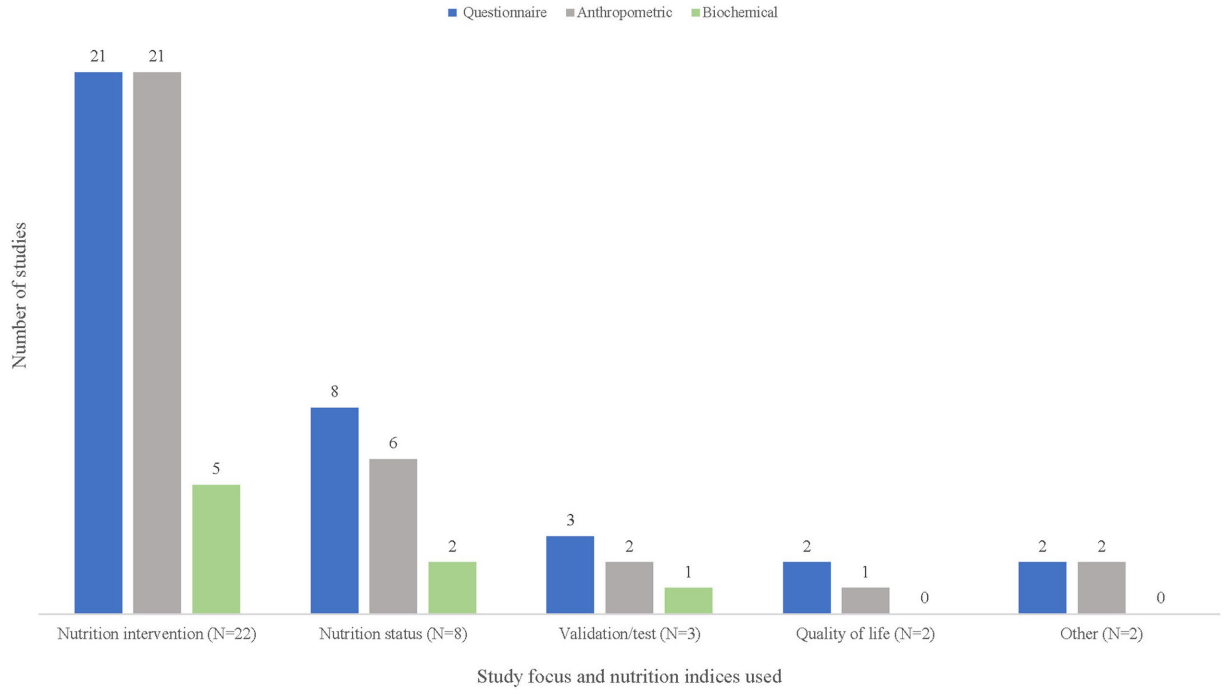


FIGURE 5
Frequency of nutrition indices used and focus for studies included in nutrition and quality of life scoping review (*N* = 37).

biochemical measures. Several studies in our review used nutrition questionnaires, most commonly the MNA ($n = 8$) or MNA-SF ($n = 5$). Both the MNA and MNA-SF are widely used (26) and have been validated for use with older adults (27, 28). The original MNA (now described as the "full" MNA) was designed as an 18-item questionnaire to be completed by a healthcare professional. It includes questions about food intake, weight loss, mobility, psychological stress/acute disease, neuropsychological problems, BMI, living arrangement, prescription drug use, pressure injuries, food consumption, and anthropometric measures (mid-arm muscle and calf circumference) and takes an estimated 10–15 min to complete (27). The MNA-SF has six items, with questions on food intake, weight loss, mobility, psychological stress/acute disease, neuropsychological problems, and BMI or calf circumference, and takes 5 min or less to complete (28). A Self-Mini Nutritional Assessment (SELF-MNA) has also been developed and validated (29) although the SELF-MNA was not used in any of the studies included in our review.

Three-quarters of the studies included anthropometric indices such as BMI, which was specifically reported in 28 studies, and they were much more common than biochemical indices which were only listed in 8 studies. This finding was expected because biochemical tests are difficult to collect in community-living populations, the measurements are costly, time-consuming, and when used by themselves without dietary and other information they are not reliable indicators of nutrition status in older adults (30).

4.1. Progress and gaps

Patient-reported outcomes are increasingly recognized as important for shared decision making, guidelines, and health policy (31). They also provide a better understanding of the factors associated with patient satisfaction and quality (32). It was heartening to note the progress made in developing and validating QoL instruments, as revealed in Siette et al.'s seminal review summarizing 29 common, validated QoL instruments (16). Validated QoL instruments are generally self-reported and questionnaire-based and thus are easy to use since they do not require physical instruments, biological measurements, or detailed training to complete. The array of instruments available today provides investigators with multiple options that are appropriate and ready for use in nutrition and other studies of factors that can impact the QoL of older adults in the community.

The recommendation made over two decades ago that more studies relating nutrition to quality of life were needed to "illustrate and strengthen claims that nutrition improves quality of life" did not appear to be heeded (15). It is puzzling why there is still such a striking lack of nutrition research in this area, particularly related to nutrition status. Between the years 2000–2022, we found only 30 nutrition research papers that investigated nutrition and/or diet among community-living older adults and included a validated general QoL instrument. Most of these studies were describing the outcomes of nutrition interventions ($n = 22$) rather than describing nutrition status ($n = 8$). Of the nutrition research papers identified, less than a third ($n = 10$) had a primary focus on QoL (i.e., where QoL was included in the study title). Thus, it appears that QoL instruments are still not yet being used routinely in nutrition studies to monitor outcomes among older adults in community settings. QoL is a complex concept that is interpreted and defined differently within and between various health disciplines (33). It may be that because of the number of instruments available to assess QoL, there was confusion on the part of nutrition researchers as to what instruments

were most appropriate for nutrition research and thus QoL outcomes were not readily assessed.

The nutrition measures in the reviewed studies were heterogeneous. Specifically, a set of consistent core nutrition measurements was absent, making the comparison of nutrition results between studies difficult. There could be several reasons for this. One is that our review of research over the last 20 years indicated that nutrition indices have evolved over that time. For example, serum albumin is no longer among the criteria used to identify malnutrition (34). Additionally, even today consensus is still lacking among nutrition researchers on a valid and reliable set of core measures for assessing nutrition and nutrition status in all its dimensions, particularly for older adults living in the community (35). In a clinical setting, the nutrition indices generally considered are those related to the five domains of nutrition assessment: (1) food or nutrition-related history, (2) biochemical data, medical tests, and procedures, (3) anthropometric measurements, (4) nutrition-focused clinical and physical findings, and (5) client history (36). Some of these more complete assessment measures may not have been included in the studies we reviewed because the studies' goals were to describe only a specific aspect of nutrition, or the measures were unfeasible/less readily available in community-living populations than might be the case in clinical settings. It is also possible that in countries without a national health program (such as the US), researchers may have been disinclined to characterize all the complexities of nutrition status when they lacked the ability/means to fully ameliorate identified problems.

Lack of clarity on what constitutes appropriate nutrition status measures may have contributed to the very limited number of QoL studies ($n = 2$) we identified that included nutrition measures. It may also be the reason why only one study had a primary focus on nutrition, as was indicated in the study title. Interestingly, a recent systematic review of QoL research in medicine and health sciences did not identify any studies on nutrition and QoL, although that research review was limited to one random week's "snapshot" because researchers were concerned about the high number of QoL articles published annually (33) and thus their timeframe differed markedly from our review of 22 years of published research.

It is disheartening that given the continued, growing emphasis on patient-centered care (37) and healthy aging (4) there is still such a gap in nutrition and QoL research and the number of studies is so limited. Many older adults have one or more chronic diseases (6) and research on chronic disease, such as primary prevention studies like PREDIMED (38), points to the importance of including nutrition in multidimensional approaches to impact health outcomes (39). However, traditional indicators such as reduced morbidity may be less meaningful for older adults themselves than subjectively assessed symptomatic improvements that may relate to their QoL (15). Indeed, defining QoL may allow healthcare providers to shift from minimizing individuals' disabilities toward maximizing their abilities (40). Several age-associated nutrition changes can also impact QoL, from decreased intake to alteration in nutrient needs, and these changes could benefit from targeted nutrition interventions if the nexus between those changes and QoL could be better elucidated (15). Further, a number of older adults face food insecurity and that can impact QoL as well (41). Such social risks for poor quality of life must be identified before the risks can be addressed by the provision of appropriate health and social services. Those conducting community-based research may not be prepared or able to do so, and this could be another reason for the limited research on nutrition and QoL. However, it is incumbent upon health professionals to investigate the scope of such problems if societal action is necessary.

An additional gap at the nexus of nutrition and QoL is the potential lack of a domain specifically involving food, diet, and eating in QoL instruments. Investigation of whether the 29 common, validated QoL instruments explicitly included food, diet, or eating-related questions was beyond the range of our scoping review. However, these are important factors in the enjoyment of life and for sustenance (42). Older adults with higher diet quality have been found to have higher QoL (43). We did identify one study in our review that also included the Satisfaction with Food-Related Life scale (44). That scale has seven questions related to the positives, negatives, pleasure, and satisfaction of food and meals and has been validated among older adults (42). Other QoL scales specific to nutrition also exist, including the Nutrition Quality of Life Survey (45), Quality of Life Factors Questionnaire (46), and an instrument for measuring QoL related to nutrition in the general population (47); but in the studies we identified none of these instruments were used.

4.2. Opportunities and implications for research and policy

There are many challenges involved in promoting independence and healthy aging in an increasingly older population. Chief among them are: determining how important factors like nutrition impact QoL, identifying actionable interventions through research, and then implementing policies that follow up on the findings. The 2022 White House Conference on Hunger, Nutrition, and Health underscored the need for intervention, research, and education on nutrition and healthy aging (9). Yet, as was evident in the limited body of research that we found, risk factors for poor QoL related to nutrition for older adults living in the community is still a gap area. This could be exacerbated because there may be differing requirements and tools for nutrition screening across various countries and populations even as there is consensus on the diagnostic criteria for malnutrition, such as the Global Leadership Initiative on Nutrition (GLIM) criteria (48). Further, even when nutrition and QoL were considered in one setting, research rarely tracked if or how nutrition status or QoL changed as older adults traversed the health and social services care chain. Only one study in our review specifically investigated care transitions and patients' hospital-to-home journeys. For those older adults who are screened and identified as positive for poor nutrition and/or decreased QoL and who have remediable problems, there is an unmet need for additional assessment, effective interventions, and continuing surveillance. Guidance documents such as those from the World Health Organization (49) and the National Academies of Sciences, Engineering, and Medicine (50) provide strategies for doing so.

Additional opportunities for future research include the need for greater collaboration between nutrition and QoL experts to ensure that appropriate instruments and indices in both areas of research are included in study design and implementation. Maintenance of QoL is one of the most important outcomes of care services for older adults (51) and yet there is a lack of nutrition and QoL studies, particularly in North America. Nutrition researchers in this region should include validated QoL measurements more frequently in their studies of

community-living older adults. The use of a consistent QoL instrument such as the SF-36 or SF-12 in North America would permit greater comparability of the results between research investigations. Overall, greater consensus among nutrition researchers on standardized, validated nutrition status core measures for community-dwelling populations (specifically on questionnaires and anthropometric measurements) could make it easier for QoL researchers to include appropriate nutrition measures and thus lead to a more complete picture of nutrition's impact on QoL in older adults.

4.3. Strengths and limitations

This review had several strengths. It updates the work of Amarantos et al. (15) and adds a nutrition perspective to the seminal work of Siette et al. (16). Also, it is one of the few studies that has considered the nexus between nutrition and QoL and identified several gaps that are important to address in considering the role of nutrition in healthy aging research and policy. Its limitations include that it focused only on community-living older adult populations in developed economies and specifically searched for research including at least one of 29 common, validated general QoL instruments used in their entirety. There is a need to consider the body of literature for additional care settings--assisted living facilities, nursing homes, and acute care hospitals--and for other countries beyond developed economies. Studies of nutrition using condition-specific QoL measurements developed for older adults with a particular disease or condition were not included in our review, and these deserve attention as well. In addition, future research could review other validated QoL instruments such as those that are nutrition-specific.

5. Conclusion

Autonomy and living at home are valued by older adults. Healthy aging and a high QoL are critical to achieving these goals. Nutrition is a fundamental and potentially modifiable factor whose influence is often ignored as a contributor to healthy aging and QoL outcomes and to date the research area on nutrition and QoL remains underdeveloped and neglected. There are valid QoL instruments and nutrition measures that could be incorporated into research among older adult populations, although the lack of consensus on specific indices, particularly for nutrition, is a barrier. It is imperative that agreement be reached on the appropriate instruments and measures to use to identify the most successful screening, assessment, and intervention strategies that ensure healthy aging and QoL of older adults.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MA, JG, KK, and JD: conceptualization. JM: research literature search. MA, JG, RC, KK, and JD: writing and reviewing. All authors have read and agreed to the submitted version of the manuscript.

Conflict of interest

MA and KK were employees and stockholders of Abbott, RC was an intern for Abbott, JD holds stock in several food and drug companies.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1225689/full#supplementary-material

References

1. United Nations, Department of Economic and Social Affairs Social Inclusion. *UNDESA World Social Report 2023*. Available at: https://www.un.org/development/desa/dspd/world-social-report/2023-2.html#:~:text=Population%20ageing%20is%20a%20defining-in%20all%20countries%20and%20areas (Accessed May 8, 2023).

2. World Health Organization. *Ageing and health*. (2022). Available at: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (Accessed May 8, 2023).

3. United Nations, Development Programme, HelpAge International, AARP. *Ageing, Older Persons and the 2030 Agenda for Sustainable Development*. Available at: https://www.un.org/development/desa/ageing/wp-content/uploads/sites/24/2017/07/UNDP_AARP_HelpAge_International_AgeingOlderpersons-and-2030-Agenda-2.pdf (Accessed May 8, 2023).

4. United Nations. World Population Ageing. (2017). Highlights. Available at: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf (Accessed May 8, 2023).

5. The Administration on Community Living, US Department of Health and Human Services. 2020 Profile of Older Americans. (2021). Available at: https://acl.gov/sites/default/files/aging%20and%20Disability%20In%20America/2020Profileolderamericans.final_.pdf (Accessed May 8, 2023).

6. Boersma P, Black LI, Ward BW. Prevalence of multiple chronic conditions among US adults, 2018. *Prev Chronic Dis*. (2020) 17:200130:E106. doi: 10.5888/pcd17.200130

7. Fong JH. Disability incidence and functional decline among Older Adults with major chronic diseases. *BMC Geriatr*. (2019) 19:323. doi: 10.1186/s12877-019-1348-z

8. US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. *Healthy people 2030, Older Adults Overview and Objectives*. Available at: https://health.gov/healthypeople/objectives-and-data/browse-objectives/older-adults. (Accessed May 8, 2023).

9. The White House. *Biden-Harris Administration National Strategy on Hunger, Nutrition, and Health*. (2022). Available at: https://www.whitehouse.gov/wp-content/uploads/2022/09/White-House-National-Strategy-on-Hunger-Nutrition-and-Health-FINAL.pdf (Accessed May 8, 2023).

10. Kringelbach ML. The pleasure of food: underlying brain mechanisms of eating and other pleasures. *Flavour*. (2015) 4:20. doi: 10.1186/s13411-014-0029-2

11. Roberts SB, Silver RE, Das SK, Fielding RA, Gilhooly CH, Jacques PF, et al. Healthy aging—nutrition matters: start early and screen often. *Adv Nutr*. (2021) 12:1438–48. doi: 10.1093/advances/nmab032

12. Dwyer JT, Gahche JJ, Weiler M, Arensberg MB. Screening community-living older adults for protein energy malnutrition and frailty: update and next steps. *J Community Health*. (2020) 45:640–60. doi: 10.1007/s10900-019-00739-1

13. Itani L, Sammarco R, Ghoch ME. Editorial: nutrition and health-related quality of life: is it an ignored outcome? *Front Nutr*. (2021) 8:778816. doi: 10.3389/fnut.2021.778816

14. United States Public Health Service Office of the Surgeon General. *Healthy People: the Surgeon General's Report on Health Promotion and Disease Prevention. 1979*. Available at: https://profiles.nlm.nih.gov/spotlight/nn/catalog/nlm:nlmuid-101584932X92-doc. (Accessed May 8, 2023).

15. Amarantos E, Martinez A, Dwyer J. Nutrition and quality of life in older adults. *J Gerontol A Biol Sci*. (2001) 56:54–64. doi: 10.1093/gerona/56.suppl_2.54

16. Siette J, Knaggs GT, Zurynski Y, Ratcliffe J, Dodds L, Westbrook J. Systematic review of 29 self-report instruments for assessing quality of life in older adults receiving aged care services. *BMJ Open*. (2021) 11:e050892. doi: 10.1136/bmjopen-2021-050892

17. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping review. *Int J Evid Based Healthc*. (2015) 13:141–6.

18. United Nations. *World Economic Situation and Prospects*. (2020). Available at: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2020_Annex.pdf (Accessed May 8, 2023).

19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. (2009) 151:264–269. doi: 10.7326/0003-4819-151-4-200908180-00135

20. Greiner W, Weijen T, Nieuwenhuizen M, Oppe S, Badia X, Busschbach J, et al. A single European currency for EQ-5D health states. Results from a six-country study. *Eur J Health Econ*. (2003) 4:222–31. doi: 10.1007/s10198-003-0182-5

21. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. (1992) 30:473–83. doi: 10.1097/00005650-199206000-00002

22. McHorney CA, Ware JE, Raczek AE. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. (1993) 31:247–63. doi: 10.1097/00005650-199303000-00006

23. Ware JE. *New England Medical Center Hospital. SF-36 Physical and Mental Health Summary Scales: a user's manual*. Boston, MA: Health Institute, New England Medical Center (1994).

24. Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. (1996) 34:220–33. doi: 10.1097/00005650-199603000-00003

25. Thompson WW, Zack MM, Krahn GL, Andresen EM, Barile JP. Health-related quality of life among older adults with and without functional limitations. *Am J Public Health*. (2012) 102:496–502. doi: 10.2105%2FAJPH.2011.300500

26. Guigoz Y, Vellas B. Nutritional assessment in older adults: MNA® 25 years of a screening tool & a reference standard for care and research; what next? *J Nutr Health Aging*. (2021) 25:528–83. doi: 10.1007/s12603-021-1601-y

27. Guigoz Y, Vellas B, Garry PJ. Mini Nutritional Assessment: a practical assessment tool for grading the nutritional state of elderly patients In: B Vellas, editor. *The Mini Nutritional Assessment (MNA), Vol. 15*. Paris: Serdi Publisher (1994). 116–22.

28. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederhom T, et al. Validation of the Mini Nutritional, Assessment, Short-form (MNA®-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging*. (2009) 13:782–8. doi: 10.1007/s12603-009-0214-7

29. Huhmann MB, Berez V, Alexander DD, Thomas DR. A self-completed nutrition screening tool for community-dwelling older adults with high reliability: a comparison study. *J Nutr Health Aging*. (2013) 17:339–44. doi: 10.1007/s12603-013-0015-x

30. Power L, Mullally D, Gibney ER, Clarke M, Visser M, Colkert D, et al. A review of the validity of malnutrition screening tools used in older adults in community and healthcare settings – a MaNuEL study. *Clin Nutr*. (2018) 24:1–13. doi: 10.1016/j.clnesp.2018.02.005

31. Calvert M, Kyte D, Mercieca-Bebber R Slade A, Chan AW, King MT. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols, the SPIRIT-PRO extension. *JAMA*. (2018) 319:483–94. doi: 10.1001/jama.2017.21903

32. Bull C, Teede H, Watson D, Callander EJ. Selecting and implementing patient-reported outcome and experience measures to assess health system performance. *JAMA Health Forum*. (2022) 3:e220326. doi: 10.1001/jamahealthforum.2022.0326

33. Haraldstad K, Wahl A, Andenaes R, Andersen JR, Andersen MH, Beisland E, et al. A systematic review of quality of life research in medicine and health sciences. *Qual Life Res*. (2019) 28:2641–50. doi: 10.1007/s11136-019-02214-9

34. Marcason W. Should albumin and prealbumin be used as indicators for malnutrition. *J Acad Nutr Diet*. (2017) 117:1144. doi: 10.1016/j.jand.2017.04.018

35. Roberts HC, Lim SER, Cox NJ, Ibrahim K. The challenge of managing undernutrition in older people with frailty. *Nutrients*. (2019) 11:808. doi: 10.3390%2Fnu11040808

36. Field LB, Hand RK. Differentiating malnutrition screening and assessment: a nutrition care process perspective. *J Acad Nutr Diet*. (2015) 115:824–8.

37. Fulmer T, Reuben DB, Auerbach J, Fick DM, Galambos C, Johnson KS. Actualizing better health and health care for older adults. *Health Aff*. (2021) 40:219–25. doi: 10.1377/hlthaff.2020.01470

38. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. (2013) 368:1279–90. doi: 10.1056/NEJMoa1200303

39. Ojo O. Nutrition and chronic conditions. *Nutrients*. (2019) 11:459. doi: 10.3390/nu11020459

40. Heide SK. Autonomy, identity and health: defining quality of life in older age. *J Med Ethics*. (2022) 48:medethics-2020-107185–356. doi: 10.1136/medethics-2020-107185

41. Russell JC, Flood VM, Yeatman H, Wang JJ, Mitchell P. Food insecurity and poor diet quality are associated with reduced quality of life in older adults. *Nutr Diet*. (2016) 73:50–8. doi: 10.1111/1747-0080.12263

42. Grunert KG, Dean M, Raats MM, Nielsen NA, Lumbers M. Food in Later Life Team. A measure of satisfaction with food-related life. *Appetite*. (2007) 49:486–93. doi: 10.1016/j.appet.2007.03.010

43. Govindaraju T, Sahle BW, McCaffrey TA, McNeil JJ, Owen A. Dietary patterns and quality of life in older adults: a systematic review. *Nutrients*. (2018) 10:971. doi: 10.3390/nu10080971

44. Husted MM, Beck AM, Ulrikkeholm LK. Involving community-dwelling older adults in activities related to meals as part of a rehabilitation program: a single-blinded cluster-controlled study. *Clin Rehabil*. (2019) 33:1185–96. doi: 10.1177/0269215519837742

45. Barr J, Schumacher G. Using focus groups to determine what constitutes quality of life in clients receiving medical nutrition therapy: first steps in the development of a nutrition quality-of-life survey. *J Am Diet Assoc*. (2003) 103:844–51. doi: 10.1016/s0002-8223(03)00385-7

46. Corle DK, Sharbaugh C, Mateski DJ, Coyne T, Paskett ED, Cahill J, et al. Self-rated quality of life measures: effect of change to a low-fat, high-fiber, fruit and vegetable enriched diet. *Ann Behav Med*. (2001) 23:198–207. doi: 10.1207/S15324796ABM2303_7

47. Schunemann HJ, Sperati F, Barba M, Santesso N, Melegari C, Aki EA, et al. An instrument to assess quality of life in relation to nutrition: item generation, item reduction and initial validation. *Health Qual Life Outcomes*. (2010) 8:26. doi: 10.1186%2F1477-7525-8-26

48. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. *Clin Nutr*. (2018) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

49. World Health Organization. *Evidence Profile: Malnutrition - Integrated Care for Older People, Guidelines on Community-Level Interventions to Manage Declines in Intrinsic Capacity*. (2017). Available at: https://www.who.int/publications/i/item/WHO-MCA-17.06.06 (Accessed May 8, 2023).

50. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Food Forum. Nutrition Across the Lifespan for Healthy Aging: Proceedings of a Workshop. Washington, DC: National Academies Press (2017).

51. van Leeuwen KM, van Loon MS, van Nes FA, Bosmans JE, de Vet HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. *PLoS One*. (2019) 14:e0213263. doi: 10.1371/journal.pone.0213263

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 23 October 2023
DOI 10.3389/fendo.2023.1210371

OPEN ACCESS

EDITED BY
Roberta Zupo,
University of Bari Aldo Moro, Italy

REVIEWED BY
Andrea Milzi,
University Hospital RWTH Aachen, Germany
Alexander E. Berezin,
Zaporizhia State Medical University, Ukraine

*CORRESPONDENCE
Tae-Jin Song
knstar@ewha.ac.kr

RECEIVED 22 April 2023
ACCEPTED 03 October 2023
PUBLISHED 23 October 2023

CITATION
Woo HG, Kim D-H, Lee H, Kang MK and Song T-J (2023) Association between changes in predicted body composition and occurrence of heart failure: a nationwide population study.
Front. Endocrinol. 14:1210371.
doi: 10.3389/fendo.2023.1210371

Association between changes in predicted body composition and occurrence of heart failure: a nationwide population study

Ho Geol Woo[1], Dong-Hyeok Kim[2], Hyungwoo Lee[3], Min Kyoung Kang[3] and Tae-Jin Song[3]*

[1]Department of Neurology, Kyung Hee University College of Medicine, Seoul, Republic of Korea, [2]Department of Cardiology, Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea, [3]Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

Background: Large population-based studies on the association between changes in body composition and the occurrence of heart failure (HF) are rare. We aimed to determine the association between changes in body composition, including the predicted body fat mass index (pBFMI), predicted appendicular skeletal muscle mass index (pASMI), and predicted lean body mass index (pLBMI), and the occurrence of HF.

Methods: For present study, 2,036,940 people who consecutively underwent national health examinations from 2010~2011 (baseline period) to 2012~2013 (follow-up period) were included. The pBFMI, pASMI, and pLBMI were indirectly investigated using validated anthropometric prediction equations from the Korean National Health and Nutrition Examination Survey cohort. The outcome was defined as at least two or more claims of HF.

Results: During a median of 7.59 years of follow-up, 22,172 participants (event rate, 1.09%) with HF were observed. Decreased changes in the pASMI and pLBMI were associated with the occurrence of HF among males (hazard ratio [HR] 0.966, 95% confidence interval (CI) [0.944-0.988]; HR 0.939, 95%CI [0.923-0.955], respectively) and females (HR 0.924, 95%CI [0.900-0.947]; HR 0.951, 95% CI [0.939-0.963], respectively). An increased change in the pBFMI was associated with the occurrence of HF in males (HR 1.017, 95%CI [1.001-1.034]). However, paradoxically, a change in the pBFMI was associated with the occurrence of HF in females (HR 0.925, 95%CI [0.909-0.942]).

Conclusion: Decreased skeletal muscle mass was related to the occurrence of HF. However, the relationship between a change in fat mass and the occurrence of HF was different and even paradoxical depending on sex.

KEYWORDS

body composition, body mass index, obesity, skeletal mass, fat mass, heart failure

1 Introduction

Heart failure (HF) is a clinical syndrome that is related to decreased cardiac contractility accompanied by impairment of the ejection of blood or ventricular filling (1). HF is a common cardiovascular disease and a leading cause of hospitalization, especially in older adults. The economic burden and prevalence of HF have been increasing worldwide (2). Despite the development of treatment and prevention tools for HF, the morbidity and mortality rates associated with HF are still high (2). Therefore, it is important to identify the hidden risk factors associated with HF. To date, risk factors for HF, including hypertension, diabetes mellitus, coronary artery occlusive disease, aortic atheroma, poor oral hygiene, smoking, and cardiomyopathy, have been suggested. However, information regarding further modifiable associations or occurrence for HF is still lacking (3, 4).

Obesity is defined as an abnormal accumulation of health-impairing fat mass, commonly assessed as a determination of a body mass index (BMI) ≥30 kg/m^2 (5). The prevalence of obesity has increased over the past few decades throughout the world, and the global burden of obesity is currently increasing rapidly (6). It is well known that obesity, especially greater levels of adiposity, is a well-established risk factor for cardiovascular disease and is associated with cardiovascular risk factors, including hypertension, insulin resistance, lipoprotein metabolism, and inflammation (7, 8). In a previous study, obesity and abdominal fat were found to be associated with an increased incidence of HF (9). However, when obesity was evaluated using BMI in patients with HF, the obesity paradox that obese patients have better long-term and short-term prognosis was observed (10). Furthermore, because BMI includes not only fat mass but also skeletal mass and lean body mass, cannot distinguish between lean body mass and fat mass, and provides no information on body fat distribution, it is necessary to check the correlation with HF using body composition rather than BMI (11).

Nevertheless, there have been few longitudinal studies targeting a general population of large sample sizes on the association of changes in body composition with the occurrence of HF. Therefore, we aimed to investigate the association between changes in body composition, including the predicted appendicular skeletal muscle mass index (pASMI), predicted body fat mass index (pBFMI), and predicted lean BMI (pLBMI), and the occurrence of HF in a longitudinal setting.

2 Materials and methods

2.1 Participants

This study was performed using the National Health Insurance Service-Health Screening (NHIS-HEALS) dataset supplied by the Korean government. In South Korea, adults older than 40 years of age are advised to undergo free health examinations in alternate years. The Korean government combined the health screening dataset with age, sex, household income, and clinical information, including diagnostic codes, prescriptions, information on treatment or procedure, hospitalization, and mortality date (12, 13). For our study, 2,139,856 people who consecutively underwent national health examinations from 2010~2011 (baseline period) to 2012~2013 (follow-up period) were included (dataset number NHIS-2021-1-715) through an identification and validation process (14–16). Among 2,139,856 participants, those (n=85,947) with at least one missing data were excluded. Those with a previous history of HF (n=16,969) were excluded. Finally, 2,036,940 participants were included in the present study (Figure 1). The present study was approved by the Institutional Review Board of Ewha Womans University Seoul Hospital (Institutional Review Board approval number: SEUMC 2022-02-018).

2.2 Change in predicted body composition and covariates

The pBFMI, pASMI, and pLBMI were indirectly evaluated by validated anthropometric prediction equations from the Korean National Health and Nutrition Examination Survey cohort (11). A previous study suggested that body fat mass, appendicular skeletal muscle mass, and lean body mass were identified using dual-energy X-ray absorptiometry, and then a prediction equation was composed using different combinations of age, anthropometric measurements (weight, height, waist circumference), serum creatinine levels, physical activity, smoking status, and alcohol intake (11). These predictive equations were validated as having high predictive power, a moderate agreement rate, and low bias in the Korean general population (11). In the present study, these prediction equations were applied to evaluate the participants' body composition. Body fat mass, appendicular skeletal muscle mass, and lean body mass were presented as indices (weight [kg] divided by height squared [m^2]); thus, pBFMI, pASMI, and pLBMI, respectively (Supplementary Methods 1). The change in the pBFMI, termed ΔpBFMI, was calculated from the difference between the baseline and follow-up periods pBFMI, and the

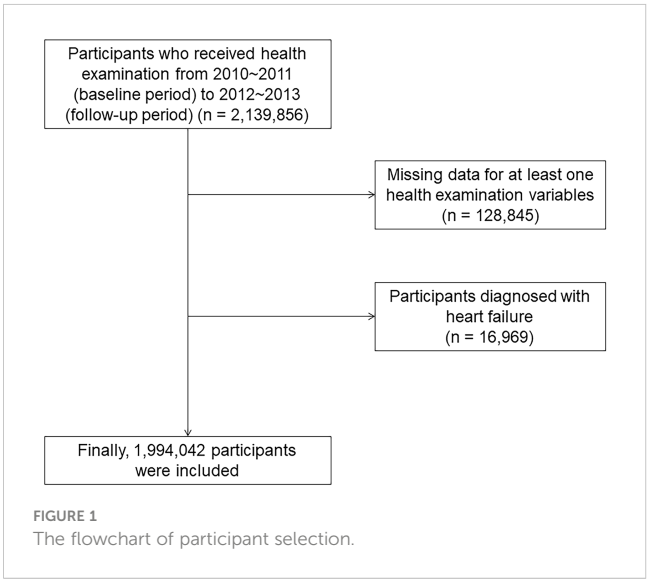


FIGURE 1
The flowchart of participant selection.

changes in the pASMI and pLBMI (ΔpASMI and ΔpLBMI) were also calculated similarly.

The detailed definitions of covariates were demonstrated in Supplementary Methods 2 and previous studies (17–19). Variables including age, sex, BMI, household income (first, second, third, or fourth quartile), smoking status (never, former, or current), alcohol intake (0, 1-2, 3-4, or ≥5 times per week), physical activity (0, 1-2, 3-4, or ≥5 times per week), comorbid disease (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, cancer, and renal disease), systolic blood pressure, fasting serum glucose, total cholesterol, estimated glomerular filtration rate, and Charlson Comorbidity Index (CCI) which is a commonly used method for evaluating comorbidities were collected (3, 18, 20). Comorbidities were defined considering the International Classification of Diseases, Tenth Revision (ICD-10) codes, history of prescriptions, and laboratory findings from the health examinations (3, 18).

2.3 Outcomes

The index date was defined as the date of the national health examination. The most recent health examination data were used for statistical analysis if more than one examination was performed during the period. Outcomes were defined as two or more claims for HF (21). Previously, the diagnostic accuracy of the ICD-10 code (I50) for HF using the NHIS dataset has been validated (3, 21). Monitoring was conducted until December 31, 2020, or the first occurrence of death or HF.

2.4 Statistical analysis

Chi-square and paired t-tests were used to compare categorical and continuous variables according to sex. The Cox proportional hazards model presented with a hazard ratio (HR) with a 95% confidence interval (CI) was used to evaluate the effect of changes in body composition (1 kg/m^2 increments in the ΔpBFMI, ΔpASMI, and ΔpLBMI) between the baseline and follow-up periods on the occurrence of HF after adjusting for all potential confounding factors. In addition, we performed an additional multivariable analysis after adjusting for all potential confounding factors, except for variables used in the prediction equations to calculate the predicted body composition, including age, smoking status, alcohol intake, and physical activity. Furthermore, we provided restricted cubic splines of change in the predicted body composition to visually estimate the association between the change in the predicted body composition (ΔpBFMI, ΔpASMI, and ΔpLBMI) and the occurrence of HF. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of the change in the predicted body composition. Stratified analyses of the effects of changes in body composition on the occurrence of HF were conducted according to the subgroups of age, household income, alcohol intake, smoking status, physical activity, systolic blood pressure, fasting serum glucose, total cholesterol, CCI, and BMI at baseline and the follow-up categories: normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥ 30 kg/m^2). To evaluate the combined effects of changes in the BMI, pASMI, pBFMI, and pLBMI, stratified analysis was additionally performed to evaluate the effect of changes in BMI during the two health examinations on the occurrence of HF according to changes in body composition. Statistical analyses were performed using R software, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Inc., Cary, NC, USA). Two-sided *P*-values less than 0.05 were considered significant.

3 Results

Table 1 shows the results of comparing the baseline characteristics of the 2,036,940 participants according to sex (n=1,070,377 for males, n=966,563 for females). During a median of 7.59 years of follow-up, 22,172 participants (event rate, 1.09%) with HF were observed. The mean age of males was 49.60 ± 13.45 years, and of females was 52.32 ± 13.65 years. Significant differences in the BMI at baseline and follow-up, household income, smoking status, alcohol intake, physical activity, systolic blood pressure,

TABLE 1 Baseline characteristics of the study participants.

Variable	Total	Male	Female	*P*-value
Number of participants	2,036,940	1,070,377	966,563	<0.001
Age, years	50.89 ± 13.61	49.60 ± 13.45	52.32 ± 13.65	<0.001
Baseline period (2010–2011)				
BMI, kg/m^2	23.79 ± 3.20	24.26 ± 3.03	23.28 ± 3.31	<0.001
pASMI, kg/m^2	19.64 ± 5.00	23.67 ± 3.19	15.17 ± 1.85	<0.001
pBFMI, kg/m^2	17.56 ± 4.69	16.11 ± 4.27	19.16 ± 4.61	<0.001
pLBMI, kg/m^2	45.74 ± 9.74	53.41 ± 6.52	37.25 ± 3.96	<0.001
Follow-up period (2012–2013)				
BMI, kg/m^2	23.86 ± 3.23	24.34 ± 3.07	23.33 ± 3.32	<0.001

(Continued)

10.3389/fendo.2023.1210371

TABLE 1 Continued

Variable	Total	Male	Female	*P*-value
pASMI, kg/m^2	19.62 ± 5.04	23.68 ± 3.26	15.13 ± 1.86	<0.001
pBFMI, kg/m^2	17.62 ± 4.74	16.17 ± 4.34	19.22 ± 4.66	<0.001
pLBMI, kg/m^2	45.79 ± 9.86	53.53 ± 6.66	37.23 ± 4.04	<0.001
Household income				<0.001
First quintile, lowest	334,222 (16.41)	126,137 (11.78)	208,085 (21.53)	
Second quintile	390,984 (19.19)	180,343 (16.85)	210,641 (21.79)	
Third quintile	571,465 (28.06)	324,611 (30.33)	246,854 (25.54)	
Fourth quintile, highest	740,269 (36.34)	439,286 (41.04)	300,983 (31.14)	
Smoking status				<0.001
Never	1,256,017 (61.66)	329,914 (30.82)	926,103 (95.81)	
Former	336,000 (16.5)	321,040 (29.99)	14,960 (1.55)	
Current	444,923 (21.84)	419,423 (39.18)	25,500 (2.64)	
Alcohol intake, days/week				<0.001
<1	1,090,488 (53.54)	353,245 (33.00)	737,243 (76.27)	
1-2	674,668 (33.12)	480,738 (44.91)	193,930 (20.06)	
3-4	195,408 (9.59)	167,853 (15.68)	27,555 (2.85)	
≥5	76,376 (3.75)	68,541 (6.40)	7,835 (0.81)	
Physical activity, days/week				<0.001
<1	1,171,086 (57.49)	530,152 (49.53)	640,934 (66.31)	
1-2	514,062 (25.24)	332,208 (31.04)	181,854 (18.81)	
3-4	222,472 (10.92)	132,221 (12.35)	90,251 (9.34)	
≥5	129,320 (6.35)	75,796 (7.08)	53,524 (5.54)	
Systolic blood pressure, mmHg	122.29 ± 12.86	124.53 ± 11.78	119.81 ± 13.53	<0.001
Fasting serum glucose, mg/dL	98.21 ± 20.59	100.38 ± 22.29	95.8 ± 18.22	<0.001
Total cholesterol, mg/dL	195.75 ± 33.63	194.59 ± 33.45	197.04 ± 33.78	<0.001
Estimated glomerular filtration rate, mL/min/1.73m^2				<0.001
<30	2,939 (0.14)	1,590 (0.15)	1,349 (0.14)	
30-60	115,170 (5.65)	54,748 (5.11)	60,422 (6.25)	
60-90	1,277,756 (62.73)	686,691 (64.15)	591,065 (61.15)	
≥90	641,075 (31.47)	327,348 (30.58)	313,727 (32.46)	
Charlson Comorbidity Index				<0.001
0	1,369,775 (67.25)	754,962 (70.53)	614,813 (63.61)	
1	446,919 (21.94)	214,619 (20.05)	232,300 (24.03)	
≥2	220,246 (10.81)	100,796 (9.42)	119,450 (12.36)	

P-values by Student's t-test and chi-square test. Data are expressed as the mean ± SD deviation or n (%).
BMI, body mass index; pASMI, predicted appendicular skeletal muscle mass index; pBFMI, predicted body fat mass index; pLBMI, predicted lean body mass index.

fasting serum glucose, total cholesterol, estimated glomerular filtration rate, and CCI were observed between males and females (Table 1). In the baseline period, the pASMI (23.67 ± 3.19 kg/m^2 for males vs. 15.17 ± 1.85 kg/m^2 for females), pBFMI (16.11 ± 4.27 kg/m^2 for males vs. 19.16 ± 4.61 kg/m^2 for females), and pLBMI (53.41 ± 6.52 kg/m^2 for males vs. 37.25 ± 3.96 kg/m^2 for females) were significantly different according to sex (P<0.001). In the follow-up period, the pASMI (23.68 ± 3.26 kg/m^2 for males vs. 15.13 ± 1.86 kg/m^2 for females), pBFMI (16.17 ± 4.34 kg/m^2 for males vs. 19.22 ± 4.66 kg/m^2 for females), and pLBMI (53.53 ± 6.66 kg/m^2 for males

vs. 37.23 ± 4.04 kg/m^2 for females) were also significantly different according to sex (P<0.001, Table 1).

Multivariate analysis showed a relationship between the occurrence of HF and changes in body composition (Table 2; Supplementary Table 1). In males, with a 1 kg/m^2 increase in the ΔpBFMI, the HR for the occurrence of HF was 1.017 (95%CI: 1.001-1.034), and the HRs for a 1 kg/m^2 increase in the ΔpASMI and ΔpLBMI were 0.924 (95%CI: 0.900-0.947) and 0.951 (95%CI: 0.939-0.963), respectively. In females, with a 1 kg/m^2 increase in the ΔpBFMI, the HR for the occurrence of HF was 0.925 (95%CI: 0.909-0.942), for a 1 kg/m^2 increase in the ΔpASMI and ΔpLBMI were 0.966 (95%CI: 0.944-0.988), and 0.939 (95%CI: 0.923-0.955), respectively. In contrast, decreases in the ΔpASMI and ΔpLBMI were associated with an increased incidence of HF in both sexes. Furthermore, a decrease in the ΔpBFMI was associated with a decreased HF incidence in males, whereas a decrease in the ΔpBFMI was associated with an increased HF incidence in females (Table 2; Supplementary Table 1 and Figure 2). For the stratified analysis, these trends and results were similar regardless of the BMI status at baseline. The occurrence-reducing effects of increased ΔpLBMI and ΔpASMI on the occurrence of HF were more prominent when the participants were less obese. Furthermore, the occurrence-reducing effect of an increased ΔpBFMI on the occurrence of HF was more prominent when female participants were less obese. In contrast to females, the occurrence-increasing effect of increased ΔpBFMI on the occurrence of HF was more prominent when male participants were less obese (Table 3; Supplementary Table 2).

Table 4 shows the effect of BMI changes during the two health examinations on the occurrence of HF according to changes in body composition. Participants who maintained a stable weight (change in BMI ± 1 kg/m^2) had a reduced incidence of HF occurrence per 1 kg/m^2 increase in ΔpLBMI and ΔpASMI for males (HR:0.928, 95% CI 0.911-0.946; HR:0.894, 95%CI 0.863-0.927, respectively) and females (HR:0.923, 95%CI 0.904-0.943; HR:0.963, 95%CI 0.935-0.993, respectively). Male participants had an increased incidence of HF per 1 kg/m^2 increase in ΔpBFMI (HR: 1.028; 95%CI: 1.005-1.050). However, female participants had a decreased incidence of HF per 1 kg/m^2 increase in ΔpBFMI (HR: 0.918; 95%CI: 0.899-0.937; Table 4).

The occurrence-reducing effects of the increase in ΔpASMI and ΔpLBMI were observed in male participants whose BMI increased from normal to obese or overweight and from overweight to obese. The occurrence-reducing effect of the increase in the ΔpASMI and ΔpLBMI was also observed in female participants whose BMI increased from normal to overweight and obese. The decrease in the ΔpBFMI showed an occurrence-reducing effect in male

TABLE 2 Hazard ratios and 95%CI of heart failure per 1 kg/m^2 increase in the change in the predicted body composition index.

Variable	Male	*P*-value	Female	*P*-value
	HR (95%CI)		HR (95%CI)	
BMI at the baseline period, kg/m^2	0.982 (0.961, 1.003)	0.096	1.043 (1.028, 1.059)	<0.001
BMI at the follow-up period, kg/m^2	1.031 (1.009, 1.053)	0.006	1.015 (1.000, 1.031)	0.047
Household income				
First quintile, lowest	1(reference)		1(reference)	
Second quintile	0.723 (0.676, 0.772)	<0.001	0.876 (0.825, 0.929)	<0.001
Third quintile	0.677 (0.638, 0.719)	<0.001	0.978 (0.926, 1.033)	0.432
Fourth quintile, highest	0.773 (0.732, 0.817)	<0.001	1.190 (1.132, 1.250)	<0.001
Systolic blood pressure, mmHg	1.025 (1.023, 1.026)	<0.001	1.031 (1.029, 1.032)	<0.001
Fasting serum glucose, mg/dL	1.001 (1.000, 1.002)	0.021	1.002 (1.001, 1.003)	<0.001
Total cholesterol, mg/dL	0.994 (0.993, 0.994)	<0.001	0.997 (0.997, 0.998)	<0.001
Charlson Comorbidity Index				
0	1(reference)		1(reference)	
1	1.991 (1.902, 2.085)	<0.001	1.861 (1.782, 1.944)	<0.001
≥2	3.549 (3.376, 3.731)	<0.001	2.661 (2.538, 2.791)	<0.001
Change in the predicted body composition index				
ΔpASMI, kg/m^2	0.924 (0.900, 0.947)	<0.001	0.966 (0.944, 0.988)	0.003
ΔpBFMI, kg/m^2	1.017 (1.001, 1.034)	0.039	0.925 (0.909, 0.942)	<0.001
ΔpLBMI, kg/m^2	0.951 (0.939, 0.963)	<0.001	0.939 (0.923, 0.955)	<0.001

The multivariable model was used for the BMI at the baseline and follow-up period, household income, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.

BMI, body mass index; CI, confidence interval; HR, hazard ratio; ΔpASMI, change in predicted appendicular skeletal muscle mass index; ΔpBFMI, change in the predicted body fat mass index; ΔpLBMI, change in the predicted lean body mass index.

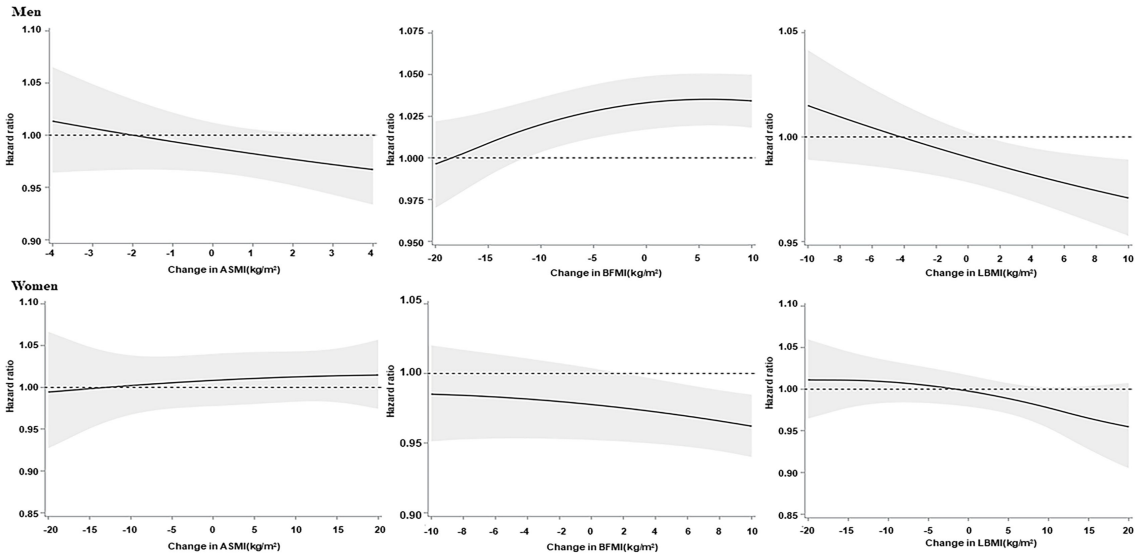


FIGURE 2
Association of the changes in the predicted body composition index with heart failure. Association of the changes in the predicted appendicular skeletal muscle mass index, body fat mass index, and lean body mass index (BMI) with heart failure. The solid lines indicate the hazard ratios, and the shaded regions show 95% confidence intervals from restricted cubic spline regression. Restricted cubic splines were constructed with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the change in the predicted appendicular skeletal muscle mass index, body fat mass index, and lean BMI. The hazard ratios (95% confidence interval) were calculated by Cox proportional hazards regression analysis after adjusting for age, BMI at baseline and follow-up, household income, smoking status, alcohol intake, physical activity, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.

participants whose BMI decreased from overweight or obese to normal and from obese to overweight. However, the increase in the ΔpBFMI showed an occurrence-reducing effect in female participants whose BMI increased from normal to obese or overweight and from overweight to obese (Table 4; Supplementary Table 3). In the subgroup analysis, there was no heterogeneity among the groups, except for age (Supplementary Table 4).

4 Discussion

In this large-scale cohort study, we found that decreased ΔpASMI and ΔpLBMI were negatively correlated with the occurrence of HF, regardless of sex. The occurrence-reducing effects of increased ΔpASMI and ΔpLBMI on the occurrence of HF were alleviated when the participants were more obese and when their BMI increased. In males, an increased ΔpBFMI showed a positive relationship with the occurrence of HF. The occurrence-increasing effect of increased ΔpBFMI on the occurrence of HF was more prominent when male participants were less obese and when the BMI of participants decreased. In contrast, decreased ΔpBFMI showed a negative relationship with the occurrence of HF in females. The occurrence-reducing effect of increased ΔpBFMI on the occurrence of HF was alleviated when the female participants were obese and when their BMI increased.

Previous studies showed that sarcopenia, which is primarily characterized by a progressive and widespread decline in skeletal muscle mass and muscle dysfunction, is common in patients with HF (about 10%) and is strongly related to the prognosis of HF (22). Also, loss of lean body mass was related to the occurrence of HF, particularly among older males (23). Various mechanisms, including malnutrition and anorexia, physical inactivity, and insulin resistance, cause an increase in muscle protein catabolism, resulting in a loss of muscle or body weight, which is associated with HF (24). Although present study could not confirm the causal relationship, in other hand, some studies suggested that muscle wasting is a consequence of HF and HF lead to several complications including musculoskeletal abnormalities and sarcopenia (25, 26). The present study showed that increased change in muscle mass had a negative relationship with the occurrence of HF, and the negative correlation was more attenuated when the participants were more obese and when the BMI of participants increased.

This study investigated sex-related differences in the association between changes in body fat mass and HF. Although the fat distribution varies according to sex, the role of obesity in the occurrence of HF in females may differ from that in males. Generally, males store sufficient fat in a visceral distribution, while females store sufficient fat in a peripheral subcutaneous distribution (27). These differences in location for stocking excessive fat have been shown to persist even after menopause. In males, visceral fat mass is associated with adiposopathy, which includes fat cell hypertrophy, increased circulating free fatty acids, and inflammatory and immune responses, leading to common metabolic diseases and HF (28, 29). The present study showed that an increased change in the body fat mass had a positive relationship with the occurrence of HF, and the occurrence-increasing effect of the increased change in body fat mass was more noticeable when the male participants were less obese and

TABLE 3 Hazard ratios and 95%CI of heart failure per 1 kg/m^2 increase in the change in the predicted body composition index stratified by the BMI group.

BMI at baseline period	Event	Person-years	ΔpASMI HR (95%CI)	*P*-value	pBFMI HR (95%CI)	*P*-value	ΔpLBMI HR (95%CI)	*P*-value
Male								
Overall	10388	44622.87	0.924 (0.900, 0.947)	<0.001	1.017 (1.001, 1.034)	0.039	0.951 (0.939, 0.963)	<0.001
Normal weight	5784	25210.77	0.889 (0.857, 0.922)	<0.001	1.035 (1.011, 1.060)	0.003	0.928 (0.911, 0.946)	<0.001
Overweight	4144	17551.2	0.932 (0.896, 0.970)	<0.001	1.011 (0.985, 1.039)	0.403	0.959 (0.940, 0.978)	<0.001
Obese	460	1860.9	1.047 (0.998, 1.099)	0.061	0.991 (0.939, 1.047)	0.757	1.027 (0.999, 1.056)	0.055
Female								
Overall	11355	48062.99	0.966 (0.944, 0.988)	0.003	0.925 (0.909, 0.942)	<0.001	0.939 (0.923, 0.955)	<0.001
Normal weight	6273	26966.99	0.954 (0.928, 0.982)	0.001	0.919 (0.899, 0.939)	<0.001	0.919 (0.901, 0.938)	<0.001
Overweight	4253	17796.32	0.988 (0.946, 1.031)	0.581	0.936 (0.907, 0.967)	<0.001	0.959 (0.930, 0.988)	0.006
Obese	829	3299.68	0.992 (0.909, 1.083)	0.862	0.988 (0.922, 1.060)	0.744	1.004 (0.954, 1.056)	0.892

The multivariable model was used for the BMI at the baseline and follow-up periods, household income, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; ΔpASMI, change in the predicted appendicular skeletal muscle mass index; ΔpBFMI, change in the predicted body fat mass index; ΔpLBMI, change in the predicted lean body mass index.

TABLE 4 Hazard ratios and 95%CI of heart failure per 1 kg/m^2 increase in the change in the predicted body composition index stratified by a change in the BMI group.

Variables	Event	Person-years	ΔpASMI HR (95%CI)	*P*-value	ΔpBFMI HR (95%CI)	*P*-value	ΔpLBMI HR (95%CI)	*P*-value
Male								
Stable weight	6995	30285.72	0.894 (0.863, 0.927)	<0.001	1.028 (1.005, 1.050)	0.014	0.928 (0.911, 0.946)	<0.001
Normal BMI at the baseline period								
Maintained normal	1346	5736.32	0.900 (0.837, 0.968)	0.004	1.041 (0.994, 1.091)	0.089	0.934 (0.898, 0.970)	<0.001
Normal to overweight	377	1628.47	0.904 (0.806, 1.013)	0.081	0.967 (0.893, 1.048)	0.411	0.945 (0.893, 1.001)	0.052
Normal to obese	7	30.44	0.970 (0.796, 1.181)	0.759	0.874 (0.675, 1.133)	0.309	0.986 (0.892, 1.089)	0.779
Overweight BMI at the baseline period								
Overweight to normal	383	1626.98	1.038 (0.925, 1.165)	0.524	1.102 (1.021, 1.19)	0.013	1.027 (0.967, 1.090)	0.382
Maintained overweight	851	3571.55	0.945 (0.863, 1.033)	0.213	0.970 (0.918, 1.024)	0.270	0.972 (0.927, 1.020)	0.248
Overweight to obese	107	440.71	0.843 (0.719, 0.988)	0.034	0.933 (0.830, 1.049)	0.247	0.917 (0.848, 0.992)	0.031

(Continued)

10.3389/fendo.2023.1210371

TABLE 4 Continued

Variables	Event	Person-years	ΔpASMI HR (95%CI)	*P*-value	ΔpBFMI HR (95%CI)	*P*-value	ΔpLBMI HR (95%CI)	*P*-value
Obese BMI at the baseline period								
Obese to normal	7	34.98	1.128 (0.928, 1.371)	0.227	1.372 (0.990, 1.904)	0.057	1.067 (0.967, 1.178)	0.197
Obese to overweight	82	327.42	1.198 (0.990, 1.451)	0.063	1.044 (0.910, 1.197)	0.539	1.094 (0.999, 1.197)	0.052
Maintained obese	135	531.47	1.069 (0.930, 1.228)	0.347	0.986 (0.881, 1.104)	0.807	1.035 (0.966, 1.109)	0.332
Female								
Stable weight	6976	29686.87	0.963 (0.935, 0.993)	0.016	0.918 (0.899, 0.937)	<0.001	0.923 (0.904, 0.943)	<0.001
Normal BMI at the baseline period								
Maintained normal	1671	7168.64	0.960 (0.906, 1.017)	0.165	0.925 (0.876, 0.978)	<0.001	0.924 (0.887, 0.962)	<0.001
Normal to overweight	453	1895.6	0.931 (0.859, 1.008)	0.078	0.896 (0.867, 0.926)	<0.001	0.910 (0.856, 0.966)	0.002
Normal to obese	8	35.45	0.958 (0.697, 1.316)	0.790	0.911 (0.725, 1.145)	0.424	0.974 (0.84, 1.131)	0.731
Overweight BMI at the baseline period								
Overweight to normal	524	2241.71	1.041 (0.962, 1.128)	0.317	1.104 (0.987, 1.235)	0.082	1.036 (0.967, 1.110)	0.317
Maintained overweight	1036	4259.37	0.908 (0.859, 0.960)	<0.001	0.938 (0.866, 1.016)	0.118	0.901 (0.851, 0.953)	<0.001
Overweight to obese	138	583.26	1.065 (0.967, 1.173)	0.199	0.983 (0.861, 1.122)	0.795	1.056 (0.949, 1.174)	0.319
Obese BMI at the baseline period								
Obese to normal	8	24.51	0.934 (0.607, 1.439)	0.758	1.085 (0.832, 1.415)	0.548	0.978 (0.799, 1.197)	0.826
Obese to overweight	139	566.92	1.013 (0.874, 1.173)	0.867	1.038 (0.942, 1.145)	0.452	1.012 (0.939, 1.090)	0.757
Maintained obese	265	1069.9	1.022 (0.893, 1.169)	0.754	0.901 (0.823, 0.987)	0.025	0.998 (0.900, 1.107)	0.971

Multivariable model was adjusted for age, BMI at baseline and follow-up, household income, smoking status, alcohol intake, physical activity, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index. BMI, body mass index; CI, confidence interval; HR, hazard ratio; ΔpASMI, change in the predicted appendicular skeletal muscle mass index; ΔpBFMI, change in the predicted body fat mass index; ΔpLBMI, change in the predicted lean body mass index.

when the BMI of participants decreased. In females, peripherally distributed fat has a negative impact on exercise intolerance (30). Also, female patients with HF were found to be in a catabolic state and have more metabolic reserves. If patients experienced malnutrition, the burden of morbidity and mortality for HF increased, and loss of muscle mass occurred, leading to advanced HF (31). In contrast, obese patients showed low adiponectin levels and a decreased catecholamine response, which led to improved HF (32). Finally, obese females showed higher fatty acid uptake and less myocardial glucose utilization compared with obese males, which resulted in differences in myocardial metabolism (33, 34). The present study showed that increased changes in the body fat mass had a negative relationship with the occurrence of HF, and the occurrence-reducing effect of the increased change in body fat mass was more alleviated when the female participants were obese and when the BMI of participants increased.

The strength of our study is that it showed an association between changes in the body composition indices and the occurrence of HF in a large sample of the Korean general population in a longitudinal setting. However, our study has several limitations. First, present study has been conducted using anthropometric prediction equations to estimate body composition. Due to time constraint and cost, measurement of body composition using accurate modalities remains challenging issue in large epidemiological studies. Therefore, we decided to proceed with present study based on previous study which developed prediction equations to indirectly assess body composition using data obtained with dual-energy X-ray absorptiometry as reference

(11). These anthropometric prediction equations from the Korean National Health and Nutrition Examination Survey cohort was validated, but it is major limitation of our study. Second, the equation for predicted body composition was estimated for the Korean population aged > 19 years; therefore, these findings may not be generalizable to other ethnicities and may not be directly applicable to different geographic and/or demographic settings. Third, although it was conducted with a longitudinal design, this is a retrospective study; therefore, we could not confirm the causal relationship or exclude confounders. Finally, because this is an epidemiologic study, our study cannot explain the basic mechanism of the association between changes in body composition and HF.

In conclusion, changes in body composition are associated with the occurrence of HF. Decreased ΔpASMI and ΔpLBMI are associated with the occurrence of HF. Furthermore, in males, increased ΔpBFMI was associated with the occurrence of HF. However, in females, decreased ΔpBFMI was associated with the occurrence of HF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board approval number: SEUMC 2022-02-018. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

T-JS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HW, D-HK, HL, MKK, and T-JS conceived of and designed the study. T-JS and HL conducted the data acquisition and statistical analyses. HW, D-HK, MKK, and T-JS interpreted data and drafted the manuscript. T-JS reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korean government (MSIT) (2022–0-00621 to T-JS, Development of artificial intelligence technology that provides dialog-based multi-modal explainability). This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI22C073600, RS-2023-00262087 to T-JS). The funding source had no role in the design, conduct, or reporting of this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1210371/full#supplementary-material

References

1. Tan LB, Williams SG, Tan DK, Cohen-Solal A. So many definitions of heart failure: are they all universally valid? A critical appraisal. *Expert Rev Cardiovasc Ther* (2010) 8(2):217–28. doi: 10.1586/erc.09.187

2. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* (2017) 3(1):7–11. doi: 10.15420/cfr.2016:25:2

3. Chang Y, Woo HG, Park J, Lee JS, Song TJ. Improved oral hygiene care is associated with decreased risk of occurrence for atrial fibrillation and heart failure: A nationwide population-based cohort study. *Eur J Prev Cardiol* (2020) 27(17):1835–45. doi: 10.1177/2047487319886018

4. Inamdar AA, Inamdar AC. Heart failure: diagnosis, management and utilization. *J Clin Med* (2016) 5(7):62. doi: 10.3390/jcm5070062

5. Obesity WHOCo and World Health O. *Obesity : Preventing and Managing the Global Epidemic : Report of a WHO Consultation*. Geneva: World Health Organization (2000).

6. Dai H, Alsalhe TA, Chalghaf N, Ricco M, Bragazzi NL, Wu J. The global burden of disease attributable to high body mass index in 195 countries and territories, 1990-2017: An analysis of the Global Burden of Disease Study. *PloS Med* (2020) 17(7): e1003198. doi: 10.1371/journal.pmed.1003198

7. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. *Circ Res* (2016) 118(11):1752–70. doi: 10.1161/CIRCRESAHA.115.306883

8. Krauss RM, Winston M, Fletcher BJ, Grundy SM. Obesity : impact on cardiovascular disease. *Circulation* (1998) 98(14):1472–6. doi: 10.1161/01.CIR.98.14.1472

9. Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, et al. Body mass index, abdominal fatness, and heart failure incidence and mortality: A systematic review and dose-response meta-analysis of prospective studies. *Circulation* (2016) 133 (7):639–49. doi: 10.1161/CIRCULATIONAHA.115.016801

10. Hall ME. Body mass index and heart failure mortality: more is less? *JACC Heart Fail* (2018) 6(3):243–5. doi: 10.1016/j.jchf.2017.12.013

11. Lee G, Chang J, Hwang SS, Son JS, Park SM. Development and validation of prediction equations for the assessment of muscle or fat mass using anthropometric measurements, serum creatinine level, and lifestyle factors among Korean adults. *Nutr Res Pract* (2021) 15(1):95–105. doi: 10.4162/nrp.2021.15.1.95

12. Park MS, Jeon J, Song TJ, Kim J. Association of periodontitis with microvascular complications of diabetes mellitus: A nationwide cohort study. *J Diabetes Complications* (2022) 36(2):108107. doi: 10.1016/j.jdiacomp.2021.108107

13. Chang Y, Lee JS, Woo HG, Ryu DR, Kim JW, Song TJ. Improved oral hygiene care and chronic kidney disease occurrence: A nationwide population-based retrospective cohort study. *Med (Baltimore)* (2021) 100(47):e27845. doi: 10.1097/MD.0000000000027845

14. Kim J, Kim HJ, Jeon J, Song TJ. Association between oral health and cardiovascular outcomes in patients with hypertension: a nationwide cohort study. *J Hypertens* (2022) 40(2):374–81. doi: 10.1097/HJH.0000000000003022

15. Chang Y, Lee JS, Lee KJ, Woo HG, Song TJ. Improved oral hygiene is associated with decreased risk of new-onset diabetes: a nationwide population-based cohort study. *Diabetologia* (2020) 63(5):924–33. doi: 10.1007/s00125-020-05112-9

16. Woo HG, Chang YK, Lee JS, Song TJ. *Association of Periodontal Disease with the Occurrence of Unruptured Cerebral Aneurysm among Adults in Korea: A Nationwide Population-Based Cohort Study Medicina (Kaunas)*, Basel, Switzerland: Licensee MDPI, Vol. 57. (2021).

17. Park J, Shin JI, Kim DH, Park J, Jeon J, Kim J, et al. Association of atrial fibrillation with infectivity and severe complications of COVID-19: A nationwide cohort study. *J Med Virol* (2022) 94(6):2422–30. doi: 10.1002/jmv.27647

18. Kim HJ, Park MS, Shin JI, Park J, Kim DH, Jeon J, et al. Associations of heart failure with susceptibility and severe complications of COVID-19: A nationwide cohort study. *J Med Virol* (2022) 94(3):1138–45. doi: 10.1002/jmv.27435

19. Lee K, Lee JS, Kim J, Lee H, Chang Y, Woo HG, et al. Oral health and gastrointestinal cancer: A nationwide cohort study. *J Clin Periodontol* (2020) 47 (7):796–808. doi: 10.1111/jcpe.13304

20. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol.* (2004) 57(12):1288–94. doi: 10.1016/j.jclinepi.2004.03.012

21. Choi EK. Cardiovascular research using the korean national health information database. *Korean Circ J* (2020) 50(9):754–72. doi: 10.4070/kcj.2020.0171

22. Sato R, Vatic M, da Fonseca GWP, von Haehling S. Sarcopenia and frailty in heart failure: is there a biomarker signature? *Curr Heart Fail Rep* (2022) 19(6):400–11. doi: 10.1007/s11897-022-00575-w

23. Forman DE, Santanasto AJ, Boudreau R, Harris T, Kanaya AM, Satterfield S, et al. Impact of incident heart failure on body composition over time in the health, aging, and body composition study population. *Circ Heart Fail* (2017) 10(9):e003915. doi: 10.1161/CIRCHEARTFAILURE.117.003915

24. Springer J, Springer JI, Anker SD. Muscle wasting and sarcopenia in heart failure and beyond: update 2017. *ESC Heart Fail* (2017) 4(4):492–8. doi: 10.1002/ehf2.12237

25. Chandrashekhar Iyer L, Vaishali K, Babu AS. Prevalence of sarcopenia in heart failure: A systematic review. *Indian Heart J* (2023) 75(1):36–42. doi: 10.1016/j.ihj.2022.12.004

26. Fülster S, Tacke M, Sandek A, Ebner N, Tschöpe C, Doehner W, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* (2012) 34(7):512–9. doi: 10.1093/eurheartj/ehs381

27. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* (1993) 58(4):463–7. doi: 10.1093/ajcn/58.4.463

28. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. *Am J Cardiol* (2012) 110(1):77–82. doi: 10.1016/j.amjcard.2012.02.050

29. Snijder M, van Dam R, Visser M, Seidell J. What aspects of body fat are particularly hazardous and how do we measure them? *Int J Epidemiol* (2005) 35(1):83–92. doi: 10.1093/ije/dyi253

30. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Cardiol* (2014) 113(7):1211–6. doi: 10.1016/j.amjcard.2013.12.031

31. Lavie CJ, De Schutter A, Alpert MA, Mehra MR, Milani RV, Ventura HO. Obesity paradox, cachexia, frailty, and heart failure. *Heart Fail Clin* (2014) 10(2):319–26. doi: 10.1016/j.hfc.2013.12.002

32. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* (2005) 112(12):1756–62. doi: 10.1161/CIRCULATIONAHA.104.530972

33. Peterson LR, Soto PF, Herrero P, Mohammed BS, Avidan MS, Schechtman KB, et al. Impact of gender on the myocardial metabolic response to obesity. *JACC Cardiovasc Imaging* (2008) 1(4):424–33. doi: 10.1016/j.jcmg.2008.05.004

34. Alagiakrishnan K, Banach M, Ahmed A, Aronow WS. Complex relationship of obesity and obesity paradox in heart failure - higher risk of developing heart failure and better outcomes in established heart failure. *Ann Med* (2016) 48(8):603–13. doi: 10.1080/07853890.2016.1197415

Frontiers in Medicine

Translating medical research and innovation into improved patient care

A multidisciplinary journal which advances our medical knowledge. It supports the translation of scientific advances into new therapies and diagnostic tools that will improve patient care.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact