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Nutrition and quality of life in the elderly

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Nutrition and quality of life in the elderly

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Editorial: Nutrition and quality of life in the elderly

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elderly, quality of life, nutrition-related metabolic diseases, chronic diseases, sarcopenia, osteoporosis, nutritional status

Editorial on the Research Topic
Nutrition and quality of life in the elderly

This Research Topic presents 15 articles that discuss strategies to identify and treat major risk factors related to poor health and suggest interventions aiming to mitigate conditions that affect old people. Sedentary behaviors and imbalanced dietary habits are among the principal contributors to these health challenges.

The risk factors related to diseases and quality of life in the elderly and the tools to identify them were evaluated in several articles included in this Research Topic. Brech et al. carried out a cross-sectional study with Brazilian elderly people over 80 years and verified the association between sociodemographic factors and quality of life with their nutritional status. The systematic review of Golmohammadi et al. verified the association between the inflammatory index of the diet and quality of life in the elderly, indicating a possible association between them.

Yang et al. followed, for 4 years, 2,601 participants with prediabetes to verify the six obesity-related indexes that are evaluated in the study could be associated with prediabetes regression. The authors identified that a low initial body roundness index, waist-to-height ratio, and Chinese visceral adiposity index, as well as a reduction in the triglyceride glucose index, were related to the regression of prediabetes to normoglycemia.

The phase angle—an index obtained from bioimpedance—is normally used as an indicator of mortality in several diseases. Langer et al. investigated the relationship between changes in phase angle and mortality and morbidity concerning cardiovascular and coronary heart disease in an 18-year follow-up study and demonstrated that phase angle can be a reliable tool in this investigation.

The study by Li, Shen et al. explored the impact of malnutrition in 662 oldest-old patients hospitalized due to acute coronary syndrome (ACS). The authors reported that malnutrition evaluated through the geriatric nutritional risk index (GNRI) was common in this population with ACS (206 patients with GNRI $\leq$ 98). Moreover, GNRI could predict all-cause mortality in the oldest-old patients with ACS.

The article by Hu et al. showed that 19.3% of the 254 patients who underwent total hip arthroplasty (THA) exhibited postoperative delirium (POD). The identified risk factors for POD in this population were neutrophil-to-albumin ratio (NAR),

prognostic nutritional index (PNI), systemic inflammation score (SIS), and age. Based on these results, the authors developed a POD predictive nomogram model with a C-index value of this model being 0.869 (95% CI = 0.820–0.918).

Ju et al. evaluated the association between the comprehensive geriatric assessment (CGA) and the nutritional status of 211 elderly patients. The Mini Nutritional Assessment (MNA) questionnaire was used to assess the nutritional status. The quality of daily living was measured through the scores of activities of daily living (ADL) and instrumental activities of daily living (IADL). History of peptic ulcer disease, high scores on the Geriatric Depression Scale (GDS), ADL, and IADL were associated with an increased risk of undernutrition.

Zhang et al. hypothesized that the gut microbiota of elderly people with hypertension may differ between two groups of participants: hypertension elderly and hypertension longevity. The hypertension longevity (with a mean age of 100 years) showed efficient acetate absorption and a microbiota composition characterized by higher abundance of *Bacteroides*, *Faecalibacterium*, and *Alistipes* and lower abundance of *Klebsiella* and *Streptococcus* compared to the hypertension elderly group (with a mean age of 70.5 years). Therefore, the microbiota may have an impact on longevity, despite high levels of systolic blood pressure. An exploratory study by O'Mahony et al. showed that the effects of a Mediterranean diet on the microbiota and health of the elderly are still poorly understood and recognized by the elderly and healthcare professionals.

The study of Wang et al. showed a relationship between serum vitamin D levels and the concentration of irisin—a myokine related to muscle mass. Lower levels of irisin were associated with sarcopenia in elderly women. Xu et al. aimed to investigate the association between the daily intake of certain minerals and the incidence of cataracts in the elderly American population. They found a strong negative association between selenium intake and the incidence of cataracts in this population.

Liu Z. et al. showed that a high intake of vitamin B_{12} was associated with an increased risk of glaucoma in participants aged 40 years or over from the USA population. The authors used data from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2008 in which dietary intake was evaluated using two 24-h dietary recalls. In total, 594 participants were included. The authors found a significant association between high intake of B_{12} and glaucoma, while normal or low doses of B_{12} intake showed no significant association.

Li, Zhu et al. proposed a study protocol to investigate the effects of vitamin K_2 in nocturnal leg cramps (NLC)—a common musculoskeletal disorder that causes sudden contractions of the leg. Menaquinone (180 μg/day) will be offered to participants over 65 years of age for 8 weeks. The study hypothesis is that vitamin K2 decreases muscle contractions, thereby alleviating NLC.

The review of Liu B. et al. discusses lipid and glucose metabolism in senescence. The authors brought together information related to decreased oxidation, increased synthesis of fatty acids, and increased glycolysis in senescent cells. Furthermore, the article discusses how external factors, such as diet, environmental pollution, stress, and temperature, can quicken cellular senescence.

Comprehensive palliative care that included local culture and traditions together with a multidisciplinary team provided longer overall survival when compared to standard oncological care offered to patients with non-small cell lung cancer, as showed by Chen et al.. Moreover, this integrative approach resulted in a higher quality of life, a lower percentage of patients with depressive symptoms, and a better nutritional status.

Assessing potential risks and methods for addressing health challenges that affect the elderly, these investigations offer valuable perspectives for supporting the health of old people. Additionally, studies examining areas such as the gut's microbiota, nutrient levels, and metabolic functions unveil promising paths for optimizing health among the elderly. By prioritizing preventive actions and tailored treatments, there are considerable opportunities to elevate the wellbeing of elderly individuals and foster healthy aging.

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Serum vitamin D status and circulating irisin levels in older adults with sarcopenia

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Background: Emerging evidence suggests sarcopenia, which is involved in the serum vitamin D deficiency and development of abnormal muscle metabolism, is predominately centered in the general older population. In the present study, we aimed to explore the relationship between the level of serum vitamin D and irisin concentrations in the older adults with sarcopenia.

Methods: A cross-sectional study was conducted which included 422 sarcopenia participants (146 males and 276 females). Sarcopenia was assessed according to the recommended diagnostic criteria of the Asia Working Group for Sarcopenia (AWGS). The levels of serum 25-hydroxyvitamin D (25(OH)D), 25-hydroxyvitamin D_2 (25(OH)D_2) and 25-hydroxyvitamin D_3 (25(OH)D_3) were determined by LC-MS/MS. Irisin levels were measured by enzyme-linked immunosorbent assay (ELISA). The relationship between serum concentration of vitamin D and irisin were determined using multiple linear regression analysis.

Results: After adjustment for potential confounding factors, a significant and positive relationship between changes in irisin across 25(OH)D, and 25(OH)D_3 was observed (standard regression coefficients of 0.150 and 0.151, respectively, $P < 0.05$). However, no significant relationship was observed between serum vitamin D concentrations and irisin levels in males.

Conclusions: This study demonstrated that a higher level of serum vitamin D is independently related to the increment of irisin in sarcopenia females, not in males. These investigations need to be verified in other large-scale prospective studies.

KEYWORDS

25-hydroxyvitamin D, 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, irisin, sarcopenia

Background

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder, the incidence of which ranges between 5 and 15% in 65-year-olds, and as high as 50% over 80 years old (1). The risk of falls, fractures, disabilities, hospitalization and mortality increased significantly with the development of sarcopenia (2, 3). An increasing body of evidence suggests that sarcopenia may affect detrimental myokines and hormonal substances metabolic abnormalities, such as irisin, myostatin, interleukin-6 and follistatin (4). Irisin, which is a hormone carried by blood and mainly produced by fibronectin type III domain containing 5 (FNDC5) in muscle tissue. It is a dependent protein of the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) (5). The expression of PGC-1α and FNDC5 in skeletal muscle are two major gene components of muscle exercise, which is a regulator protein and a precursor of irisin, respectively. In fact, irisin is a potential bridge between muscle and other tissues and organs, primarily responsible for energy metabolism and acts as a positive regulating factor of muscle mass (6). A significant decrease in the irisin level is signed to be a biomarker of muscle weakness and atrophy (7). A cross-sectional study indicated that per 1.0 ng/mL decrease of irisin was associated with an increased prevalence of sarcopenia, with an odds ratio of 1.95 (95% CI: 1.33–2.87) (8). Another study showed that the circulating irisin was significantly lower in the sarcopenia group, and the high irisin was associated with lower odds of sarcopenia in postmenopausal women (9).

The pathophysiology mechanisms of sarcopenia involve the alteration of serum micronutrient status (10). Vitamin D is discovered to be the earliest pro-steroid hormone to arise on earth. It is reported that more than 1 billion individuals are possessing vitamin D insufficiency or deficiency, especially in the older population (11). The deficiency of vitamin D due to sarcopenia is thought to underlie the pathogenesis of low muscle mass, muscle strength, and muscle function (12). Vitamin D thus performs a critical role in the regulation of skeletal muscle metabolic homeostasis. Previous studies have indicated that the level of vitamin D is evaluated as an explanation for the reason of sarcopenia (10, 13, 14).

Many animal studies explored the detailed mechanism of serum vitamin D and irisin on skeletal muscle (15, 16). Compelling evidence has shown that sarcopenia induced lower serum irisin. Moreover, recent studies have demonstrated that several possible risk factors of sarcopenia included irisin and 25(OH)D (9). Therefore, clarifying the common mechanisms of irisin and vitamin D is a crucial step toward providing early prevention and treatment. We speculate that vitamin D and irisin have inherent conjunction during the prevalence and progression of sarcopenia. However, human studies on the relationship between vitamin D status and irisin in the older population with sarcopenia remained unknown. The study aimed to investigate whether serum vitamin D concentrations are related to the level of irisin among older individuals with sarcopenia.

Methods

Study participants

The Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSIH) Cohort Study is a prospective cohort involving >100,000 study participants, a large prospective dynamic cohort study initially designed to investigate the relationships between chronic low-grade systemic inflammation and health status. Additional information on the study design of the TCLSIH has been examined elsewhere (17). At the time of enrollment, participants attended a self-designed structured questionnaire survey including sociodemographic characteristics, diet, lifestyle, household income, occupation, and educational level, etc., and completed comprehensive health examinations. The study procedures were provided by the Institutional Review Board of Tianjin Medical University, and all participants provided written informed consent.

The assessment of sarcopenia was followed the diagnostic approach of the AWGS (18). Participants were recruited as sarcopenia patients according to the following conditions: (1) low muscle mass, the skeletal muscle mass index (SMI) was calculated as follows: SMI (kg/m^2) = appendicular muscle mass (kilograms) / (height [meter])^2, which was an effective measure of sarcopenia. The cutoff values of SMI were 7.0 kg/m^2 in men and 5.7 kg/m^2 in women by using Bioelectrical Impedance Analysis. (2) low muscle strength. A handgrip strength was measured by a hand-held dynamometer (EH101; CAMRY, Guangdong, China). In the criteria, sarcopenia was defined as grip strength < 26 kg for men and < 18 kg for women. (3) low physical performance. Gait speed over a distance of 4 meter was measured to evaluate physical performance. Studies have shown that the reference value for low physical capacity was < 1 m/s (19). According to the above diagnostic criteria, a total of 463 participants have attended this research. Participants with incomplete data collection on questionnaire and error measurement of irisin and vitamin D values were excluded (n = 41). As a result of these exclusions and diagnosis of sarcopenia, 422 participants (females, 65.4%) were included in this cross-sectional study.

Measurement of vitamin D

Study nurses collected the sarcopenia older participants anthropometric details and blood samples. The fasting blood samples were routinely drawn from participants using

venipuncture. Blood samples were protected from light and isolated the serum immediately. Stabilized samples were stored at −80°C. Vitamin D in the serum is in the form of 25(OH)D_2 and 25(OH)D_3, which were measured using a liquid chromatography–triple quadrupole mass spectrometry (LC-MS/MS, SCIEX Triple Quad 4500MD). The concentration of 25(OH)D was the sum of 25(OH)D_2 and 25(OH)D_3. According to the manufacturer's notes, the coefficient of variance of intra- and inter assay were both <15%. The linear ranges were 2.0–100 ng/mL for 25(OH)D_2 and 4.0–200 ng/mL for 25(OH)D_3.

Measurement of irisin

To assess irisin, blood samples were centrifuged for 5 min at 3000rpm/min, then serum was stored at −80°C. Serum irisin was determined by the principle of competitive enzyme immunoassay according to ELISA kit (Cat. no: EK-067-29, Phoenix Pharmaceuticals Inc., CA, USA). The maximal intra- CV and inter-assay CV were <10 and <15%, respectively, meanwhile, the normal detection range was 5.8–23.2 ng/ ml supported by the manufacturer. The kit was commercially reliable and highly sensitive.

Measurement of other variables

Height and body weight were measured by using a calibrated balance scale. Body mass index (BMI, kg/m^2) was calculated as weight divided by height. Body fat composition was assessed by a multifrequency bioelectrical impedance analyzer (In-Body720; Biospace Co, Seoul, Korea). With full consent, age, sex, marital status, educational level, household income, employment status, smoking status, alcohol-consumption status, physical activity, living alone status and the use of nutritional supplement were obtained from the health questionnaire records. Baseline values of individual history of diseases (cardiovascular disease, stroke, cancer, diabetes, hypertension, and hyperlipidemia) were obtained through collecting personal health records and relevant biochemical index evaluation (20). The dietary pattern and total energy intake values were assessed from the food frequency questionnaire (FFQ). Dietary pattern divided into three categories: "sweets," "healthy," and "animal foods" dietary pattern. Depressive symptoms were evaluated based on the 20-item of the Chinese version of the Self-Rating Depression Scale (SDS) with cutoff value of 45 (21). A fasting blood sample was drawn and collection data was recorded. For information about the sunlight exposure, it was quantified asking the participant to provide the outdoor activity time in summer/autumn or winter/spring (22).

Statistical analysis

Statistical analyses of the data were conducted with Analysis System 9.3 edition for Windows (SAS Institute Inc., Gary, NC, USA). Study population characteristics according to sex are reported as means (with 95% confidence interval, CI) for continuous variables and percentages for categorical variables. The concentrations of serum 25[OH]D, 25[OH]D_2 and 25[OH]D_3 were used as independent variable, and the level of serum irisin was used as dependent variable separately. The relationship between serum vitamin D and irisin was assessed using multiple linear regression analysis adjusted for age, BMI, physical activity, smoking status, drinking status, history of diseases (cardiovascular disease, stroke, cancer, hypertension, hyperlipidemia, and diabetes), total energy intake, dietary pattern, education level, married status, living alone status, employment status, depressive symptoms and season of average outdoor time, body fat ratio and the use of nutritional supplement. β and standard β values were calculated. All tests were two- tailed and $P < 0.05$ was defined as statistically significant.

Results

The study sample included 422 sarcopenia subjects aged 69.9 years (range: from 66.1 to 74.1 years), all baseline characteristics are shown in Table 1. There were 146 men and 276 women with complete data for sarcopenia analyses. Multiple linear regression analyses were presented to confirm the crude and adjusted relationship between serum vitamin D concentration and irisin in Table 2. Results of analysis showed a positive relationship between serum 25(OH)D and 25(OH)D_3 levels and irisin in females using age- and BMI-adjusted model, standard regression coefficient (SRC) = 0.135, $P < 0.05$ and SRC = 0.132, $P < 0.05$ respectively. After adjusting for potential confounders, irisin distinctly showed a significant relationship with 25(OH)D [SRC = 0.150; $P < 0.05$], and 25(OH)D_3 [SRC = 0.151; $P < 0.05$] in females. However, no significant interactions between 25(OH)D_2 and irisin were observed in the final models [SRC = 0.032; $P = 0.606$]. Additionally, in males, the crude SRC of irisin across serum vitamin D were presented. Adjusted irisin levels across serum 25(OH)D, 25(OH)D_2 and 25(OH)D_3, the values were SRC = −0.073, $P = 0.423$; SRC = −0.096, $P = 0.304$ and SRC = −0.071, $P = 0.434$ respectively. The analysis with multiple linear regressions did not indicate nonlinear relationship between 25(OH)D, 25(OH)D_2 and 25(OH)D_3 concentrations and irisin in males.

Discussion

Previous studies not only have shown the relationship between sarcopenia and 25(OH)D (23, 24), but also proved

TABLE 1 Baseline characteristics of participants ($n = 422$).

Characteristics	All	Men (34.6%)	Women (65.4%)	*P* value[a]
Number of participants	422	146	276	
Age (years)	69.9 (66.1, 74.1) [b]	72.7 (68.0, 76.9)	68.7 (65.8, 72.7)	<0.0001
BMI (kg/m^2)	23.7 (21.8, 25.8)	23.5 (21.4, 25.0)	24.1 (22.0, 26.0)	0.0551
Body fat ratio (%)	33.6 (27.0, 38.6)	26.7 (22.1, 31.5)	37.0 (31.7 40.9)	<0.0001
Total energy intake (kcal/day)	1,909.5 (1,519.2, 2,385.9)	2,193.1 (1,773.2, 2,677.1)	1,799.0 (1,404.8, 2,191.8)	<0.0001
"Sweets" dietary pattern score	−0.20 (−0.61, 0.48)	0.02 (−0.52, 0.80)	−0.24 (−0.74, 0.25)	0.017
"Healthy" dietary pattern score	−0.30 (−0.51, 0.24)	−0.34 (−0.54, 0.20)	−0.28 (−0.51, 0.27)	0.52
"Animal foods" dietary pattern score	−0.40 (−0.73, 0.17)	−0.04 (−0.66, 0.78)	−0.46 (−0.75, −0.13)	<0.0001
SDS score[c]	36.0 (29.0, 41.0)	35.0 (28.0, 41.0)	36.0 (29.0, 41.0)	0.18
Smoking status (%)				<0.0001
Current smoker	36.65[d]	48.25	30.48	
Ex-smoker	7.77	14.69	4.09	
Non-smoker	55.58	37.06	65.43	
Alcohol drinking status (%)				<0.0001
Everyday	4.05	16.67	0.00	
Sometime	6.76	22.22	1.79	
Ex-drinker	4.05	16.67	0.00	
Non-drinker	85.14	44.44	98.21	
PA (≥23 MET × hour/week, %)	33.18	40.41	29.53	0.055
Education level (≥middle school, %)	14.37	22.95	9.27	<0.001
Marital status (married, %)	99.14	97.62	100.0	0.021
Living alone (yes, %)	13.12	12.90	13.24	0.93
History of disease (%)				
Hypertension	50.71	50.68	50.72	0.53
Hyperlipidemia	46.68	34.25	53.26	<0.0001
Stroke	5.69	6.16	5.43	<0.0001
Cancer	0.24	0.00	0.36	<0.0001
Diabetes	13.74	13.0	14.13	<0.0001
Season of average time outdoors				
Summer (≥3 h/d, %)	59.94	77.69	50.00	<0.0001
Winner (≥3 h/d, %)	59.05	76.86	49.07	<0.0001
Use of dietary supplements (yes, %)	0.60	0.84	0.46	0.67

BMI, body mass index; PA, physical activity.
[a]Wilcoxon rank-sum test or chi-square test.
[b]Continuous variables are expressed as medians (interquartile range) (all such values).
[c]SDS score were evaluated based on the 20-item of the Chinese version of the Self-Rating Depression Scale.
[d]Categorical variables are expressed as percentages (all such values).

that irisin showed potentially far-reaching effects on muscle function (25, 26). In the present study, we firstly investigate the relationship between serum 25(OH)D status and the circulating levels of irisin in a sarcopenia population. Our results showed that the changes in irisin have a strongly analogous relationship with serum 25(OH)D and 25(OH)D_3 levels in females, but not in males, implicated that serum are rich in 25(OH)D and 25(OH)D_3, which may inhibit lower irisin levels induced by sarcopenia in older adults.

In the current study, we adjusted multiple recognized confounding factors. First, we calculated an unadjusted regression model to identify any differences in irisin according to types of serum 25(OH)D concentration. Second, several studies have revealed that irisin is related to age and BMI (27, 28), therefore, we adjusted for these two variables. After adjustment, there is a statistical significantly relationship between 25(OH)D and 25(OH)D_3 and the level of irisin was observed. Finally, sociodemographic variables, lifestyle factors, medical history, total energy intake and seasonal differences of outdoor time are closely associated with sarcopenia (17). Therefore, we further adjusted for smoking status, drinking status, educational level, occupation, married status, living alone status, family history of the disease, individual history of the disease, total energy intake and outdoor time. After all adjustments were

TABLE 2 Adjusted relationships of serum vitamin D levels and the circulating irisin in sarcopenia ($n = 422$).

Irisin concentration (ng/mL)	25-hydroxyvitamin D (ng/mL)				25-hydroxyvitamin D_2 (ng/mL)				25-hydroxyvitamin D_3 (ng/mL)			
	β	Standardized β	Standard Error	t Value	*P* Value[a]	β	Standardized β	Standard Error	t Value	*P* Value[a]	β	Standardized β	Standard Error	t Value	*P* Value[a]
Male ($N = 146$)															
Model 1[b]	−0.101	−0.052	0.161	−0.63	0.531	−0.071	−0.089	0.067	−1.07	0.285	−0.098	−0.052	0.158	−0.62	0.534
Model 2[c]	−0.106	−0.055	0.161	−0.66	0.510	−0.084	−0.105	0.067	−1.26	0.209	−0.102	−0.054	0.158	−0.65	0.518
Model 3[d]	−0.141	−0.073	0.175	−0.80	0.423	−0.077	−0.096	0.074	−1.03	0.304	−0.134	−0.071	0.170	−0.78	0.434
Female ($N = 276$)															
Model 1[b]	0.163	0.134	0.073	2.23	<0.05	0.039	0.068	0.034	1.13	0.260	0.156	0.131	0.072	2.18	<0.05
Model 2[c]	0.165	0.135	0.073	2.26	<0.05	0.037	0.065	0.034	1.07	0.283	0.158	0.132	0.071	2.22	<0.05
Model 3[d]	0.183	0.150	0.075	2.46	<0.05	0.018	0.032	0.035	0.52	0.606	0.180	0.151	0.073	2.46	<0.05

[a]Obtained by using multiple linear regression analysis.
[b]Unadjusted model.
[c]Adjusted for age, BMI.
[d]Adjusted for age, BMI, physical activity, smoking status, alcohol-consumption status, individual history of diseases (cardiovascular disease, stroke, cancer, hypertension, hyperlipidemia, and diabetes), total energy intake, dietary pattern score, education level, married status, employment status, SDS score, living alone status, season of average outdoor time, body fat ratio, the use of dietary supplements.

made, the standard regression coefficient of female sarcopenia participants with irisin were 0.143 and 0.145 in interaction with 25(OH)D and 25(OH)D_3. However, males did not show any significant difference. The gender-specific difference between the concentration of irisin and vitamin D in this study seem to be explained by the innately higher amount of subcutaneous fat mass in women, which may stimulate a higher biological activity and lead to a higher irisin concentration (29). At the same time, subcutaneous adipose tissue is closely related to estrogen, which may absorb more vitamin D molecules produced from the skin because of its fat-soluble properties (30). These results indicate that the associated changes in serum vitamin D and irisin are more affected by estrogen levels and body fat content. Studies are needed to confirm this hypothesis.

Sarcopenia is a hallmark of the aging process. The occurrence of sarcopenia causes abnormality in many physiological and biochemical indicators (1, 13, 25). A meta-analysis reported by Olivier showed that vitamin D supplements increased muscle strength in people who had 25(OH)D levels < 30 nmol/L (approximately 12 ng/mL), and seemed more valid in older people over 65 years (31), which suggested that in the sarcopenia older population with lower levels of serum 25(OH)D, vitamin D performed a small but significant positive effect. A previous study showed that the cut-off value of serum irisin level of 8.46 ng/mL performed maximal sensitivity (68%) and specificity (69%), the relationship between irisin and sarcopenia was not limited by the adjustment of BMI and age (8), indicated that irisin is a novel and independent predictor for sarcopenia. Previous studies demonstrated that irisin was a stronger determinant of bone mineral status (32), increasing bone formation and decreasing bone resorption, leading to reduced risk of osteoporosis. Irisin had been shown to play an important role in promoting osteoblastogenesis and reducing osteoclastogenesis (33). Therefore, we speculate the beneficial effects of irisin on bone protection in postmenopausal women with sarcopenia. Although there are several studies underlined the impact of sarcopenia on serum 25(OH)D and irisin respectively, few studies have evaluated the biochemical parameter of cross interaction in older sarcopenia participants. These results imply that earlier vitamin D supplementation is needed to preserve irisin at a higher level, to delay the development of sarcopenia in the older population.

Previous animal studies have probed that lower serum 25(OH)D reduced the energy homeostasis and irisin levels (34). Serum 25(OH)D concentrations affect the expression of the parathyroid hormone (S-PTH), which might lead to an activation of PGC1α and result in high irisin secretion into the blood (35, 36). Of note, there is no statistical relationship between 25(OH)D_2 and irisin in females. Romagnoli et al. (37) found that serum 25(OH)D_2 seems to be less efficient than 25(OH)D_3 in decreasing S-PTH levels. We speculated that the changes of irisin in patients with sarcopenia may have an impact on the inverse relationship between S-PTH concentrations

and 25(OH)D_3. The changes in serum 25(OH)D_2 was not significant and will require further investigation. Moreover, vitamin D receptor expression affects the functional response of muscle cells to 25(OH)D, which is expressed in human skeletal muscle. VDR expression is down-regulated with age and sarcopenia (38). Further studies will be clarified the exact mechanisms of 25(OH)D mediating the effect of irisin on older sarcopenia participants.

The major strength of this study is that we first report the relationship between serum vitamin D and concentrations of irisin with sarcopenia in the general population. Moreover, multiple potential confounders were considered in this study, such as sociodemographic factors, health status, dietary patterns and seasonal influences. This study has several limitations. First, having only included older sarcopenia participants in cross-sectional design, causality could not be provided. Second, participants were recruited from a single area and the included sample was relatively small, which might have negatively affected the power of data analysis. In addition, some hormonal levels might have been overlooked due to the limited on sample collection. Although these may influence the metabolic levels the irisin and vitamin D in sarcopenia (39), it indicated that the analysis of data were relatively stable over time according to our published studies. Besides, we could not investigate familial and genetic details prior to the study, though irisin levels can be maternally inherited. More research is necessary to detect the relationship between these observations in terms of genetic inheritance (40).

Conclusions

In conclusion, this study revealed that 25(OH)D is positively related to the concentration of irisin in sarcopenia females. The prevalence of sarcopenia increased stepwise because of the risk factors, further prospective epidemiologic studies with to replicate our findings and investigate the underlying mechanisms that will be done in the future. Therefore, further studies with large sarcopenia participants needed to confirm our results.

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 studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Tianjin Medical University with the reference number of TMUhMEC 201430. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW and YG analyzed data and wrote the paper. JH, HW, GM, QZ, LL, SZ, XuW, JZ, SS, XiW, MZ, QJ, KS, JH, BZ, and GD conducted data collection or management. PD and KN designed the research and had primary responsibility for the final content. All authors contributed to the article and approved the submitted version.

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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.

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Is there any association between dietary inflammatory index and quality of life? A systematic review

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Background: The inflammatory potential of unhealthy diets can lead to the development of chronic diseases and also exacerbating their complications. Therefore, the present systematic review aimed to evaluate the association of dietary inflammatory index (DII) and quality of life (QOL) in human subjects.

Methods: A systematic search was conducted in PubMed, Web of Science, and Scopus databases, using the combination of all search terms related to DII and QOL until May 2022. All eligible human studies published in English were included.

Results: Three hundred twenty-seven studies were obtained from the first systematic search of the databases although, only eight studies were eligible for the evaluation. Seven studies reported that there was a significant reverse association between DII scores and overall QOL and/or its subscales in different populations including patients with asthma, osteoarthritis, hemodialysis patients, multiple sclerosis, obese women, and also in healthy subjects. While, one study on postmenopausal women found no evidence of this association.

Conclusion: This systematic review demonstrated that an anti-inflammatory diet might be associated with better QOL. However, future well-designed clinical trials can provide better conclusions especially regarding the quantifying of this relationship.

KEYWORDS

anti-inflammatory diet, chronic disease, dietary inflammatory index, inflammation, quality of life

Introduction

The term Quality of Life (QOL) was first introduced in 1970s, as the multi-dimensional concept of well-being and health status regarding the physical, mental, emotional, and social aspects of life (1). QOL usually decreases during the aging and diseases (2, 3). It has been documented that low-grade inflammation, increasing pro-inflammatory cytokines in the body, is associated with different chronic disease (4–9), as well as impaired neurodevelopment (10) and adverse mental health outcomes (11), which can affect various aspects of patients' QOL (12). Therefore, reversing the inflammatory pathways can increase QOL of patients.

Emerging evidence showed that healthy eating is associated with low inflammatory responses and can be a cost-effective intervention to improve the QOL. It was reported that a Western dietary pattern with high consumption of refined grains, processed meats, butter, and high-fat dairy products causes inflammation in the body. Whereas, a healthy diet like the Mediterranean diet which includes whole grains, vegetables, fish, and olive oil, can prevent inflammation or suppress inflammatory pathways (13–16). For this purpose, Shivappa et al. developed a tool to assess the inflammatory potential of the diet called the Dietary Inflammatory Index (DII) (17). Higher DII scores are associated with inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) (18, 19). Studies have shown that DII is associated with various diseases such as breast cancer (20), colorectal cancer (21), osteoarthritis (22), metabolic syndrome (23), and asthma (24).

Therefore, this study was conducted with the hypothesis that the inflammatory potential of the diet can lead to the development or progression of chronic diseases complications and thus decreases patients' QOL. To the best of our knowledge, this is the first systematic review that has summarized and concluded the outcomes of related studies to assess the impact of DII on QOL.

Methods

The search strategy

This study was performed according to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 statement. We searched through PubMed/Medline, Web of Science, and Scopus for relevant papers published in English until May 2022 using the following keywords: "dietary inflammatory score" OR "dietary inflammatory index" OR "DII" OR "inflammatory diet" OR "inflammatory potential of diet" OR "dietary inflammation potential" OR "potential inflammatory intake" OR "anti-inflammatory diet" OR "pro-inflammatory diet" in title/abstract AND "quality of life" OR "QOL" OR "health-related QOL" OR "HRQOL" OR "World Health Organization Quality of Life-Brief" OR "WHOQOL" OR "PedsQL" in the title/abstract.

The screening of studies

All detected articles were saved in an EndNote software file and duplicate articles were removed. Then, unrelated articles were identified and deleted by reviewing the titles and abstracts. The full text of remaining articles was then screened for eligibility and data extraction by two independent researchers. Discrepancies between the two authors were resolved by a third researcher.

Inclusion and exclusion criteria

Studies were included if they examined the association of a DII score and QOL. There was no restriction on study design and all English articles were eligible. Moreover, studies that assessed the association of DII with QOL in patients with knee osteoarthritis, multiple sclerosis (MS), asthma, and hemodialysis were included in this review.

Data extraction and quality assessment

The data were collected according to a standard extraction form to obtain the information about the first author's name, geographical area, study design, population/sample size, mean ages of participants, interventional/control diet, duration of intervention, QOL/DII/food intake assessment tools, and the main outcomes.

For assessment of the articles quality, the adapted version of the Newcastle–Ottawa Scale (NOS) checklist was used for cross-sectional studies as it was shown in **Supplementary Table 1** (25) and the Jadad checklist was used for experimental studies as it was shown in **Supplementary Table 2** (26). In the NOS checklist, the score of ≥7 was interpreted as a low risk of bias,

Abbreviations: AQLQ, asthma quality of life questionnaire; BDNF, brain derived neurotropic factor; DASH, dietary approaches to stop hypertension; DII, dietary inflammatory index; EQ-5D, EuroQOL-5D; FFQ, food frequency questionnaire; GPCRs, G protein-coupled receptors; HF, heart failure; 24HR, 24-hour food recall; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IR, insulin resistance; MS, multiple sclerosis; MSQOL-54, multiple sclerosis quality of life; P, pain; PF, physical function; PH, physical health; PRISMA-P, preferred reporting items for systematic reviews and meta-analyses protocols; QOL, quality of life; RCT, randomized control trial; ROS, reactive oxygen species; RP, role limitation due to physical health; SCFAs, short-chain fatty acids; SF, social function; SF-12, short-form 12; SF-36, short-form 36; TNF-α, tumor necrosis factor.

scores between 4 and 6 were interpreted as a high risk of bias, and the score of <4 was interpreted as a very high risk of bias (27). In the Jadad checklist, the score of ≥3 was considered to have superior quality (26).

Results

Selection of studies

As it was shown in **Figure 1**, 327 potentially relevant articles were obtained by the search strategy. Of these records, 50 were excluded due to duplicate studies. Then, of 277 remained articles, 263 studies were excluded because they did not meet the inclusion criteria. Finally, 8 articles were included for analysis.

Characteristics of included studies

The study population of included studies were as follow: knee osteoarthritis (n = 1) (28), asthma (n = 1) (29), MS (n = 1) (30), hemodialysis patients (n = 1) (31), women with obesity or overweight (n = 1) (32), postmenopausal women (n = 1) (33), healthy people (n = 2) (34, 35). The details of each study are summarized in **Table 1**.

The population of studies were over 20 years of age, except for one research on children aged 11–12 (35). Of 8 included studies, 2 were randomized controlled trial (RCT) using the anti-inflammatory diets as the intervention for 10 (29) and 12 (30) weeks (see **Table 1**) and 6 articles were cross-sectional in design (28, 31–35).

Different questionnaires were used to assess QOL across the studies including Child and adult version of the Child Health Utility-9D (35), Short-Form 36 (SF-36) (28, 31, 32), Short-Form 12 (SF-12) (34), EuroQOL-5D (EQ-5D) (33), Asthma quality of life questionnaire (AQLQ) (29) and Multiple Sclerosis Quality of Life (MSQOL-54) (30).

There was also a heterogeneity in the assessment of dietary inflammatory index between studies. The food intake assessment tools were food frequency questionnaire (FFQ) (28, 30, 32, 35), 3-day food record (33), 3-day or 2-day 24-hour food recall (29, 31, 34).

Quality of the articles

Using the NOS checklist, it was determined that four cross-sectional studies had a high risk of bias (28, 31–33) and two of them had a low risk of bias (34, 35). Jadad's checklist also showed that all interventional studies had superior quality (29, 30). The

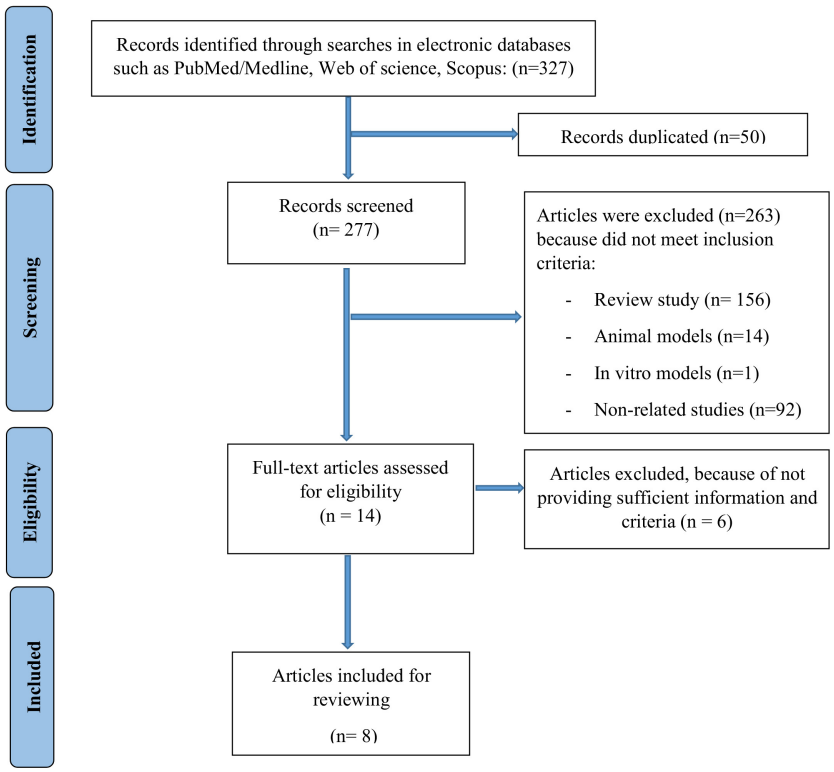

FIGURE 1
Flowchart of the studies search and selection.

TABLE 1 Summary of included studies.

References, country	Type of study	Population/ Sample size	Age (year)	Interventional diet	Control diet	Duration of intervention (weeks)	Quality of life assessment tools	DII assessment method	Food intake assessment tools	Main outcomes
Lycett et al. (35), Australia	Cross-sectional	Children n = 1,759 and adults n = 1,812	11.5 ± 0.5 and 43.7 ± 5.2	–	–	–	Child and adult version of the Child Health Utility-9D	26 food parameters	60 items FFQ	Higher DII scores were associated with lower QOL.
Song et al. (33), Korean	Cross-sectional	Postmenopausal women n = 132	45–70	–	–	–	EQ-5D	38 food parameters	3-day food record	QOL did not show a significant difference across the DII tertiles.
Kuczmarski et al. (34), USA	Cross-sectional	Urban African American and White adults n = 1,907	48.38 ± 0.21	–	–	–	SF-12	35 food parameters	4-day 24-h dietary recalls	Higher DII scores were associated with lower QOL.
Yaseri et al. (31), Iran	Cross-sectional	Hemodialysis patients n = 83	56.7 ± 12.6	–	–	–	SF-36	45 food parameters	3-day 24-h dietary recalls	Higher DII scores were associated with lower QOL.
Tabrizi et al. (32), Iran	Cross-sectional	Reproductive-aged women with obesity or overweight n = 278	31.40 ± 10.89	–	–	–	SF-36	24 food parameters	168 items FFQ	Higher DII scores were associated with lower QOL.
Toopchizadeh et al. (28), Iran	Cross-sectional	Knee osteoarthritis patients n = 220	≥45	–	–	–	SF-36	29 food parameters	168 items FFQ	Highest DII score was associated with lower QOL in terms of physical function, role limitation due to physical health, social function, and pain scales and physical health subscale.
Yucel et al. (29), Turkey	RCT	Obese asthmatic patients Intervention (n = 29) Control (n = 26)	Intervention.: 50.4 ± 10.4 Control.: 50.3 ± 10.0	–	No dietary recommendation	10 weeks	AQLQ	24 food parameters	2-day 24-h dietary recalls	AQLQ scores increased in the intervention group.
Mousavi-Shirazi-Fard et al. (30), Iran	RCT	Relapsing-remitting MS patients Intervention (n = 50) Control (n = 50)	Intervention: 35.20 ± 6.61 Control: 36.26 ± 7.23	Anti-inflammatory diet	Healthy diet	12 weeks	MSQOL-54	35 food parameters	147 items FFQ	Physical and mental components of MSQOL-54 was improved between and within the two groups after the intervention.

AQLQ, asthma quality of life questionnaire; DII, dietary inflammatory index; EQ-5D, EuroQOL-5D; FFQ, food frequency questionnaire; MS, multiple sclerosis; MSQOL-54, multiple sclerosis quality of life; QOL, quality of life; RCT, randomized control trial; SF-12, short-form 12; SF-36, short-form 36.

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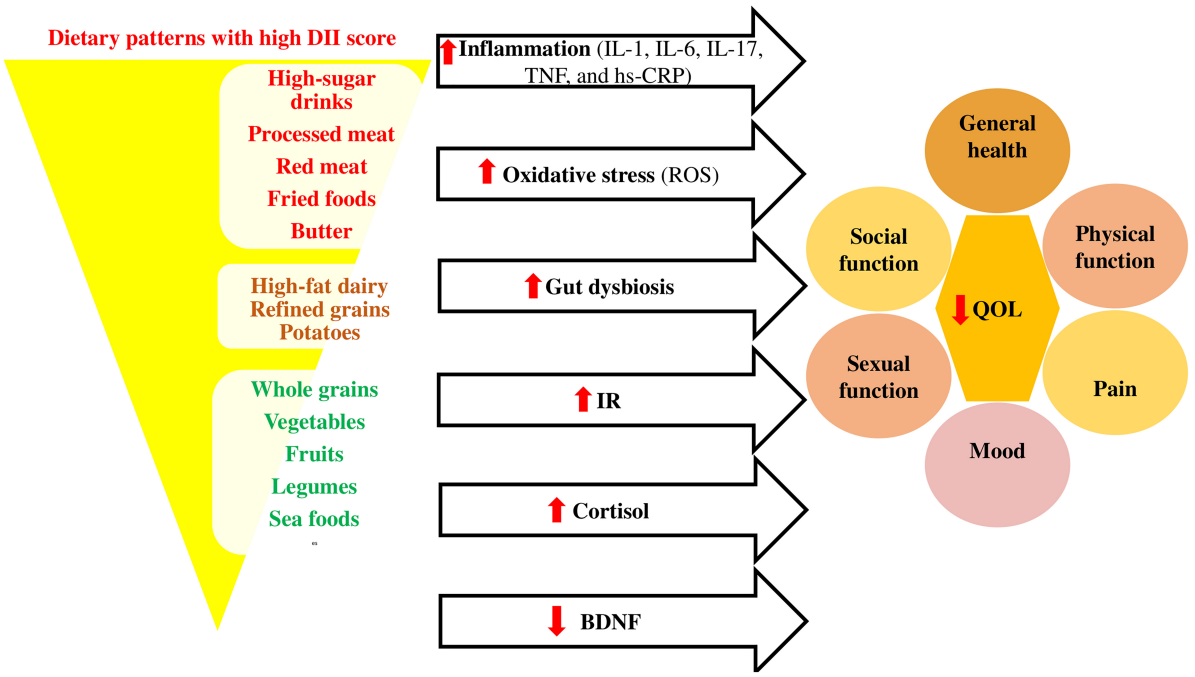

FIGURE 2
Association between pro-inflammatory diets and quality of life. Pro-inflammatory diets like Western diets (98) affect the inflammatory cytokines (99, 100), oxidative stress (101), gut microbiota composition (102), insulin resistance (IR) (103), cortisol (104), and brain derived neurotropic factor (BDNF) (105) levels, causing decrease in quality of life through its effects on different dimensions. BDNF, brain derived neurotropic factor; DII, dietary inflammatory index; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IR, insulin resistance; QOL, quality of life; ROS, reactive oxygen species; TNF, tumor necrosis factor.

scores obtained from the NOS and Jadad checklists are shown in **Supplementary Tables 1**, **2**.

Association between the dietary inflammatory index and quality of life

Five out of six cross-sectional studies found that higher DII scores were significantly associated with lower QOL (28, 31, 32, 34, 35). But the results of one cross-sectional study on post-menopausal women did not show any significant differences in QOL across the DII tertiles (33).

Moreover, the results of clinical trials showed that consumption of anti-inflammatory diet for 10 and 12 weeks significantly increased patients' quality of life in terms of different physical and/or mental components (29, 30).

Discussion

To the best of our knowledge, the present study is the first systematic review of the association between DII and QOL. The majority of the studies included in this review showed the negative relationship between DII with QOL and/or its domains, with the exception of one study showing no association (33).

Healthy dietary patterns such as the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) promote eating healthy foods, which can reduce inflammation in the body (36–39), while Western dietary pattern has inflammatory properties (40). The effect of dietary patterns on QOL have also been previously studied and our results are consistent with these studies. Results of a systematic review by Govindaraju et al. showed that healthy dietary patterns like Mediterranean diet were associated with better QOL (41). Another review study found that in contrast to the Western and unhealthy diet, the Mediterranean diet was associated with better QOL in both physical and mental domains (42). Wu et al. reported that diet quality and dietary behavior were positively associated with various aspects of QOL, including physical, psychosocial, school, and emotional functioning in children and adolescents (43). Results of a most recent study showed that adherence to the Mediterranean diet was positively associated with quality of life in children and adolescents (44). Moreover, adhering to the DASH pattern led to the improvement of QOL in patients with heart failure (HF) during 3 months (45). It was also reported that healthy dietary patterns were associated with better sleep status, sexual function, and physical activity (46–50).

The most important mechanism for the health effects of the aforementioned healthy dietary patterns can be justified by reducing inflammation, suppressing pro-inflammatory

responses, and the antioxidant effects. In this regard, focusing on the effect of diet in modulation of inflammation caused to the development of DII first in 2009 (51). DII is a validated dietary score that was introduced to assess the potential effects of people's diet on their inflammatory status and health outcomes. Accordingly, a high DII score reflects the pro-inflammatory potential of diet, while the low scores of DII reflect the anti-inflammatory effect of diet (52).

It was reported that high DII scores were positively associated with systemic inflammation and also decreased lung function in people with asthma (24). Moreover, it was reported that consumption of a pro-inflammatory diet may have important role in knee osteoarthritis pathology (53). Studies showed a positive association between DII scores with postmenopausal complications such as osteoarthritis (33), lower bone density (54, 55), higher menopause-specific somatic score (56), hip fracture risk (54), increased risk of breast cancer (20), and proximal colorectal cancer (21).

Bohlouli et al. showed that adherence to an anti-inflammatory diet such as the Mediterranean diet improved fatigue severity in relapsing-remitting MS (57). Cross-sectional studies showed that the body composition and anthropometric measurements were directly associated with DII scores (58, 59). There are evidence that high DII scores have been positively associated with an increased risk of obesity in non-obese individuals and also the prevalence of overweight and obesity (60). Recently, Ferreira et al. showed that the comorbidities of obesity decreased after improving the DII scores of participants (61).

Dietary inflammatory index can trigger inflammatory responses in the body (24, 62) and the inflammatory cytokines are related to low QOL due to physical disability, psychosocial burdens, pain, mood, and sexual function (63–72) in different conditions and diseases like respiratory tract diseases (24, 73–75), osteoarthritis and synovitis (76, 77), MS (78), obesity (79, 80), postmenopausal women (81, 82), and hemodialysis patients (83).

However, Song et al. showed that there was no significant relationship between DII scores and QOL in post-menopausal women, which may be due to the low sample size of the study (33).

Figure 2 shows the association between pro-inflammatory diets and quality of life in different conditions.

Healthy dietary patterns with low DII scores can also change the gut microbiota composition and correct the gut dysbiosis (84). These diets emphasize the consumption of vegetables, fruits, whole grain, beans, legumes, nuts, seeds, and olive oil (85) and improve the microbiome diversity by increasing growth of Bacteroides, Lactobacili, Bifidobacteria, Faecalibacterium, Oscillospira, Roseburia, Ruminococci, and their metabolic activities and decreasing growth of Firmicutes and Proteobacteria (86). Therefore, the production of short-chain fatty acids (SCFAs) will increase in the feces (84). SCFAs, especially butyrate bind to epithelial and immune cell G protein-coupled receptors (GPCRs) which leads to maintaining the integrity of the intestine and preventing inflammation, oxidative stress, and insulin resistance (87), while the western diets lead to metabolic endotoxemia by increasing intestinal permeability (86). Indeed, gut dysbiosis can affect various aspects of QOL, including physical and mental health (88–92).

The antidepressant effect of healthy diets with low DII score can also be explained through decreasing cortisol (93) and increasing brain derived neurotropic factor (BDNF) (94–97). Several limitations in the present study should be clarified when interpreting the results of this review including: (a) The number of studies on the association of DII and QOL was limited. (b) There was heterogeneity between studies' populations (different diseases or conditions) and also questionnaires which assessed the QOL, DII, and food intake. (c) The majority of included studies in this systematic review were cross-sectional studies, which did not show causal and temporal associations. (d) The instruments used to examine diet and quality of life were both self-reported, which may be subject to recall and reporting biases.

Conclusion

This systematic review demonstrated that an anti-inflammatory diet might be associated with better QOL. However, future well-designed clinical trials on various disease can provide better conclusions especially regarding the quantifying of this relationship.

Data availability statement

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

Author contributions

MG and SN contributed to designing the study, searching for resources, and writing the manuscript. MG, SK, VE, and JM cooperated in writing the manuscript. RS contributed to English revising of the manuscript. RM and MM cooperated in literature search. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1067468/full#supplementary-material

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Protection effect of gut microbiota composition and acetate absorption against hypertension-induced damages on the longevity population in Guangxi, China

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Introduction: Recent evidence supports a role for the gut microbe-metabolites in longevity. However, the phenomenon of hypertension is more common in the longevity area and whether hypertension is associated with longevity remains unclear. Here, we hypothesize that the levels of gut microbiota, SCFAs, and urine metabolites were different between hypertension elderly and hypertension longevity.

Methods: We recruited 46 elderly volunteers from Donglan County, Guangxi, and 32 were selected and included in the experiment. The subjects with hypertension were divided into two groups according to age, Hypertension Elderly (HTE, aged 70.5 ± 8.59, n = 19) and Hypertension Longevity (HTL, aged 100 ± 5.72, n = 13). The gut microbiota, SCFAs, and urine metabolites were determined by three-generation 16S rRNA full-length sequencing, GC-MS, and ^{1}H-NMR, respectively.

Results: Compared with the HTL group, the HTE group had higher levels of hypertension-related genera *Klebsiella* and *Streptococcus*, while having lower levels of the SCFA-producing genera *Bacteroides*, *Faecalibacterium*, and *Alistipes*. Based on LEFse analysis, *Klebsiella pneumoniae*, *Lactobacillus gasseri*, *Streptococcus salivarius, Ruminococcus, Actinomyces, Rikenellaceae, f_Saccharimonadaceae, Clostridium perfringens*, and *Bacteroids, Faecalibacterium prausnitzii, Parabacteroides, Alistipes* were biomarkers that showed significant differences between the groups. In addition, the microbial pathways associated with *K. pneumoniae* and *E. coli* may promote hypertension, while *A. muciniphila* may play a role in reversing the development of hypertension in long-lived elderly.

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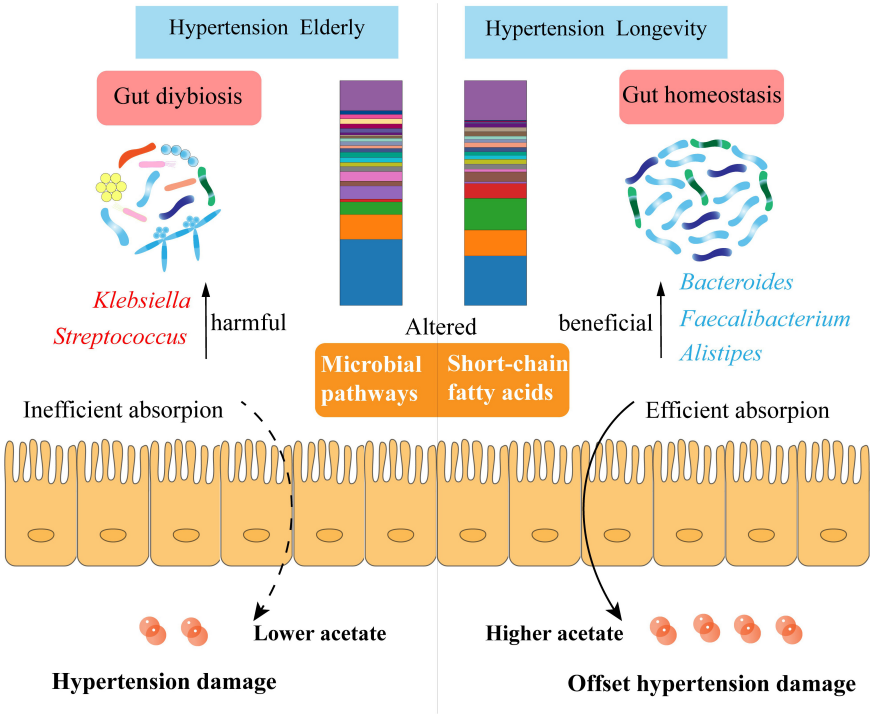

GRAPHICAL ABSTRACT
Summary of the study findings.

Metabolomics revealed that HTL contained a lower concentration of fecal acetate and propionate than HTE, while it contained a higher concentration of serum acetate and urine acetate. Furthermore, their immune cells exhibited no significant changes in SCFAs receptors.

Conclusion: Although long-lived elderly have extremely high systolic blood pressure, their unique gut microbiota composition and efficient acetate absorption in the colon may offset the damages caused by hypertension and maintain healthy homeostasis.

KEYWORDS

gut microbiota, hypertension, longevity, short-chain fatty acids, urine metabolites

Introduction

Hypertension is a major cause of cardiovascular disease and has become a public health problem worldwide. The pathogenesis of hypertension involves multiple factors, including genetics, environment, hormones, and inflammation (1). There is increasing evidence that the gut microbiota plays an essential role in the development and pathogenesis of hypertension (2). The gastrointestinal tract is the largest immune interface with the environment in the human body. An association between hypertension and gut microbiota has been found in human and animal models (3). In hypertensive patients, the α-diversity of gut microbiota was decreased and highly correlated with gram-negative flora, including increased genera *Klebsiella*, *Streptococcus*, *Parabacteria*, *Desulfovibrio*, and *Prevotella* (4), while some short-chain fatty acid-producing bacteria, such as *Faecalibacterium*, *Roseburia spp* will be reduced (5). It was also found that high blood pressure is correlated to gut dysbiosis in spontaneously hypertensive rats (6). Germ-free mice transplanted with fecal bacteria from hypertensive humans developed gut microbiota similar

to their donors and increased systolic and diastolic blood pressure after 8 weeks (2). Together, these studies suggest that hypertensive patients have disturbed gut microbiota and an increase in some of the characteristic genera associated with hypertension.

Changes in gut microbiota can lead to changes in microbial-derived metabolites. Among them, short-chain fatty acids (SCFAs), as the product of bacterial fermentation of dietary fiber, are closely related to health (7). SCFAs are produced and absorbed in the colon and excreted in the feces, so fecal SCFAs reflect levels that cannot be absorbed in the colon (8). Previous research indicated that the efficient absorption of acetate, propionate, and butyrate in the colon decreased the blood pressure in hypertensive experimental animals (9, 10), which was further confirmed by the higher levels of fecal SCFAs in hypertensive patients (11). Therefore, fecal SCFAs can be used as a surrogate index of the absorption of SCFAs in the body.

Numerous studies have used the longevity population to study the relationship between gut microbiota and longevity (12–14). The gut microbiota of centenarians is rich in health-related bacteria such as *Akkermansia*, *Christensenellaceae*, and *Bifidobacterium* (15), which produce high levels of specific secondary bile acids and effectively inhibit gram-positive pathogenic bacteria (16). It has a higher ability of glycolysis and fermentation to generate short-chain fatty acids (17). However, long-lived elderly and their offspring have widespread hypertension (18). Most of them live in remote mountain villages, such as Bama in Guangxi (19), Sardinia (17), rural Korea (20), and Moscow (21), etc., are rarely affected by the modern urbanization environment. Bama, Donglan, and Fengshan are the three most famous longevity populations in Guangxi, and which prevalence of the three counties was 35.6, 31.4, and 28.5 centenarians/100,000 citizens in 2019, respectively (13). In our previous study, 66.7% of the population aged >60 in this longevity area had SBP≥140 mmHg (22). This co-existence of longevity and hypertension is well worth investigating. We hypothesize that these long-lived populations have unique gut microbiota and microbial-derived metabolites that offsets hypertension damage and thus maintain healthy homeostasis.

Based on the above, this study conducts a cross-sectional study of gut microbiota, urine metabolites, SCFAs, and their receptors in longevity areas in Donglan County, Guangxi, through three generations of 16S full-length sequencing, metabolomics, and qPCR, respectively. Analyzing the particularity of gut microbiota composition of long-lived people with hypertension, and combing the corresponding metabolites to explain the relationship between longevity and hypertension, can provide a reference for the prevention and treatment of hypertension.

Materials and methods

Participant recruitment and study groups

This research was approved by the Ethics Committee of Guangxi University (approval number: gxdxyxll05). For the experiment design, 46 subjects from Donglan County, Hechi City, Guangxi, were recruited, and all subjects signed written informed consent. The general conditions of the research subjects were recorded, including their age, gender, height, weight, and blood pressure of the subjects. The age information was verified by comparing the ID card or household registration. Clinical and medical history were collected based on the self-report and physical examination reports (**Supplementary Table 1**). Blood pressure (BP) was measured using a calibrated arm electronic sphygmomanometer (Omron). When measuring blood pressure, subjects were asked to sit still for 5 min with their feet flat on the floor without crossing them, and their upper arms were relaxed and placed on a table at the same level as the heart. Two measurements were taken 1 min apart, and if systolic BP was >15 mm Hg apart or diastolic BP > 10 mm Hg apart, a third measurement was performed and averaged. Inclusion criteria: (i) age ≥ 60 years, and either sex, (ii) body mass index (BMI) 17–25 kg/m^2, (iii) systolic blood pressure (SBP) ≥ 140 mmHg, and not using BP-lowering medication, (iv) from autochthonous families, none was coming from other regions originally. Exclusion criteria: (i) history of chronic medical conditions (diabetes, gastroenteritis, chronic kidney disease, morbid obesity, chronic pancreatitis, or other malabsorption disorder), (ii) use of probiotics, prebiotics, or antimicrobial medication (antibiotic or antifungal treatments) 1 year before sampling. Four participants were excluded due to high BMI, four were excluded due to the SBP lower than 140 mmHg, and five were excluded due to chronic medical conditions. One participant dropped out due to unwillingness to continue (**Supplementary Figure 1**). Following criteria, a total of 32 participants remained: 19 participants aged 60–90 were divided into Hypertension-Elderly (HTE, average 70.5) group, and 13 participants aged 92+ were divided into Hypertension-Longevity (HTL, average 100). The characteristics of the participants are shown in **Table 1**.

Dietary assessment

Participants' dietary and nutritional status was assessed using a semi-quantitative food frequency questionnaire (FFQ), which was recorded for consecutive 7-days at home (23, 24). All participants were asked to adopt the mode of individual dining and were urged to maintain their usual eating patterns at home during the dietary survey. Trained investigators used

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TABLE 1 Demographics and clinical characteristics of participants.

	Hypertension elderly (*N* = 19)	Hypertension longevity (*N* = 13)	Total (*N* = 32)	*p*-value
Sex				
Male	10 (52.6%)	4 (30.8%)	14 (43.8%)	
Female	9 (47.4%)	9 (69.2%)	18 (56.3%)	
Age (years)				<0.001
Mean (SD)	70.5 (8.59)	100 (5.72)	82.6 (12.6)	
Median [min, max]	70.0 [60.0, 88.0]	101 [92.0, 109]	81.5 [60.0, 109]	
BMI				0.323
Mean (SD)	21.7 (2.32)	20.9 (2.26)	21.4 (2.29)	
Median [min, max]	22.0[17.3, 24.8]	21.5 [17.1, 24.2]	21.6 [17.1, 24.8]	
SBP (mmHg)				0.305
Mean (SD)	154 (14.8)	163 (22.6)	157 (18.5)	
Median [min, max]	148 [140, 190]	163 [141, 207]	148 [140, 207]	
DBP (mmHg)				0.223
Mean (SD)	90.1 (9.26)	86.9 (6.70)	88.8 (8.35)	
Median [min, max]	90.0 [69.0, 108]	88.0 [75.0, 98.5]	89.0 [69.0, 108]	
Pulse				0.472
Mean (SD)	75.2 (9.07)	73.7 (8.47)	74.6 (8.72)	
Median [min, max]	74.0 [59.0, 91.0]	71.0 [61.0, 95.5]	73.3 [59.0, 95.5]	

Data are shown as mean (SD) or numbers and percentages. *P*-value from Mann–Whitney. $P < 0.05$ is statistically significant. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

electronic food scales, measuring cups, and spoons to weigh and record each food and drink the participants consumed. For unmeasurable food, the standard portion size was used. Qualified dietitians evaluated and verified the dietary data at a dietary survey location for quality control purposes. Dietary data was converted to nutritional consumption levels according to the 2022 Dietary Guidelines for Chinese Residents. The average daily nutritional intake was determined by multiplying the food consumed (in grams) or the portion size consumed by the nutrient content per 100 g of the food listed in the guideline (25).

16S rRNA third-generation full-length sequencing of gut microbiota

Our study followed guidelines for gut microbiota studies in hypertension (26) and the STORMS (Strengthening the Organization and Reporting of Microbiome Studies) reporting (27) (**Supplementary Table 2**). Fecal samples of the participants were collected by themselves or their family members with an icebox at home in sterilized empty tubes (for SCFA determination) or tubes containing RNAlater (Thermo Scientific) for microbial DNA extraction. Morning urine samples were collected in sterilized empty tubes with an icebox. Tubes were immediately stored in a small car refrigerator (Alpicool, A30) at −20°C for <24 h. Then, the samples were transported to the laboratory by professionals and stored at −80°C after dispensing into 2 mL sterilized EP tubes until analysis. DNA was extracted using the Stool Genomic DNA Extraction Kit (Solarbio) according to the manufacturer's instructions. After extraction, PCR amplification of the full-length region of bacterial 16S rRNA was performed using universal primers 27F (5′-AGRGTTTGATYNTGGCTCAG-3′), 1492R (5′-TASGGHTACCTTGTTASGACTT-3′), and purified with magicpure size selection DNA beads (TANGEN Biotech Corporation Ltd., Beijing, China).

Subsequently, the quality inspection was performed on the formed sequencing library, and processing, including barcode recognition, was performed on the high-quality circular consensus sequencing (CCS) sequence obtained. The generated optimization CCS was clustered at 97% similarity (USEARCH, version 10.0), and its species classification was obtained based on the operational taxonomic unit (OTU) sequence composition. The platforms of 16S: Silva database and RDP Classifier were used to analyze species annotation and taxonomy and gut microbiota diversity. Alpha diversity analysis was performed to examine the species richness and diversity within a single sample, and each

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TABLE 2 The daily average intake of nutrients in the HTE and HTL.

	HTE	HTL	*p*
Nutrients			
Energy(Kcal)	1514.69 ± 215.64	1315.94 ± 218.92	0.011
Protein(g)	61.34 ± 12.22	54.31 ± 11.94	0.099
Fat(g)	36.09 ± 11.25	25.97 ± 10.76	0.008
SFA (g)	9.02 ± 2.80	6.54 ± 2.83	0.013
MUFA (g)	8.24 ± 3.41	5.21 ± 3.43	0.014
PUFA (g)	12.47 ± 4.03	8.84 ± 4.56	0.009
Carbohydrate(g)	114.47 ± 21.08	95.74 ± 17.63	0.016
Dietary Fiber(g)	29.84 ± 5.44	27.09 ± 2.44	0.343
Cholesterol (mg)	105.49 ± 43.22	89.50 ± 39.29	0.170
Vitamin A (μgRE)	847.94 ± 151.54	751.17 ± 97.72	0.071
Thiamine (mg)	0.69 ± 0.11	0.58 ± 0.10	0.010
Riboflavin (mg)	1.07 ± 0.18	0.92 ± 0.17	0.010
Vitamin C (mg)	51.14 ± 12.71	41.51 ± 9.12	0.147
Vitamin E (mg)	9.38 ± 3.73	6.23 ± 3.57	0.020
Vitamin K (μg)	84.72 ± 19.90	82.75 ± 16.81	0.677
Folic acid (μg)	237.43 ± 54.80	190.97 ± 40.69	0.018
Nicotinic acid (mg)	15.85 ± 4.15	14.51 ± 3.58	0.170
Phosphorus (mg)	650.13 ± 127.38	550.49 ± 124.28	0.049
Sodium (mg)	466.55 ± 209.35	360.47 ± 199.06	0.158
Potassium (mg)	2042.27 ± 330.72	1809.42 ± 262.95	0.041
Magnesium (mg)	210.18 ± 36.94	185.43 ± 29.66	0.223
Calcium (mg)	191.36 ± 34.67	159.92 ± 33.93	0.022
Iron (mg)	21.03 ± 33.85	21.45 ± 33.92	0.108
Zinc (mg)	6.35 ± 2.04	5.31 ± 2.16	0.037
Selenium (μg)	16.04 ± 6.99	11.74 ± 7.47	0.099
Manganese (mg)	3.77 ± 1.08	2.91 ± 1.12	0.008
Diversity of food			
Number of different food items consumed by participants, *item/d	12.47 ± 0.77	11.69 ± 1.44	0.170

*Only accounting for food items with >10 g that participants consumed both within and outside of the study. Condiments were not included. SFA, saturated fatty acid; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

sample's ACE, Chao, Shannon, and Simpson indices were calculated. The differences in the community composition and structure of different samples were compared through Beta diversity analysis. Finally, Metastats analysis was carried out to compare the significant differences between the groups at the genus level, and linear discriminant analysis effect size (LEfSe) analysis was used to screen biomarkers that were statistically different between the groups (criteria: LDA score > 3.5). The raw sequencing data generated in this study have been deposited to the NCBI SRA database (BioProject: PRJNA888351).

Fecal short-chain fatty acid measurement

Serum SCFAs were measured in 400 μL, and fecal SCFAs were measured from 0.2 g of fecal sample, all in triplicates. For the fecal sample extraction, 0.2 g of −80°C frozen feces were mixed with 2 mL ultra-pure water in a centrifuge tube. Samples were shaken for 2 min and centrifuged at 12,000 rpm for 20 min (4°C). After centrifugation, 1 mL supernatant was mixed with 0.25 mL of 25% metaphosphoric acid, kept in ice bath at −20°C for 2 h. After thawed, the samples were centrifuged

at 12,000 rpm for 10 min (4°C). The supernatant (1 mL) was mixed with 1 mL ethyl acetate, vortexed and centrifuged for 12,000 rpm for 5 min (4°C) to obtain the clear organic layer, which was aspirated and filtered through an organic green membrane into the cold GC glass vials for analysis. For the serum sample extraction, 400 μL serum was mixed with 50 μL of 25% metaphosphoric acid and kept in ice bath at −20°C for 2 h. Follow steps were similar to fecal extraction and took care to add proportion. The analysis of acetate, propionate, isobutyrate, butyrate, isovalerate, and valerate was performed by gas chromatography-mass spectrometry (Agilent 7890A Series) using a capillary DB-Wax column (30 m, 0.25 μm, 0.25 μm; SGE, Cromlab SL, Barcelona, Spain), coupled with a flame ionization detector (GC-FID). The column temperature was programmed at 80°C, reached 110°C at a rate of 10°C/min, maintained for 1 min, then increased to 160°C at 4°C/min, and maintained 1 min (total run time 17.5 min). Helium was the carrier gas (0.5 mL/min). The injection was carried out with a split injector (1:100) at 220°C, the detector temperature was 250°C, and 1 μL of the solution was injected into the GC-FID system. The SCFAs was identified according to standard compounds' retention time of standard compounds (acetate, propionate, isobutyrate, butyrate, isovalerate, and valerate; Sigma-Aldrich).

Analysis of urine metabolites based on ^{1}H-nuclear magnetic resonance

Aliquots of 500 μL of urine were transferred into a 2.0 mL centrifuge tube and added with 500 μL of 100 mM phosphate buffer containing 0.05% TSP-labeled heavy water (10% heavy water, K_2HPO_4/NaH_2PO_4, PH = 7.4). The mixtures were vortexed and centrifuged (15 min, 12,000 × rpm, 4°C) to obtain the urine supernatant.

^{1}H-NMR analysis

The prepared urine supernatant (550 uL) was placed on the Bruker AVANCE 500 MHZ nuclear magnetic resonance spectrometer of the Prodigy liquid nitrogen cryogenic probe for NMR spectrum detection. The pre-saturation method suppressed the water peak, and the NOESY pulse sequence was used. The specific setting parameters are sampling times NS = 64, temperature 25°C, spectrum width SWH = 10,000 Hz, measurement frequency SF = 500.13 MHz, relaxation delay D1 = 2 s, number of sampling points TD = 65,536, sampling time AQ = 3.277 s, mixing time 0.1 s, O1P = 4.7ppm, FID resolution 0.245.

^{1}H-NMR spectrum processing and data analysis

The Fourier transform of the fecal ^{1}H-NMR spectrum was performed using MestReNova NMR data processing software (Mestrelab Research, Spain), and the phases and baseline were adjusted. The chemical shift of TSP (δ 0.0) was taken as the standard to calibrate the chemical shift. The water peak within the range of δ 4.70–5.00 was excised, and the NMR spectra with δ 0.60–9.00 were segmented with equal width in the unit of 0.01 for segment integration, and the data were normalized. The above data were stored in Excel tables for statistical analysis.

Blood expression of SCFA receptors and transporters

The three main SCFA-sensing receptors GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A (HCAR2) have a role in cardiovascular dysfunction (28). As these receptors are highly expressed in immune cells (29), we quantified the mRNA expression of the 3 receptors in circulating immune cells in 30 participants. Since no blood samples were collected from the participants, we selected 30 samples(15 in HTE and 15 in HTL) from long-lived populations with hypertension characteristics collected earlier (23). The basic information of these samples is presented in **Supplementary Table 3**. Whole blood was treated with Red Blood Cell Lysis Buffer (ThermoFisher Scientific), and RNA was extracted using the Total RNA Extraction Kit (Solarbio). RNA was quantified in a Nanodrop Spectrophotometer, and the first-strand complementary synthesis reaction (cDNA) was made using the BeyoRT^{TM} III First Strand cDNA Synthesis Kit (Beyotime). SYBR Green I was used in a Roche LIGHTCYCLER 96 Real-time quantitative PCR (qPCR) system (Roche Diagnostics Co., Ltd., Basel, Switzerland), with GAPDH as housekeeping genes (**Supplementary Table 4**). All expression experiments were run in duplicates, and significance was assessed by the 2−ΔΔ CT method.

Statistics and analysis

Microbiome data were analyzed as explained above. Graphs were generated using GraphPad Prism version 9.0. Adobe Illustrator version 2020 was used to figure combinations and graphical abstract drawings. All the analyses were performed using SPSS version 26.0 (SPSS Inc., United States) and a 5% significance level. The data were presented as mean ± SD values. The Mann–Whitney U test was used to determine the statistical difference between the two groups gut microbiota, SCFAs, and urine metabolites. A spearman correlation test was conducted to explore correlations between the differential genus and significant microbial pathways and nutrient intake. Pearson correlation analysis was performed to examine correlations between blood pressure and levels of SCFAs, and urine metabolites, after adjustment for age and BMI. Further analyses were conducted using simple linear regression models for BP, acetate, butyrate, and propionate.

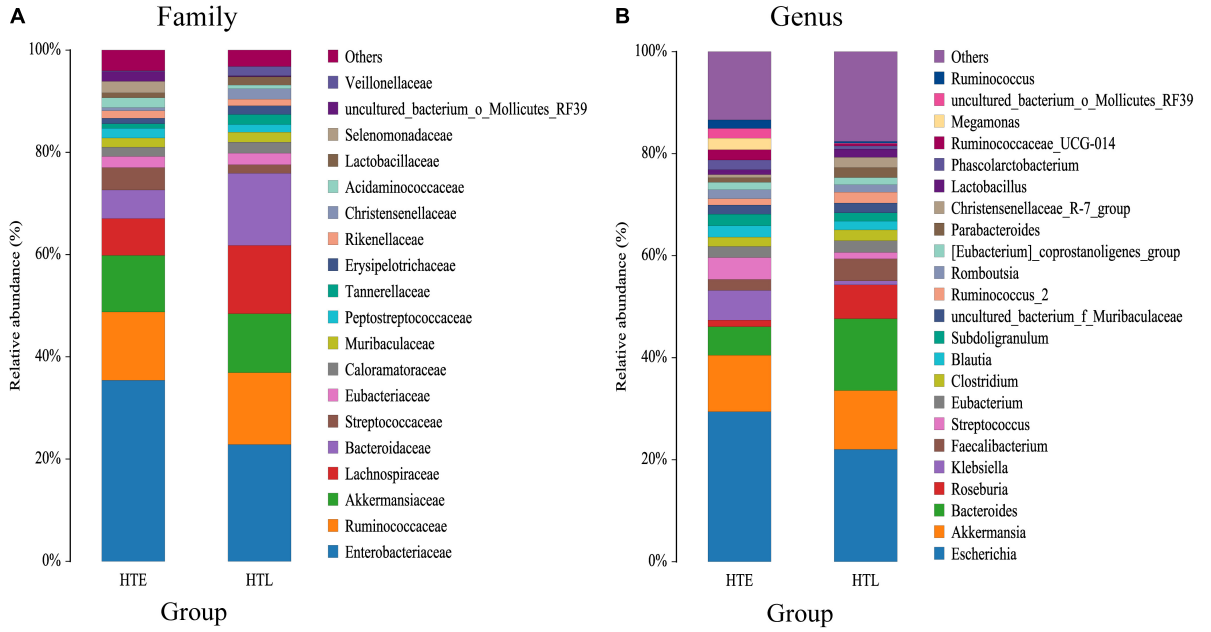

FIGURE 1
Bar chart of the relative abundance (%) gut microbiota profiles. The taxa with average relative abundance above 1% are displayed at the family **(A)**, and genus **(B)** levels.

Results

Nutrient intake in subjects

The nutrient intake levels in the two groups are presented in Table 2. The two groups had significantly different nutrient intake levels. Notably, the level of energy, fat, saturated fatty acid (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), carbohydrate, thiamine, riboflavin, vitamin E, folic acid, phosphorus, potassium, calcium, zinc, and manganese were significantly lower in subjects in the HTL compared with the group HTE ($p < 0.05$). Furthermore, the intake of protein, dietary fiber, cholesterol, vitamin C, vitamin K, nicotinic acid, phosphorus, sodium, magnesium, iron, and selenium were at the same level between the groups. In addition, there were no significant differences in the number of food items consumed by participants, probably due to the similar dietary habits of the participants in the longevity areas. The spearman correlation was used to calculate the relationship between genus and nutrient intake (Supplementary Figure 2). The genus of *Faecalibacterium* was positively correlated with sodium, whereas the genus of *Subdoligranulum* was positively correlated with energy, fat, SFA, PUFA, vitamin A, thiamine, riboflavin, vitamin E, phosphorus, magnesium, calcium, iron, and zinc. *Clostridium* was negatively correlated with vitamin A, iron, and zinc. *Christensenellaceae_R7_group* had a negative correlation with vitamin C.

Analysis of gut microbiota characteristics between group

Through high-throughput sequencing and sequence screening, 400,724 CCS sequences were obtained through the Barcode identification of 32 samples after sequencing. Each sample generated at least 10,254 CCS sequences, with an average of 12,523 CCS sequences. Operational taxonomic units (OTUs) were divided according to 97% sequence similarity, and a total of 360 OTUs were obtained for subsequent analysis. Through the Shannon curve and the rank abund curve, it was found that the number of OTUs in all samples increased with the increase in sequencing amount and eventually plateaued, indicating that the sequencing volume is sufficient to achieve the ideal sequencing depth (Supplementary Figure 3). The shared and unique OTUs within and between groups were analyzed and plotted as Venn diagrams. HTL had six shared OTU features, HTE had three shared OTU features, and 306 shared OTU features between the two groups (Supplementary Figure 4). Alpha diversity was assessed by five parameters and showed no significant difference between HTE and HTL (Supplementary Table 5).

A total of 11 phylum were dominated by *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Verrucomicrobiota*, which accounted for 97.32% (HTE) and 99.01% (HTL), respectively. The ratio of *Firmicutes* to *Bacteroidetes*(F/B) of HTL (2.14) was significantly lower than HTE (3.71). Figure 1 shows species with relative abundances greater than 1% at the family and

TABLE 3 The significant difference genus and species between HTE and HTL.

Taxa	Median, range[1] (%)		*p*-value
	HTE	HTL	
Genus			
Bacteroides	5.57, 0.57–10.57	8.06, 4.61–22.73	0.033
Klebsiella	3.73, 0.55–8.53	0.31, 0.03–1.57	0.005
Streptococcus	0.67, 0.23–5.45	0.28, 0.02–0.66	0.059
Faecalibacterim	1.02, 0.03–2.55	2.91, 0.20–7.49	0.03
Parabacteroides	0.18, 0.02–0.42	0.40, 0.16–3.04	0.037
Ruminococcus	0.64, 0.18–2.63	0.13, 0.06–0.45	0.018
Alistipes	0.11, 0.04–0.38	0.88, 0.39–2.078	<0.001
Erysipelotrichaceae_UCG-003	0.02, 0.00–0.34	0.33, 0.03–1.22	0.041
Species			
Klebsiella pneumoniae	3.73, 0.55–8.53	0.31, 0.03–1.57	0.005
Faecalibacterium prausnitzii	1.02, 0.03–2.55	2.91, 0.20–7.49	0.03
Streptococcus salivarius	0.24, 0.11–1.05	0.01, 0.00–0.33	0.007
Clostridium perfringens	0.05, 0.01–0.15	0.00, 0.00–0.04	0.049
g_Erysipelotrichaceae_UCG-003	0.02, 0.00–0.34	0.33, 0.03–1.22	0.041
Bacteroides massiliensis	0.00, 0.00–0.09	0.37, 0.02–0.73	0.02
Bacteroides caccae	0.01, 0.00–0.03	0.42, 0.06–0.79	0.008
Alistipes putredinis	0.03, 0.00–0.22	0.31, 0.04–1.16	0.022
Alistipes finegoldii	0.00, 0.00–0.04	0.20, 0.09–0.83	<0.001
Parabacteroides_sp	0.04, 0.00–0.16	0.22, 0.07–0.70	0.018
Lactobacillus mucosae	0.01, 0.00–0.04	0.00, 0.00–0.00	0.049

[1]Range represents the up quartile and the lower quartile.

genus levels. Both groups were dominated by five families, *Enterobacteriaceae*, *Ruminococcaceae*, *Akkermansiaceae*, *Bacteroidaceae*, and *Lachnospiraceae*, with cumulative abundances of 72.61% (HTE) and 75.90% (HTL), respectively. Compared with HTL, the HTE group had much higher levels of the hypertension-related bacteria genera *Klebsiella* and *Streptococcus* (+655% and +242%), while it had lower levels of SCFA-producing bacteria *Bacteroides* (−60%), *Roseburia* (−80%), *Faecalibacterium* (−50%), and *Alistipes* (−79%), respectively. Table 3 further presents the significant difference between the groups in taxa at the genus and species level. The above results showed that the HTE experienced gut dysbiosis, while HTL were abundant in SCFA-producing bacteria. These results are consistent with the commonly reported hypertensive gut genera in addition to identifying two new health-associated bacterial genera (**Supplementary Table 6**).

The LEfSe method was used to analyze and screen out the biomarker with an LDA score > 3.5. A total of 23 differential species were found between the two groups, *Klebsiella pneumoniae*, *Lactobacillus gasseri*, *Streptococcus salivarius*, *Ruminococcus*, *Actinomyces*, *Rikenellaceae*, *f_Saccharimonadaceae*, *Clostridium perfringens* in the HTE and *Bacteroids, Faecalibacterium prausnitzii*, *Parabacteroides*, *Alistipes* in the HTL group, respectively (**Figure 2**).

Hypertension-related microbial pathways

PICRUSTs2 was performed to predict the functional prediction of KEGG microbial pathways in gut microbiota, and a total of 248 Class3 microbial pathways were obtained. The biosynthesis of secondary metabolites, biosynthesis of antibiotics, microbial metabolism in diverse environments, and biosynthesis of amino acids were significantly enriched in both HTE and HTL groups. There were 114 Class3 microbial pathways with relative abundance greater than 0.1% and 16 microbial pathways were significantly different between HTE and HTL groups, including ABC transporters, alanine, aspartate and glutamate metabolism, arginine biosynthesis, benzoate degradation, degradation of aromatic compounds, GABAergic synapse, glycosaminoglycan metabolism, inositol

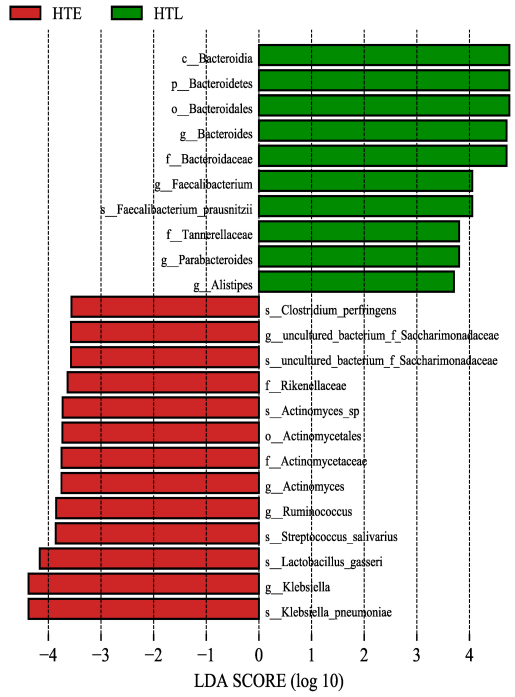

FIGURE 2
The gut microbiome taxa linear discriminant analysis effect sizes. Predicted gut microbiome taxa that are different between hypertension elderly and hypertension longevity, with a linear discriminant analysis (LDA) score of least 3.5.

phosphate metabolism, lysosome, other glycan degradation, phosphotransferase system (PTS), propanoate degradation, quorum sensing, selenocompound metabolism, sphingolipid metabolism, and tyrosine metabolism (**Supplementary Table 7**). The correlations between the top 20 species and 16 significant microbial pathways were further analyzed by Spearman correlation (**Figure 3**). Interestingly, the association of the hypertensive marker species *Klebsiella pneumoniae* with microbial pathways was consistent with *Escherichia coli*, but the correlation was reversed for *Akkermansia muciniphila*.

Fecal short-chain fatty acid levels

Six short-chain fatty acids (SCFAs) in fecal samples, namely acetate, propionate, isobutyrate, butyrate, isovalerate, and valerate, were qualitatively detected by GC-MS. Acetate ($p = 0.008$) and propionate ($p = 0.033$) were significantly lower in HTL feces than in HTE (**Figures 4A, C**). Correlation analysis showed that there was no correlation between SBP and SCFAs, but DBP was negatively correlated with acetate ($r = -0.368$, $p = 0.045$) and propionate ($r = -0.387$, $p = 0.035$) (**Figures 4B, D**). There were significant correlations between SCFAs, and acetate was significantly positively correlated with propionate ($r = 0.708$, $p = 0.000$), butyrate ($r = 0.545$, $p = 0.002$), and valerate ($r = 0.453$, $p = 0.012$) (correlation results after adjusted for age and BMI).

Statistical analysis of urine metabolites

Through urine ^{1}H-NMR metabolomic analysis, 36 metabolites were identified (**Supplementary Figure 5**). Compared with HTE, urine acetate ($p < 0.001$), pyruvate ($p = 0.022$), alanine ($p = 0.014$), and acetoacetate ($p = 0.010$) were significantly higher in HTL, while creatinine was significantly lower ($p = 0.041$) (**Figure 5**). **Supplementary Table 8** shows the urine metabolites significantly associated with SBP and DBP. In particular, N-acetyl glycoprotein was negatively correlated with both SBP and DBP (correlation results were adjusted by age and BMI).

SCFAs and receptors

To further explore the relationship between SCFAs and hypertension, we then directly measured the levels of serum SCFAs and plasma SCFAs receptors. Since no blood samples were collected from the participants, 30 samples (15 in HTE and 15 in HTL) from long-lived populations with hypertension characteristics collected earlier were selected (23). Hypertension long-lived elderly had higher serum acetate levels than hypertension elderly ($p = 0.011$) (**Figure 6A**). There were no significant differences between the groups' levels of serum propionate, butyrate (**Figures 6B, C**), isobutyrate, valerate, and isovalerate. We then quantified the mRNA levels of SCFA-sensing receptors, GPR41, GPR43, and GPR109A, in white blood cells from these samples. There were no changes in the expression of GPR41, GPR43, and GPR019A (**Figures 6D–F**).

Discussion

This study is the first cross-sectional study to explore the phenomenon of hypertension in long-lived populations. Microbiome and metabolomic techniques were conducted to characterize the gut microbiota, urine metabolites, and SCFAs of longevity populations with hypertension. The HTE group experienced gut dysbiosis, similar to those reported in hypertensive patients (2, 28), such as higher levels of *Klebsiella* and *Streptococcus*, but not in the HTL group. The HTL group had higher *Bacteroides*, *Faecalibacterium*, and *Alistipes*, which may protect the long-lived elderly against hypertension-induced damage. In addition, the microbial pathways associated with *K. pneumoniae* and *E. coli* may promote hypertension, while

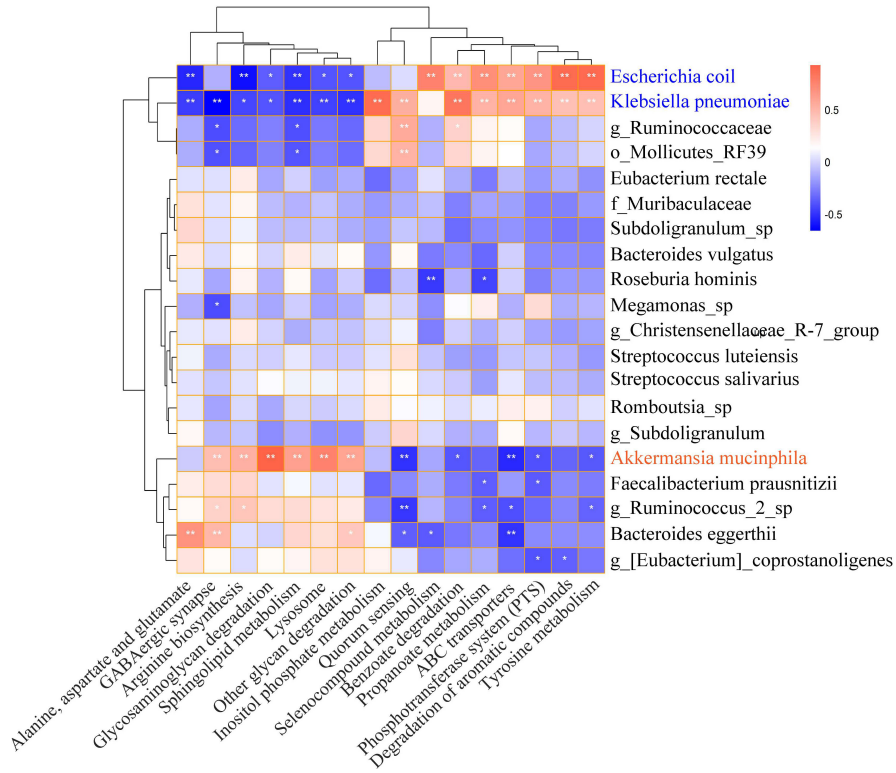

FIGURE 3
Heat map of Spearman correlation between significantly microbial pathways and top 20 abundance species. The *X*-axis indicates the significantly different microbial pathways, and the *Y*-axis indicates the top 20 levels of species. Red represents positive correlation, and blue represents negative correlation. The stronger the color, the closer the number is to the Spearman correlation value of 1 or −1, *indicates significant correlation, $*p < 0.05$, $**p < 0.01$.

A. muciniphila may play a role in reversing the development of hypertension in long-lived elderly. Fecal SCFAs levels showed that fecal acetate and propionate in the HTL group were significantly lower, while urine acetate was significantly higher than in the HTE group. Furthermore, HTL exhibited higher serum acetate, but their immune cells expressed no significant changes in SCFAs receptors. In conclusion, our study revealed that hypertension elderly experienced gut dysbiosis, while hypertension long-lived elderly had a unique microbiome and efficient acetate absorption capability in the colon, which can offset the damage of hypertension and maintain healthy homeostasis.

Compared to HTL, the HTE group had significantly higher levels of F/B, and more hypertension-related genera increased in the HTE group, such as *Klebsiella* and *Streptococcus*. F/B has been used to assess the stability of gut microbiota. A higher value indicates a more disordered intestinal flora and a greater the possibility of hypertension. These conclusions have been verified in hypertensive patients (30) and spontaneously hypertensive rats (6). From the characteristics of gut microbiota, compared with the control population, hypertensive patients always have a higher abundance of *Klebsiella*, *Clostridium*, *Streptococcus*, *Porphyromonas*, and *Actinomyces*, and a lower abundance of *Bacteroides*, *Faecalibacterium*, *Roseburia* than the control population (2). In this study, the disturbance of gut microbiota in the HTE group was similar to the previous report, but the HTL group was quite different. The HTL group had higher *Bacteroides*, *Faecalibacterium*, and *Alistipes* than the HTE group. *Bacteroides* and *Alistipes* are important acetate and propionate producing bacteria (31), and *Faecalibacterium* are important butyrate-producing bacteria (32), which are biomarkers to distinguish hypertensive patients in the average population (11). These genera are essential for maintaining health, suggesting that the HTL group has a health-relevant gut microbiome profile.

The search for biomarkers with significant differences between groups (**Figure 3**) has implications for exploring the phenomenon of hypertension in long-lived people and can explore the relationship between gut microbiota and hypertension at the species level. *Bacteroides*, *F. prausnitzii*, *Parabacteroides*, and *Alistipes* were enriched in HTL. *F.prausnitzii* can produce butyrate, which affects blood pressure through vasodilation or plasminogen activator inhibitor-1 (33). *Alistipes* are a producer of acetate and propionate and

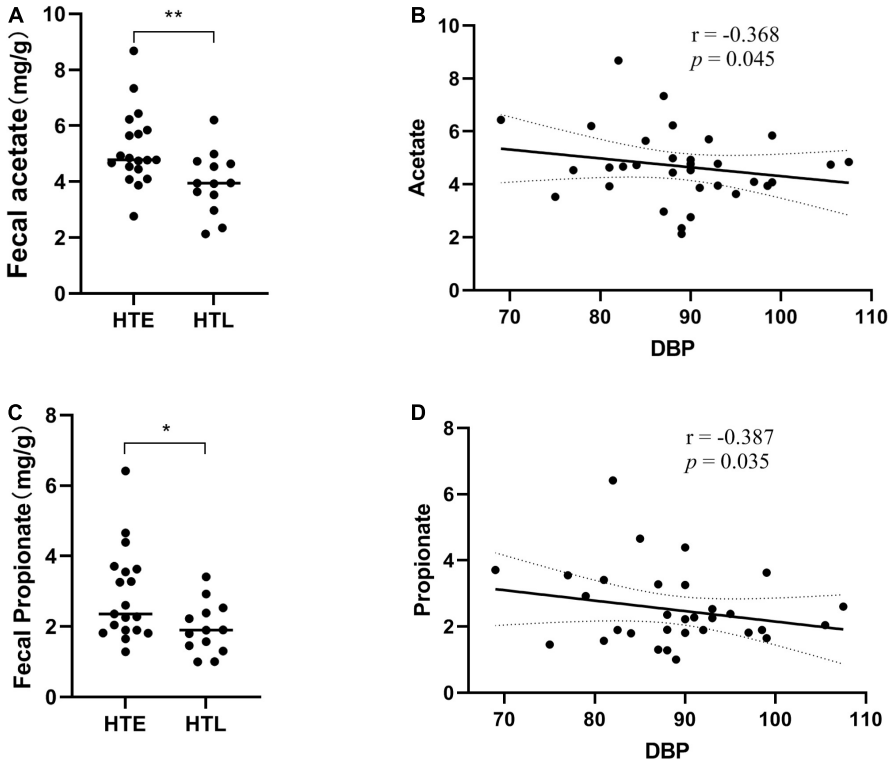

FIGURE 4
Fecal levels of gut microbial metabolites short-chain fatty acids (SCFAs) in association with hypertension. **(A)** Acetate, **(B)** the correlation analysis between acetate and diastolic blood pressure (DBP), **(C)** propionate, **(D)** the correlation analysis between propionate and diastolic blood pressure (DBP). Sample size: n = 19 hypertension elderly and 13 hypertension longevity. *Indicates $p < 0.05$, **$p < 0.01$.

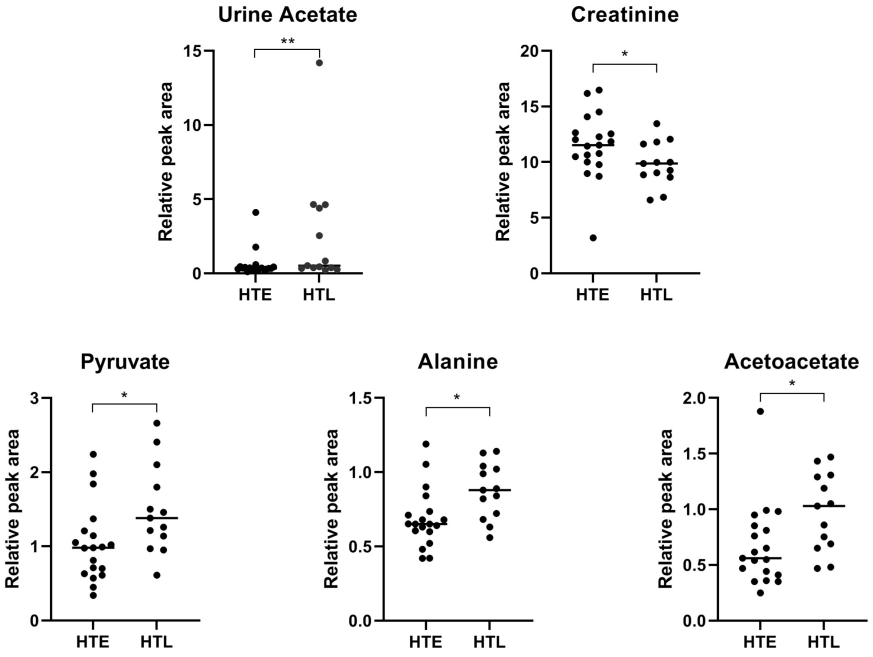

FIGURE 5
Urine metabolites with significant differences between groups. Sample size: n = 19 hypertension elderly and 13 hypertension longevity. *Indicates $p < 0.05$. **$P < 0.01$.

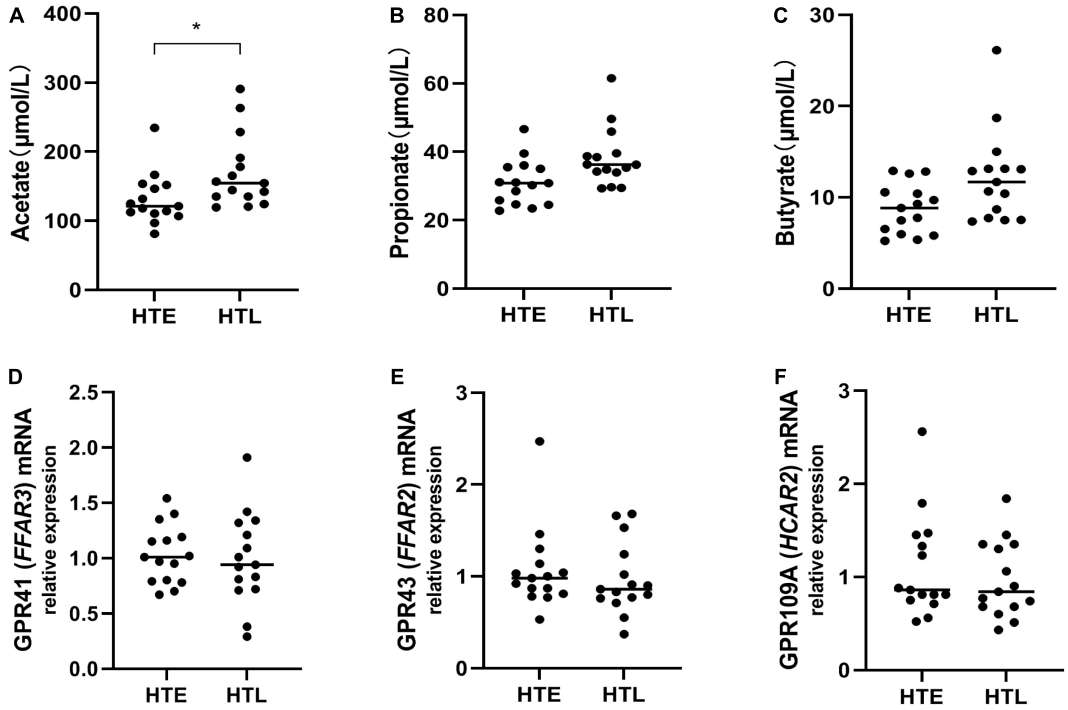

FIGURE 6
Plasma levels of short-chain fatty acids (SCFAs) and relative expression of short-chain fatty acids (SCFAs)-sensing receptors. **(A)** Acetate, **(B)** propionate, **(C)** butyrate, the mRNA expression in white blood cells between groups, while there are no change in GPR41 **(D)**, GPR43 **(E)**, and GPR109A **(F)**. Sample size: n = 15 hypertension elderly and 15 hypertension longevity. *Indicates $p < 0.05$.

play a protective role in cardiovascular diseases (34). *Alistipes finegoldii* belonging to the genus *Alistipes* is a species that protects the integrity of the intestinal barrier against colitis (35), which contributes to the absorption of energy substances in the colon. Compared to the HEL group, the HTE had higher levels of *Klebsiella pneumoniae*, and *Streptococcus salivarius*, a further extension of the genus-level species (*Klebsiella* and *Streptococcus*) reported in previous studies (4). The severity of hypertension was associated with an increased abundance of these two species (36). The enrichment of *K. pneumoniae* directly contributes to blood pressure elevation and hypertension pathogenesis, and it causes intestinal damage, fecal metabolic changes, and renal shifts may be integrated mediators (23).

The correlation analysis showed that *Klebsiella pneumoniae* and *Escherichia coli* might be associated with the microbial pathways of hypertension, while *Akkermansia muciniphila* was the opposite. As we know, *E. coli* is an opportunistic pathogen, the most abundant intestinal flora in the longevity population in this study, which was reported to be associated with the development of hypertension during follow-up (37). Moreover, both *E. coli* and *K. pneumoniae* have been reported to be significantly enriched in carotid atherosclerosis and hypertension patients, which generated lipopolysaccharide (LPS) (38) and Trimethylamine (TMA) (39). LPS can be transferred to the bloodstream when the intestinal barrier function is impaired, causing asymptomatic hypoendotoxemia (40). TMA is converted by liver enzymes to TMAO, which causes cardiovascular damage (41) and exacerbates angiotensin II-induced hypertension (42). Based on these findings, we inferred that *E. coli* and *K. pneumoniae* have similar microbial pathways and may be involved in the development of hypertension. On the contrary, the abundance of *A. muciniphila* is negatively associated with obesity, type 2 diabetes, and hypertension (43, 44). Therefore, as a new generation of probiotics, the microbial pathway of *A.muciniphila* is significantly different from that of *K. pneumoniae* and *E. coli.* It may play a role in reversing the development of hypertension, and its specific mechanism needs further exploration.

Besides gut microbiota, the changes in SCFAs were also correlated to blood pressure (45). The concentrations of fecal acetate and propionate in the HTL group were significantly lower, while urine acetate was significantly higher than HTE. Furthermore, HTL exhibited higher serum acetate, but their immune cells expressed no significant changes in SCFAs receptors. A common explanation is that the lower fecal SCFAs in the long-lived elderly may be due to the reduction of SCFA-producing bacteria and the decreased metabolic activity of the gut microbiota (46). However, the relative abundance of SCFA-producing bacteria such as *Bacteroides*, *Faecalibacterium*, and

Alistipes was higher in HTL than in HTE, and there was no significant difference in dietary fiber intake between the two groups, so it would not be lower from the perspective of SCFAs production. Everything gets interesting when explained in terms of SCFA uptake levels. SCFAs are efficiently absorbed in the colon, and less than 5% are excreted in the feces. Fecal SCFAs reflect SCFAs that cannot be absorbed in the host colon (3) and are surrogate indicators of colonic SCFAs absorption. Fecal SCFAs concentrations are more representative of SCFAs uptake than their production (8). Fecal SCFAs are significantly increased, and serum SCFAs are significantly decreased in hypertensive patients, indicating that the adequate absorption level of SCFAs in hypertensive patients is lower (11). Higher levels of fecal SCFAs are associated with gut dysbiosis, obesity, and hypertension, presumably due to the lower absorption rate of SCFAs in the gut (47). In contrast, participants with lower blood pressure had lower levels of fecal SCFAs and higher levels of SCFA-producing bacteria, which may promote intestinal absorption of SCFAs (5). Above all, these SCFA-producing bacteria have two functions: they produce SCFAs and promote the absorption of SCFAs in the human intestine, with their activity contributing to the maintenance of low levels of fecal SCFAs and higher levels of blood SCFAs and even urine of the host.

More importantly, we noticed that the acetate level in the HTL group was lower in the fecal and higher in the blood and urine compared to the HTE group. It is important to note that most SCFAs are consumed in the gastrointestinal tract and liver. The remaining SCFAs (mainly acetate) can be transported to other organs *via* the bloodstream to regulate the host's metabolism, physiology and energy balance (48). Acetate and propionate both enter the portal venous circulation and peripheral blood, but they play different roles. The propionate is mainly used for glycoisogenesis in the liver, which is then metabolized to CO_2 through the tricarboxylic acid cycle and other metabolic pathways. In contrast, acetate enters the systemic circulation and reaches peripheral tissues, which activates signaling *via* binding to 3 G-protein–coupled receptors, with GPR43 being the most predominant of these receptors (9). These receptors are highly expressed in immune cells, including T, B, and innate lymphoid cells, and activate anti-inflammatory downstream pathways to decrease blood pressure (49). The high absorption of acetate in the colon and more urine excretion of the HTL group supports the hypothesis that the HTL group have unique gut microbiota and efficient acetate absorption capacity, which can offset hypertension damage and thus maintain healthy homeostasis.

Although this research used a relatively small sample size and did not include a healthy control group, our study took advantage of the only longevity and hypertension cohort published to date with well-characterized BP monitoring in both men and women, all untreated for BP-lowering medication. This study is also the only cohort with detailed information regarding diet, urine metabolites, plasma, fecal SCFAs, and their receptors, which allowed us to explore the interplay between the gut microbiome, diet, urine metabolites, SCFAs, and their receptors regard to longevity. Future studies should expand the sample size and use ambulatory BP monitoring to minimize intra-individual variation in samples. Meanwhile, due to the limitation of 16S rRNA sequencing, future studies will use metagenome to uncover the species that play a crucial role in the association between longevity and hypertension.

Conclusion

In conclusion, we found that people in longevity areas of Guangxi, China, generally with hypertension. Hypertension elderly had much higher levels of hypertension-related bacteria *Klebsiella* and *Streptococcus*, while hypertension long-lived elderly had higher levels of short-chain fatty acid-producing bacteria (*Bacteroides*, *Faecalibacterium*, *Alistipes*). Moreover, *K. pneumoniae* and *E. coli* may play a role in promoting hypertension, while *A. muciniphila* may play a role in reversing the development of hypertension. SCFAs further suggest that acetate can be effectively absorbed in the colon of long-lived elderly with hypertension to offset the negative effects of hypertension. An important mechanism may be driven by SCFA-producing bacteria and their main metabolite, acetate, associated with hypertension longevity. The enrichment of SCFA-producing bacteria, such as *Bacteroides spp*, *Faecalibacterium spp*, and *Alistipes spp* may promote efficient acetate absorption in the colon and represent a new target for BP therapy in the future.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://www.ncbi.nlm.nih.gov/bioproject/PRJNA888351.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee, Guangxi University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QL, ZQ, and QZ conceived and designed the experiments. QZ, NM, YL, HZ, RL, KH, HL, XY, and JM contributed sample collection, investigation, and data analysis. QZ wrote the original draft. QL, DH, ZZ, YL, and ZQ contributed to review and edit. QL, ZQ, and YL contributed to final approval of the publication. QL, ZQ, YL, and QZ are accountable for all the aspects of the work. All authors have read and agreed to the published version of the manuscript.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1070223/full#supplementary-material

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Older adults and healthcare professionals have limited awareness of the link between the Mediterranean diet and the gut microbiome for healthy aging

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Objectives: Strategies to improve the gut microbiome through consuming an improved diet, including adopting the Mediterranean Diet (MD), may promote healthy aging. We explored older adults' and healthcare professionals' (HCPs) perspectives of the MD, gut health, and microbiome for their role in healthy aging.

Design: Phenomenological qualitative.

Setting: Community-dwelling older adults and HCPs in primary and secondary care in Ireland.

Participants: Older adults (aged 55 + years), recruited through social, retirement and disease-support groups. HCPs recruited through researcher networks and professional associations.

Measurements: Semi-structured 1:1 interviews and focus groups (FGs) conducted remotely with older adults and HCPs separately. Interviews/FGs were recorded, transcribed, and coded using inductive thematic analysis.

Results: Forty-seven older adults were recruited (50% male; 49% aged 60–69 years; 28% 70 +), and 26 HCPs including dietitians (*n* = 8); geriatricians (*n* = 6); clinical therapists (*n* = 4); nurses, pharmacists, catering managers, and meal-delivery service coordinators (*n* = 2 each). Older adults considered the MD *"a nice way to enjoy food,"* good for cardiovascular health and longevity, but with accessibility and acceptability challenges (increased salads/fish, different food environments, socio-cultural differences). HCPs felt the MD is included in healthy eating advice, but not overtly, mostly through the promotion of mixed-fiber intake. Older adults considered "live" yogurt and probiotics, and to a lesser extent fiber, to maintain a "healthy gut," suggesting the gut has *"something to do with"* cognitive and digestive health. Overall, microbiota-health effects were considered *"not common knowledge"* among most older adults, but becoming more topical among both professionals and the public with advancing scientific communication.

Conclusion: While "gut health" was considered important, specific effects of the MD on gut microbiota, and the significance of this for healthy aging, was under-recognized. Future efforts should explain the importance to older adults of maintaining the gut microbiota through diet, while appreciating perspectives of probiotic products and supplements.

KEYWORDS

gut microbiota, Mediterranean diet, healthcare professionals, older adults, healthy aging, aging, microbiome, science communication

1. Introduction

Nutrition and diet play a key role in promoting health and contributing to a healthy aging process (1, 2). In particular, the Mediterranean Diet (MD) is suggested as a dietary strategy for addressing multiple age-related issues such as frailty and neurodegenerative decline (3, 4). The MD involves a varied wholefood diet, with higher consumption of fiber through fruits, vegetables and legumes, as well as unsaturated fats through nuts, olive oil and fish, and less red meat and dairy (5). Adopting the MD may facilitate healthy aging by promoting a favorable gut microbiota profile, modulating the gut-brain axis and preventing age-related decline (2, 6, 7).

Recently, the NU-AGE dietary trial specifically showed that the MD contributed to optimal gut microbiota, better global cognitive ability and episodic memory, reduced bone loss, and improved immune function and blood pressure among a cohort of older adults from five countries (8). Diet alters gut microbiota in a way which impacts upon the rate of health decline in older age (9, 10), mediating the gut-microbiota and immune system interplay (11). Consequently, the potential translation of these findings to health advice is advancing to actionable recommendations. For example, a personalized diet has been proposed for people with neurodegenerative disease to positively influence microbiota signatures (12). Furthermore, with changes in gut microbiota potentially influencing serotoninergic function in older age (13), the therapeutic potential for improving mental health *via* gut microbiota modulation has also gathered much attention (14, 15).

Despite potential for improved health through optimized gut microbiota, there are barriers to incorporating the MD in Northern Europe, including the perceived difficulty of adopting the diet while living in a colder climate, cultural differences, demand for convenience, or overall acceptability (16–18). There are differences in the foods typically consumed as part of the MD and Irish diet, as has been described previously (17). For instance, the current Irish diet is relatively low in fruit, vegetables, fish and nuts/seeds, with olive oil used in very small amounts, but relatively high intake of red meat, poultry, dairy, processed grains, and confectionary (19). Barriers to promoting maintenance of gut microbiota may also exist. One study of consumer receptivity to clinical microbiota interventions in a Middle-Eastern population found that the role of the gut microbiota in health, particularly the gut–brain axis, was poorly understood in both scientific and public communities (20). Experts have previously noted the need for clinical intervention studies which prove the role of microbiota as a key aspect in health in order for adapted medical and public health education (21).

To our knowledge, no study has been carried out in an Irish population of current awareness and perspectives of the MD and gut microbiota in the context of healthy aging. We thus explored older adults (55 + years of age) and healthcare professionals' (HCPs) perspectives of the MD and gut microbiota for their role in healthy aging, using qualitative methods. This enquiry forms part of a wider project which aims to develop a novel food product by harnessing key nutrients of the MD to promote optimal gut microbiota in older age. Exploring stakeholder perceptions through qualitative enquiry can frame the context for implementing targeted dietary intervention through functional food products, as well as wider promotion of healthy eating strategies within a Western European cohort.

2. Materials and methods

This study followed a phenomenological qualitative design and is reported in adherence to COREQ guidelines (22) (**Supplementary material**). A phenomenological approach was considered appropriate by the researchers to yield an in-depth exploration of older adults' and HCPs' lived experience and perception of the MD and gut microbiota in relation to healthy aging (23). Consideration was also given to different qualitative health research methodologies used in nutrition research, with the principles of qualitative description closely aligned to the chosen research methods (24). Full ethical approval has been granted (SREC 2021-079).

2.1. Recruitment and data collection

Adults aged 55 + years ("55 + adults") were recruited through social, community and retirement groups, and disease-specific support groups. The researcher (LoM; female research assistant trained in qualitative methods) contacted organizations, requesting to share study information with members as appropriate (email, newsletters, social-media, word-of-mouth). Interested participants were invited to contact the researcher. Purposive sampling included a gender balance and range of ages, and inclusion of people with relevant diseases (stroke, arthritis, etc.). HCPs/stakeholders were recruited through researcher networks and relevant national professional associations. There were no sampling criteria for HCPs/stakeholders. Recruitment continued until data saturation was reached.

Interviews and focus-groups were conducted with 55 + adults and HCPs in Ireland from July 2021 to January 2022. Two semi-structured schedules were developed by the research team, for 55 + adults

(Supplementary File 1) and for HCPs/stakeholders (Supplementary File 2). Three pilot interviews were conducted with 55 + adults and the schedule was refined accordingly. LoM attended a Public Patient Involvement (PPI) meeting with an age advocacy and activity organization (Age and Opportunity) to explore perspectives during recruitment and data collection (e.g., saying "food" rather than "diet" to avoid confusion with a restrictive or prescribed diet). The schedule for HCPs/stakeholders was used flexibly to suit professional roles. Participants chose a one-off 1:1 interview or focus-group to accommodate personal preferences and time commitments. Written consent, informed by a participant information leaflet, was obtained. Interviews/focus-groups were conducted remotely using Microsoft Teams® and recorded using the software's inbuilt function, or by telephone and audio-recorded using the research laptop. Recordings were assigned numerical codes and erased following transcription. Anonymized transcripts were used for analysis. LoM conducted all interviews/focus-groups and transcribed 80% of data, with assistance from the research team. LoM had no prior relationship with study participants, who understood her as the study's research assistant. Field notes were taken; data not transcribed by LoM were read through before coding to ensure data familiarization.

2.2. Data analysis

Inductive thematic analysis was used (25), supported by NVivo 12. LoM coded an initial subset (15%; 6/41) of transcripts using a data-driven approach before applying these codes to remaining transcripts, with additions/revisions as required. Four transcripts were reviewed by a second coder (EoS; female senior researcher), to ensure quality and consistency. Throughout the coding process, a list of themes and sub-themes was derived, adapted, and refined. For demographic data, valid percentages are reported.

3. Results

A total of 47 adults aged 55 + and 26 HCPs took part. This included 25 interviews (17 adults aged 55 +, and 8 HCPs), along with 16 focus-groups, each with 2–5 participants (30 adults and 18 HCPs took part this way). Interviews/focus-groups lasted, on average, 45?min with 55 + adults and 43 min with HCPs. Six focus-groups with 55 + adults proceeded with only two participants due to the other planned participants' unexpected non-attendance.

Participant demographics are outlined in Table 1. Most 55 + adults were aged 60–69 years (n = 23; 48.9%), with four aged 80 + years, and equal numbers of males (n = 23) and females (n = 23). One person identified as non-binary. Most were recruited *via* social/community or retirement groups (n = 33), and several through disease support groups e.g., stroke, Parkinson's disease, and arthritis (n = 11). Three were recruited from an organization within the Traveling community, a particularly hard-to-reach ethnic group (26). There were more female (n = 21; 81%) HCPs than males (n = 5; 19%), with occupations described below.

Nine key themes were identified in the data which could be organized into three domains, an overview of which is described below (Figure 1). Participant quotations are presented to illustrate thematic findings, attributed to the 55 + adults (abbreviated as OA) and HCPs (disciplines included). An overview of quotations can be found in Supplementary File 3.

3.1. Perception of the Mediterranean diet

3.1.1. Foods considered to form part of the MD

Most 55 + adults understood foods included in the MD, though there were some areas of uncertainty. HCPs did not specifically discuss older adults' understanding of the MD composition but suggested it may depend on whether the person had traveled to Mediterranean countries, and that the MD "*is not what they're (older person) used to*" (see subtheme "Acceptability: Socio-cultural and habitual differences of the MD"). Indeed, many 55 + adults associated the MD with foods eaten in Mediterranean countries, including fresh salads, olive oil and fish, and noted the visual attraction of colorful and seasonal fruit and vegetables, speaking favorably of home-growing and local production. However, some felt that the MD was "*vague,*" and were uncertain that all perceived components could be regarded as beneficial to health. Some considered pasta, pizza, breads and wine may also be consumed in the MD; *"I wouldn't think it includes all the red wine and sugars. . . even pastas. . . a clear definition of the MD is hard to get. . . Is it just vegetables?. . . and lots of oil?" (OA#30).*

While some were aware there might be "*limited amounts of meat*" and more fish or plant-based dishes, few discussed reduced red meat or dairy as a feature of the MD. Some were concerned about achieving sufficient protein intake if not eating meat regularly, or believed meat was needed for sustenance. Some commented on the inclusion of nuts, beans, legumes, and wholegrains while others did not; "*I suppose*

TABLE 1 Demographic characteristics of study participants (N = 73).

		N (%)
Participant type	Older adult (55 + adults)	47 (64.4)
	Healthcare professional	26 (35.6)
Age (55 + adults)	<60	11 (23.4)
	60–69	23 (48.9)
	70–79	9 (19.1)
	80 +	4 (8.6)
Employment status (55 + adults)	Retired	28 (59.6)
	In employment or self employed	19 (40.4)
Residential province (All participants)	Connacht	5 (7.0)
	Leinster	35 (49.3)
	Munster	30 (42.3)
	Ulster	1 (1.4)
HCP occupation	Dietitian	8 (30.7)
	Geriatrician	6 (23.1)
	Clinical therapist*	4 (15.4)
	Pharmacist	2 (7.7)
	Clinical nurse (one manager; one nurse specialist)	2 (7.7)
	Catering manager (one community-based; one residential)	2 (7.7)
	Meal delivery service coordinator	2 (7.7)

*Speech and language therapist (n = 2), physiotherapist (n = 1), occupational therapist (n = 1).

Perception of the Mediterranean Diet	**Foods considered to form part of a Mediterranean diet** included salads, olive oil and fish but sometimes also pasta, pizza and red wine.
	Perceived benefits of the Mediterranean diet to health included longevity, cardiovascular and cognitive health, but the social and lifestyle benefits were also considered important.
Perception of the gut microbiota	**A new and emerging science** to both older adults and HCPs, who describe learning about it from a variety of sources.
	Health benefits are "not common knowledge" and sometimes included mental health and cognitive function, but mostly digestive gut health and motility benefits.
	Probiotic supplements are considered for use 'every now and then' such as after a course of antibiotics.
Challenges in promoting a Mediterranean Diet for gut microbiota benefit for healthy ageing	**Little awareness of the Mediterranean diet and gut microbiota linkage for healthy ageing,** as some considered benefits of fibre from fruit and vegetables, but most thought of probiotic yoghurt, supplements and fermented foods as 'good for the gut'. There are also gaps in HCP awareness.
	Acceptability challenges as socio-cultural and habitual differences to the Mediterranean Diet may make it challenging to introduce; 'its not what they're used to'
	Accessibility challenges as the Mediterranean Diet could be difficult to access given it's unique food environment.
	Tailoring communication to promote the Mediterranean diet and gut microbiota may be useful

FIGURE 1
Themes identified in the data organized by domain.

they eat a lot of fish, and they grow their own food. I don't know necessarily what the food is, I think there's nuts involved?" (OA#4).

Several 55 + adults used olive oil and spoke of cod-liver oil supplements for Omega-3; "*our mother used to spoon us cod liver oil. . . (it's) good for your bones and builds you up" (OA#55).* Others had "*heard something about*" taking a spoonful of olive oil to "*stave off dementia*" or that oil is carcinogenic if burnt. Several understood the difference between saturated and unsaturated fats within the MD, while others were divided on the healthfulness of fats; *"I always think oil is unhealthy, even olive oil. . . that's just oil? you're eating lots of fats?" (OA#4).* One person considered that all fats were part of the MD *". . .in the MD, it's ok to eat cheese, use cream, butter" (OA#16).*

3.1.2. Perceived benefits of the Mediterranean diet to health

The MD was considered by both HCPs and 55 + adults to have cardiovascular and longevity benefits, with few people noting benefits for cognitive health; *"I think there's some place in Italy where they all live to a hundred. . . it's supposed to be something to do with their diet" (OA#20).* Another had doubts about the evidence; *"from a consumer's point of view, I never saw any evidence that it (MD) will extend my life" – (OA#30).* Many 55 + adults felt the MD could help to prevent heart disease and was good for lipid profiles; *"I think that it has beneficial effects on, let's say, if you have high cholesterol" (OA#28).* One person, living with arthritis, suggested the diet could reduce inflammation.

While HCPs were not explicitly asked about the health benefits of the MD (as it was assumed most would be familiar with this), most described it generally in terms of healthy eating, while only some cited its role for specific diseases; *"there's most information there with regards to prevention of dementia" (Dietitian #4).* Some dietitians and geriatricians spoke about what they felt was "*relatively weak*" evidence from epidemiological study of the MD and disease outcomes in older cohorts; *"The problem with diet and relating it to chronic illness prevention, the studies are far few and between and not robust in some cases" (Dietitian #4).* Others had questions about the preventative potential of MD foods alone in achieving health benefits in an older population; *"I would have thought the evidence starts with these populations where it is their whole food diet that they've had that's helped to prevent against whatever diseases" (Dietitian #5).* For people

already living with moderate to severe neurodegenerative disease, geriatricians were most concerned about "*whatever [nutrients] you can get into them (patients),*" particularly adequate energy and protein intake, rather than a MD approach.

Both 55 + adults and HCPs suggested that the MD could have social and wellbeing benefits. One geriatrician suggested that the MD may have benefits due to its social structure; "*. . . certain lifestyles or behaviours that are not related specifically to the type of food that you eat. . . but can be around how you organise mealtimes" (Geriatrician #6).* Separately, another questioned whether the diet was still beneficial *"if you extract the social component" (Pharmacist #15).*

3.2. Perceptions of the gut microbiota

3.2.1. The gut microbiome is a new and emerging science

Some 55 + adults spoke about their increased awareness of the microbiota in recent years; *"I know that there's a lot of research going on now on the gut microbiome. . . and I would wonder about certain things, would they be helpful for me. . . like the probiotics" (OA#10).* They have heard about the gut microbiota from a variety of sources including product advertisement, TV or radio, health professionals, scientists, books, or their own research; *"I've heard a lot about it on the radio. . . dietitians and nutritionists and people talking about how important it is to have a balanced microbiome" (OA#5).* Several others were aware of the microbiome from research in a nearby university: "*in (University College Cork). . . doing terrific work on the gut. . . relating it to the brain and depression*" *(OA#28).*

HCPs acknowledged the abundance of new discoveries around the microbiota, with one dietitian noting they have been "*struggling to keep on top of it" (Dietitian #3).* Another felt research advancements were important because of the role of the gut microbiome in mental health; *"You see a lot of people with irritable bowel syndrome. . . related to anxiety and the gut. . . I think having that research about the gut microbiome is really important for all round health, not just for digestive health, but mental health" (Dietitian #3).*

3.2.2. Perceived health benefits are "not common knowledge"

Both HCPs and 55 + adults felt effects of the gut microbiota on different aspects of health were "*not common knowledge*" among most older adults. There appeared only a vague understanding of the gut-brain association among 55 + adults; *"I don't quite understand the relationship between healthy gut and healthy body, and not ageing and dementia. . . how far is it actual proved scientific knowledge. . . that the healthy gut does prevent dementia?" (OA#63).* A few discussed how different foods affect their mood, such as confectionary and convenience foods. Others considered the gut microbiota had "something to do with" cognitive health*; "I have read about it. . . there's some bacteria in the brain. . . but I let the details go" (OA#64).* For others, the association with dementia was "*a new angle,*" noting they *"wouldn't have made the connection with dementia." (OA#52).*

More frequently, 55 + adults related the gut microbiota or "healthy gut" to digestive health and motility, for instance "*an absence of indigestion and digestive disorders,*" or the "*mechanical*" breakdown of food. Dietitians also considered bowel health and the effects of fiber; "*you would be looking at fibre and fluid intake, not necessarily very probiotic effective food, but just the overall fibre their diet provides" (Dietitian #7).* One geriatrician discussed the potential interest in probiotic foods like yogurts for their preventive potential against antibiotic-associated diarrhoea. Many participants recognized yogurts to have gut benefits; *"Anything I see in the line of live cultures. . . yoghurts and things. . . I don't know what it actually means but I presume it's something fairly good" (OA#46).* Several 55 + adults thought of a "*gut cleansing*" or "*clearing*" effect, suggesting fasting was part of maintaining gut health "*you go 12 hours to 14 hours with no food, isn't that another way of doing that. . . clearing your gut?" (OA#42).* A couple discussed eating linseeds to "*help take out some of the. . . poisons*" from the gut.

It was suggested that maintaining the gut microbiota is seen as a local issue rather than something with systemic effects; "*there's so many things that it affects. . . but they're (older adults) not aware of the other general health benefits to everything, that it's not just gut" (Dietitian #1).* Only some considered wider effects, for instance, one person with arthritis had some understanding of the microbiome's role in inflammation; "*there's some good bacteria and bad bacteria and if the good bacteria win, you won't have leaky gut and you won't have inflammation" (OA#2).* One dietitian was interested in immunity benefits from maintaining gut microbiota, particularly in the context of COVID-19, while another considered the microbiota as important when looking at "*overall health*" of an older cohort and "*not just their malnutrition risk and management*" *(Dietitian #4*).

3.2.3. Probiotic supplements are considered for use "every now and then"

Many 55 + adults associated a healthy microbiota with taking probiotic supplements; *"I look after my biome by. . . taking a supplement and eating live yoghurt" (OA#21).* They suggested their sporadic and restorative use; "*the antibiotics have done so much damage to your system and then the probiotics, you take them to counteract that" (OA#1).* Some 55 + adults implied that gut health was only something to be concerned about every now and then; *"my gut is probably a bit leaky, as we get older. . . so every so often I'll take a product that is meant to kind of help repair the gut a bit" (OA#25).* Several indicated they would be more aware of gut health if they suffered from issues like constipation or irritable bowel syndrome, suggesting they don't worry about gut health because they don't have any trouble with it; *"Am I going to start changing the way I eat to try and tweak my gut microflora?. . . I don't think I've got a problem, so I don't think I need to do anything about it" (OA#3).*

One geriatrician described that they were "*cynical*" of probiotic products; *". . . anecdotally, the probiotics are dead by the time they reach your small intestine. . . where they're needed." (Geriatrician #5).* One dietitian felt instead that fruit and vegetables were best "*avenue*" for benefiting the gut microbiota over supplements which they felt can be "*quite an extreme measure." (Dietitian #2).*

3.3. Challenges in promoting a Mediterranean diet for gut microbiota benefit for healthy aging

3.3.1. Little awareness of the Mediterranean diet and microbiota linkage for healthy aging

Few participants, including HCPs, specifically discussed the role of the MD in optimizing gut microbiota profiles. Those who did

discuss any association between the two mostly suggested digestive gut health and motility could be optimized through the consumption of dietary fiber, mainly by intake of fruits, vegetables, and salads. For instance, several 55 + adults spoke about how a "*balanced and varied*" diet of colorful fruit and vegetables could be beneficial for gut health. Others felt fruit, nuts and seeds were good to "*keep the tummy active*" or that "*fibre is what feeds the microbiome.*" While participants recognized the microbiota benefit from yogurts, one person didn't feel yogurts fit into the MD; "*. . . I don't think I'd associate yoghurts now with Mediterranean diet but apparently, they're supposed to be good for your gut" (OA#20).*

Some 55 + adults felt there were microbiota benefits to be gained from diets other than the MD, such as the Japanese or Korean diet due to its fermented food content. Many 55 + adults described that they ate foods such as kombucha, kimchi, sauerkraut, and kefir *"because of the good bacteria" (OA#64).* These diets were considered by one person as healthier than the MD; "*The ultimate healthy diet, I think you'd be looking at Japanese macrobiotic sort of diet. . . Whereas the Mediterranean diet. . . it's a nice way to enjoy food" (OA#19)*

3.3.2. Acceptability: Socio-cultural and habitual differences of the Mediterranean diet; "it's not what they're used to"

Some 55 + adults and HCPs felt that implementing the MD in Ireland might be difficult to align with existing cultures and traditions; "*it's something different from what we'd be used to" (physiotherapist #10).* The Mediterranean style of eating late in the evening might not suit Irish traditions, where for many older adults the main meal is typically eaten mid-day; *"I'm not sure that many Irish people would be able to cope with eating as late in the evening as they do" (OA#24).* Several others felt Irish cultures around high meat and dairy consumption may make it hard to introduce some of the plant-based or fish elements of the MD; *"I'm not a great fan of oily fish. . . I'm more a meat and two veg sort of fellow" (OA#21).* Others commented on the Irish Catholic tradition of having fish on Friday, and that the idea of having fish any other day "*might need a little bit of encouragement" (Meal-delivery service coordinator #17).*

There were several perceived differences between Mediterranean salads vs. in Ireland where many salads have rich sauces or are starch-based; "*. . . potato salad and coleslaw. I think in Ireland a lot of people see that as a salad" (OA#1).* Some 55 + adults felt that adopting salads as a dietary staple would be difficult because of the colder climate; "*no cold food. . . your gut doesn't like it in the winter" (OA#23).* There was a sense that what we have in Ireland can be 'just as good' as the MD; *"what's wrong with having an Irish diet and looking at our own seasonal foods and maybe bringing something that doesn't have to travel as far" (OA#26).*

3.3.3. Accessibility: The Mediterranean diet in different food environments

Both 55 + adults and HCPs felt the MD might be difficult to access in Ireland in terms of produce availability and location of retail outlets relative to where older people lived. Produce sold in Mediterranean open-air food markets were considered local, fresh, affordable and of better quality than imported produce; "*The fruit and veg, seasonality. . .. if you're in the Mediterranean, there would be more opportunities to eat fresh, it's more accessible" (Dietitian#4).* One person felt that more support for horticulture in Ireland is needed to make salads more accessible, while someone else described fresh fish as less accessible if living inland. Others, including HCPs, felt access to the MD might be impeded by cooking requirements, cost, and acquisition of multiple ingredients; *"The affordability of a MD and the effort required to accumulate the parts of it might be a barrier for people on reduced income and with people with reduced mobility. Maybe not everything is readily available in their local corner store" (Pharmacist #15).*

3.3.4. Tailoring communication to promote the Mediterranean diet and gut microbiota

Some 55 + adults and HCPs discussed how language could help to implement the MD. Sometimes, the word "diet" was seen as requiring an entire dietary restriction; *"if I went on the Mediterranean diet. . ." (OA#3); ". . . does it have to be full Mediterranean diet or can it be incorporated?" (OA#S20).* Several dietitians noted how their advice on the MD would be "*subtle*"; *"It's overlapping with. . . increase fish, get your fruit and veg in there. It's indirectly Mediterranean without calling it that" (Dietitian #1).* Others spoke about how they use "*small steps*" to explain components of the MD instead of "*diving into olive oil, chickpeas, and lentils. . ." (Dietitian #3).* Similarly, one dietitian noted how they would tend to explain the *"simplified version"* of the gut microbiome; "*. . . it's not necessarily something I mention to them, but it's in my head. . . if they were talking about the good stuff in the yoghurt. . . I would talk about the probiotic, again not the technical terms" (Dietitian #1).*

4. Discussion

This study explored Irish older adults' and HCPs' perspectives of the MD, gut health, and microbiome in terms of supporting healthy aging. Both stakeholder groups considered the importance to health of the MD and gut microbiota separately, with little recognition of the specific role of the MD in promoting a favorable gut microbiota profile and thus contributing toward healthy aging. There were varying perceptions of the link between gut microbiota and gut health, how to maintain it, and which physiological and aging processes it may affect. Many older adults in particular perceived the gut microbiota role mainly in terms of digestive health rather than overall physical or cognitive health. Older adults and professionals perceived challenges in promoting the MD to an older population in Ireland.

Several 55 + adults and HCPs perceived there to be a beneficial role of fiber from fruits, vegetables, salads, nuts and seeds in promoting gut health. However, many associated gut microbiota maintenance with products such as "live" yogurts or probiotic supplements and did not specifically reference the MD or Mediterranean foods. This perception that probiotic supplements and products are required to maintain gut health suggests the influence of marketing in shaping public perceptions. Some 55 + adults perceived there to be microbiota benefits from other diets like the Asian diet, for a similar contribution to longevity as the MD, *via* its fermented food components. While the literature can support both of these perspectives (27, 28), there may be a missed opportunity for the promotion of the role of the MD in gut microbiome health and its involvement with healthy aging processes (8). In addition, some 55 + adults were of the opinion that a fasting effect of gut "*cleansing*" or *"clearing"* was beneficial for gut health. Despite some research in this area (29), these perspectives highlight the need for differentiation

of "gut microbiome" and "gut health" in the public perception and experience (30).

Participants recounted learning about the gut microbiota from various sources such as health and nutrition professionals and consumer-directed advertising. There appeared to be a blurred distinction between digestive "gut health" and "microbiota health," as well as self-perceived knowledge gaps. For instance, one dietician suggested they were "*struggling to keep on top of*" gut microbiota research, pointing to the potential for additional professional education activities to increase HCP knowledge. Many 55 + adults and HCPs discussed bowel motility or digestive conditions when asked about the gut microbiota, with only a handful suggesting that there could be systemic benefits to immunity or inflammation, with little regard for age-specific effects. Thus, it appeared that gut health is often perceived as a local issue and not something which affects the wider body. The perspectives observed in our sample are not uncommon. A cross-sectional survey distributed among adults in the United Arab Emirates found that while respondents understood a basic definition of the microbiota, they lacked understanding of its role in disease protection and immunity, with HCP knowledge not significantly higher than that of non-HCPs (31).

Linked to this, gut health was seen to be only in need of attention "*every now and then,*" perhaps after a course of antibiotics or if someone was concerned about digestion. This may partly reflect the increased promotion of and demand for probiotics and prebiotics from consumers (32), and indeed their perceived sporadic usage. One study showed that despite recommendations for probiotic foods and supplements to be used consistently (33), up to 30% of people who use probiotics do so only intermittently or in an *ad hoc* manner (34, 35).

As research increasingly demonstrates the importance of diet, and particularly the MD (8), for gut microbiota benefit (36), public and professional receptivity to the MD as a dietary strategy for healthy aging is important. Many 55 + adults considered the MD as healthy and recognized cardiovascular and longevity benefits, consistent with research messaging (5). Many described their familiarity and experience with various food components of the diet, such as salads, olive oil, and fish. However, our study suggests adaptability challenges for the MD in Ireland. For instance, the perception among some 55 + adults that foods like pasta and pizza equate to the MD diet, and their varying perspectives on olive oil or fish oil as either having benefits for brain health ("staving off dementia") or as being "*unhealthy*" or "*carcinogenic,*" suggests a poor understanding of the MD and its key constituents. There were also recurring suggestions that the MD is just "*a nice way to enjoy food,*" with benefits only attributing to a "*whole-diet approach*" rather than its components.

While some dietitians pointed out that the MD is already *"subtly"* included in healthy eating advice, consideration of evidence-based health benefits from the MD for older adults as demonstrated in published observational and trial data were not to the fore. Some dietitians and geriatricians suggested that epidemiological study of the effects of Mediterranean foods in older cohorts had "*not covered itself in glory.*" Indeed, the longevity effects of the MD were considered difficult to "unbundle" from the effects of lifestyle practices (37). This is despite adherence to Mediterranean dietary patterns being associated with longevity, reduced risk of overall mortality, cardiovascular diseases, overall cancer incidence, and neurodegenerative diseases (2).

Many participants appeared to consider the MD as an "all-or-nothing" approach; the concept of adopting some elements of the MD as a solution to acceptability and accessibility challenges did not arise. While there are many unique socio-cultural elements to the Mediterranean way of eating (38), both older adults and HCPs in this study considered experiential factors such as dietary meal staples and the timing of the meals as potentially challenging to align within existing long-standing traditions. Participants also felt accessibility issues might inhibit the diet in a non-Mediterranean region, considering unique food environments or the need to overcome availability barriers in different consumer retail and supply-chains (16). Such differences have indeed been noted in the literature (16, 39). Overall, the apparent "all-or-nothing" perception of implementing the MD, combined with existing HCP opinions of epidemiological evidence, may be limiting the perceived promotion and acceptability of MD adoption in a non-Mediterranean culture and environment.

To promote adoption of the MD in an older cohort, efforts might focus on increasing stakeholders' knowledge of what constitutes a MD and what does not, as well as public and professional understandings of the health benefits associated with the MD. For instance, it has been already suggested to incorporate the key principles of the MD into current Irish Food Pyramid guidance (17). Health promotion should include information on the gut microbiota in terms of its effects on body health, and not just "gut health." Public health promotion campaigns, as well as targeted education for health and nutrition professionals, may be useful in this regard.

4.1. Strengths and limitations

We involved an adequate sample size, appropriate gender balance and range of ages. There was specific inclusion of 55 + adults from a range of social, retirement and disease-specific groups, including people from potentially marginalized groups such as the Traveling community and LGTBQ + community (26). While we collected information such as age, gender, area of residence and employment status (retired/not) from the older adults, we did not collect racial-ethnic data, education level or socioeconomic status, which is a limitation.

Most of the HCPs recruited were predominantly in contact with older adults with established disease, and we acknowledge the absence of primary care HCPs such as GPs and public health nurses (PHNs) who may have more experience with fitter, community-dwelling older adults. Thus, there may have been a mismatch between our older person sample and older people as envisioned by the HCPs. Professional networks known to the research team were contacted, but due to an ongoing protracted COVID-19 wave, no GPs or PHNs were available to participate. Nevertheless, exploring the views of 55 + adults and HCPs simultaneously allowed identification of important potential knowledge gaps for future health promotion and science communication.

We acknowledge the limitations of a qualitative study in terms of data generalizability, and we recommend that the themes determined in this study are explored further in a large population survey.

5. Conclusion

Older adults and HCPs describe being increasingly aware of research examining how the gut microbiota relates to aging processes and the interplay which exists with diet; however, the translation of

research findings to public and professional understanding appears incomplete. This is not entirely unexpected. There appears to be knowledge gaps in both stakeholder groups in recognizing that the Mediterranean diet promotes gut microbiota profiles linked to healthy aging. While individuals considered the effects of fiber through fruits and vegetables and probiotic yogurts and supplements in promoting digestive health, there was little awareness of the systemic effects of the MD *via* promoting beneficial microbiota in terms of preventing disease in old age. Some references were made to inflammation, mental health and immunity, however, disparities remained toward the role of the MD in promoting healthy gut microbiota signatures. Separately, challenges in perception, acceptability, and accessibility may exist in implementing the MD in a non-Mediterranean culture and environment. These insights should be considered in future science communication and health promotion efforts to improve public and professional understanding of the role of the MD in promoting the gut microbiota for healthy aging.

Data availability statement

The datasets presented in this article are not readily available because participants were only asked for their consent to quotation/publication of extracts from the focus-groups and interviews. They did not give their consent to having any other data made publicly available or shared with other research groups. Requests to access the datasets should be directed to corresponding author.

Ethics statement

This study and all procedures involving research participants were approved by the Social Research Ethics Committee at University College Cork (SREC/2021/079). Written informed consent was obtained from all study subjects prior to their participation in interviews/focus groups via a participant information leaflet which included details of the study, the right to withdrawal, data protection policies and procedures, and a consent form attached. Verbal consent was confirmed and recorded at the start of each interview/focus group.

Author contributions

ST, EA, and PO'T conceived and designed the study. LO'M collected the data. LO'M checked and coded the transcripts with assistance from EO'S. LO'M conducted and interpreted the analyses with guidance from EO'S and ST. LO'M drafted the manuscript with input from EO'S and ST. EO'C, AT, MH, JH, and SK acted as external expert advisors on the project. All authors reviewed, provided feedback on, and approved the final draft of the manuscript.

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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/fnut.2023.1104238/full#supplementary-material

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Selenium intake help prevent age-related cataract formation: Evidence from NHANES 2001–2008

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Introduction: Cataract is one of the leading causes of blindness and visual impairment, about 16 million people around the world. Trace elements play an important role in a variety of the processes in human body. This study aimed to investigate the association between daily dietary intake of trace elements and age-related cataract incidence based on data from the National Health and Nutrition Examination Survey (NHANES) 2001–2008.

Methods: Iron, zinc, copper, and selenium were conducted in this study among subjects aged 50 years and older for African Americans and 55 and older in US adults. Multivariate logistic regression analysis was used in different models to investigate the association of trace elements intake and cataract.

Results: After screening, 7,525 subjects were ultimately included in this study. A significant negative association was found between selenium intake and cataract incidence in adjusted models using multivariate logistic regression analysis (model 1: OR = 0.998, 95% CI = 0.997–1.000; model 2: OR = 0.997, 95% CI = 0.995–1.000; and model 3: OR = 0.998, 95% CI = 0.995–1.000). After dividing selenium intake into quintiles, significant negative associations between selenium intake and cataract were observed in the first quintile of model 3, the fourth and fifth quintiles of all models. In subgroup analyses adjusted for age and sex, a significant negative association was observed only in women aged 65–74 years.

Discussion: Our study points out that maintaining daily dietary selenium intake at higher levels is helpful for cataract prevention, and that increasing daily dietary selenium intake in American women aged 65–74 years may contribute to the prevention of age-related cataract. The intakes of iron, zinc, copper may not be associated with age-related cataract.

KEYWORDS

cataract, trace elements, National Health and Nutrition Examination Survey (NHANES), selenium, cross-sectional study

1. Introduction

Cataract is usually defined as opacification of the lens. Cataract is one of the leading causes of blindness and visual impairment, about 16 million people around the world (1–5). More than 541,000 cataract extraction procedures are performed at a cost of more than $3.8 billion each year in the United States (6). This indicates that cataract has a serious burden on human health and socioeconomy. Age related cataract is usually defined as cataract occurring at age 50 and older (7). Oxidative stress mechanisms is considered to have a part in the pathological process of cataract formation: when oxidative damage in the lens continuously accumulates until its intrinsic antioxidant capacity is exceeded, it will lead to the aggregation of lens proteins and apoptosis of human lens epithelial cells (8, 9). Epidemiological studies have revealed several risk factors for age related cataract, such as age, obesity, diabetes, smoking, and low socioeconomic status (10–14).

Currently cataract treatment modalities for which efficacy has been affirmed are surgery only, and the most commonly used surgical strategy is phacoemulsification and lens replacement (15). Small incision cataract surgery has been widely used, which accelerates the post-operative recovery of patients and improves the quality of post-operative vision (4). However, because the complications associated with cataract surgery similarly affect the visual quality of patients, such as posterior capsular disruption, retinal detachment, progressive myopic traction maculopathy, etc. (16–18). Therefore, effective prevention of cataractogenesis is perhaps the best way to combat the visual damage brought about by cataracts.

Trace elements in the human body include copper, selenium, zinc, manganese, cobalt, chromium, and molybdenum, among others, which function as co-factors or as prosthetic groups located in the enzymes (19–23). The role of these trace elements in diseases is the focus of current research. Currently, researchers have observed that differences in trace element levels exist in the aqueous humor, lens, plasma of cataract patients (24, 25). This difference is similarly present in other age-related eye diseases (26). Shearer et al. found that only selenium was able to cause cataract alone, and that seven other trace elements prevented cataract induced by selenium, with mercury showing the strongest protective ability (27). Selenite also has a strong ability to induce cataract, and because of this property, a rat model of selenite induced cataract has been widely used in cataract related research (28–30). These studies were all able to indicate the close relationship between trace elements and cataract. However, recently Post et al. found that low serum selenium levels maybe a risk factor of age-related cataract (31). This is in contrast to previous findings, perhaps indicating that the effect of selenium on cataract remains to be explored in a deeper step. The effects of other trace elements on cataracts and the specific molecular mechanism are also urgent to be confirmed by further studies.

To further explore the relationship between trace elements and cataract, we carried out this study. This study used National Health and Nutrition Examination Survey (NHANES) database and aimed to analyze the association between trace element intake and incidence of cataract, which may provide a foundation for guiding trace element supplementation.

2. Materials and methods

2.1. Data source and subjects selection

This study is based on NHANES data from 2001 to 2008. NHANES is a national cross-sectional research program aimed to assess the physical status of ordinary Americans, performed by the National Center for Health Statistics (NCHS). The NHANES subjects were all U.S. non-institutionalized civilian participants, all of whom had accepted comprehensive measurements. Each cycle of NHANES is an independent cross-sectional survey. The NCHS research ethics review board approved the survey protocol for NHANES. All participants gave written informed consent (32).

Referred to previous studies, we set the inclusion criteria for age as 50 years or older for non-Hispanic blacks and 55 years or older for other races (33). In the study, a total of 28,332 subjects who underwent ophthalmic examination were identified, and 7,525 subjects were finally included. 20,807 subjects were excluded for the following reasons: (1) No valid data on cataract diagnosis; (2) No valid data on trace element intake; (3) Not meeting the above age inclusion criteria.

2.2. Cataract identification criteria

National Health and Nutrition Examination Survey asked participants aged 20 years and older if they had undergone ophthalmic surgery for cataracts prior to their ocular examination (34). If participants answered yes, they were defined as having cataract in this study. Participants with non-response or uncertain response were excluded. Because of the increased rate and lower threshold for cataract surgery in the United States (4, 35), self-reported cataract surgery may be able to represent clinically meaningful cataract. This defining criterion for cataract has also been used in previous studies (36, 37).

2.3. Determination of intake of various trace elements and daily energy intake

Dietary data were collected in the in-person interview using the Automated Multiple Pass Method (AMPM). Participants recalled all of the foods they had consumed on the previous day and told staff. The staff calculated the amount of various nutrients they ingested daily based on what the subjects said. The AMPM is a USDA′s dietary data collection instrument and a fully computerized recall method. The NHANES Mobile Examination Center (MEC) provided a set of measuring guides that facilitated participants to describe the amount of foods they had ingested (38).

Four trace elements of iron, copper, zinc, selenium were included in our study. Because in the NHANES dietary survey database, there are no dietary intake data for other trace elements except these four. Daily energy intake was used to represent the total amount of food the participants consumed on a daily basis.

2.4. Covariates assessment

We selected demographic variables such as age, race/ethnicity, sex, and education level to be included as covariates in this study. These demographic data were obtained through computer-assisted face-to-face interviews (39). Social status and living status affect physical wellbeing. But these indicators could not be quantified, so we took the above demographic data to evaluate the social status and living status of participants.

Diabetes mellitus, smoking, obesity/overweight are all risk factors for age-related cataract, therefore (40–44), they were also included as covariates in this study. Diabetes status was defined by self-reported diagnosis (45). Smoking status was defined by serum cotinine levels to reflect both direct and indirect smoking quantity (46, 47). Obesity/overweight was reflected by body mass index (BMI). BMI was calculated by the weight in kilograms divided by the square of height in meters (kg/m^2) (48).

2.5. Statistical analysis

All statistical analyses were performed using SAS 9.4. NHANES uses a stratified, multistage sampling method, so we incorporated sampling weights and strata, sampling units in our statistical analysis to account for the complex sampling design. For continuous variables, we used means and standard errors (SE) expressed with *t*-test to compare participants′ characteristic variables. For categorical variables, we expressed percentages and SE with the Rao Scott Chi-square test to compare participants′ characteristic variables. Logistic regression models were used to determine the association of various trace element intakes with the presence of cataracts. To better determine their association, we selected three models. Model 1 was adjusted by age, race, gender, and education level to correct the influence of demographic characteristics. Model 2 = Model 1 and adjusted by diabetes, BMI and daily energy intake to correct the influence of daily food intake, obesity, and diabetes. Model 3 = Model 2 and adjusted by serum cotinine to correct the influence of smoking. Since a significant association between selenium and cataract was observed, to better investigate the association between the two, we further performed quintile regression between selenium and cataract after dividing the intake levels of selenium into quintiles. Finally, because age and sex were the most prominent risk factors, we performed subgroup analyses for age and sex. Because of the setting of the inclusion criteria, participants 50–54 years of age were all black, and to avoid this selection bias, subgroup analyses were performed starting at age 55 in each decade as one group. Gender was grouped in males and females. All statistical analysis results with a two-tailed p value < 0.05 were considered significant.

3. Results

3.1. Description of baseline information of the study sample

Table 1 shows the demographic data as well as other characteristic data of the participants with and without cataracts. Of all included participants, 1,570 had cataracts, 18.10% of the total after weighting, 5,955 did not have cataracts, and 81.90% of the total after weighting. Participants with cataracts all had significantly lower intakes of trace elements, including iron (13.948 vs. 14.812 mg), zinc (10.269 vs. 11.114 mg), copper (1.151 vs. 1.261 mg), selenium (85.698 vs. 98.267 μg). Significant differences were also observed in other covariates. Older age, female sex, non-Hispanic white race, and lower educational level groups were all more likely to have cataracts.

3.2. Association between the intake of iron, zinc, copper, selenium, and the presence of cataract

Table 2 shows the associations that existed between the intake of various trace elements and cataract as addressed by multivariate logistic regression models. A significant negative association between selenium intake and incident cataract was shown in all models (model 1: OR = 0.998, 95% CI = 0.997–1.000; model 2: OR = 0.997, 95% CI = 0.995–1.000; model 3: OR = 0.998, 95% CI = 0.995–1.000). No significant association with cataract was observed for the intakes of iron, zinc, copper.

3.3. Relationship of different quintiles of selenium with the presence of cataract

Table 3 demonstrates the analysis of the association of different grades of selenium intake with cataract after dividing selenium intake into quintiles. The quintiles of selenium intake levels were 55.9, 75.9, 97.4, and 129.6 μg. In the first quintile of model 3 (OR = 0.985, 95% CI = 0.971–0.999), and the fourth (model 1: OR = 0.979, 95% CI = 0.960–0.998; model 2: OR = 0.979, 95% CI = 0.958–1.000; model 3: OR = 0.977, 95% CI = 0.956–0.998) and fifth quintiles (model 1: OR = 0.996, 95% CI = 0.992–0.999; model 2: OR = 0.996, 95% CI = 0.992–1.000; model 3: OR = 0.996, 95% CI = 0.992–0.999) of all models, we observed a significant negative association between selenium intake and cataract.

3.4. Subgroup analyses for age and sex

Table 4 presents the association of cataracts and selenium in male and female participants at different ages. In accordance with our results, we only observed a significant negative association in women aged 65–74 years in all models (model 1: OR = 0.994, 95% CI = 0.990–0.999; model 2: OR = 0.992, 95% CI = 0.985–1.000; model 3: OR = 0.992, 95% CI = 0.984–1.000). No significant association was observed at other ages for women and at all ages for men.

4. Discussion

Our study included large-scale cross-sectional data from four NHANES cycles. Logistic regression results showed a significant negative association between selenium intake and cataract. There was no significant associations between the intake of iron, copper, and zinc and cataract. Therefore, our study points out that increasing selenium intake in daily diet may decrease the risk of cataract. This notion was subsequently confirmed in the multivariable logistic

regression model performed after dividing selenium intake into quintiles. Because significant negative associations were observed in the first quintile of model 3, the fourth, and fifth quintiles of all models, we hypothesized that maintaining daily dietary selenium intake at lower or higher levels is helpful for cataract prevention. In subgroup analyses adjusted for age and sex, the inverse association of selenium intake with cataract was observed only among US women 65–74 years of age. Four trace elements, iron, zinc, copper, and selenium, have a non-negligible role in the human body and they are involved in all aspects of human physiological activities (49–54), as well as in the visual system (55–57). Oxidative stress mechanism played an important role in the pathological process of cataract, in which iron, zinc, copper were involved (58–64). However, the relationship between these three trace elements and cataract could not be well confirmed in the current study (62, 65–71). This is consistent with our study, which perhaps indicated that the intake of these three trace elements had a negligible relationship with cataract.

In our results, selenium was the only significant variable, which deserves our high attention. All the time, rats with high-dose selenite intake have frequently been used to prepare animal models of

TABLE 1 Baseline information for the study sample.

Variables		Cataract (+)	Cataract (−)	*p*-value
Continuous variables, mean (SD)				
Unweighted counts		1570	5955	
Age (years)		75.040 (0.288)	64.840 (0.167)	<0.001
Iron intake (mg)		13.948 (0.235)	14.812 (0.193)	<0.001
Zinc intake (mg)		10.269 (0.214)	11.114 (0.241)	0.001
Copper intake (mg)		1.151 (0.0308)	1.261 (0.0220)	<0.001
Selenium intake (μg)		85.698 (1.309)	98.267 (1.284)	<0.001
Energy (kcal)		1672.820 (19.086)	1886.280 (20.793)	<0.001
BMI (kg/m^2)		28.051 (0.190)	28.862 (0.118)	<0.001
Serum cotinine (ng/mL)		28.932 (2.518)	50.664 (2.167)	<0.001
Category variables, (%)				
Cataract		18.100 (0.700)	81.900 (0.700)	
Gender	Male	35.800 (1.200)	46.800 (0.700)	<0.001
	Female	64.200 (1.200)	53.200 (0.700)	
Race	Mexican American	2.700 (0.500)	4.100 (0.600)	<0.001
	Other Hispanic	2.300 (0.600)	2.700 (0.600)	
	Non-Hispanic white	84.900 (1.500)	76.600 (1.800)	
	Non-Hispanic black	6.600 (0.800)	12.800 (1.300)	
	Other race–including multi-racial	3.600 (0.600)	3.700 (0.500)	
Education level	Less than 9th grade	16.000 (1.200)	9.000 (0.700)	<0.001
	9–11th grade (Includes 12th grade with no diploma)	16.300 (1.400)	12.300 (0.700)	
	High school grad/GED or equivalent	26.700 (1.700)	27.700 (1.000)	
	Some college or AA degree	24.200 (1.300)	25.000 (1.000)	
	College graduate or above	16.800 (1.600)	26.000 (1.400)	
Diabetes mellitus	(+)	27.000 (1.500)	16.200 (0.800)	<0.001
	(−)	73.000 (1.500)	83.800 (0.800)	

TABLE 2 Association between intake of iron, zinc, copper, selenium and cataract.

Variables	Model 1[a] OR (95% CI)	*p*-value	Model 2[b] OR (95% CI)	*p*-value	Model 3[c] OR (95% CI)	*p*-value
Iron intake	0.999 (0.986∼1.0130)	0.901	0.993 (0.978∼1.00900)	0.370	0.994 (0.978∼1.00900)	0.436
Zinc intake	1.00800 (0.996∼1.0200)	0.179	1.00900 (0.997∼1.0210)	0.138	1.00900 (0.997∼1.0210)	0.154
Copper intake	0.996 (0.937∼1.0590)	0.897	0.987 (0.927∼1.0520)	0.695	0.984 (0.920∼1.0520)	0.625
Selenium intake	0.998 (0.997∼1.000)	0.0481	0.997 (0.995∼1.000)	0.0184	0.998 (0.995∼1.000)	0.0275

[a]Model 1: adjusted for age, race, gender, educational level.
[b]Model 2:further adjusted for diabetes mellitus, BMI, daily energy intake.
[c]Model 3: further adjusted for serum cotinine.

TABLE 3 Association between selenium intake levels and cataract in different quintiles.

Variables		Model 1[a] OR (95% CI)	*p*-value	Model 2[b] OR (95% CI)	*p*-value	Model 3[c] OR (95% CI)	*p*-value
Selenium intake	Q1 (<55.9 μg)	0.995 (0.980∼1.010)	0.512	0.988 (0.974∼1.002)	0.0815	0.985 (0.971∼0.999)	0.0422
	Q2 (55.9∼75.9 μg)	0.992 (0.957∼1.028)	0.647	0.987 (0.949∼1.0280)	0.527	0.985 (0.945∼1.0280)	0.490
	Q3 (75.9∼97.4 μg)	0.993 (0.963∼1.0250)	0.678	0.990 (0.961∼1.0190)	0.477	0.990 (0.960∼1.0200)	0.486
	Q4 (97.4∼129.6 μg)	0.979 (0.960∼0.998)	0.0318	0.979 (0.958∼1.000)	0.452	0.977 (0.956∼0.998)	0.0343
	Q5 (>129.6 μg)	0.996 (0.992∼0.999)	0.0172	0.996 (0.992∼1.000)	0.0305	0.996 (0.992∼0.999)	0.0273

[a]Model 1: adjusted for age, race, gender, educational level.
[b]Model 2:further adjusted for diabetes mellitus, BMI, daily energy intake.
[c]Model 3: further adjusted for serum cotinine.

TABLE 4 Association between selenium intake and cataract in different ages and sex.

Variables		Model 1[a] OR (95% CI)	*p*-value	Model 2[b] OR (95% CI)	*p*-value	Model 3[c] OR (95% CI)	*p*-value
Male	55∼64 years	0.995 (0.988∼1.00300)	0.191	0.998 (0.985∼1.0110)	0.763	0.998 (0.985∼1.0120)	0.809
	65∼74 years	1.000 (0.996∼1.00400)	0.968	1.00300 (0.998∼1.00800)	0.189	1.00300 (0.998∼1.00700)	0.219
	75∼85 years	1.000 (0.997∼1.00300)	0.902	0.998 (0.994∼1.00200)	0.255	0.998 (0.994∼1.00200)	0.307
Female	55∼64 years	1.003 (0.997∼1.00800)	0.312	0.990 (0.961∼1.0190)	0.943	1.00100 (0.994∼1.00800)	0.822
	65∼74 years	0.994 (0.990∼0.999)	0.0235	0.992 (0.985∼1.000)	0.0433	0.992 (0.984∼1.000)	0.0387
	75∼85 years	0.997 (0.993∼1.00200)	0.233	0.996 (0.991∼1.00100)	0.120	0.996 (0.991∼1.00100)	0.141

[a]Model 1: adjusted for race, educational level.
[b]Model 2:further adjusted for diabetes mellitus, BMI, daily energy intake.
[c]Model 3: further adjusted for serum cotinine.

cataract, which is able to laterally reflect the promoting effect of high-dose selenium on cataract (28, 72). Post et al.'s cross-sectional findings showed that low-serum selenium showed a positive association with age-related cataract only in the first quartile range of serum selenium levels (OR = 7.969, $p < 0.01$) (31). While the results of the SELECT Eye Endpoints (SEE) study conducted by Christen et al. indicated that an additional 200 μg/d of L-selenomethionine daily as a supplement source of selenium during an average 5.6 years of follow-up failed to observe a protect effect of selenium on age-related cataract (33). In the study of Xiangjia Zhu et al., after oral supplementation of different doses of selenium to rats with cataract induced by naphthalene solution, the slowing of the increase of lens density or the decrease of turbid density could be observed at all selenium intake doses. And they also observed an elevation of glutathione peroxidase (GPx) activity in the lens of Se supplemented group rats. This suggests that selenium supplementation is able to slow down the development of naphthalene induced cataract by slowing down oxidative stress (73). These above results suggest that the effect of selenium on cataract remains inconclusive, which is still a topic of investigation. Dietary intake is the main body′s access to selenium and selenium in food includes both organic and inorganic forms. The organic forms of selenium include selenomethionine and selenocysteine, and their bioavailability is high, up to 90–95%; the inorganic form of selenium includes selenite, selenides, etc., and its bioavailability is low, only 80–85% (54). The effects of these two forms of selenium on cataract are distinct. For the organic form of selenium, after the tRNA mediated incorporation of selenocysteine, these selenium can synthesize a variety of selenoproteins, including GPx and thioredoxin reductases (TrxR), among others, which have a powerful antioxidant capacity; organic forms of selenium or are able to prevent cataractogenesis by combating oxidative stress (54, 74–76). The inorganic form of selenium is in the oxidation state; this might aggravate oxidative stress and thus promote cataract (74). In addition, selenite is also able to promote cataracts through mechanisms such as altered epithelial metabolism, calcium accumulation, calpain induced proteolysis, crystallin precipitation, phase transition, and cytoskeletal loss (28). Notably, Huang et al. also found that the effect of selenite on the lens changed over time, with a 30% decrease in DNA replication in lens epithelial cells observed at 6–12 h after administration of the selenite into rats, but an 80% increase in DNA replication in lens epithelial cells was observed by 24 h. This suggests that selenite, after a period of action on the lens, has an effect that shifts from damage caused by oxidative stress to repair of the lens epithelium (77). Combined with our results, we speculate that the reason that selenium only has a protective effect on cataract at lower and higher doses may be the gap in bioavailability between the organic and inorganic forms of selenium and the different maintenance times of high concentrations of selenite within the lens resulting in different effects. Because the bioavailability of the organic form of selenium is greater than that of the inorganic form, at low dietary doses of selenium, the organic form of selenium absorbed by the body predominates, at which point the organic form of selenium exerts antioxidant effects through a series of biological metabolism, thereby playing a protective role against cataracts. But when selenium intake increases, the uptake of inorganic forms of selenium increases in the body, and a range of damaging effects on the lens begin to manifest. Since at this time the protective effect exerted by the organic form of selenium was similarly enhanced with increasing dose, it did not show an absolute cataract promoting negative effect. However, as selenium intake continues to rise to higher levels, it is sufficient within the lens to maintain higher selenite concentrations for an extended period of time at which point the reparative effects of selenite on lens cells begin to manifest and, together with selenoproteins, exert a protective effect on the lens, thereby against cataracts. The reason why selenium

gradually exerted different effects on cataract at different intake levels is because the main aggregation sites of selenium in the human body are liver, muscle, kidney. Of the selenium ingested by humans, the dose of selenium able to aggregate into lens is low. Thus, only when a large change in selenium intake occurs can it lead to an influential change in the amount of selenium accumulated within the lens, resulting in a potent effect on the lens (78). However, although we found a protective role of selenium in cataract, because selenium is an essential nutrient for humans, prevention of cataract by reducing selenium intake seems an unwise regimen. Therefore, we more recommend that elderly people prevent cataract by moderately increasing their intake of selenium in their daily diet.

In the results of subgroup analysis, no significant association was observed in males of all ages. This is similar to the findings of Christen et al. (33). A significant negative association was observed in women aged 65–74 years, suggesting that increased selenium intake may be a protective factor for women in this age group of cataract. This result is presented, perhaps because of the role that estrogen withdrawal plays in cataracts (79). Another NHANES study showed that the mean age at menopause among US women enrolled in the study from 2001 to 2008 was 49.9 years (80). The course of cataracts is long, ranging from the onset of pathological changes to patients′ self-conscious symptoms for up to several years. And when visual symptoms occur, the time that patients go to the hospital and undergo cataract surgery is delayed because of personal psychological or socioeconomic factors. The results observed in our study should therefore be broadly consistent with the actual situation. Taken together, for women, taking selenium supplements at the beginning of menopause may help prevent cataract.

In the present study, since no direct data were available on the prevalence of cataracts in NHANES 2001–2008, we can only roughly estimate the prevalence of cataracts by cataract surgery status. This approach has been widely used in previous cataract studies using the NHANES database (36, 37, 81, 82). However, the plausibility of this approach has not been discussed in detail in previous studies, but we believe it is necessary. First, the study by Varma et al. estimated that the prevalence of cataract was 19.50% in the US population (83), and the meta-analysis by Hashemi et al. indicated that the worldwide cataract prevalence was approximately 17.20% (84). While in the present study, cataract surgery accounted for 18.10% of all participants, which was consistent with the above data. Second, in terms of cataract surgical coverage (CSC), CSC was defined as the percentage of cataract patients who underwent cataract surgery as a percentage of the total number of cataract patients (85). To the best of our knowledge, there are no studies conducted on CSCs for the US population, but based on the Rapid Assessment of Avoidable Blindness (RAAB) survey data, researchers have conducted extensive studies on CSCs for other countries, for example, Tabin et al.'s study indicated that CSCs can reach 50–70% in most developing countries (85), while Szabó et al. indicated that CSCs in Hungary, which is the same developed country as the US, are even higher up to 90% (86). Based on the above data, we can predict that the United States, as a developed country and with a high level of medical care, should also have CSCs at a high level, and most cataract patients are able to undergo cataract surgery. Finally the reduced cost of cataract surgery and the higher health gains for patients after surgery are also reasons for increased CSCs (87). Taken together, we believe that the cataract surgery data in this paper are broadly representative of the prevalence of cataract.

Although our study benefited from a reasonable sampling design to obtain a large sample size and nationally representative population, there are still certain limitations of this study that deserve to be explored. First, according to the NHANES method of ophthalmological examination, we can only know patients who have had cataract surgery and give a rough estimate of cataract occurrence in terms of cataract surgery status. The inability to detect those patients who had cataracts but remained unoperated would therefore make us underestimate the incidence of cataracts in our study. Second, cataracts are divided into subtypes, each of which has some differences in pathogenesis and risk factors that are not available in NHANES ophthalmological examination results. Third, dietary nutrient intake data were verbally ascertained through participants′ recall, and although based on the NHANES complete and rigorous measurement method, which enables accurate access to dietary nutrient data for a large proportion of participants, there may still be a small proportion of participants with varying degrees of recall bias. Fourth, because the contents of these trace elements in serum, aqueous humor, lens were not present in the results of the 2001–2008 NHANES study, these findings may be affected by other factors, such as different levels of subject digestive absorption, which could not be eliminated by adjustment. Finally, as a cross-sectional study, causality between observed variables cannot be directly concluded. However, our study also has a number of irreplaceable strengths. First, this is the first study to investigate the association between trace element intake and the risk of incident cataract through a nationally representative population-based survey. Second, to the best of our knowledge, this is the first study to report that high and low selenium intakes are protective against cataracts. Third, this is also the first study to report differential effects of selenium intake on cataracts in different genders. Fourth, it is also the first study that has explored the availability of data from cataract related studies in NHANES 2001–2008 in detail.

5. Conclusion

Our study points out that maintaining daily dietary selenium intake at higher levels is helpful for cataract prevention, and that increasing daily dietary selenium intake in American women aged 65–74 years may contribute to the prevention of age-related cataract. The intakes of iron, zinc, copper may not be associated with the incidence of age-related cataract.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

Approval for data collection was obtained from the NCHS Research Institutional/Ethics Review Board (IRB/ERB) (Protocol #98-12, Protocol #2005-06, Continuation of Protocol #2005-06). The patients/participants provided their written informed consent to participate in this study.

Author contributions

BX: conceptualization, software, investigation, resources, and data curation. BX and JZ: methodology. ZY and JZ: supervision and project administration. BX, ZY, and JZ: writing—original draft preparation and writing—review and editing. ZY: funding acquisition. BX and ZL: formal analysis. ZY and ZL: validation. All authors have read and agreed to the published version of the manuscript.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1042893/full#supplementary-material

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Effect of vitamin K2 in the treatment of nocturnal leg cramps in the older population: Study protocol of a randomized, double-blind, controlled trial

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Introduction: Nocturnal leg cramps (NLCs) are sudden contractions of the leg muscles, usually in the posterior calf muscles at night, affecting sleep quality. Because the precise pathophysiology of NCLs is unclear, different interventions have been proposed. There is conflicting evidence regarding the efficacy of conventional interventions in preventing cramps. Thus, the present study aims to investigate the effects of vitamin K2 for NLCs in a prospective randomized, double-blind, controlled trial.

Methods and analysis: This multicenter, randomized, double-blind, placebo-controlled clinical study will enroll older age (≥65-year-old) with two or more documented episodes of NLCs during 2weeks of screening. Participants will be randomized to receive vitamin K2 or a similar-looking placebo for 8weeks in a 1:1 ratio. Follow-up visits will be scheduled each week at the beginning of 4-week intervention, then participants will be visited semimonthly. The primary outcome is the difference in the mean number of NLCs per week in the vitamin K2 and placebo arms. The secondary outcomes include the severity and duration of NLCs in the vitamin K2 and placebo arms. Two hundred patients will be needed, for this two-treatment parallel design study, to achieve a probability is 90% that the study will detect a treatment difference at a two-sided 0.04 significance level, if the difference between treatments is 3.6 (difference in means between treatment arms) NLC events.

Discussion: Nocturnal Leg Cramps (NLCs) are a common musculoskeletal disorder in the general population, but effective and safe interventions have not been established. Our previous study has shown vitamin K2 was effective to reduce the frequency, severity, and duration of dialysis-related muscle cramps with a good safety profile. This randomized controlled trial (RCT) of rigorous methodological design will help to establish the effectiveness of vitamin K2 for the management of NLCs in older population. The findings of this RCT will encourage the studies of vitamin K2 in musculoskeletal disorders.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier, NCT05547750.

KEYWORDS

vitamin K2, nocturnal leg cramps, older population, muscle cramps, randomized controlled trial

1. Introduction

Nocturnal leg cramps (NLCs) are spontaneous contractions of muscles. The gastrocnemius is commonly involved (1), lasting from a few seconds to a few minutes (2). Patients might wake up with pain during attacks, making it difficult to sleep for a short period. It commonly occurs >60-year-old (3). The medical history and physical examination are usually sufficient to differentiate nocturnal leg cramps from other conditions, such as restless legs syndrome, claudication, myositis, and peripheral neuropathy. Factors that may lead to leg cramps attacks include hemodialysis, electrolyte imbalance, metabolic disorders, and congenital disorders (4). The cramps can be relieved by passive stretching of the gastrocnemius and deep tissue massage, but such prevention is limited, especially in patients with refractory muscle cramps (5). Quinine has been shown to be effective in treating NLCs but is not recommended by the US Food and Drug Administration due to severe side effects (6). Magnesium supplements are often used as a preventative treatment for NLCs (7, 8); however, their effectiveness is controversial (2, 9, 10). Magnesium supplements are widely marketed for the prophylaxis of NLCs since a double-blind, placebo-controlled study proved their effectiveness in pregnant women (11). However, magnesium administration did not show significant benefits in NLCs in double-blind, placebo-controlled studies (12, 13). Meta-analysis of some randomized control trials (RCTs) showed that magnesium therapy did not appear to be effective in the treatment of NLCs in the general population, but may have a negligible effect in pregnant women (14). Therefore, seeking new approaches to manage NLCs is imperative.

Vitamin K is a fat-soluble vitamin involved in carboxylation and activating several dependent proteins. It is found in two isoforms (phylloquinone (vitamin K1) and menaquinone (vitamin K2)) that differ in length and degree of saturation of the side chain. In addition to their role in coagulation, vitamin K-dependent proteins are involved in vascular calcification and osteoporosis physiology. Accumulating evidence has shown the beneficial effects of vitamin K2 supplementation on cardiovascular and bone health (15).

Another study revealed that vitamin K3 relieved muscle cramps by effectuating the voltage-dependent calcium channels to release the calcium stored in the cells, thus reducing the frequency of muscular contractions (16). To the best of our knowledge, no study has yet investigated the efficacy of vitamin K in NLCs. In addition, vitamin K2 has a good safety profile compared to other medications. Our pilot study demonstrated that vitamin K2 supplementation decreases the frequency, duration, and severity of muscle cramps in hemodialysis patients (17). To further investigate the efficacy and safety of vitamin K2 in NLCs, we designed this prospective, multicenter, randomized, double-blind trial.

2. Methods and analysis

2.1. Objective

The objective of the present study is to evaluate the efficacy and safety of vitamin K2 in the older population with NLCs.

2.2. Trial design

This prospective, multicenter RCT will recruit participants from two tertiary hospitals, Chengdu Third People's Hospital and Affiliated Hospital of North Sichuan Medical College, with the diagnosis of NLCs. This manuscript is according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (18).

The study will conduct as a randomized controlled, double-blinded trial. The subjects screened with NLCs will be randomly assigned to two arms: the vitamin K2 arm (vitamin K2 180 μg/day) and the placebo arm. The arms would consist of an equal number of participants, and the study would be conducted double-blind between the participants and the researchers during observation. The overall framework is to compare the treatment outcomes between the two groups.

A total of 200 participants will be randomly assigned to the two study groups using a 1:1 randomization protocol ($n = 100$/group). The vitamin K2 arm takes vitamin K2 180 μg/day at bedtime and the placebo arm takes a placebo at bedtime for 8 weeks. The frequency of muscle cramps and the duration and severity of each attack in both arms will be recorded every week (Figure 1).

Medical evaluation and enrolment procedure. All participants will be recruited through recruitment advertisement from September 2022 to September 2023. Potential participants suffering from NLCs are willing to participate in this study. In that case, they may contact the research assistant, who will make a medical history interview to screen the participants. Eligible participants will be invited to participate in a physical examination to confirm NLC diagnosis and assess eligibility for participation in the study.

2.3. Inclusion criteria

1. Unexplained cramps occurred two or more times in 2 weeks.
2. Age ≥ 65-year-old.

2.4. Exclusion criteria

1. Cramps caused by specific metabolic diseases and specific neuropathies (hypothyroidism, hemodialysis, hypoglycemia, alcoholism, amyotrophic lateral sclerosis, poliomyelitis complications, lumbar spinal stenosis, Parkinson's disease, radiculopathies, and motor neuron diseases).
2. Suffering from malignant tumors (breast cancer, prostate cancer, lymphoma, and multiple myeloma).
3. Taking diuretics, or vitamin K antagonist.
4. Taking supplements with vitamin K2 within 2 months before enrollment.

A research assistant will meet with the eligible participants after the medical evaluation and obtain their written informed consent. All participants' demographic variables, such as age, sex, medical history, and lifestyle (smoking and alcohol use), will be collected before intervention (baseline). Participants will also be asked relevant questions about the duration of symptoms and previous treatments.

Randomization and blinding participants will be classified into two intervention groups at a ratio of 1:1, using a computer-generated

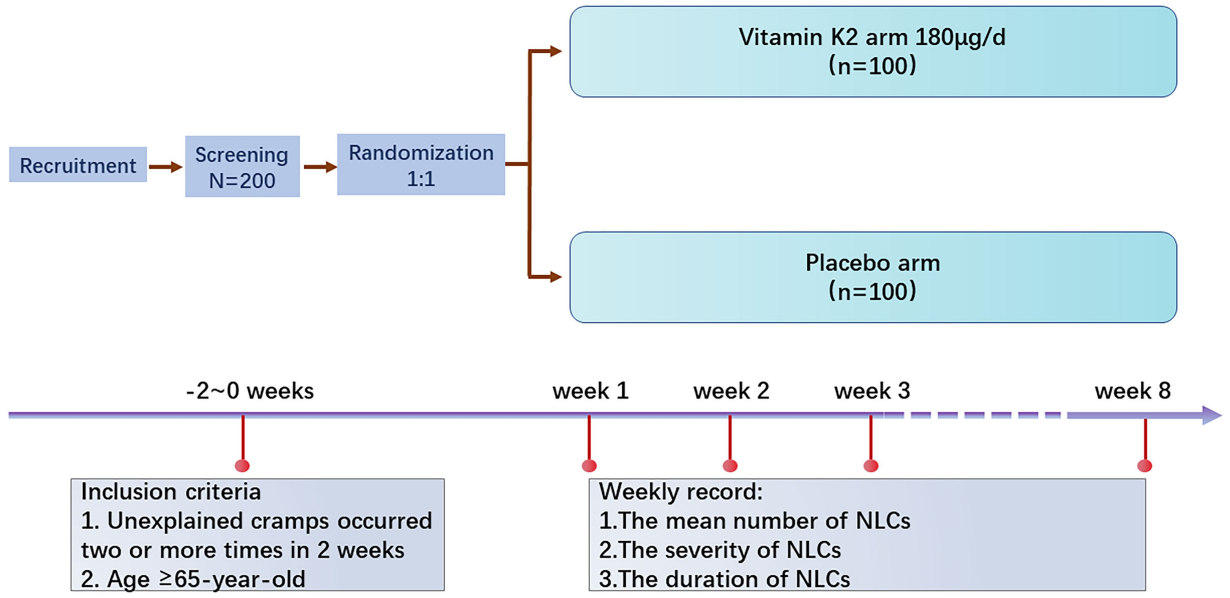

FIGURE 1
Study design and flow chart.

randomized sequence with varying unknown block sizes for all study centers without stratification. A research assistant not involved in clinical care and participant evaluations will prepare sequentially numbered, opaque, sealed envelopes based on a random list and ensure that anyone will not access or influence the allocation data. The participants, outcome assessor, and statistician will be blinded to group allocation and not involved in the treatment procedures.

3. Intervention description

3.1. Vitamin K2

Vitamin K2 is a fat-soluble and one of the body's indispensable vitamins. It is mainly synthesized by gut bacteria in the body and plays a role in the mitochondrial electron transport chain (19). It boosts calcium metabolism, acts on osteoblasts, and promotes bone tissue calcification. It also inhibits osteoclasts from causing bone resorption, thus increasing bone density, and preventing osteoporosis (20). Furthermore, it regulates the use of calcium and promotes the inhibition of vascular calcification by matrix Gla protein (MGP) activity (21). Vitamin K2 supplementation at recommended dosage does not affect vitamin K-dependent coagulation factors' activity. It does not enhance the carboxylation of prothrombin in healthy individuals. Vitamin K2 administration does not alter the hemostatic balance in healthy populations without anticoagulation treatment. Thus, vitamin K2 is deemed to have a good safety profile (22).

3.2. Placebo

Placebo tablets appear similar to those of vitamin K2, and the participants are unaware whether they are assigned to the vitamin K2 or the placebo group.

Criteria for trial termination or withdrawal participants may withdraw from the trial voluntarily for personal reasons or terminate it if they become unwell due to the treatment. During the experiment, researchers will record all adverse events.

4. Data management

Data will be collected at baseline and every week after random assignment (Table 1). Phone calls from research assistants will be programmed each week to maximize participant compliance in subsequent assessments. A registered participant will be excluded from the study if exclusion criteria are detected after registration. Researchers will record the cause and date of suspension. The consent to use data collected before the participant's withdrawal will be included in the informed consent form. We will perform all data analyses according to the intention to treat principle, and the analysis, data collection, and processing will be blinded with respect to treatment group assignment. Randomized participants who do not complete the study will be included in their assigned study groups for the primary analysis.

5. Primary endpoint

The mean number of NLCs attacks per week (During the 8-week investigation, the differences in the frequency of attacks will be recorded and compared between vitamin K2 and placebo arms).

6. Key secondary endpoints

1. Duration of muscle cramps in minutes (During the 8-week investigation, the differences in the duration of attacks will be recorded and compared between vitamin K2 and placebo arms).

TABLE 1 Study evaluation procedures and timeline.

Trail phase	Screening −2week	Baseline 0week	Intervention							
			1week	2week	3week	4week	5week	6week	7week	8week
Sign the informed consent form	×									
Determine eligibility	×									
Obtain medical and demographic data		×								
Fill in the general information	×									
Comorbidities and treatment			×	×	×	×	×	×	×	×
Outcome measures										
The mean number of NLCs			×	×	×	×	×	×	×	×
The severity of NLCs			×	×	×	×	×	×	×	×
The duration of NLCs			×	×	×	×	×	×	×	×
Physical examination						×				×

2. The severity of muscle cramps using a 1–10 analog scale (During the 8-week investigation, pain severity during attacks will be recorded and compared between vitamin K2 and placebo arms). The participants will be asked to record the severity of cramping with a 1–10 analog scale. That is, 1–3 points, mild pain, tolerable, does not affect sleep; 4–6 points, moderate pain, affects sleep, also tolerable; 7–10 points, sharp pain, intolerable.

7. Adverse events

All adverse events, defined as negative or unwanted reactions to intervention, will be recorded based on the symptoms reported by the patients and observations by a researcher at every visit. Follow-up visits will be scheduled each week in the beginning of 4-week intervention, then participants will be visited semimonthly of adverse events monitoring.

8. Sample size

The difference in the number of episodes of NLCs during the treatment period of 8 weeks, will serve as the sole primary efficacy endpoint for this study. We calculated that a total of 200 patients will be needed, for this two-treatment parallel design study, to achieve a probability is 90 percent that the study will detect a treatment difference at a two-sided 0.04 significance level, if the true difference between treatments is 3.6 (difference in means between treatment groups) NLC events. This is based on the assumption that the standard deviation of the mean number of NLC events is 8.

9. Statistical methods

SPSS statistical software is used for data analysis. Non-parametric tests (Mann–Whitney U test) are used for non-normal data. Results are given as medians with 95% confidence intervals (CI). Approximately normally distributed data are described as means and standard deviations. Other statistical tests used include Student's t-tests for continuous normally distributed data and Chi-Square tests for categorical data are stated with the results.

10. Quality assurance/monitoring/management

In order to standardize the procedures of staff training and learning, such as participant recruitment, outcome measures, data import, security, and management and analysis, a manual of operations and procedures and a case report form will be developed, including the monitoring plans to assure participant protection and data integrity, thus facilitating consistency in protocol implementation and data collection. The investigators, physicians, research assistants, outcome assessors, and statisticians should be trained in good clinical practice. The trained project managers will visit each center for monitoring to ensure data quality and compliance with the trial protocol.

All data will be stored electronically and strictly in a database with secure and restricted access. Encryption will be used for data transmission, and any information identifying individuals will be removed. Data will only be de-identified for analysis after this study.

11. Discussion

NLCs are a common cause of sleep disturbance among the older population. Although experienced by most people at some point in life, there is little concern about leg cramps because of their sporadic and infrequent occurrence. However, in patients with frequent NLCs, an annoying physical symptom may cause significant distress and nighttime disturbance. Forceful stretching is often the most straightforward remedy. Nonpharmacological methods of preventing leg cramps have not been proven effective for most people (2). In terms of pharmacological treatments, quinine (23) and magnesium (2, 7, 9, 10, 13) have been studied extensively; however, the results on the exact efficacy remain controversial. Other medications, such as calcium channel blockers, vitamin E, vitamin B complex, and antiepileptic medications (6, 24, 25), might alleviate NLCs, but their efficacy is not yet defined due to the low methodological quality of the trials.

Previously, we demonstrated that vitamin K2 supplementation decreases the frequency, duration, and severity of muscle cramps and is safe for hemodialysis patients (17).

NLC diagnosis criteria is based on subjective report without objective evaluation and parameters, which poses a limitation to this study.

To the best of our knowledge, this is the first to investigate the efficacy and safety of vitamin K2 in the treatment and prevention NLCs. The findings of this RCT will encourage further studies of vitamin K2 in musculoskeletal disorder.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Third People's Hospital of Chengdu (approval No. 2022-S17). Written informed consent to participate in this study was provided by the participants.

Author contributions

JT designed the study. JT, LW, YL, and RZ completed the research ethics registration and were responsible for the observation of patients in hospital. JT and YL drafted and submitted the manuscript. All authors contributed to the article and approved the submitted version.

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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

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Geriatric nutritional risk index predicts all-cause mortality in the oldest-old patients with acute coronary syndrome: A 10-year cohort study

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Background and objective: Nutritional status assessment in acute coronary syndrome (ACS) patients has been neglected for a long time. The geriatric nutritional risk index (GNRI) is a sensitive indicator for assessing the nutritional status of the elderly. This study aims to explore the association between GNRI and all-cause mortality in the oldest-old patients with ACS.

Methods: The patients who met the inclusion criteria were consecutively enrolled from January 2006 to December 2012. Clinical data were collected on admission, and all subjects were followed after being discharged. The nutritional status was evaluated using GNRI. The relationship between GNRI and all-cause mortality was assessed by using different analyses.

Results: A total of 662 patients with a mean age of 81.87±2.14years old were included in our study, and followed (median: 63months, IQR 51–71). Patients whose GNRI≤98 were reported as at risk of malnutrition (31.11%, n=206). In multivariable analysis, we found that for each SD increase in GNRI, the risk of all-cause mortality lowered by 23%, and the HR for GNRI≤98 was 1.39 (95% CI 1.04–1.86). After stratifying patients into three groups by tertiles of GNRI, we found that the HRs for tertile 2 and tertile 3 were 1.49 (95% CI 1.02–2.19) and 1.74 (95% CI 1.22–2.50), respectively. The trend test revealed a dose–response relationship between GNRI and all-cause mortality in the oldest-old with ACS. Lastly, in subgroup analyses, we found a reliable association between GNRI and all-cause mortality.

Conclusion: Malnutrition is common in the oldest-old patients with ACS, and GNRI could predict their long-term all-cause mortality in a dose-dependent manner. GNRI may be a prospective index for risk-stratification and secondary-prevention in the oldest-old patients with ACS.

KEYWORDS

oldest old, acute coronary syndrome, malnutrition, GNRI, mortality

1. Introduction

Acute coronary syndrome (ACS) is one of the leading causes of morbidity and mortality worldwide (1, 2). Aging is a vital risk factor for its prevalence and poor clinical outcomes. Almost a third of patients admitted for ACS and two-thirds of those dying from ACS are >75 years old (3, 4). Multi-comorbidities, complicated coronary artery lesions, and high prevalence of frailty in the oldest-old have increased the risk of re-infarcted, bleeding complications, and mortality when compared to younger patients (5–7).

Malnutrition is a common but under-recognized problem in hospitalized patients and caused detrimental and extensive impacts on clinical results with negative and far-reaching consequences for clinical outcomes (8, 9). As estimated, about 30–60% of hospitalized patients are malnourished. It not only leads to a high economic burden but is associated with longer hospital stays and higher mortality (10, 11). A higher prevalence of malnutrition has been found in the elderly (12). Recently, the side effects of malnutrition in cardiovascular diseases have come under the researchers' spotlight. Clinical studies have demonstrated that malnutritional status has negative effects on people affected by cardiovascular diseases including ACS (13–16).

Geriatric nutritional risk index (GNRI) was first created by Bouillanne et al. to identify nutritional-related complications among the elderly (17–19). It has been used to assess the nutritional status of patients with heart failure (20), chronic kidney disease (CKD) (21), tumors (22), etc. And many studies have revealed that GNRI was significantly associated with vascular calcification, length of hospital stay, and mortality (23, 24). However, studies about the relationship between GNRI and the prognosis of ACS have seldom been conducted (25).

Herein our study aimed to explore the relationship between GNRI and all-cause mortality of the oldest-old ACS patients, investigate the predictive value of GNRI on patients; long-term prognosis, and assess the effectiveness of the risk-stratify for them.

2. Methods

2.1. Study design and population

From January 2006 to December 2012, 720 patients aged ≥80 admitted to the cardiology department of the Chinese People's Liberation Army (PLA) General Hospital for coronary angiography due to ACS symptoms, were enrolled (Figure 1). A total of 699 patients signed their informed consent. The exclusion criteria were: (1) patients with severe valvular heart disease, severe pulmonary hypertension, severe liver or renal insufficiency, rheumatoid arthritis, infectious diseases, and malignant tumors; (2) patients with familial hypertriglyceridemia (triglyceride ≥5.65 mmol/L); and (3) patients with neuropsychiatric problems that prevent them cooperating with the researchers. Most critically, our study followed the Declaration of Helsinki and was certified by the Chinese PLA General Hospital's Ethics Service Center.

To confirm the diagnosis of coronary heart disease, the cardiac intervention center of the PLA General Hospital performed coronary intervention and perioperative treatment according to current guidelines. All of the angiography results were analyzed using the same image analysis tool. Loading doses of aspirin (300 mg) and clopidogrel (300 mg) were administered before the intervention. The degree of coronary stenosis was determined using the Gensini score (26), and two experienced experts trained the recorders. Individualized interventions, such as intensive medication therapy, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG), were administered based on coronary angiography results, and long-term follow-up was conducted after being discharged.

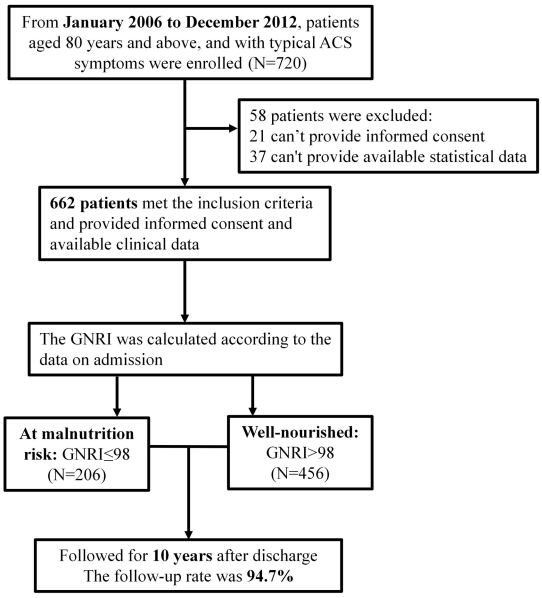

FIGURE 1
Flow chart of patient enrollment, grouping, and follow-up.

2.2. Data collection and index evaluation

We collected demographic data (age and gender), anthropometric data [height, body weight, BMI, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP)], laboratory data [total cholesterol (TC), triglycerides (TG), low-density lipid-cholesterol (LDL-C), high-density lipid-cholesterol (HDL-C), estimated glomerular filtration rate (eGFR), fasting plasma glucose (FPG), uric acid (UA), albumin], left ventricular ejection fraction (LVEF), comorbidity data [diabetes mellitus type 2 (T2DM), hypertension, stroke, prior myocardial infarction (MI), hyperlipidemia and chronic kidney disease (CKD)], smoking, drug-usage data [aspirin, clopidogrel, statins, β-blocker and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)], coronary lesions data[left anterior descending branch (LAD), left circumflex branch (LCX), right coronary artery (RCA), left main coronary artery (LM), multivessel lesions and Gensini score] and treatment data (intensive medications, PCI and CABG).

The body mass index (BMI) was calculated as follows:

$$\mathrm{BMI} = \mathrm{height}\left(\mathrm{m}^2\right) / \left[\mathrm{weight}\left(\mathrm{kg}\right)\right]^2$$

According to WHO criteria in the Asian population, patients could be classified as overweight (BMI > 24.9 kg/m^2), normal-weight (BMI 18.5–24.9 kg/m^2), and under-weight (BMI < 18.5 kg/m^2) (27).

The eGFR was calculated by the Chinese modified Modification of Diet in Renal Disease equation:

$$\mathrm{eGFR}\left(\mathrm{ml/min/1.73m^2}\right) = 175 \times \text{standardlized creatinine}\left(\mathrm{mg/dl}\right)^{-1.234} \times \text{age}\left(\text{years old}\right)^{-0.179} \times 0.79$$

Standardized creatinine (Scr) was calculated by the calibration equation:

$$\mathrm{Scr}\left(\mathrm{mg/dl}\right) = 0.795 \times \left[\text{enzymatic method Scr}\left(\mathrm{mg/dl}\right)\right] + 0.29$$

Chronic kidney disease was defined as eGFR <60 ml/min/1.73 m^2.

The diagnostic criteria for diabetes mellitus type 2 (T2DM) were: FPG ≥ 7.0 mmol/L; and (or) random blood glucose (RBG) ≥ 11.1 mmol/L; blood glucose ≥11.1 mmol/L 2 h after oral glucose tolerance test (OGTT).

Hyperlipidemia was defined as the use of lipid-lowering drugs or total serum cholesterol ≥240 mg/dl.

Based on coronary angiography results, the multivessel lesion was defined as having more than 2 vessels with significant diameter stenosis of 50%.

2.3. Assessment of nutritional status

The geriatric nutritional risk index (GNRI) was used in this study to assess the nutritional status of the oldest-old patients with ACS. GNRI is calculated as follow (17):

$$\mathrm{GNRI} = 1.489 \times \text{albumin}\left(\mathrm{g/L}\right) + 41.7 \times \left(\text{weight / ideal weight}\right)\left(\mathrm{kg}\right)$$

The ideal weight was calculated as follows: 22 × square of height (m^2) (18). It is worth noting that GNRI was created to identify and predict nutritional-related complications (17). The original GNRI cut-off values and grades of nutrition-related risk were: severe risk (GNRI <82), moderate risk (GNRI 82–92), low risk (GNRI 92–98), and no risk (GNRI >98). Patients were often considered as having a normal nutritional status if their GNRI >98 (19). Hence, we used 98 as the cut-off value in the present study. GNRI >98 was defined as well-nourished, while GNRI≤98 was defined as at malnutrition risk.

2.4. Endpoint and follow-up

The follow-up period lasted up to 10 years performed every 12 months after discharge *via* outpatient visits, telephone records, or medical records of outcomes. During the follow-up period, 37 patients were lost follow-up, leaving 662 (94.7%) patients enrolled in the final statistical analysis. All-cause mortality (cardiac and non-cardiac) was the ultimate endpoint of our research.

2.5. Statistical analysis

The baseline characteristics of the participants were shown according to GNRI >98 and GNRI ≤98. The measurement data of normal distribution were expressed as mean ± SD, and the *T*-test was used for homogeneity of variance. If the variance is not uniform, the rank-sum test was used. Non-normally distributed measurements were represented by the median and interquartile range (IQR). Statistical data were expressed by quantity, the chi-square test was used to evaluate differences between groups, and an analysis of variance was used to compare data between groups. Pearson correlation test was used to evaluate the correlation between GNRI and clinical parameters. Unadjusted survival curves were generated using log-rank tests in Kaplan–Meier plots. Univariate Cox regression analysis (HR, 95% CI) was used to identify the factors associated with all-cause mortality. $p < 0.05$ was considered statistically significant. The Cox proportional hazards model was used to estimate the association between GNRI and all-cause mortality. We built three regression models: model 1 is the unadjusted model, model 2 is the partially adjusted model (age and gender), and model 3 is the completely adjusted model (age, gender, diabetes, stroke, CKD, aspirin, eGFR, FPG, UA, EF, Gensini score, LM lesions, multivessel lesions, and HDL-C). The GNRI was transformed into three classification variables for the primary analysis. For the trend test, the new categorical variables were recorded as continuous variables and entered into the regression model. We also standardized the GNRI and then put it into a regression model to determine the relationship between the change in GNRI per SD and all-cause mortality. In addition, we performed a subgroup analysis to explore whether the relationship between GNRI and all-cause mortality could be modified by the following variables: gender, diabetes, hypertension, prior MI, hyperlipidemia, CKD, smoking, LM lesions, and multivessel lesions. Interactions between GNRI and the above variables were tested. Results were reported as HR and 95% CI. Two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using the statistical software packages R (28) and Empower Stats (29).

3. Results

3.1. Baseline characteristics and malnutrition assessment

There were 662 oldest-old patients with ACS enrolled in our study, 71.9% ($n = 476$) of whom were males (Table 1). The mean age of the participants was 81.87 ± 2.14 years old (IQR 80–89), and the average GNRI at admission was 102.47 ± 11.06. According to GNRI, the patients were classified as well-nourished (GNRI >98, $n = 456$, 68.89%), and at malnutrition risk (GNRI ≤98, $n = 206$, 31.11%). Patients with low GNRI had lower body weight, BMI, SBP, LVEF, albumin, and eGFR, while they have higher height and heart rate. There were no statistical differences in TC, TG, LDL-C, HDL-C, FPG, and UA between the two groups. Patients at malnutrition risk had a higher proportion of CKD but a lower proportion of hypertension. There was no significant difference in the prevalence of other common

TABLE 1 Baseline characteristics of all participants (*N*=662).

Variable	Total	GNRI >98	GNRI ≤98	*d*-value	*p*-Value
N	662	456	206		–
Demographic data					
Age (year old)	81.87 ± 2.14	81.83 ± 2.11	81.98 ± 2.20	−0.0701	0.398
Female	186 (28.10%)	135 (29.61%)	51 (24.76%)	0.1079	0.199
Anthropometric data					
Height (cm)	165.32 ± 8.25	164.81 ± 8.61	166.46 ± 7.27	−0.1806	0.017
Body weight (kg)	67.20 ± 10.68	69.74 ± 10.16	61.55 ± 9.63	0.8191	<0.001
BMI (kg/m^2)	24.57 ± 3.40	25.64 ± 2.97	22.19 ± 3.08	1.1482	<0.001
Heart rate (bpm)	74.81 ± 14.02	74.01 ± 13.47	76.57 ± 15.07	−0.183	0.029
SBP (mmHg)	137.08 ± 21.79	138.41 ± 21.10	134.15 ± 23.02	0.1962	0.020
DBP (mmHg)	71.44 ± 12.12	71.73 ± 12.07	70.78 ± 12.23	0.0784	0.350
Laboratory data					
TC (mmol/L)	4.11 ± 0.97	3.94 ± 1.09	3.87 ± 1.18	0.0626	0.443
TG (mmol/L)	1.39 ± 0.72	1.43 ± 1.02	1.30 ± 0.95	0.1302	0.133
LDL-C (mmol/L)	2.36 ± 0.84	2.21 ± 0.77	2.11 ± 0.76	0.1304	0.109
HDL-C (mmol/L)	1.13 ± 0.36	1.15 ± 0.31	1.15 ± 0.39	0	0.803
eGFR (ml/min/1.73 m^2)	70.85 ± 23.11	72.16 ± 24.16	67.97 ± 20.35	0.1818	0.031
FPG (mmol/L)	7.05 ± 4.13	6.91 ± 4.45	7.34 ± 3.32	−0.1041	0.224
UA (μmol/L)	351.59 ± 149.66	355.77 ± 164.12	342.34 ± 110.98	0.0897	0.285
Albumin (g/L)	37.54 ± 5.98	39.85 ± 4.22	32.45 ± 6.17	1.5073	<0.001
GNRI	102.47 ± 11.06	107.93 ± 7.31	90.38 ± 7.94	2.3365	<0.001
LVEF (%)	55.65 ± 9.91	56.73 ± 9.23	53.28 ± 10.92	0.3525	<0.001
Comorbidity data					
T2DM	231 (34.89%)	157 (34.43%)	74 (35.92%)	0.0313	0.709
Hypertension	511 (77.19%)	363 (79.61%)	148 (71.84%)	0.1849	0.028
Stroke	138 (20.85%)	94 (20.61%)	44 (21.36%)	0.0184	0.827
Prior MI	120 (18.13%)	82 (17.98%)	38 (18.45%)	0.012	0.886
Hyperlipidemia	151 (22.81%)	111 (24.34%)	40 (19.42%)	0.1175	0.162
CKD	78 (11.78%)	43 (9.43%)	35 (16.99%)	0.2364	0.005
Smoking	164 (24.77%)	112 (24.56%)	52 (25.24%)	0.0158	0.851
Medication data					
Aspirin	642 (96.98%)	444 (97.37%)	198 (96.12%)	0.0731	0.384
Clopidogrel	632 (95.47%)	435 (95.39%)	197 (95.63%)	0.0114	0.892
Statins	615 (92.90%)	426 (93.42%)	189 (91.75%)	0.0651	0.438
β-blocker	418 (63.14%)	286 (62.72%)	132 (64.08%)	0.0282	0.737
ACEI/ARB	364 (54.98%)	252 (55.26%)	112 (54.37%)	0.018	0.830
Coronary lesions					
LAD lesions	560 (84.59%)	385 (84.43%)	175 (84.95%)	0.0145	0.863
LCX lesions	383 (57.85%)	256 (56.14%)	127 (61.65%)	0.1116	0.184
RCA lesions	429 (64.80%)	282 (61.84%)	147 (71.36%)	0.1991	0.018
LM lesions	109 (16.47%)	73 (16.01%)	36 (17.48%)	0.0395	0.638
Multivessel lesions	466 (70.39%)	306 (67.11%)	160 (77.67%)	0.2314	0.006
Gensini score	53.65 ± 42.65	50.89 ± 41.63	59.77 ± 44.31	−0.209	0.013

(Continued)

TABLE 1 (Continued)

Variable	Total	GNRI >98	GNRI ≤98	*d*-value	*p*-Value
Treatment				0.0158	0.851
Intensive medication	241 (36.40%)	167 (36.62%)	74 (35.92%)		
PCI	405 (61.18%)	279 (61.18%)	126 (61.17%)		
CABG	16 (2.42%)	10 (2.19%)	6 (2.91%)		

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein-cholesterol; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein-cholesterol; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary; SBP, systolic blood pressure; TC, total cholesterol; T2DM, diabetes mellitus type 2; TG, triglycerides; UA, uric acid.

complications such as diabetes, hyperlipidemia, or stroke. What is more, we noticed that patients with low GNRI were more likely to have RCA lesions and multivessel lesions, and got a higher Gensini score. In terms of smoking behavior, medication usage, and treatment manners, there was no significant difference between the two groups.

We further analyzed GNRI in patients with different BMI and albumin levels (Figure 2). The high prevalence of malnutrition was found in patients with BMI <18.5 kg/m^2 (94.12%), and patients with albumin<35 g/L (74.68%). What is more, there were substantial malnutritional patients in the normal-to over-weight groups.

3.2. Association between GNRI and all-cause mortality

The participants were followed for a median of 63 months (IQR 51–74). There were 201 endpoint-events during the follow-up, with 82 occurring in the low GNRI group and 119 in the other. As a nutritional screening index, GNRI was associated with many traditional cardiovascular risk factors (Supplementary Table 1). In univariate analysis (Table 2), a strong positive association was found between all-cause mortality and age, diabetes, stroke, CKD, FPG, Gensini scores, LM lesions, and multivessel lesions. Meanwhile, aspirin, HDL-C, eGFR, LVEF, albumin, and GNRI (HR = 0.97, 95% CI [0.96, 0.99]) were closely associated with a reduction in all-cause mortality. However, male, hypertension, BMI, TC, and LDL-C did not show a significant association with the outcome.

We further assessed the association between GNRI and all-cause mortality by multivariable Cox regression analysis (Table 3 and Figure 3). For each SD increase in GNRI, the risk of all-cause mortality was lowered by 23%. And when compared with the high GNRI group, the HR of all-cause mortality in the low GNRI group was 1.39 (95% CI [1.04, 1.86], $p < 0.05$). Then we divided the patients into three groups according to the tertiles of GNRI. Compared with tertile 1, the HRs of tertile 2 and tertile 3 were 1.49 (95% CI [1.02, 2.19], $p < 0.05$) and 1.74 (95% CI [1.22, 2.50], $p < 0.01$), respectively. Subsequently, the trend test revealed a dose–response between GNRI and all-cause mortality.

3.3. Survival analyses of GNRI and all-cause mortality

According to the Kaplan–Meier survival analysis (Figure 4A), we found that patients with high GNRI had a longer survival time ($p < 0.001$). Then we further divided GNRI into the tertiles and analyzed them. As shown in Figure 4B, all-cause mortality in tertile 3 was significantly lower than in tertile 1 and tertile 2 ($p < 0.001$).

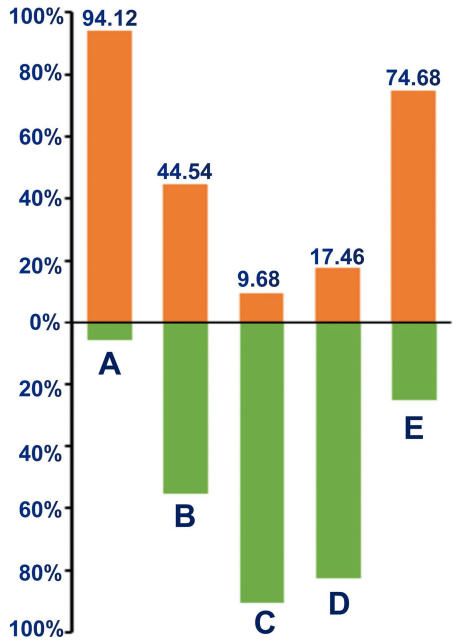

FIGURE 2
Percentage of malnutrition according to BMI and albumin. **(A)** Under-weight (BMI <18.5kg/m^2); **(B)** Normal-weight (BMI 18.5–24.9kg/m^2); **(C)** overweight (BMI >24.9kg/m^2); **(D)** normal-albumin (≥35g/L); **(E)** hypo-albumin (<35g/L).

3.4. Subgroup analyses

In the subgroup analysis (Figure 5), we adjusted sex, age, diabetes, stroke, CKD, aspirin, eGFR, FPG, UA, LVEF, Gensini score, LM lesions, multivessel lesions, and HDL-C except for the stratified variables. The results showed that low GNRI was associated with increased all-cause mortality in those males, with diabetes mellitus, with previous MI, without multivessel lesions, and without LM lesions. But the values of p for interaction were all >0.05, suggesting the inverse association between low GNRI with all-cause mortality across all those subgroups.

4. Discussion

In this study, we collected clinical data from 662 oldest-old patients with ACS who received coronary angiography and followed for 10 years. As far as we know, this's the first study to investigate the association between GNRI and all-cause mortality in the oldest-old patients with ACS. Our key findings were the following: (1) the

TABLE 2 Univariate Cox regression analyses for independent variables associated with all-cause mortality.

Variable	All-cause mortality	
	HR (95% CI)	*p* value
Male	1.05 (0.77, 1.43)	0.777
Age (year)	1.08 (1.02, 1.15)	0.012
BMI (kg/m^2)	0.96 (0.92, 1.00)	0.084
SBP (mmHg)	0.99 (0.99, 1.00)	0.058
DBP (mmHg)	0.99 (0.98, 1.01)	0.337
TC (mmol/L)	1.09 (0.98, 1.20)	0.101
TG (mmol/L)	1.06 (0.95, 1.19)	0.314
LDL-C(mmol/L)	1.05 (0.88, 1.26)	0.594
HDL-C(mmol/L)	0.53 (0.33, 0.83)	0.006
eGFR(ml/min/1.73m^2)	0.98 (0.97, 0.98)	<0.001
FPG (mmol/L)	1.05 (1.03, 1.06)	<0.001
UA (μmol/L)	1.00 (1.00, 1.00)	0.004
albumin	0.96 (0.94, 0.98)	<0.001
GNRI	0.97 (0.96, 0.99)	<0.001
LVEF	0.96(0.95, 0.98)	<0.001
T2DM	1.46 (1.10, 1.93)	0.008
Hypertension	1.07 (0.76, 1.49)	0.712
Stroke	1.50 (1.09, 2.04)	0.012
Prior MI	1.05 (0.75, 1.49)	0.764
Hyperlipidemia	0.81 (0.57, 1.15)	0.230
CKD	2.30 (1.62, 3.25)	<0.001
Smoking	1.08 (0.78, 1.48)	0.648
Aspirin	0.38 (0.21, 0.70)	0.002
Clopidogrel	0.60 (0.34, 1.05)	0.071
Statins	0.98 (0.59, 1.64)	0.951
β-blocker	1.06 (0.80, 1.42)	0.672
ACEI/ARB	1.11 (0.84, 1.48)	0.450
LM lesions	1.53 (1.09, 2.14)	0.014
Multivessel lesions	1.44 (1.04, 2.00)	0.030
Gensini score	1.01 (1.00, 1.01)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure; TC, total cholesterol; T2DM, diabetes mellitus type 2; TG, triglycerides; UA, uric acid.

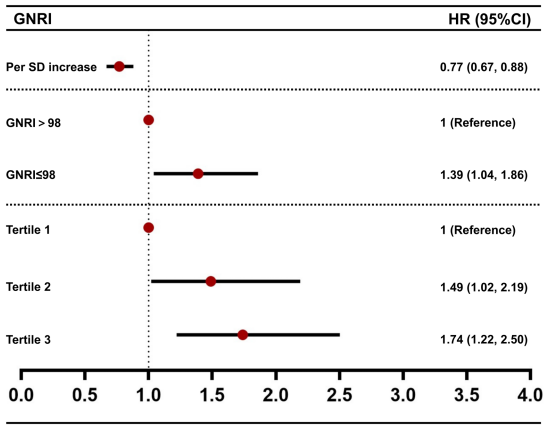

FIGURE 3
Forest plot of the association between GNRI and all-cause mortality. HR values were from model 3 of Table 3.

prevalence of malnutrition risk was high in the oldest-old patients with ACS; (2) as a reliable tool for assessing the nutritional status of the elderly, GNRI is associated with many traditional cardiovascular risk factors; (3) low GNRI is an independent risk factor of all-cause mortality in a dose-dependent manner; (4) GNRI has a stable predictive ability for all-cause mortality; and (5) GNRI is a prospective indicator to stratify the risk of all-cause mortality in the oldest-old patients with ACS.

Aging and diseases, especially cardiovascular diseases, are the risk factors for malnutrition (30–32). The oldest-old (elderly >80 years old) tend to have a higher malnutrition risk than those 65–80 years old (33). Despite its high prevalence and negative impact on short-and long-term prognosis, malnutrition remains underdiagnosed. One of the reasons is the lack of a broadly acknowledged definition and diagnostic criterion, and assessing patients' nutritional status in an emergency like ACS is even more challenging. GNRI seems a promising index because that it can be readily calculated using three objective measurements: serum albumin concentration, height, and body weight. GNRI was strongly associated with poor outcomes in elderly emergency surgery patients, according to Jia et al. (34). Therefore, we picked GNRI as the screening tool for malnutrition in the oldest-old patients with ACS and further assess the association between GNRI and the prognosis of the oldest-old ACS patients.

Serum albumin and BMI are common nutrition indicators; however, they are affected by dehydration, heart failure, inflammation, and other factors (9, 35). In comparison, GNRI is more reliable. It is not simply an overlap of albumin and BMI. Adding GNRI to a baseline model of established risk factors increased the predictive effect of mortality beyond BMI or serum albumin (36, 37). GNRI performed much better than serum albumin level alone in predicting MACE in patients receiving the PCI with rotational atherectomy in the previous study (38). Lots of studies have been conducted to investigate the relationship between GNRI and the prognosis of some chronic diseases, such as chronic heart failure, CKD, and tumors. And the results revealed that low GNRI correlated with longer hospital stays and high mortality. However, few studies evaluated the association between GNRI and the prognosis of elderly patients with ACS, let alone the oldest-old patients. To our knowledge, this was the first time to confirm that a low GNRI was an independent predictor of long-term prognosis in the oldest-old patients with ACS.

Common nutrition screening tools include subjective global assessment (SGA), mini nutritional assessment (MNA), MNA-short form (MNA-SF), prognostic nutritional index (PNI), controlling nutritional status (CONUT), etc. (35, 39). These methods are sensitive to subjective biases and have limitations in terms of time, personnel, and the potential for overdiagnosis. Several studies have compared GNRI with them (40, 41). Wafaa et al. (25) demonstrated that GNRI

TABLE 3 Multivariable Cox regression analyses for the association between GNRI and all-cause mortality.

GNRI	Deaths, *N* (%)	HR (95% CI)		
		Model 1	Model 2	Model 3
Per SD increase	201 (28.8%)	0.75 (0.66, 0.85)***	0.76 (0.67, 0.86)***	0.77 (0.67, 0.88)***
>98	119 (26.1%)	1 (Reference)	1 (Reference)	1 (Reference)
≤98	82 (39.8%)	1.70 (1.28, 2.25)***	1.69 (1.27, 2.23)***	1.39 (1.04, 1.86)*
Tertile 1	51 (23.1%)	1 (Reference)	1 (Reference)	1 (Reference)
Tertile 2	62 (28.2%)	1.34 (0.92, 1.94)	1.33 (0.92, 1.93)	1.49 (1.02, 2.19)*
Tertile 3	88 (39.8%)	2.03 (1.43, 2.86)***	1.99 (1.41, 2.82)***	1.74 (1.22, 2.50)**
p for trend		<0.001	<0.001	0.003

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$.
Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for sex, age, diabetes, stroke, CKD, aspirin, eGFR, FPG, UA, LVEF, Gensini score, LM lesions, and multivessel lesions.

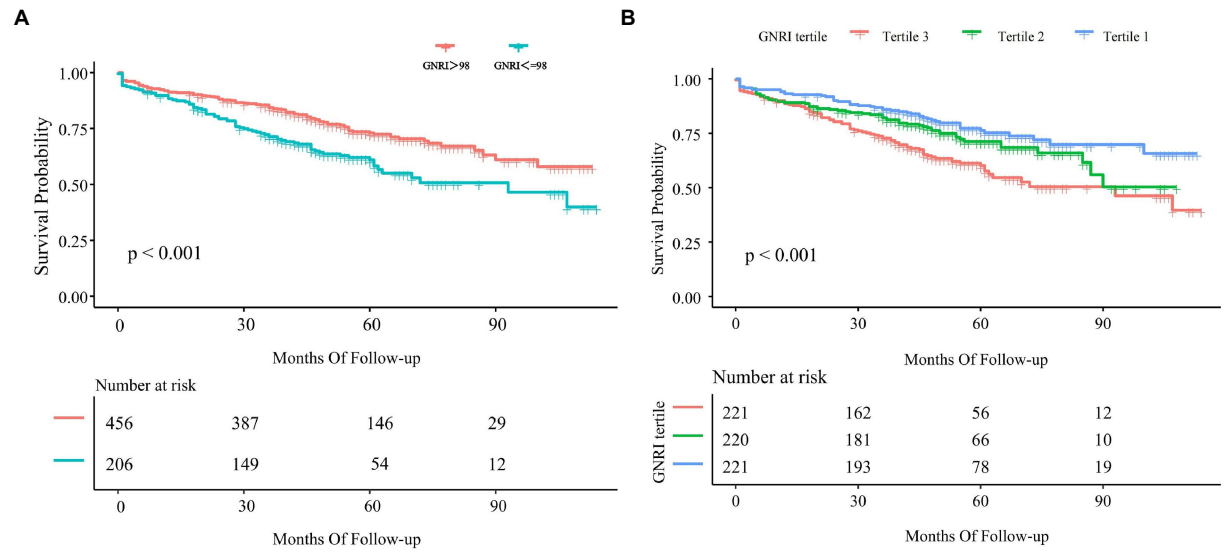

FIGURE 4
Kaplan–Meier curve of GNRI and all-cause mortality. **(A)** Kaplan–Meier survival curve for all-cause mortality by GNRI 98. **(B)** Kaplan–Meier curve for all-cause mortality by tertiles of GNRI. The result was shown as the Kaplan–Meier curve and *p*-value.

had a stronger predictive value for describing and classifying nutritional status and nutritional-related problems in elderly hospitalized patients. The GNRI was created as a nutrition-related risk index to recognize and anticipate nutritional-related problems. In the present study, we noticed that a low GNRI at admission was a robust predictor for all-cause mortality in the oldest-old individuals with ACS.

In our study, the GNRI was found to have a positive correlation with BMI, eGFR, LVEF, and serum albumin concentration. The roles of abnormal glucose and lipid metabolism in the pathogenesis of ACS have been widely acknowledged (26). Surprisingly, we did not find an association like in other studies (36, 37, 42) between GNRI and FPG, TC, TG, LDL-C, or HDL-C. Our distinct subjects may explain the differences. As we all know, malnutrition is more common in the elderly due to decreased appetite, impaired digestion and absorption ability, and the impact of diseases (43). So, in our oldest-old patients, hyperglycemia and hyperlipidemia were relatively less prevalent. And our patients followed prescriptions more strictly (92.90% vs. 78.7%) so that maintained their superior blood glucose and cholesterol levels.

CKD is a severe risk factor for coronary artery disease (CAD) (44, 45). Patients with CKD generated atherosclerotic plaque as a result of traditional (hyperlipidemia, hypertension, diabetes mellitus, smoking, and so on) and non-traditional (uremia-related cardiovascular disease risk factors such as inflammation, aberrant calcium-phosphorus metabolism, and so on) risk factors (46, 47). As eGFR declines, this progress gets even worse. Herein our study, we discovered the correlation between GNRI and eGFR which may further inspire researchers to explore the relationship between nutritional status and cardio-renal syndrome.

Obesity has been considered a traditional risk factor for cardiovascular diseases. Herein the present study, we found that there were substantial malnutritional patients in the normal-to over-weight patients who may be seen as relatively strong before, and our findings may provide evidence supporting the existence of the obesity paradox (48, 49). Inflammation is a crucial factor in the development of ACS, and it also makes a significant contribution to malnutrition. The malnutrition-inflammation-atherosclerosis (MIA) syndrome has already been proposed as a crucial component of geriatric syndrome

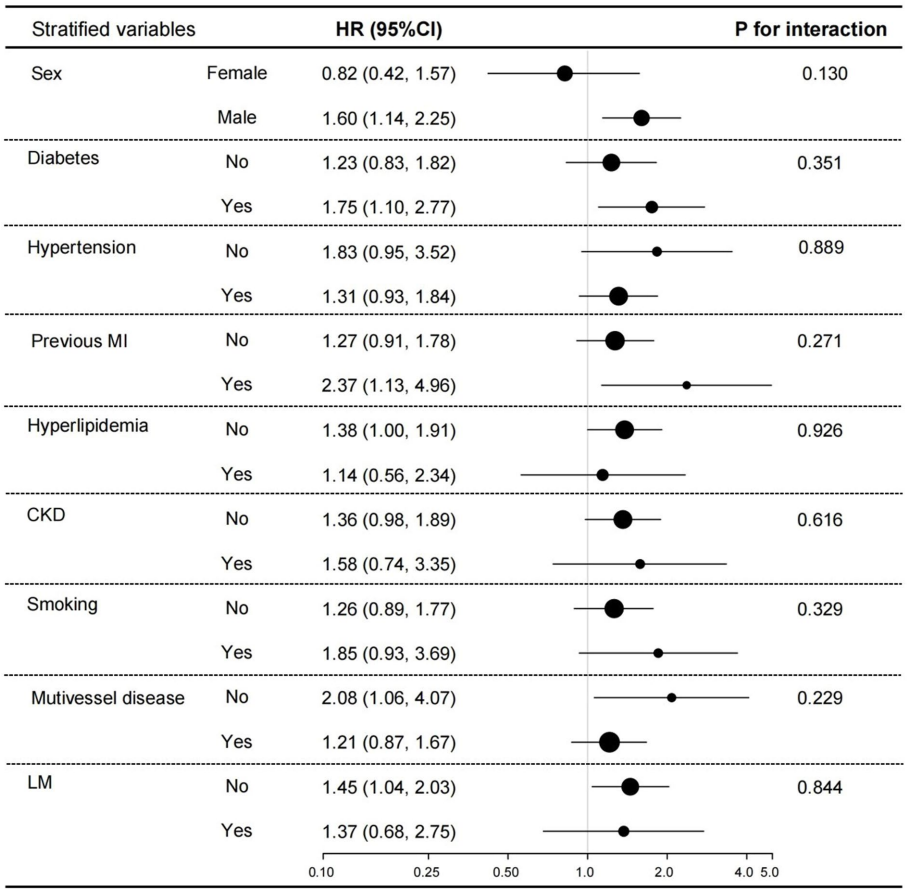

FIGURE 5
Subgroup analyses for the association between GNRI and all-cause mortality. Adjusted sex, age, diabetes, stroke, CKD, aspirin, eGFR, FPG, UA, LVEF, Gensini score, LM lesions, multivessel lesions, and HDL-C.

(50–52). GNRI was strongly associated with the progression of atherosclerosis in elderly CAD patients (53). In the present study, we found that patients with a low GNRI were more prone to developing multivesicular lesions and got a higher Gensini score. This was the first to report an association between GNRI and the location and severity of the culprit coronary arteries.

There have been reported that effective nutritional interventions could significantly reduce the length of hospital stay and mortality of malnutritional patients (54, 55). By using GNRI, one can quickly recognize the risk of malnutrition and then take measures to improve nutritional status, and the prognosis gets ultimately enhanced. The GNRI was created to assess and forecast nutritionally associated problems. In multi-variate analysis and subgroup analysis, we demonstrated that GNRI stably predicts all-cause mortality of the oldest-old patients in a dose-manner. Based on these, we concluded that the GNRI could serve as a perspective index for risk-stratification and secondary prevention of the oldest-old patients with ACS.

4.1. Strengths and limitations

This was the first time enrolled oldest-old patients with ACS, assessed their nutritional status with GNRI on admission, and followed for 10 years. Then we evaluated the association between GNRI and long-term all-cause mortality. In the end, we demonstrated that GNRI is a nutrition assessing tool with prominent advantages, and it may be a hopeful tool to quickly and accurately evaluate nutritional status and predict their prognosis. The results of our study were reliable and practical for clinical use.

However, there were some deficits inevitably. First, this was a single-center cohort study and all participants were Chinese and our was something old, so some selection bias existed. Second, we did not record dietary intake, physical activity, and other factors during the follow-up that may affect nutritional status. Finally, we took 98 as the cut-off value of GNRI, it may need further adjustment according to race or age, etc.

5. Conclusion

In this study, we confirmed that low GNRI was an independent predictive factor for all-cause death in the oldest-old patients with ACS, and the relationship between the two was dose-dependent. GNRI may be a perspective index for risk stratification in the oldest-old patients with ACS.

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 human participants were reviewed and approved by Chinese PLA General Hospital's Ethics Service Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL, JS, and XH: conducted research and wrote the paper. YL and YS: analyzed the data. YJ, JW, and HL: conducted research. ZF: designed research and had primary responsibility for final content. 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1129978/full#supplementary-material

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Relationship between high dose intake of vitamin B12 and glaucoma: Evidence from NHANES 2005–2008 among United States adults

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Objective: Glaucoma has currently become the second leading cause of blindness in the world. Serum vitamin B12 level has been found to be involved in the development and progression of glaucoma. We performed the present study to confirm this association.

Methods: This cross-sectional study included 594 participants aged 40 years and older in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2008. Retinal imaging was performed using the Ophthalmic Digital Imaging system (Retinography) to assess the retina for the presence of features of glaucomatous lesions. Logistic regression models were used to assess the association between dietary vitamin intake and glaucoma.

Results: After screening, 594 subjects were finally included. Among all vitamin intakes, we observed significant differences between the two groups for vitamin B12 intake (5.93 vs. 4.77 mg, p=0.033). According to the logistic regression results, the intake of vitamin B12 was significantly positively associated with glaucoma (model 1: OR=1.078, 95% CI=1.019–1.141; model 2: OR=1.092, 95% CI=1.031–1.158; model 3: OR=1.092, 95% CI=1.029–1.158). After performing a quantile regression, we observed a significant positive association between vitamin B12 intake and incident glaucoma in the fourth quartile (model 1: OR=1.133, 95% CI=1.060–1.210; model 2: OR=1.141, 95% CI=1.072–1.215; model 3: OR=1.146, 95% CI=1.071–1.226).

Conclusions: Therefore, the above results, high-dose intake of vitamin B12 may promote the development of glaucoma.

KEYWORDS

vitamin B12, glaucoma, national health and nutrition examination survey, nutrition epidemiology, cross-sectional study

1. Introduction

Glaucoma, a neurodegenerative disease, is the second leading cause of irreversible blindness, with a worldwide prevalence of 3.5% among people aged 40 to 80 years (1). With an increasing proportion of the elderly population, 111.8 million people are expected to have glaucoma by

2040 (2). The common types of glaucoma include primary open-angle glaucoma (POAG), primary closed-angle glaucoma (PCAG) and normal tension glaucoma (NTG). Commonalities between all types of glaucoma result in damage to the optic nerve, apoptosis of retinal optic ganglion cells and visual field.

defects (3–7). Retinal ganglion cell apoptosis may be the result of impaired blood supply to the head of the optic ganglion or direct toxic effects of multiple cytotoxic substances (8–10). Glaucoma is a multi-factorial disorder, and a strong association has been found between increasing age and sex and disease progression, while other factors including hypertension, genetic variation, and other environmental risk factors may also affect it (11–13). Vascular theory and mechanical theory are the two main mechanisms of glaucoma pathogenesis. For mechanical reasons, high intraocular pressure can damage ganglion cell axons (14). The vascular theory suggests that increased intraocular pressure and other risk factors contribute to insufficient blood flow to the eyes, which can cause damage to the optic nerve (15). The precise mechanism of glaucoma remains to be determined.

Vitamin B12 (cobalamin) therapy can reduce oxidative stress damage and inflammation levels of the nervous system, and it can promote the regulation of the antiviral activity and immune system, especially when combined with folic acid (16–22). Vitamin B12 (cobalamin) deficiency is the only vitamin deficiency definitively associated with optic neuropathy characterized by slow-progressing optic atrophy (23). Recent study indicates that vitamin B12 can alleviate COVID-19 symptoms, through its analgesic function and role in neuromuscular disorders (24). A cross-sectional study showed, that vitamin B12 intake was positively correlated with plasma concentration (25). Previous prospective studies have evaluated the correlation of B vitamin intake with risk of exfoliation glaucoma or exfoliation glaucoma suspect (EG/EGS) risk. Until now, there has still been conflicting results in different studies. Several authors found that vitamin B12 intake was not correlated with EG/EGS risk in different types of glaucoma (26–29). Some studies demonstrated that serum vitamin B12 levels are decreased in glaucoma patients (6, 12), but others found them to be elevated in NTG, POAG and EXG (7, 8, 11). A meta analysis demonstrated that high-dose intake of vitamins A and B, but not vitamins C, D, or E, was associated with a low prevalence of glaucoma (30, 31).

Overall, the sample size of the glaucoma group in the above studies was small (ranging from approximately 15 to 290), and the proper dose of vitamin B12 intake for glaucoma remains inconclusive. Therefore, we conducted the present study on the basis of data from national health and nutrition examination survey (NHANES) 2005–2008 aiming to further identify the evidence provided for the appropriate dose of vitamin B12 nutritional therapy for glaucoma.

2. Materials and methods

2.1. Data source and subject selection

This study is based on data from NHANES 2005–2008. NHANES is a large nationwide cross-sectional study performed by the national center for health statistics (NCHS). NHANES subjects were all U.S. masses randomly selected on the basis of a sampling design, who underwent universal examination and signed an informed con-sent form. The NCHS research ethics review board approved the survey protocol for NHANES (32).

2.2. Defining criteria for glaucoma

Participants aged 40 years or older underwent binocular non-mydriatic fundus photography in the Mobile Examination Center (MEC) using the Canon Non-Mydriatic Retinal Camera CR6-45NM. Digital images were graded at the University of Wisconsin. The optic disc images were classified into 4 severity levels, no, possible, probable, definite (33). To better assess the potential risk of vitamin intake on the occurrence of glaucoma, in this study, "possible, probable and definite" were all considered to have glaucoma or a greater likelihood of developing glaucoma, and thus these subjects were all defined as having glaucoma.

2.3. Determination of vitamin intake and daily energy intake

Dietary data were collected in the in-person interview using the automated multiple pass method (AMPM). The AMPM is a USDA' dietary data collection instrument and a fully computerized recall method. The NHANES (MEC) provided a set of measuring guides that facilitated participants' ability to describe the amount of foods they had ingested (34, 35). NHANES performed dietary data statistics for two consecutive days, and we considered the mean of two daily dietary data for each subject as the final dietary intake data in an effort to obtain an outcome that more closely approximated the true level of life. Our study included all vitamin data that appeared in NHANES 2005–2008.

2.4. Assessment of covariates

Sociodemographic variables including age, race/ethnicity, sex and educational level were obtained by computer-assisted in-person interview (36). Daily intake of calories and diabetes mellitus were defined by subject's self-report (34, 35, 37).

2.5. Statistical analysis

All statistical analyses were performed using SAS 9.4 and R software 4.1.3. NHANES uses a stratified, multistage sampling method, so we incorporated sampling weights and strata, and sampling units in our statistical analysis to account for the complex sampling design. Continuous variables were presented with mean and standard error (SE), and categorical variables were presented with percentage and SE; the chi-square test or T-test was used to compare patients' demographic characteristics. Logistic regression models were used to determine the association of vitamin intake with the presence of glaucoma. Model 1 was adjusted by age, race, sex, and educational level. Model 2 = model 1 and adjusted by daily energy intake. Model 3 = model 2 and adjusted by diabetes mellitus. Since a significant association between vitamin B12 and glaucoma was observed, we further performed quantile regression between vitamin B12 and glaucoma. In response to the above logistic regression results, we have created additional forest plots to show them more clearly.

3. Results

3.1. Description of baseline information of the study sample

On the basis of the study design of NHANES, we selected a total of 14,440 subjects for inclusion in this study. After screening, 594 subjects were finally included, and 13,846 subjects were excluded because of missing dietary data or ophthalmological examination data. The detailed flow is shown in Figure 1. Table 1 shows the demographic data as well as other characteristic data of the participants with and without glaucoma. Among the tested population, the number of subjects with or suspected glaucoma accounted for 41.9% after weighting. Of all covariates, only age differed significantly between the two groups (55.66 vs. 63.29 years, $p < 0.001$). Among all vitamin intakes, we observed significant differences between the two groups for three vitamins, retinol (474.49 vs. 401.42 mg, $p = 0.014$), vitamin A (704.61 vs. 605.62 mg, $p = 0.0040$), and vitamin B12 (5.93 vs. 4.77 mg, $p = 0.033$).

3.2. Association between the intake of retinol, vitamin a, and vitamin B12 and the presence of glaucoma

Table 2 and Figure 2 show the associations that existed between the intake of retinol, vitamin A and, vitamin B12 and glaucoma as addressed by multivariate logistic regression models. A significant positive association between vitamin B12 intake and incident glaucoma was shown in all models (model 1: OR = 1.078, 95% CI = 1.019–1.141; model 2: OR = 1.092, 95%CI = 1.031–1.158; model 3: OR = 1.092, 95% CI = 1.029–1.158). No significant association with glaucoma was observed for the intakes of retinol and vitamin A.

3.3. Relationship of different quartiles of vitamin B12 with the presence of glaucoma

Table 3 and Figure 3 demonstrate the analysis of the association of different grades of vitamin B12 intake with glaucoma after dividing vitamin B12 intake into quartiles. Significant positive correlations between the fourth quartiles (Q4, high dose of vitamin B12 intake) and the prevalence of glaucoma were seen in all models (model 1: OR = 1.133, 95%CI = 1.060–1.210; model 2: OR = 1.141, 95% CI = 1.072–1.215; model 3: OR = 1.146, 95% CI = 1.071–1.226). No significant association with glaucoma was observed for the intakes of vitamin B12 in the first quartiles (Q1, low dose of vitamin B12 intake), the second quartiles (Q2, normal dose of vitamin B12 intake) and the third quartiles (Q3, normal dose of vitamin B12 intake).

4. Discussion

In this study, the potential correlation between vitamin B12 intake and glaucoma was investigated by analyzing the NHANES database. Our results suggest that there is no significant correlation between normal or low doses of vitamin B12 intake and glaucoma, but that there is significant correlation between high dose intake of vitamin B12 and glaucoma.

According to past experience, the clinical consequences of multiple doses of oral vitamin B12 as a nutritional therapy for glaucoma have not been definitively studied (38). Studies have found that the main reason for high levels of serum cobalamin is the presence of potentially life-threatening diseases, and early diagnosis is often a decisive predictor (39, 40). Cobalt is a nerve agent that can cause optical neuropathy and retinopathy. Apostoli et al. injected cobalt alone intravenously, and observed optic nerve damage and loss of cochlear hair cells (41). This study, along with one by Carelli et al. exploited similarities between mitochondrial disease and cobalt-induced optic neuropathy (41, 42). Other studies have shown similar

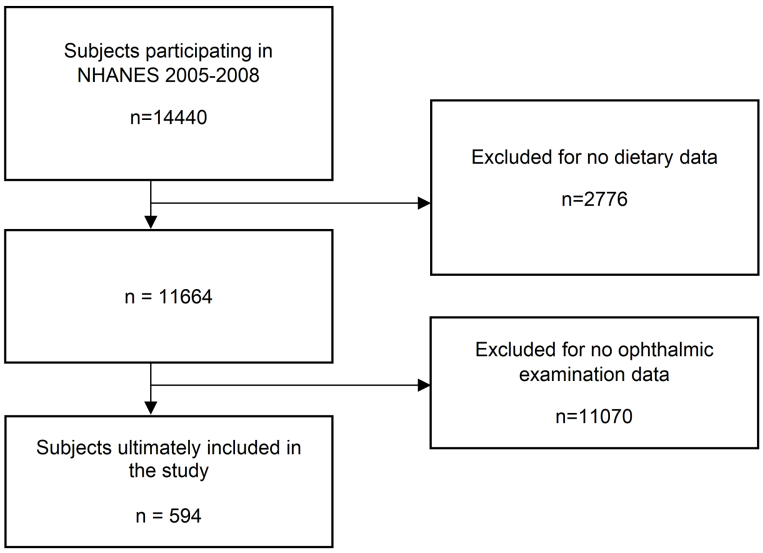

FIGURE 1
Screening process of the included studies.

TABLE 1 Baseline information for the study sample.

Variables		Glaucoma (+)	Glaucoma (–)	*p*-Value
Continuous variables, mean (SE)				
Age (years)		63.29 (1.07)	55.66 (0.81)	<0.001
Vitamin E (mg)		7.23 (0.43)	7.31 (0.38)	0.85
Retinol (mg)		474.49 (27.83)	401.42 (16.60)	0.014
Vitamin A (mg)		704.61 (31.88)	605.62 (32.88)	0.0040
Vitamin B1 (μg)		1.60 (0.067)	1.56 (0.062)	0.54
Vitamin B2 (mg)		2.29 (0.11)	2.15 (0.082)	0.32
Niacin (mg)		23.37 (0.98)	23.64 (0.74)	0.78
Vitamin B6 (mg)		2.01 (0.085)	1.90 (0.065)	0.17
Total folate (mg)		386.13 (16.94)	402.037 (18.46)	0.20
Vitamin B12 (mg)		5.93 (0.52)	4.77 (0.19)	0.033
Vitamin C (mg)		92.72 (5.58)	86.19 (5.38)	0.25
Vitamin K (mg)		108.12 (10.64)	112.26 (14.079)	0.70
Energy (kcal)		1947.51 (73.27)	2053.12 (61.18)	0.16
Category variables, (%)				
Glaucoma		41.90 (2.10)	58.10 (2.10)	
Gender	Male	52.70 (4.50)	45.10 (3.90)	0.25
	Female	47.30 (4.50)	54.90 (3.90)	
Race	Mexican American	4.40 (1.10)	7.70 (1.20)	0.36
	Other Hispanic	1.50 (0.70)	3.70 (1.20)	
	Non-Hispanic White	69.80 (4.60)	65.20 (4.40)	
	Non-Hispanic Black	18.00 (3.00)	17.70 (2.90)	
	Other Race—Including Multi-Racial	6.30 (2.90)	5.60 (1.90)	
Education Level	Less Than 9th Grade	6.40 (2.00)	4.40 (1.40)	0.85
	9–11th Grade (Includes 12th grade with no diploma)	13.00 (2.50)	11.30 (1.80)	
	High School Grad/GED or Equivalent	23.30 (3.60)	25.40 (2.90)	
	Some College or AA degree	31.50 (3.80)	33.10 (3.10)	
	College Graduate or above	25.80 (4.40)	25.80 (3.80)	
Diabetes mellitus	(+)	19.30 (3.20)	12.30 (2.50)	0.086
	(–)	80.70 (3.20)	87.70 (2.50)	

TABLE 2 Association between intake of retinol, vitamin A, vitamin B12 and glaucoma.

Variables	Model 1[a] OR (95% CI)	*p*-Value	Model 2[b] OR (95% CI)	*p*-Value	Model 3[c] OR (95% CI)	*p*-Value
Retinol intake	1.000 (0.998–1.002)	0.99	1.000 (0.998–1.003)	0.84	1.000 (0.998–1.003)	0.84
Vitamin A intake	1.000 (0.998–1.002)	0.93	1.000 (0.998–1.002)	0.98	1.000 (0.998–1.002)	0.98
Vitamin B12 intake	1.078 (1.019–1.141)	0.011	1.092 (1.031–1.158)	0.0041	1.092 (1.029–1.158)	0.0048

[a]Model 1: adjusted for age, race, gender, educational level.
[b]Model 2: further adjusted for daily energy intake.
[c]Model 3: further adjusted for diabetes mellitus.

toxic effects of cobalt on the eye, such as optic nerve atrophy; however, as reported by Apostoli et al., the concentration required to produce this effect is 1/80 compared to the previous study (43). Our results showed that high-dose vitamin B12 intake may cause optic neuropathy and play a role in the development of glaucoma, consistent with these previous studies on cobalt induced visual impairment and neuropathy.

Variables	OR	95%CI	*p* value
Model 1			
Retinol intake	1.000	0.998 to 1.002	0.99
Vitamin A intake	1.000	0.998 to 1.002	0.93
Vitamin B12 intake	1.078	1.019 to 1.141	0.011
Model 2			
Retinol intake	1.000	0.998 to 1.003	0.84
Vitamin A intake	1.000	0.998 to 1.002	0.98
Vitamin B12 intake	1.092	1.031 to 1.158	0.0041
Model 3			
Retinol intake	1.000	0.998 to 1.003	0.84
Vitamin A intake	1.000	0.998 to 1.002	0.98
Vitamin B12 intake	1.092	1.029 to 1.158	0.0048

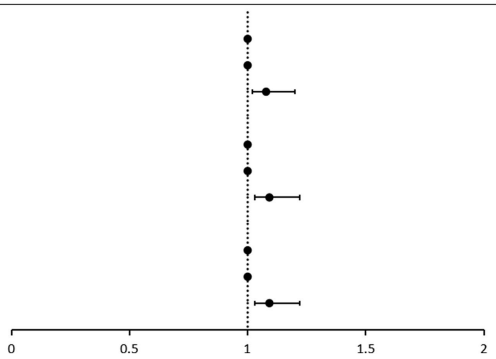

FIGURE 2
Forest plot of logistic regression results.

Variables	OR	95%CI	*p* value
Model 1			
Q1	1.199	0.463 to 3.103	0.70
Q2	0.965	0.251 to 3.714	0.96
Q3	0.834	0.396 to 1.757	0.62
Q4	1.133	1.060 to 1.210	0.00070
Model 2			
Q1	1.103	0.479 to 2.541	0.81
Q2	0.938	0.231 to 3.815	0.93
Q3	0.844	0.401 to 1.778	0.64
Q4	1.141	1.072 to 1.215	0.00020
Model 3			
Q1	1.079	0.456 to 2.554	0.86
Q2	0.958	0.236 to 3.899	0.95
Q3	0.840	0.397 to 1.780	0.63
Q4	1.146	1.071 to 1.226	0.00040

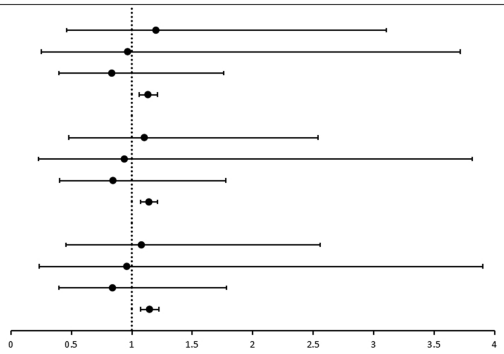

FIGURE 3
Forest plot of quantile regression results.

TABLE 3 Association between vitamin B12 intake levels and glaucoma in different quartiles.

Variables		Model 1[a] OR (95% CI)	*p*-Value	Model 2[b] OR (95% CI)	*p*-Value	Model 3[c] OR (95% CI)	*p*-Value
Vitamin B12 intake	Q1	1.199 (0.463–3.103)	0.70	1.103 (0.479–2.541)	0.81	1.079 (0.456–2.554)	0.86
	Q2	0.965 (0.251–3.714)	0.96	0.938 (0.231–3.815)	0.93	0.958 (0.236–3.899)	0.95
	Q3	0.834 (0.396–1.757)	0.62	0.844 (0.401–1.778)	0.64	0.840 (0.397–1.780)	0.63
	Q4	1.133 (1.060–1.210)	0.00070	1.141 (1.072–1.215)	0.00020	1.146 (1.071–1.226)	0.00040

[a]Model 1: adjusted for age, race, gender, educational level.
[b]Model 2: further adjusted for daily energy intake.
[c]Model 3: further adjusted for diabetes mellitus.

There are three major pathological mechanisms underlying increased cobalamin in serum, and these mechanisms arise from any pathological factors, including: a direct increase of vitamin B12 in plasma *via* overuse or medical use; a direct increase in the level of vitamin B12 in the plasma due to release from the body *via* excessive secretion or excretion disorders; and lack of vitamin B12 levels or lack of affinity (44). Excess vitamin B12 intake when indoors is usually relatively undetected according to ANAMNEA data. In addition, long-term pastoral use of vitamin B12 may lead to the formation of an autoantibody to TK II, which leads to a decrease in its clearance (45, 46). A positive association has been observed between intake and plasma concentrations for vitamin B12 in physically active people

(25). An increase in plasma vitamin B12 may indicate a functional deficit, with clinical results similar to vitamin B12 deficiency, which can lead to increased homocysteine levels, optic neuropathy, and more seriously, irreversible damage to the nervous system (47–54). This is presumed to be another mechanism of high doses of vitamin B12 as a risk factor for glaucoma development.

The strengths of this study included the focus on the relationship between vitamin B12 intake and glaucoma, and the relatively large sample size, but there were some limitations. First, the data of NHANES ophthalmology examination could not clearly indicate the type of glaucoma that the subject had and could not reveal the relationship between vitamin B12 and different types of glaucoma. Additionally, the diet data obtained from the self-reported recall of the subject could have had some errors.

There were also individual differences in the bioavailability of vitamin B12 in each participant, resulting in differences in serum vitamin concentrations (29). Therefore, further controlled trials or epidemiological peer studies are required to confirm the serious consequences of high doses of vitamin B12 in different types of glaucoma. Moreover, to further investigate the direct relationship between vitamin B12 and glaucoma, future research should be devoted to the analysis of serum vitamin levels. Despite the limitations, this study is valuable in light of the association between high-dose intake of vitamin B12 and glaucoma.

5. Conclusion

High-dose vitamin B12 intake may contribute to the development of glaucoma, which casts a new light on a warning about dietary intake doses and any drug administration.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/index.htm.

Author contributions

YH: conceptualization. BX and ZL: methodology, software, formal analysis, investigation, resources, and data curation. ZY and JZ: validation, supervision, project administration, and funding acquisition. ZY, JZ, YW, YH, and BX: writing—original draft preparation, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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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.

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Can change in phase angle predict the risk of morbidity and mortality during an 18-year follow-up period? A cohort study among adults

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Introduction: Phase angle (PhA, degrees), measured *via* bioimpedance (BIA, 50 kHz), is an index that has been used as an indicator of nutritional status and mortality in several clinical situations. This study aimed to determine the relationship between 6-year changes in PhA and total mortality as well as the risk of incident morbidity and mortality from cardiovascular disease (CVD) and coronary heart disease (CHD) during 18 years of follow-up among otherwise healthy adults.

Methods: A random subset ($n = 1{,}987$) of 35–65 years old men and women was examined at the baseline in 1987/1988 and 6 years later in 1993/1994. Measures included weight, height, and whole-body BIA, from which PhA was calculated. Information on lifestyle was obtained through a questionnaire. The associations between 6-year PhA changes (ΔPhA) and incident CVD and CHD were assessed by Cox proportional hazard models. The median value of ΔPhA was used as the reference value. The hazard ratio (HR) model and confidence intervals (CIs) of incident CVD and CHD were used according to the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of ΔPhA.

Results: During 18 years of follow-up, 205 women and 289 men died. A higher risk of both total mortality and incident CVD was present below the 50th percentile ($\Delta = -0.85°$). The highest risk was observed below the 5th percentile ($\Delta PhA = -2.60°$) in relation to total mortality (HR: 1.55; 95% CI: 1.10–2.19) and incident CVD (HR: 1.52; 95% CI: 1.16–2.00).

Discussion: The larger the decrease in PhA, the higher the risk of early mortality and incident CVD over the subsequent 18 years. PhA is a reliable and easy measure that may help identify those apparently healthy individuals who may be at increased risk of future CVD or dying prematurely. More studies are needed to confirm our results before it can be definitively concluded that PhA changes can improve clinical risk prediction.

KEYWORDS

bioelectrical impedance analysis, phase angle, nutritional status, mortality, cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the leading risk factor for early mortality worldwide (1). In 2019, an estimated 17.9 million people died from CVD, representing 32% of all global deaths. Coronary heart disease (CHD) is the most common type of heart disease, killing ∼360,900 people in 2019, and ∼2 in 10 deaths from CHD happen in adults younger than 65 years old (2). While being physically inactive can increase the risk of myocardial infarction by >10%, adopting a generally healthy physically active lifestyle can further lower the risk of CVDs (3). Other behaviors such as cessation of tobacco use, reducing salt in the diet, eating more fruit and vegetables, and avoiding harmful alcohol use may also help decrease the risk of CVDs (1). During the development of CVD, subtle changes in body water may occur that, as suggested earlier, maybe the first sign of future increased risk of CVD (4), and changes, especially an increase in extracellular body water, as measured by bioelectrical impedance analysis (BIA), were suggested as a simple and easy to measure early prognostic marker to identify individuals in need of CVD prevention intervention (4).

Bioelectrical impedance analysis (BIA) is an indirect method used to estimate body composition, including body water, in a safe, fast, and non-invasive approach compared with other methods. Phase angle (PhA), determined by BIA at a frequency of 50 kHz (5), is an indicator of hydration and nutritional status as well as cell membrane integrity (6). PhA has been studied as a marker of morbidity and mortality in several diseases (7) and healthy populations (8). It has also been shown to be an indicator of general health status (9) and a prognostic survival factor in several diseases (hemodialysis patients, HIV infection, and cancers) (10–12). Low PhA (<5.0°) indicates a compromised status of cell membranes and an imbalance of body water distribution, whereas a high PhA indicates better nutritional status and body cell mass (6, 13). Toso et al. (10) found a significant association between a low PhA (<4.5°) and shorter survival in patients with advanced cancer. Thus, PhA can be used as a prognostic marker for morbidity and mortality in different clinical situations as well as among initially healthy individuals (7, 8).

While previous studies have used PhA to assess disease severity among patients or predict morbidity and mortality using a single time-point measure of PhA, it remains unknown if a change in PhA is also associated with an increased risk of morbidity and mortality among people free from primary chronic disease (8). Therefore, we aimed to determine the relationship between 6-year changes in PhA and 18-year incident morbidity and mortality from CVD and CHD in a random population sample of healthy adult Danish men and women. We hypothesized a reduction in PhA to be independently associated with an increased risk of morbidity and mortality from CVD and CHD, and that associations would be modified by sex and physical activity.

Materials and methods

Study population

The study is part of the Danish Monitoring Trends in Cardiovascular Disease (MONICA) study, a longitudinal population-based study sampled among people from the greater Copenhagen area. Figure 1 shows the eligibility of the participants in the study, starting with the baseline MONICA cohort first examined in 1982/1983 as an age-stratified sample from subjects born in 1922, 1932, 1942, and 1952 selected randomly from the Danish Civil Registration System among individuals living in the greater Copenhagen area. The present study was based on measurements, including anthropometric and bioelectrical impedance, taken at the two follow-up surveys conducted in 1987/1988 and 1993/1994. Information about educational level, health behaviors, and prevalent major chronic diseases (cancer, CVD, or diabetes) was assessed *via* questionnaires and from record linkage to the National Patient Register (14). Participants who were of non-Danish origin were excluded, as well as all the participants who were diagnosed with cancer, CVD, or a self-reported diagnosis of diabetes before the 1993/1994 examination.

Ethics statement

All participants gave written informed consent, and the ethical committee approved the study protocol of Copenhagen country. The study is under the Declaration of Helsinki for study with human subjects.

Anthropometrics

Measurements for each participant were taken at the baseline (1987/1988) and after 6 years (1993/1994). Body weight (kg) was measured using a lever balance to the nearest 0.1 kg, and body height (cm) was measured using a wall-mounted stadiometer to the nearest 0.1 cm, following the recommended protocols from the World Health Organization (15).

Bioelectrical impedance analysis

In 1987/1988, bioelectrical impedance measurements were taken on the right side of the body using a single frequency (50 kHz) BIA-103 RJL system analyzer (RJL Systems, Detroit, MI) and in 1993/1994 using the ImpediMed SEAC multi-frequency analyzer. Devices were calibrated against reference circuits and were technically accurate (16). Participants were overnight fasted and were instructed to remove all objects containing metal before measurement. All BIA measurements were taken with participants supine, with the arms and legs relaxed and slightly abducted from the body. Electrodes from the AccuSensor (Carbo Cone M45, Lynn Medical, Wixom, MI) were placed on the dorsal surfaces of the right hand and foot, at the distal metacarpals and metatarsals, respectively, and between the distal prominence of the radius and the ulna at the wrist and the medial and lateral malleoli at the ankle. The devices provided both the value of resistance (R) and reactance (Xc) in ohm (Ω), at 50 kHz, to calculate the PhA at this frequency in degrees as follows: PhA = arctangent (Xc/R) × (180°/π) (5).

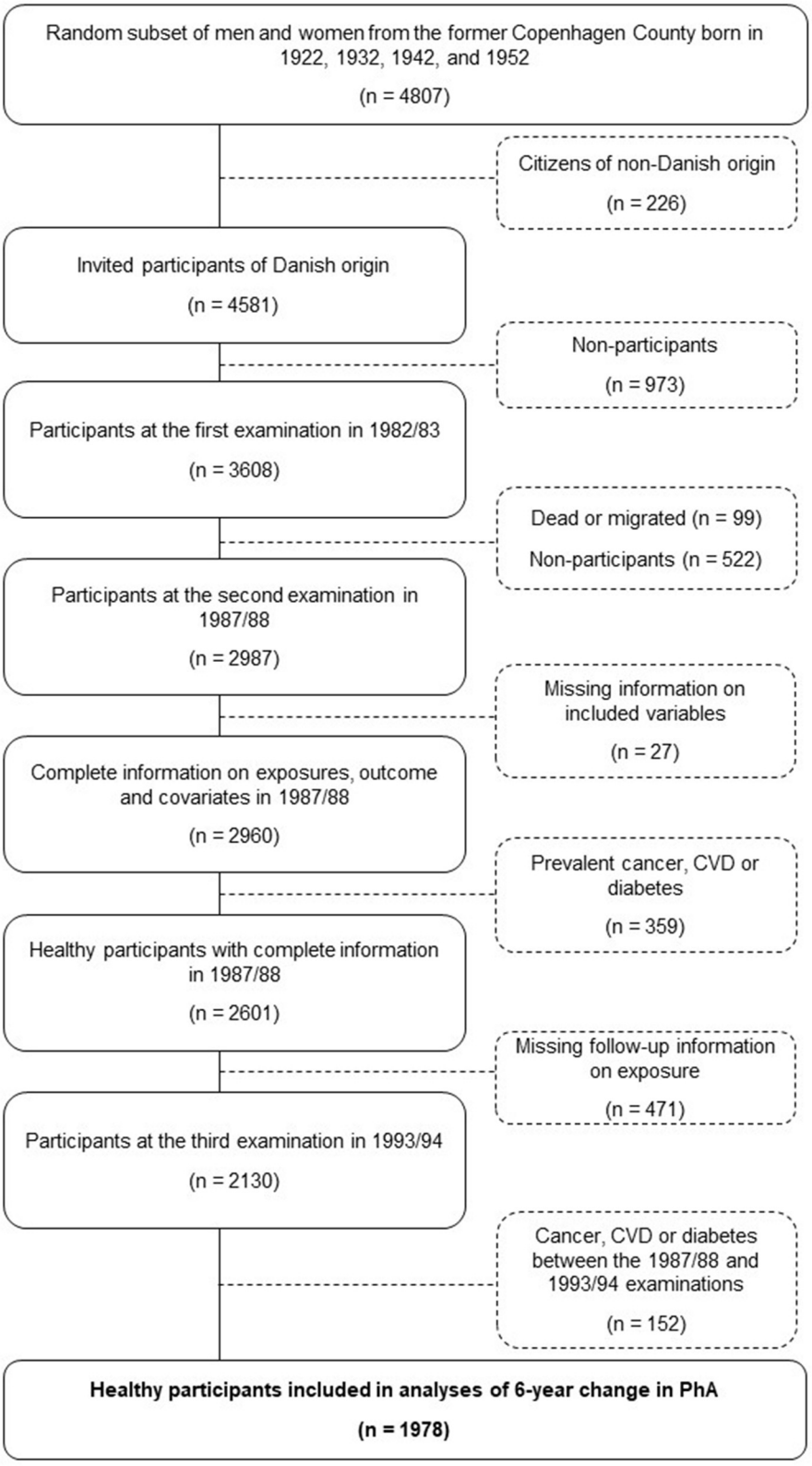

FIGURE 1
Flowchart of the study sample.

TABLE 1 Descriptive characteristics of the study participants at the 1987/1988 examination stratified by sex and mortality.

Variables	Women			Men		
	Censored ($n = 778$)	Dead ($n = 205$)	p-value	Censored ($n = 547$)	Dead ($n = 289$)	p-value
Age (years)	45.7 (35.9, 55.6)	65.5 (55.7, 65.9)	**<0.001**	45.7 (35.9, 46.5)	56.0 (46.3, 65.7)	**<0.001**
Weight (kg)	62.8 (57.7, 69.9)	63.3 (56.5, 71.9)	0.96	78.2 (71.5, 86.2)	78.6 (70.2, 87.3)	0.99
Height (cm)	164.0 (160.5, 168.0)	161.0 (157.5, 164.5)	**<0.001**	177.0 (172.5, 181.5)	173.5 (170.0, 178.0)	**<0.001**
R (Ω)	568 (527, 606)	565 (526, 610)	0.97	460 (432, 495)	464 (438, 501)	0.09
Δ R (Ω)	0.0 (−21.0, 20.0)	3.0 (−17.0, 23.0)	0.17	−1.0 (−14.0, 12.0)	2.0 (−14.0, 17.0)	0.05
Xc (Ω)	61.0 (56.0, 68.0)	58.0 (52.0, 66.0)	**<0.001**	57.0 (52.0, 63.0)	57.0 (51.0, 64.0)	0.11
Δ Xc (Ω)	−8.0 (−14.0, −3.0)	−9.0 (−15.0, −4.0)	0.09	−7.0 (−12.0, −3.0)	−9.0 (−14.0, −4.0)	**<0.001**
PhA (°)	6.2 (5.8, 6.8)	5.8 (5.4, 6.6)	**<0.001**	7.1 (6.6, 7.7)	6.9 (6.2, 7.6)	**<0.001**
Δ PhA (°)	−0.8 (−1.3, −0.3)	−0.9 (−1.4, −0.5)	**0.01**	−0.8 (−1.4, −0.4)	−1.1 (−1.8, −0.6)	**<0.001**
CVD cases (%)	272 (35.0%)	138 (67.3%)	**<0.001**	275 (39.0%)	173 (59.9%)	**<0.001**
CHD cases (%)	62 (8.0%)	34 (16.6%)	**<0.001**	100 (14.2%)	59 (20.4%)	**0.02**
Physical activity level, *n* (%)						
Sedentary	682 (87.7%)	181 (88.3%)	0.81	496 (70.3%)	236 (81.7%)	**<0.001**
Active	96 (12.3%)	24 (11.7%)		210 (29.7%)	53 (18.3%)	
Smoking (pack/y)	3.8 (0.0, 15.8)	11.5 (0.0, 25.0)	**<0.001**	11.0 (0.0, 23.8)	26.3 (10.5, 41.0)	**<0.001**
Alcohol intake (units/wk)	3.0 (1.0, 7.0)	3.0 (0.0, 7.0)	0.21	8.0 (4.0, 17.0)	10.0 (4.0, 21.0)	0.06
Educational level, *n* (%)						
Primary	199 (25.6%)	96 (46.8%)	**<0.001**	152 (21.5%)	135 (46.7%)	**<0.001**
Beyond primary	579 (74.4%)	109 (53.2%)		554 (78.5%)	154 (53.3%)	

R, resistance; Xc, reactance; PhA, phase angle; Δ, 6-year change; CVD, cardiovascular disease; CHD, coronary heart disease. Results presented as median (interquartile range) unless otherwise stated. Bold values indicate statistically significant (censored vs. dead group), $p < 0.05$.

Endpoint

Information on incident CVD, CHD, and mortality was recovered from the Danish National Patient Registry, Cause of Death Register, and Central Person Register. Survival time was parameterized as the time until CVD (both fatal and non-fatal cases) or censoring event in the year, with age as the underlying time scale. Total CVD and CHD cases were identified based on International Classification of Disease codes 390 through 458 (8th edition) and 100 through 199 (10th edition). The subjects were followed until 4 October 2012, for an average of 18 years or a total of 46,831 persons per year.

Covariates

Information on lifestyle factors was recovered through a detailed self-administered questionnaire at the baseline. Physical activity was categorized into sedentary (almost completely inactive, such as reading or watching television) and physically active [light activity at least 4 h/week (e.g., riding a bicycle or walking to work, walking, or skiing with the family, or gardening) or hard activity at least 3 h/week (e.g., heavy gardening, running, calisthenics, tennis, or regular hard physical training for competition, such as running events, soccer, racing, and European handball)] (17). Smoking behavior was defined as pack per year (20 cigarettes/pack) and computed as the product of smoking duration and cigarettes per day, divided by 20. Alcohol intake was defined as the number of standard drinks (12 g of alcohol each) per week. Both smoking and alcohol intake were included as continuous variables. The level of education was categorized into the primary level (<10 grade) and the above primary level (>10 grade) of regular schooling.

Statistical analysis

Characteristics of study participants were presented for men and women, according to mortality status as the median and corresponding interquartile range for continuous variables and as absolute numbers and percentages for categorical variables. Between-group differences were tested using the Wilcoxon rank-sum test or chi-square test. The associations between 6-year change in PhA and total mortality, incident CVD, and incident CHD older than 18 years were assessed using Cox proportional hazard regression models. Since the study cohort comprises four different birth cohorts with only a slight variation in age within the birth cohorts, time since follow-up examination was chosen as the underlying time scale instead of age. Both crude and adjusted models were conducted. The crude model was only adjusted for age and baseline level of PhA. The adjusted model was additionally

TABLE 2 Hazard ratio (HR) model and confidence intervals (CIs)* of total mortality, incident cardiovascular disease (CVD), and incident coronary heart disease (CHD) according to percentiles of 6-year change in phase angle (ΔPhA).

Percentile	Δ PhA	Total mortality						CVD						CHD					
		Crude			Adjusted			Crude			Adjusted			Crude			Adjusted		
		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
5th	−2.60	1.10	0.80	1.52	1.55	1.10	2.19	1.30	1.00	1.68	1.52	1.16	2.00	0.83	0.51	1.33	1.29	0.77	2.16
10th	−2.06	1.06	0.86	1.31	1.34	1.08	1.67	1.19	1.01	1.41	1.32	1.11	1.58	0.90	0.66	1.23	1.22	0.87	1.70
25th	−1.39	1.02	0.94	1.11	1.12	1.03	1.22	1.07	1.01	1.14	1.12	1.05	1.20	0.99	0.88	1.12	1.12	0.98	1.28
50th	−0.85	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
75th	−0.41	1.00	0.91	1.09	0.94	0.86	1.02	0.96	0.90	1.02	0.93	0.87	1.00	0.94	0.82	1.08	0.87	0.76	1.00
90th	−0.07	1.00	0.84	1.19	0.90	0.77	1.06	0.93	0.82	1.06	0.89	0.78	1.02	0.87	0.67	1.14	0.77	0.58	1.00
95th	0.16	1.00	0.79	1.26	0.87	0.71	1.09	0.91	0.77	1.08	0.87	0.72	1.03	0.83	0.58	1.19	0.70	0.49	1.01

*Crude model was adjusted for age and baseline level of PhA. The adjusted model was additionally adjusted for sex, weight, height, smoking, alcohol intake, physical activity, and level of education.

adjusted for sex, weight, height, smoking, alcohol intake, physical activity, and level of education. The median value of a 6-year change in PhA was used as the reference value. To explore non-linear associations, all results were presented using restricted cubic splines with three knots placed at equally spaced percentiles of the exposure. All the reported plots represent the hazard ratio (HR) model as cubic spline functions for the 1st−99th percentile range of the exposure variable, avoiding not interpreting extreme values for which there were only limited data.

Effect modification between a 6-year change in PhA and sex or physical activity was examined by adding product terms to the model, and stratified analyses were conducted if statistically significant interaction was observed. The assumption of proportional hazards in the models was tested using Schoenfeld residuals.

All statistical tests were two-tailed with a significance level of $p < 0.05$. Analyses were performed using Stata SE 14 (StataCorp LLC, College Station, Texas, United States).

Results

Table 1 presents the general characteristics of participants included in the study, stratified by sex and mortality. During follow-up, a total of 205 women and 289 men died. Women who died during follow-up had a higher incidence of CVD (67.3% vs. 35.0%) and CHD (16.6% vs. 8.0%), were older and shorter, had lower Xc and PhA values, and had a greater decrease in PhA over the 6-year study period than women who were censored (−0.9° vs. −0.8°, $p = 0.006$). They also had a lower educational level and smoked more compared to women who were censored ($p < 0.001$). Men who died during follow-up had a higher incidence of CVD (59.9% vs. 39.0%) and CHD (20.4% vs. 14.2%), were older and shorter, had a lower PhA values, and had a greater 6-year decrease in Xc and PhA (−1.1° vs. −0.8°, $p < 0.001$) values than men who were censored. They also were less physically active, had lower education levels, and smoked more compared to men who were censored ($p < 0.001$).

No evidence was found of an interaction between physical activity level and change in PhA on total mortality ($p = 0.50$), incident CVD ($p = 0.27$), or incident CHD ($p = 0.50$); moreover, no interaction between sex and change in PhA was found on total mortality ($p = 0.96$), incident CVD ($p = 0.29$), or incident CHD ($p = 0.84$). Thus, we did not stratify the analyses, but rather in addition to the baseline level of PhA and age, weight, height, smoking, alcohol intake, and level of education adjusted for both sex and physical activity in the fully adjusted regression models.

Table 2 shows crude and adjusted HRs (95% CIs) estimated from a Cox regression spline model of total mortality, incident CVD, and incident CHD, according to the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of 6-years change in PhA (ΔPhA) among participants. After adjustment for covariates, a statistically significant association between a 6-year decrease in the PhA value ($\Delta = -0.85°$) with the risk of total mortality and incident CVD was present below the 50th percentile ($p < 0.001$). The highest risk was observed below the 5th percentile ($\Delta PhA = -2.60°$) in relation to total mortality (HR: 1.55; 95% CI: 1.10–2.19) and incident CVD (HR: 1.52; 95% CI: 1.16–2.00). We found no statistically significant association between a 6-year change in PhA and the risk of developing CHD.

Figure 2 illustrates the crude and adjusted restricted cubic splines of the association between a 6-year change in PhA and total mortality, incident CVD, and incident CHD. A threshold effect of a 6-year change in PhA on total mortality and incident CVD was evident at around a decrease in PhA of −0.85°. Below this threshold, a higher risk of total mortality and incident CVD was observed, while no further risk reduction was observed above $\Delta PhA = -0.85°$. A similar but not significant pattern of a threshold was seen for the association between the 6-year change in PhA and incident CHD.

Discussion

This study aimed to determine the relationship between 6-year changes in PhA and subsequent 18-year total mortality or incident CVD and CHD among initially healthy (free from primary chronic disease) adult Danish men and women. Our findings indicated that men and women who were older than 6 years decreased the value of PhA by more than 1° had an increased risk of total mortality and incident CVD. An association between a low value of PhA and

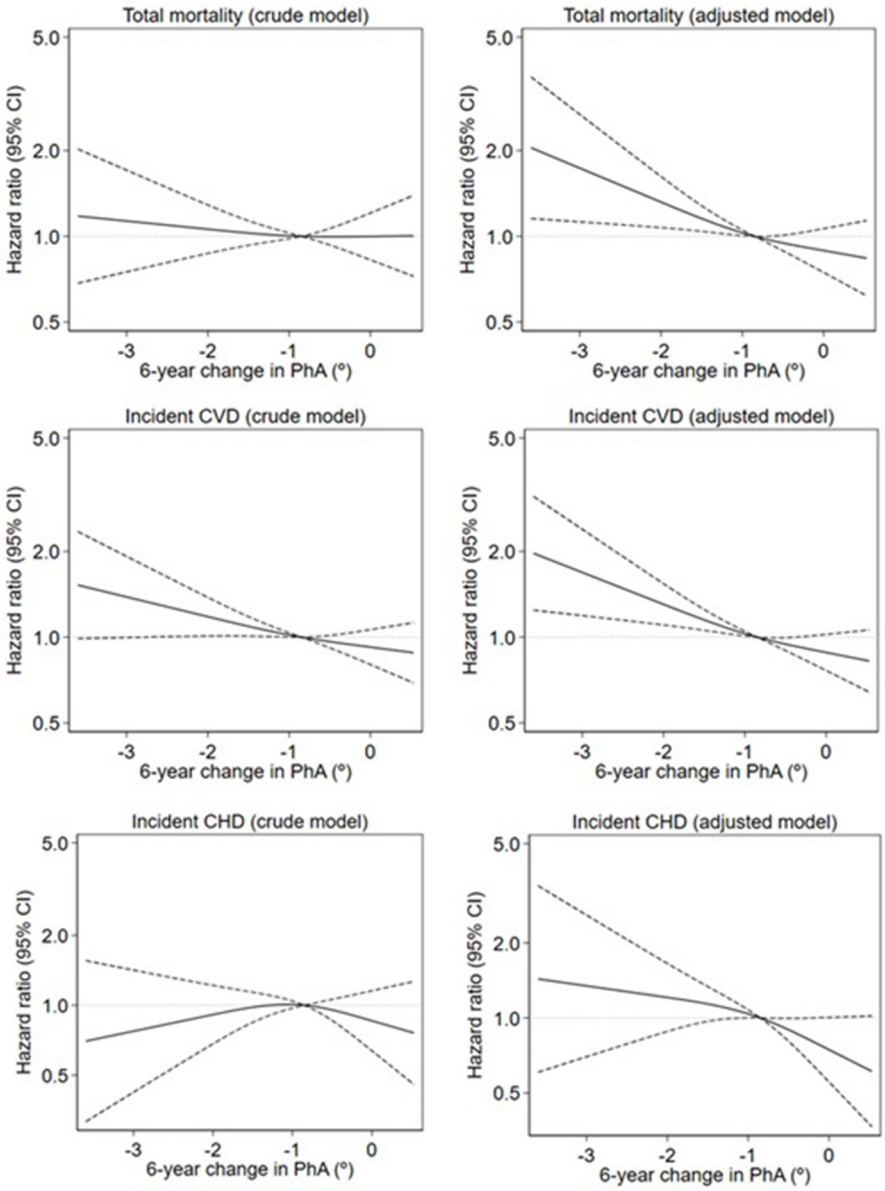

FIGURE 2
Crude and adjusted restricted cubic splines of the association between 6-year change in phase angle (PhA) and total mortality, incident cardiovascular disease (CVD), and incident coronary heart disease (CHD). Mortality is estimated by hazard ratios (smoothed lines) with 95% confidence intervals (dashed lines) estimated from a Cox regression spline model. The crude models were adjusted only for age and baseline level of PhA. The adjusted models were additionally adjusted for weight, height, smoking, alcohol intake, physical activity, and level of education. The median value of change in PhA is the reference value (hazard ratios of 1.00, indicated by the horizontal dotted line). Only the 1st–99th percentile of exposure is shown.

mortality risk has been shown previously among individuals with and without heart diseases (18–20) and hospitalized patients (21–23). However, to the best of our knowledge, no previous studies have examined if a measured change over time in PhA may be predictive of a future increased risk of early overall mortality or cardiovascular disease. Our results suggest that changes in PhA occurring almost 20 years earlier seem predictive of future mortality and CVD risk.

The present study builds on our previous findings in which a lower PhA value was associated with a higher incidence of CVD over 24 years in a group of adult Danish men and women free from primary chronic disease (8). In this previous study, among women, a higher risk of incident CVD was found when PhA was <6.6°; however, among men, no significant association was found. It is well known that sex, age, and physical activity are some of the main factors to influence the PhA value (24, 25); however, in the present study, the morbidity and mortality risk related to changes in PhA was significant and not different among men and women. In addition, we found no evidence that associations between PhA changes and subsequent morbidity and mortality risk were different for subjects reporting high and non-daily physical activity. However, in a previous study with young healthy adults

(26), army cadets (27), and older women (28), after a period of physical training, participants have shown an increase in the value of PhA. It is speculated that since participants included in the present study did not have a higher level of physical activity (compared to other studies), this may be a factor that did not influence the relationship between PhA and risk of CVD and mortality. The present findings show that changes in PhA were associated with an increased risk of total mortality and incident CVD, suggesting that PhA may be used as an important early prognostic tool for the survival and prevention of CVD.

A decrease in PhA would indicate that cell membranes may have become more compromised leading to an imbalance of body water distribution and potential accumulation in extracellular water, imbalances that may not be clinically visible or otherwise discovered (29, 30). In accordance, previous studies have reported that an excess of extracellular water was associated with the development of cardiovascular morbidity and mortality among older adults (4, 18, 19). In the present study, for most individuals, PhA decreased over the 6-year observation period; however, the increased risk of early mortality and CVD morbidity was mainly present below, but not above the 50th percentile, indicating a threshold effect of loss of PhA below which the risk of developing CVD and dying prematurely increased with a greater decrease in the PhA value ($\Delta = -0.85^{\circ}$). The highest risk was observed below the 5th percentile ($\Delta\text{PhA} = -2.60^{\circ}$) in relation to total mortality (HR: 1.55; 95% CI: 1.10–2.19) and incident CVD (HR: 1.52; 95% CI: 1.16–2.00). We found no statistically significant association between a 6-year change in PhA and the risk of developing CHD, possibly related to the lower number of individuals developing CHD than developing CVD.

The main strength of this study was that our sample included participants who were initially free of primary chronic disease and were followed for almost two decades for the development of premature mortality and incident CVD, providing a unique opportunity to investigate our hypothesis. Moreover, the Danish MONICA study had a very high participation rate (78.8%) (31). In addition, we have no reason to believe that the associations we have found would be different in other Western populations of generally Caucasian origin. Hence, our results may suggest a good model of health behaviors apply to other similar populations.

A potential limitation of our study is that the information on general lifestyle factors was obtained by a self-questionnaire, which, however, would have led to attenuation rather than inflation of the association between changes in PhA and CVD risk but may have masked potential significant associations between PhA change and CHD. Although we adjusted our analyses for several potential confounders, as in most observational studies, it is still likely that some unmeasured or residual confounding remained. As an example, our analyses were not adjusted for any measure of diet quality, which is a known risk factor for CVD and a predictor for mortality (32).

Our findings suggest that a decrease in PhA value over a 6-year period of more than 0.85° was associated with an increased subsequent risk of early mortality and incident CVD. This safe, reliable, and easily obtainable measure of PhA from BIA, which is indicative of changes in cell membrane health and fluid balance, may help identify those otherwise healthy (free from primary chronic disease) adults who are at an increased risk of future incident CVD or dying prematurely. However, to the best of our knowledge, this study is the first to examine if changes in PhA are predictive of future CVD morbidity and total mortality, more studies are still needed before it can be firmly concluded that PhA changes can improve clinical risk prediction.

Data availability statement

Data from the Monica study cannot be made publicly available for ethical and legal reasons. Public availability may compromise participant privacy, and this would not comply with Danish legislation. Access to the data requires an application submitted to and subsequently approved by the steering committee. Contact BH (Berit.Lilienthal.Heitmann@regionh.dk) or the Research Unit for Dietary Studies at The Parker Institute (bfh-eek@regionh.dk).

Ethics statement

All participants gave written informed consent, and the study was approved by the Local Ethics Committee of Copenhagen County. The study was conducted in accordance with the Helsinki Declaration.

Author contributions

RL, LW, and BH designed the study. BH carried out data collection, provided all needed materials, and funding acquisition to conduct the study. SL performed the statistical analysis, analyzed the results, and created the figures. LW helped to analyze the impedance data. RL together with LW and BH drafted the manuscript. LW, BH, and SL revised the manuscript and added their valuable expertise to the discussion section. All authors approved the final version of the manuscript.

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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

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Associations of obesity-related indices with prediabetes regression to normoglycemia among Chinese middle-aged and older adults: a prospective study

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Background: Prediabetes is associated with increased cardiovascular risk and all-cause mortality, while its regression will decrease the risks. This study investigated the associations of six obesity-related indices (waist-to-height ratio (WHtR), body roundness index (BRI), conicity index (CI), body shape index (ABSI), Chinese visceral adiposity index (CVAI), and triglyceride glucose (TyG) index) with prediabetes regression based on the China Health and Retirement Longitudinal Study (CHARLS), enrolling middle-aged and older adults.

Methods: We included 2,601 participants with prediabetes from CHARLS, who were followed up from 2011–2012 to 2015–2016, with blood samples collected for measuring fasting plasma glucose and hemoglobin A1c. All the obesity-related indices at baseline and their dynamic changes were calculated and categorized into tertiles. Logistic regression analysis was applied to obtain the odds ratio (OR) and 95% confidence intervals (CIs). Attributable fractions (AFs) and 95% CIs of these indices and the dynamic changes were calculated with the AF package in R software, and the cutoff values of initial obesity-related indices were obtained by the receiver operating characteristic (ROC) analysis.

Results: During the 4-year follow-up period, 562 (21.61%) participants regressed from prediabetes to normoglycemia. They had lower initial BRI, WHtR, CI, ABSI, CVAI, and TyG than those who did not ($P < 0.05$). After multivariable adjustment, participants in the first tertile of initial BRI (OR, 1.45, 95%CIs, 1.09–1.93), WHtR (OR, 1.46, 95%CIs, 1.10–1.95), and CVAI (OR, 1.47, 95%CIs, 1.11–1.93) had increased odds of prediabetes regression compared with those in the highest tertile. Participants with decreased TyG (OR, 2.08; 95%CIs, 1.61–2.70) also had increased odds of prediabetes regression compared with those with increased TyG. The cutoff values of initial obesity-related indices were 4.374 for BRI, 0.568 for WHtR, 8.621 for TyG, 1.320 for CI, 0.083 for ABSI, and 106.152 for CVAI, respectively. The AFs were 21.10% for BRI < 4.374, 20.85% for WHtR < 0.568, 17.48% for CVAI < 107.794, and 17.55% for ΔTyG < 0, respectively.

Conclusion: Low initial BRI, WHtR, and CVAI, as well as TyG reduction, were significantly related to prediabetes regression to normoglycemia, and the AFs were around 20%. Less abdominal fat and insulin resistance reduction would benefit future health outcomes among people with prediabetes.

KEYWORDS

obesity, obesity-related indices, prediabetes regression, abdominal fat, insulin resistance

Introduction

Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is defined as a blood glucose level higher than normal but lower than the thresholds of diabetes (1–3). Globally, there are around 374 million people living with IGT, and there will be more than 470 million people with IGT by 2030 (4, 5). In China, the estimated prevalence of prediabetes was 35.2% among Chinese adults between 2015 and 2017 (6). Prediabetes has been associated with a significantly increased risk of cardiovascular diseases, chronic kidney disease, cancer, and all-cause mortality (7, 8), while the regression to normoglycemia could reduce the risks (9). Therefore, it is of crucial importance to identify modifiable factors to aid in regressing from prediabetes to normoglycemia.

Several factors such as body weight loss, structured physical activity, and metformin use have been associated with prediabetes regression, while obesity may be detrimental to this process (7, 10–14). Obesity is considered a major risk factor for prediabetes and diabetes, while its role in prediabetes regression to normoglycemia is still mixed. The KORA F4 cohort study found the reduction of body mass index (BMI) and waist circumference (WC), instead of initial BMI and WC, contributed to the reversing from prediabetes, defined by hemoglobin A1c (HbA1c), to normal glucose tolerance (NGT) in older Germany adults (14, 15). Nevertheless, Kowall et al. reported that the reduction of BMI and WC had no effect on glucose-defined prediabetes regression (15). Evidence suggested that BMI and WC have some drawbacks to evaluate obesity and metabolism abnormality (16, 17). BMI can only identify general obesity (17), while WC could identify abdominal obesity, but it does not account for differences in body height (16, 17).

Waist-to-height ratio (WHtR), body roundness index (BRI), conicity index (CI), body shape index (ABSI), and Chinese visceral adiposity index (CVAI) are surrogate markers for abdominal obesity and have been shown to be more correlated with metabolic abnormality than BMI and WC (17–19). A Chinese cohort study suggested BRI and WHtR as the best anthropometric indices for predicting diabetes risk (20). However, no prior study has explored the relationship between these indices and prediabetes regression. Meanwhile, the triglyceride glucose (TyG) index is also a marker of obesity and is highly associated with insulin resistance (IR) (21). Previous studies indicated that TyG was more suitable for the determination of IR than HOMI-IR and had a great ability to identify prediabetes and diabetes (22, 23). However, its association with prediabetes regression to normoglycemia is still unclear.

Although several obesity-related indices have been associated with prediabetes and diabetes, studies investigating these indices in relation to prediabetes regression are lacking. Therefore, this study aimed to investigate the associations of obesity-related indices and their dynamic changes with prediabetes regression to normoglycemia in middle-aged and older adults from the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Study population

The present study used data from the CHARLS, which enrolled a nationally representative sample of community dwellers aged ≥45 years in China. The design of CHARLS has been described in detail elsewhere (24). A total of 17,708 participants from 450 urban communities and rural areas in 28 provinces of China were recruited from 2011 to 2012 (Wave 1). They were followed up every 2 years, and there were three subsequent follow-ups. In this study, data from Wave 1 and Wave 3 (2015–2016) were used because blood samples were only collected in the two waves.

Of 17,708 participants, we excluded 436 participants aged <45 years, 5,989 participants with missing data on fasting plasma glucose (FPG) and HbA1c, 1,768 participants unable to calculate obesity-related indices, and 5,651 participants without prediabetes. At the follow-up, we further excluded 417 participants who lost to follow-up, 804 participants with missing data on FPG and HbA1c, and 42 participants unable to calculate these indices. Finally, a total of 2,601 participants were included in the present study. Details regarding the study population selection are presented in Figure 1.

Data collection

Fasting blood samples were collected for measurements of FPG, HbA1c, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-c), and low-density lipoprotein-cholesterol (LDL-c). FPG, TG, TC, HDL-c, and LDL-c were measured by an enzymatic colorimetric test method, whereas the HbA1c assay was performed by the boronate affinity high-performance liquid chromatography (HPLC) method. Height and weight were measured via standard methods, with participants wearing light clothes without shoes. WC was measured to the nearest ± 0.5 cm at the minimum circumference between the lowest ribs. BMI was calculated by dividing weight (kg) by height squared (m^2). Obesity-related indices were calculated by following formulas (19, 25) and were categorized into tertiles.

$$BRI = 364.2 - 365.5 \times [1 - \pi^{-2} WC_{(m)}^2 height^{-2}{}_{(m)}]^{1/2}$$

$$WHtR = WC_{(cm)}/height_{(cm)}$$

$$TyG = \ln(TG_{(mg/dL)} \times FPG_{(mg/dL)}/2)$$

$$CI = [WC_{(m)}] \times 0.109^{-1} \times [weight_{(kg)}/height_{(m)}]^{-1/2}$$

$$ABSI = [WC_{(m)}] BMI^{-2/3} height_{(m)}^{-1/2}$$

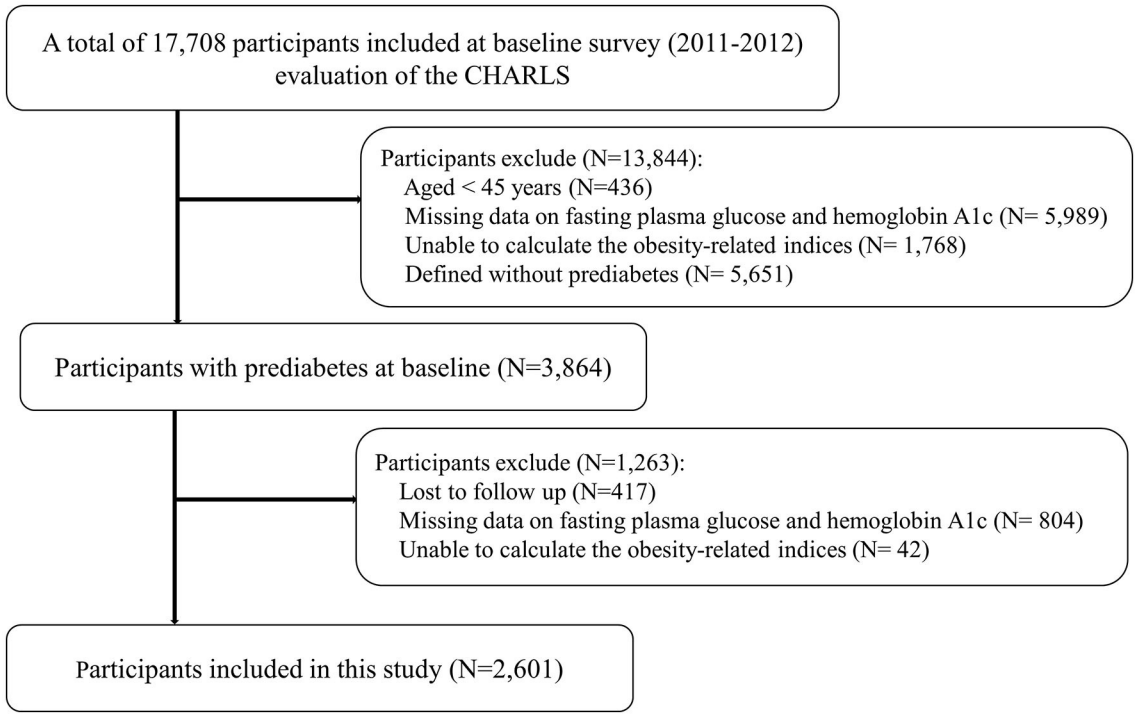

FIGURE 1
Study flow chart.

$$\text{CVAI}: \text{CVAI} = -267.93 + 0.68\times\text{age} + 0.03\times\text{BMI} + 4\times\text{WC} + 22\times\log\text{TG}_{(\text{mmol/l})} - 16.32\times\text{HDL} - \text{c}_{(\text{mmol/l})} \text{ in males}$$

$$\text{CVAI} = -187.32 + 1.71\times\text{age} + 4.23\times\text{BMI} + 1.12\times\text{WC} + 39.76\times\log\text{TG}_{(\text{mmol/l})} - 11.66\times\text{HDL} - \text{c}_{(\text{mmol/l})} \text{ in females.}$$

Dynamic changes in the indices were calculated by subtracting the baseline values from those of the follow-up and were categorized into tertiles (decreased, stable, and increased).

Definition of prediabetes, diabetes, and normoglycemia

According to the criteria of the American Diabetes Association (7), prediabetes was defined as FPG in the range of 5.6–6.9 mmol/L or HbA1c in the range of 5.7–6.4%; normoglycemia was as FPG $<$ 5.6 mmol/L and HbA1c $<$ 5.7%; and diabetes was as FPG $\geq$ 7.0 mmol/L, HbA1c $\geq$ 6.5%, self-reported history, and/or the use of anti-diabetic medications.

Covariates

Participants reported their sociodemographic characteristics, including age, gender, education level (primary school or below, middle school, and high school or above), place of residence, marital status, and smoking and drinking history. Hypertension was determined by either clinical diagnosis or self-reported hypotensive treatment or SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg. Dyslipidemia was defined as TC $\geq$ 6.22 mmol/L, TG $\geq$ 2.26 mmol/L, HDL-c $<$ 1.04 mmol/L, LDL-c $\geq$ 4.14 mmol/L, or self-reported dyslipidemia (26, 27). Additionally, TG, TC, LDL-c, HDL-c, FPG, and HBA1c at the baseline were included in confounders.

Statistical analysis

The normality of continuous variables was inspected visually by QQ-plot, which suggested no serious violations of normality assumptions. Continuous variables in our study are presented as means ± standard deviations, and the two groups were compared using the *t*-test. Categorical variables are presented as frequency (*n*, %), and the two groups were compared using the chi-square test. Multiple logistic regression analysis was conducted to assess the association of obesity-related indices and their dynamic changes with regression to normoglycemia. According to previous research (7), three different models were introduced as follows: Model 1, without adjustment; Model 2, adjusted for age and gender; and Model 3, further adjusted for the covariates including place of residence, marital status, educational level, history of smoking and drinking, presence of hypertension and dyslipidemia, SBP, DBP, TG, TC, LDL-c, HDL-c, FPG, and HbA1c at the baseline.

Subgroup analyses were performed to evaluate the association between obesity-related indices and prediabetes regression stratified by age. In the sensitivity analysis, we used the 1999 World Health Organization (WHO) criteria for diabetic status to assess

the association of obesity-related indices with the regression of prediabetes (28). Prediabetes was defined as FPG 6.1–6.9 mmol/L; normoglycemia was defined as FPG < 6.1 mmol/L, and diabetes was defined as FPG ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, self-reported history, and/or the use of anti-diabetic medications. In addition, we further performed sensitivity analysis based on multinomial logistic regression in which three outcome groups were taken into consideration over follow-up: regression to normoglycemia, progression to diabetes, and remained as prediabetes and progression to diabetes group was used as the reference.

Population attributable fraction (PAF) and attributable fraction (AF) are the embodiments of the percentage reduction of a given outcome that is expected if there is no exposure (29). The details of AF and the formula were described elsewhere (30). AFs and 95%CI were calculated with the AF package in R software, which allows for confounder-adjusted estimation of AFs for cohort studies (30). Here, we defined the exposure as low levels of initial obesity-related indices and their reduction to obtain the AFs. To calculate AFs, we obtained the cutoff values of initial obesity-related indices by the receiver operating characteristic (ROC) analysis. Then, we defined the initial values lower than the corresponding cutoff values as the exposure and the dynamic change lower than 0 as the exposure in AF analysis.

Pearson's correlation analysis was performed to assess the correlations between obesity-related indices, fasting glucose, and HbA1c.

All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R language environment (version 3.3.1, http://www.r-project.org). A two-sided p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 2,601 participants with prediabetes at the baseline were included in this study. The basic characteristics are shown in Table 1. The mean age (SD) of participants was 59.34 (8.67) years old, and 1,194 (45.9%) participants were men. During the 4-year follow-up period, 562 participants regressed to normoglycemia. They showed a lower prevalence of dyslipidemia and lower initial SBP, WC, BMI, TG, TC, LDL, FPG, and HbA1c ($P < 0.05$) than those who did not regress to normoglycemia. Participants who regressed to normoglycemia also had lower BRI, WHtR, TyG, CI, ABSI, and CVAI ($P < 0.05$) than participants who did not regress to normoglycemia.

Initial obesity-related indices at baseline and prediabetes regression

The association of obesity-related indices at baseline with prediabetes regression is presented in Table 2. Initial BRI, WHtR, and CVAI showed a significant association with prediabetes regression. In the unadjusted model (Model 1), compared with the highest tertile, the ORs of the first tertile were 1.99 (95%CIs, 1.57–2.53) for BRI, 2.00 (95%CIs, 1.58–2.55) for WHtR, and 1.79 (95%CIs, 1.42–2.29) for CVAI, respectively. After adjusting for potential confounders (Model 3), the ORs were 1.45 (95%CIs, 1.09–1.93) for BRI, 1.46 (95%CIs, 1.10–1.95) for WHtR, and 1.47 (95%CIs, 1.11–1.93) for CVAI, respectively. However, there was no significant association between initial CI, ABSI, TyG, and prediabetes regression. In addition, elevated WC showed decreased odds of regression from prediabetes to normoglycemia (OR, 0.989; 95%CIs, 0.981–0.998), while there was no significant association between BMI and prediabetes regression to normoglycemia (Supplementary Table S1).

The sensitivity analyses suggested BRI, WHtR, CI, and CVAI were significantly associated with prediabetes regression (Supplementary Tables S2, S4). In the subgroup analyses, the associations of BRI, WHtR, CI, and CVAI with prediabetes regression to normoglycemia were significant in the subgroups of participants aged ≥60 years, not drinking group, and participants with high HbA1c level. Initial BRI and WHtR in the group aged <60 years and female group, WHtR in the low HbA1c level group, and CVAI in the male group were also significantly associated with prediabetes regression (Supplementary Figures S1, S3, S5, S7).

Dynamic changes of obesity-related indices with prediabetes regression

The association of dynamic changes of obesity-related indices with prediabetes regression is presented in Table 3. ΔTyG showed a significant association with prediabetes regression to normoglycemia. In the unadjusted model (Model 1), compared with the highest tertile, the OR of the first tertile of ΔTyG was 1.90 (95%CIs: 1.51–2.40). After adjusting for potential confounders (Model 3), the OR was 2.19 (95%CIs: 1.68–2.85). Nevertheless, ΔBRI, ΔWHtR, ΔCI, ΔABSI, and ΔCVAI showed no significant association with prediabetes regression to normoglycemia. In addition, ΔBMI and ΔWC showed no significant association with prediabetes regression to normoglycemia (Supplementary Table S1).

The sensitivity analyses suggested that TyG reduction was associated with prediabetes regression to normoglycemia (Supplementary Tables S3, S5). However, the reduction of BRI, WHtR, and CI also showed a significant association with prediabetes regression to normoglycemia. In the subgroup analyses, TyG reduction was associated with prediabetes regression to normoglycemia in all the subgroups while the reduction of other indices was not, which was consistent with the primary analyses (Supplementary Figures S2, S4, S6, S8).

Attributable fractions of obesity-related indices

The AFs of obesity-related indices and their dynamic changes are shown in Table 4. We obtained the cutoff values by ROC curves, and they were 4.374 for BRI, 0.568 for WHtR, 8.621 for TyG, 1.320 for CI, 0.083 for ABSI, and 106.152 for CVAI, respectively (Supplementary Table S6, Supplementary Figure S9). Low initial BRI (BRI < 4.374), WHtR (WHtR < 0.568), and

TABLE 1 Baseline characteristics of participants stratified by glycemic condition.

Characteristic	Total	Regression to normoglycemia		*P*
		No	Yes	
No. of subjects	2,601	2,039	562	
Age, years	59.34 ± 8.67	59.69 ± 8.62	58.21 ± 8.76	<0.001
Male, *n* (%)	1,195 (45.9)	904 (44.3)	291 (51.8)	0.002
Place of residence, *n* (%)				0.743
Rural	2,175 (83.6)	1,702 (83.5)	473 (84.2)	
Urban	426 (16.4)	337 (16.5)	89 (15.8)	
Marital status, *n* (%)				0.982
Married	2,274 (87.4)	1,728 (84.7)	492 (87.5)	
Not married	2,274 (12.6)	311 (15.3)	70 (12.5)	
Education level				0.035
Primary school or below	1,858 (71.4)	1,479 (72.5)	379 (67.4)	
Middle school	537 (20.6)	410 (20.1)	127 (22.6)	
High school or above	206 (7.9)	150 (7.4)	56 (10.0)	
Smoking, *n* (%)	1,615 (62.1)	1,277 (62.6)	338 (60.1)	0.344
Drinking, *n* (%)	845 (32.5)	647 (31.7)	198 (35.2)	0.118
Chronic diseases history				
Hypertension, *n* (%)	1,097 (42.2)	878 (43.1)	219 (39.0)	0.090
Dyslipidemia, *n* (%)	941 (36.2)	758 (37.2)	183 (32.6)	0.049
WC (cm)	85.07 ± 12.42	85.63 ± 12.42	83.03 ± 12.25	<0.001
SBP (mmHg)	131.46 ± 24.52	131.83 ± 23.35	130.12 ± 28.31	0.004
DBP (mmHg)	76.17 ± 11.96	76.34 ± 11.88	75.58 ± 12.23	0.138
TC (mmol/L)	5.10 ± 0.99	5.15 ± 0.99	4.91 ± 0.99	<0.001
TG (mmol/L)	1.52 ± 0.97	1.52 ± 0.95	1.49 ± 1.05	0.045
LDL-c (mmol/L)	3.09 ± 0.93	3.14 ± 0.93	2.91 ± 0.91	<0.001
HDL-c (mmol/L)	1.33 ± 0.40	1.33 ± 0.40	1.33 ± 0.40	0.819
FPG (mmol/L)	6.02 ± 0.37	6.03 ± 0.38	5.99 ± 0.34	0.002
HbAlc (%)	5.20 ± 0.42	5.25 ± 0.42	5.01 ± 0.39	<0.001
BMI	23.80 ± 3.84	23.93 ± 3.85	23.36 ± 3.80	<0.001
BRI	4.26 ± 1,52	4.35 ± 1.54	3.94 ± 1.38	<0.001
WHtR	0.54 ± 1.31	0.54 ± 0.08	0.52 ± 0.08	<0.001
TyG	8.74 ± 0.55	8.75 ± 0.54	8.70 ± 0.57	0.023
CI	1.27 ± 0.14	1.28 ± 0.14	1.26 ± 0.15	<0.001
ABSI	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.001
CVAI	97.54 ± 43.54	99.59 ± 43.65	90.11 ± 42.34	<0.001

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; BMI, body mass index; BRI, body roundness index; WHtR, waist-to-height ratio; TyG, triglyceride glucose index; CI, conicity index; ABSI, a body shape index; CVAI, Chinese visceral adiposity index.

CVAI (CVAI < 107.794), as well as TyG reduction (ΔTyG < 0) had significant effects on prediabetes regression (BRI: AF 21.10%, 95%CIs: 10.14–32.07%; WHtR: AF 20.85%, 95%CIs: 9.91–31.80%; CVAI, AF 17.48%, 95%CIs: 7.60–27.36%; ΔTyG: AF 17.55%, 95%CIs: 10.25–24.85%), while low initial TyG and the reduction of BRI, WHtR, CI, ABSI, and CVAI showed no significant association with prediabetes regression.

The correlations between obesity-related indices, fasting glucose, and HbA1c are shown in Figure 2. The initial BRI, WHtR, and CVAI had a stronger correlation with the dynamic

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TABLE 2 Initial obesity-related indices and prediabetes regression.

Variables	No. of cases/total	Model 1[a] OR (95% CIs)	Model 2[b] OR (95% CIs)	Model 3[c] OR (95% CIs)
BRI				
Tertile 1 (<3.582)	226/866	1.99 (1.57, 2.53)	1.84 (1.43, 2.37)	1.45 (1.09, 1.93)
Tertile 2 (3.582–4.818)	205/867	1.74 (1.37, 2.23)	1.63 (1.27, 2.09)	1.38 (1.06, 1.81)
Tertile 3 (>4.818)	131/868	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		<0.001	<0.001	0.015
WHtR				
Tertile 1 (<0.512)	226/866	2.00 (1.58, 2.55)	1.86 (1.44, 2.39)	1.46 (1.10, 1.95)
Tertile 2 (0.512–0.572)	206/868	1.76 (1.38, 2.25)	1.65 (1.29, 2.12)	1.40 (1.07, 1.83)
Tertile 3 (>0.572)	130/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		<0.001	<0.001	0.013
TyG				
Tertile 1 (<8.463)	206/866	1.26 (1.00, 1.59)	1.27 (1.00, 1.60)	1.20 (0.84, 1.70)
Tertile 2 (8.463–8.934)	184/868	1.09 (0.86, 1.37)	1.11 (0.88, 1.41)	1.14 (0.84, 1.55)
Tertile 3 (>8.934)	172/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.046	0.046	0.543
CI				
Tertile 1 (<1.254)	216/867	1.67 (1.32, 2.11)	1.46 (1.14, 1.87)	1.19 (0.92, 1.57)
Tertile 2 (1.254–1.324)	202/866	1.53 (1.21, 1.94)	1.37 (1.07, 1.75)	1.20 (0.93, 1.56)
Tertile 3 (>1.324)	144/868	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		<0.001	0.003	0.211
ABSI				
Tertile 1 (<0.081)	203/866	1.30 (1.04, 1.65)	1.11 (0.86, 1.41)	0.96 (0.74, 1.25)
Tertile 2 (0.081–0.085)	194/867	1.23 (0.97, 1.55)	1.09 (0.85, 1.38)	0.79 (0.79, 1.31)
Tertile 3 (>0.085)	165/868	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.025	0.435	0.747
CVAI				
Tertile 1 (<81.131)	216/867	1.76 (1.38, 2.23)	1.61 (1.26, 2.05)	1.33 (1.01, 1.77)
Tertile 2 (81.131–114.538)	211/867	1.59 (1.25, 2.01)	1.55 (1.22, 1.97)	1.26 (0.97, 1.64)
Tertile 3 (>114.538)	135/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		<0.001	<0.001	<0.001

Abbreviations are the same as presented in Table 1; OR, odds ratio; CIs, confidence intervals.
[a] Unadjusted.
[b] Adjusted for age and gender.
[c] Adjusted for age, gender, place of residence, marital status, educational level, history of smoking and drinking, presence of hypertension, dyslipidemia, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, fasting plasma glucose, and hemoglobin A1c at baseline (for TyG, except triglycerides and fasting plasma glucose; for CVAI, except triglycerides and high-density lipoprotein-cholesterol).

changes in FPG (ΔFPG) and HbA1c (ΔHbA1c) than other initial indices. ΔTyG had a stronger correlation with the dynamic changes in ΔFPG and ΔHbA1c than other indices. In addition, BRI, WHtR, CI, and CVAI showed a strong correlation with each other. ΔBRI, ΔWHtR, ΔCI, ΔABSI, and ΔCVAI showed a strong correlation with each other but a weak correlation with ΔTyG.

Discussion

In the present study, we investigated the association of six obesity-related indices and their dynamic changes with prediabetes regression to normoglycemia among Chinese adults aged ≥45 years during a 4-year follow-up. Our results suggested that low initial BRI, WHtR, and CVAI, as well as TyG reduction were positively

TABLE 3 Dynamic changes in obesity-related indices and prediabetes regression.

Variables	No. of cases/total	Model 1[a] OR (95% CIs)	Model 2[b] OR (95% CIs)	Model 3[c] OR (95% CIs)
ΔBRI				
Decreased (<-0.188)	185/866	1.00 (0.80, 1.26)	1.04 (0.82, 1.31)	1.14 (0.90, 1.46)
Stable (−0.188 to 0.461)	192/867	1.05 (0.84, 1.32)	1.04 (0.82, 1.30)	1.05 (0.82, 1.34)
Increased (>0.461)	185/868	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.98	0.766	0.284
ΔWHtR				
Decreased (<-0.009)	187/867	1.00 (0.80, 1.26)	1.03 (0.82, 1.30)	1.14 (0.89, 1.45)
Stable (−0.009 to 0.023)	188/867	1.01 (0.80, 1.27)	1.00 (0.79, 1.26)	1.02 (0.80, 1.29)
Increased (>0.023)	187/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.998	0.776	0.307
ΔTyG				
Decrease (<-0.214)	238/867	1.90 (1.51, 2.40)	1.90 (1.51, 2.41)	2.08 (1.61, 2.70)
Stable (−0.214 to 0.224)	180/867	1.32 (1.03, 1.68)	1.35 (1.06, 1.73)	1.37 (1.06, 1.77)
Increased (>0.224)	144/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		<0.001	<0.001	<0.001
ΔCI < 0				
Decreased (<-0.025)	174/867	0.95 (0.75, 1.2)	0.98 (0.77, 1.24)	1.03 (0.81, 1.32)
Stable (−0.025 to 0.038)	207/867	1.19 (0.95, 1.49)	1.15 (0.92, 1.45)	1.15 (0.91, 1.46)
Increased (>0.038)	181/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.683	0.876	0.783
ΔABSI < 0				
Decreased (<-0.002)	171/866	0.89 (0.7, 1.12)	0.91 (0.72, 1.15)	0.74 (0.74, 1.21)
Stable (−0.002 to 0.002)	203/868	1.1 (0.88, 1.38)	1.06 (0.84, 1.33)	1.02 (0.80, 1.30)
Increased (>0.002)	188/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.327	0.437	0.664
ΔCVAI < 0				
Decreased (<-1.367)	191/867	1.06 (0.85, 1.34)	1.10 (0.87, 1.38)	1.18 (0.93, 1.51)
Stable (−1.367 to 15.666)	184/867	0.97 (0.77, 1.22)	1.02 (0.81, 1.29)	1.02 (0.80, 1.31)
Increased (>15.666)	187/867	1 (Ref.)	1 (Ref.)	1 (Ref.)
P for trend		0.861	0.597	0.275

OR, odds ratio; CIs, confidence intervals; ΔBRI, dynamic change of body roundness index; ΔWHtR, dynamic change of waist-to-height ratio; ΔTyG, dynamic change of triglyceride glucose index; ΔCI, dynamic change of conicity index; ΔABSI, dynamic change of a body shape index; ΔCVAI, dynamic change of Chinese visceral adiposity index.

[a]Unadjusted.

[b]Adjusted for age and gender.

[c]Adjusted for age, gender, place of residence, marital status, educational level, history of smoking and drinking, presence of hypertension, dyslipidemia, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, fasting plasma glucose, and hemoglobin A1c at baseline (for ΔTyG, except triglycerides and fasting plasma glucose; for ΔCVAI, except triglycerides and high-density lipoprotein-cholesterol).

associated with the prediabetes regression. Furthermore, the AFs of low initial BRI, WHtR, and CVAI, as well as TyG reduction were all around 20%.

In the present study, 562 (21.61%) participants with prediabetes regressed to normoglycemia. Similarly, the KORA S4 study found that 27.3% of participants reversed from HbA1c-defined prediabetes to normal HbA1c levels, while only 9.3% of participants regressed from glucose-defined prediabetes to NGT based on ADA criteria (15). Moreover, a 10-year follow-up study in Japan reported that 17.1% of participants with prediabetes regressed to normal glucose tolerance (12). The different rates of prediabetes regression may be due to the different definitions of prediabetes, study population, and follow-up years. In the present study, prediabetes was defined using HbA1c and FPG according to the

TABLE 4 Attributable fractions of obesity-related indices.

Variables	Model 1[a]		Model 2[b]		Model 3[c]	
	AF% (95%CIs)	*P*-value	AF% (95%CIs)	*P*-value	AF% (95%CIs)	*P*-value
BRI < 4.734	28.07 (18.03, 38.11)	<0.001	28.99 (19.40, 38.59)	<0.001	21.10 (10.14, 32.07)	<0.001
WHtR < 0.568	27.75 (17.72, 37.78)	<0.001	28.70 (19.12, 38.28)	<0.001	20.85 (9.91, 31.80)	<0.001
TyG < 8.621	7.55 (0.53, 14.58)	0.035	8.89 (2.21, 15.56)	0.009	6.26 (−2.15, 14.68)	0.144
CI < 1.320	23.37 (13.97, 32.77)	<0.001	18.11 (7.77, 28.47)	<0.001	9.57 (−1.61, 20.74)	0.093
ABSI < 0.083	13.57 (6.04, 21.10)	<0.001	9.26 (1.17, 17.36)	0.025	5.99 (−2.13, 14.10)	0.148
CVAI < 106.152	23.52 (15.05, 31.99)	<0.001	21.14 (12.41, 29.88)	<0.001	13.53 (3.43, 23.63)	0.008
ΔBRI < 0	3.28 (−3.03, 9.59)	0.308	3.05 (−3.26, 9.37)	0.343	5.62 (−0.41, 11.65)	0.068
ΔWHtR < 0	3.28 (−3.03, 9.59)	0.308	3.05 (−3.26, 9.37)	0.343	5.62 (−0.41, 11.65)	0.068
ΔTyG < 0	18.32 (11.63, 26.19)	<0.001	18.61 (11.32, 25.90)	<0.001	17.55 (10.25, 24.85)	<0.001
ΔCI < 0	−0.07 (−6.63, 6.49)	0.894	1.04 (−5.47, 7.54)	0.755	2.88 (−3.42, 9.18)	0.37
ΔABSI < 0	−2.99 (−9.75, 3.76)	0.385	−2.07 (−8.76, 4.63)	0.545	−0.23 (−6.73, 6.27)	0.945
ΔCVAI < 0	0.09 (−5.41, 5.50)	0.974	0.36 (−5.15, 5.87)	0.898	2.21 (−3.07, 7.48)	0.413

AF, attributable fraction.
Abbreviations are the same as presented in Tables 2, 3.
[a] Unadjusted.
[b] Adjusted for age and gender.
[c] Adjusted for age, gender, place of residence, marital status, educational level, history of smoking and drinking, presence of hypertension, dyslipidemia, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and hemoglobin A1c at baseline (for TyG and ΔTyG, except triglycerides and fasting plasma glucose; for CVAI and ΔCVAI, except triglycerides and high-density lipoprotein-cholesterol).

ADA criteria, while in the KORA F4 cohort study (15), prediabetes and normoglycemia were defined only using HbA1c or blood glucose. Furthermore, various characteristics of participants may also explain the different results. Participants aged 45 years and above were included in our study and most of them came from Chinese rural areas, which suggested that the lifestyle of our participants may be different from other study populations.

Abdominal obesity was suggested as a risk of diabetes and may prevent prediabetes regression to normoglycemia (31). BRI, WHtR, and CVAI were recognized as good markers of abdominal fat (18). Although several studies focused on the association of several obesity-related indices with diabetes (32–34), studies on their relationship with prediabetes are lacking. Liu et al. (20) reported that people with higher BRI and WHtR showed an increased risk of developing diabetes. Cai et al. (33) reported that increases in BRI and WHtR were related to an elevated risk of diabetes among Chinese older adults. CVAI, an obesity-related index based on the Chinese population, showed a positive association with diabetes and metabolic abnormality (19). De et al. (35) reported that people who regressed from prediabetes to normoglycemia had lower WHtR than people who did not regress. The present study demonstrated that low initial levels of BRI, WHtR and CVAI were positively associated with prediabetes regression, which indicated that less abdominal fat may contribute to prediabetes regression to normoglycemia. The abdominal fat, a marker of excess ectopic fat, has more metabolically activity than subcutaneous fat. It can secrete a variety of lipoxins associated with metabolic abnormality, hyperinsulinemia, and impaired insulin secretion, damage pancreatic β-cells, increase insulin resistance, and enhance inflammatory responses, thus increasing the risk of diabetes (36).

Notably, the initial CI and ABSI, as well as the reduction of BRI, WHtR, CI, and CVAI also showed significant association with prediabetes regression in the sensitivity analyses based on WHO criteria and the sensitivity analyses based on multinomial logistic regression, which were inconsistent with the results based on ADA criteria. On the one hand, it may be due to the WHO criteria having higher FPG levels to meet prediabetes and do not offer any recommendation on HbA1c criteria for prediabetes. Therefore, fewer people were diagnosed with prediabetes, and a high rate of prediabetes regression to normoglycemia was presented. On the other hand, we made the progression to the diabetes group as the reference in multinomial logistic regression, and the results showed that prediabetes participants with lower initial obesity-related indices and/or the reduction of obesity-related indices contribute to regress to normoglycemia. These sensitivity analysis results suggested lower initial obesity-related indices and/or the reduction of obesity-related indices contribute to a better health outcome among people with prediabetes. However, a longer follow-up period is needed to further identify whether BRI and WHtR reduction contribute to prediabetes regression. For the CI and ABSI showed no significant association with prediabetes in the primary analysis, there may be other explanations besides the diagnostic criteria and analytical methods above. Previous studies reported that CI and ABSI had a low ability to identify prediabetes status (25). In addition, ABSI, which had little correlation with height, weight, or BMI, was originally established to predict mortality in a follow-up cohort, and it may be not a good index to evaluate obesity status (37). CI was highly related to ABSI, and our study also suggested that they had very weak correlations with FPG, HbA1c, and their dynamic changes. Therefore, the two indices may not be good indices to evaluate prediabetes regression.

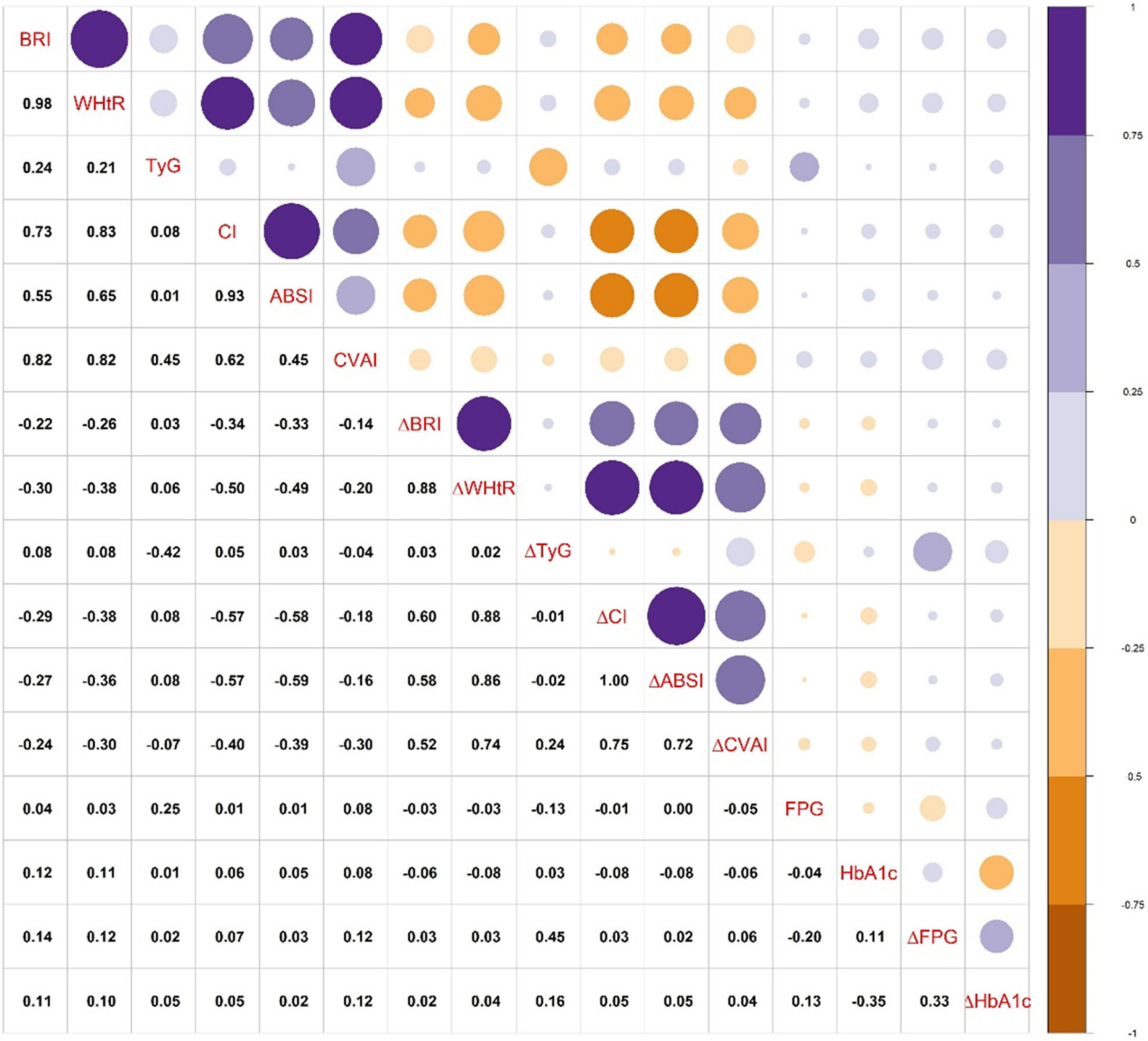

FIGURE 2
The correlations between obesity-related indices, fasting glucose, and HbA1c. Abbreviations are the same as presented in Tables 2, 3. ΔFPG, dynamic change of FPG; ΔHbA1c, dynamic change of HbA1c.

In the present study, we demonstrated that TyG reduction contributed to prediabetes regression. TyG, calculated by FPG and TG and developed by Simental–Mendia et al. (38), is recognized as a reliable marker for IR (21). Some evidence indicated that its discriminatory ability for IR was better than that of the HOMA-IR and TyG, specifically reflected muscle-related IR (22, 23, 39). Zhang et al. found that increasing TyG elevated the cumulative increased risk of incident diabetes after 6 years of follow-up among 5,706 Chinese rural participants (40). Previous studies reported that TG increment accelerated the progression of prediabetes to diabetes, while TG reduction helped patients with prediabetes regress to normoglycemia (35, 41). In addition, high TG level in the blood has been proven to inhibit insulin activity in muscle and interfere with glucose uptake, while TG overload in islets would impair the function of β cells (42). When both fatty acids and glucose are elevated, the accumulation of metabolites derived from fatty-acid esterification impaired the function of pancreatic β cells (21, 42). Previous research suggested that the capacity for insulin secretion and IR was closely affected by TG and FPG levels (43). Improved pancreatic β-cell function and insulin sensitivity have been shown to increase the odds of reaching normal glucose regulation from prediabetes (31). Our study demonstrated that TyG reduction promoted the progress of prediabetes regression to normoglycemia.

In addition, we further investigated the AFs of obesity-related indices for prediabetes regression. Previous research reported PAFs for diabetes attributable to being overweight, which suggests

increases in BMI were responsible for 58% of type 2 diabetes globally. Although several studies have explored the influencing factors of regression from prediabetes to normoglycemia (5, 13, 15), the AFs of the predictors of regression from prediabetes to normoglycemia are lacking. In the present study, the AFs of obesity-related indices were around 20%, which suggested that around 20% of cases regressed to normoglycemia would be attributable to low initial BRI, WHtR, CVAI, or TyG reduction. As a large number of middle-aged and older adults suffered from prediabetes in China (6), the present study suggested that many people with prediabetes would benefit from the prevention of abdominal obesity or the reduction of IR.

The strengths of this study include a prospective cohort study design with a large sample of Chinese middle-aged and older adults. Furthermore, six obesity-related indices have been adopted to access their association with prediabetes regression. In addition, we calculated the AFs of the obesity-related indices and their dynamic changes to make their contributions to prediabetes regression clear.

There are some limitations in this study that should be acknowledged. First, the CHARLS included adults aged 45 years and older from 28 provinces, and the generalization of our findings may not be applicable to all Chinese adults. Second, although our study has controlled for several confounders, some unmeasured variables, such as dietary habits, cardiorespiratory fitness, and metformin use were not included. Third, despite FPG and HbA1c having been used to define prediabetes, the lack of 2 h of post-prandial glucose data from the oral glucose tolerance test may bias the results reported. However, the same criteria have been used in the previous study (7), and the sensitivity analyses also showed consistent results.

In conclusion, our study suggested that low initial BRI, WHtR, and CVAI, as well as TyG reduction, were associated with increased odds of regression to normoglycemia among Chinese middle-aged and older adults with prediabetes. Furthermore, the TyG index can be used as a long-term observation index since its dynamic reduction is beneficial to prediabetes regression. In addition, this study provides more evidence showing that initial obesity-related indices, especially their cutoff values, could be used to identify individuals with prediabetes who are likely to return to normoglycemia. Given that it is difficult for those with prediabetes and a high obesity-related index to return to normoglycemia, more effective lifestyle interventions are warranted to control the conditions in this population.

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.

Author contributions

HY, MinjZ, and JN contributed to the data acquisition, analysis, and results explanation. MinzZ and GL contributed to the results explanation. HY, QH, and RC drafted the manuscript. HY and QH revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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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/fnut.2023.1075225/full#supplementary-material

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Lipid and glucose metabolism in senescence

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Senescence is an inevitable biological process. Disturbances in glucose and lipid metabolism are essential features of cellular senescence. Given the important roles of these types of metabolism, we review the evidence for how key metabolic enzymes influence senescence and how senescence-related secretory phenotypes, autophagy, apoptosis, insulin signaling pathways, and environmental factors modulate glucose and lipid homeostasis. We also discuss the metabolic alterations in abnormal senescence diseases and anti-cancer therapies that target senescence through metabolic interventions. Our work offers insights for developing pharmacological strategies to combat senescence and cancer.

KEYWORDS

senescence, lipid metabolism, glycolysis, CPT1, ACOX1, ACC, TCA, PPP

1. Introduction

Senescence is a universal and complex biological process that affects all living organisms. While senescence contributes to embryonic development and limits tumorigenesis and tissue damage (1), it involves dynamic biological, environmental, physiological, psychological, behavioral, and social process changes leading to progressive declines in biological functions and physiological processes and increased susceptibility to disease, disability, and death (2, 3). The senescence process increases the risk of chronic diseases such as diabetic neurodegenerative diseases, metabolic syndrome, and cardiovascular disease, which have become more prevalent in the elderly population (4). Therefore, understanding the mechanisms and factors that influence senescence and its consequences is crucial for developing interventions to prevent, diagnose, treat, and delay age-related diseases and improve healthspan (the portion of life spent in good health).

Senescence and cell death are two different but interrelated phenomena. Cell death is the irreversible loss of cell viability and function that can occur through different mechanisms, including apoptosis, autophagy, necrosis, and senescence (5). In 2019, the International Cell Senescence Association reached a consensus on the characteristics and biomarkers of cellular senescence (6). They concluded that cellular senescence is not the same as cell death and that senescent cells remain metabolically active for some time and show distinct changes, with four characteristics typical of cell cycle arrest, senescence-related secretory phenotypes (SRSPs), macromolecular damage, and metabolic disorders. Senescent cells show reduced mitochondrial function, impaired adenosine triphosphate (ATP) production, and increased production of reactive oxygen species (ROS), which cause protein and lipid damage (macromolecular damage). Disorders in glucose and lipid metabolism are among the results and further drive the progression of senescence (7, 8).

Lipids may influence cell activity by altering cytomembrane composition, energy reserves, secondary messenger signaling, and gene expression (9–11). A common component of

biological lipid species is fatty acids. One of the signs of senescence is fatty acid metabolic dysregulation, which is related to the transformation from catabolism to synthesis. A decline in fatty acid oxidation (FAO) capacity determines lipid imbalance and age-related obesity (12). Tissue-specific stem cells repair tissue damage and maintain tissue homeostasis. Unbalanced stem cell self-renewal can cause harmful effects such as disease and senescence. Age-related declines in FAO levels harm stem cell maintenance and activity, driving stem cell senescence (13). The imbalance between nuclear receptors (liver-X-receptor α, retinoid acid receptor α, and peroxisome proliferator-activated receptor α [PPARα]) and their target genes (ATP-binding cassette transporter A1, sterol regulatory element binding protein 1c [SREBP1c], and fatty acid synthase [FAS]) likely drives hepatic steatosis in aged patients (14). Moreover, H_2O_2-induced senescence is significantly decreased by inhibiting lipogenesis using FAS inhibitors or silencing SREBP1 and ATP citrate lyase (15). All these pieces of evidence indicate that fatty acid metabolism seriously affects senescence. Targeting the key enzymes of fatty acid metabolism is the most direct and scientific means to screen for anti-senescence drugs or promote tumor senescence treatment.

Glucose metabolism is also involved in the regulation of intracellular senescence. Glucose transporters (GLUTs), members of the membrane transporter family, transport extracellular glucose into the cell. GLUT1 is highly expressed in senescent cells and increases glucose uptake (16, 17). In contrast, under low-concentration glucose culture conditions, drug-induced senescence in lung cancer cells (17) or replicative senescence of human fibroblasts (18) and stem cells (19) cultured *in vitro* is delayed (20). Glucose transported into cells by GLUTs is catalyzed to pyruvate via glycolysis enzymes. The levels of multiple glycolytic enzymes, including hexokinases (HKs), lactate dehydrogenase A (LDHA), and pyruvate kinase (PK), are increased in senescent cells (21). Finally, the metabolites generated by pyruvate entering the tricarboxylic acid (TCA) cycle, including α-ketoglutaric acid (αKG) (22–24) and citrate (25, 26), significantly inhibit intracellular senescence.

This review aims to clarify the relationship between lipids, glucose metabolism, and senescence.

2. Lipids and senescence

2.1. Fatty acid catabolism and senescence

Fatty acid catabolism includes mitochondrial β-oxidation of saturated fatty acids, peroxisomal β-oxidation of very-long-chain fatty acids, α-oxidation of branched-chain fatty acids, ω-oxidation, and ketone formation (27–31). Mitochondrial β-oxidation of saturated fatty acids and peroxisomal β-oxidation of very-long-chain fatty acids are generally the primary metabolic pathways, and carnitine palmitoyl transferase 1 (CPT1) and acyl-CoA oxidase 1 (ACOX1) play crucial roles as rate-limiting enzymes.

2.1.1. Mitochondrial β-oxidation

Under sufficient oxygen supply, medium- and long-chain fatty acids can be decomposed into acetyl-CoA, which can be further completely oxidized into CO_2, H_2O, and significant energy. The whole process of converting acyl CoA to acetyl-CoA, called mitochondrial β-FAO, occurs in the mitochondrial matrix (32). CPT1 assists acyl CoA in the transmembrane entry into the mitochondria and is the primary rate-limiting enzyme (33). All three isoforms of CPT1 (CPT1A, CPT1B, and CPT1C) are associated with senescence. Comparison with proteomic analysis of adult mouse kidneys revealed significantly lower CPT1A expression in aged mice (34). In diabetic nephropathy, a common disease associated with senescence, CPT1A expression is similarly suppressed (35). The same trend in CPT1B expression has been observed in aged rats (36). In addition, deletion of the novel biomarker CPT1C induced mitochondrial dysfunction, leading to senescence-like growth inhibition and cellular senescence in six cancer cell types, including pancreatic cancer cells, and inhibited cancer growth *in vivo* (37). While these findings suggest that senescence is inextricably linked to the absence of CPT1, the exact mechanism is not yet clear.

In recent years, scholars have made progress in this regard (Figure 1). Telomeres, the protective caps on the ends of chromosomes, guard genetic material during cell division. Telomeres shorten with each cell division until they reach a critical length that triggers cellular senescence or apoptosis (38). Telomere shortening is one of the hallmarks of senescence, as it reflects the cumulative damage and stress that cells experience over time. In human hepatoma (HepG2) cells, the knockdown of patatin-like phospholipase domain-containing 2 (also called adipose triglyceride lipase [ATGL]) and CPT1, two crucial genes for lipolysis, results in reduced telomere length (39).

In addition, the cell cycle regulates cell differentiation, proliferation, and senescence. Moreover, senescent cells are blocked in certain growth phases. Treatment with linoleic and oleic acids significantly increased CPT1 expression and S-phase ratio in primary bovine satellite cells and promoted cell proliferation, while decreasing the G0/G1 phase ratio (40). Long-chain fatty acyl-CoA synthase 1, which catalyzes the bioconversion of exogenous or *de novo* synthesized fatty acids to fatty acyl-CoA, promoted tumor progression by reducing CPT1 activity and the number of prostate cancer cells remaining in the G1/S phase (41). The triggers of senescence ultimately converge on the $p53/p21^{CIP1}$ and $p16^{INK4A}$/pRb pathways, which induce cell cycle arrest (42, 43). The proto-oncogene c-MYC is involved in cell cycle progression, apoptosis, and cellular transformation. CPT depletion, especially CPT1C, leads to cellular senescence by blocking the cell proliferation-promoting and cell cycle progression effects of the c-MYC/p27/cyclin D1 signaling axis (44). CPT1 overexpression increases ATP production from FAO sources and drives cell cycle operation in pulmonary artery smooth muscle cells by inhibiting the adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)-p53-p21 signaling pathway (45). CPT1A also represses p21 expression by inhibiting forkhead box O (FoxO), which must be phosphorylated by various protein kinases such as AMPK, c-Jun N-terminal protein kinase (JNK), and p38 to perform their functions (46).

The loss of stem cell number and function is also a visual manifestation of senescence. This age-related change underlays some adverse consequences of senescence. Mihaylova et al. (47) showed that interference with CPT1A reversed fasting-induced enhancement of intestinal stem cell activity and that CPT1A deficiency reduced ISC number and function. Moreover, CPT1A-mediated FAO facilitates the maintenance of neural stem/progenitor cell quiescence (48, 49). Chronic inflammation is a defining characteristic of senescence and has been dubbed "inflamm-senescence" (50). Mitochondrial FAO with CPT1 drives anti-inflammatory protective effects due to its ability

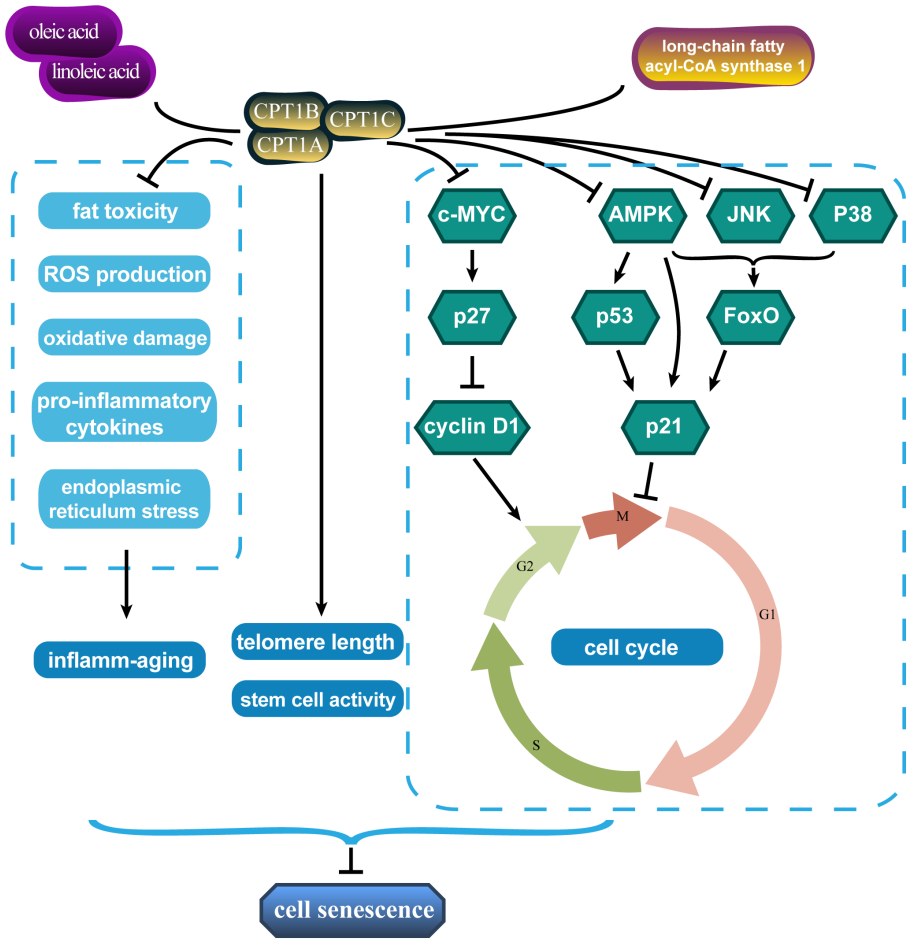

FIGURE 1
Carnitine palmitoyl transferases affect senescence through multiple pathways. CPT1, carnitine palmitoyl transferase 1.

to remove pro-inflammatory compounds such as saturated fatty acids by reducing fat toxicity and ROS production and attenuating palmitic acid-induced pro-inflammatory cytokines, oxidative damage, and endoplasmic reticulum stress (51, 52).

In conclusion, these results tentatively explain the anti-senescence effects of mitochondrial β-oxidation and CPT1. Targeted increase or inhibition of CPT1 expression for different diseases may reduce age-related senescence damage or inhibit tumor progression.

2.1.2. Peroxisomal β-oxidation

Mitochondrial β-oxidation metabolizes common saturated fatty acids. However, some fatty acids, such as very long-chain fatty acids (VLCFAs, with >22 carbons), require the peroxisomal β-oxidation-dependent pathway to be converted into chain-shortened acyl-CoA, which is then transported to the mitochondria for complete oxidation (53). ACOX1 catalyzes its rate-limiting step. Numerous senescence-related diseases are directly related to fatty acid peroxisome β-oxidation. Age-related reduction in liver peroxisomal β-oxidation was accompanied by altered brain fatty acid composition and decreased ACOX1 and PPARα expression in old rats (54). In senescence and age-related degenerative diseases, peroxisome β-oxidation and ACOX1 are significantly reduced (55). In the early stages of Alzheimer's disease (AD), ACOX1 and its transcriptional regulators PPARα and peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1α) are induced to be highly expressed due to damaged mitochondria and increased oxidative stress but are significantly reduced in late stages (56). Moreover, decreased ACOX1, CPT1, and PPARα expression in leptin-resistant elderly rats is the basis of age- and lipid-related diseases (57).

ACOX1 deficiency leading to the accumulation of specific metabolites may affect the biogenesis of the peroxisome itself and/or the homeostasis of other cellular organelles such as the mitochondria and endoplasmic reticulum (Figure 2). Inflammation plays an important role in senescence. The main characteristics of pseudo-neonatal adrenoleukodystrophy (a neurodegenerative disease) are VLCFA accumulation and inflammatory demyelination due to activation of the IL-1 inflammatory pathway. The main cause of this lesion is the absence of ACOX1 (58). Fibroblasts from an ACOX1-deficient patient showed downregulation of numerous cytokines and chemokine mRNAs, including CXCL14 and CXCL12, which are relevant to the regulation of cellular homeostasis (58). Mice lacking ACOX1 also exhibited elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and induced T cell polarization (59). However, inflammation resolution is a dynamic biosynthetically active process governed by a superfamily of bioactive lipids known as specialized pro-resolving mediators

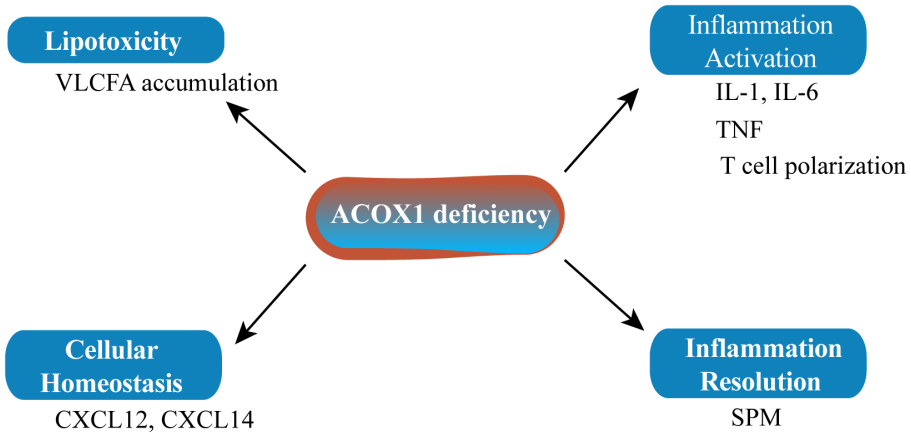

FIGURE 2
ACOX1 deletion affects cellular homeostasis. SPM, specialized pro-resolving mediator.

(SPMs), which enhance the remission of inflammatory reactions (60). SPMs can regulate autophagy, change the release of cytokines/chemokines, and affect the migration and function of leukocytes to alleviate inflammation and delay the senescence process. As it is upstream of SPM biosynthesis, ACOX1 has become a potential anti-senescence protein (61, 62).

PPARα, a subtype of PPARs (including α, β/δ, and γ) and a transcriptional activator of *ACOX1* and *CPT1*, regulates the fatty acid β-oxidation pathway (63, 64). PPARα activity and expression decreased in various aged-animal organs, including the liver and heart (65, 66). These reductions are most likely directly connected to lipid metabolic abnormalities and elevated levels of inflammatory mediators in elderly animals (67). Fatty acid-binding protein-1 (FABP1) binds to free fatty acids by upregulating PPARα and protects the liver from fat toxicity (68). Senescence decreases FABP1 levels, which alters PPARα and causes β-oxidation damage, increasing the morbidity of non-alcoholic fatty liver disease (69). PPARα depletion inhibits cell proliferation and induces cell senescence by reducing the expression of the target gene *CPT1C* (70).

Drugs targeting PPARα may have the potential to fight age-related diseases such as atherosclerosis, vascular diseases, and AD (71). The receptor for advanced glycation end product (RAGE) plays a crucial role in senescence-related vascular disorders, liver damage, and insulin resistance (72–74). Wan et al. (75) observed elevated RAGE levels at the molecular level, which was associated with lower PPARα and β-oxidation levels and was responsible for the deposition of hepatic TG in aged mice. Thus, the RAGE/PPARα regulator axis may be a therapeutic target for fatty liver disease associated with senescence. In *Caenorhabditis elegans*, the administration of ω-3 polyunsaturated fatty acids (α-linolenic acid) increased longevity by activating the transcription factors NHR-49/PPARα (76). Oleoylethanolamide (OEA) can interact with hepatocyte nuclear factor 4 and PPARα and promote their transcriptional activity. Worms treated with OEA showed PPARα activation and increased lifespans (77).

Fenofibrate, a PPARα agonist, reduces the number of senescent cells by increasing apoptosis and autophagy flux and prevents cartilage degeneration caused by senescent and osteoarthritis (78). Proanthocyanidins correct lipid metabolism disorders and treat senescence-related diseases by regulating key enzymes, including PPARα and CPT1 (79). In a d-galactose-induced senescent mouse model, mussel peptides mitigated lipid metabolic diseases and the senescence phenotype by preserving glucose and lipid homeostasis and increasing PPARα/PPARγ expression levels (80). These findings suggest that PPARs may be essential targets in lipid signaling pathways that promote lifespan. Age-related modifications in PPARα in humans have not been explicitly proven, and determining whether the results of animal experiments are applicable to humans is difficult. However, these results provide molecular support for the anti-senescence application of PPAR agonists (e.g., fibrates).

2.1.3. Fatty acid α-/ω-oxidation

Fatty acid α-oxidation occurs in the peroxisomes of cells. This process involves the degradation of branched-chain fatty acids, such as phytanic acid, produced by the body or obtained through dietary intake. Phytanic acid is a 20-carbon fatty acid with a methyl group at the γ-carbon, which prevents it from undergoing β-oxidation (81). Therefore, phytanic acid is oxidized at the α-carbon, which is adjacent to the carboxyl group and loses one carbon atom as CO_2. Phytanoyl-CoA hydroxylase is involved in this process. The resulting product, pristanic acid, can then enter the β-oxidation pathway and generate acetyl-CoA and propionyl-CoA. Fatty acid α-oxidation and senescence are related in several aspects. First, fatty acid α-oxidation is impaired in some senescence-related diseases, such as Refsum disease, a rare genetic disorder that causes the accumulation of phytanic acid in various tissues and plasma, leading to neurological symptoms such as peripheral neuropathy, ataxia, retinitis pigmentosa, and deafness (82). Second, fatty acid α-oxidation generates ROS as by-products (83), which can cause oxidative stress and damage to cellular components, including DNA, proteins, and lipids. Oxidative stress is a major contributor to senescence and age-related diseases such as neurodegeneration, cancer, and diabetes. Third, α-oxidation of fatty acids is also regulated by PPARs (84), the latter in relation to senescence as discussed above regarding peroxisomal β-oxidation.

Fatty acid ω-oxidation occurs in the endoplasmic reticulum of some cells, especially in the liver and kidney (29). This process involves the monooxygenase-catalyzed oxidation of the fatty acid ω-carbon (the carbon furthest from the carboxyl group), followed by

successive oxidations of the β-carbon until the fatty acid chain is shortened by two carbon atoms. This mechanism exists to break down large, water-insoluble fatty acids that, in greater quantities, would be hazardous to cells (85). The ω-oxidation of fatty acids accelerates the rate of fatty acid degradation as feedback to various stressors such as hypoxia, inflammation, and stimulation by exogenous substances. These substances increase the demand for FAO and detoxification. Correspondingly, the omega-oxidation of fatty acids reduces the likelihood that these stressors will lead to senescence and age-related diseases.

2.2. Fatty acid synthesis and senescence

Triglycerides, phospholipids, sphingolipids, and cholesterol lipids are all produced by a series of enzymatic reactions between fatty acids and different chemical groups. Therefore, the regulation of fatty acid synthesis affects the metabolic homeostasis of lipids to a certain extent.

2.2.1. Acetyl-CoA carboxylase

Acetyl-CoA carboxylase (ACC) catalyzes the rate-limiting step of *de novo* fatty acid synthesis (86). Among the two subtypes, ACC1 and ACC2, the former locates in the cytoplasm and is used for fatty acid synthesis by converting acetyl coenzyme A into malonyl coenzyme A. ACC2 is located on the cytoplasmic surface of mitochondria, and the product is used to inhibit CPT1 from reducing FAO (87). SiRNA silencing of SREBP1 significantly reduced the expression of its downstream target genes *ACC*, *FAS*, and ATP citrate lyase, and weakened H_2O_2-induced senescence (15). ACC1-dependent lipogenesis is the fundamental metabolic pathway downstream of AMPK, which induces autophagy and maintains cell survival during yeast senescence (88). This evidence suggests that ACC directly modulates the senescence phenotype, and several drugs targeting ACC to slow senescence already exist. Citrate treatment can increase ACC1 expression, promote excessive lipid biosynthesis, and lead to tumor cell senescence and growth inhibition (26). The AD candidate drugs CMS121 and J147 play anti-senescence neuroprotective roles by inhibiting ACC1 and increasing acetyl-CoA levels (89). Resveratrol plays an anti-senescence role by increasing ACC phosphorylation and enhancing mitochondrial lipolysis ability (90). AMPK, the upstream negative regulator of ACC, also shows some anti-senescence activity.

2.2.2. AMP-activated protein kinase

Lipid metabolism depends heavily on AMPK. AMPK enhances lipolysis by upregulating ATGL expression (91). AMPK can also suppress lipid production by inhibiting ACC activation by phosphorylating ACC1 (Ser 79 Ala) and ACC2 (Ser 212 Ala) (92) and downregulating SREBP1c expression (93, 94). AMPK affects organism senescence directly or indirectly in a variety of ways. For example, dietary restrictions delay the senescence of many species, in which AMPK is widely involved. In *C. elegans*, AMPK and dietary restriction increase FAO through mitochondrial-peroxisome coordination, thereby maintaining homeostasis and plasticity within the mitochondrial network to extend life (95). Greer et al. (96) also reported that the lifetime extension due to food restriction in *C. elegans* was mediated through the AMPK-FoxO (transcription factors) pathway. AMPKα subunit AAK-2 is activated by either a mutation that reduces insulin-like signaling or an environmental stressor that increases the AMP:ATP ratio, which can extend lifespan *in C. elegans* (97, 98). A similar situation exists in mice. For instance, the pharmacological stimulation of AMPK can imitate caloric restriction (induced comparable gene expression patterns) and provide extensive protection against age-related diseases (99). Fibroblast growth factor 21 can exhibit anti-senescence effects by elevating the expression of AMPK, which regulates lipid and glucose metabolic balance (100), blocking the p53 signaling pathway in an AMPK-dependent manner (101). As an AMPK agonist, metformin plays a dual role in cancer prevention and anti-senescence (102, 103). Fruit flies' lifespans also increased by overexpressing AMPK (104).

AMPK also regulates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inflammatory pathway (105), mammalian target of rapamycin (mTOR) C1 autophagy-related protein, and PGC-1α, P53/HIF-1α senescence-related signaling to achieve anti-senescence effects (106, 107). In detail, by phosphorylating mTORC1, ULK1, and PIK3C3/VPS34 complexes, AMPK directly stimulates autophagy (108). Inhibiting mTOR signaling plays a crucial role in mammalian senescence by reducing the accumulation of protein toxicity and oxidative stress (99), increasing autophagy to clear damaged proteins and organelles (109), and enhancing the self-renewal capacity of hematopoietic stem cells (110) and intestinal stem cells (111). Metformin can reduce cartilage degeneration in senescence-related osteoarthritis models by modulating AMPK/mTOR (112).

2.3. Ketone bodies and senescence

Ketone bodies are endogenous metabolites produced by the liver from fatty acids and ketogenic amino acids when glucose availability is low, such as during fasting, caloric restriction, or prolonged exercise (113). Ketone bodies can be used as an alternative fuel source by many tissues, especially the brain, heart, and skeletal muscle, when glucose is scarce or absent (114). These bodies can also cross the blood–brain barrier and supply energy to the central nervous system.

Ketone bodies are scary to clinicians because of the high mortality rate of ketoacidosis; however, in reality, the ketone bodies have signaling functions that regulate inflammation, epigenetics, oxidative stress, and other cellular processes by binding to specific receptors and enzymes (115–117). The bodies may also modulate gene expression and protein synthesis. Ketone bodies are linked to multiple mechanisms of senescence and resilience, such as glucose sparing, mitochondrial biogenesis, autophagy, and hormesis (118–121); thus, they have anti-cancer, anti-angiogenic, and anti-atherogenic effects. Ketone bodies also reduce neuroinflammation and β-amyloid and tau accumulation, and improve memory and healthy lifespan in a senescent mouse model (114).

The most well-known ketone body, 3-hydroxybutyrate (3-OHB), binds to specific hydroxycarboxylic acid receptors to inhibit histone deacetylases, free fatty acid receptors, and nucleotide oligomerization domain (NOD)-like receptor protein 3 inflammasomes. This initially inhibits lipolysis, inflammation, oxidative stress, cancer growth, angiogenesis, and atherosclerosis, and may increase lifespan associated with exercise and caloric restriction (122). In addition to helping treat other neurological conditions including dementia, the ketone body/ketogenic diet has been successfully utilized to reduce seizures (123). Additionally, 3-OHB protects muscle proteins from damage caused by

systemic inflammation and is a crucial part of the metabolic defense against insulin-induced hypoglycemia (124).

2.4. Phospholipids and senescence

Phospholipids are major components of biological membranes and consist of a glycerol backbone, two fatty acid chains, and a polar head group. Phospholipids are essential for membrane structure, fluidity, and function, as well as for intracellular signaling, trafficking, and metabolism (125). Phospholipids are synthesized in different cellular compartments by various enzymes and transported by specific carriers or vesicles. Phospholipids mainly include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and cardiolipin. Phospholipids can also be degraded or modified by phospholipases, acyltransferases, and other enzymes that regulate their turnover and diversity (126).

Phospholipids play important roles in senescence and age-related diseases. Senescence is associated with changes in phospholipid composition, metabolism, and transport in different tissues and organs. These changes may affect membrane integrity, fluidity, and function, as well as cellular signaling and homeostasis (127, 128). For example, senescence leads to decreased unsaturated fatty acid levels and increased saturated fatty acid levels in phospholipids, which may impair membrane fluidity and increase oxidative stress (129). Senescence also alters the levels of specific phospholipid species, such as phosphatidylcholine, phosphatidylethanolamine, and cardiolipin, which may affect mitochondrial function and biogenesis (130).

Phospholipid interventions may have beneficial effects on senescence and lifespan. Dietary supplementation or genetic manipulation of phospholipids or their precursors can modulate membrane properties, cellular signaling, and mitochondrial function in various model organisms. For instance, phosphatidylcholine or choline supplementation improved cognitive function and memory in aged rodents (131). Overexpression of cardiolipin synthase or supplementation of cardiolipin precursors can enhance mitochondrial function and extend lifespan in yeast, worms, flies, and mice (132).

2.5. Sphingolipids and senescence

Sphingolipids are a diverse class of lipids that are involved in various cellular processes such as membrane structure, signal transduction, cell cycle regulation, apoptosis, senescence, and inflammation (133). Sphingolipids are synthesized *de novo* in the endoplasmic reticulum from non-sphingolipid precursors, such as serine and palmitoyl-CoA, and then further modified in the Golgi apparatus and other organelles to generate a variety of complex sphingolipids with different polar head groups (134). The major bioactive sphingolipids include ceramide (Cer), sphingosine, sphingosine-1-phosphate (S1P), and ceramide-1-phosphate, which can act as second messengers or ligands for specific receptors to modulate cellular responses (135).

Sphingolipids have been implicated in the regulation of senescence and age-related diseases, as they can affect several hallmarks of senescence such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (136). In general, Cer and its derivatives induce cellular senescence and promote senescence phenotypes, while S1P and its receptor signaling delay senescence and extend lifespan (137). For example, sphingolipids are involved in sarcopenia, an age-related disorder of loss of skeletal muscle mass and function. Park et al. (133) recently reported that Cer and glucosylceramide accumulate in the skeletal muscle of a senescent mouse model and that deleting serine palmitoyltransferase (SPT), the rate-limiting enzyme for sphingolipid biosynthesis, or using the SPT inhibitor myriocin to inhibit sphingolipid synthesis prevents sarcopenia and improves muscle health. In addition, SPT deletion or myriocin treatment enhances mitochondrial function, autophagy, and proteostasis in aged muscle cells, suggesting that sphingolipids may impair these processes by affecting endoplasmic reticulum stress and calcium homeostasis.

2.6. Sterols and senescence

Sterols are essential components of eukaryotic cell membranes, where they regulate membrane fluidity, permeability, and microdomain formation. Sterols also have important roles in animal physiology, as they are precursors of steroid hormones such as glucocorticoids, mineralocorticoids, androgens, estrogens, and progestins, which modulate various metabolic, reproductive, and immune functions (138). Sterols are synthesized from acetyl-CoA through a complex pathway that involves more than 20 enzymes and intermediates (139). The first steps of sterol biosynthesis occur in the cytosol and endoplasmic reticulum, where acetyl-CoA is converted to mevalonate by three enzymes: acetoacetyl-CoA thiolase, HMG-CoA synthase, and HMG-CoA reductase. Mevalonate is then converted to isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), which are the building blocks of isoprenoids. IPP and DMAPP are used to synthesize geranyl pyrophosphate, farnesyl pyrophosphate, and squalene, which are the precursors of sterols and other isoprenoids such as ubiquinone, dolichol, and prenylated proteins (140). The final steps of sterol biosynthesis involve the cyclization of squalene to form lanosterol, which is then converted to cholesterol by a series of modifications such as hydroxylation, demethylation, reduction, and isomerization. Take cholesterol, the predominant sterol in animals, for example, which is integral and indispensable to neuronal physiology during both development and adulthood. As a major component of cell membranes and a precursor to steroid hormones, it helps regulate ion permeability, cell shape, intercellular interactions, and transmembrane signaling. Inherited diseases with mutations in cholesterol-related genes lead to impaired brain function. In these cases, brain cholesterol defects may be secondary to pathogenic factors and lead to functional deficits through altered synaptic function. Defects in brain cholesterol metabolism may lead to neurological syndromes such as AD, Huntington's disease, and Parkinson's disease, and even cognitive deficits (141–143).

3. Glucose metabolism and senescence

3.1. Glycolysis

The Warburg effect reveals that tumor cells prefer ATP production by glycolysis over oxidative phosphorylation even in the presence of abundant oxygen (144). The Warburg effect plays an important role in the inhibition of cellular senescence and tumor promotion (145).

Glycolysis is upregulated in most senescence phenotypes. Glycolytic gene overexpression promotes altered cancer metabolism in a variety of tumor cells. LDHA, involved in the conversion of pyruvate to lactate, was significantly increased in radiotherapy-induced senescent HCT-116 and MDA-MB-231 cells (146, 147). Lactate liberation acidulates the extracellular environment involved in SRSPs (146). Lactic acid-induced acidic intracellular pH activates Snail to promote epithelial-mesenchymal transition. Increased Snail expression facilitated lung cancer cells to escape oncogene-induced senescence by directly suppressing $p16^{INK4a}$ expression (21). In this way, LDHA expression in senescent fibroblasts promotes PC3 cell invasion in the co-culture of senescent fibroblasts and PC3 cells (148). Pharmacological inhibition of LDHA induces tumor cell senescence by suppressing heat shock response (149). Aurora-A, a serine/threonine kinase, can directly bind to the transcription factor SOX8 to promote the expression of glycolytic and senescence genes, including *LDHA*, *HK2*, *P16*, and *hTERT* in cisplatin-resistant ovarian cancer cells (150). Consequently, radiotherapy/chemotherapy-induced senescent cancer cells exhibit glycolytic vulnerability.

Beyond radiotherapy- and chemotherapy-induced senescent cancer cells, glycolysis is also activated in non-neoplastic senescent cells. The levels of intermediate metabolites of glycolysis, including 3-phosphoglycerate, glucose 6-phosphate, fructose 6-phosphate, and phosphoenolpyruvate, are significantly increased in senescent fibroblasts, which highlights increased glycolytic flux to promote pyruvate and lactate production (151). Senescent spermatogonial stem cells exhibit JNK phosphorylation and enhanced glycolytic capacity compared with young cells (152). Senescence fibroblasts exhibit a significant increase in glucose consumption (18). Increased glycolysis appears to be mediated by the overexpression of multiple glycolytic enzymes in distinct kinds of induced senescence. First, GLUT proteins are encoded by *SLC2*. GLUTs 1–4 have widely established roles as glucose transporters (153). GLUT1 is overexpressed in aged lungs and regulates fibrogenesis (154). In this way, hyperglycemia-induced GLUT1 overexpression activates the mTOR pathway to increase P16 and P21 levels while promoting macrophage establishment of the SRSP response (16). Second, HKs catalyze the phosphorylation of glucose as the first rate-limiting step in glycolysis (155). HK1 and HK2 (154) isozymes are highly expressed in replicative senescence human fibroblasts (18). Third, PK, the rate-limiting enzyme in the final step of glycolysis, catalyzes pyruvate production. The levels of this enzyme are upregulated in replicative senescence fibroblasts due to increased TCA activity and oxygen consumption (156). In conclusion, glycolysis is increased in replicative senescent cells, but the regulatory mechanism of elevated enzyme expression and activity needs to be further characterized.

3.2. TCA cycle

Tumor cells maintain cell proliferation by activating glycolysis to provide energy and precursors. Pyruvate, a glycolytic terminal product, enters the TCA cycle to produce metabolic intermediates that inhibit cellular senescence (157). Citrate is the product catalyzed by citrate synthase in the initiation of the TCA cycle. Recently, citrate has been reported to extend lifespan through mTOR and AMPK. However, citrate treatment results in cellular senescence and inhibits the proliferation of MCF-7 and HCT116 cancer cells (26). Mechanistically, DNA damage pathways coupled with MAPK and mTOR pathways lead to citrate-induced cellular senescence (26). αKG, a metabolite catalyzed by isocitrate dehydrogenase (IDH), extends the lifespan of *C. elegans* (23), *Drosophila* (158), and mice (22); attenuates mouse age-related bone loss (24); and delays age-related fertility decline in mammals (159). Sustaining this biological activity requires a continuous supply of ATP from mitochondria; however, the partial inhibition of the electron transport chain by αKG reportedly extends the lifespan of *C. elegans* and mammalian cells (23). Mechanistically, αKG inhibits intracellular senescence by regulating the expression of histone epigenetic modifications of BMP signaling proteins (24). In addition, αKG prolongs *Drosophila* lifespan by activating AMPK and inhibiting mTOR (158). The IDH1 R132H mutant indirectly promotes senescence of malignant glioma cells by reducing αKG production (160).

3.3. Pentose phosphate pathway

Abnormal glucose metabolism in cancer cells activates arrested cellular senescence. Cancer cells not only show active glycolysis for sufficient energy but also precursors from the pentose phosphate pathway (PPP) for intracellular biosynthesis (161). G6PD-mediated oxidative PPP (oxPPP) provides NADPH to counteract oxidative stress, while non-oxPPP generates ribose-5-phosphate (R5P) to provide precursors for nucleotide synthesis (161). G6PD, a unique rate-limiting enzyme in the PPP, is involved in counteracting cellular senescence. Mechanistically, G6PD knockdown increases the levels of P21, a classical marker of senescence, which promotes HCC and HCT116 cell senescence (162). In addition, TAp73 enhances cell cycle inhibitory protein P21 by regulating metabolism (163). TAp73 directly activates G6PD to increase PPP flow to inhibit cancer cell senescence (164). Thus, G6PD may mediate, at least in part, the regulation of the senescence phenotype of cancer cells by TAp73. G6PD also regulates cellular senescence by affecting telomerase activity (165, 166). G6PD-deficient fibroblasts exhibit delayed growth and accelerated senescence. Ectopic expression of the human telomerase reverse transcriptase hTERT activated telomerase activity to prevent cellular senescence in G6PD-deficient fibroblasts (166). Thus, the knockdown of hTERT significantly reduces G6PD expression and telomerase activity to promote cancer cell senescence (165). 6-phosphogluconate dehydrogenase (6PGD) is a key enzyme in oxPPP. Pharmacological inhibition of 6PGD induces cellular senescence and MCF-7 cell cycle arrest (167). Non-oxPPP also regulates cellular senescence. Supplementation of ribose 5-phosphate in drug-induced senescent human dermal fibroblasts significantly inhibited cell enlargement, a morphological alteration of cellular senescence (168). In addition, hTERT knockdown inhibited the expression and activity of transketolase, a key enzyme of non-oxppp; increased cancer cell senescence; and reduced tumor burden in a mouse model of heterotypic xenograft (165).

4. Lipid and glucose metabolism and SRSPs

SRSPs describe the diverse array of proinflammatory and profibrotic factors secreted by senescent cells (169). SRSPs include

cytokines, chemokines, growth factors, proteases, and extracellular matrix components that can affect the surrounding tissue microenvironment and modulate various biological processes, including inflammation, immunity, tissue remodeling, and tumorigenesis (170). SRSPs are considered crucial drivers of chronic inflammation and senescence phenotypes, as they accumulate throughout normal senescence and in age-related diseases. SRSPs can have both beneficial and detrimental effects on the organism, depending on the expression context and duration. While SRSPs can promote wound healing, tissue repair, and immune surveillance by stimulating cell proliferation, angiogenesis, and immune cell recruitment (170), they can also induce cellular senescence in neighboring cells, disrupt tissue homeostasis and function, and facilitate the development and progression of age-related diseases such as cancer, neurodegeneration, cardiovascular disease, diabetes, and osteoporosis (171, 172).

Growing evidence has shown that lipid metabolism and SRSPs are interconnected at multiple levels. For instance, some lipids (such as ceramides, S1P, and prostaglandins) can modulate the expression or activity of key regulators of SRSPs, including p53, NF-κB, p38 MAPK, JNK, mTOR, IL-1α/β, and STAT3 (173–175). Conversely, some SRSP factors, such as IL-1β, IL-6, IL-8, and TNF-α, can affect lipid metabolism by altering lipogenic enzymes (e.g., FAS, ACLY, and ACC), lipolytic enzymes (e.g., ATGL, hormone-sensitive lipase [HSL], and MGL), lipid transport proteins (e.g., CD36 and FABP4), fatty acid oxidases (e.g., CPT1A, CPT2, and ACADL), and PPAR expression or activity to influence lipid metabolism (173, 176). SRSP factors can also regulate lipids by affecting key signaling pathways such as the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR and sphingosine kinase 1/S1P pathways.

Disturbances in glucose metabolism can also induce cellular senescence and SRSPs in various tissues, such as pancreatic beta cells, endothelial cells, neurons, astrocytes, myocytes, and adipocytes (177–179). Conversely, SRSPs can modulate its metabolic activity by altering the expression and activity of key metabolic enzymes and transcription factors such as AMPK (180), PGC-1α, sirtuin 1 (181), FoxO (182), NF-κB (183), and nuclear factor erythroid 2-related factor 2 (184). These factors can regulate various aspects of glucose metabolism such as glycolysis, gluconeogenesis, glycogen synthesis and breakdown, pentose phosphate pathway, and the hexosamine biosynthetic pathway. SRSPs can also impair glucose uptake and utilization in these tissues by interfering with insulin signaling and inducing insulin resistance (185).

5. Apoptosis, autophagy, and senescence

Apoptosis and autophagy are two major forms of programmed cell death that play important roles in senescence and age-related diseases. Apoptosis is a regulated process of cell elimination that involves the activation of caspases, cleavage of cellular substrates, and formation of apoptotic bodies that are phagocytosed by macrophages or neighboring cells (186). Autophagy is a catabolic process of self-digestion that involves the formation of double-membrane vesicles called autophagosomes, which engulf cytoplasmic components and deliver them to lysosomes for degradation (187). Both apoptosis and autophagy are essential for maintaining cellular homeostasis, tissue integrity, and organismal health, as they remove damaged or redundant cells and organelles, recycle nutrients, and regulate inflammation and immunity (188). However, both processes also decline with senescence, leading to the accumulation of dysfunctional cells and organelles, oxidative stress, chronic inflammation, and impaired tissue repair and regeneration (189).

The relationship between apoptosis and autophagy in senescence is complex and context-dependent. On the one hand, apoptosis and autophagy can cooperate or compensate for each other to maintain cellular quality control and prevent senescence or tumorigenesis. For example, autophagy can remove damaged mitochondria that produce ROS and trigger apoptosis (190). Autophagy can also degrade pro-apoptotic factors or inhibit apoptotic signaling pathways, thus protecting cells from excessive or inappropriate cell death. On the other hand, apoptosis and autophagy can antagonize or compete to modulate cellular fate and function. For instance, apoptosis can inhibit autophagy by cleaving autophagy-related proteins or blocking autophagosome-lysosome fusion. Apoptosis can also induce autophagy as a survival mechanism or a secondary mode of cell death when caspase activation is impaired or overwhelmed (191).

The balance between apoptosis and autophagy in senescence is influenced by various factors, including genetic background, environmental stimuli, hormonal status, metabolic state, and disease conditions. Lipid and glucose metabolism are the two main pathways that provide energy and substrates for cellular function and survival. Dysregulation of lipid or glucose metabolism can affect the balance between apoptosis and autophagy. Lipid metabolism is regulated by various factors, including hormones, nutrients, and oxygen levels. Lipid metabolism can modulate apoptosis and autophagy by affecting the production of ROS, activation of signaling pathways, and formation of lipid droplets or membrane structures (192). For example, excessive lipid accumulation can induce oxidative stress and ER stress, which can trigger apoptosis or autophagy by activating the JNK, p53, or PKR-like endoplasmic reticulum kinase (PERK) pathways (193–195). Conversely, lipid depletion can also induce apoptosis or autophagy by impairing mitochondrial function, reducing ATP levels, or activating the AMPK pathway (196, 197). Moreover, lipid metabolism can influence autophagic membrane initiation and elongation by providing phospholipids or fatty acids as precursors or modulators (198). Lipid metabolism can be regulated by autophagy through the degradation of lipid droplets or lipogenic enzymes in a process called lipophagy (199).

Similarly, glucose metabolism can regulate apoptosis and autophagy by affecting the production of ROS, activation of signaling pathways, and maintenance of energy homeostasis. For example, high glucose levels can induce oxidative stress and ER stress, which can trigger apoptosis or autophagy by activating the p38 MAPK, NF-κB, or CHOP pathways (200–202). Conversely, low glucose levels can also induce apoptosis or autophagy by impairing mitochondrial function, reducing ATP levels, or activating the AMPK pathway (203). Moreover, glucose metabolism can influence autophagy induction and progression by providing hexosamines or acetyl-CoA as regulators (204, 205). Furthermore, glucose metabolism can be regulated by autophagy through the degradation of glycogen granules or glycolytic enzymes in a process called glycophagy (206).

6. Insulin signaling

The relationship between insulin signaling and glucose and lipid metabolism is essential for maintaining energy homeostasis and preventing metabolic diseases. Insulin stimulates glucose uptake, utilization, and storage by activating the PI3K/Akt pathway and downstream targets such as GLUT4, glycogen synthase, and HK (207). Insulin also stimulates lipid synthesis and storage by activating the same pathway and downstream targets such as SREBPs, ACC, and FAS (208). Insulin also inhibits glucose production by suppressing the expression and activity of enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), or lipolysis, such as HSL and ATGL (209). However, insulin signaling and glucose and lipid metabolism can be disrupted by various factors such as obesity, inflammation, oxidative stress, endoplasmic reticulum stress, and senescence. These factors can impair insulin action and induce insulin resistance by interfering with insulin receptor function or downstream signaling components. For instance, oxidative stress can reduce insulin receptor tyrosine phosphorylation and Akt activation by increasing the activity of protein tyrosine phosphatase 1B or protein kinase C (PKC) (210). Inflammation can also impair insulin signaling by inducing the production of pro-inflammatory cytokines such as TNF-α and IL-6, which can activate serine/threonine kinases such as JNK or inhibitor of nuclear factor κB kinase subunit β (IKKβ), that can phosphorylate insulin receptor substrate 1 (IRS-1) on serine residues and inhibit its tyrosine phosphorylation (211). Mitochondrial dysfunction can impair lipid oxidation and increase lipid accumulation in non-adipose tissues such as skeletal muscle or liver, which can cause lipotoxicity and impair insulin action by activating PKC, JNK, or IKKβ (212). Endoplasmic reticulum stress can also induce insulin resistance by activating the unfolded protein response (UPR), which can suppress insulin receptor expression or activate JNK or PERK, which can phosphorylate IRS-1 on serine residues and inhibit its tyrosine phosphorylation (213). Conversely, senescence can also affect insulin signaling and glucose and lipid metabolism by reducing the expression or activity of insulin receptors or their substrates, increasing the levels of inflammatory cytokines or oxidative stress markers, impairing mitochondrial function or autophagy, or altering the composition or function of gut microbiota.

Several transcription factors play pivotal roles in modulating insulin action and lipid homeostasis in response to senescence. For example, FoxO transcription factors, which are downstream targets of the PI3K/Akt pathway, have been implicated in regulating glucose and lipid metabolism, oxidative stress resistance, inflammation, autophagy, and lifespan in various organisms (214). FoxO factors can induce the expression of genes involved in gluconeogenesis such as *PEPCK* and *G6Pase*, or genes involved in FAO such as *CPT1* or *ACOX*, thereby antagonizing the effects of insulin on glucose and lipid metabolism (215). FoxO factors can also induce the expression of genes involved in antioxidant defense such as superoxide dismutase or catalase, or genes involved in anti-inflammatory responses, such as *IL-10* or suppressor of cytokine signaling 3, thereby protecting against oxidative stress and inflammation induced by senescence (216). FoxO factors can also induce the expression of genes involved in autophagy, such as *LC3* or *Atg12*, thereby promoting the clearance of damaged organelles or proteins accumulated during senescence (217). Moreover, FoxO factors can regulate lifespan by modulating the activity of the insulin/insulin-like growth factor signaling (IIS) pathway or other longevity pathways, such as sirtuins or mechanistic/mTOR (218).

7. Environmental factors affecting senescence

7.1. Nutrition

Glucose is one of the main sources of cellular energy. Excessive glucose intake and abnormally elevated circulating blood glucose levels are associated with chronic diseases such as obesity and diabetes. On the one hand, the metabolic changes caused by hyperglycemia and diabetes promote cellular senescence, leading to tissue dysfunction and various complications such as diabetic retinopathy. Pancreatic β-cells sense elevated blood glucose levels and secrete insulin correspondingly to maintain blood glucose levels within a narrow range. Glycolysis is increased in diabetic β-cells, which inhibits β-cell function (219). Increased numbers of SA-β-gal+ cells in the pancreas of healthy older adults compared with younger adults and further increases in the number of SA-β-gal+ cells in the pancreas of patients with type 2 diabetes (T2D) compared with non-diabetic patients suggest that β-cell senescence may contribute to T2D pathogenesis (220). A diabetic environment and SRSPs are considered drivers of diabetic retinopathy senescence *in vitro* and *in vivo*. High glucose exposure accelerates cellular senescence (20). High concentrations of 25 mM glucose in culture accelerated the senescence of human retinal microvascular endothelial cells. However, glycolysis was significantly reduced rather than increased in an *in vitro* model of senescence. The presence of a negative feedback regulatory mechanism in an *in vitro* model may reduce levels of the glucose transport proteins GLUT1 and GLUT3 and the glycolytic enzyme PFKFB3, affecting the rate of glucose transport (221). On the other hand, cellular senescence may also affect insulin secretion and sensitivity, thereby increasing the risk of developing diabetes. Adipose precursor cells affect neighboring non-senescent cells through the secretion of SRSP factors such as activin A, IL-6, and TNFα, leading to impaired adipogenesis and reduced insulin sensitivity, which may also be involved in T2D progression (222).

Abnormal lipid accumulation during senescence is mainly caused by increased fatty acid uptake, *de novo* lipogenesis, and decreased FAO processes. Mitochondrial integrity and autophagy induction are also diminished during senescence, leading to decreased lipolysis. These changes further impart lipotoxicity to the cell, depleting energy in the tissues and altering cellular signaling, thereby accelerating senescence and the early onset of age-related diseases (223). Multiple adipogenesis enzymes are upregulated in senescent hepatocytes, including FAS, ACC, and stearoyl-CoA desaturase (SCD) (224). In addition to lipid synthesis, excessive lipid intake increases FAO in the mitochondria and the ROS produced, leading to mitochondrial DNA damage and mitochondrial dysfunction (225). Excessive lipid intake inhibits autophagy activation signaling and reduces autophagy levels. Reduced autophagy levels lead to the accumulation of large amounts of waste products and toxins in the cell, interfering with cellular function and homeostasis and accelerating cellular senescence (226). Excess saturated fatty acids activate the NF-κB and JNK signaling pathways

by binding to Toll-like receptor 4 on the cell surface, thereby inducing the expression and release of inflammatory factors (227, 228).

7.2. Stress

Stress can impair glucose and lipid metabolism by altering the levels of insulin, leptin, cortisol, and other hormones that modulate appetite, energy expenditure, and glucose uptake (229). Stress can also induce lipotoxicity, which is the accumulation of excess lipids and their metabolites in non-adipose tissues, such as the liver, muscle, heart, and brain (230). Lipotoxicity can cause cellular damage, inflammation, insulin resistance, and apoptosis, leading to metabolic disorders and age-related diseases (230). Moreover, stress can affect the mitochondrial function and autophagy of cells, which are involved in glucose and lipid metabolism (231). Mitochondria are organelles that produce energy from glucose and fatty acids, while autophagy is the process that degrades damaged or excess cellular components, such as lipids. Stress can induce mitochondrial stress, which is the imbalance between mitochondrial biogenesis and degradation, resulting in mitochondrial dysfunction, oxidative stress, and impaired energy metabolism (231). Stress can also modulate autophagy, which can have both beneficial and detrimental effects on senescence depending on the stress type and duration. Autophagy can enhance stress resistance and protein homeostasis by removing damaged mitochondria and lipids, but it can also promote cell death and inflammation by activating ferroptosis, a form of iron-dependent lipid peroxidation.

7.3. Environment pollution

Environmental pollution, especially air pollution, can expose the body to various harmful substances, such as particulate matter, ozone, nitrogen dioxide, and polycyclic aromatic hydrocarbons. These substances can induce oxidative stress, inflammation, and endothelial dysfunction, which can impair glucose and lipid metabolism (232–234). Oxidative stress can damage DNA, proteins, and lipids, leading to cellular senescence and apoptosis (234). Inflammation can alter the levels of cytokines, such as IL-6 and TNF-α, which can affect the secretion and action of insulin, a hormone that regulates glucose uptake (233).

7.4. Temperature

Glucose and lipid metabolism are regulated by various hormones, enzymes, and signaling pathways that respond to temperature changes, such as thermogenesis, cold exposure, or heat stress (223, 235, 236). Temperature can modulate glucose and lipid metabolism by altering the levels of adipokines, thyroid hormones, catecholamines, and other hormones that modulate energy balance, thermoregulation, and glucose uptake. Temperature can also affect lipid lipolysis and oxidation, which are the processes that break down and utilize lipids for energy. Lipolysis is the hydrolysis of triglycerides into fatty acids and glycerol, while oxidation is the conversion of fatty acids into acetyl-CoA, which is used by the Krebs cycle. Temperature can induce lipolysis and oxidation by activating HSL, ATGL, and CPT, which are enzymes that catalyze lipid breakdown and transport. Temperature can also affect the glycerolipid metabolism and signaling of cells, which are involved in glucose and lipid metabolism (223). Therefore, temperature can influence senescence through multiple aspects of glucose and lipid metabolism that affect cellular health and function (Figure 3).

8. Abnormal senescence

8.1. Premature ovarian insufficiency

Premature ovarian insufficiency (POI) is the condition of ovarian function decline leading to amenorrhea for over a year before 40 years of age (237), which may be associated with genetic, medical, immunological, environmental, and other factors. POI is associated with metabolic disturbances, including glucose and lipid metabolism, which may increase the risk of long-term complications, such as cardiovascular diseases and osteoporosis (238). Glucose metabolism is regulated by insulin. Estrogen, the main ovarian hormone, modulates insulin sensitivity and glucose homeostasis by influencing insulin secretion, signaling, and action in various tissues. Estrogen deficiency in POI may impair glucose metabolism and lead to insulin resistance, hyperglycemia, or diabetes mellitus (239). Estrogen also affects lipid metabolism by regulating the expression and activity of enzymes and receptors involved in lipid synthesis, transport, and degradation (240). Zhou et al. (238) found that patients with POI had higher levels of plasma glucose, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR, a marker of insulin resistance), plasma triglycerides, total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B compared with healthy controls. Moreover, they identified several metabolites related to glucose metabolism and lipid metabolism that were altered in patients with POI, including lactate, pyruvate, citrate, carnitine, acylcarnitine, glycerol, and glycerophospholipids. In conclusion, POI affects not only ovarian function but also metabolic health. POI patients may have impaired glucose and lipid metabolism due to estrogen deficiency, which may increase their risks of developing metabolic disorders or cardiovascular diseases. Therefore, it is important to monitor and manage the metabolic status of POI patients and provide appropriate hormonal replacement therapy or lifestyle interventions to prevent or reduce the adverse outcomes associated with POI.

8.2. Platelet senescence

Platelets are cell fragments without nuclei that participate in hemostasis and thrombosis. The lifespan of platelets is usually 7–10 days, and as age increases, the quantity and function of platelets decrease, resulting in increased bleeding propensity (241). The levels of lipid peroxides in platelets increase during senescence. Lipid peroxidation is important for cell function. It causes extensive damage to cell membranes and subcellular granules, leading to enzyme inactivation and destruction, and inhibition of metabolic pathways and cell division. The accumulation of lipid peroxidation products in aged platelets may cause cumulative damage to the membrane structure of platelets and their subcellular granules (such as alpha

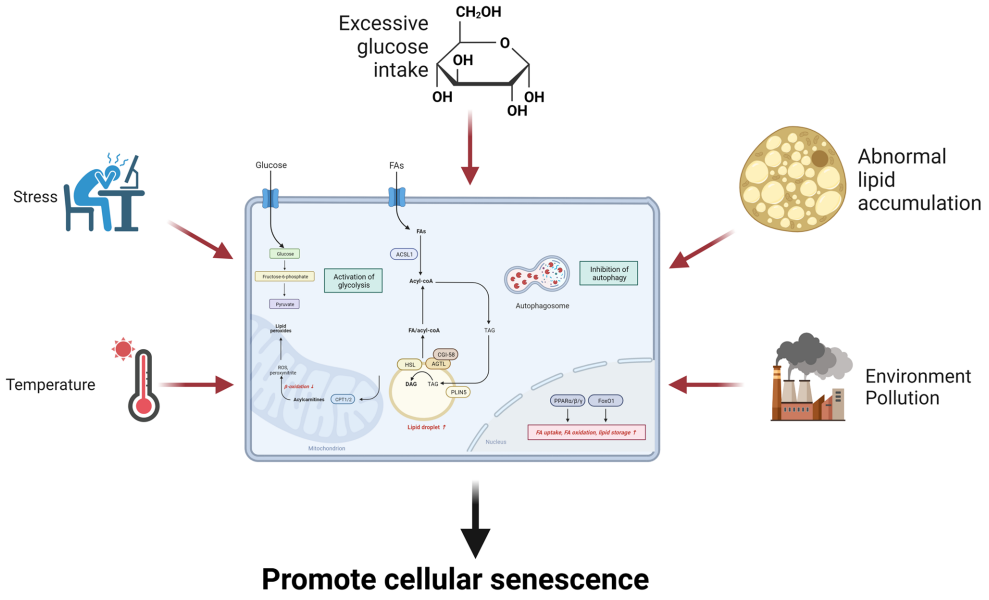

FIGURE 3
Environmental factors influence senescence through glucose and lipid metabolism. Environmental factors such as excessive glucose intake, lipid overaccumulation, stress, environmental pollution, and temperature can promote cellular senescence by increasing glycolysis and inhibiting fatty acid oxidation.

granules, mitochondria, and the endoplasmic reticulum). Lipid peroxidation may directly affect metabolic pathways by reducing the activity of lipid-dependent enzymes such as NADH- or succinate-cytochrome c reductase or indirectly by releasing lysosomal enzymes from alpha granules (242). Platelets have a rich glycocalyx on their surface, and platelet glycosylation plays an important role in physiological hemostasis mechanisms, regulating platelet-receptor protein interactions, and dynamically remodeling surface glycosylation through their own glucose metabolism system. Platelet glycosylation also participates in platelet senescence and clearance to regulate platelet count; meanwhile, platelet glycosylation abnormalities are closely related to primary immune thrombocytopenia, coronary heart disease, and related diseases, and are potential targets for anti-platelet therapy (243).

8.3. Down syndrome

Down syndrome (DS) is a genetic disorder caused by an extra copy of chromosome 21, which results in cognitive impairment, physical abnormalities, and increased risks of age-related comorbidities. Individuals with DS typically exhibit premature senescence phenomena, including skin senescence, graying hair, cataracts, osteoporosis, atherosclerosis, immune decline, and memory loss (244). Likewise, the glucose and lipid metabolism of patients with DS also changes, mainly manifesting as reduced serum cholesterol levels, increased triglyceride levels, increased insulin resistance, abnormal glucose tolerance, etc. These changes may be related to genetic abnormalities, oxidative stress, mitochondrial dysfunction, and other factors in these patients. Moreover, many changes occur in the brain lipids of patients with DS, including a significant reduction in esterified polyunsaturated fatty acids, especially fatty acids esterified into phosphatidylinositol and phosphatidylserine.

9. Anti-cancer treatment and senescence

Lipid and glucose metabolism are two essential metabolic pathways that provide energy and building blocks for cancer cells. Cancer cells reprogram their lipid and glucose metabolism to support their rapid growth, survival, invasion, and resistance to therapy.

Cancer cells increase their lipid biosynthesis by upregulating enzymes such as FAS, ACC, and SCD, which are often driven by oncogenic signals such as KRAS, MYC, and PI3K/AKT (245, 246). Cancer cells also enhance their lipid uptake by expressing more lipoprotein receptors, such as low-density lipoprotein receptor (LDLR) and scavenger receptor class B type I (SR-BI), and lipid transporters, such as fatty acid transport proteins and FABPs (245, 247). Moreover, cancer cells can mobilize lipids from adipose tissue or surrounding stromal cells through lipolysis or lipophagy (245, 248). Lipids can be stored in lipid droplets or oxidized through mitochondrial β-oxidation to generate ATP and acetyl-CoA, which can fuel the TCA cycle and oxidative phosphorylation. Lipids can also modulate various signaling pathways, such as RAS, PI3K/AKT, and nuclear receptors, to regulate cell proliferation, survival, migration, and inflammation (245).

In response to this feature, ongoing efforts aim to adapt lipid metabolism as an anti-cancer drug. Some approaches are used in preclinical models *in vitro* and *in vivo*, and some drugs have entered

clinical trials. Inhibiting lipid biosynthesis enzymes, such as FAS (TVB-2640) (249), ACC (Soraphen A) (250), and SCD (A939572) (251), can induce endoplasmic reticulum stress and activate the unfolded protein response, leading to cell cycle arrest, apoptosis, or senescence. By blocking lipid uptake receptors like LDLR (GW3965) (252) or SR-BI (ML279) (253), less cholesterol and other lipids are available for membrane production and signaling. This blocking can also impair mitochondrial beta-oxidation and increase the accumulation of toxic lipids, such as ceramide and ROS, by inhibiting the lipid oxidase CPT1 (etomoxir) (254). Inhibition of COX-2 or LPA receptors, lipid signaling molecules, modulates various pathways involved in cancer cell proliferation, survival, migration, angiogenesis, and inflammation (255, 256). Finally, cancer progression can also be inhibited by altering the biophysical properties (fluidity, curvature, and permeability) of the membrane bilayer through the localization and activity of membrane-associated proteins and receptors, as typified by statins that reduce cholesterol concentrations in the plasma membrane and affecting lipid raft clustering and displacement of receptors in non-raft domains (257).

The main pathway of glucose metabolism in cancer cells is aerobic glycolysis, also known as the Warburg effect (258). This is a phenomenon in which cancer cells preferentially convert glucose into lactate, even in the presence of oxygen and functional mitochondria. Aerobic glycolysis allows cancer cells to rapidly consume glucose and produce ATP while avoiding the production of ROS that can damage DNA and proteins. Moreover, aerobic glycolysis provides cancer cells with various metabolic intermediates that can be used for the synthesis of nucleotides, amino acids, and lipids (259). To support aerobic glycolysis, cancer cells increase their glucose uptake by overexpressing GLUTs, especially GLUT1 (260). Cancer cells also upregulate key glycolytic enzymes, such as HK2, phosphofructokinase 1, pyruvate kinase M2, and LDHA, which are often regulated by oncogenic signals, such as KRAS, MYC, and HIF1α (261). However, aerobic glycolysis is not the only mode of glucose metabolism in cancer cells. Some cancer cells can also use oxidative phosphorylation (OXPHOS) to generate ATP from glucose-derived pyruvate in the mitochondria. OXPHOS can be activated in cancer cells under conditions, such as hypoxia, nutrient deprivation, or drug resistance (262). OXPHOS is more efficient than glycolysis in terms of ATP production per glucose molecule but also generates more ROS. OXPHOS can also provide cancer cells with acetyl-CoA and NADH, which can modulate various signaling pathways, such as histone acetylation and sirtuin activity. To support OXPHOS, cancer cells can modulate their pyruvate metabolism by regulating the expression or activity of pyruvate dehydrogenase, pyruvate dehydrogenase kinase, or pyruvate carboxylase. Cancer cells can also use alternative substrates for OXPHOS, such as glutamine, fatty acids, or ketone bodies (261).

Cellular senescence can occur in both normal and cancer cells and has complex dependence effects on cancer development and treatment. On the one hand, cellular senescence is a cancer suppressor mechanism that prevents the proliferation of damaged or malignant cells. SRSPs secreted by senescent cells recruit and activate immune cells to remove senescent cells (263). Some immune cells, such as T helper 1 cells, can also trigger cancer cell senescence by secreting inflammatory cytokines. In addition, cellular senescence enhances the expression of cancer-associated antigens and immunogenic molecules on cancer cells, making them more susceptible to recognition and clearance by T cells. Thus, T cells are a key component of cancer immunotherapy (263). On the other hand, cellular senescence can also adversely affect T cell immunity and cancer therapy. First, senescent cells accumulate in cancers and normal tissues, releasing SRSPs with pro-tumorigenic effects such as promoting angiogenesis, invasion, metastasis, and drug resistance. Second, T cell senescence decreases their proliferation, cytokine production, and cytotoxicity and increases the expression of inhibitory receptors and pro-apoptotic molecules (264, 265).

Therefore, cellular senescence is a double-edged sword that can influence T cell immunity and cancer therapy in different ways. Understanding the molecular mechanisms and interactions between how sugar and lipid metabolism regulate T cell senescence could provide new insights and strategies for improving anti-cancer therapy. T cell metabolism is tightly linked to T cell activation, differentiation, and function. T cells undergo metabolic reprogramming upon antigen stimulation, switching from a quiescent state that relies on oxidative phosphorylation to a highly glycolytic state that supports rapid proliferation and effector functions (173). However, chronic or excessive stimulation can lead to T cell exhaustion or senescence, which are associated with metabolic dysregulation, such as impaired glucose uptake, reduced glycolytic capacity, and altered mitochondrial function (266). In addition to glucose metabolism, lipid metabolism plays a crucial role in regulating T cell immunity. Senescent T cells have reduced FAO capacity and increased dependence on FAS. Targeting FAS with pharmacological inhibitors or gene knockdown induces apoptosis in senescent non-functional T cells and improves anti-cancer immunity. Conversely, enhancing FAO with pharmacological activators or gene overexpression can prevent or reverse T cell senescence and exhaustion by restoring mitochondrial function and reducing oxidative stress (267).

10. Conclusion

The relationships between different types of lipid components, glucose metabolites, and senescence have been reported (268, 269). However, an in-depth study of the regulatory relationships of the key enzymes is necessary to screen anti-senescence drugs. New anti-cancer drugs may also be developed by targeting tumor cell senescence.

Various aspects of glucose and lipid metabolism are closely related to senescence. In lipid metabolism, decreased fatty acid catabolism is directly related to senescence onset, including mitochondrial β-oxidation (34, 36, 37, 57, 270), peroxisomal β-oxidation (54, 55), α-oxidation (82, 84), and ω-oxidation (85). The most prominent key enzymes include CPT1 and ACOX1. Drugs such as fenofibrate can exert anti-senescence effects by targeting PPARα, the gene upstream of *CPT1* and *ACOX1* (Figure 4). Meanwhile, increased fatty acid synthesis aggravates lipotoxicity, and both direct inhibition of ACC and indirect regulation via AMPK/SREBP1 can exert anti-senescence activity (89). In addition to fatty acid catabolism and synthesis, acetyl coenzyme A undergoes a variety of pathways to ketone bodies, phospholipids, sphingolipids, and sterols, which perform a wide

range of biological functions and exert pro- or anti-senescence effects (Figure 5). The effects of these lipids on senescence often depend on the amount, subtype, and state of the cellular microenvironment. For example, appropriate levels of ketone bodies are beneficial for the central nervous system's energy supply, maintenance of mitochondrial biogenesis, and attenuation of oxidative stress; however, excessive ketone bodies can lead to ketoacidosis and even death (118). Cer induces cellular senescence, whereas S1P, another sphingolipid component, delays senescence and extends lifespans (133, 137).

Multiple glucose metabolism pathways are involved in the regulation of intracellular senescence. Several rate-limiting enzymes in glycolysis, including HK2 and PK, are highly expressed in senescent cells (150, 156). Although the pharmacological activation of Nrf2 increases HK2 expression (18), other mechanisms require further investigation. Several key enzymes of the PPP, a branch of the glycolytic pathway, are also involved in the regulation of intracellular senescence. The key enzymes promote cellular senescence by upregulating P21, P16, and telomerase activity (163). Notably, the dietary TCA-cycling metabolites citrate and αKG delay cellular senescence (23–26). Therefore, supplementation of these metabolites may provide an effective intervention for the treatment of senescence-related dysfunction (Figure 6).

Environmental factors can affect senescence through glucose and lipid metabolism, which are essential for energy production and cellular function. Alterations in the external environment such as nutrition, stress, environment, pollution, and temperature accelerate cellular senescence by regulating glucose and lipid metabolism through a variety of hormones, enzymes, and signaling pathways. Thus, targeting aberrant metabolism may delay normal cellular senescence.

In summary, fatty acid and glucose metabolism are essential in the maintenance of normal cellular function, both of which are disturbed by senescence. Conversely, disturbances in fatty acid and glucose metabolism can further lead to senescence. Two pathway-related enzymes and metabolites are involved in the regulation of cellular senescence. While many advances have been made in recent years, several important issues must still be addressed, including: (a) What are the initiating factors of senescence and metabolic disorders? (b) While reports suggest a

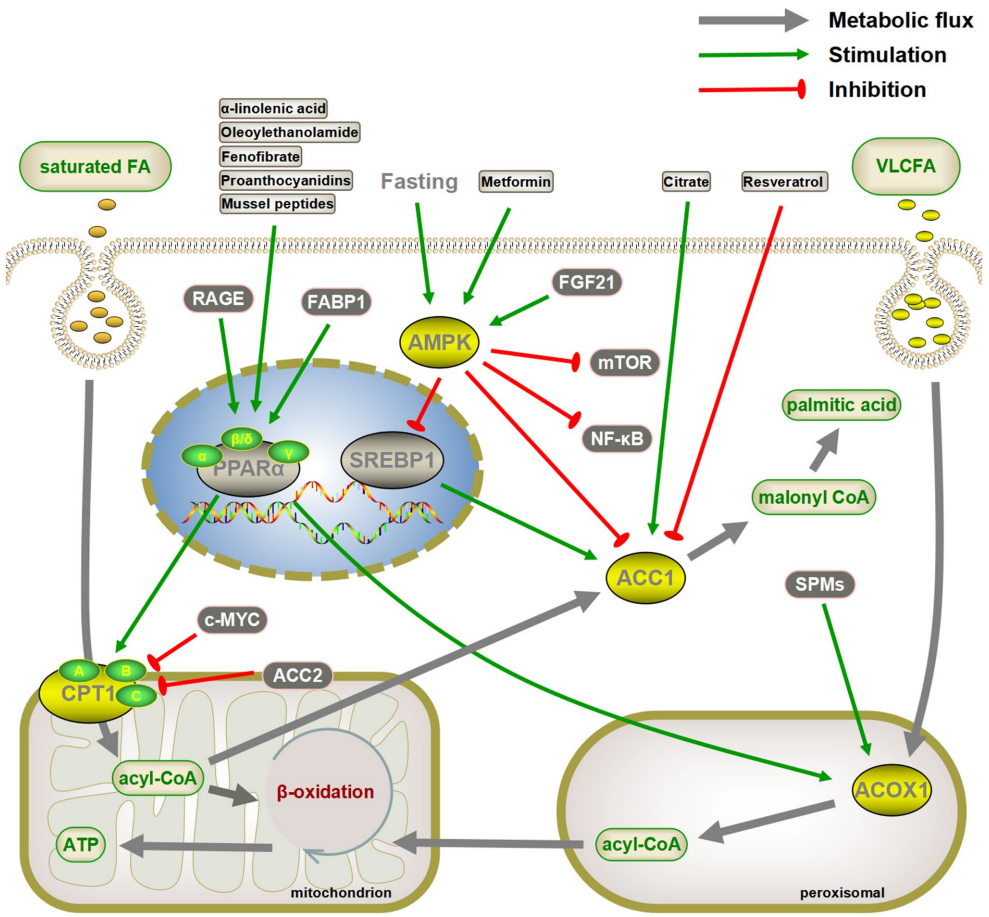

FIGURE 4
Targeting critical enzymes of fatty acid synthesis and catabolism to delay senescence. Activation of CPT1 and ACOX1 directly or indirectly through the peroxisome proliferator-activated receptor α (PPARα) pathway promotes fatty acid oxidation, both of which may have a senescence-delaying effect. Similarly, inhibiting fatty acid synthesis by the AMPK/SREBP1/ACC pathway is also beneficial in slowing down senescence. AMPK also inhibits senescence by inhibiting the mTOR and NF-κB pathways. The gray arrows represent normal metabolic pathways. The green pointed and blunt red arrows represent activating and inhibiting effects, respectively.

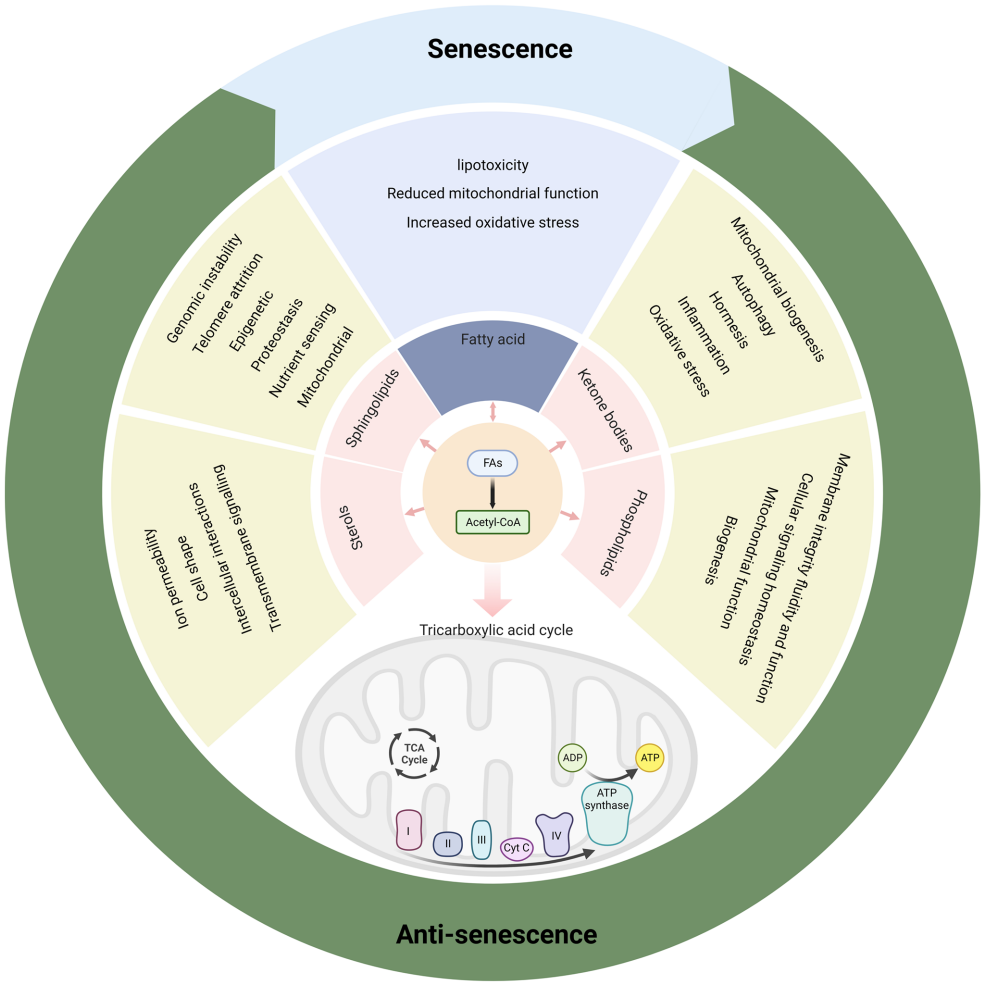

FIGURE 5
Various metabolic products of fatty acids have rich biological functions and affect senescence.

correlation between metabolic disorders and senescence, the true causal relationship remains undetermined. (c) Anti-senescence therapies proven to work in humans are scarce. Understanding the role of enzymes and metabolites in fatty acid and glucose metabolism may provide answers for a more comprehensive understanding of senescence.

Author contributions

BL and QM investigated and wrote the first draft of the manuscript. XG and HS wrote sections of the manuscript. ZX and YW contributed to conception the study and acquire funds. HZ contributed to design of the study and acquire funds. BL, QM, XG, HS, ZX, YW, and HZ were involved in drafting, revising the manuscript, and agree to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

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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.

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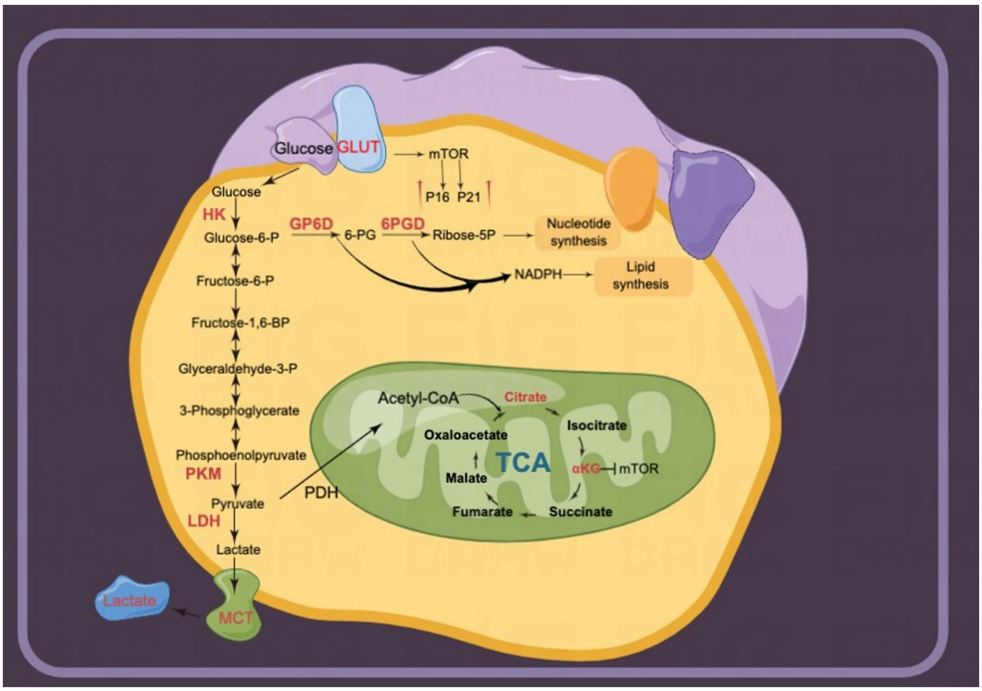

FIGURE 6
Glucose metabolism is upregulated in senescent cells. Multiple enzymes of glycolysis are upregulated. For instance, lactate release mediated by monocarboxylate transporters (MCTs) is involved in senescence-related secretory phenotypes (SRSPs). Several metabolites in the tricarboxylic acid (TCA) cycle, including α-ketoglutarate (αKG) and citrate, delay senescence.

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Combined early palliative care for non-small-cell lung cancer patients: a randomized controlled trial in Chongqing, China

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Purpose: More effective approaches are needed to improve the prognosis of non-small-cell lung cancer (NSCLC) patients. Thus, we used the E-warm model to assess how early integration of interdisciplinary palliative care was related to the quality of life (QoL), psychological functioning, pain management, and nutrition factors of NSCLC patients.

Methods: This randomized controlled trial enrolled 280 newly diagnosed NSCLC patients, which were randomly divided (1:1) into combined early palliative care (CEPC) and standard oncological care (SC) groups. At baseline and after 24 weeks, the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale, Hospital Anxiety and Depression Scale (HADS), and the Patient Health Questionnaire-9 (PHQ-9) were used to assess QoL and psychological function, respectively. The Numerical Rating Scale (NRS) and Patient-Generated Subjective Global Assessment (PG-SGA) were used to assess cancer patients' pain and nutrition levels. The primary outcome was overall survival (OS). Secondary outcomes comprised changes in the QoL, psychological functioning, pain, and nutrition state. The intention-to-treat method was applied for analysis. This study was registered at www.chictr.org.cn (ChiCTR2200062617).

Results: Of the 140 patients enrolled in the CEPC and SC groups, 102 and 82 completed the research. The CEPC group presented higher QoL than the SC group ($p < 0.05$). Additionally, fewer patients presented depressive symptoms in the CEPC group than in the SC group ($p < 0.05$), as well as better nutritional status ($p = 0.007$) and pain management ($p = 0.003$). Compared to the SC group, CEPC patients had significantly longer OS (20.4 *vs.* 24.6 months, $p = 0.042$; HR: 0.19; 95% CI: 0.04-0.85, $p = 0.029$).

Conclusion: With combined early palliative care, NSCLC patients lived longer, had better QoL, were psychologically stable, were in less pain, and were more nutritionally satisfied.

KEYWORDS

combined early palliative care, non-small-cell lung cancer (NLSCLC), overall survival (OS), pain management (MeSH), psychological status, nutritional level

Introduction

About 85% of lung cancers are non-small-cell lung cancers (NSCLC), which leads to a poor quality of life (QoL) and high symptom burdens (1–4). It is common for NSCLC patients to be diagnosed at an advanced stage and, therefore, lose the opportunity to undergo radical resection (5–7). Moreover, NSCLC patients are often malnourished, in pain, and psychologically distressed, contributing to poor QoL and short survival (8, 9). Thus, NSCLC patients need high-quality, low-medical-burden interventions to improve their QoL, nutrition, psychological well-being, and survival.

Palliative care focused on managing symptoms and providing psychosocial support can improve a patient's quality of life and care (10, 11). For advanced cancer patients, palliative care has accumulated substantial evidence supporting its integration into oncology practice (12–15). There has been a rapid expansion in palliative care services worldwide, but China is experiencing a fundamentally different situation. Several factors contribute to the problem, including limited healthcare resources, policies, low awareness, and local cultural norms (16–19). Palliative care in China is still in its infancy (20, 21). In the greater China region, models of palliative care that delivered specialist palliative care services in various settings were reported (21), including hospitals (22), inpatient hospice units (23, 24), nursing home (25), and home-based care (26–28). Furthermore, few studies have focused on the collaborative experience of various specialists in early palliative care models, as well as the impact of China's unique population characteristics and different regional cultural customs on palliative care. Therefore, in our endeavor to promote and develop a palliative care model tailored to the Chinese context, it is crucial to address the following aspects. In order to maintain the integrity and organization of the palliative care system, it is imperative to establish a comprehensive framework consisting of co-built wards, palliative communities, palliative homes, and hospices (29). Special emphasis should be placed on providing comprehensive support to patients and their families, ensuring their comfort, and offering ongoing assistance to survivors in their mourning process (29). Additionally, it is crucial to consider the influence of China's distinct population characteristics and cultural customs across various regions on the implementation of palliative care. Consequently, developing an appropriate palliative care pattern for Chinese circumstances is urgently needed.

E-warm pattern interventions are interdisciplinary palliative care technologies considering Chinese culture and circumstances (30). The E-warm model is defined as Early, Whole, Assessment, Re-evaluation, and MDT Management by acknowledging and incorporating local culture and traditions into practices (30). By implementing the E-warm model, our primary objective is to establish a comprehensive palliative care system and procedure that embodies Chinese attributes, encompassing diverse professional teams and intervention cycles, in order to deliver comprehensive, holistic, family-centered, and continuous care to patients and their families. Herein, we investigated the effectiveness of the combined early palliative care for NSCLC patients on the QoL, psychological well-being, pain, and nutrition state.

Abbreviations: CEPC, combined early palliative care; ECOG, Eastern Cooperative Oncology Group; FACT-L, Functional Assessment of Cancer Therapy-Lung; HADS, Hospital Anxiety and Depression Scale; LCS, lung-cancer subscale; MDT, Multi disciplinary team; NRS, Numerical Rating Scale; NSCLC, non-small-cell lung cancer; PG-SGA, Patient-Generated Subjective Global Assessment; PHQ-9, Patient Health Questionnaire-9; QoL, quality of life; OS, overall survival; SC, standard oncological care; TOI, Trial Outcome Index.

Methods

Study design and patients

An open, randomized, controlled trial was conducted from October 7, 2019, to October 25, 2021, in newly diagnosed NSCLC patients at the Chongqing University Cancer Hospital in Chongqing, China. The inclusion criteria considered inpatients and outpatient, and patients could be followed up in an outpatient or inpatient setting after being recruited. The study was open to patients who had Stage IIIB to IV advanced NSCLC within eight weeks of enrollment, treatment naïve or have not received disease-directed treatments, were 18 years or older, had a baseline Eastern Cooperative Oncology Group (ECOG) from 0 to 2, had expected survival time at least 24 weeks and had sufficient reading and cognitive skills. Patients who have already received palliative care services were not eligible.

The Chongqing University University Cancer Hospital's Ethics Committee approved this study (CZLS2019177), registered at http://www.chictr.org.cn/ (ChiCTR2200062617). The study design was not revised after it began.

Procedures

A flowchart of the combined early palliative care (CEPC) team process is shown in Supplementary Figure S1. The medical oncologists made medical decisions following the NCCN Guidelines and patient preferences (31). The E-warm model, which encompasses the principles of Early, Whole, Assessment, Re-evaluation, and MDT Management, is proposed (30). The term "Early" denotes the importance of early intervention, particularly in the context of advanced tumor patients, where early palliative care should be integrated into their anti-cancer treatment. The concept of "Whole" emphasizes the need for palliative care to be integrated throughout the entire cancer treatment process. "Evaluation" highlights the significance of dynamic assessment, allowing for continuous improvement of intervention strategies based on clinical feedback. Lastly, "MDT Management" underscores the necessity of Multi-Disciplinary Treatment being consistently applied throughout cancer treatment. In order to maintain the integrity and organization of the palliative care system, it is imperative to establish a comprehensive framework consisting of co-built wards, palliative communities, palliative homes, and hospices. Special emphasis should be placed on providing comprehensive support to patients and their families, ensuring their comfort, and offering ongoing assistance to survivors in their mourning process. Additionally, it is crucial to consider the influence of China's distinct population characteristics and cultural customs across various regions on the implementation of palliative care. Currently, the E-warm model represents an initial palliative care approach that aligns with the aforementioned Chinese cultural customs and characteristics. The E-warm model focuses on establishing a palliative care system and procedure that incorporates Chinese characteristics, encompassing diverse professional teams and intervention cycles, in order to provide patients and their families with comprehensive, holistic, family-centered, and continuous care. For further details, please refer to the Supplementary Appendix.

A 1:1 randomization without stratification was used to assign eligible patients to either of the two groups within eight weeks of diagnosis. Professionals working for Palliative Care Services provided support and care for inpatients and outpatients. For 24 weeks, beginning within the first week of enrollment and continuing every month, patients met with a medical oncologist, an oncology nurse specialist, a dietitian, and a psychologist in the CEPC group. It was up to the patient, oncologist, or CEPC team to schedule additional palliative care visits. Randomly assigned SC patients did not have nutrition, pain, or psychology assessments except because of patient or oncologist requests. A single patient from the SC group did not cross over to the CEPC group if they received nutritional, psychological, or cancer pain consultations. Oncologic care was routinely provided to all study participants.

The early palliative care in the CEPC group focused on four basic elements: QoL, nutrition level, pain management, and psychological support (1). The QoL was evaluated by oncologists using the FACT-L scale, including the lung-cancer subscale (LCS) and Trial Outcome Index (TOI), which appraise the multidimensionality of the health-related QoL (function and symptom) (30) (2). Besides PG-SGA, dietitians assessed each patient's nutritional intake, physical exams, and hematology tests. A nutritional intervention was initiated following the assessment results (3). Oncologists used an NRS to assess pain, and pain treatment was provided to the patient when necessary (4). The HADS, which evaluates anxiety (HADS-A) and depression (HADS-D) symptoms, and the Patient Health Questionnaire-9 (PHQ-9) were used by psychologists for psychological evaluations (8, 32). Psychologists provided psychotherapy to each patient and administered psychotropic medications when necessary.

The primary outcome was overall survival (OS). Secondary outcomes included changes in the QoL, nutrition state, pain, and psychological functioning. After enrollment, both groups were assessed every four weeks for QoL, nutritional level, pain status, and psychological factors. During CEPC weekly meetings, members discussed trial-related issues and potential solutions to improve the process to ensure all patients received coordinated interventions.

Statistical analysis

SPSS 22.0 was used to analyze the data. Descriptive statistics were used to estimate frequency distributions, means, and standard deviations. For categorical variables, Fisher's exact and χ^2 tests were used to assess differences between groups for baseline characteristics and clinical outcomes. Independent-sample Student's t-tests were used for continuous variables. Kaplan-Meier plots and log-rank tests were performed to determine whether combining early palliative care with other forms of treatment led to better OS. Data were analyzed based on the intention-to-treat method. Patients were randomly assigned, including those who died or were not followed up. An intention-to-treat analysis was performed using the last observation as the outcome. A per-protocol analysis of participants who fulfilled the protocol's eligibility requirements was performed (see Supplementary Table S1). Statistical significance was defined as $p < 0.05$.

Results

A total of 528 NSCLC patients were assessed for participation. Finally, 280 were enrolled and randomly (1:1) assigned to CEPC or standard oncologic care (Figure 1). Ultimately, all 280 patients were included in the intention-to-treat analysis, and 184 patients were analyzed per protocol, 102 in the CEPC group and 82 in the SC group. The compliance at 24 weeks was 72.86 and 58.57% in the CEPC and SC groups. Both groups had similar demographics and baseline clinical characteristics (Table 1). Between the SC and CEPC groups, 24.29% (34/140) *vs*. 60.71% (85/140) received nutritional consultations, 20.00% (28/140) *vs*. 22.14% (31/140) received psychological consultations, and 27.14% (38/140) *vs*. 40.00% (56/140) received pain medications over the 24 weeks. Additionally, 41.43% (58/140) of patients in the SC group and 22.86% (32/140) in the CEPC group were no longer being followed up or died at the cutoff date (April 25, 2022).

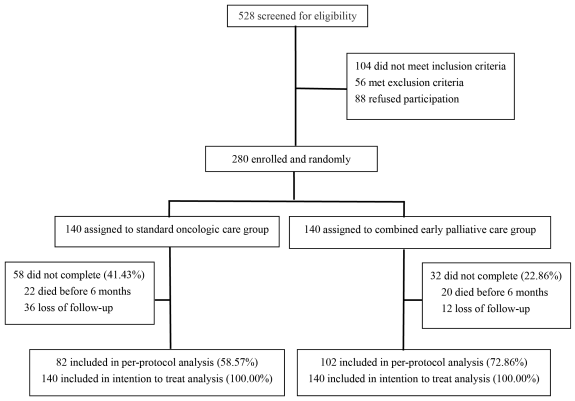

FIGURE 1
Trial profile.

Baseline characteristics

The baseline characteristics were similar for both groups (Table 1). Patients were matched on age, sex, height, weight, BMI, ECOG, smoking state, histology, and neoplasm staging. The groups did not differ regarding the baseline nutritional assessment, pain evaluation, emotional symptoms, or QoL (Table 1).

Key characteristics at baseline and 24 weeks

In the SC group, the baseline nutrition assessment and pain level did not significantly differ at baseline and after 24 weeks (Table 2). In contrast, the level of PG-SGA, NRS, HADS, PHQ-9, and QoL of the CEPC group markedly improved after 24 weeks ($p < 0.05$, Table 2). Subsequent analysis of participants who completed the 24-week intervention revealed no statistical differences in factors such as age, gender, and cancer stage between the SC group and CEPC group (see Supplementary Table S1).

Nutrition, pain, mood symptoms, health-related QoL, and survival analysis

CEPC and SC patients were assessed by PG-SGA at baseline, and after 24 weeks, all participants were re-assessed. Additionally, the CEPC group (14.29 *vs.* 22.86%, severe malnutrition; 47.86 *vs.* 55.71%, moderate or mild malnutrition; and 37.86 *vs.* 22.86%, no malnutrition) had a better nutrition level than the SC group ($p = 0.007$) (Table 3). Moreover, the CEPC group had a much lower NRS score than the SC group after 24 weeks ($p = 0.003$) (Table 3).

Furthermore, the CEPC group had significantly lower levels of anxiety and depression at 24 weeks when assessed by both HADS and PHQ-9 ($p < 0.05$) than SC group patients. Nonetheless, the proportion of patients prescribed antidepressant drugs was similar (about 20%, $p = 1.000$). In the PHQ-9 depression severity test, the groups significantly differed, considering depression severity scores ($p = 0.020$). The per-protocol analyses showed similar results for HADS mood symptoms (Supplementary Table S1).

In the present study, a total of 15 patients (10.71%) in the SC group received palliative care consultations upon request, either by

TABLE 1 Patients' Demographic and Baseline Characteristics.

Characteristic	Standard Care (n=140)	Combined Early Palliative Care (n=140)	$t/\chi^2/Z$	*P*
Age, years	62.9±10.36	62.02±10.36	0.71	0.478
Sex—no.(%)			0.16	0.690
Male	99 (70.71 %)	102 (72.86%)		
Female	41 (29.29%)	38 (27.14%)		
Height,cm	162.3±7.27	161.94±7.61	0.40	0.693
Weight, kg	59.26±9.52	59.09±10.21	0.14	0.887
BMI, kg/m 2	22.48±2.98	22.5±3.35	-0.06	0.954
Waist, cm	83.23±8.01	82.77±8.66	0.41	0.684
ECOG—no.(%)			1.77	0.412

(Continued)

TABLE 1 Continued

Characteristic	Standard Care (n=140)	Combined Early Palliative Care (n=140)	$t/\chi^2/Z$	*P*
0	20 (14.29%)	16 (11.43%)		
1	71 (50.71%)	82 (58.57%)		
2	49 (35.00%)	42 (30.00%)		
Smoking status—no.(%)			0.02	0.900
Former	93 (66.4%)	92 (65.71%)		
Never	47 (33.57%)	48 (34.29%)		
Histology—no.(%)			0.81	0.668
Adenocarcinoma	91 (65.00%)	97 (69.29%)		
Squamous cell	47 (33.57%)	42 (30.00%)		
Other	2 (1.43%)	1 (0.71%)		
AJCC cancer stage—no.(%)			0.52	0.771
IIIB	15 (10.71%)	18 (12.86%)		
IIIC	14 (10.00%)	16 (11.43%)		
IV	111 (79.29%)	106 (75.71%)		
PG-SGA score—no.(%)			0.02	0.990
0–1	19 (13.57%)	19 (13.57%)		
2–8	87 (62.14%)	86 (61.43%)		
≥9	34 (24.29%)	35 (25.00%)		
NRS score—no.(%)			0.27	0.874
No pain (0)	67 (47.86%)	65 (46.33%)		
Mild pain (1-3)	55 (39.29%)	54 (38.57%)		
Moderate pain (4–6)	18 (12.86%)	21 (15.00%)		
Severe pain (7-10)	0	0		
Assessment of mood symptoms				
HADS				
Anxiety subscale (HADS-A)	3.54±2.73	3.91±3.09	-0.32	0.746
Depression subscale (HADS-D)	4.41±3.51	4.16±3.28	-1.272	0.203
PHQ-9 Depression severity			2.18	0.535
No (0-4)	93 (66.43%)	89 (63.57%)		
Mild (5-9)	38 (27.14%)	46 (32.86%)		
Moderate(10-14)	8 (5.71%)	4 (2.86%)		
Moderately severe(15-19)	1(0.71%)	1(0.71%)		
Scores on quality-of-life measures				
FACT-L scale	106.14±12.66	105.94±12.16	0.14	0.892
Lung-cancer subscale	27.84±4.14	28.08±3.67	-0.51	0.612
Trial Outcome Index	67.18±9.53	67.51±8.54	-0.30	0.762

Data are means ±SD or n (%). Percentages might not total 100% because of rounding. Abbreviations: ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; PG-SGA, Patient-Generated Subjective Global Assessment; NRS, Numerical Rating Scale; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire-9; FACT-L, Functional Assessment of Cancer Therapy-Lung.

TABLE 2 Patients' key characteristics at baseline and 24 weeks by intention-to-treat analysis.

Characteristic	Standard Care		*P*	Combined Early Palliative Care		*P*
	Baseline (n=140)	6 months (n=140)		Baseline(n=140)	6 months (n=140)	
PG-SGA score—no.(%)			0.221			<0.001
0–1	19 (13.57%)	30 (21.43%)		19 (13.57%)	53 (37.86%)	
2–8	87 (62.14%)	78 (55.71%)		86 (61.43%)	67 (47.86%)	
≥9	34 (24.29%)	32 (22.86%)		35 (25.00%)	20 (14.29%)	
NRS score—no.(%)			0.396			<0.001
No pain (0)	67 (47.86%)	76 (54.29%)		65 (46.33%)	103 (73.57%)	
Mild pain (1-3)	55 (39.29%)	52 (37.14%)		54 (38.57%)	29 (20.71%)	
Moderate pain (4–6)	18 (12.86%)	12 (8.57%)		21 (15.00%)	8 (5.71%)	
Severe pain (7-10)	0	0		0	0	
Assessment of mood symptoms						
HADS						
Anxiety subscale (HADS-A)	3.54 ± 2.73	2.66 ± 2.86	0.009	3.91 ± 3.09	1.45 ± 2.86	<0.001
Depression subscale (HADS-D)	4.41 ± 3.51	3.54 ± 4.61	0.074	4.16 ± 3.28	1.5 ± 2.05	<0.001
PHQ-9 major depressive syndrome			0.011			<0.001
Depression severity	93 (66.43%)	111 (79.29%)		89 (63.57%)	127 (90.71%)	
No (0-4)	38 (27.14%)	20 (14.29%)		46 (32.86%)	12 (8.57%)	
Mild (5-9)	8 (5.71%)	4 (2.86%)		4 (2.86%)	1 (0.71%)	
Severe pain (7-10)	1(0.71%)	5 (3.57%)		1(0.71%)	0	
Scores on quality-of-life measures						
FACT-L scale	106.14 ± 12.66	111.66 ± 14.9	0.001	105.94 ± 12.16	117.81 ± 11.15	<0.001
Lung-cancer subscale	27.84 ± 4.14	29.64 ± 3.94	<0.001	28.08 ± 3.67	30.9 ± 2.96	<0.001
Trial Outcome Index	67.18 ± 9.53	70.66 ± 11.35	0.006	67.51 ± 8.54	75.62 ± 8.62	<0.001

Data are means ± standard deviations (SD) or n (%). Percentages might not total 100% because of rounding. This test was conducted with by intention-to-treat analysis.
Data are means ± SD or n (%). Percentages might not total 100% because of rounding. PG-SGA, Patient-Generated Subjective Global Assessment; NRS, Numerical Rating Scale; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire-9; FACT-L, Functional Assessment of Cancer Therapy-Lung.

the patient or the oncologist, within the initial 24-week period. The primary purpose of these consultations was to address symptom management. Among these patients, 11 received a single visit, while 4 received two visits.

The combined early palliative care treatment significantly affected the QoL, improving not only the FACT-L scale (117.81 ± 11.15 *vs.* 111.66 ± 14.90; $p < 0.001$) but also the LCS (30.90 ± 2.96 *vs.* 29.64 ± 3.94; $p = 0.003$) and TOI (75.62 ± 8.62 *vs.* 70.66 ± 11.35; $p < 0.001$) than the SC group after 24 weeks (Table 3). From baseline to the 24th week, CEPC patients increased their mean FACT-L score by 11.77 points and SC patients by only 5.51 points ($p < 0.001$) (Figure 2). CEPC patients had significantly better survival than SC patients (median OS, 24.6 *vs.* 20.4 months, $p = 0.042$; HR, 0.19; 95% CI, 0.04 to 0.85, $p = 0.029$, Figure 3).

Discussion

This study examined the effects of combined early palliative care (according to the E-warm concept) for NSCLC patients. When palliative care was integrated early into standard oncology care, NSCLC patients presented a clinically meaningful improvement in QoL, nutritional state, pain management, psychological level, and survival benefit. NSCLC patients have shorter survival when depressed, a poor nutritional level, and lower QoL (31). Further, when Early Palliative Care is integrated with Standard Oncologic Care, anticancer therapy can be optimally and appropriately administered, especially in the final stages of the illness (8, 32, 33). By receiving early referrals to palliative care, patients might manage their symptoms better, improving their condition and

TABLE 3 Intention to treat analyses of patients' characteristics at 24 weeks.

Characteristic	Standard Care (n=140)	Combined Early Palliative Care (n=140)	$t/\chi^2/Z$	*P*值
Height,cm	161.99 ± 7.31	161.89 ± 7.91	0.11	0.915
Weight, kg	60.02 ± 9.27	60.38 ± 10.79	-0.27	0.788
BMI, kg/m 2	22.83 ± 2.95	22.96 ± 3.55	-0.31	0.759
Waist, cm	82.01 ± 8.78	84.08 ± 7.23	-2.82	0.090
PG-SGA score—no.(%)			9.98	**0.007**
No malnutrition (0–1)	30 (21.43%)	53 (37.86%)		
Mild or moderate malnutrition (2–8)	78 (55.71%)	67 (47.86%)		
Severe malnutrition (≥9)	32 (22.86%)	20 (14.29%)		
NRS score—no.(%)			11.40	**0.003**
No pain (0)	76 (54.29%)	103 (73.57%)		
Mild pain (1-3)	52 (37.14%)	29 (20.71%)		
Moderate pain (4–6)	12 (8.57%)	8 (5.71%)		
Severe pain (7-10)	0	0		
Assessment of mood symptoms				
HADS				
Anxiety subscale (HADS-A)	2.66 ± 2.86	1.45 ± 2.86	4.13	< **0.001**
Depression subscale (HADS-D)	3.54 ± 4.61	1.5 ± 2.05	4.77	< **0.001**
PHQ-9 Depression severity			9.88	**0.020**
No (0-4)	111 (79.29%)	127 (90.71%)		
Mild (5-9)	20 (14.29%)	12 (8.57%)		
Moderate(10-14)	4 (2.86%)	1 (0.71%)		
Moderately severe(15-19)	5 (3.57%)	0		
Scores on quality-of-life measures				
FACT-L scale	111.66 ± 14.90	117.81 ± 11.15	-3.907	< **0.001**
Lung-cancer subscale	29.64 ± 3.94	30.90 ± 2.96	-3.017	**0.003**
Trial Outcome Index	70.66 ± 11.35	75.62 ± 8.62	-4.12	< **0.001**

Data are means ± standard deviations (SD) or n (%). Percentages might not total 100% because of rounding. This test was conducted with by intention-to-treat analysis.
Data are means ± SD or n (%). Percentages might not total 100% because of rounding. PG-SGA, Patient-Generated Subjective Global Assessment; NRS, Numerical Rating Scale; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire-9; FACT-L, Functional Assessment of Cancer Therapy-Lung.

having a longer life expectancy (9, 34). Nevertheless, future studies are required to confirm these hypotheses.

Considering the progressive nature of NSCLC, improving patients' quality of life, nutrition level, pain management, and psychological status is a major challenge (7). Our previous study has shown that early palliative care improved patients' QoL in the FACT-L (30), consistent with this study and previous reports on metastatic NSCL patients in the New England Journal of Medicine (10). Palliative care integration in oncology care has been shown to improve quality of life in three previous trials at 12 weeks (8, 35, 36), and in three other trials at later time points (37–39). At 24 weeks, the intervention proposed in our trial significantly improved quality of life.

As a result of our findings, early and planned palliative care consultations are critical for patients to discuss all aspects of palliative care at their own pace. These approach contrasts with the usual care group, in which palliative care consultations were only arranged on demand and often. In the era of rapid development of targeted therapy and immunotherapy, comparing patients assigned to CEPC and those assigned to SC is of great interest. The CEPC group had better survival benefits and QoL. Besides, the depression scores significantly differed between the two groups. Thus, this did not result from a difference in antidepressant use between the groups.

Previous studies have demonstrated the benefits of supportive care in terms of QoL, symptom control, and mood management

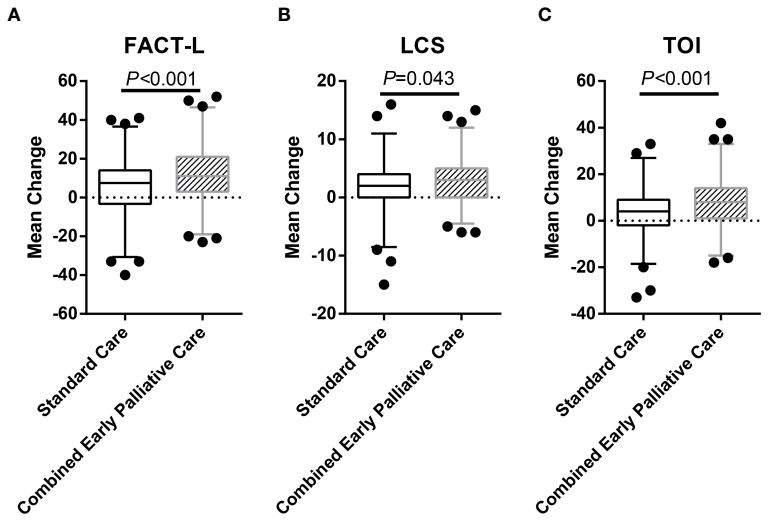

FIGURE 2
Mean Change in Quality-of-Life Scores from Baseline to 24 Weeks in the Two Study Groups. The study group was the independent variable, and the two-sided independent-sample Student's t-tests showed a trend toward a significant between-group difference in the mean (± SD) change in scores from baseline to 24 weeks on the FACT-L scale (5.51 ± 14.04 in the SC group *vs*. 11.77 ± 14.89 in the CEPC group; differences between groups, 6.26; 95% confidence interval (CI), 2.83 to 9.68; $p < 0.001$) **(A)**. A significant between-group difference was detected in the mean change in scores on the LCS (1.80 ± 4.33 and 2.80 ± 3.81 in the two groups, respectively; the difference between groups, 0.99; 95% CI, 0.03 to 1.96; $p = 0.043$) **(B)**, as well as a significant between-group difference in the mean change in TOI scores(3.45 ± 10.41 *vs*. 8.03 ± 10.83; the difference between groups, 4.58; 95% CI, 2.07 to 7.09; $p < 0.001$) **(C)**. Data from 140 patients in the SC group and 140 patients in the CEPC group by intention-to-treat analysis. I bars indicate 95% confidence intervals.

(30, 40, 41). Similar to previous studies (8, 38), we observed an improvement in overall survival. Despite the lack of a clear mechanism behind a better overall survival in this setting, more aggressive early palliative care treatment regimens have been suggested as an explanation (8, 38). There is evidence that the improved nutritional and psychological status of the CEPC group may contribute to the prolonged OS. Anxiety and depression have been linked to a significant increase in cancer-specific mortality (42). Furthermore, individualized nutritional interventions have been shown to reduce 30-day mortality (43). Impacts of nutrition

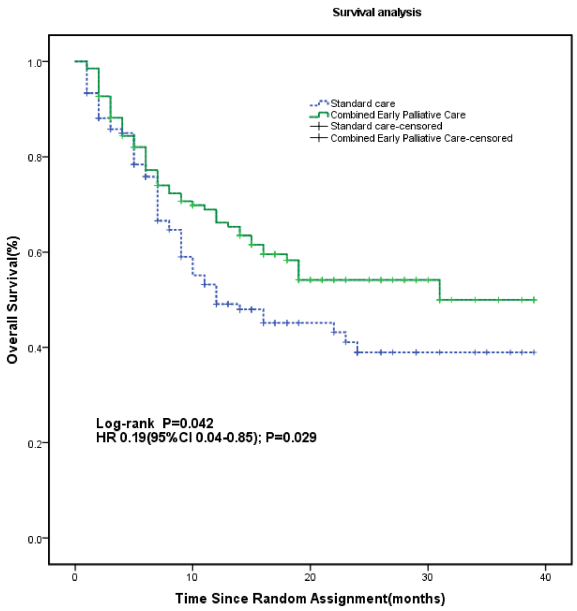

FIGURE 3
Kaplan-Meier Survival Estimates According to Study Group. The survival rate was calculated from enrollment through the time of death if it occurred during the study period or until January 1, 2023, when the data were censored. The median OS was 24.6 months (95% CI, 21.8 to 27.5) for patients assigned to the CEPC group (n = 140 patients) compared to 20.4 months (95% CI, 17.4 to 23.4) for patients in the SC group (n = 140 patients) (HR, 0.19; 95% CI, 0.04 to 0.85; $p = 0.029$). HR, hazard ratio.

and psychological status may play a significant role in immune response (41, 44–46), which improves long-term prognosis. There have, however, been few studies specifically investigating the effectiveness of multiple support systems in cancer patients.

In a recent study, nutrition and psychology interdisciplinary palliative care enhanced the OS in advanced esophagogastric cancer patients by alleviating symptoms (32). Our findings are similar to those from other researchers in which CEPC improved the QoL of advanced cancer patients (35, 47, 48). Our intervention might have had an effect on aggressive treatment choices of patients because the role of the effect of combined early palliative care group in our trial was large.

This randomized controlled trial has several advantages. First, palliative care interventions were provided for 24 weeks, and many studies have shorter intervention times (8, 35, 47, 49). Furthermore, no model of palliative care is suitable for Chinese conditions. Moreover, our study provided a Chinese-oriented model for palliative care.

However, our current study also has some limitations. First, it was conducted at a single institution, with only Chinese patients. Thus, its generalizability to people from different races and settings might be limited. An additional optimization is needed to customize this palliative care model to meet the needs of different cultures and resources. Second, a potential bias was introduced because participants and investigators were not masked in the group assignment. Finally, the intention-to-treat analysis is conservative if all missing data are carried forward from the last observation. This would suggest that the treatment effect of combined early palliative care might be greater than what we reported here.

In summary, we examined combined early palliative care (based on the E-warm concept) among NSCLC patients. Early palliative care may benefit survival rates, quality of life, psychological well-being, pain management, and nutrition. It would be beneficial to optimize and standardize further.

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.

Ethics statement

The Ethics Committee of the Chongqing University Cancer Hospital approved this study (CZLS201917). Informed consent was obtained from all patients before they participated in the study.

Author contributions

MC and HuY initiated the project, designed and performed experiments, analysed the data and drafted the manuscript. LY, HoY, HC, LL, LM, SL, LT, SW enrolled and followed up the patients. HuY and MC designed the project, obtained funding, helped with the writing of the paper, and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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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/fonc.2023.1184961/full#supplementary-material

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Inflammatory and nutritional markers predict the risk of post-operative delirium in elderly patients following total hip arthroplasty

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Objectives: This study intended to explore whether albumin-associated inflammatory and nutritional markers could predict post-operative delirium (POD) in older patients after total hip arthroplasty (THA). In addition, we established a nomogram model for POD prediction.

Methods: Totally, 254 elderly cases who received THA were included. Clinical and laboratory data of these patients were retrospectively collected. Albumin-associated inflammatory and nutritional markers included neutrophil-to-albumin ratio (NAR), CRP-to-albumin ratio (CAR), prognostic nutritional index (PNI), and systemic inflammation score (SIS). The LASSO, univariate and multivariate logistic regression analyses were utilized to screen risk factors. A nomogram model was developed according to the results of multivariate regression analyses.

Results: Among 254 patients, 49 cases had POD with an incidence of 19.3%. LASSO regression and multivariate logistic analyses suggested that preoperative NAR, preoperative PNI, preoperative SIS, and age >75 years were risk factors for POD. A nomogram model was developed according to the results of multivariate logistic analyses. The calibration curve suggested that the predicted probability of this nomogram model was in good line with the actual probability. The DCA showed that this nomogram model had net benefits for the prediction of POD for elderly patients following THA.

Conclusion: Albumin-associated inflammatory and nutritional markers including NAR, PNI, and SIS could predict POD in elderly patients following THA.

KEYWORDS

post-operative delirium, total hip arthroplasty, inflammatory markers, nutritional markers, nomogram

1. Introduction

Delirium, a neuropsychiatric syndrome, is characterized by an acute change in awareness, attention and cognition. It could affect up to 15–50% of elderly patients undergoing surgery (1). A meta-analysis showed that the overall incidence of delirium was 23% (2). Multiple risk factors included acute medical illness, drug use, trauma or surgery could trigger delirium (3). Delirium was reported to be associated with prolonged hospital stay time, higher complications, higher morbidity, and mortality (4–7). Although delirium was a common syndrome, most of cases were undocumented and unrecognized by the clinicians (8–10). Therefore, identifying biomarkers may help to the early detection of delirium, which is necessary for patients and clinicians.

Delirium is a primary post-operative complication in elderly patients with total hip arthroplasty (THA) (11, 12). A recent meta-analysis revealed that the incidences of post-operative delirium (POD) in patients with THA or total knee arthroplasty (TKA) varied significantly (0–48%), with a median incidence of 14.8%; most of the studies ranged from 10 to 15% (11). Although the pathogenesis of delirium is poorly understood, inflammation was a well-established factor involved in the development of delirium (13–15). In addition, studies suggested that hypoalbuminemia was an independent risk factor for POD in surgical patients (16–18), indicating that malnutrition was related to the risk of POD. Albumin (Alb), a protein in acute inflammatory response, is used to evaluate the nutritional status of patients receiving surgery. Therefore, we aimed to investigate whether Alb-derived markers integrating inflammation and nutrition could be the significant predictors for POD in elderly patients following THA. These Alb-associated inflammatory and nutritional markers were as follows: neutrophil-to-albumin ratio (NAR), CRP-to-albumin ratio (CAR), prognostic nutritional index (PNI), and systemic inflammation score (SIS).

2. Patients and methods

2.1. Participants

The enrollment flowchart of elderly patients receiving THA is presented in **Supplementary Figure 1**. Eventually, 254 patients following THA were included in this study from January 2019 to December 2022. Patients were included when they conformed to the following criteria: (1) patients received THA for the first time; (2) patients were Han nationality; and (3) age >60 years. Exclusion criteria included: (1) patients with neurological or psychiatric disorders; (2) patients with post-operative infections; (3) patients did not have complete data; (4) patients had a family history of mental illness; and (5) patients used antipsychotic medications in recent 3 months. All cases signed informed consent. This study was approved by the Ethics Committees of the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. This study was in line with the *Helsinki declaration*.

2.2. Diagnosis of POD

The diagnosis of POD was based on the criteria of Confusion Assessment Method (CAM) (19). The CAM instrument had the following four criteria: (I) inattention, (II) acute onset and fluctuating course, (III) altered consciousness, and (IV) disorganized thinking. The diagnosis of delirium required the presence of criterion (I) and (II), and either criterion (III) or (IV). Within 7 days after surgery, POD status was assessed for patients receiving THA. POD was determined at the same period every-day. Patients would not be evaluated after surgery beyond 7 days.

2.3. Data collection

The baseline characteristics including age, smoking, sex, hypertension, drinking, body mass index (BMI), diabetes mellitus, position of THA, anesthesia time, and surgery time were collected. Routine laboratory indexes were performed, including neutrophil, monocyte, lymphocyte, CRP, and Alb. The blood indicators were collected after admission within 24 h. The definitions of lymphocyte/monocyte ratio (LMR), NAR, neutrophil/lymphocyte ratio (NLR), SIS, CAR, and PNI are shown in **Supplementary Table 1**.

2.4. Statistical analysis

The data were presented as numbers (%) or median (with interquartile range) or means (± standard deviations). Categorical variables were calculated by Fisher exact test or Chi-square test, while continuous variables were determined by *t*-test (normally distributed variables) or Mann-Whitney *U*-test (non-normally distributed variables). The variance inflation factor (VIF) and tolerance were used to evaluate collinearity between variables. LASSO regression, and univariate and multivariate logistic analyses were utilized to find independent risk factors. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of markers for POD. The C-index value, calibration plots, and decision curve analysis (DCA) were analyzed in the nomogram model, which was based on the findings of multivariate logistic analyses. A P-value < 0.05 indicated statistically significant. SPSS (version 21.0, Chicago, IL, USA), MedCalc software, R software (version 4.1.3), and Graphpad Prism (version 8.0) were used.

3. Results

3.1. Patient characteristics

A total of 254 elderly cases after THA were analyzed, including 167 females (65.7%) and 87 males (34.3%). The average age of cases was 68.07 ± 5.68 years. Forty-nine cases with POD occurred, with a proportion of 19.3% (**Table 1**). The age of POD group was older than that in non-POD group (**Table 1**). The THA position between these two groups was significantly different (**Table 1**). The

TABLE 1 Clinicopathological characteristics for elderly patients following total hip arthroplasty.

Variables	Overall	Non-POD	POD	*P*-value
Sample size, *n*	254	205	49	
Sex, *n* (%)				0.351
Male	87 (34.3%)	73 (35.6%)	14 (28.6%)	
Female	167 (65.7%)	132 (64.4%)	35 (71.4%)	
Age, mean (SD), years	68.07 ± 5.68	67.25 ± 5.02	71.51 ± 6.93	<0.001*
BMI, mean (SD), kg/m^2	24.84 ± 3.74	24.99 ± 3.83	24.21 ± 3.29	0.190
Smoking, *n* (%)				0.888
Yes	17 (6.7%)	13 (6.3%)	4 (8.2%)	
No	237 (93.3%)	192 (93.7%)	45 (91.8%)	
Drinking, *n* (%)				0.726
Yes	10 (3.9%)	9 (4.4%)	1 (2.0%)	
No	244 (96.1%)	196 (95.6%)	48 (98.0%)	
Hypertension, *n* (%)				0.898
Yes	81 (31.9%)	65 (31.7%)	16 (32.7%)	
No	173 (68.1%)	140 (68.3%)	33 (67.3%)	
Diabetes mellitus, *n* (%)				0.934
Yes	32 (12.6%)	26 (12.7%)	6 (12.2%)	
No	222 (87.4%)	179 (87.3%)	43 (87.8%)	
Position, *n* (%)				<0.001*
Left	132 (52.0%)	97 (47.3%)	35 (71.4%)	
Right	119 (46.9%)	107 (52.2%)	12 (24.5%)	
Double	3 (1.1%)	1 (0.5%)	2 (4.1%)	
Surgery time, mean ± SD, h	1.82 ± 0.55	1.80 ± 0.53	1.93 ± 0.62	0.135
Anesthesia time, mean ± SD, h	2.16 ± 0.60	2.12 ± 0.59	2.31 ± 0.65	0.045*

*P-value < 0.05. BMI, body mass index; POD, post-operative delirium.

anesthesia time of POD group was significantly longer than that in non-POD group (Table 1). No significant differences were shown in sex, BMI, smoking, drinking, hypertension, diabetes mellitus, position, and surgery time (Table 1). The results of laboratory tests for these patients are listed in Table 2. The cases with SIS = 0 or 1 or 2 were 33 (13.0%), 115 (45.3%), and 106 (41.7%), respectively. Cases were divided into low group (SIS = 0 or 1) and high group (SIS = 2). The values of NAR and CAR in POD group were remarkedly higher than that in non-POD group; the value of PNI in POD group was markedly lower than that in non-POD group (Figure 1).

3.2. Diagnostic value of Alb-associated inflammatory and nutritional markers for POD

The diagnostic abilities of Alb-associated nutritional markers (NAR, CAR, and PNI) were analyzed (Table 3). ROC curve analyses showed that NAR, CAR, and PNI could predict the occurrence of POD with AUC values of 0.829 (cut-off value = 0.12, sensitivity = 77.55%, specificity = 76.59%, and Youden index = 0.5414), 0.765 (cut-off value = 0.19, sensitivity = 53.06%, specificity = 94.15%, and Youden index = 0.4721), and 0.819 (cut-off value = 43.85, sensitivity = 83.67%, specificity = 72.20%, and Youden index = 0.5587), respectively. Totally, the diagnostic abilities of preoperative Alb-associated inflammatory and nutritional markers for POD were good (Figure 2).

3.3. Predictive factors of POD

LASSO regression, univariate and multivariate logistic analyses were to obtain risk factors of POD. Univariate logistic analysis indicated that age >75 years, high NAR, high neutrophil, low PNI, low Alb, and high SIS were risk factors for POD (Supplementary Table 3). LASSO regression (Figure 3) indicated that age, NAR, PNI, and SIS were selected into multivariate logistic analysis. In addition, the tolerance was >0.1, and VIF was <5 for the abovementioned factors (Supplementary Table 4), suggesting no collinearity among these variables. Multivariate logistic analyses (Figure 4) showed that age >75 years, high NAR, low PNI, and high SIS could predict POD in elderly patients following THA (Table 4).

Last, we developed a nomogram model to predict POD in older patients following THA. Factors from LASSO regression and multivariate logistic analyses were utilized to develop it. The nomogram model was based on age (≥75 vs. <75 years), NAR (high vs. low), PNI (low vs. high), and SIS (high vs. low) (Figure 5). This model showed a good discriminatory ability with a c-index value of 0.869 (95% CI = 0.820–0.918). The calibration curve showed that the nomogram predictive model indicated a good

TABLE 2 Laboratory tests of elderly patients following total hip arthroplasty.

Variables	Non-POD	POD
Neutrophil, median (IQR), 10^9/L	3.73 (2.46–4.72)	4.95 (4.11–5.63)
Monocyte, median (IQR), 10^9/L	0.45 (0.29–0.61)	0.53 (0.42–0.72)
Lymphocyte, median (IQR), 10^9/L	1.07 (0.82–1.47)	0.86 (0.59–1.17)
Albumin, median (IQR), g/L	40.70 (37.95–43.10)	35.50 (32.00–38.40)
CRP, median (IQR), mg/L	5.20 (4.10–6.40)	6.50 (4.55–8.15)
NAR, median (IQR)	0.09 (0.06–0.12)	0.14 (0.12–0.17)
LMR, median (IQR)	2.33 (1.49–4.68)	1.62 (0.96–2.30)
CAR, median (IQR)	0.13 (0.10–0.16)	0.19 (0.13–0.23)
PNI, median (IQR)	46.15 (43.18–49.03)	40.40 (35.65–43.15)
SIS		
0	33 (16.1%)	0 (0%)
1	106 (51.8%)	9 (18.4%)
2	66 (32.2%)	40 (81.6%)

IQR, interquartile range; CRP, C-reactive protein; NAR, neutrophil/albumin ratio; LMR, lymphocyte/monocyte/ratio; CAR, CRP/albumin ratio, PNI, prognostic nutritional index; SIS, systemic inflammation score.

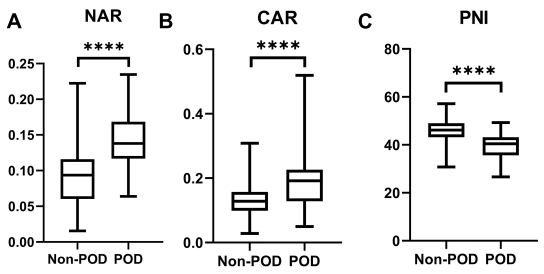

FIGURE 1
The preoperative values of NAR **(A)**, CAR **(B)**, and PNI **(C)** between POD group and non-POD group (****indicated $P < 0.001$).

consistency between the observational probability and predicted probability (Figure 6). The DCA suggested that this model had net benefits for the prediction of POD in elderly patients following THA (Figure 7).

4. Discussion

This study showed that age >75 years, and Alb-associated inflammatory and nutritional markers (NAR, PNI, and SIS) were predictive factors for POD in elderly patients following THA, suggesting that evaluating the preoperative inflammatory and nutritional status was necessary for elderly patients following THA.

4.1. Alb

Previous studies have demonstrated that hypoalbuminemia was significantly associated with an increased risk of delirium (18, 20–22). Chu et al. showed that Alb ≤ 32.26 g/L was a predictive factor for POD in cases with hip fracture (23). Another study from India suggested that Alb ≤ 35 g/L could predict POD in geriatric patients with hip fracture (24). In this study, we observed that Alb ≤ 39.8 g/L could not predict the POD among the elderly patients following THA. Obviously, the Alb level in this study was remarkedly higher than that of other studies, which may be a potential reason for inconsistent results. It is of note that PNI, CAR, SIS, and NAR consisting of Alb may be more accurate markers that reflected the physical condition including inflammation and nutrition status in predicting post-operative complications than a single index such as Alb (25). Therefore, we investigated aforementioned biomarkers including PNI, CAR, SIS, and NAR in this study. The associations between these indicators and POD are summarized in **Supplementary Table 2**.

4.2. PNI

Malnutrition was a risk factor for POD after primary total joint arthroplasty (24, 26–28). PNI, a new nutritional indicator, was calculated by lymphocyte count and serum Alb level. The impact of PNI on post-operative complications including POD following orthopedic surgery was reported before (29, 30). Acarbaş et al. found that preoperative PNI was associated with perioperative adverse events including POD in patients undergoing spinal surgery (29), which was replicated in their further study (30). Several Japanese studies observed an association between PNI and POD after orthopedic surgery (31–34); however, a study by Kobayashi et al. did not (35). We thought different sample sizes, clinical heterogeneity, different definitions of POD may explain these inconsistencies. Chen et al. from China found that preoperative PNI was related to POD after total joint arthroplasty (36). Xing et al. showed that preoperative PNI was related to POD after hip fracture surgery (37). In this study, we showed that low preoperative PNI was an independent predictor for POD following THA. In addition, preoperative PNI could predict POD of non-cardiac surgery (38) and colorectal cancer surgery (39).

TABLE 3 Receiver operating characteristic (ROC) curves of preoperative markers for predicting the post-operative delirium among elderly patients following total hip arthroplasty.

Variables	Cut-off values	Sensitivity%	Specificity%	AUC (95%)	Youden index
NAR	0.12	77.55	76.59	0.829	0.5414
CAR	0.19	53.06	94.15	0.765	0.4721
PNI	43.85	83.67	72.20	0.819	0.5587

AUC, area under curve; NAR, neutrophil/albumin ratio; CAR, CRP/albumin ratio, PNI, prognostic nutritional index.

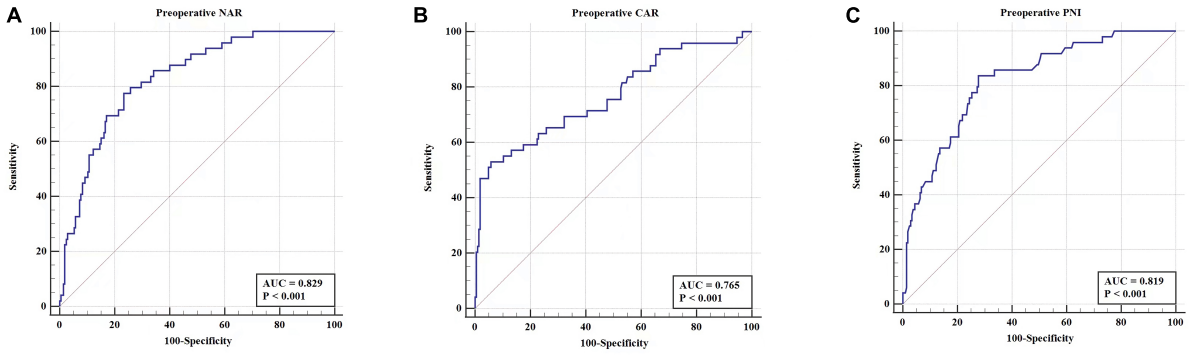

FIGURE 2
The diagnostic abilities of preoperative values of NAR **(A)**, CAR **(B)**, PNI **(C)** in predicting POD among patients following THA.

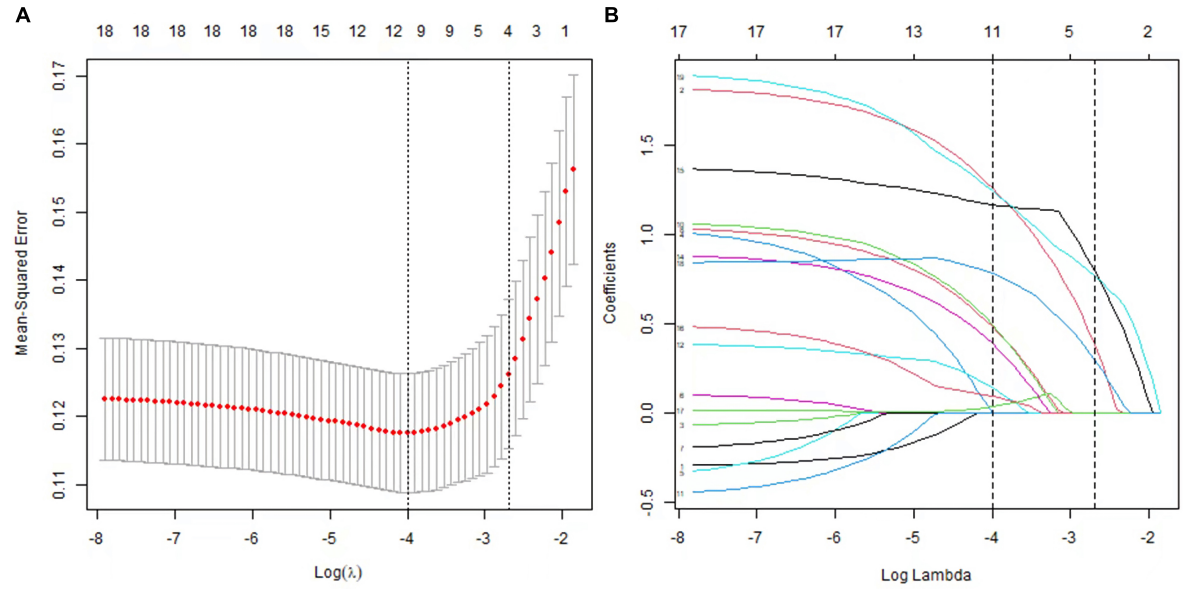

FIGURE 3
Predictor selection using the LASSO logistic regression model. **(A)** Identification of the optimal penalization coefficient lambda in the Lasso model using 10-fold cross-validation and the minimum criterion. **(B)** Lasso coefficient profiles of the potential predictors.

TABLE 4 **Multivariate logistics regression analyses for post-operative delirium in elderly patients following total hip arthroplasty.**

Variables	B	S.E.	Wals	OR (95% CI)	*P*-value
Age (≥75 vs. <75 years)	1.805	0.546	10.928	6.08 (2.09–17.72)	0.001*
NAR (high vs. low)	2.058	0.493	17.408	7.83 (2.98–20.58)	<0.001*
PNI (low vs. high)	1.245	0.542	5.275	3.47 (1.20–10.04)	0.022*
SIS (high vs. low)	1.385	0.502	7.612	3.99 (1.49–10.68)	0.006*

*P-value < 0.05. NAR, neutrophil/albumin ratio; PNI, prognostic nutritional index; SIS, systemic inflammation score.

4.3. CAR

Regarding CAR, Yang et al. indicated that preoperative CAR was not related to the occurrence of POD in cases undergoing lumbar spinal surgery (40). Peng et al. found that preoperative CAR was a significant predictor for POD for older patients receiving total joint arthroplasty (41). A Korean study indicated that preoperative CAR had an association with POD in older patients undergoing hip fracture surgery (42). In addition, Zhang et al. suggested that preoperative CAR may predict POD in older patients (>60 years old) after total knee arthroplasty (43). However, we thought the findings by Zhang et al. were controversial (43). In multivariate logistic regression analyses, they showed that the *P*-value for CAR was larger than 0.05 (43), indicating that CAR was not an independent risk factor for POD. Herein, we showed that patients with a high CAR

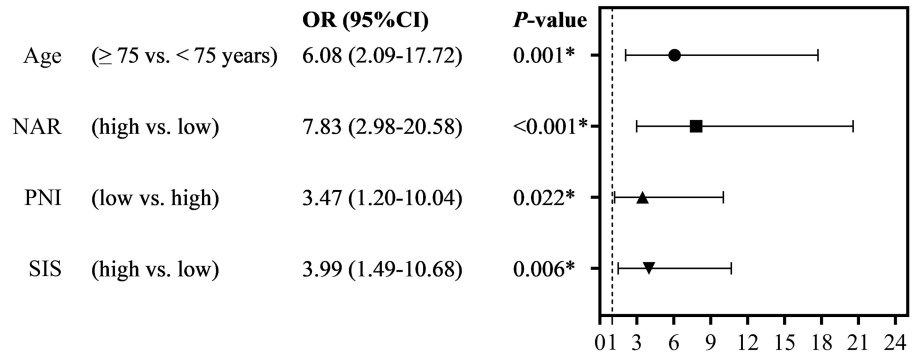

FIGURE 4
The multivariate logistic regression analyses of the independent predictor of POD (*indicated that they showed statistical differences).

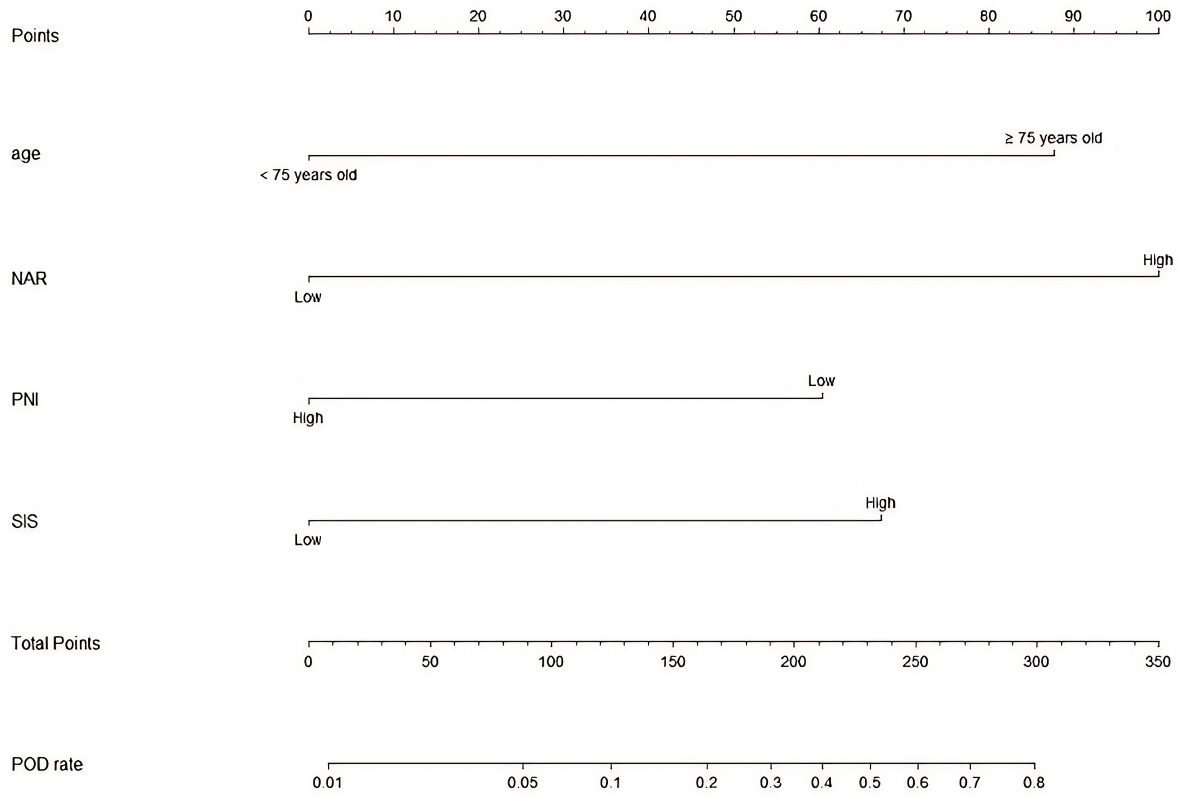

FIGURE 5
A predictive nomogram model for the prediction of POD.

had a higher percentage of POD after THA in this study. However, the lasso regression analysis showed that preoperative CAR could not predict POD for older patients receiving THA in this study. Further studies in other races are urgently needed in the future.

4.4. NAR

NAR, consisting of neutrophil and Alb, is a promising biomarker for predicting the prognosis of cancer (44–47). Günay et al. showed that higher NAR after lower extremity amputation was significantly associated with early mortality after extremity amputation (48). Chen et al. found that NAR was related to all-cause mortality in patients with stroke (49). A study revealed that NAR was associated with a higher risk of low cognitive performance (50). In addition, NAR could reflect the increased inflammatory status in patients with schizophrenia (51). Xie et al. showed that NAR was a reliable biomarker for post-operative complications in patients with colorectal cancer after surgical treatment (52). Up to date, no studies have explored the relationship between NAR and POD in older cases after THA. In this study, we found that high

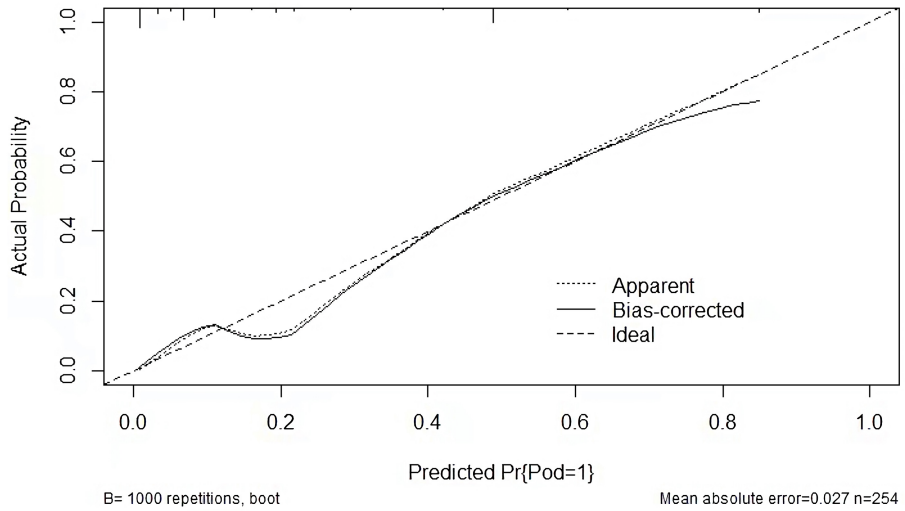

FIGURE 6
Calibration curve of the prediction nomogram.

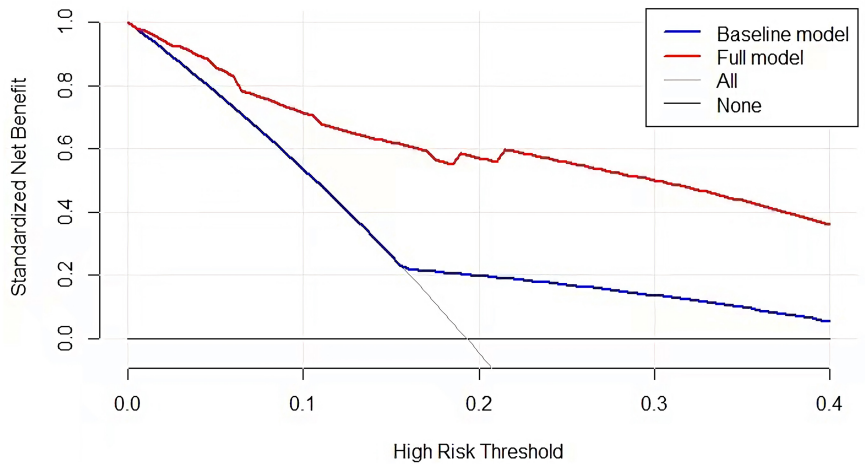

FIGURE 7
Decision curve for nomogram model to predict the risk of POD.

CAR could predict POD for older patients receiving THA. NAR could reflect the status of inflammation and nutrition; thus, higher NAR may indicate the higher inflammation and malnutrition of patients. It may be the reason why higher NAR was significantly associated with POD in patients with THA.

4.5. SIS

SIS consisted of Alb and LMR, which could also reflect nutrition and inflammation status. SIS was mainly reported to be associated with the survival of cancers (53–55). In addition, SIS was associated with post-operative complications in surgical patients (56–58). Therefore, we intended to investigate the association between SIS and POD among elderly patients receiving THA. Results of this study showed that high SIS was significantly related with the risk of POD after THA among older patients. To the knowledge, this is the first study to show that preoperative SIS could predict POD in older patients after THA. Further studies in other races and regions should be conducted in future.

4.6. Other factors

Inflammation may play a dominant role in the development of delirium. In a recent meta-analysis by Wang et al., they showed that CRP showed a significant association with POD (59). Adamis et al. indicated that CRP was a significant predictor for the types of surgery; however, this effect was predominant in the acute orthopedic surgery and elective abdominal surgery (60). In this study, we found that preoperative CRP could not predict POD among elderly patients after THA. The surgery may aggravate inflammatory response with elevated levels of CRP. Therefore, we

thought that the association between post-operative CRP and POD may become stronger. However, we did not evaluate post-operative CRP in this study. Last but not least, this study showed that older age (≥75 years) was a significant predictor for POD after THA. Advanced age was regarded as an accepted predictor for delirium (3, 61). However, Zhang et al. suggested that older age was not a risk factor for POD after total knee arthroplasty (43).

Last, we performed a nomogram predictive model to assess the POD based on the multivariate logistic regression analyses. The C-index value of this model was 0.869 (95% CI = 0.820–0.918). The calibration curve showed that the nomogram model indicated a good consistency between the observational probability and predicted probability. The DCA suggested that this model had net benefits for the prediction of POD in elderly patients following THA.

This study showed several limitations. First, our study was retrospective; thus, a potential selection bias may exist. Second, the sample size was not large enough, which may underpower the findings in this study. Third, post-operative factors that affecting the development of POD were not investigated in this study. Last, we did not split the dataset into training and validation datasets during the modeling process due to the small sample size in this study. The lack of external validation for the predictive model was a limitation of this study.

5. Conclusion

This study observes an association between Alb-associated inflammatory and nutritional markers (NAR, PNI, and SIS) and the occurrence of POD in elderly patients following THA. Prospective studies are needed to explore preoperative inflammatory and nutritional markers of POD.

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 the Ethics Committees of the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

YH and JW: study design and project administration. WH: data collection and analysis, and writing. ZS, HS, and JW: revised the manuscript. All authors approved the final 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1158851/full#supplementary-material

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Quality of life and socio-demographic factors associated with nutritional risk in Brazilian community-dwelling individuals aged 80 and over: cluster analysis and ensemble methods

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Introduction: The aim of the present study was to use cluster analysis and ensemble methods to evaluate the association between quality of life, socio-demographic factors to predict nutritional risk in community-dwelling Brazilians aged 80 and over.

Methods: This cross-sectional study included 104 individuals, both sexes, from different community locations. Firstly, the participants answered the sociodemographic questionnaire, and were sampled for anthropometric data. Subsequently, the Mini-Mental State Examination (MMSE) was applied, and Mini Nutritional Assessment Questionnaire (MAN) was used to evaluate their nutritional status. Finally, quality of life (QoL) was assessed by a brief version of World Health Organizations' Quality of Life (WHOQOL-BREF) questionnaire and its older adults' version (WHOQOL-OLD).

Results: The K-means algorithm was used to identify clusters of individuals regarding quality-of-life characteristics. In addition, Random Forest (RF) and eXtreme Gradient Boosting (XGBoost) algorithms were used to predict nutritional risk. Four major clusters were derived. Although there was a higher proportion of individuals aged 80 and over with nutritional risk in cluster 2 and a lower proportion in cluster 3, there was no statistically significant association. Cluster 1 showed the highest scores for psychological, social, and environmental domains, while cluster 4 exhibited the worst scores for the social and environmental domains of WHOQOL-BREF and for autonomy, past, present, and future activities, and intimacy of WHOQOL-OLD.

Conclusion: Handgrip, household income, and MMSE were the most important predictors of nutritional. On the other hand, sex, self-reported health, and number of teeth showed the lowest levels of influence in the construction of models to evaluate nutritional risk. Taken together, there was no association between clusters based on quality-of-life domains and nutritional risk, however, predictive models can be used as a complementary tool to evaluate nutritional risk in individuals aged 80 and over.

KEYWORDS
aged, quality of life, nutritional risk, cross-sectional study, machine learning

1 Introduction

The over 80 years demographic group has been increasing steadily worldwide and, although this fact should be celebrated by humanity, increased life expectancy may bring along a higher frequency of chronic diseases, which could impair a person's ability to perform daily activities, as well as their independence and autonomy. Consequently, it may enhance physical fragilities, as well as social and psychological vulnerabilities, which could trigger negative feelings and decrease aging-associated quality of life (1).

Quality of life (QoL) has been defined by the World Health Organization (WHO) as the subjects' perception about socio-cultural and value systems in which they are inserted and regarding their goals, expectations, and concerns. Therefore, to keep the general population's QoL at a higher level, it is necessary to consider some aspects, namely physical and psychological health, as well as to obtain satisfactory levels in other domains, such as psychological, social relations, and environmental (2). In addition, higher scores of QoL for older adults considers additional domains, such as autonomy, sensorial functioning, social participation, past, present, and future activities, as well as death and dying.

In Brazil, a country in development, individuals aged 80 and over represent 2% of the population (3); with an estimated increase of this group to 2.2% by 2030, and 4.07% by 2040 (4). Thus, this accelerated growing of the number of oldest-old in a country with countless socioeconomic inequalities must be considered in an attempt to improve public policies focusing on lifelong health.

Dietary and lifestyle patterns are undeniably relevant for both the physical and psychological conditions of all individuals, contributing for prevention of health-related problems as well as maintenance, and promotion of health; they also contribute to the well-being that impacts quality of life (5). However, the Brazilian Institute of Geography and Statistics has reported that food insecurity in the Brazilian population has increased from 2013 to 2018 (6). Salles-Costa et al. (7) described an increased number of people experiencing food insecurity in the aforementioned period (from 2.9 to 5.6 million). On the other hand, households having at least one older adult present lower prevalence of food insecurity, probably due to the Continuous Benefit Installment program, which also contributed for poverty reduction in Brazil from 2004 to 2013 (8).

Food insecurity (FI) is characterized by irregular access to food, and has a negative impact on food intake, nutritional status and health of older people. Approximately 2.37 billion people worldwide were affected by moderate or severe food insecurity in 2021 due to environmental and socio-economic conditions (9). A recent systematic review included 22 studies of different worldwide regions, being 18.2% Europeans 13.6% Asian, 9.1% African, and 13.6% Latin American populations, and concluded food insecurity was associated with malnutrition (45.5%) and with overweight (27.3%) in older adults (10). In Portugal (11) and Iceland (12) nutritional risk was considered a critical factor for the health of older adults', primarily affecting those living alone, which increases the health concerns as well as QoL of older subjects (11, 12).

The prevalence of FI in studies among Brazilian community-dwelling older people varies, depending on the region. In 2021, 7% of the population were living in poverty and 19% in extreme poverty (<US$1.90 *per capita*/day), revealing the social inequalities of Brazil. In a recent study on food insecurity in older people covered by a program of the Family Health Strategy in Northeast Brazil, the prevalence was 63.5% in households with older people (38.4% mild FI and 25.1% moderate/severe FI), a scenario that was exacerbated after the pandemic period (9).

Although there are studies about older adults, only a handful of them have associated quality of life and socio-demographic factors with nutritional risk, which renders studies using machine learning of fundamental importance, particularly for a country with so many inequalities and where longevity increases at such a high pace. The aim of the present study was to use cluster analysis and ensemble methods to evaluate the association between quality of life, socio-demographic factors to predict nutritional risk in community-dwelling Brazilians aged 80 and over.

2 Materials and methods

2.1 Study design and ethics

This cross-sectional study was approved by the Research Ethics Committee of São Judas Tadeu University (CAAE 49987615.3.0000.5404 and approval number 09069419.8.0000.0089).

2.2 Participants

Participants were invited to participate from partner reference centers of the state of São Paulo, Brazil, where ongoing health promotion activities are performed for older adults. The invitation was writing and by word of mouth. Thus, this was a non-probability convenience sample, in which they were included aged 80 and over subjects, able to communicate and cognition preserved enough to answer the questionnaire inclusion criteria. An investigator carefully presented the aims, risks, benefits of the study, and freedom of participation, as well as confidentiality for all aged 80 and over subjects, moment who had opportunity to decline. Then, who agreed to participate of the study signed an information sheet and a consent form. They were excluded who did not finish answering the questionnaires too were.

Thus, the data collection occurred from October 2016 to October 2017, in four Institutions from São Paulo state: Casa do Idoso Norte (North Older Adults' House, São José dos Campos city), Centro Integrado de Saúde e Educação (Moacyr Rodrigues Moacyr Rodrigues- Aging Health and Education Integrated Center, São Caetano do Sul city), Escola Superior de Educação Física (Superior

School of Physical Education, Jundiaí city) and Universidade São Judas Tadeu (São Paulo city). The institutions located in São José dos Campos, São Caetano do Sul and Jundiaí are reference centers for the older adults' population, since they have medical care and socializing spaces exclusive for people over 60.

The self-reported sociodemographic characteristics (age, sex, ethno-racial features, marital status, schooling, household income), self-reported health conditions and number of teeth were obtained from aged 80 and over subjects with the printed questionnaire by interview with a multidisciplinary staff previously trained and with experience in gerontological assessment (biomedical, physiotherapist, psychologists, and nutritionist).

2.3 Mini-mental state examination

The Mini-Mental State Examination (MMSE) (13) was used to assess the participants' cognitive status. MMSE comprises questions divided into seven categories: orientation regarding time and place (5 points each), memorizing of three words (3 points), attention and simple mathematical calculation (5 points), remembering of three words (3 points), language (aphasia and apraxia, 8 points) and constructional skills (1 point). The MMSE score ranged from a minimum of 0 to a maximum total of 30 points. The cut-off point for cognitive decline considers schooling level, and this study used 18–19 and 24–25, according to the absence and presence of previous formal schooling, respectively (14).

2.4 Quality of life

QoL of the individuals aged 80 and over was evaluated using the WHOQOL-BREF and WHOQOL-OLD instruments. The WHOQOL-BREF was translated and validated in Brazil by Fleck et al. (15), and it consists of 26 items, two of which relate to global QoL and health in general, and the remaining 24 are organized into four domains (physical, psychological, environmental, and social relationships). The WHOQOL-OLD is a specific instrument for evaluation of QoL in older adults, and it was validated for Brazil's older population by Chachamovich et al. (16). This instrument comprises 24 items divided into six domains: sensory abilities, autonomy, past-present-future activities, social participation, death and dying, and intimacy; it should be applied along with WHOQOL-BREF. In both instruments, the scoring answer is based on the Likert scale, varying from 1 to 5, according to satisfaction degree. The final scores vary from 0 to 100, and they are proportional with QoL; a score of 100 means the best QoL.

2.5 Strength test

Maximal handgrip strength was determined using a hydraulic hand dynamometer (model Jamar® by JLW Instruments, Chicago, IL, United States). All participants were tested while seated, elbow flexed at 90° with forearm and wrist in a neutral position, hips and knees flexed at 90°, feet on the ground, in accordance with the guidelines of the American Society of Hand Therapists (17). The testing protocol consisted of three repetitions of 5 s in maximal isometric contractions of the dominant hand, with a rest period of at least 60 s. The highest strength value among the three attempts was considered for analysis, and results were shown in kilogram/force (Kg/f).

2.6 Mini nutritional assessment® and short form

The MNA® is a validated nutrition screening tool to identify individuals aged 65 and over at nutritional risk (18). Originally, the instrument comprised 18 questions, and the MNA Short Form (19) consists of 6 questions and streamlines the screening process while retaining the validity and accuracy of the original MNA® to identify older adults who are malnourished or at risk of malnutrition. The MNA-SF comprises simple measurements and six questions that can be completed in less than 5 min: anthropometric measurements (body mass index, weight loss); global assessment (mobility); and dietary questionnaire and subjective assessment (food intake, neuropsychological problems, acute disease). A total score of MNA-SF <8, 8–11, and >11 indicates malnutrition, risk of malnutrition, and no malnutrition, respectively. Those who did not complete the questionnaire were excluded.

2.7 Statistical analysis

All analyzes were performed in R, version 4.1.0 (R Foundation for Statistical Computing). Data were tested for normality using the Shapiro–Wilk test, revealing non-normal distribution. Kruskal-Wallis, Bonferroni, and Dunn's nonparametric tests were used to evaluate the presence of differences in sociodemographic (age, sex, race, marital status, schooling, household income) and health variables (self-reported health and number of teeth) by cluster, in muscular strength, MMSE, WHOQOL-BREF and WHOQOL-OLD domains. The numerical variables were presented as medians and interquartile ranges, or mean and standard deviation, while categorical variables were shown as frequencies (%). Associations between the categorical variables were tested using Chi-squared and Fisher Exact tests. The level of significance was established at 5% ($p \leq 0.05$) for all analyzes.

Initially, clustering analysis (unsupervised machine learning) was used to derive groups of participants based on quality-of-life scores, and the association of the clusters with nutritional risk was tested. Subsequently, two classifier algorithms were used, Random Forest and eXtreme Gradient Boosting based on the ensemble strategy as part of the techniques of supervised machine learning to predict nutritional risk (Figure 1).

The characteristics of each machine learning algorithm is briefly described below.

2.7.1 Machine learning

One of the most useful tasks in ML is that of labeling, assigning each data point a certain tag, label, or a numerical value according to some prespecified criterion. Semi-supervised or partially supervised learning refers to a class of ML techniques which combine labeled and unlabeled data to build classifiers (20). Additionally, an ensemble method is a set of classifiers whose individual decisions are combined in some way (typically by weighted or unweighted voting) to classify new examples. Ensemble methods are known to perform better than

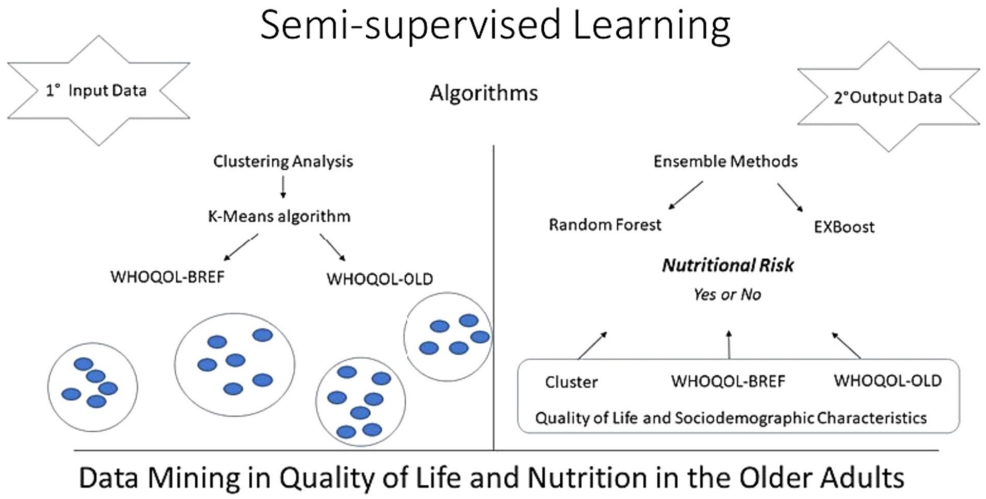

FIGURE 1
Conceptual model of quality of life and nutritional risk in the older adults.

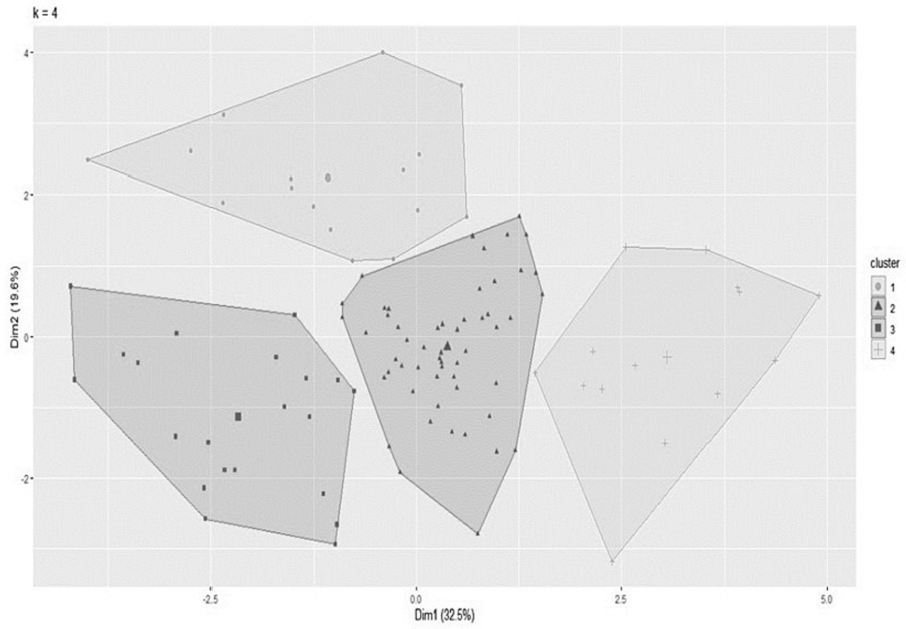

FIGURE 2
Cluster of individuals aged 80 and over performed by K-Means algorithm.

other algorithms, because they help to reduce false positive rates (21). Random Forest and eXtreme Gradient Boosting are based on the ensemble strategy and perform well in many tasks.

2.7.2 Unsupervised learning and clustering analysis

K-means clustering algorithm was used to identify the clusters based on WHOQOL-BREF and WHOQOL-OLD domains. The following packages were used: cluster and factoextra. The QoL scores were converted to z-scores and input into the algorithm. Standardized data were used to ensure all features have equal influence on the clustering procedure. Clustering distance measurements were carried out using Euclidean distances. Each data point was categorized by calculating the distance between the point to each group centroid and then classifying the point closest to it (22). Centroids were recomputed based on the classified points, and the process was then repeated until the centroids no longer changed. Four clusters were retained considering homogeneity in the groups that were derived in the analysis (Figure 2) and considering the optimal number of clusters by average silhouette width (Supplementary Figure S1). Interpretability of characteristics for each group was examined to confirm the optimal number of clusters, and whether a group was sufficiently large for an adequate statistical power, that is, at least 10% of the total sample (23).

2.7.3 Supervised learning, random forest, and XGBoost algorithm

The Random Forest (RF) and eXtreme Gradient Boosting (XGBoost) were used to predict the nutritional risk of each participant. The training stage of the classifier algorithms was based on the following predictors: age, sex, household income, self-reported health, handgrip, MMSE, number of teeth. These predictors were defined considering the models' best performance in the test stage and evaluation metrics, such as accuracy and area under the curve. Sociodemographic data were used together with cluster and QoL characteristics to build three different models: (1) based on the Cluster; (2) WHOQOL-BREF; (3) WHOQOL-OLD.

The RF algorithm generates several decision trees, and each tree is trained with a random distribution. A major advantage of the RF is the ease of measuring the relative importance of each attribute for the prediction by analyzing how many nodes in the trees use a given attribute to reduce the overall impurity of the forest (22). The RF model was built through the Random Forest function, which is part of the package of the same name. Analysis was performed using the following established basic parameters (Supplementary Table S1): number of trees, minimum size of terminal nodes, number of variables used in each tree, and seed for reproducibility. The eXtreme Gradient Boosting algorithm (XGBoost) is also used as an efficient, popular implementation of gradient-boosted decision trees. XGBoost strictly prioritizes computational speed and model performance, with good accuracy using most data sets. The analysis was performed using the following established, basic parameters (Supplementary Table S1): number of trees, minimum size of terminal nodes and number of variables used in each tree, max number of boosting iterations, maximum depth of a tree, and seed for reproducibility.

2.7.4 Feature selection and model assessment

The predictors used by the classifier algorithms were ranked according to the importance of their influence on the class prediction (with or without nutritional risk). The order of importance was based on the importance function of a RF model (randomForest package) and XGBoost model (EIX package). Concordance between the outcome class (nutritional risk) and the classification scheme provided by the algorithms was calculated. The accuracy was determined using confusionMatrix (e1071 package); in new individuals, for whom the risk label was not known by the algorithm, only information regarding the sociodemographic data and QoL characteristics were used. In general, values equal to 0.5 correspond to the performance of a random classifier, values smaller than 0.6 (and greater than 0.5) indicate moderate predictive performance and values greater than 0.7 indicate good predictive performance. Furthermore, other evaluation metrics were calculated, such as sensitivity, specificity, area under curve, positive and negative predictive values (24).

3 Results

The present study managed to recruit a sample of 104 older people in the period determined for collection, mostly women (69.23%), who declared themselves white (82.69%), with a median age of 82 years and 4 years of age education (Table 1).

Figure 2 illustrates the result of the final cluster analysis using the K-means algorithm, resulting in four groups used to perform clustering. Figure 2 shows the clusters that were derived based on the QoL data. The sum between the two dimensions, which corresponds to the Y (19.6%) and X (32.5%) axes of the graph, explains a total of 52.1% of the QoL variability in the sample. Furthermore, it shows that there was no overlap between the clusters, a fact that indicates that the K-means algorithm was able to group individuals in such a way that participants from the same group are more homogeneous among themselves when compared to participants who are in other clusters. The figure is used as an initial indicator of model performance, additionally comparisons between clusters are described in Tables 1, 2, which allow us to characterize each cluster and make comparisons between them. Other subdivisions were tested during the analysis, but they did not show better intra-cluster homogeneity and differences between the groups, resulting in overlapping and small subgroups (data not shown).

The clusters' sociodemographic characteristics are shown in Table 1. From the original data set ($n = 104$), four major clusters were derived: cluster 1 ($n = 16$, 15.7%), cluster 2 ($n = 21$, 20.6%), cluster 3 ($n = 51$, 50.0%) and cluster 4 ($n = 14$, 13.7%). Although there was a higher proportion of individuals aged 80 and over with nutritional risk in cluster 2, and a smaller proportion in cluster 3, there was no statistical association between nutritional risk and the cluster derived from QoL data (WHOQOL-BREF and WHOQOL-OLD scores). On the other hand, there were more men in cluster 4, while cluster 3 had the highest proportion of women ($p < 0.05$). In addition, there was a higher proportion of individuals who were unmarried in cluster 3 ($p < 0.05$).

Table 2 shows the mean/median and standard deviation/interquartile range for WHOQOL-BREF and OLD scores by cluster of individuals aged 80 and over. Regarding WHOQOL-BREF, higher scores were present in cluster 1 and 2 when compared to clusters 3 and 4 for the physical domain ($p < 0.05$). Also, cluster 1 showed the highest scores for psychological, social, and environmental domains, while cluster 4 presented the worst scores for social and environmental domains. Similar findings were found regarding cluster 4 in the WHOQOL-OLD analysis, the worst scores in comparison to other clusters were for the following domains: autonomy, past-present-future activities, and intimacy. On the other hand, the highest scores for the abovementioned domains were observed in cluster 2, which was also the case for the social participation domain. No statistical difference between clusters was noteworthy for the death and dying domain ($p > 0.05$).

Regardless of the classifier built with QoL data according to WHOQOL-BREF, OLD or the Cluster, the RF algorithm showed the highest values for accuracy and area under the curve. Although the XGBoost algorithm exhibited greater accuracy (>0.70) for all models based on predictors of quality of life associated to sociodemographic characteristics, its specificity was the lowest when compared to the RF algorithm. This finding suggests a lower ability of the XGBoost algorithm to identify individuals at nutritional risk. All metrics used to evaluate the performance of the RF and XGBoost models are shown in Table 3.

Regarding level of importance, handgrip, household income, and MMSE were the most important predictors of nutritional risks. On the other hand, sex, number of teeth and self-reported health showed the

TABLE 1 Description of sociodemographic and nutritional status characteristics by cluster.

	Overall		Cluster 1		Cluster 2		Cluster 3		Cluster 4		*p* value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Nutritional Status*											
Without risk	72	70.59	11	68.75	12	57.14	36	70.59	9	64.29	0.717
With risk	30	29.41	5	31.25	9	42.86	15	29.41	5	35.71	
Sex											
Male	32	30.77	4	25.00	6	28.57	12	22.64	10	71.43	<0.050
Female	72	69.23	12	75.00	15	71.43	41	77.36	4	28.57	
Ethno-racial features											
Not White	18	17.31	2	12.50	4	19.05	9	16.98	3	21.43	0.922
White	86	82.69	14	87.50	17	80.95	44	83.02	11	78.57	
Married											
No	67	64.42	10	62.50	15	71.43	38	71.70	4	28.57	<0.050
Yes	37	35.58	6	37.50	6	28.57	15	28.30	10	71.43	
Self-report health*											
Worst	24	23.53	2	12.50	4	19.05	14	26.92	4	30.77	0.632
Equal	61	59.80	11	68.75	12	57.14	32	61.54	6	46.15	
Better	17	16.67	3	18.75	5	23.81	6	11.54	3	23.08	

	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (years)	82	80–84	81	80–84	81	80–84	82	80–84	83	81–88
Schooling (years)	4	4–8	6	4–11	4	4–8	4	4–8	4	4–8
Household Income	1874	0–3,368	1887	0–4,168	2000	0–3,300	1874	0–3,000	1,068	0–3,500
Hand Grip	18	14–23	22	16–25	20	15–22	17	12–22	18	16–23
Mini Mental	25	22–27	25	21–26	25	22–26	26	21–28	23	22–26
Number of Teeth	0	0–1	0	0–2	0	0–1	0	0–1	0	0–1

P values are derived from Chi-Squared or Fisher Exact tests (continuous and categorical variables). The level of significance was established at 5% ($p \leq 0.050$). IQR, interquartile range.
*Exclusion of 2 individuals aged 80 and over presenting malnutrition ($n = 102$).

TABLE 2 Description of scores of all domains of quality of life by cluster.

	Cluster 1		Cluster 2		Cluster 3		Cluster 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
WHOQOL-BREF								
DOM1–Physical	81.25[b,c]	17.37	74.58[e]	15.41	66.46[b]	13.23	59.69[c,e]	10.98
DOM2–Psychological	86.20[a,b,c]	7.09	75.98[a e]	9.94	69.77[b,f]	9.05	58.63[c,f]	8.56
DOM3–Social	90.10[a,b,c]	8.18	71.57[a,e]	13.20	68.26[b,f]	12.96	57.74[c,e,f]	10.06
DOM4–Environmental	87.89[a,b,c]	8.68	73.16[a,e]	9.25	67.89[b,f]	9.35	55.80[c,e,f]	6.57
WHOQOL-OLD								
Autonomy	58.33[a,c]	13.93	87.50[a,d,e]	10.27	63.35[d,f]	11.40	44.7[c,e,f]	12.46
Past, Present and Future Activities	71.88[a,c]	16.32	90.77[a,d,e]	8.97	73.58[d,f]	11.27	55.29[c,e,f]	17.28
Social Participation	71.35[a]	14.46	90.48[a,d,e]	9.81	69.32[d]	12.19	60.10[e]	13.63
Death and Dying	62.50	25.56	80.95	20.10	63.49	27.42	67.79	26.98
Sensory Abilities*	62.65	43.75–93.75	87.50[e]	81.25–93.75	75.00	62.50–93.75	50.00[e]	37.50–81.25
Intimacy*	68.75[a,b,c]	59.38–81.25	93.75[a,d,e]	87.50–100.00	75.00[b,d,f]	68.75–81.25	50.00[c,e,f]	50.00–56.25

P values were derived from a Bonferroni test or Dunn's test, and statistical significance were represented with different letters: [a]cluster 1 e 2; [b]cluster 1 e 3; [c]cluster 1 e 4; [d]cluster 2 e 3; [e]cluster 2 e 4; [f]cluster 3 e 4. *Median and Interquartile Range. DOM, domain.

lowest levels of influence in the construction of models to evaluate nutritional risk (Figure 3). RF models exhibited better consistency to identify physical domain scores in the WHOQOL-BREF instrument (Figure 4). Feature selection was performed for both algorithms, and the results of the XGBoost model are presented as Supplementary material, due its lower performance, while the main predictors of nutritional risk analyzed by RF were ordered in accordance with their level of importance in Figures 3–5.

TABLE 3 Performance measures of the ensemble algorithms.

Algorithm	Random forest			XGBoost		
Random forest	Cluster	BREF	OLD	Cluster	BREF	OLD
Accuracy	0.80	0.78	0.87	0.74	0.71	0.76
95% CI	0.65; 0.90	0.63; 0.89	0.73; 0.95	0.66; 0.84	0.56; 0.80	0.55; 0.83
Sensibility	0.80	0.80	0.85	0.80	0.75	0.85
Specificity	0.80	0.76	0.88	0.64	0.68	0.60
Positive predictive value	0.76	0.73	0.85	0.64	0.65	0.63
Negative predictive value	0.83	0.83	0.88	0.80	0.77	0.83
Prevalence	0.44	0.44	0.44	0.44	0.44	0.44
Detection Rate	0.36	0.36	0.38	0.35	0.33	0.38
AUC	0.87	0.86	0.85	0.72	0.72	0.73

Predictors: age, sex, income, health assessment, hand grip, mini mental, number of teeth. AUC, area under the curve measure.

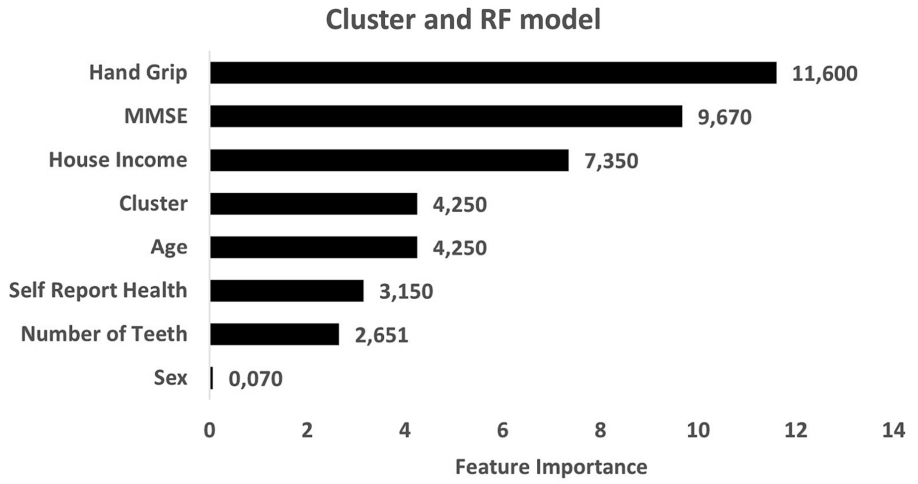

FIGURE 3
Predictors of nutritional risk with cluster quality of life and sociodemographic characteristics, self-reported-health and number of teeth, Mini-Mental State Examination (MMSE), and handgrip to individuals aged 80 and over analyzed by Random Forest model.

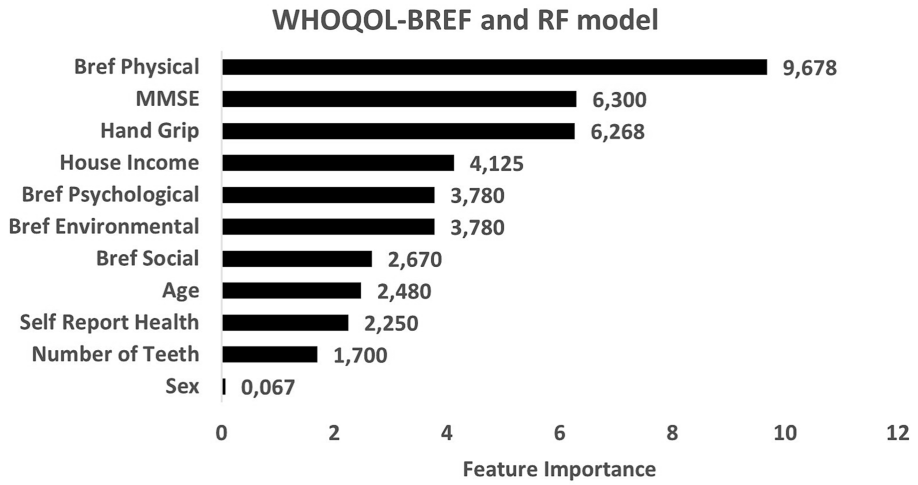

FIGURE 4
Predictors of nutritional risk with scores of WHOQOL-BREF and sociodemographic characteristics, self-reported-health and number of teeth, Mini-Mental State Examination (MMSE), and handgrip to individuals aged 80 and over analyzed by Random Forest model.

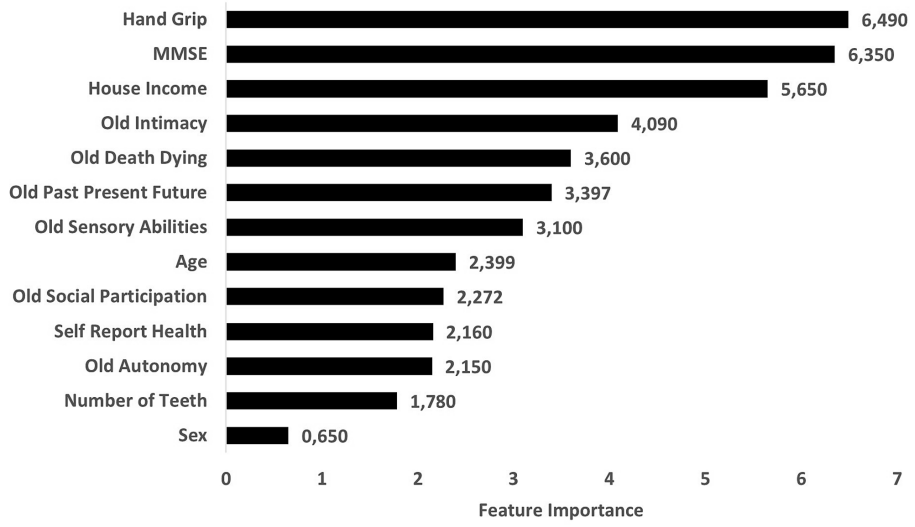

FIGURE 5
Predictors of nutritional risk with scores of WHOQOL-OLD and sociodemographic characteristics, self-reported-health and number of teeth, Mini-Mental State Examination (MMSE), and handgrip to individuals aged 80 and over analyzed by Random Forest model.

4 Discussion

The findings of the current study showed that, among the four clusters formed by the K-means algorithm, the predictors of nutritional risk for Brazilian community-dwelling individuals aged 80 and over were lower muscular strength, income, and cognitive capacity. Although there was no difference between clusters in relation nutritional risk, there was an association with female sex and unmarried status. Regarding quality of life, there was no association between nutritional risk and the clusters derived from the analysis. In the ensemble methods, the RF analysis had the best accuracy, sensitivity, and specificity, and the predictors with the highest importance in the model constructions were handgrip, household income, and MMSE.

Overall, the main predictors of nutritional risk for older adults were those associated with frailty, which, in the present study, were assessed through physical condition and cognition. According to Morley et al. (25), frailty is characterized as a dynamic and multifactorial clinical state that determines imbalance of homeostatic reserves associated with a reduction in the ability to respond to minor injuries, and an increased risk of dependence; quality of life is directly impacted by increased dependence. The systematic review and meta-analysis conducted by Kojima et al. (26) demonstrated a consistent inverse association between frailty/pre-frailty and quality of life among community-dwelling older adults, despite high heterogeneity and possible risk of biases in this population.

Furthermore, the present study identified that the intrinsic capacity of individuals aged 80 and over was a predictor of nutritional risk, represented by handgrip and MMSE. WHO (27) defines intrinsic capacity as the combination of an individual's physical and mental abilities. In the Integrated Care for Older People (ICOPE) guidelines, functional ability was defined as the combination and interaction of intrinsic capacity with the environment in which an older adult life. Thus, the evaluation of intrinsic capacity allows to identify conditions associated with its decline, providing an alternative to intervene in halting, decreasing, or reversing it, which, in turn, improves health and QoL of individuals aged 80 and over.

Some studies (28–31), mainly cohort studies, with oldest-old people and centenarians and using the geriatric nutritional risk index (GNRI), have associated nutritional risk with various aspects of health, not just the classic ones, observed in the present study, such as cognition, nutrient status (e.g., selenium), sexual hormones and bone blurriness, in addition to abdominal obesity.

Frailty is recognized as an important predictor of adverse health events (32–34), as demonstrated in the systematic review and meta-analysis conducted by Crocker et al. (35) which observed an association between frailty and QoL in all domains studied. Divergent results were noted in the present study, which showed no association between nutritional risk and QoL with cluster analysis. A possible explanation could be that the present study included community-dwelling individuals aged 80 and over who regularly attended reference centers, with medical care and socializing spaces for the older adults' population, which may not represent the health and social conditions of most individuals aged 80 and over.

It's important to mention that to our knowledge there are few studies with individuals over 80 years old from São Paulo, which impedes a better comparison with the results of the present study. However, when we look at recent data from the demographic Census (36), Brazil has about 208 million habitants, and it is estimated that 15% comprise the older population (about 31 million) and 1.8% (200.000) are over 80 years old in São Paulo.

Therefore, individuals aged 80 and over included in the present study partially represent the Brazilian older adults, as described by Mirandola and Morsch (37). Based on the National Health Survey (NHS) performed by Brazilian Institute of Geography and Statistics (BIGS), enrollment 1,498 aged 80 and over people from all over the

country, in relation of ethno-racial features: 55.7% self-declared to be white, 42.7% black or brown, 1.1% yellow and 0.4% self-reported as indigenous (37). The higher proportion of white ethno-racial features among the participants included in the present study could be explained by locations where data was collected.

In addition, the NHS-BIGS study showed that 34.7% of Brazilians individuals aged 80 and over are unable to read and write, and among the remaining (65.3%): 20% were literate in courses for adults, 35.3% presented elementary education attended on regular or supplemental, 5% attended high school and another 5% presented an university degree. It's important to note that Brazil is a very large country with many socio-economic and cultural differences among regions, and in the present study the southeast individuals aged 80 and over self-reported 6 years of schooling (median), while in the study conducted by Amorim (38) with 135 individuals aged 80 and over from the Teresina, in the state of Piauí (northeast region) found that 62.1% of the participants were illiterate. In this way, the high proportion of Brazilians individuals aged 80 and over who only have an elementary education is a reflection of the social organization of the beginning of the last century, when education was not a priority and younger people had to choose between work or study in order to contribute to the family income (37, 39).

In the present study, it was also detected an association between nutritional risk and unmarried status in individuals aged 80 and over. A few studies associated nutritional risk and marital status, but other studies observed some association with weight loss and sarcopenia. Alexandre et al. (40) described an association between absence of marital life and sarcopenia to older adults who participated of the Health, Well-being, and Aging study in 2010 (SABE study), while Góes et al. (41) related that unmarried men lose weight at a higher rate, showing a higher risk of sarcopenia for older adults living in Southern Brazil (EpiFloripa Study).

Household income was another predictor of nutritional risk, corroborating with other studies found in the scientific literature. Rossi et al. (42) states that insufficient income gets in the way of obtaining enough food to meet physiological and psychological needs, which consequently may promote food insecurity, highlighting the importance of identifying those at risk, in order to demand greater efforts to implement public policies to reduce social inequities, and thus contribute for the prevention, maintenance, and promotion healthy aging (43, 44). Based on data from the NHS-BIGS, the monthly income of Brazilian individuals aged 80 and over was R$ 2087.00 (USD 417.40) ± R$ 4358.73 (USD 871.75) (37), in accordance as observed in the present study. In general, the low income of Brazilians individuals aged 80 and over has been described in some studies (45, 46), however, the discrepancies observed in the incomes could be explained by the region in which the studies were conducted. The studies that described long-lived people with higher income levels (2 to 3 minimum-wages) were carried out in the municipality of Marilia, a municipality in the state of São Paulo (47), in the south of state of Minas Gerais (48) and the Brazilian Federal District (49), while the studies that observed an average income of 1 minimum wage were conducted in the city of Recife, state of Pernambuco (50). The participants of the present study live in São Paulo, one of the richest states in the federation and has better health services that can contribute to better living conditions when compared to other regions of the country. In addition, the increase in the older adults population creates numerous challenges, influencing consumption, the transfer of benefits, taxes, pensions, jobs, family organization and the health sector. Almost all of the individuals aged 80 and over participants of this study declared that their income came from retirement and/or a pension (94.2%, data not shown), which highlights the importance of the federal government benefits for Brazilian individuals aged 80 and over.

Taken together, our findings are in accordance with other studies that show a low purchasing power is one of the characteristics of the older population in Brazil and social benefits are the main income source (46, 47, 51). This national scenario requires the state to formulate and implement public policies to assist this population, especially associated with social security. This issue deserves to be widely and carefully discussed since the growing social security deficit is a consequence of the model in which the contributions paid by active workers are intended to cover the costs of benefits for retirees and pensioners (52).

There was an association between nutritional risk and female sex in this study, a very common finding in studies with older adults (53–56). In a longitudinal study conducted with community-dwelling older adults in Spain (57) association was observed between nutritional risk and female sex, as well as with the physical and psychological domains of the WHOQOL-BREF.

The feminization of old age is a phenomenon highlighted by gerontological literature and there is a predominance of women in the Brazilian older old population, with some small variations in the proportions among regions (37, 38, 45, 46, 58–64). Ferreira (58) showed that 60,4% of individuals aged 80 and over including in Health, Wellbeing and Aging Study (SABE), under the coordination of the Pan American Health Organization, were women. The feminization of aging is not an exclusively Brazilian phenomenon, but is also observed elsewhere in the world and needs attention (37, 46, 65–68). Collerton et al. (67) studied individuals aged 80 and over in the United Kingdom and reported that 59.9% of the women. The same was observed in the Niklasson et al. (66) study with older adults in Sweden, with 79.4% of women. Several factors may be associated with this increased expectancy for women, such as regular medical care, observed mainly in women aged 80 and over (69). Porciúncula et al. (50) reported that older adult men are more exposed to acute lethal diseases, such as heart ischemia. The predominance of the female population among the individuals aged 80 and over has important repercussions on the demands for public policies, since various studies show that despite living longer, women are susceptible to developing functional disabilities and multiple health problems and live with them for longer (37, 70).

The population aging may be considered a successful episode for any society, but it can also be a challenge to ensure, to these individuals to gain years of life, but also quality to live these additional years (71).

Noteworthy no association with nutritional risk and number of teeth has been detected, all participants of the present study self-reported with edentulism or severe tooth loss (IQR 0–1, Table 1) and the use of dental prostheses. This data could be justified by the whole history of the Brazilian individual aged 80 and over and their access to health services, in which the traditional model exposed them to a mutilating practice that solved pain on a one-off basis (72). Unfortunately, studies that address the oral health condition of the Brazilian population are scarce, despite tooth loss harming the quality

of life and health (73–75). According to the National Health Survey (PNS), 75% of Brazilian older adults self-reported the use of some type of dental prosthesis (76), and the prevalence of tooth loss among older adults remained high (77). Thus, the improvement in the oral health conditions of Brazilian older adults remains a challenge to public health, which needs to emphasize preventive measures to avoid total edentulism, as well as planning the prosthetic rehabilitation of tooth loss.

Although cluster analysis is a commonly useful method for characterization of data sets, mainly when there is no previous knowledge about the data correlation, this analysis has not detected any associations between clusters and nutritional risk. Thus, this method was used in the initial stage of the predictive model's construction, allowing to rank QoL scores and sociodemographic characteristics in predicting nutritional risk. Random Forest was the method that presented the best performance for predicting nutritional risk (higher accuracy, sensitivity, and specificity). The comparison between RF and XBGoost model allowed us to verify the consistency among the variables which are most important to predict nutritional risk, and the performance of these ensemble methods. Several set models have been tested by both algorithms to improve predictive ability, and they have been frequently used with good results in the healthcare field (78–80).

It was very complicated to compare the results of the present study with previous studies found in scientific literature, due to the scarcity of studies with a similar proposal that considered the use of machine learning methods to predict nutritional risk in individuals aged 80 and over. Despite this, Lee et al. (81) used five algorithms to identify the factors that affect the health-related quality of life of older adults with chronic diseases, including RF. The authors demonstrated that the stepwise logistic regression (SLR) model was the most accurate (0.93), and the most important predictors were income, diagnosis of chronic disease, depression, discomfort, and perceivedhealth status. Prati (82) investigated the variables correlates of QoL, such as happiness, and life satisfaction in European adults aged 50 and over, using machine learning techniques, and concluded that the most important categories were physical health and subjective life circumstances. In addition, the most important categories correlating with happiness were sociodemographic factors, country of residence, and psychological variables (82).

In the present study, physical condition (evaluated by WHOQOL-BREF and handgrip) and cognitive performance (evaluated by MMSE) were the main predictors of nutritional risk by RF analysis. However, when WHOQOL-OLD was used as a predictor, the variables of muscle strength, income, and cognition presented higher levels of influence. Alonso et al. (83) suggested that lower handgrip strength is correlated with muscle strength in the lower limbs, which could be used as a proxy indicator of overall strength for screening older adults, since muscle weakness decreases functional capacity, which, in turn, can lead to dependence. In a recent study, Peterson et al. (84) provided initial evidence of age acceleration in older people with lower handgrip strength and loss of strength over time. Taken together, these findings suggest that the maintenance of muscle strength positively influences healthy aging and QoL.

Cognition appeared as one of the main predictors in both models used in the present study. According to Kwan et al. (85), dietary pattern is a modifiable risk factor associated with cognitive frailty. Neuroinflammation and oxidative stress are some of the mechanisms that affect the cognitive capacity of older adults, and weight loss, reduced energy, and reduced nutrient intake are associated with changes in body composition, physical abilities, and increased risk of frailty.

The main clinical implications are related to the importance of conducting multidimensional studies in an attempt to identify the physical, psychological, and social conditions, as well as their connections. Health professionals must be attentive to detect the decline of physical and cognitive capacity, as well as nutritional risk of individuals aged 80 and over.

Nutritional risk is a modifiable condition that affects quality of life. Older adults with cognitive and physical frailty who show signs of malnutrition need to be monitored, since interventions should be implemented to prevent worsening of the situation, and even to reverse it altogether. Another important point regards results that reinforce the need to implement social programs for vulnerable families with older adults, contributing to their access to healthy foods. In addition, the findings show the fundamental importance of specific, interdisciplinary interventions to preserve the independence and autonomy of individuals aged 80 and over.

5 Limitations

It is important to mention that, although this is a multicenter study, data were collected in convenient locations, and it was only possible to obtain a small, non-probabilistic sample size. Therefore, there is a selection bias in the sample, since the participants had a specific sociodemographic (as ethno-racial features; schooling; number of teeth) profile and may not represent the general characteristics of the Brazilian population and is not representative of individuals aged 80 or over. In addition, individuals aged 80 and over can present sensory alterations, mainly cognitive, auditory, and visual, which could influence their ability to remember and self-report their health conditions and QoL. The exclusion of other factors in the tests of predictors set evaluated in the present study may have also influenced its outcomes. Finally, the findings do not imply causality due to the cross-sectional nature of the study.

6 Final considerations

Our findings demonstrate that for individuals aged 80 and over including in the present study, several factors can predict nutritional risk, such as lower muscle strength, worse cognitive ability, lower income, female sex, and unmarried status. However, there was no significant association between nutritional risk and quality of life (QoL) and cannot be representative for all individuals aged 80 or over. In addition, the study showed that the random forest (RF) analysis method presented better accuracy, sensitivity, and specificity when compared to other ensemble methods, for the sample of the study. This suggests that machine learning could be a useful tool for predicting nutritional

risk for individuals aged 80 and over, but need to be confirm if it would be also useful for other individuals aged 80 or over. Overall, the study highlights the importance of assessing nutritional risk in individuals aged 80 and over and identifying the associated factors to contribute to development interdisciplinary interventions proposals.

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 Research Ethics Committee of São Judas Tadeu University (CAAE 49987615.3.0000.5404 and approval number 09069419.8.0000.0089). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AA, MB, AM-L, and RA: conception and design of the research, conceptualization, project administration, methodology, resources, and supervision. GB, VS, AA, MB, and RA: design of the paper, writing, and reviewing of manuscript. VS, AA, and GB: interpretation and analysis of the data. GB, GM, and DS: acquisition of the data. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1183058/full#supplementary-material

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The role of comprehensive geriatric assessment in the identification of different nutritional status in geriatric patients: a real-world, cross-sectional study

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Background: Malnutrition is an often unrecognized problem, but it is common in older patients and leads to adverse outcomes.

Aims: The purpose of this study is to analyze the prevalence of the risk of undernutrition in elderly patients and the correlation between CGA and nutritional status, and to determine the nutritional status of elderly patients.

Methods: This is a real-world cross-sectional study of continuously enrolled elderly patients aged 65years or older with a complete CGA database. CGA inventory was prepared by compiling and screening general information, body composition and blood biochemical results. MNA was also conducted for each elderly patient to screen for malnutrition. A multivariable logistic regression analysis was used to determine the association between the CGA and nutritional assessment.

Result: The average age of the 211 selected elderly patients (160 men and 51 women) was 79.60 ± 9.24 years, and their ages ranged from 65 to 96 years. After controlling for confounders, patients with a history of PUD (OR = 2.353, $p = 0.044$), increased ADLs & IADLs scores (OR = 1.051, $p = 0.042$) or GDS scores (OR = 6.078, $p < 0.001$) may increase the incidence of the risk of undernutrition respectively, while an increase in BMI (OR = 0.858, $p = 0.032$) may lower the incidence of malnutrition risk. In addition, increased ADLs & IADLs scores (OR = 1.096, $p = 0.002$) or GDS scores (OR = 11.228, $p < 0.001$) may increase the incidence of undernutrition. However, increased MMSE (OR = 0.705, $p < 0.001$), BMI (OR = 0.762, $p = 0.034$), UAC (OR = 0.765, $p = 0.048$) and CC (OR = 0.721, $p = 0.003$) may decrease the incidence of undernutrition, respectively.

Conclusion: The study found that the prevalence of risk of undernutrition in elderly patients was the highest. Risk of undernutrition was independently associated with peptic ulcer disease, ADLs & IADLs, GDS and BMI. However, we found that when the nutritional status reached the level of undernutrition, it was related to more factors, including ADLs & IADLs, MMSE, GDS, BMI, UAC and CC. Determining the level of malnutrition through CGA may help to prevent and intervene malnutrition as early as possible.

KEYWORDS

comprehensive geriatric assessment, nutritional status, Mini nutritional assessment, real-world, multivariable logistic regression analysis

1 Introduction

Malnutrition is a chronic and often imperceptible process and identifying it at an early stage is crucial to reduce adverse outcomes (1). There are many related factors to malnutrition during the aging process, which may seriously affect the health status of the elderly (2). In addition, as people grow older, they are more likely to suffer from chronic diseases such as heart disease, cancer and diabetes, which will increase the risk of cognitive decline, weakness and disability. As is well known, improving nutrition will bring tangible benefits to the elderly, and many age-related diseases and conditions can be prevented, adjusted or improved by increasing nutritional levels (3). However, malnutrition in elderly patients has often been overlooked so far, so there is an urgent need to identify methods for malnutrition in order to prevent and treat it in a timely manner.

Comprehensive Geriatric Assessment (CGA) is a multi-dimensional and multidisciplinary diagnosis and treatment process, which assesses the physical diseases, psychological and functional abilities of the elderly; identifies high-risk patients; and further guides the disease prevention, treatment and follow-up (4, 5). It may also help to formulate long-term diagnosis and treatment plans (6). One study on health workers has shown that the CGA is related to nutritional indicators (7). In clinical practice, it has been found that elderly patients are willing to accept CGA, which may help identify the nutritional status of the elderly in clinical practice.

In this study, we hypothesized that CGA was related to nutritional status. If the hypothesis holds, we can use CGA to identify the different nutritional status of elderly patients, which can lead to early prevention and treatment.

2 Methods

2.1 Participants

This is a real-world cross-sectional study. We conducted an experimental study on consecutive outpatients and inpatients in the cadre ward department of the First Hospital of Jilin University from June 2020 to June 2021. The inclusion criteria were the elderly patients who had a complete CGA database and were 65 years old or older. The exclusion criteria were patients younger than 65 years old who did not participate in CGA or whose data were incomplete. The study was in line with the Helsinki Declaration and was approved by the Ethics Committee of the First Hospital of Jilin University (2021–478).

2.2 The process of CGA

The personnel conducting CGA receive specialized training in scale evaluation and instrument inspection (8). The detailed CGA assessment tools vary depending on institutions, medical environments and needs, but the definition of CGA is consistent, including the assessment of needs in multiple fields and the development of treatment plans (9). The measurement process of this study was personally tested by the same physician from the Cadre Ward Department of the First Hospital of Jilin University. Firstly, routine examinations should be conducted on enrolled patients. The collection of general information by face-to-face inquiry includes gender, age, educational background, smoking history, drinking history, sports and chronic diseases, such as cardiovascular disease (CVD), diabetes and peptic ulcer disease (PUD). The evaluation of the scale includes quality of daily life, cognitive test and geriatric depression scale. The evaluator dictates the survey content and records the patient's answers. The next step for human body composition testing includes body mass index (BMI), upper arm circumference (UAC), calf circumference (CC), body fat percentage, and visceral fat area. Collect fasting venous blood from all patients the morning after admission and send them to the Laboratory Department of the First Hospital of Jilin University. After the results are reported, collect data on hemoglobin, albumin, prealbumin, triglycerides and low-density lipoprotein cholesterol (LDL-C). The experimental personnel collect and organize the data, and a total of 211 valid and complete data were obtained.

2.3 Detailed content of CGA

2.3.1 General information

Collect personal information of patients, including gender, age, educational background, smoking history, drinking history, exercise (It refers to the patient walks for a total of more than 1 h per day and more than 5 days per week.) and chronic diseases (It refers to non-communicable chronic diseases, most commonly diabetes, obesity, metabolic syndrome, chronic kidney disease, cardiovascular disease, cancer and chronic respiratory diseases) (10). The patient has been diagnosed with the disease in the past and is in the process of disease monitoring and treatment.

2.3.2 Quality of daily living

The living ability of elderly people was measured with the activities of daily living and instrumental activities of daily living (ADLs & IADLs). The ADLs & IADLs are important to older adults (11). ADLs includes physical care activities. These activities are essential for living in the social world. They enable people to obtain basic survival and well-being, such as eating, dressing, bathing and toileting; IADLs includes activities of daily life in families and communities, which usually are more complex than ADLs, such as making phone calls, taking medicine, financial management, purchasing groceries and housekeeping services (12). When the total score is greater than 16, it indicates that the patient has functional decline to varying degrees.

2.3.3 Cognitive tests

Cognitive dysfunction was assessed using the Mini Mental State Examination (MMSE), a widely used cognitive test (13). The total MMSE score ranges from 0 to 30 (14), which consists of 30 items, including orientation tests, short-term memory and recall tests, attention and computing ability tests, naming tests, oral command tests, judgment tests and repeated pentagons tests (15). Cognitive impairment is evaluated based on differences in educational levels. A score of less than 18 was used to define cognitive impairment in participants without any formal education, less than 21 for those with six or fewer years of education, and less than 25 for those with more than six years of education (16, 17). All patients in this article have more than 6 years of education, the cut-off point for MMSE is 24, and a score of 24 or lower indicates cognitive impairment, which has been widely used as a screening tool in epidemiological research (17, 18).

2.3.4 Geriatric depression

Depression was determined using the 30-item Geriatric Depression Scale (GDS) (19), which is a standardized self-reported questionnaire consisting of 30 dichotomous questions. Sum of the 30 items produced a score ranging from 0 to 30, with greater values indicating increased severity. A GDS score of 11 or above is considered depression (20, 21). One study on depression in elderly people in Amsterdam showed that the GDS-30 scale with a critical value of 11 is the most effective in screening for depression in terms of sensitivity and specificity for screening for severe and mild depression (22). And other studies have shown this cutoff has been shown to have 100% sensitivity and 84% specificity with other depression criteria (23).

2.3.5 Body composition

Height and weight were measured according to clinical standards. BMI is calculated by dividing weight (kg) by height (m^2).

Measure the UAC at the level of the thickest part of the biceps muscle when the upper arm drops naturally (accurate to 0.1 cm). Participants stood with their feet shoulder-width apart and measured the CC around the most prominent part of the gastrocnemius muscle (accurate to 0.1 cm). During the experiment, we tried our best to appease the patients and encourage them to cooperate with our measurements. We strictly followed the experimental steps and methods when measuring height, weight, UAC, and CC, proficiently used measuring instruments, accurately read, and conducted three measurements to minimize possible measurement errors and ensure the accuracy and reliability of the measurement results.

Body fat percentage and visceral fat area were measured by bioelectrical impedance analysis (BIA) using the Inbody S10 (Biospace, Seoul, Korea) (24).

2.3.6 Blood biochemical results

Blood biochemical indicators such as hemoglobin, albumin, prealbumin, triglycerides, and LDL-C were obtained from the test results in electronic medical record.

2.4 Nutritional assessment

Nutritional status was assessed using the Mini Nutritional Assessment (MNA) questionnaire, which included 18 questions related to important factors of nutritional status, including food intake, weight loss, mobility, whether there is acute stress or disease, neurological problems, drug intake, BMI, UAC and CC. The highest score is 30 points. A score of 24 or more indicates a good nutritional status, a score between 23.5 and 17 indicates a risk of undernutrition, and a score below 17 indicates undernutrition (25). According to the MNA score results, the experiment was divided into three groups: normal nutrition group for scores ≥24, risk of undernutrition group for scores 17–23.5, and undernutrition group for scores <17.

2.5 Data analysis

The SPSS/WIN 23.0 software (IBM Corp., Armonk, NY, United States) and GraphPad Prism 8 (GraphPad Prism Software Inc., San Diego, CA, United States) were used for the statistical analysis. The Kolmogorov–Smirnov test was used to test the normality of the continuous variables. According to the distribution characteristics of data, continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), and Student's t-test or Mann–Whitney U-test was used to test the difference between the two groups. The categorical variables were expressed as absolute values and percentages, and chi-squared test were used to test the differences between the two groups. A multivariable logistic regression analysis was used to determine the correlation between PUD, ADLs & IADLs, MMSE, GDS, BMI, UAC, CC and MNA. Variables with $p < 0.05$ were selected for the multivariate analysis. The values of $p < 0.05$ were considered statistically significant.

3 Results

3.1 Baseline data of general characteristics, chronic diseases, ADLs & IADLs, MMSE and GDS

The average age of the 211 selected elderly patients (160 men and 51 women) was 79.60 ± 9.24 years, and their ages ranged from 65 to 96 years. As shown in Table 1, among the elderly patients, the incidence rate of undernutrition risk is the highest (43.60%), and older patients have poorer nutritional status. Among them, the median age of normal nutritional patients ($n = 85$, 40.28%) was 76.00, the median age of patients at risk of undernutrition ($n = 92$, 43.60%) was 81.50 and the median age of undernutritional patients ($n = 34$, 16.11%) was 90.00. Compared to patients with normal nutrition, the number of malnourished patients who exercise regularly is smaller. Moreover, as the nutritional status worsens, the ability of daily living of the elderly gradually declined, and the prevalence of related chronic diseases also gradually increased, especially CVD, PUD, depression and cognitive disorders ($p < 0.05$).

3.2 Baseline data of the anthropometric parameters and the blood biochemical indicators

As shown in Table 2, with the gradual decrease of BMI, UAC and CC, the nutritional status gradually deteriorates. Compared with elderly patients with normal nutrition, patients at risk of undernutrition and undernutrition have lower hemoglobin, albumin, prealbumin and triglyceride ($p < 0.05$).

3.3 Multivariable logistic regression analysis for risk of undernutrition.

As shown in Table 3 and Figure 1, we analyzed the relationship between factors in CGA and risk of undernutrition. In model 1, after adjusting the age and the type of chronic diseases, patients with PUD were 2.353 times more likely to be at risk of undernutrition than those without PUD (95%CI: 1.024–5.408, $p = 0.044$). The probability of developing the risk of undernutrition increases by 5.1% for each

TABLE 1 Baseline data of general characteristics, chronic diseases, ADLs & IADLs, MMSE and GDS.

Variable	Normal Nutrition (85, 40.28%)	Risk of Undernutrition (92, 43.60%)	*p*	Undernutrition (34, 16.11%)	*p*
Gender, male, *n* (%)	70 (82.4)	66 (71.7)	0.094	24 (70.6)	0.155
Age, median (IQR), years	76.00 (68.00, 86.50)	81.50 (73.25, 88.00)	0.030	90.00 (87.50, 92.00)	0.001
Education background, *n* (%)			0.186		0.212
College degree or above	71 (83.5)	83 (90.2)		25 (73.5)	
Less than a college degree	14 (16.5)	9 (9.8)		9 (26.5)	
Smoke, *n* (%)	31 (36.5)	39 (42.4)	0.421	13 (38.2)	0.857
Drink, *n* (%)	35 (41.2)	39 (42.4)	0.870	15 (44.1)	0.769
Exercise, *n* (%)	59 (69.4)	57 (62.0)	0.297	11 (32.4)	<0.001
Types of chronic diseases, *n* (%)			0.007		0.024
≥3	24 (28.2)	44 (47.8)		17 (50.0)	
<3	61 (71.8)	48 (52.2)		17 (50.0)	
CVD, *n* (%)	31 (36.5)	47 (51.1)	0.050	20 (58.8)	0.026
Diabetes, *n* (%)	26 (30.6)	28 (30.4)	0.982	13 (38.2)	0.422
PUD, *n* (%)	11 (12.9)	26 (28.3)	0.012	10 (29.4)	0.033
ADLs & IADLs, median (IQR)	16.00 (14.00, 19.50)	20.00 (14.00, 28.00)	0.002	27.25 (20.00, 43.00)	<0.001
MMSE, median (IQR)	27.00 (25.00, 29.00)	27.00 (24.00, 28.00)	0.056	23.00 (19.00, 25.25)	<0.001
GDS, median (IQR)	7 (8.2)	36 (39.1)	<0.001	20 (58.8)	<0.001

IQR, interquartile range; CVD, cardiovascular disease; PUD, peptic ulcer disease; ADLs & IADLs, Activities of daily living and instrumental activities of daily living; MMSE, Mini-mental State Examination; GDS, Geriatric Depression Scale.

TABLE 2 Baseline data of the anthropometric parameters and the blood biochemical indicators.

Variable	Normal Nutrition (85, 40.28%)	Risk of Undernutrition (92, 43.60%)	*p*	Undernutrition (34, 16.11%)	*p*
BMI, median (IQR), kg/m^2	24.80 (23.05, 26.65)	24.00 (22.50, 25.50)	0.006	22.60 (24.80, 27.78)	<0.001
UAC, median (IQR), cm	27.40 (26.10, 28.80)	26.35 (25.40, 27.95)	0.004	24.80 (22.40, 26.03)	<0.001
CC, mean ± SD, cm	34.08 ± 3.77	32.40 ± 3.05	0.001	29.47 ± 2.90	<0.001
Body fat percentage, mean ± SD, %	30.32 ± 7.24	29.69 ± 7.52	0.570	30.07 ± 8.39	0.872
Visceral fat area, median (IQR), cm^2	80.60 (64.00, 108.50)	79.10 (61.75, 89.95)	0.288	72.30 (55.70, 106.33)	0.436
HGB, mean ± SD, g/L	138.25 ± 19.93	130.12 ± 19.92	0.007	125.47 ± 18.30	0.002
Alb, median (IQR), g/L	38.40 (36.65, 42.05)	35.95 (34.60, 37.88)	<0.001	35.75 (32.73, 37.23)	<0.001
Prealbumin, median (IQR), g/L	0.23 (0.19, 0.29)	0.21 (0.18, 0.26)	0.120	0.19 (0.14, 0.26)	0.006
TC, median (IQR), mmol/L	1.41 (0.99, 1.94)	1.16 (0.83, 1.61)	0.011	1.03 (0.58, 1.67)	0.011
LDL-C, mean ± SD, mmol/L	2.93 ± 0.91	2.87 ± 0.85	0.660	2.75 ± 1.03	0.345

BMI, body mass index; IQR, interquartile range; UAC, upper arm circumference; CC, calf circumference; HGB, hemoglobin; Alb, albumin; TC, triglycerides; LDL-C, low density lipoprotein cholesterol.

1- point increase in ADLs & IADLs (95%CI: 1.002–1.102, $p = 0.042$). In addition, depressed patients are 6.078 times more likely to suffer from the risk of undernutrition than those without depression (95%CI: 2.408–15.338, $p < 0.001$); In model 2, after adjusting for age, types of chronic diseases, PUD, ADLs & IADLs and GDS, for every 1 point increase in BMI, the elderly patients were 14.2% less likely to be at risk of undernutrition (95%CI: 0.746–0.987, $p = 0.032$). The area under the receiver operating characteristic of comprehensive PUD, ADL, GDS and BMI is 0.756.

3.4 Multivariable logistic regression analysis for undernutrition

As shown in Table 4 and Figure 2, we analyzed the relationship between factors in CGA and undernutrition. In model 1, after adjusting the age, exercise and the type of chronic diseases, the probability of undernutrition increases by 9.6% for each 1-point increase in ADLs & IADLs (95%CI: 1.035–1.161, $p = 0.002$), the probability of undernutrition decreased by 29.5% for each 1 value

TABLE 3 Multivariable logistic regression analysis for the risk of undernutrition.

Variates	Crude		Adjusted	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Model 1				
PUD	2.650 (1.216, 5.776)	0.014	2.353 (1.024, 5.408)	0.044
ADLs & IADLs	1.063 (1.021, 1.107)	0.003	1.051 (1.002, 1.102)	0.042
GDS	7.163 (7.973, 17.259)	<0.001	6.078 (2.408, 15.338)	<0.001
Model 2				
BMI	0.842 (0.743, 0.955)	0.007	0.858 (0.746, 0.987)	0.032
UAC	0.835 (0.733, 0.952)	0.007	0.869 (0.752, 1.005)	0.059
CC	0.865 (0.790, 0.948)	0.002	0.944 (0.852, 1.047)	0.276
HGB	0.979 (0.964, 0.995)	0.009	0.985 (0.967, 1.004)	0.119
Alb	0.878 (0.813, 0.948)	0.001	0.940 (0.861, 1.026)	0.168
TC	0.669 (0.439, 1.022)	0.063	0.749 (0.465, 1.206)	0.234

PUD, peptic ulcer disease; ADLs & IADLs, Activities of daily living and instrumental activities of daily living; GDS, Geriatric Depression Scale; BMI, body mass index; UAC, upper arm circumference; CC, calf circumference; HGB, hemoglobin; Alb, albumin; TC, triglycerides; Model 1: Adjusted for age, types of chronic diseases; Model 2: Adjusted for age, types of chronic diseases, PUD, ADLs & IADLs, GDS.

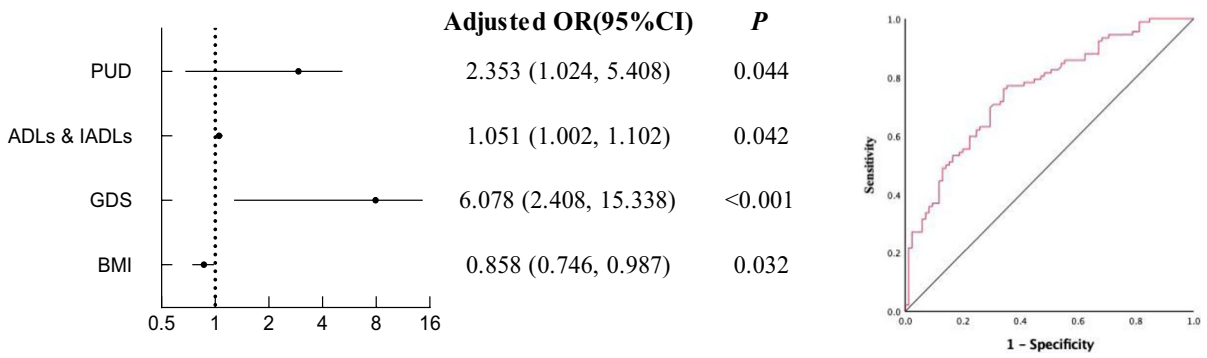

FIGURE 1
Multivariable logistic regression analysis for risk of undernutrition and the receiver operating characteristic of comprehensive PUD, ADL, GDS and BMI.

increase in MMSE (95%CI: 0.592–0.839, $p < 0.001$). In addition, depressed patients are 11.228 times more likely to suffer from undernutrition than those without depression (95%CI: 3.585–35.165, $p < 0.001$); In model 2, after adjusting for age, exercise, types of chronic diseases, CVD, PUD, ADLs & IADLs, MMSE and GDS, for each 1-point increase in BMI, the probability of undernutrition decreased by 23.8% (95%CI: 0.593–0.979, $p = 0.034$), for each 1-point increase in UAC, the probability of undernutrition decreased by 23.5% (95%CI: 0.587–0.998, $p = 0.048$), or for each 1-point increase in CC, the probability of undernutrition decreased by 27.9% (95%CI: 0.582–0.894, $p = 0.003$). The area under the receiver operating characteristic of comprehensive ADLs & IADLs, MMSE, GDS, BMI, UAC and CC is 0.753.

4 Discussion

Our study is the first to report the identification of different nutrition in elderly patients by CGA in the real world. Our results showed that many parameters of CGA are related to nutrition. In analyzing this relationship, we found that PUD, ADLs & IADLs, GDS, BMI, MMSE, UAC, CC were independently associated with nutritional status in elderly patients. The area under the ROC curve of the combined indicators under different nutritional states is greater than 0.7, therefore, the combination of corresponding indicators has certain diagnostic value for different nutritional states.

Scholars at home and abroad have been keen on the study of malnutrition and have found many factors related to malnutrition. Previous studies have demonstrated that PUD is associated with malnutrition (26). People with peptic ulcers such as duodenal ulcers often experience hunger or nocturnal abdominal pain, while people with gastric ulcers often experience postprandial abdominal pain, nausea, vomiting and weight loss (27).

Several large sample studies on the elderly have shown that depression is also related to malnutrition and these two diseases are common among the elderly in China (28, 29). And depression is a common mental illness characterized by decreased appetite, self-care, apathy and physical weakness. These characteristics may well explain the relationship between malnutrition and depression (30). In addition, the ability of daily living in elderly patients gradually

TABLE 4 Multivariable logistic regression analysis for undernutrition.

Variates	Crude		Adjusted	
	OR (95%CI)	*P*	OR (95%CI)	*p*
Model 1				
CVD	2.488 (1.103, 5.613)	0.028	1.677 (0.684, 4.342)	0.287
PUD	2.803 (1.060, 7.411)	0.038	2.598 (0.807, 8.359)	0.109
ADLs & IADLs	1.128 (1.074, 1.185)	<0.001	1.096 (1.035, 1.161)	0.002
MMSE	0.690 (0.593, 0.804)	<0.001	0.705 (0.592, 0.839)	<0.001
GDS	15.918 (5.673, 44.666)	<0.001	11.228 (3.585, 35.165)	<0.001
Model 2				
BMI	0.721 (0.609, 0.853)	<0.001	0.762 (0.593, 0.979)	0.034
UAC	0.651 (0.533, 0.795)	<0.001	0.765 (0.587, 0.998)	0.048
CC	0.697 (0.601, 0.808)	<0.001	0.721 (0.582, 0.894)	0.003
HGB	0.968 (0.947, 0.989)	0.003	0.990 (0.960, 1.021)	0.536
Alb	0.799 (0.710, 0.898)	<0.001	0.931 (0.789, 1.099)	0.399
Prealbumin	0.000 (0.000, 0.049)	0.005	0.000 (0.000, 14.711)	0.141
TC	0.644 (0.360, 1.153)	0.139	0.962 (0.408, 2.269)	0.930

CVD, cardiovascular disease; PUD, peptic ulcer disease; ADLs & IADLs, Activities of daily living and instrumental activities of daily living; MMSE, Mini-mental State Examination; GDS, Geriatric Depression Scale; BMI, body mass index; UAC, upper arm circumference; CC, calf circumference; HGB, hemoglobin; Alb, albumin; TC, triglycerides; Model 1: Adjusted for age, exercise, types of chronic diseases; Model 2: Adjusted for age, exercise, types of chronic diseases, CVD, PUD, ADLs & IADLs, MMSE, GDS.

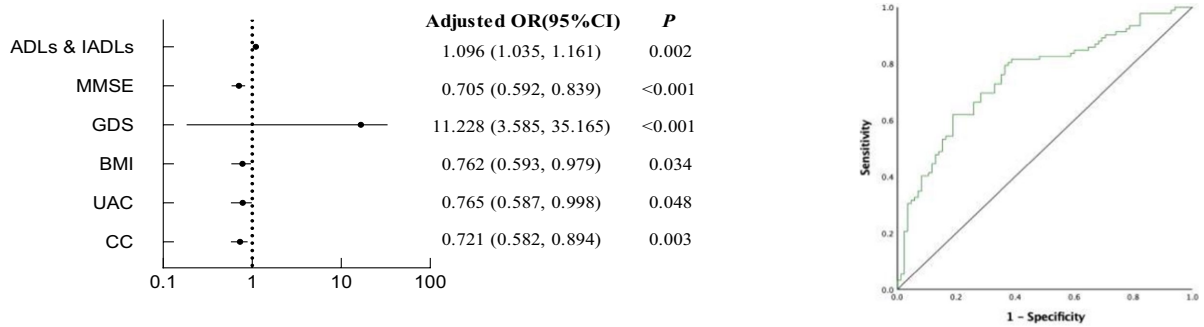

FIGURE 2
Multivariable logistic regression analysis for undernutrition and receiver operating characteristic of comprehensive ADLs & IADLs, MMSE, GDS, BMI, UAC and CC.

decreases with age, and it has been reported that poor ability of daily living is associated with malnutrition (31). Others have found a link between nutritional status and cognition (32), the decline of cognitive function may affect the nutritional status, leading to a reduction in nutrient intake, and the resulting weight loss and malnutrition, which in turn may worsen cognitive function (33). Another important aspect is that there are many important indicators involved in nutritional assessment, such as BMI, UAC and CC (34, 35), which are valuable information for common nutrition-related diseases (36). Therefore, factors related to chronic diseases and body composition can affect the nutritional status of patients, and malnutrition can in turn affect the course of disease (37).

As age advances, the elderly are more likely to suffer from malnutrition or chronic energy deficiency, due to the deterioration of various physical functions, economic dependence and social isolation. Several small studies have demonstrated that the prevalence of malnutrition in the elderly ranges from 14 to 52% (38–40). It is well known that malnutrition is an underrecognized and undertreated problem throughout the health care system. Clinically, hospital malnutrition may lead to an increase in the number and severity of disease complications by increasing morbidity and mortality (41). The objective of this study was to analyze the factors of undernutrition and risk of undernutrition in order to identify different levels of nutrition. Through the identification of different nutritional conditions, early prevention and appropriate intervention can be carried out.

Previous studies have also analyzed the correlation between CGA parameters and nutrition. One of the cross-sectional studies of health professionals showed that CGA was associated with nutrition-related factors such as sarcopenia, sarcopenic dysphagia, cachexia. The appropriate care plan, including rehabilitation and nutrition management are provided according to the patient's condition (7).

Another study of older adults showed that age, drinking, chronic diseases, depression, BMI, ADLs & IADLs, number of recent falls, cognitive impairment, insomnia, low hemoglobin and albumin levels were independently associated with malnutrition. CGA can provide detailed information of elderly patients and is of great value for nutritional assessment (42). However, different from previous studies, this study was a real-world cross-sectional study that included elderly patients in outpatients and inpatients over a continuous period of time. In this study, we not only analyzed the general characteristics, scales and blood biochemical indicators of patients, but also included body composition factors such as UAC, CC, body fat percentage and visceral fat area. More importantly, this study specifically analyzed the different factors in CGA related to different levels of nutrition, so as to more specifically identify the current level of malnutrition in addition to more targeted prevention and treatment. This is a real-world cross-sectional study aimed at understanding the real living conditions of elderly patients and examining the relevance of geriatric diseases to the field of geriatric assessment, contributing to the prevention of many diseases and reducing the growing disease burden of the elderly.

There are some limitations to consider in our study. Firstly, since the patients included in our study are all patients in the cadre ward of the First Hospital of Jilin University, and these patients are groups with relatively high educational level, socioeconomic status and healthcare treatment level, and there is no significant difference. Considering that the impact on the experiment is small, there is not too much elaboration on this part of mixed factors in the experiment. In the future experiment, multi center, large sample research is very valuable, and excluding the possible confounding factors mentioned above may have more generalizability for the experimental results. Secondly, because this experiment is a small sample cross-sectional study, the results can only show the correlation between various factors and nutrition, which limits the ability to infer the causal relationship between malnutrition and observed results. Therefore, large sample cohort study in the future is very worthwhile and valuable and is very meaningful for malnutrition identification. Thirdly, based on clinical experience and literature review, it has been learned that medication use in the elderly may have an impact on their nutritional status. However, in this experiment, we did not include multiple medication use in the elderly. It is necessary to enrich the CGA database in future studies, such as including factors related to multiple medication use. Our CGA only included a small number of factors. In the future, it is necessary to further enrich the CGA content to have a more comprehensive understanding of nutrition-related factors in elderly patients.

5 Conclusion

The study found that the prevalence of risk of undernutrition in elderly patients was the highest. Risk of undernutrition was independently associated with peptic ulcer disease, ADLs & IADLs, GDS and BMI. However, we found that when the nutritional status reached the level of undernutrition, it was related to more factors, including ADLs & IADLs, MMSE, GDS, BMI, UAC and CC. Determining the level of malnutrition through CGA may help to prevent and intervene malnutrition as early as possible. And we found that the combination of corresponding indicators has significant diagnostic value for different nutritional states. It is suggested that the elderly should take appropriate exercise according to their physical conditions, improve their quality of life, improve their mood, eat high protein, low salt and low-fat food and regularly go to community hospital for medical treatment.

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.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Hospital of Jilin University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YJ, JL, and XL drafted the manuscript. YJ and XL revised the manuscript. KZ, DY, and MC drew the figures. XL, DY, and HJ were responsible for the data acquisition. YMJ and JYL performed the data analysis. YJ, HJ, and MC performed the statistical analyses. YJ, KZ and JL conceived of and designed the study. All authors contributed to the article and approved the submitted version.

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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

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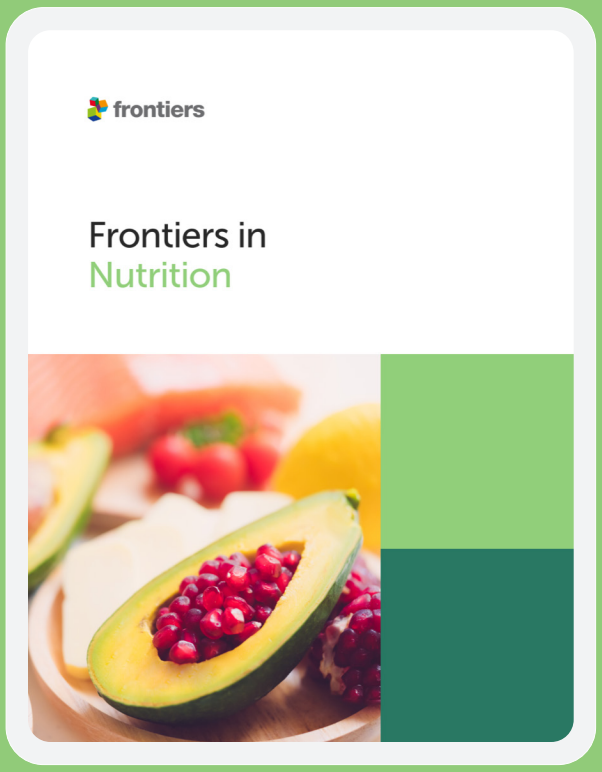

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