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Review

The Association between Dietary Inflammatory Index and Aging Biomarkers/ Conditions: A Systematic Review and Dose-Response Meta-Analysis

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Abstract

OBJECTIVES: We performed a current study to examine the association between dietary inflammatory index (DII) score and older age-related muscle conditions, including sarcopenia, low muscle mass, low muscle strength, frailty, and/or disability.

DESIGN: Systematic review and dose-response meta-analysis.

SETTING: A systematic literature search was performed using Scopus, PubMed/MEDLINE, and ISI Web of Science without limitation until October 04, 2022. Relative risk (RR) and 95% confidence interval (CI) were pooled by applying a random-effects model, while validated methods examined assess quality and publication bias via Newcastle-Ottawa Scale, Egger's regression asymmetry, and Begg's rank correlation tests respectively. A dose-response meta-analysis was conducted to estimate the RRs per 1-unit increment in DII scores.

PARTICIPANTS: Adults (≥18 years).

MEASURES: The risk of older age-related muscle conditions (sarcopenia, low muscle mass, low muscle strength, frailty, and/or disability).

RESULTS: Data were available from 19 studies with 68079 participants. Results revealed that a higher DII score was significantly related to an increased risk of sarcopenia (RR=1.50; 95% CI: 1.26, 1.79; I2=53.3%; p<0.001; n=10; sample size =43097), low muscle strength (RR=1.47; 95% CI: 1.24, 1.74; I2=6.6%; p<0.001; n=4; sample size =9339), frailty (RR=1.61; 95% CI: 1.41, 1.84; I2=0.0%; p<0.001; study=5; participant=3882) and disability (RR=1.41; 95% CI: 1.16, 1.72; I2=58.4%; p=0.001; n=5; sample size =13760), but not low muscle mass (RR=1.24; 95% CI: 0.98, 1.56; I2=49.3%; p=0.069; n=4; sample size =11222). Additionally, results of the linear dose-response indicated that an increase of one point in the DII score was related to a 14% higher risk of sarcopenia, 6% higher risk of low muscle mass, 7% higher risk of low muscle strength, and a 7% higher risk of disability in adults. Non-linear dose-response relationships also revealed a positive linear association between the DII score and the risk of sarcopenia ($P_{nonlinearity}$ = 0.097, $P_{dose\text{-}response}$<0.001), frailty ($P_{nonlinearity}$ = 0.844, $P_{dose\text{-}response}$=0.010) and disability ($P_{nonlinearity}$ = 0.596, $P_{dose\text{-}response}$=0.007).

CONCLUSION: Adherence to a pro-inflammatory diet was significantly associated with a higher risk of sarcopenia and other age-associated adverse effects such as low muscle strength, disability, and frailty. These results indicate a necessity to prioritize the reduction of pro-inflammatory diets to help promote overall older age-related muscle conditions.

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Key words: Dietary inflammatory index, older age-related muscle condition, meta-analysis, sarcopenia.

Introduction

Sarcopenia is defined as a progressive and generalized older age-related muscle condition that occurs with aging and/or immobility (1). It is characterized by the degenerative loss of skeletal muscle mass, muscle strength, and physical performance (1), leading to an increased risk of serious complications and hospitalizations (2). From a mechanistic perspective, the loss of skeletal muscle mass relates to the intricate balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). When rates of MPS are less than MPB over an extended period of time, a negative net muscle protein balance ensues, subsequently decreasing muscle mass (3, 4). Physical activity (e.g., resistance training (5), high-intensity interval training (6), walking-related physical activity (7), and aerobic exercise (8)) and nutritional strategies (e.g., protein ingestion (9)) can help improve and maintain skeletal muscle mass with advancing age which is crucial to increasing the independence and health span of older adults (4). However, chronic systemic inflammation (10), characterized by increased concentrations of mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-), and C-reactive protein (CRP) (11, 12), is implicated in net negative muscle protein balance and decreased muscle mass and strength in older adults. Elevated circulating concentrations of such pro-inflammatory markers may lead to dysbiosis and vascular dysfunction (13), subsequently impairing amino acid delivery to skeletal muscle. This condition leads to reduced MPS while increasing MPB, resulting in muscle weakness and atrophy. In addition, because of shared metabolic signaling pathways, aging-induced inflammation may contribute to impaired protein anabolism. Taken together, dysregulated anabolic signaling related to systemic inflammation is likely to be implicated

in the anabolic resistance of MPS rates with aging (10). Nonetheless, alterations in dietary habits, such as adherence to a Mediterranean diet (14) may significantly influence the management of chronic systemic inflammation (15) and lead to increased muscle mass and strength (16).

The dietary inflammation index (DII) estimates the overall inflammatory potential of a diet based on the pro and anti-inflammatory properties of various dietary ingredients (17). Higher DII scores indicate a more pro-inflammatory diet, reflected in higher plasma concentrations of inflammatory markers (18). Indeed, a study in older Australian males with higher energy-adjusted DII scores was shown to have a lower appendicular lean mass after controlling for body mass index (BMI), although no association was found between DII and changes in handgrip strength over three years (19). Another study from the same population indicated that a more pro-inflammatory diet was associated with lower muscle mass and reduced muscular performance, as assessed by Timed-Up-and-Go (20). Furthermore, a diet with a higher pro-inflammatory potential was shown to be related to a higher risk of sarcopenia as evidenced by lower muscle mass among a community-dwelling elderly population (21). In contrast, another study showed an increased DII score to not be associated with decreases in knee extensor strength, whole lower-limb muscle strength, or handgrip strength in a cohort of older Australian adults (22). A recent meta-analysis investigated the association between DII and sarcopenia including 11 studies with 19,954 participants (23). The results indicated that the DII score was related to sarcopenia, and the risk of sarcopenia increased by 1.22 times for each 1-point increase in the DII score. Collectively, these results show heterogeneity in the literature regarding the effects of high DII scores on changes in skeletal muscle mass and strength in older adults. We, therefore, performed a systematic review and dose-response meta-analysis to assess the association between DII score and older age-related muscle conditions, including sarcopenia, low muscle mass, low muscle strength, frailty, and/or disability. We used a dose-response meta-analysis to evaluate the association of older age-related muscle conditions on sarcopenia measures.

Methods

This systematic review and dose-response meta-analysis was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24). The study protocol was registered with the international prospective register of systematic reviews database (PROSPERO) under the registration number CRD42022364880.

Literature Search and Selection

A systematic search was performed using Scopus, PubMed/MEDLINE, and ISI Web of Science without limitation until October 04, 2022. The search strategy is reported in Supplementary Table 1. Data from grey literature sources such as letters, reviews, notes, conference abstracts, reports, case reports, and short surveys were retrieved from a manual search of references noted in original research studies published in one of the above databases.

Inclusion and Exclusion Criteria

Inclusion criteria included observational research (cross-sectional, case-control, or cohort) in adults (≥18 years), reporting data on the association between DII score and the risk of older age-related muscle condition (sarcopenia, low muscle mass, low muscle strength, frailty and/or disability) and providing effect estimates in the form of odds ratios (OR), relative risk (RR), or hazard ratio (HR) stating at least 95% confidence interval (95% CI). We included studies with the presence of sarcopenia (1) as an endpoint without restriction for the reported outcomes and methods of assessment. Exclusion criteria were as follows: (1) studies undertaken in children and adolescents (<18 years), (2) without sufficient data, and (3) as well as studies with an overlap in population, exposure, and the outcome variable. Article titles and abstracts and, subsequently, full-text reviews obtained from database searches meeting the inclusion criteria were assessed by two researchers (SM and PA). Any disagreement of opinion regarding study inclusion/exclusion criteria was resolved by consensus following discussion. The PICOS tool for individual studies provided the basis for study inclusion as follows a) population: adults (≥18 years), b) intervention: none, c) comparison: dietary inflammatory index, d) outcome: the risk of older age-related muscle condition (sarcopenia, low muscle mass, low muscle strength, frailty and/or disability), and e) study design: observational research (cross-sectional, case-control, or cohort) (Supplementary Table 2).

Data Extraction

Two researchers (SM and ST) extracted the following data from articles meeting the inclusion criteria: a) first author's name, year of publication, and country of origin; b) study characteristics (design, follow-up period, and source of data health status); c) participant characteristics (number of participants/cases, age, and sex); d) DII score evaluation method; e) muscle health reported outcomes; f) main study results (outcomes), and g) covariates utilized for adjustments in multivariate analyses. Any disagreement of opinion regarding data extraction features was resolved by consensus following the discussion.

Quality Assessment

Two investigators (SM and MZ) performed the quality evaluation of each selected article by applying the Newcastle-Ottawa Scale (NOS) (25). The NOS was developed to evaluate the risk of bias in non-randomized prospective cohort research for systematic reviews or meta-analyses and allocates a maximum of 9 points in three broad domains: study group selection (four points), study group comparability (two points); and exposure and outcomes ascertainment for case-control or

Table 1. Characteristics of included studies

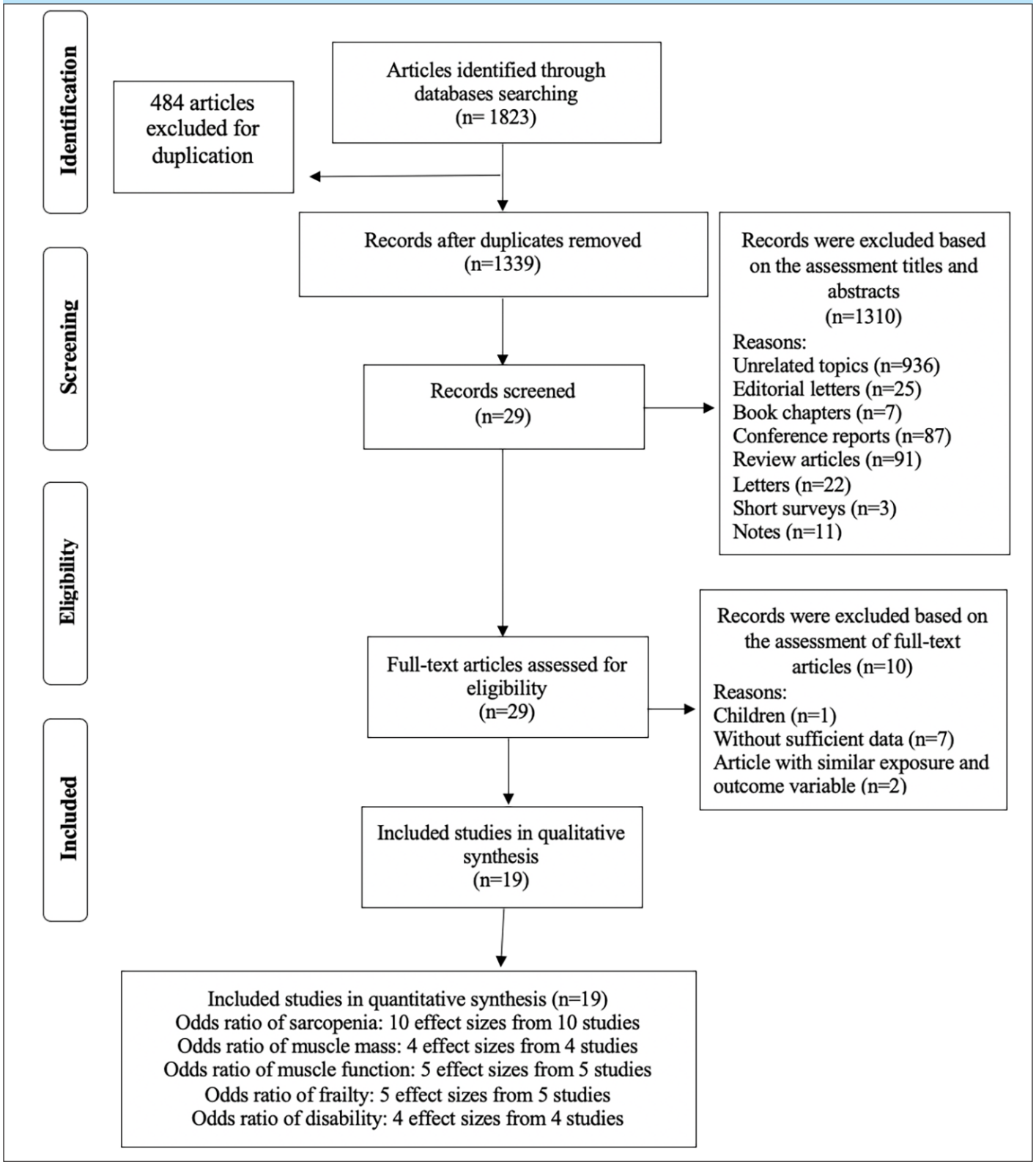
Author (year; location)	Study design / Follow up (years) / Source of data/ Health status	Population/ Age/(women/ men)	Muscle health outcomes	DII assessment method	Outcomes	Adjusted variables	Quality score
Tomata et al. (2018, Japan)	Cohort study /12 year / Tsurugaya Project/ Community-dwelling older individuals aged ≥70 years	N= 739 / Age = 75.5 ± 4.7 years/ (390 / 349)	Disability	Self-administered brief diet history questionnaire (BDHQ)	A higher DII score increased the risk of disability (HR=1.26; 95%CI: 1.01,1.57)	History of disease, education level, social support, smoking, depressive symptoms, cognitive function, number of remaining teeth, BMI and serum albumin.	+9/10
Kim et al. (2018, Korea)	Cross-sectional study /-/ Community-dwelling older/ individuals aged 70–85 years	N= 321 / Age = 75.98 ± 3.77 years/ (218 / 103)	Frailty Low muscle strength	24-h dietary recall	Higher DII score increased the risk of frailty (OR=1.64; 95%CI: 1.25,2.17), and low muscle strength risks (OR=1.34; 95%CI: 1.13, 1.60)	Age, chewing ability, and energy intake	+6/10
Shivappa et al. (2018, USA)	Cohort study /8 years/ the Osteoarthritis Initiative (OAI)/ participants with knee osteoarthritis or at high risk.	N= 4421 /Age = 61.3 ± 9.3 years/ (2564/ 1857)	Frailty	FFQ	A higher DII score increased the risk of frailty (HR=1.37; 95%CI: 1.01,1.89)	Age, sex, race, education level, BMI, yearly income, smoking, comorbidity index, physical activity, CES-D, and number of frailty indexes at the baseline	+9/10
Lohman et al. (2018, USA)	Cross-sectional study /-/ National Health and Nutrition Examination Survey (NHANES: 2007–2014 / adults age >60 years	N= 7182 / Age = 70.37 ±0.18 years/ (4004 / 3178)	Frailty 1483.2213	24-h dietary recall	A higher DII score increased the risk of frailty (OR=2.07; 95%CI: 1.13,2.80)	Age, sex, smoking status, comorbidity burden; including obesity DII interaction	+8/10
Laclaustra et al. (2019, Spain)	Cohort study /2-year/ Seniors-ENRICA study/ community-dwelling individuals ≥ 60 years old	N= 1948 / Age = 68.4 ± 6.2 years/ (1003 / 945)	Frailty, Disability, Low muscle strength	Diet history using Spanish food composition tables.	Higher DII scores increased the risk of frailty (HR=2.48; 95%CI: 1.42,4.44), disability (HR=1.96; 95%CI: 1.03,3.86), and low muscle strength risks (HR=1.82; 95%CI: 1.27, 2.64)	Age, sex, education, smoking status, BMI, energy intake, diagnosed diseases, time spent watching TV, and leisure-time physical activity.	8/10
Bagheri et al. (2020, Iran)	Cross-sectional study /-/ elderly people	N= 300 / Age = 66.7 ± 7.7 years/ (150 / 150)	Sarcopenia, Low muscle strength, Low muscle mass	FFQ	Higher DII score increase the risk of sarcopenia (OR=2.18; 95%CI: 1.01,4.74), but not abnormal hand grip strength (OR=0.97; 95%CI: 0.49,1.89) and low muscle mass risks (OR=1.38; 95%CI: 0.72, 2.63)	Age, sex, energy intake, physical activity, smoking, alcohol consumption, medication use, and positive history of the disease.	+6/10
Geng et al. (2021, USA)	Cross-sectional study /-/ Nutrition Examination Survey (NHANES)- 1999 to 2006 / Healthy subjects	N= 25,781 / Age = 45.44 ± 12.22 years/ (12177 / 13604)	Sarcopenia	24-h dietary recall	A higher DII score increased the risk of sarcopenia (OR=1.12; 95%CI: 1.07,1.13)	Age, sex, race, ratio of family income to poverty, education level, BMI, comorbidity index, smoking, alcohol intake per week, and physical activity	+9/10
Gojanovic et al. (2021, Australia)	Cross-sectional study /-/ Geelong Osteoporosis Study (GOS) / Older adults	N= 809 / Age = 66.4/ (278 / 531)	Sarcopenia	FFQ	A higher DII score increased the risk of sarcopenia (OR=1.34; 95%CI: 1.08,1.67)	Age, sex, and body fat percentage	+7/10
Oliveira et al. (2021, Brazil)	Cross-sectional study /-/ individuals aged 60 years or older	N= 135 / Age = 70.33 ± 7.1 years/ (77 /58)	Frailty	FFQ	A higher DII score increased the risk of frailty (OR=1.58; 95%CI: 1.29,1.93)	Age, depressive symptoms, cognitive performance, functional capacity, and years of schooling	+6/10
Son et al. (2021, Japan)	Cross-sectional /-/ Kashiwa-based study individuals/ aged 60 years or older	N= 1,254 / Age = 74.6±5.5 years/ (- /1254)	Sarcopenia, Low muscle strength, Low muscle mass,	Self-administered brief diet history questionnaire (BDHQ	Men in the highest tertile of the E-adjusted DII showed a 2.89-times (95% CI: 1.04-8.04) higher risk of sarcopenia than those in the lowest tertile. Regarding its components (low muscle mass/strength/ function), men in the highest tertile did not have significantly greater odds, respectively.	Aage, education level, protein intake, physical activity, medical history, eating alone, Lubben Social Network Scale (LSNS) social ties, Geriatric Depression Scale (GDS), and Geriatric Oral Health Assessment Index (GOHAI) score.	+8/10
Wang et al. (2021, USA)	Cross-sectional study /-/ the National Health and Nutrition Examination Survey (NHANES): 2007-2016)/ Participants aged 60 years and above	N= 6,893 / Age =60 ≤ years/ (3536 /3536)	Disability	24-h dietary recall	A higher DII score increased the risk of Disability (OR=1.97; 95%CI: 1.37,2.82)	Age, sex, self-reported race and ethnicity, marriage, status, education, annual household income, BMI, physical activity, smoking status, energy intake, hypertension, diabetes, arthritis, stroke, and cancer	+8/10

Table 1 (continued). Characteristics of included studies

Author (year; location)	Study design / Follow up (years) / Source of data/ Health status	Population/ Age/(women/ men)	Muscle health outcomes	DII assessment method	Outcomes	Adjusted variables	Quality score
Bian et al. (2022, China)	Cross-sectional study /-/ Crohn's disease patients from Ruijin Hospital in Shanghai	N= 140 / Age = 32.59 ± 10.24 years/ (39 / 101)	Sarcopenia, Low muscle strength, Low muscle mass,	FFQ	Higher DII score increased the risk of sarcopenia (OR=9.59; 95%CI: 1.69,54.42) and low muscle mass risks (OR=5.77; 95%CI: 1.06, 31.35), but not low muscle strength (OR=1.26; 95%CI: 0.33,4.83)	Age, sex, BMI, smoking status, alcohol consumption, nutritional status, disease activity, total energy intake, disease duration, montreal classification-location, and montreal classification-behaviour	+6/10
Chen et al. (2022, USA)	Cross-sectional study /-/ the National Health and Nutrition Examination Survey (NHANES)/ Healthy subjects	N= 6082 / Age = 37.22 ± 12.52 years/ (3,162/ 2920)	Sarcopenia, Low muscle mass, Weakness	24-h dietary recall	Higher DII score increased the risk of sarcopenia (OR=1.17; 95%CI: 1.00,1.37) and low muscle mass risks (OR=1.11; 95%CI: 1.05, 1.18) but not weakness (OR=1.05; 95%CI: 0.94, 1.18)	Age, sex, race, educational level, marriage status, family poverty income ratio, smoking status, drinking status, physical activity level, BMI status, diabetes, and hypertension	+9/10
Chen et al. (2022, USA)	Cross-sectional study /-/ Nutrition Examination Survey (NHANES) 1999–2002/ individuals over 50 years of age	N= 1863 / Age = 62.1±9.5 years/ (950/ 913)	Low muscle mass, Low muscle strength	24-h dietary recall	Higher DII score increased the risk of low muscle mass risks (OR=1.45; 95%CI: 1.03, 2.06) and low muscle strength (OR=1.56; 95%CI: 1.08, 2.25)	Age, sex, race, education, marital status, nativity, smoking, physical activity level, BMI, Chronic disease, energy, and protein	+8/10
Huang et al. (2022, USA)	Cross-sectional study /-/ Nutrition Examination Survey (NHANES) / adult with chronic kidney disease participants	N= 2,569/ Age = 55.6 ± 18.1years/ (1410/1159)	Sarcopenia	24-h dietary recall	A higher DII score increased the risk of sarcopenia (OR=1.98; 95%CI: 1.32,2.98)	Age, gender, race, income, physical activity, smoking, alcohol drinking, diabetes, hypertension, overweight, central obesity, dyslipidemia, cancer, arthritis, heart disease, eGFR, ACR, hypoalbuminemia, low energy intake, low protein intake, CRP, WBC, NLR, and NHANES strata	+8/10
Inoue et al. (2022, Japan)	Cross-sectional study /-/ the Frailty Registry Study/ older adults	N= 304/ Age = 77.6 ± 6.3 years/ (203/101)	Sarcopenia Low muscle mass, Low muscle strength	Self-administered brief diet history questionnaire (BDHQ)	Higher DII score increased the risk of sarcopenia (OR=3.40; 95%CI: 1.11,10.39) and low muscle strength (OR=2.49; 95%CI: 1.36, 4.56), but not low muscle mass risks	Age, sex, comorbidity, physical activity, BMI, energy, and protein intake	+6/10
Masuda et al. (2022, Japan)	Cross-sectional study /-/ -/ older people aged 65 years or older	N= 1642/ Age = 75.6 ± 7.4 years/ (930/712)	Disability	FFQ	Higher DII score increased the risk of sarcopenia (OR=1.26; 95%CI: 1.16,1.36)	Sex, age, BMI, education, economic status, and energy intake	+8/10
Millar et al. (2022, USA)	Cohort study /12 years / Framingham Heart Study (FHS)/ Healthy subjects	N= 1701/ Age = 58 ± 8 years/ (935/766)	Frailty	FFQ	Higher DII score increased the risk of frailty (HR=2.07; 95%CI: 1.13,2.80)	Age and sex, energy intake, depressive symptoms, diabetes, cardiovascular disease, and cancer	+9/10
Su et al. (2022, China)	Cohort study /14 years / The Mr. OS and Ms. OS (Hong Kong) Cohort Stud/ community-dwelling Chinese men and women	N= 3995/ Age = 72.39 ± 5.01years/ (1997/1998)	Sarcopenia	FFQ	DII score was not significantly associated with the risk of sarcopenia among men (OR=1.45; 95%CI: 0.88,2.35) or women (OR=1.13; 95%CI: 0.73,1.74)	Age, BMI, current smoking, previous fracture, hypertension, diabetes, chronic obstructive lung disease, cardiovascular disease, rheumatoid arthritis, nonsteroidal anti-inflammatory agent use, osteoporosis medication, vitamin D status, and physical activity	+9/10

Abbreviations: BMI, body mass index; HR, hazard ratio; FFQ: food-frequency questionnaire; OR, odds ratio

Figure 1. Flow chart of the process of the study selection



cohort studies (three points). Studies scoring 7-9 are deemed high quality/low risk of bias, whereas a score of 0-3 indicates a high risk of bias. The consensus of the NOS quality evaluation of selected articles is displayed in Table 1.

Statistical Analyses and Data Synthesis

Statistical analyses were performed by STATA version 14.0 (StataCorp, College Station, TX, USA) and SPSS version 25.0 (IBM, Armonk, NY, USA). The RR and 95% CI were

established as overall effect sizes in this research, similar to effect estimates reported by original studies meeting the inclusion criteria for this meta-analysis (26). The synthesized effect estimates for this research were reported as pooled relative risk (RR) with 95% CI. Due to anticipated heterogeneity between studies, effect estimates were calculated using the DerSimonian-Laird weighted random-effects model (27). Firstly, a pairwise meta-analysis was carried out by combining the effect size results for the highest and lowest categories of DII scores. Heterogeneity in the articles was examined by the Cochran Q and I-squared (I^2) statistics where the I^2 value was estimated from [(Q-df)/Q×100%]; Q being the χ^2 value and df the corresponding degrees of freedom. Between-study heterogeneity was considered significant when the Cochran Q statistic was significant ($p<0.01$) or $I^2>50\%$; more specifically, low, moderate, high, and extreme heterogeneity was defined based on the I^2 statistics cut-offs of <25%, 25-50%, 50-75%, and >75%, respectively. Additionally, subgroup analyses were performed to assess any feasible results effects due to the study setting (cross-sectional or cohort), study region of origin (USA, Europe, Australia, and Asia), the study population (general adults, elderly, special diseases), number of cases (<1000 or >1000), number of participants (<2000 or 2000), the mean age of participants (<50 or >50), dietary evaluation method (food frequency questionnaires, 24h recall, or brief diet history questionnaire) case ascertainment (Asian Working Group for Sarcopenia [AWGS], European Working Group on Sarcopenia [EWGSOP], and Foundation for the National Institutes for Health [FNIH]), and other covariate adjustments to data. Sensitivity analysis was performed by omitting each study and assessing the remaining pooled effect estimates. Publication bias was assessed by visual inspection of funnel plots, formal testing by Egger's regression asymmetry, and Begg's rank correlation tests (28, 29), with results regarded as significant at $p<0.05$.

A dose-response meta-analysis was conducted to estimate the RRs per 1-unit increment in DII scores (30-32) based on the method introduced by Greenland and colleagues (33, 34). To implement this process, studies needed to report the number of cases (i.e., participants with incidence) and non-cases (i.e., participants without incidence) or person-years (i.e., the number of people in the study and the amount of time each person spends in the study) and the median point of DII score across more than three categories of DII. Ultimately, a one-stage linear mixed-effects meta-analysis was undertaken to model the dose-response associations through the estimation and combining of study-specific slope lines used to obtain an average slope in a single stage. The linear mixed-effects meta-analysis includes studies with two categories of exposures (at least two effect sizes) in the dose-response analysis.

Quality of evidence

The general certainty of evidence across studies was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group guidelines. Based on the GRADE assessment criteria, the quality of evidence was ranked into four classes: high, moderate, low, and very low (35).

Results

Study Characteristics

We found 1823 studies through a database search and reference lists. Then omitting duplicates, 1339 records remained (Figure 1). Following the review of the title and abstract of these studies, 1310 publications were excluded. The remaining 29 full-text articles were assessed, with a further ten studies excluded for the following reasons: one study was performed on children, seven studies reported insufficient data (data were indicated as β coefficient or mean [SE]), and two studies conducted similar papulation (Supplemental Table 3). Finally, nineteen studies met our inclusion criteria and were selected for the current meta-analysis (36-54).

The general characteristics of selected studies are displayed in Table 1 and reported below: fourteen were cross-sectional (36, 39, 42, 43, 45-54), and five had a cohort setting (37, 38, 40, 41, 44). All of the selected studies were published between 2018 and 2022 and were conducted in USA (36, 40, 41, 43, 47, 51, 52), Japan (37, 39, 42, 46), Korea (45), Spain (44), Brazil (50), China (38, 53), Australia (48) and Iran (54). The study-specific, maximally adjusted RR was reported for 68079 participants across the selected articles and was pooled for meta-analysis to evaluate the associations between DII score and the risk of sarcopenia, low muscle mass and strength, frailty, or disability. Regarding study outcomes. Sarcopenia risk was reported in ten studies (38, 39, 46-49, 51-54), four studies documented low muscle mass risk (39, 51-53), five reported low muscle strength (39, 45, 46, 51, 53), five documented frailty (40, 41, 43, 45, 50) and four reported the risk of disability (36, 37, 42, 44). The Newcastle-Ottawa scale (55) was used for the quality evaluation of selected articles and indicated fourteen studies of high quality (36-44, 47-49, 51, 52) and five of medium quality (45, 46, 50, 53, 54) (Supplementary Table 4). In addition, our outcomes revealed that the level of agreement between investigators for data collection as well as for quality evaluation was appropriate (Kappa = 0.779).

Dietary inflammatory index and adult muscle health

Our outcomes revealed that a higher DII score was significantly related to an increased risk of sarcopenia (RR=1.50; 95% CI: 1.26, 1.79; I2=53.3%; $p<0.001$; n=10), low muscle strength (RR=1.47; 95% CI: 1.24, 1.74; I2=6.6%; $p<0.001$; n=5), frailty (RR=1.61; 95% CI: 1.41, 1.84; I2=0.0%; $p<0.001$; n=5) and disability (RR=1.41; 95% CI: 1.16, 1.72; I2=58.4%; p=0.001; n=4), but not low muscle mass (RR=1.24; 95% CI: 0.98, 1.56; I2=49.3%; p=0.069; n=4) (Table 2 and Supplemental Figure 1). High heterogeneity levels were observed among studies that reported the risk of sarcopenia. All subgroups analysis indicated a significant relationship between higher DII scores and increased sarcopenia risk in

Table 2. Dietary Inflammatory Index and the risk of muscle health

	Highest vs. lowest category meta-analysis						Dose-response meta-analysis					Quality of evidence
	Studies, n	RR (95% CI)	P value	I^2, %	P heterogeneity	Dose, unit	Studies, n	RR (95% CI)	P value	I^2, %	P heterogeneity	
Sarcopenia	10	1.50 (1.26, 1.79)	<0.001	53.3	0.023	1	8	1.14 (1.08, 1.19)	<0.001	39.9	0.113	●●●● High
Low muscle mass	4	1.24 (0.98, 1.56)	0.069	49.3	0.116	1	3	1.06 (1.00, 1.12)	0.036	25.4	0.262	●●○○ Low
Low muscle strength	5	1.47 (1.24, 1.74)	<0.001	6.6	0.369	1	3	1.07 (1.02, 1.13)	0.010	0.0	0.381	●●●○ Medium
Frailty	5	1.61 (1.41, 1.84)	<0.001	0.0	0.571	1	2	1.07 (0.97, 1.19)	0.167	58.6	0.120	●●●○ Medium
Disability	4	1.41 (1.16, 1.72)	0.001	58.4	0.066	1	1	1.07 (1.02, 1.12)	0.005	-	-	●●●○ Medium

Abbreviations: ASMI; appendicular skeletal muscle mass index, RR; relative risk, CI; Confidence Interval.

adults (Table 3). The observed heterogeneity was attenuated by study design subgroup analysis (Table 3). Since the number of studies included for the rest of the endpoints is less than or equal to 5 studies (5 studies for frailty and muscle strength and 4 for disability and muscle mass), it was not possible to conduct a subgroup analysis for them. Therefore, we were able to report subgroup results just for the relation between sarcopenia and DII.

Linear dose-response analysis

The results of the linear dose-response analysis are illustrated in Table 2 and Supplemental Figure 2. We observed that a 1-unit increment in DII score was related to a 14% higher risk of sarcopenia (RR=1.14; 95% CI: 1.08, 1.19; I2=39.9%; p<0.001; n=8), a 6% higher risk of low muscle mass (RR=1.06; 95% CI: 1.00, 1.12; I2=25.9%; p=0.036; n=3), a 7% higher risk of low muscle strength (RR=1.07; 95% CI: 1.02, 1.13; I2=0.0%; p=0.010; n=3), and a 7% higher risk of disability (RR=1.07; 95% CI: 1.02, 1.12; p=0.005; n=1) in adults. However, our results did not indicate linear dose-response association DII score and frailty (RR=1.07; 95% CI: 0.97, 1.19; I2=58.6%; p=0.167; n=2), (Table 2 and Supplemental Figure 2).

Non-linear dose-response analysis

Non-linear dose-response relationships revealed a positive linear association between the DII score and the risk of sarcopenia (Pnonlinearity = 0.097, Pdose-response<0.001, Figure 2). Furthermore, the risk of low muscle mass was slightly increased when increasing the DII score from the less pro-inflammatory boundary toward the more pro-inflammatory boundary. The slope was slightly flattening from the DII score of -1 to 1 level, while it was not statistically significant (Pnonlinearity = 0.412, Pdose-response=0.095; Figure 3). Moreover, there was no association between DII score with risk of low muscle strength (Pnonlinearity = 0.433, Pdose-response=0.067; Figure 4). Furthermore, there was a positive linear association between DII score with frailty (Pnonlinearity = 0.844, Pdose-response=0.010; Figure 5) and disability (Pnonlinearity = 0.596, Pdose-response=0.007; Figure 6).

Figure 2. Non-linear dose–response association between dietary inflammatory index and the risk of sarcopenia

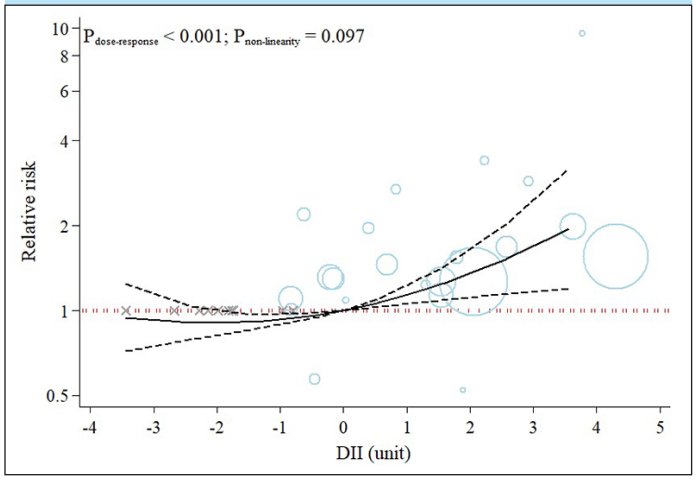
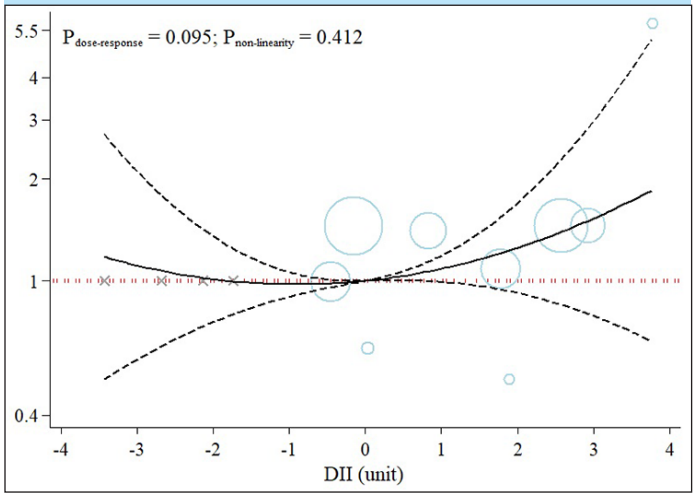


Figure 3. Non-linear dose–response association between dietary inflammatory index and the risk of low muscle mass



Sensitivity analyses

The sensitivity analysis for the highest to the lowest meta-analysis for risk of muscle health including sarcopenia, low muscle mass, low muscle strength, frailty, and disability indicated that effect sizes were not influenced by one specific study (Supplemental Figure 3).

Table 3. Subgroup analyses of Dietary Inflammatory Index and the risk of Sarcopenia (Highest vs. lowest category meta-analysis)

Sub-groups	n	Relative Risk (95%CI), P-value	I2 (%), $P_{heterogeneity}$	$P_{between}$
All studies	10	1.50 (1.26, 1.79), <0.001	53.3	0.023
Study design				0.064
Cohort	3	1.21 (1.06, 1.38), 0.006	0.0	0.407
Cross-Sectional	7	1.68 (1.35, 2.09), <0.001	39.2	0.130
Region				0.056
USA	4	1.49 (1.18, 1.87), 0.001	69.9	0.019
Europe	1	3.40 (1.11, 10.40), 0.032	-	-
Asia	4	1.88 (1.03, 3.42), 0.039	54.2	0.088
Australia	1	1.33 (1.05, 1.69), 0.019	-	-
Population				0.156
General adults	2	1.34 (1.02, 1.77), 0.036	83.2	0.015
Elderly	6	1.42 (1.19, 1.69), <0.001	0.1	0.415
Special disease (IBD, CKD)	2	3.45 (0.79, 15.07), 0.100	66.7	0.083
Number of Cases				0.528
<100	6	1.53 (1.13, 2.07), 0.006	57.2	0.039
>100	4	1.55 (1.34, 1.79), <0.001	3.5	0.375
Number of participants				0.072
<2000	6	1.82 (1.27, 2.62), 0.001	41.7	0.127
>2000	4	1.41 (1.14, 1.74), 0.002	69.0	0.022
Age				0.527
<50	3	1.45 (1.02, 2.05), 0.037	81.6	0.004
>50	7	1.54 (1.27, 1.86), <0.001	16.5	0.304
Dietary assessment				0.517
FFQ	4	1.52 (1.05, 2.21), 0.027	54.7	0.085
24h Recall	4	1.49 (1.18, 1.87), 0.001	69.9	0.019
BDHQ	2	2.31 (1.11, 4.84), 0.026	0.0	0.370
Case ascertainment				0.245
AWGS	4	2.19 (1.04, 4.63), 0.040	61.1	0.053
EWGSOP	2	1.48 (0.99, 2.19), 0.053	30.3	0.231
FNIH	2	1.34 (1.02, 1.77), 0.034	83.2	0.015
Not report	2	1.86 (1.35, 2.55), <0.001	0.0	0.621
Adjustments				
Body mass index				0.459
Yes	5	1.45 (1.10, 1.90), 0.08	71.0	0.008
No	5	1.54 (1.28, 1.84), <0.001	0.0	0.425
Smoking status				0.986
Yes	7	1.52 (1.23, 1.89), <0.001	63.3	0.011
No	3	1.57 (1.01, 2.45), 0.045	27.7	0.251
Physical activity				0.673
Yes	8	1.57 (1.26, 1.96), <0.001	63.0	0.008
No	2	1.35 (1.07, 1.70), 0.011	0.0	0.618
Alcohol intake				0.722
Yes	6	1.49 (1.19, 1.86), <0.001	67.0	0.010
No	4	1.62 (1.14, 2.32), 0.008	23.5	0.270
Energy intake				0.066
Yes	4	2.02 (1.44, 2.84), <0.001	17.4	0.304
No	6	1.35 (1.16, 1.58), <0.001	45.0	0.106

1. Calculated by Random-effects model; BDHQ; brief diet history questionnaire, AWGS; Asian Working Group for Sarcopenia, EWGSOP, European Working Group on Sarcopenia, FNIH; Foundation for the National Institutes for Health.

Figure 4. Non-linear dose–response association between dietary inflammatory index and the risk of low muscle strength

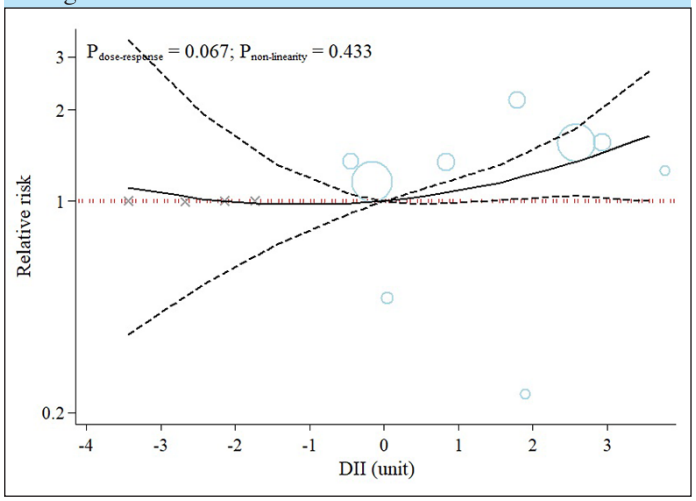


Figure 5. Non-linear dose–response association between dietary inflammatory index and the risk of frailty

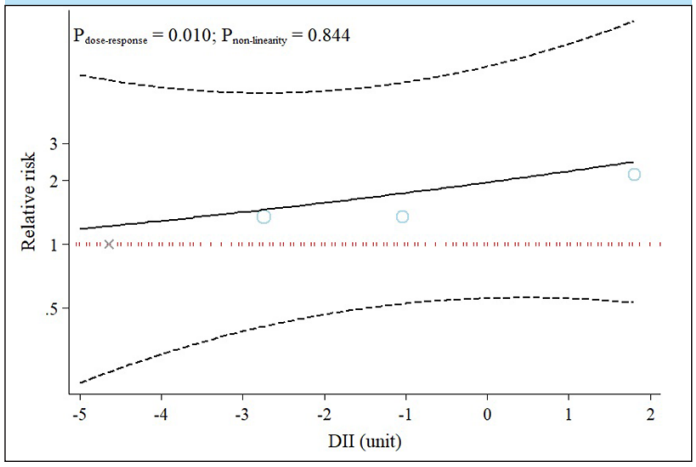
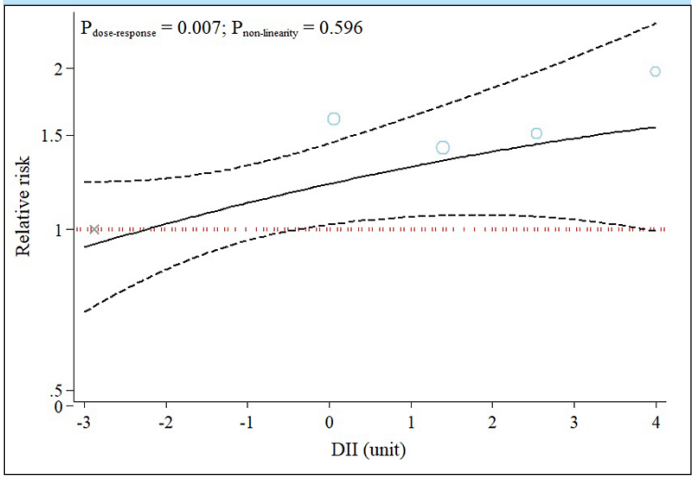


Figure 6. Non-linear dose–response association between dietary inflammatory index and the risk of disability



Publication bias

No evidence of publication bias was found in articles related to the association with an enhanced risk of low muscle mass (p = 0.256, Egger's test; p = 0.174, Begg's), low muscle strength (p = 0.725, Egger's test; p = 0.624, Begg's test), frailty (p = 0.247, Egger's test; p = 0.327, Begg's test), and disability (p = 0.183, Egger's test; p = 0.174, Begg's test). However, Egger's test (p = 0.022) indicated publication bias for studies evaluating the association between DII score and the risk of sarcopenia and was not approved by Begg's test (p = 0.060). As shown in Supplemental Figure 4, the funnel plot was asymmetrical for the association between the DII score and the risk of sarcopenia, which indicated publication bias (Supplemental Figure 4-A).

Quality of evidence

The GRADE guideline was employed to determine the quality of evidence across articles for sarcopenia, low muscle mass, low muscle strength, frailty, or disability results associated with associations between DII score and relative risk of muscle health disorders. The evidence for our outcomes indicated the associations between DII score and sarcopenia risk to be of high quality (Table 2). The outcomes of low muscle strength, frailty, and disability were downgraded to a moderate level. Moreover, low muscle mass was categorized as low quality (Table 2).

Discussion

The present systematic review and dose-response meta-analysis investigated the association between higher dietary inflammatory index (DII) scores representing a pro-inflammatory diet and older age-related muscle conditions, including sarcopenia, reduced muscle mass and strength, and adverse health outcomes such as frailty and disability. In the pooled analysis, we found that an elevated DII was negatively associated with low muscle strength. Moreover, there were significant associations between the highest DII and lowest category score to increase the risk of sarcopenia, frailty, and disability by 50, 61, and 41 %, respectively. Subgroup analysis based on study setting, region of origin, population cohort, number of cases, total number and mean age of participants, dietary evaluation method, case ascertainment, BMI, smoking status, physical activity, energy intake, and alcohol consumption revealed similar results regarding relation between a pro-inflammatory diet and sarcopenia.

Sarcopenia is characterized by a gradual decrease in muscle strength, mass, and function, as well as a diminished ability to regenerate muscle tissue, with advancing age (56). Along with neuropathic, hormonal, immunological, nutritional, and physical activity factors contributing to the progressive loss of skeletal muscle, chronic inflammation has also been recognized as a causative factor in the loss of muscle mass, strength, and functionality (57). The physiological mechanisms underlying such muscle impairments with age-related inflammation are not fully understood. Insulin resistance, oxidative stress, increased

rates of MPB, and adipose tissue accumulation induced by low-grade inflammation, may each have direct or indirect effects on muscle wasting (56). The predictive role of circulating cytokines in potential sarcopenia diagnosis has also been investigated (58). Pro-inflammatory cytokines such as IL-6, TNF-α, and CRP have been shown to increase in adults with sarcopenia (56). In this regard, results from previous meta-analyses have reported higher CRP levels in individuals with sarcopenia (59) and elevated CRP and IL-6 concentrations in individuals with frailty (60). The result of this recognized role of chronic inflammation in attenuating skeletal muscle mass and function is a growing interest in the context of nutritional factors and dietary patterns mediating inflammatory processes. Accordingly, results from a cross-sectional study including 1514 men and 1528 women revealed that adherence to a traditional Mediterranean diet was associated with a significant reduction in CRP and IL-6 concentrations (61). Moreover, a vegan diet rich in polyphenols with antioxidants and anti-inflammatory properties was associated with lower CRP concentrations than a mixed diet (62). Regarding food items, the consumption of fruit and vegetables (63), whole grains (64), olive oil (65), and fish (66) have been proposed to reduce pro-inflammatory mediators such as CRP, IL-6, and TNF-α. In contrast, there is growing evidence that a diet rich in sugar, refined flour, saturated fats, and red and processed meats can induce inflammation by elevating the activation of transcription factors such as Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and promoting the expression of inflammatory genes (67, 68). Furthermore, pro-inflammatory effects of excess circulatory fatty acids have also been shown to significantly dampen MPS responses (69-71).

The DII provides a reliable and easy-to-compare tool for assessing dietary inflammatory potential based on anti- and pro-inflammatory components of the overall diet (72). Our results of the linear dose-response indicated that a 1-unit increment in DII score was related to a 14% higher risk of sarcopenia and a 7% higher risk of disability in adults. Non-linear dose-response relationships also revealed a positive linear association between the DII score and the risk of sarcopenia, frailty, and disability. A recent meta-analysis study conducted by Diao et al. including eleven observational studies revealed similar results regarding the association between higher DII and the risk of sarcopenia. In this study, 1 point increment in the DII score was associated with a 1.22 times increase in the risk of sarcopenia (23). The authors also performed subgroups based on sex (male and female), sarcopenia determinants (muscle mass, muscle strength, and physical performance), region of participants (Asia, Americas, and Oceania), and basic disease (general population and people with basic diseases) (29). In regards to the novelty of the present work, we included eight more studies (n=19) with subgroups performed on sarcopenia, low muscle mass, low muscle strength, frailty, disability, study setting (cross-sectional or cohort), the study region of origin (USA, Europe, Australia, and Asia), the study population (general adults, elderly, special diseases), number of cases (<1000 or >1000), number of participants (<2000 or 2000), the mean age of participants (<50 or >50), dietary evaluation method (food frequency questionnaires, 24h recall, or brief diet history questionnaire) case ascertainment (Asian Working Group for Sarcopenia [AWGS], European Working Group on Sarcopenia [EWGSOP], and Foundation for the National Institutes for Health [FNIH]) along with linear and non-linear dose-response analyses.

The role of DII in sarcopenia, frailty, and disability has been investigated in recent observational studies. For instance, in a cohort study conducted on individuals over 60 years, higher adherence to a pro-inflammatory diet was significantly associated with a higher risk of frailty and disability and low muscle strength (73). Results from a longitudinal study over 15 years in middle-aged men (50 years at baseline and 64 at follow-up) showed that adherence to an anti-inflammatory diet and obtaining higher scores on a traditional dietary pattern characterized by greater consumption of whole grains and nuts and a wider variety of plant foods and animal foods, including non-processed fish promote skeletal muscle index (SMI) measured by dual-energy X-ray absorptiometry (DXA) (74). In contrast, a negative association between a pro-inflammatory diet and muscle function (assessed by Timed Up and Go [TUG] (75)) was observed in middle-aged and older males over a 15-year period (76). In another study, Gojanovic et al. reported a positive association between DII and the risk of sarcopenia among older Australians (20). These results are in line with our results indicating a positive association between adherence to an inflammatory diet and the risk of sarcopenia and its subsequent effects including disability and frailty. While no positive association between DII score and risk of low muscle mass was observed in the current non-linear dose-response, the linear dose-response analysis showed that a 1-unit increase in DII score was associated with a 6% higher risk of low muscle mass and a 7% higher risk of low muscle strength. In this regard, previous work has reported a higher DII score to be associated with lower muscle mass and function (77).

Potential mechanisms underlying the association between DII and muscle mass and sarcopenia are likely attributed to the pro-inflammatory and anti-inflammatory dietary components included in the DII. There is consensus that long-term diets rich in pro-inflammatory foods, including high-sugar foods, refined grains, red and processed meats, and fried foods, tend to increase inflammation, which may attenuate MPS and increase muscle hypertrophy, ultimately leading to sarcopenia (15, 69-71). Mechanisms by which dietary sugar can induce low-grade inflammation are an increase in Toll-like receptor 4 (TLR4) and, as a result, activation of Nuclear factor-ϰB (NF-ϰB) and AMP-activated protein kinase (AMPK) signaling leading to upregulation of inflammatory factors, modulation of T-cell inflammation and impairment of gut barriers through reduction of short-chain fatty acids production in the gut (77). In addition, studies have shown that a high-fat diet can shift the gut microbiota population by activating the TLR4 pathway, which increases intestinal permeability and elevates circulating levels of lipopolysaccharides and free fatty acids, resulting in pro-inflammatory cytokines production (78). On the other hand, a potential mechanism of action may be diet-induced oxidative stress as a hallmark of age-related inflammation, which affects muscle mass health (10). It is indicated that anti-inflammatory food sources, which gained negative value in measuring DII,

including protein, iron, magnesium, zinc, thiamine, riboflavin, niacin, vitamin B6, b-carotene, vitamin A, vitamin C, folate, dietary fiber, pepper, onion, and garlic can attenuate low-grade chronic inflammation through their antioxidant capacity (79-81). Overall, due to the overlapping effects which predispose older adults to muscle loss and dysfunction (82), it would appear that adherence to an anti-inflammatory diet can protect elderly individuals against several chronic diseases through anti-inflammation effects.

Regarding the effect of individuals age on the relationship between DII and skeletal muscle mass disorders, it should be noted that among the included studies in our meta-analysis, only 4 studies investigated the relationship between DII and sarcopenia or muscle mass in individuals with an average age of less than 60 years. For instance, 2 recent cross-sectional studies reported a significant relationship between higher DII and increased risk of sarcopenia and low muscle mass in individuals with mean age lower than 40 years (52, 53). Since, subgroup analysis based on the age of participants (>50 or <50) showed no changes in the association between higher DII and the risk of sarcopenia, it seems that this association is independent of the age of participants. Regarding DII scoring of different regions, it should mention that among included studies, 9 studies were conducted in the Americas, 8 in Asia, 1 in Europe, and 1 in the Oceania region. In all included studies DII scoring method designed by Shivappa was used (17), but food parameters used in most studies were less than 45 items, from 19 to 45 items. Although some of the food parameters used in the original DII scoring method were not available in the dataset of these countries, previous studies reported that using 27 or 28 parameters instead of 45 parameters did not influence the predictive capability of DII (83, 84). Moreover, Subgroup analyses based on region showed a significant association between higher DII scores and risk of sarcopenia in all 4 regions.

Study strengths and limitations

The present meta-analysis has several notable strengths, including the novelty of pooled observational data on the relationship between the dietary inflammatory index and older age-related muscle condition, dose-response analyses, GRADE assessment of evidence, and adjustment of pooled data for several confounding variables. In regards to the novelty of the present work, we included eight more studies (n=19) with various analyses and more subgroups. Therefore, the results of the present study might have a higher degree of utility and practicality compared to the previous one (23).

Our study also has some limitations. The majority of included studies used a cross-sectional design, which is unable to imply causative association. Furthermore, dietary information was obtained from 24-h recall or food frequency questionnaires, which can be prone to recall bias. Using food information acquired by the 24-h recall cannot reflect long-term dietary patterns, and the data are exposed to large intra-person variability, resulting in misclassified categorization in the DII tertiles or quartiles. In addition, the varied number of DII components measured in previous studies caused a wide range of DII scores, making it difficult to draw consistent conclusions. Nonetheless, subgroup analysis and meta-regression were employed to identify potential sources of heterogeneity. Moreover, sensitivity analysis and tests for publication bias confirmed the consistency of the primary results.

Conclusion

This is the first meta-analysis to specifically investigate the association between DII and the risk of sarcopenia-related outcomes centered on low muscle mass, strength, function, and their consequences altogether. Our results demonstrate a positive relationship between adherence to a pro-inflammatory diet and increased risk of sarcopenia and associated age-related adverse effects such as low muscle strength, disability, and frailty. Considering the established role of inflammation in attenuated muscle health with advancing age, the collective results of our work advocating for adherence to dietary patterns emphasize a reduction in pro-inflammatory components to promote overall skeletal muscle health in older adults. Further prospective studies with large sample sizes and diverse ages, genders, and nationalities are required to broaden our knowledge regarding this association.

Ethical standard: This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest: The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication.

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