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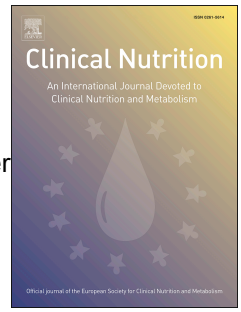

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The inflammatory potential of diet is related to incident frailty and slow walking in older adults

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ABSTRACT

BACKGROUND: Certain foods and dietary patterns have been associated with both inflammation and frailty. As chronic inflammation may play a role in frailty and disability, we examined the association of the inflammatory potential of diet with these outcomes.

METHODS: Data were taken from 1948 community-dwelling individuals ≥60 years old from the Seniors-ENRICA cohort, who were recruited in 2008-2010 and followed-up through 2012. Baseline diet data, obtained with a validated diet history, was used to calculate Shivappa's Dietary Inflammatory Index (DII), an "a priori" pattern score which is based on known associations of foods and nutrients with inflammation, and Tabung's Empirical Dietary Inflammatory Index (EDII), an "a posteriori" pattern score which was statistically derived from an epidemiological study. At follow-up, incident frailty was assessed with Fried's criteria, and incident limitation in instrumental activities of daily living (IADL) with the Lawton-Brody index. Statistical analyses were performed with logistic regression, and adjusted for the main confounders.

RESULTS: Compared with individuals in the lowest tertile of DII, those in the highest tertile showed higher risk of frailty (odds ratio [OR] 2.48; 95% confidence interval [CI]: 1.42, 4.44, p-trend=0.001) and IADL disability (OR: 1.96; 95% CI: 1.03, 3.86, p-trend=0.035). By contrast, EDII did not show an association with these outcomes. The DII score was associated with slow gait speed, both as a low score in the Short Physical Performance Battery test (OR: 1.82; 95% CI: 1.27, 2.62, p-trend=0.001) and as a positive Fried's criterion (OR: 1.64; 95% CI: 1.08, 2.51, p-trend=0.021), which use different thresholds.

CONCLUSIONS: DII predicted frailty and IADL while EDII did not. DII is able to measure diet healthiness in terms of physical decline in addition to avoidance of inflammation.

Keywords: Frailty, Dietary patterns, Inflammation, Disability, Cohort

INTRODUCTION

Ageing is associated with progressive limitations in physical functioning and with disability. The frailty syndrome[1] is a criteria-based condition which heralds the disability process, and identifies older adults with increased risk of death, hospitalization and falls[2]. Lifestyle, in particular physical activity and diet, has strong influence on the aging process[3]. In particular, diet[4], studied as specific foods and nutrients[4,5] or as patterns[6–8] has been associated with the risk of frailty and disability in older adults.

Chronic inflammation may play a role in the pathophysiology of frailty, although further research should still clarify the actual mechanisms[9]. Shivappa et al. proposed the dietary inflammatory index (DII), which captures *a priori*-defined dietary patterns linked to higher inflammatory markers, based on published evidence[10] and thus can be used to link diet and inflammation. Very recently, an empirical (*a posteriori*) dietary inflammatory index (EDII) has been developed using prospective data from the large Nurses' Health Study[11]. DII has demonstrated association with several diseases, including those leading world mortality and morbidity: cardiovascular diseases[12,13], which share risk factors with frailty, and cancer[14], but also metabolic syndrome[15] and depression[16] among others. Only a previous article has examined the association between an inflammatory index and the risk of frailty[17] and none has assessed the association with disability. As both indices differ in the way they were developed it is possible that their information is not equivalent and it would be worth analyzing the association of both with aging-related outcomes.

Thus, we hypothesized that inflammatory dietary patterns are associated with higher risk of frailty and disability, and we tested this hypothesis with data from the Seniors-ENRICA cohort of older adults in Spain.

METHODS

Study design and participants

The Seniors-ENRICA study is a cohort of 2614 community-dwelling individuals aged 60 years or older, who were recruited between 2008 and 2010 and have been followed-up through 2012[18]. Among survivors (n=2519), we excluded 9 participants with dementia or Alzheimer disease at baseline, 12 with missing data on diet, and 550 on questionnaires or function tests, for a final sample size of 1948 (See Flowchart). At baseline, physical and laboratory examinations, a frailty assessment, and several health questionnaires, including a diet history and a Lawton and Brody scale, were performed. At follow-up, the same procedures were repeated with the addition of some others like the Short Physical Performance Battery (SPPB). This study describes the longitudinal association of baseline dietary inflammatory indices with aging-related outcomes: a reduced physical performance, frailty, and disability. Specific exclusions to select participants at risk for each analysis are described below, in the statistical analyses section (see Flowchart). Informed consent in writing was obtained from all participants, and the study was approved by the Clinical Research Ethics Committee of the *La Paz* University Hospital in Madrid.

Exposure measurements: Diet and inflammatory dietary indices

A computer-based diet history was used to collect the participant's regular diet. The interview collected information from 880 different foods and the nutrient intake from them is calculated using Spanish food composition tables. This diet history is

validated[19] and provides an estimate in daily grams of foods and nutrients that represents the average intake during a year.

To assess the inflammatory components of diet, we used the DII and EDII. The DII was calculated according to Shivappa's procedure[10]. In brief, 32 (see list on appendix) of the possible 45 items (daily amounts of food or nutrients) were normalized using the world averages and standard deviations provided in the procedure[10]. Those values were then converted to centered percentile scores that were subsequently multiplied by each provided parameter factor ("food parameter effect score")[10]. The sum of the 32 values resulted in a DII score for each participant. A higher DII score indicates a greater diet's inflammatory component.

EDII calculation was based on 18 food groups (see list on appendix), ascertained as daily portions[11]. We summed daily intake of foods in each of the 18 groups, and then converted the values to portions by dividing them for a group-specific portion size. Group values were multiplied by the group-specific inflammatory coefficient[11] and summed together. Finally, we substracted the mean of these values and divided it by their standard deviation to compute a standardized score. The higher the EDII score the higher the inflammatory component of diet.

Outcome measurements: Low physical performance, frailty, and disability

In each participant, to asses a reduced physical performance, we used the Short Physical Performance Battery (SPPB) to evaluate lower extremity function[20]. The SPPB includes three component tests performed in order: 1) Balance: the capacity of holding a standing position with three hierarchical dispositions of feet; 2) Gait speed, across 2.44 meters; 3) Chair stand, evaluating the capacity and time needed to rise from a chair five times consecutively without using the arms[20]. A scale between 0 and 4, predefined for

each test, is used to score each component and the scores are subsequently summed together (SPPB range 0-12). The standard cut-off score used to detect functional limitation is ≤9[21]. Additional analyses of each SPPB component were performed using a cut-off <2, i.e., scores of 0 or 1. Such score in any single component implies that the maximum sum could never exceed 9, i.e., SPPB≤9, even with a maximum score, i.e., four, in the other two components.

The presence of three of the following five Fried criteria[22] was used to define frailty: 1) Exhaustion, identified with an affirmative response on any of the two following questions from the Center for Epidemiologic Studies Depression Scale[23]: “I feel that anything I do is a big effort” or “I feel that I cannot keep on doing things” at least 3-4 days a week; 2) Low physical activity, identified when self-reported walking was ≤ 2.5 h/week in men and ≤ 2 h/week in women[24]; 3) Slow gait speed, considered as the lowest cohort-specific quintile in the 2.44 meters walking speed test of the SPPB, adjusted for sex and height[20].; 4) Unintentional weight loss, when ≥ 4.5 kg of body weight was lost in the preceding year; 5) Muscle weakness, when grip strength measured with a Jamar dynamometer (highest of two consecutive measurements in the dominant hand) and adjusted for sex and body mass index (BMI) was in the cohort-specific lowest quintile[25].

Lawton and Brody scale was used to assess disability in instrumental activities of daily living (IADL)[26]. It includes questions about the ability for shopping, phoning, preparing meals, doing housework, laundry, using the transportation, taking medication, and managing finances. Meals and housework questions were only considered for women, because of Spanish cultural issues. A reported difficulty in any of the items classified the participant as having disability.

Other variables

Age, sex, education, smoking status, measured weight and height, from which body mass index (BMI) was calculated, diagnosed diseases, time spent watching TV, and leisure-time physical activity (using the EPIC cohort questionnaire) were collected during the baseline interview and physical exam using standard procedures. Also the MEDAS score[27] assessing conformance of dietary patterns to the Mediterranean diet was calculated.

Statistical analyses

Participants were classified in sex-specific tertiles for each dietary inflammatory index (cut-off values on Table 1 footnote). Logistic regression was used to estimate inter-tertile odds ratios (OR) and their 95% confidence interval (CI) using the first tertile (less inflammatory pattern) as reference. A trend significance test was performed considering the tertile assignation as numeric. Regression models were built with three levels of adjustment: Model 1 is adjusted for age, sex, and education; Model 2 is additionally adjusted for smoking status, BMI, energy intake, and diagnosed diseases; Model 3 is additionally adjusted for time spent watching TV and leisure-time physical activity. These were segregated from Model 2 because they can be considered either as confounders or as intermediate variables of the studied associations. Providing Model 2 and 3 separately allows interpreting the results from one or the other approach.

Exclusion of participants exhibiting the target characteristic or a proxy at baseline was done separately for each outcome (see Flowchart), i.e., for analysis of each outcome, participants with it at baseline were considered not at risk and removed. Unfortunately, SPPB was not performed at baseline and participants were excluded from the analyses of incident reduced physical performance (measured at follow-up as low SPPB and low SPPB components) using as a proxy for baseline low physical performance an item

from a baseline questionnaire: answering “a lot” to the question “Does your current health or fitness limit you for walking several blocks (a few hundred meters)?”. Of these participants excluded for having an affirmative baseline answer to that question, 80% had low SPPB at follow-up. See the discussion section for an analysis of the consequences of this approximation. Frail participants at baseline were excluded from analyses of the development of frailty outcome. Only robust participants, i.e. without any criteria, were considered at risk for the frailty components analysis. The Lawton and Brody test at baseline was used to exclude participants with any difficulty already at baseline from incident disability analyses. The number at risk for each subsample is reported in the tables and in the Flowchart.

We performed as sensitivity analyses stratification by age (more or less than 70 y) and by BMI (normal weight, overweight, or obesity).

RESULTS

At baseline, both inflammatory indices were higher in women, and in those with greater BMI and TV watching time, those who suffered diabetes, and those who were less adherent to Mediterranean dietary patterns. Inflammatory indices differed in the way they were associated with age, level of education, and energy intake; among older, less educated, and people with less caloric diets, DII was higher, but on the contrary, EDII was lower. DII showed higher scores associated with performing less leisure-time physical activity and with being current smoker, but EDII showed no association (Table 1).

A low (≤9) score in the SPPB at follow-up showed ORs above one for both DII and EDII, but it did not reach statistical significance. Higher DII was associated with increased risk of frailty (OR for the highest vs lowest tertile: 2.48, 95% CI 1.42, 4.44, p

for trend = 0.001) and IADL disability (OR: 1.96, 95% CI 1.03, 3.86, p for trend = 0.035) at follow-up, independently of age, sex, education, smoking status, BMI, energy intake, diagnosed diseases, TV watching time, and leisure-time physical activity. However, EDII did not show an association with the risk of frailty or IADL disability (Table 2).

Additionally we examined the association of the DII or EDII with the components of the SPPB and each frailty criterion. Higher scores on both indices were associated with a low score in the gait speed SPPB test; specifically, the OR (95% CI) for the highest versus lowest tertile was 1.82 (1.27, 2.62, p for trend = 0.001) for DII and 1.39 (0.99, 1.96, p for trend = 0.056) for EDII. The frailty criterion that showed a significant association with DII was slowness, using a different threshold that the one used for SPPB scoring, with OR 1.64 (95% CI 1.08, 2.51, p-trend = 0.021). Unintentional weight loss also showed a tendency to be associated with DII, with OR 1.71 (0.97, 3.03, p-trend = 0.059), but without reaching the level of significance. For completeness, the associations of frailty components with EDII were studied but, as expected, no association was found, consistently with the absence of a pattern of frailty across EDII tertiles (Appendix Table 1).

Similar results were observed when analyses were stratified by age or BMI categories (data not shown).

DISCUSSION

In this cohort of older adults followed up for 3 years, DII at baseline was associated with later presence of slow walking speed. DII was associated with development of frailty and of a positive Lawton and Brody test, indicating IADL disability.

Diet has been linked with both frailty[6,7,28] and inflammatory markers[10,29]. Nutritionally deficient diets, on the one hand, may accelerate musculoskeletal decline through compromising protein synthesis, producing sarcopenia, and loss of muscle strength. On the other hand, obesity is a condition that predicts future frailty[30,31], probably favoring low physical activity and fatigue. Interestingly, not only specific deficiencies or obesogenic diets affect future frailty; dietary patterns recognized for providing protective health effects for several chronic diseases, such as the Mediterranean diet, also confer protection against incident frailty[6].

Regular intake of several individual foods and nutrients, like vitamins, antioxidants, n-3 fatty acids, and alcohol, modify inflammatory markers[10]. Also the Mediterranean dietary pattern is associated with reduced markers of inflammation[29]. Based on published evidence, Shivappa et al.[10] developed DII, an a priori dietary pattern that provides a quantitative assessment of the inflammatory potential of a particular diet. We found that Shivappa's index predicts incident frailty and disability for IADL after adjustment for confounders. A second index, EDII, has been developed as an *a posteriori* dietary pattern applying reduced rank regression to Nurses' Health Study data[11]. The selection of foods and their weighting in this index were tuned to capture cytokine levels in that sample. EDII was not linked to the reduced physical performance, frailty, or disability outcomes.

In our data DII and EDII also showed differing association with socio-demographics, lifestyle, and other potential confounders, suggesting that they capture different information from the analyzed diets. Our aim was to gather information on dietary patterns that may affect healthy aging and to identify which index of dietary inflammatory potential does capture better information of a relevant pattern. Our goal was not to compare the indices in their capacity for detecting inflammation, which

should be addressed with other methods, including biological assessment of inflammation. We propose some explanations for why association of the indices with frailty differ. The indices are different in development, structure, and potential uses, which could explain the distinct results, at least partially. DII is an index based mainly on nutrients, minerals, and some condiments (usually consumed in small quantities and supplying a minimum amount of energy), and as such, it requires more details in data collection and availability of appropriate food composition tables. Due to the high complexity of nutrient-based indices, they are used mainly in research. Nonetheless, given that most nutrients and minerals considered are usually present in many foods, when those nutrients are active principles, nutrient-based indices are able to capture better the hidden relationship between diets and outcomes because they take into account elementary components from the entire diet. In addition, DII is based in previous knowledge of associations and their possible physiological pathways, and each component of the index has already received attention in trying to explain the biological plausibility of its association with inflammation. On the contrary, EDII is a food-based index, in particular based on food groups. Indices of this kind are more suitable for clinical use (screening, risk communication, and interventions) but they are more difficult to be applied across countries and cultures because food components and their relevance in the diet may vary substantially. Also, they are usually less sensitive to small effects of active principles because foods, and food groups, may contain antagonistic principles that partially neutralize each other. EDII was derived statistically, and a common criticism on *a posteriori* indices is that they underperform when ported from the population in which they were derived to other populations. Furthermore, healthy or unhealthy aging is likely to depend on nutrients that act as

active principles, thus DII seems to capture better the underlying association than EDII in which only food groups are considered.

Among the theories addressing frailty pathogenesis, chronic inflammation has been proposed as a key underlying mechanism[32]. Several studies have shown increased levels of interleukin-6 (IL-6) [33], C-reactive protein[34], and leukocytes[33] among frail community-dwellers, as well as among frail residents in nursing homes and assisted living facilities[35]. Thus, frailty could be considered an inflammatory status. In the search for a pathophysiological explanation, proposed intermediate links between chronic inflammation and frailty are muscular wasting, producing sarcopenia, endocrine dysregulation including cortisol and the somatotropin axes, cardiovascular diseases, and nutritional dysregulation with deficiency of micronutrients[32]. Nonetheless, these theories have not been proven so far, and a recent meta-analysis of studies on the prospective association between baseline C-reactive protein or interleukin-6 and frailty rendered non-significant results after combining data of 3402 participants with a median follow-up of 3 years[9]. Our results, in which inflammatory dietary patterns significantly predict incident frailty, support the pathogenic implication of inflammatory mechanisms in frailty.

In order to obtain a deeper insight of the aspects of physical decline which are most affected by the inflammatory dietary patterns, we analyzed the components of the SPPB and frailty. We found a significant association of DII with slow gait speed (which is a component of SPPB and frailty, with different thresholds), and borderline significant association of EDII with the gait speed component of the SPPB. Gait speed is the objective physical performance test most associated with frailty diagnosis and it predicts most endpoints that frailty predisposes to[36]: death, falls, disability, and hospitalization. Slow gait alone is associated with a pro-inflammatory pattern of

cytokines[37], but a study of inflammatory and walking speed trajectories did not find evidence of any interactive effect of them on mortality[38]. Again, cross-sectional evidence of association between inflammation and gait speed is clear[39], but longitudinal evidence suggests that a common cause, such as adiposity could be responsible of the joint development of both[40]. We found a statistically significant prospective association between inflammatory potential of diet and slowness. The kind of diet represented by the DII and EDII could be responsible of producing both effects: activating pro-inflammatory mechanisms and producing physical decline. In fact, both DII and EDII were inversely associated with MEDAS, which measures adherence to a Mediterranean diet, which is considered to be healthy and, as mentioned before, associated with lower inflammation[29] and decreased frailty risk[6].

This study benefits from a prospective design, a detailed measurement of diet with a validated instrument, as well as a reasonably large sample size. Outcome measurements have been collected by trained staff undergoing a strict re-training schedule to ensure homogeneity and objectivity. There are also some limitations in our analyses. First, only 32 of 45 Shivappa's items were available in our dietary data. Fortunately, DII was conceived to be calculated with the amount of items available in each research context and two thirds is around the fraction regularly used in other studies. Second, applying *a posteriori* patterns (EDII) to populations other than that where they were developed can bias associations towards the null. Third, differences in habitual diets across countries may create heterogeneity on the foods providing the inflammatory or anti-inflammatory effects; also some associations of the inflammatory dietary indices with socio-demographic and lifestyle variables may vary across populations. In our analyses, adjusting for these variables was used to control confounding but also to tackle with those differences; however, we cannot rule out some residual confounding. The lack of

SPPB at baseline implies an incomplete exclusion of low SPPB prevalent cases for the analysis. This could artificially show a spurious longitudinal association due to contamination from cross-sectional association but given that we do not find such longitudinal association, even with the potential contamination, we believe that the approximation does not affect the results reported.

In conclusion, the different dietary inflammatory indices seem to capture non-overlapping information on the inflammatory characteristics of diet. Higher inflammatory potential of diet measured by DII but not EDII is associated with future frailty and IADL disability. Our results provide additional evidence for the role of inflammation on frailty, and shows that DII is able to measure diet healthiness in terms of physical decline in addition to avoidance of inflammation.

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ML, FRA, and ELG designed research; ML conducted research; PGC, JRB, AG, EGE, and ELG collected data; FRA and JRB designed the initial cohort; ML and ELG analyzed data; ML, FRA, and ELG drafted the manuscript; The rest of the authors

361 contributed important intellectual content to the final paper; ML had primary

362 responsibility for final content. All authors read and approved the final manuscript.

363 The authors have no potential conflicts of interest.

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501 FIGURE CAPTION
502
503 Flowchart: Steps sequence of participant exclusions to conform the analytic sample.

Table 1. Characteristics of the study participants across sex-specific tertiles of the Dietary Inflammatory Indices

		Dietary Inflammatory Index (DII)				Empirical Dietary Inflammatory Index (EDII)			
	Overall	Tertile 1	Tertile 2	Tertile 3	P-trend	Tertile 1	Tertile 2	Tertile 3	P-trend
N	1948	650	648	650		650	648	650	
Men	48.5	48.5	48.5	48.5	-	48.5	48.5	48.5	-
Age, y	68.4 (6.2)	67.7 (5.8)	68.1 (6.0)	69.4 (6.5)	<0.001	69.1 (6.4)	68.3 (6.1)	67.8 (6.0)	<0.001
Education									
Primary or less	52.9	49.2	50.2	59.4	<0.001	52.6	56.0	50.2	0.374
Secondary	24.9	28.0	26.2	20.6	0.002	27.2	22.5	25.1	0.370
University	22.1	22.8	23.6	20.0	0.229	20.2	21.5	24.8	0.045
BMI, kg/m^2	28.5 (4.3)	28.2 (4.3)	28.5 (4.1)	28.7 (4.5)	0.042	28.2 (4.0)	28.2 (4.2)	29.1 (4.6)	<0.001
Energy intake, kcal/d	2034.6 (572.8)	2285.4 (557.7)	2080.6 (521.2)	1737.8 (499.2)	<0.001	1801.2 (507.0)	2001.9 (519.0)	2300.5 (576.6)	<0.001
Time spent watching TV,h/wk	17.7 (10.9)	16.9 (10.1)	17.2 (10.1)	19.2 (12.3)	<0.001	17.0 (11.0)	17.9 (10.7)	18.2 (11.0)	0.049
Leisure-time physical activity, MET-h/wk	22.0 (15.3)	23.1 (15.1)	21.7 (15.2)	21.1 (15.6)	0.021	22.4 (15.0)	22.4 (15.8)	21.1 (15.1)	0.118
MEDAS	7.2 (1.8)	8.2 (1.8)	6.9 (1.8)	6.5 (1.5)	<0.001	7.6 (1.7)	7.2 (1.7)	6.7 (2.0)	<0.001
Smoking status									
Current smoker	11.4	9.1	11.7	13.5	0.012	12.5	10.8	11.1	0.433
Former smoker	30.3	30.2	33.5	27.4	0.278	30.3	31.2	29.5	0.763
Never smoker	58.2	60.8	54.8	59.1	0.536	57.2	58.0	59.4	0.431
Diagnosed diseases									
Diabetes	15.0	12.0	14.4	18.6	0.001	12.3	13.7	18.9	0.001
Bronchitis or asthma	7.3	8.0	7.4	6.6	0.339	9.2	5.4	7.4	0.203
Cardiovascular disease	5.1	4.6	5.9	4.9	0.802	4.5	4.9	6.0	0.210
Osteo-muscular disease	47.7	49.2	46.8	47.2	0.470	48.8	45.5	48.9	0.956
Depression	7.8	7.2	7.1	9.1	0.215	6.9	7.3	9.2	0.122
Cancer	2.0	1.5	2.5	2.0	0.553	2.6	1.2	2.2	0.553

Data shown as percentage and mean (standard deviation). P values calculated from t-tests or Chi-squared-tests. Cut-off values for Dietary Inflammatory Index tertiles were -0.69 and 0.93 for men and -0.02 and 1.85 for women. Cut-off values for Empirical Dietary Inflammatory Index tertiles were -0.293 and 0.467 for men and -0.535 and 1.220 for women.

BMI, Body Mass Index, MET, metabolic equivalent, MEDAS, MEditerranean Diet Adherence Score (0-14)

Mean (standard deviations) and percentage (number) are reported for continuous and categorical variables respectively.

Table 2. Odds ratios (95% Confidence Interval) for the association of Dietary Inflammatory Indices with reduced physical performance, frailty and disability

	Dietary Inflammatory Index (DII)				Empirical Dietary Inflammatory Index (EDII)			
	Tertile 1	Tertile 2	Tertile 3	P-trend	Tertile 1	Tertile 2	Tertile 3	P-trend
Low physical performance (SPPB<=9), n/N	**209/626**	**238/630**	**253/613**	**700/1869**	**235/626**	**215/620**	**250/623**	**700/1869**
Model 1	Ref.	1.18 (0.92,1.50)	1.18 (0.93,1.51)	0.180	Ref.	0.92 (0.72,1.17)	1.29 (1.01,1.65)	0.040
Model 2	Ref.	1.21 (0.94,1.56)	1.25 (0.95,1.65)	0.113	Ref.	0.93 (0.72,1.20)	1.18 (0.90,1.55)	0.243
Model 3	Ref.	1.19 (0.92,1.53)	1.22 (0.92,1.62)	0.159	Ref.	0.94 (0.73,1.21)	1.18 (0.90,1.55)	0.240
Frailty, n/N	**25/641**	**35/640**	**67/634**	**127/1915**	**46/640**	**37/637**	**44/638**	**127/1915**
Model 1	Ref.	1.33 (0.78,2.30)	2.30 (1.43,3.80)	<0.001	Ref.	0.82 (0.52,1.31)	1.10 (0.71,1.73)	0.681
Model 2	Ref.	1.32 (0.76,2.34)	2.60 (1.50,4.61)	<0.001	Ref.	0.85 (0.52,1.38)	0.84 (0.50,1.41)	0.502
Model 3	Ref.	1.33 (0.75,2.37)	2.48 (1.42,4.44)	0.001	Ref.	0.82 (0.50,1.34)	0.77 (0.45,1.30)	0.319
IADL disability, n/N	**17/605**	**22/591**	**42/572**	**81/1768**	**32/602**	**23/586**	**26/580**	**81/1768**
Model 1	Ref.	1.26 (0.66,2.45)	2.21 (1.24,4.07)	0.005	Ref.	0.79 (0.45,1.38)	1.01 (0.58,1.75)	0.999
Model 2	Ref.	1.22 (0.62,2.41)	2.03 (1.07,3.99)	0.026	Ref.	0.88 (0.49,1.56)	1.14 (0.61,2.10)	0.734
Model 3	Ref.	1.20 (0.62,2.38)	1.96 (1.03,3.86)	0.035	Ref.	0.87 (0.48,1.56)	1.10 (0.59,2.05)	0.796

n/N, number of cases/number at risk. SPPB, short physical performance battery. IADL, instrumental activities of daily living

Odds ratios and 95% confidence interval were estimated with logistic regression models with different levels of adjustment. Model 1 is adjusted for age, sex, and education; Model 2 is additionally adjusted for smoking status, body mass index, energy intake, diagnosed diseases; Model 3 is additionally adjusted for time spent watching TV and leisure-time physical activity. Trend is calculated with the tertile number as a continuous variable.

Appendix

Appendix Table 1. Odds ratios (95% Confidence Interval) for the association between Dietary Inflammatory Indices and the components of the Short Physical Performance Battery test and the Frailty criteria

	Dietary Inflammatory Index (DII)				Empirical Dietary Inflammatory Index (EDII)			
	Tertile 1	Tertile 2	Tertile 3	P-trend	Tertile 1	Tertile 2	Tertile 3	P-trend
Short Physical Performance Battery								
Balance test score < 2, n/N	**13/626**	**14/630**	**17/613**	**44/1869**	**15/626**	**15/620**	**14/623**	**44/1869**
Model 3	Ref.	1.00 (0.44,2.26)	1.02 (0.43,2.45)	0.955	Ref.	1.01 (0.47,2.20)	0.92 (0.39,2.15)	0.853
Gait speed test < 2, n/N	**75/626**	**100/630**	**118/613**	**293/1869**	**89/626**	**90/620**	**114/623**	**293/1869**
Model 3	Ref.	1.44 (1.03,2.01)	1.82 (1.27,2.62)	0.001	Ref.	1.09 (0.78,1.51)	1.39 (0.99,1.96)	0.056
Chair stand test < 2, n/N	**163/626**	**188/630**	**202/613**	**553/1869**	**183/626**	**177/620**	**193/623**	**553/1869**
Model 3	Ref.	1.19 (0.91,1.55)	1.25 (0.93,1.67)	0.132	Ref.	1.04 (0.80,1.36)	1.14 (0.86,1.50)	0.375
Frailty								
Exhaustion, n/N	**38/550**	**46/519**	**51/494**	**135/1563**	**47/535**	**40/515**	**48/513**	**135/1563**
Model 3	Ref.	1.27 (0.79,2.04)	1.35 (0.81,2.25)	0.249	Ref.	0.94 (0.59,1.49)	1.27 (0.78,2.04)	0.354
Low levels of activity, n/N	**77/550**	**70/519**	**66/494**	**213/1563**	**76/535**	**56/515**	**81/513**	**213/1563**
Model 3	Ref.	1.04 (0.71,1.51)	1.17 (0.78,1.78)	0.457	Ref.	0.72 (0.48,1.06)	0.90 (0.61,1.34)	0.611
Slow gait speed, n/N	**58/547**	**56/517**	**78/490**	**192/1554**	**65/533**	**50/510**	**77/511**	**192/1554**
Model 3	Ref.	1.05 (0.70,1.57)	1.64 (1.08,2.51)	0.021	Ref.	0.84 (0.56,1.26)	1.33 (0.89,1.99)	0.166
Unintentional weight loss, n/N	**32/544**	**41/516**	**34/488**	**107/1548**	**36/533**	**34/510**	**37/505**	**107/1548**
Model 3	Ref.	1.60 (0.97,2.67)	1.71 (0.97,3.03)	0.059	Ref.	0.87 (0.52,1.44)	0.72 (0.42,1.23)	0.228
Muscle weakness, n/N	**148/550**	**128/517**	**178/494**	**454/1561**	**157/535**	**145/514**	**152/512**	**454/1561**
Model 3	Ref.	0.79 (0.58,1.07)	1.17 (0.84,1.61)	0.385	Ref.	1.11 (0.83,1.50)	1.31 (0.95,1.81)	0.096

n/N, number of cases/number at risk.

Odds ratios and 95% confidence interval were estimated with logistic regression. Analyses were adjusted as in Model 3 in Table 2. Trend is calculated with the tertile number as a continuous variable.

531 Dietary Inflammatory Index parameters used

Food or nutrient[10]	Present in ENRICA
Alcohol (g)	Yes
Vitamin B12 (ug)	Yes
Vitamin B6 (mg)	Yes
b-Carotene (ug)	Yes
Caffeine (g)	Yes
Carbohydrate (g)	Yes
Cholesterol (mg)	Yes
Energy (kcal)	Yes
Eugenol (mg)	No
Total fat (g)	Yes
Fibre (g)	Yes
Folic acid (ug)	Yes
Garlic (g)	Yes
Ginger (g)	No
Fe (mg)	Yes
Mg (mg)	Yes
MUFA (g)	Yes
Niacin (mg)	Yes
n-3 Fatty acids (g)	Yes
n-6 Fatty acids (g)	Yes
Onion (g)	Yes
Protein (g)	Yes
PUFA (g)	Yes
Riboflavin (mg)	Yes
Saffron (g)	No
Saturated fat (g)	Yes
Se (ug)	Yes
Thiamin (mg)	Yes
Trans fat (g)	Yes
Turmeric (mg)	No
Vitamin A (RE)	Yes
Vitamin C (mg)	Yes
Vitamin D (ug)	Yes
Vitamin E (mg)	Yes
Zn (mg)	Yes
Green/black tea (g)	Yes
Flavan-3-ol (mg)	No
Flavones (mg)	No
Flavonols (mg)	No
Flavonones (mg)	No
Anthocyanidins (mg)	No
Isoflavones (mg)	No
Pepper (g)	No
Thyme/oregano (mg)	No
Rosemary (mg)	No

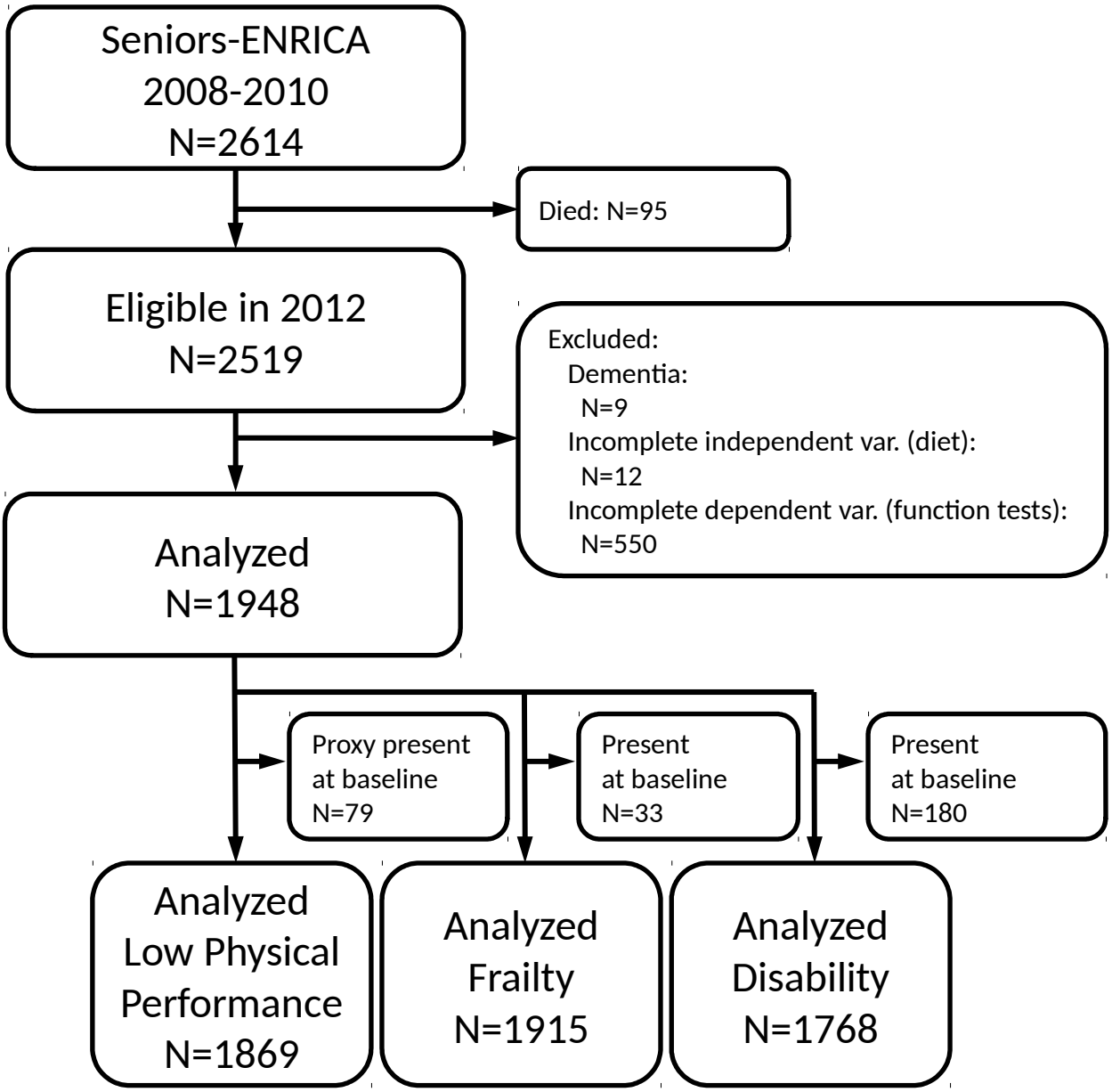
532

533

534 Empirical Dietary Inflammatory Index food groups. Tabung et al.[11]
535

Pro-inflammatory
Processed meat
Red meat
Organ meat
Other fish
Other vegetables
Refined grains
High-energy beverages
Low-energy beverages
Tomatoes
Anti-inflammatory
Beer
Wine
Tea
Coffee
Dark yellow vegetables
Leafy green vegetables
Snacks
Fruit juice
Pizza

536


Seniors-ENRICA
2008-2010
N=2614
Died: N=95
Eligible in 2012
N=2519
Excluded:
Dementia:
N=9
Incomplete independent var. (diet):
N=12
Incomplete dependent var. (function tests):
N=550
Analyzed
N=1948
Proxy present
at baseline
N=79
Present
at baseline
N=33
Present
at baseline
N=180
Analyzed
Low Physical
Performance
N=1869
Analyzed
Frailty
N=1915
Analyzed
Disability
N=1768