CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Changes in Dietary Intake of Animal and Vegetable Protein and Unhealthy Aging

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ABSTRACT

BACKGROUND: Animal and vegetable-based proteins differ on their effect on many health outcomes, but their relationship with unhealthy aging is uncertain. Thus, we examined the association between changes in animal and vegetable protein intake and unhealthy aging in older adults.

METHODS: Data came from 1951 individuals aged ≥60 years recruited in the Seniors-ENRICA cohort in 2008-2010 (wave 0) and followed-up in 2012 (wave 1), 2015 (wave 2), and 2017 (wave 3). Dietary protein intake was measured with a validated diet history at waves 0 and 1, and unhealthy aging was measured with a 52-item health deficit accumulation index at each wave.

RESULTS: Compared with participants with a >2% decrease in energy intake from vegetable protein from wave 0 to wave 1, those with a >2% increase showed less deficit accumulation over 3.2 years (multivariable β [95% confidence interval (CI)]: -1.05 [-2.03, -0.06]), 6 years (-1.28 [-2.51, -0.03]), and 8.2 years of follow-up (-1.68 [-3.27, -0.09]). No associations were found for animal protein. Less deficit accumulation over 8.2 years was observed when substituting 1% of energy from vegetable protein for an equal amount of carbohydrate or fat (-0.50 [-0.93, -0.07]), animal protein (-0.44 [-0.81, -0.07]), dairy protein (-0.51 [-0.91, -0.12]), or meat protein (-0.44 [-0.84, -0.04]).

CONCLUSIONS: Increasing dietary intake of vegetable protein may delay unhealthy aging when replacing carbohydrates, fats, or animal protein, especially from meat and dairy.

 • The American Journal of Medicine (2019) 000:1−9

KEYWORDS: Animal protein; Cohort study; Unhealthy aging; Vegetable protein

INTRODUCTION

The report on aging and health published by the World Health Organization (WHO) in 2015 defines healthy aging as "the process of developing and maintaining the functional ability that enables wellbeing in older age" and emphasizes the benefits of maintaining healthy behaviors through life, particularly engaging in physical activity and keeping an adequate nutrition, especially in older age.[1]

During aging, numerous physiological changes contribute to a decrease in food and energy intake, such as reduced appetite, loss of acuity of taste, smell and sight, or difficulties chewing and swallowing.[2] Although energy requirements decline with age as a result of a reduced basal metabolic rate,[3] the requirements for other essential nutrients may in fact increase in later life. Specifically, a greater protein intake is needed to compensate for age-related decreases in skeletal muscle mass, strength, and function.[4] The current

Funding: This work was mainly supported by FIS grants 16/609,16/1512 and 18/287 (Instituto de Salud Carlos III, State Secretary of R+D+I and FEDER/FSE), CIBERESP, the Salamander Project (JPI-A Healthy Diet for a Healthy Life, State Secretary of R+D+I PCIN-2016-145), and Cátedra de Epidemiología y Control del Riesgo Cardiovascular at UAM. The funding agencies had no role in study design, data collection and analysis, interpretation of results, manuscript preparation or in the decision to submit this manuscript for publication.

Conflicts of Interest: None.

Authorship: All authors had access to the data and a role in writing this manuscript.

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https://doi.org/10.1016/j.amjmed.2019.06.051

US Recommended Dietary Allowance for protein of 0.8 g/kg/day is based on short-term nitrogen balance studies,[5] which may not be the best methods to estimate optimal protein requirements in older adults, so studies assessing the effects of different amounts of protein intake on clinically important outcomes are essential.[6,7] More recent recommendations using this approach propose an average daily intake of 1.0-1.2 g/kg/day for older adults and even higher for those with acute or chronic diseases.[8] These recommendations are supported by growing evidence of the beneficial effect of higher intakes of dietary total protein on muscle mass and strength,[2,9−11] physical functioning,[2,9,11−14] hip fracture,[15,16] and frailty.[11,17−20]

The source of dietary protein is also important because other components of high-protein foods may influence health outcomes and account for the effects attributed to protein. Although research in this field is relatively recent, it has shown opposite effects of animal and vegetable protein on clinically important outcomes, such as type 2 diabetes, cardiovascular disease, and all-cause and cardiovascular mortality, with beneficial effects of vegetable protein and detrimental effects of animal protein.[21−25] These findings and the fact that substitution of vegetable protein for animal protein has been associated with lower risk of mortality[23] stresses the importance of protein sources and warrants more research in this area.

The purpose of this work was to examine if changes in dietary intake of animal and vegetable protein are associated with changes in a health deficit accumulation index (DAI) in older adults. Using changes in dietary intake instead of baseline intake is a more potent approach because they mimic dietary intervention in clinical trials. The DAI is a good indicator of unhealthy aging and constitutes a clinically important end point because it has shown to predict adverse outcomes such as death, institutionalization, or hospitalization.[26−28]

CLINICAL SIGNIFICANCE

- Higher intake of vegetable protein was associated with less deficit accumulation.
- Replacing fat, carbohydrate, or animal protein (especially from meat and dairy) with plant protein led to less deficit accumulation.
- Including vegetable protein in the diet instead of other macronutrients may delay unhealthy aging.

SUBJECTS AND METHODS

Study Design and Population

This study has been conducted using data from the Seniors-ENRICA cohort, whose methods have been reported elsewhere.[28,29] Briefly, the participants in the cohort were selected in 2008-2010 by stratified cluster sampling of the community-dwelling population ages 60 and older in Spain, and followed-up for a median of 8.2 years (range: 6.8-9.1) through 2017. At baseline (wave 0), a telephone interview was performed to obtain information on sociodemographic, lifestyle, and morbidity data, and two home visits were conducted to collect biological samples, perform a physical examination, obtain data on prescribed medications and functional limitations, and record a diet history.[29] Additional follow-ups were performed in 2012 (wave 1), 2015 (wave 2), and 2017 (wave 3) (Supplemental Figure 1 in Supplementary material 1). Study participants provided written informed consent, and the Clinical Research Ethics Committee of La Paz University Hospital in Madrid approved the study.

Study Variables

Dietary Protein Intake. At waves 0 and 1, habitual dietary intake in the previous year was estimated with a validated computerized diet history developed from the one used in the EPIC cohort study in Spain.[29] Energy and nutrient intake was estimated using standard composition tables for Spain. The diet history exhibited good validity for assessing protein intake, with Pearson correlation coefficients with seven 24-h recalls obtained over 1 year of 0.62 for both animal and vegetable protein.[30] Macronutrients were expressed as percentages of total energy intake, and changes in total energy and macronutrient intake from wave 0 to wave 1 were calculated.

Deficit Accumulation Index. At each wave, unhealthy aging was measured using a 52-item DAI with 4 domains: functional impairments, self-reported health/vitality, mental health, and morbidities/use of health services. The overall and domain-specific DAI scores were calculated as the total sum of points assigned to each deficit divided by the number of deficits considered and further multiplied by 100 to obtain a range from 0 (lowest) to 100% (highest deficit accumulation). A detailed description of this index is provided in the Methodological Appendix and Supplemental Table 1 (available online).[28]

We calculated changes in the DAI from wave 0 to wave 1 (median follow-up: 3.2 years), wave 2 (6.0 years), and wave 3 (8.2 years) (Supplemental Figure 1, available online). Negative changes indicate health improvement, whereas positive changes indicate health deterioration.

Potential Confounders. At each wave, we collected information on sociodemographic and lifestyle characteristics including age, sex, educational level, tobacco smoking, alcohol consumption, leisure-time physical activity (in metabolic equivalents of task-hour/week), and time watching TV (in h/d). As a measure of diet quality, we used intake of fruits and vegetables (except legumes and tubers), monounsaturated fats and n-3 polyunsaturated fats (in g/d). Also, weight and height were measured in standardized conditions[31] to calculate the body mass index (BMI) as the weight (in kg) divided by the squared height (in m).

Statistical Analysis

Details about study participants' disposition are presented in Supplemental Figure 2 in Supplementary material 1. The

Table 1 Baseline Characteristics of Study Participants by Categories of Change in Protein Intake From Wave 0 to Wave 1.

	Change in animal protein intake (% en)				Change in vegetable protein intake (% en)			
	<−2%	−2% to <0%	0% to 2%	>2%	<−1%	−1% to <0%	0% to 1%	>1%
	n = 562	n = 400	n = 422	n = 567	n = 449	n = 531	n = 519	n = 452
Age (years)	69.1 (6.4)	68.7 (6.5)	68.3 (6.6)	68.4 (6.2)	68.7 (6.3)	69.1 (6.7)	68.2 (6.1)	68.4 (6.5)
Sex — men, No. (%)	261 (46.4)	208 (52.0)	207 (49.1)	268 (47.3)	201 (44.8)	268 (50.5)	265 (51.1)	210 (46.5)
Educational level — primary or less, No. (%)	297 (52.9)	212 (53.0)	220 (52.1)	312 (55.0)	253 (56.4)	293 (55.2)	253 (48.8)	242 (53.5)
Tobacco smoking — current smoker, No. (%)	61 (10.9)	50 (12.5)	45 (10.7)	62 (10.9)	54 (12.0)	54 (10.2)	66 (12.7)	44 (9.7)
Alcohol consumption — current drinker, No. (%)	260 (46.3)	220 (55.0)	235 (55.7)	296 (52.2)	207 (46.1)	277 (52.2)	297 (57.2)	230 (50.9)
Leisure-time physical activity (MET-h/week)	21.5 (14.9)	22.3 (16.1)	22.6 (14.6)	21.3 (15.9)	21.4 (16.0)	21.7 (14.8)	22.1 (15.8)	22.1 (14.9)
Time watching TV (h/day)	2.6 (1.6)	2.5 (1.5)	2.6 (1.6)	2.5 (1.6)	2.6 (1.6)	2.6 (1.7)	2.4 (1.4)	2.5 (1.6)
BMI (kg/m^2)	28.7 (4.4)	28.4 (4.0)	28.0 (4.3)	28.5 (4.3)	28.6 (4.4)	28.4 (4.3)	28.2 (4.1)	28.7 (4.3)
Energy intake (kcal/day)	1869 (540)	2000 (543)	2072 (547)	2189 (569)	1963 (539)	2024 (557)	2112 (569)	2021 (583)
Animal protein intake (g/day)	74.7 (15.6)	62.9 (12.2)	56.9 (13.8)	49.6 (13.1)	56.6 (15.1)	59.3 (15.5)	61.9 (16.8)	67.0 (18.8)
Vegetable protein intake (g/day)	28.0 (6.1)	30.8 (6.2)	32.0 (7.3)	32.9 (6.8)	36.4 (5.9)	31.8 (5.3)	29.5 (6.0)	25.9 (6.1)
Fat intake (g/day)	84.5 (13.2)	82.2 (13.7)	81.4 (14.2)	80.8 (14.6)	77.7 (13.2)	80.6 (12.7)	84.1 (14.0)	86.8 (14.6)
Carbohydrate intake (g/day)	198 (33.1)	211 (33.6)	219 (35.1)	227 (35.2)	226 (32.2)	217 (29.6)	208 (36.9)	200 (40.2)
Alcohol intake (g/day)	10.0 (13.5)	10.8 (15.3)	9.9 (15.4)	9.8 (17.7)	7.9 (11.7)	10.2 (16.0)	11.0 (17.0)	11.1 (16.5)
Fruit and vegetable intake (g/day)	513 (237)	553 (251)	584 (252)	583 (277)	562 (263)	591 (275)	554 (253)	515 (226)
Monounsaturated fat intake (g/day)	36.6 (7.5)	36.0 (7.7)	36.2 (8.5)	35.8 (8.5)	34.2 (7.7)	35.7 (7.6)	37.1 (8.2)	37.4 (8.3)
n-3 polyunsaturated fat intake (g/day)	2.31 (1.24)	2.11 (0.98)	2.03 (1.03)	1.90 (1.20)	2.02 (1.15)	1.99 (1.02)	2.11 (1.12)	2.26 (1.28)
DAI	17.7 (10.1)	17.1 (10.0)	16.4 (8.8)	17.3 (8.9)	17.7 (9.0)	17.3 (9.9)	16.6 (9.1)	17.3 (9.9)

Values are means (standard deviations) unless indicated.
% en = percentage of energy intake; BMI = body mass index; DAI = deficit accumulation index; MET = metabolic equivalent of task.

Table 2 Beta Coefficients (95% Confidence Intervals) for the Association of Changes in Protein Intake From Wave 0 to Wave 1 With Changes in the DAI.

	Change in animal protein intake (% en)					
	<−2%	−2% to <0%	0% to 2%	>2%	*P* trend	per 1% increase
Change in the DAI over 3.2 years						
No.	562	400	422	567		1951
Model 1	Ref.	−0.58 (−1.46 to 0.31)	−0.02 (−0.91 to 0.87)	0.01 (−0.87 to 0.88)	0.74	−0.00 (−0.10 to 0.09)
Model 2	Ref.	−0.51 (−1.39 to 0.37)	0.03 (−0.86 to 0.91)	0.06 (−0.81 to 0.93)	0.67	0.01 (−0.09 to 0.10)
Model 3	Ref.	−0.56 (−1.44 to 0.32)	−0.05 (−0.94 to 0.84)	−0.04 (−0.93 to 0.85)	0.84	−0.01 (−0.11 to 0.09)
Change in the DAI over 6 years						
No.	446	295	339	440		1520
Model 1	Ref.	−0.75 (−1.90 to 0.40)	−0.54 (−1.66 to 0.59)	−0.32 (−1.43 to 0.81)	0.66	−0.07 (−0.19 to 0.05)
Model 2[a]	Ref.	−0.63 (−1.76 to 0.50)	−0.36 (−1.47 to 0.75)	−0.15 (−1.26 to 0.95)	0.88	−0.04 (−0.16 to 0.08)
Model 3[a]	Ref.	−0.65 (−1.78 to 0.49)	−0.34 (−1.47 to 0.78)	−0.15 (−1.28 to 0.99)	0.91	−0.04 (−0.16 to 0.08)
Change in the DAI over 8.2 years						
No.	230	171	184	227		812
Model 1	Ref.	−0.37 (−1.87 to 1.12)	−0.62 (−2.12 to 0.88)	−0.38 (−1.90 to 1.15)	0.58	−0.01 (−0.18 to 0.15)
Model 2[b]	Ref.	−0.50 (−1.97 to 0.97)	−0.63 (−2.09 to 0.84)	−0.57 (−2.05 to 0.92)	0.45	−0.04 (−0.20 to 0.12)
Model 3[b]	Ref.	−0.55 (−2.02 to 0.93)	−0.68 (−2.16 to 0.80)	−0.63 (−2.13 to 0.88)	0.41	−0.04 (−0.21 to 0.12)

Table 2 (continued)

	Change in vegetable protein intake (% en)					
	<−1%	−1% to <0%	0% to 1%	>1%	*P* trend	per 1% increase
Change in the DAI over 3.2 years						
No.	449	531	519	452		1951
Model 1	Ref.	−0.60 (−1.46 to 0.27)	−0.40 (−1.29 to 0.49)	−1.03 (−1.99 to −0.07)*	0.07	−0.26 (−0.50 to −0.01)*
Model 2	Ref.	−0.60 (−1.46 to 0.26)	−0.40 (−1.28 to 0.48)	−0.98 (−1.93 to −0.02)*	0.09	−0.23 (−0.47 to 0.02)
Model 3	Ref.	−0.66 (−1.52 to 0.21)	−0.47 (−1.37 to 0.43)	−1.05 (−2.03 to −0.06)*	0.07	−0.26 (−0.52 to −0.01)*
Change in the DAI over 6 years						
No.	358	400	401	361		1520
Model 1	Ref.	−0.84 (−1.95 to 0.27)	−0.65 (−1.79 to 0.49)	−1.35 (−2.56 to −0.14)*	0.05	−0.32 (−0.64 to −0.01)*
Model 2[a]	Ref.	−0.65 (−1.76 to 0.50)	−0.40 (−1.53 to 0.72)	−1.22 (−2.42 to −0.03)*	0.08	−0.26 (−0.57 to 0.05)
Model 3[a]	Ref.	−0.66 (−1.76 to 0.44)	−0.42 (−1.57 to 0.72)	−1.28 (−2.51 to −0.03)*	0.08	−0.28 (−0.60 to 0.05)
Change in the DAI over 8.2 years						
No.	191	207	219	195		812
Model 1	Ref.	−0.24 (−1.71 to 1.23)	−0.68 (−2.16 to 0.81)	−1.34 (−2.94 to 0.27)	0.09	−0.41 (−0.83 to 0.02)
Model 2[b]	Ref.	−0.23 (−1.66 to 1.21)	−0.73 (−2.18 to 0.72)	−1.74 (−3.30 to −0.17)*	0.03	−0.51 (−0.93 to −0.09)*
Model 3[b]	Ref.	−0.26 (−1.70 to 1.19)	−0.69 (−2.16 to 0.78)	−1.68 (−3.27 to −0.09)*	0.04	−0.50 (−0.93 to −0.07)*

Model 1: Linear regression model adjusted for sex, age, educational level (primary or less, secondary, or university) and DAI at wave 0, and changes in energy intake (kcal/day), alcohol intake (<−1, −1 to 0, 0 to 1, >1% en), and complementary, animal or vegetable, protein intake (% en) from wave 0 to wave 1.

Model 2: As model 1 and further adjusted for changes in smoking status (remained never, current to former and remained former, or never/former to current and remained current), alcohol consumption status (remained never, current to former and remained former, or never/former to current and remained current), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), and body mass index (kg/m^2) from wave 0 to wave 1.

Model 3: As model 2 and further adjusted for changes in intake of fruits and vegetables (g/day) (quartiles), monounsaturated fats (g/day) (quartiles), and n-3 polyunsaturated fats (g/day) (quartiles) from wave 0 to wave 1.

[a]Adjusted for changes from wave 0 to wave 2 for lifestyle variables.

[b]Adjusted for changes from wave 0 to wave 3.

**P* < 0.05.

% en = percentage of energy intake; DAI = deficit accumulation index; MET = metabolic equivalent of task.

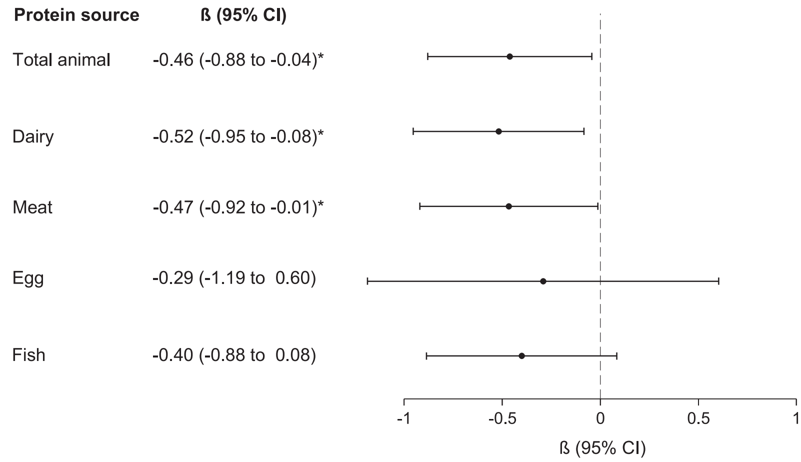

Figure 1 Change in the DAI over 8.2 years associated with replacement of 1% of energy from animal protein sources with vegetable protein. Linear regression model adjusted for sex, age, educational level (primary or less, secondary, or university), and DAI at wave 0, changes in energy intake (kcal/day), vegetable protein intake (% en), animal protein intake from all sources except the one being examined (% en), fat intake (% en), carbohydrate intake (% en), and alcohol intake (% en) from wave 0 to wave 1, and changes in smoking status (remained never, current to former and remained former, or never/former to current and remained current), alcohol consumption status (remained never, current to former and remained former, or never/former to current and remained current), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), and body mass index (kg/m^2) from wave 0 to wave 3. *$P < 0.05$. % en = percentage of energy intake; CI = confidence interval; DAI = deficit accumulation index.

analytical sample comprised 1951 individuals for analyses of change in the DAI over 3.2 years of follow-up, 1520 for analyses of change in the DAI over 6 years, and 812 for analyses of change in the DAI over 8.2 years.

The association of changes in animal or vegetable protein intake from wave 0 to wave 1 (in quartiles) with change in the DAI over 3.2 years was summarized with β coefficients and their 95% confidence intervals (CIs) obtained from linear regression. We used nutrient density models with adjustment for changes in energy intake and in the percentages of energy from animal protein, vegetable protein, and alcohol. In these models, the coefficient for a particular macronutrient (animal or vegetable protein) is interpreted as the effect of replacing those macronutrients not included in the model (in our case, fats and carbohydrates) with an equal amount of energy from such macronutrients, independent of energy intake and the macronutrients included in the model (in our case, alcohol and the complementary protein). We chose these particular models with no adjustment for fats and carbohydrates for our main analyses because protein from animal foods is usually accompanied by fats and protein from most plant foods is usually accompanied by carbohydrates. Thus, we would expect animal protein to replace mostly carbohydrates, and vegetable protein to replace mostly fats. However, we also built additional models adjusting for change in fats or carbohydrates.

Three models were tested: Model 1 adjusted for sex, age, educational level, and the DAI at wave 0; Model 2 further adjusted for changes in tobacco smoking, alcohol consumption, leisure-time physical activity, time watching TV, and BMI from wave 0 to wave 1; and Model 3 further adjusted for changes in intake of fruits and vegetables, monounsaturated fats, and n-3 polyunsaturated fats from wave 0 to wave 1. Similar analyses were conducted to assess the association of changes in animal or vegetable protein intake from wave 0 to wave 1 with changes in the DAI over 6 years and 8.2 years of follow-up; in these cases, models were adjusted for changes in lifestyle variables from wave 0 to wave 2 and from wave 0 to wave 3, respectively. We also examined the association between the replacement of 1% of energy from different animal protein sources (dairy, meat, egg, or fish) with an equal amount of energy from vegetable protein, and changes in the DAI. This was done by using models that included energy intake, and the percentages of energy from vegetable protein, animal protein from all sources except the one being examined, and other macronutrients (fat, carbohydrates, and alcohol).

Lastly, to check the robustness of results, analyses for the change in the DAI in the longest follow-up were stratified by sex, age, physical activity, BMI, diet quality assessed with the Mediterranean Diet Adherence Screener (MEDAS), DAI score, and main chronic diseases at baseline; interaction terms defined as the product of change in protein intake by such variables were tested. Becauase interactions with sex were not significant, results for men and women are presented combined.

Statistical significance was set at two-sided $P < 0.05$. Analyses were performed with Stata®, version 13.1.

RESULTS

Among study participants, animal and vegetable protein accounted for about 12% and 6% of total energy intake, respectively. The average baseline distribution of protein intake according to dietary source was: meat (5.18% of energy intake), dairy (3.26%), refined grains (2.97%), fish (2.84%), legumes (0.82%), eggs (0.61%), fruit (0.58%), vegetables (0.56%), whole grains (0.34%), tubers (0.19%), and nuts (0.15%). Detailed information on the consumption of macronutrients at waves 0 and 1 is presented in Supplemental Tables 2 and 3 (online).

There was no substantial variation in baseline sociodemographic and lifestyle characteristics of study participant across categories of change in animal or vegetable protein intake, except for dietary intake. Compared with individuals who decreased animal protein intake from wave 0 to wave 1, those who increased intake had higher baseline intakes of energy, vegetable protein, carbohydrate, and fruit and vegetables and lower baseline intakes of animal protein, total fat, and n-3 polyunsaturated fat; and those who increased vegetable protein intake had higher baseline intakes of energy, animal protein, total fat, monounsaturated fat, and n-3 polyunsaturated fat and lower baseline intakes of vegetable protein, carbohydrate, and fruit and vegetables (Table 1).

The associations of changes in animal and vegetable protein intake from wave 0 to wave 1 at the expense of carbohydrate and fat with changes in the DAI from wave 0 to wave 1, wave 2, or wave 3 are shown in Table 2. No associations were found between change in animal protein intake and changes in the DAI. Compared with participants with a decrease >2% in energy intake from vegetable protein, those with an increase >2% showed less deficit accumulation over 3.2 years (β [95% CI] = −1.05 [−2.03, −0.06]), 6 years (−1.28 [−2.51, −0.03]), and 8.2 years (−1.68 [−3.27, −0.09]). The magnitude of the association between increasing vegetable protein intake and deficit accumulation grew with the duration of follow-up, with the largest association observed for change in the DAI over 8.2 years (β [95% CI] = −0.50 per 1% increase of energy from vegetable protein [−0.93, −0.07]). Similar results were obtained when analyses were adjusted for change in fats (−0.49 per 1% increase of energy from vegetable protein [−0.93, −0.05]) or carbohydrates (−0.52 [−0.99, −0.06]).

The associations between the replacement of 1% of energy from different animal protein sources with an equal amount of energy from vegetable protein, and the change in the DAI from wave 0 to wave 3 are presented in Figure 1. Replacing total animal protein, dairy protein, or meat protein with vegetable protein led to significantly less deficit accumulation over 8.2 years, whereas replacement of egg protein or fish protein did not show a statistically significant association with deficit accumulation. Finally, we found no evidence that the study associations varied across subgroups of sex, age, physical activity, BMI, MEDAS score, deficit accumulation, and prevalent chronic disease at baseline (Supplemental Figure 3, online).

DISCUSSION

In this cohort of older adults in Spain, we found that increasing dietary intake of vegetable protein at the expense of other macronutrients was associated with less deficit accumulation over time, an association that became stronger with the duration of follow-up. An increase of 1% of energy in vegetable protein (corresponding to about 5 g/d as an average) was associated with a decrease in the DAI of 0.50 in a period of 8 years. Because we had previously observed an average annual increase in the DAI of 0.74 in this cohort[28], such increase in vegetable protein corresponds to a delay in unhealthy aging of approximately 8 months, that is, 1 month per year, which is clinically relevant. In addition, substitution of 1% of energy from vegetable protein for an equal amount of total animal protein, dairy protein, or meat protein also led to significantly less deficit accumulation.

Previous studies examining specific effects of protein from different sources have reported beneficial effects of higher intakes of animal protein on muscle mass[9,32] and strength,[33]functional performance,[9] hip fracture (only in men),[15] and frailty,[34] but detrimental effects on type 2 diabetes[21,22] and cardiovascular mortality.[23] Vegetable protein, on the other hand, has been associated with lower risk of muscle loss,[35] frailty,[36] hip fracture,[15] type 2 diabetes,[22] and cardiovascular and all-cause mortality.[23] Previous research also reports associations between the substitution of vegetable protein for animal protein and a lower risk of type 2 diabetes[22] and mortality.[23] Among animal protein sources, higher intakes of red or processed meat have been associated with higher risk of type 2 diabetes, cardiovascular disease, some cancers, and all-cause and cardiovascular mortality,[37−40] and higher dairy intake has been related to more cardiovascular mortality.[40] In line with these findings, in our study, substituting vegetable protein for animal protein from meat and dairy led to less deficit accumulation over time. Among vegetable protein sources, higher consumption of fruits and vegetables have been associated with a lower risk of type 2 diabetes, cardiovascular disease, frailty, and mortality;[41−45] higher intake of nuts has been associated with a lower risk of type 2 diabetes, cardiovascular disease, and all-cause and cardiovascular mortality;[45,46] higher intake of legumes has been related to a lower risk of ischemic heart disease;[47] and higher consumption of whole grains has been associated with a lower risk of type 2 diabetes, cardiovascular disease, colorectal cancer, and mortality.[44,45,48,49] Biological mechanisms for the beneficial health effects of vegetable protein are unknown: Effects may be due to the amino acid composition of specific foods, other components present in the food sources of vegetable protein, and lifestyles associated with specific dietary patterns,[50] so it is difficult to conclude that the observed effects are attributable only to protein per se. One might think that the beneficial associations observed for vegetable protein could also be the result of the observed reduction in fat intake accompanying the increase in vegetable protein (Supplemental Table 3 in Supplementary material 1). However, adjustment for change in fat intake did not materially modify the association. Besides, consistently with the distribution of vegetable protein sources in a study in 8 European countries,[51] half of the vegetable protein consumed in our cohort derived from refined grains, which have been associated with higher risk of type 2 diabetes, cardiovascular disease, and other chronic conditions,[52] suggesting that the beneficial effect of vegetable protein observed in our study might, at least partly, reside in protein.

This study has strengths and limitations. Among the strengths is the instrument used to measure dietary intake, a validated diet history with good correlation with seven 24-h recalls obtained over 1 year.[30] Another strength is the design of the study because the assessment of the influence of changes in protein intake resembles the approach used in dietary intervention trials. In addition, linking changes in diet during a short period of time to changes in deficit accumulation over longer follow-ups reinforces the advantages of the prospective design, intended to establish the temporality of the associations, and helps reduce reverse causation. A further strength is the approach to unhealthy aging used because the DAI is conceptually sound (reflects all health dimensions of aging) and predicts well many adverse outcomes in older adults.[26,27] Lastly, adjustment for changes in many sociodemographic and lifestyle variables reduced residual confounding. Among the limitations are the self-reported nature of dietary information and the high rates of losses to follow-up, although similar to other population-based cohorts of older adults.[53] Finally, as in any observational study, we cannot entirely rule out residual confounding, despite the measures taken to reduce it.

CONCLUSIONS

Increasing dietary intake of vegetable protein may delay unhealthy aging when replacing carbohydrates, fats, or animal protein, especially from meat and dairy. Whether the potential benefits of plant protein-rich foods are entirely the result of protein itself or may also result from other diet-related components needs further investigation.

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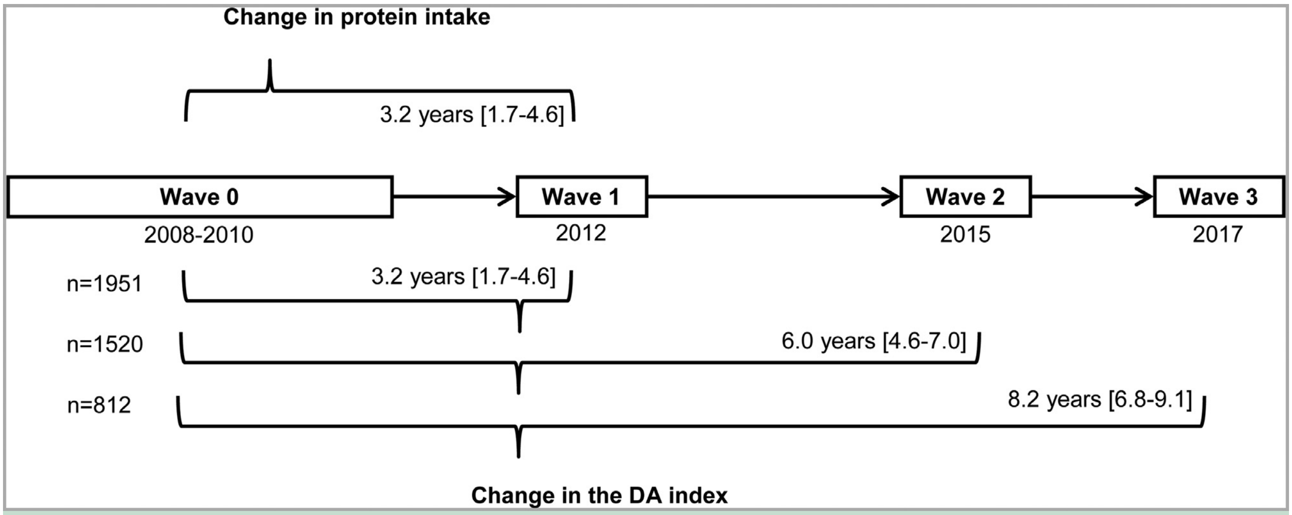
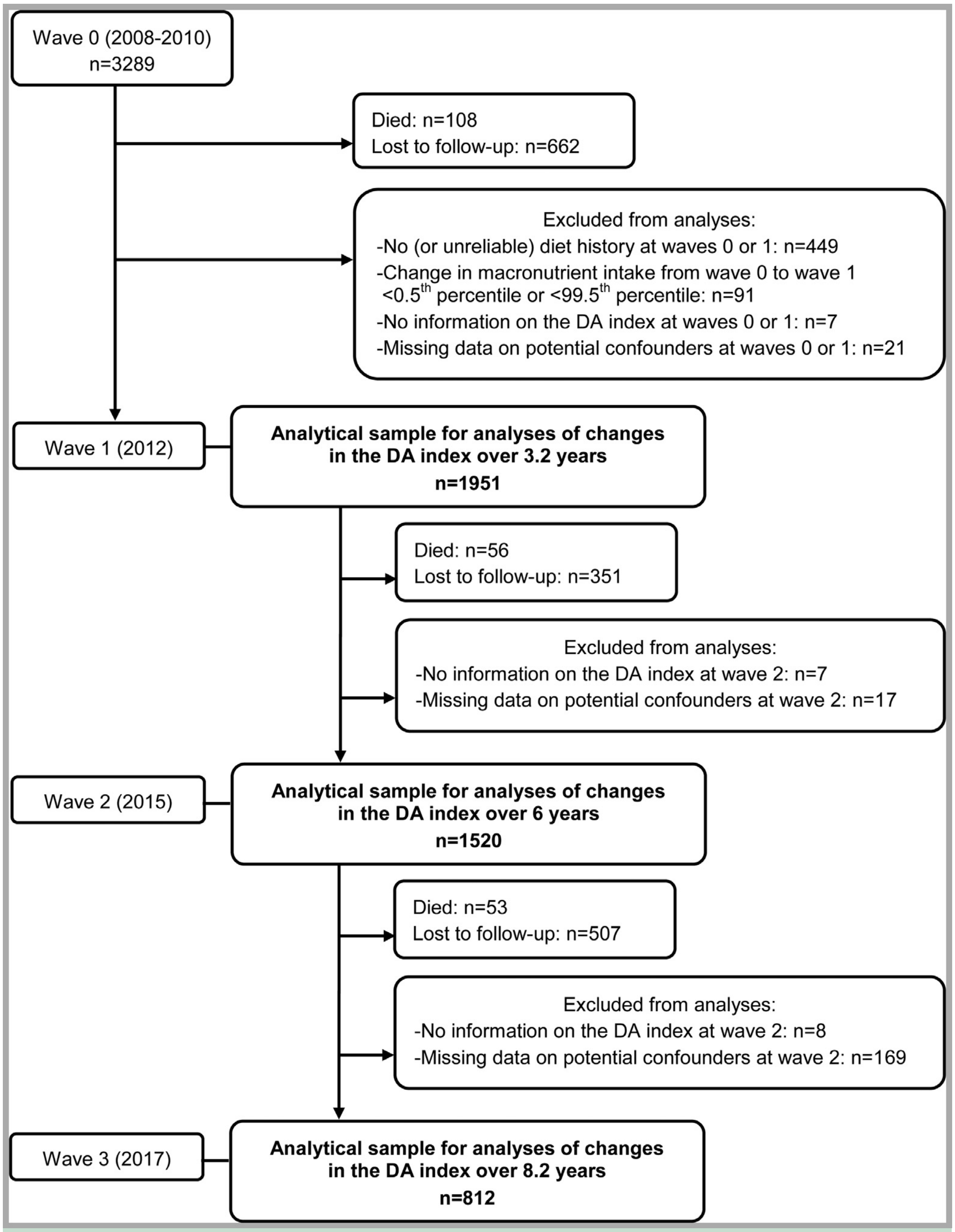
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2019.06.051.

APPENDIX A. SUPPLEMENTARY DATA



Supplemental Figure 1 Study diagram.



Supplemental Figure 2 Participant flow chart.

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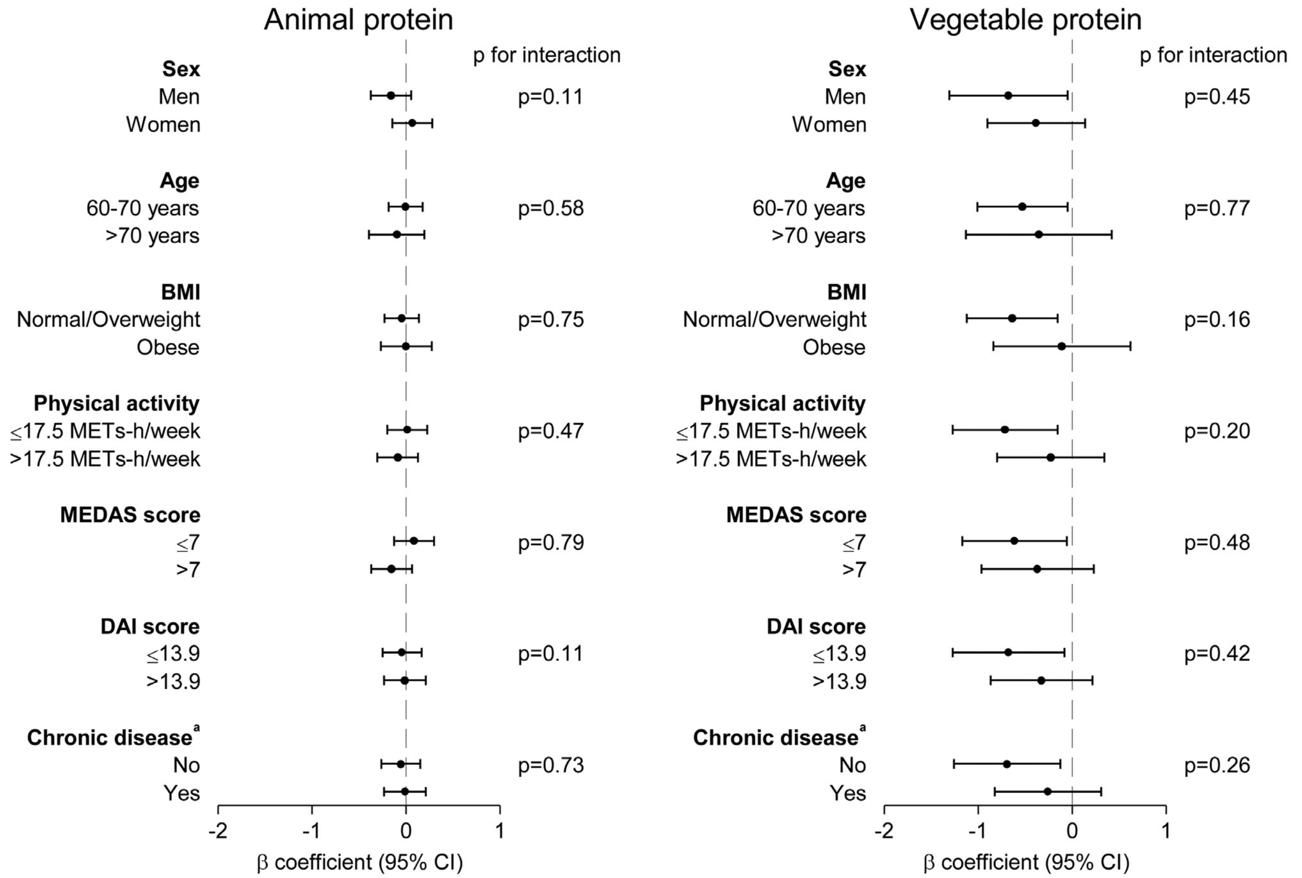

Supplemental Figure 3 Change in the DAI over 8.2 years associated with replacement of 1% of energy from fat and carbohydrate with animal or vegetable protein, stratified by sex, age, leisure-time physical activity, BMI, MEDAS score, DAI score and main chronic diseases at baseline. Linear regression models adjusted as Model 3 in Table 2. a Including cardiovascular disease (stroke, myocardial infarction and chronic heart failure), osteomuscular disease (osteoarthritis and arthritis) and cancer. BMI = body mass index; CI = confidence interval; DAI = deficit accumulation index; MEDAS = Mediterranean Diet Adherence Screener; MET = metabolic equivalent of task.

Supplemental Table 1 Health deficits and domains included in the deficit accumulation index.

Health deficits	Cut-point and score
Functional impairments domain	
Physical impairments	
ADL disabilities	
Help bathing	No=0, Yes=1
Help eating	No=0, Yes=1
Health dressing	No=0, Yes=1
Incontinence	No=0, Yes=1
Help using the toilet	No=0, Yes=1
IADL disabilities	
Help shopping	No=0, Yes=1
Help with housework	No=0, Yes=1
Help preparing meals	No=0, Yes=1
Help taking medications	No=0, Yes=1
Help with finances	No=0, Yes=1
Agility disability	
Limitation bending or kneeling	No=0, Yes=1
Mobility disability	
Limitation to lift/carry a shopping bag	No=0, Yes=1
Limitation to walk several blocks	No=0, Yes=1
Limitations in moderate activities	No=0, Yes=1
Limitations in climbing several flights of stairs	No=0, Yes=1
Decreased life-space mobility	No=0, Yes=1
Limitation in lower-extremity physical performance	
Poor balance	No=0, Yes=1
Unable to complete 5 chair stands	No=0, Yes=1
Slowness	No=0, Yes=1
Low grip strength	No=0, Yes=1
Low physical activity	No=0, Yes=1
Cognitive impairment	
Poor cognitive function	MMSE 24=0; 20 to <24=0.25; 18 to <20 =0.5; 11 to <18=0.75; <11=1
Self-rated health and vitality domain	
Self-rating of health	excellent=0; very good= 0.25; good=0.5; fair=0.75; poor=1
Doing less as a result of physical health	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Limited in activities as a result of physical health	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Health interfered with social activities	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Pain interfered with normal work	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Not having energy	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Unintentional weight loss	No=0, Yes=1
Mental health domain	
Accomplishing less than would like because of any emotional problem	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Doing activities less carefully than usual	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Not feeling calm and peaceful	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Feeling down-hearted and blue	never=0; rarely=0.25; sometimes=0.5; most of the time=0.75; always=1
Not being able to face up to problems	No=0, Yes=1
Feeling helpless	No=0, Yes=1
Morbidities and use of health services domain	
Morbidities and polymedication	
Heart attack	No=0, Yes=1
Heart failure	No=0, Yes=1
Stroke	No=0, Yes=1
Cancer	No=0, Yes=1
Respiratory disease	No=0, Yes=1
Arthritis	No=0, Yes=1
Osteoarthritis	No=0, Yes=1
Hip fracture	No=0, Yes=1
Parkinson's disease	No=0, Yes=1
Periodontal disease	No=0, Yes=1

Supplemental Table 1 (*Continued*)

Health deficits	Cut-point and score
Diabetes	No=0, Yes=1
Depression	No=0, Yes=1
Unhealthy body mass index	18.5 to <25=0; 25 to <30=0.5; <18.5 or 30=1
High blood pressure	No=0, Yes=1
Use of 3 or more medications	No=0, Yes=1
Use of health services	
High frequency of outpatient health care or consultation in last 12 months	rarely=0; once or twice a year=0.25; every two or three months=0.5; once or twice a month=0.75; almost every day=1
At least one overnight stay in a hospital in last 12 months	No=0, Yes=1

ADL = activities of daily living; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Examination.

Supplemental Table 2 Mean (SD) of total energy and macronutrient intake (n=1951).

		Wave 0	Wave 1
kcal/day	Total energy	2033 (564)	2006 (449)
% en	Animal protein	12.3 (3.6)	12.2 (3.0)
	Vegetable protein	6.1 (1.4)	6.1 (1.2)
	Fats	36.0 (6.4)	36.5 (6.0)
	Carbohydrates	42.4 (7.1)	42.3 (6.5)
	Alcohol	3.2 (5.0)	2.9 (4.1)
g/day	Animal protein	61.2 (16.9)	60.8 (14.6)
	Vegetable protein	30.9 (6.9)	30.5 (6.1)
	Fats	82.3 (14.0)	82.0 (13.2)
	Carbohydrates	213 (36.1)	210 (32.2)
	Alcohol	10.1 (15.6)	8.7 (12.2)
g/kg/day	Animal protein	0.84 (0.26)	0.85 (0.24)
	Vegetable protein	0.43 (0.13)	0.43 (0.12)
	Fats	1.14 (0.28)	1.15 (0.27)
	Carbohydrates	2.97 (0.77)	2.96 (0.74)
	Alcohol	0.13 (0.20)	0.12 (0.16)

% en = percentage of energy intake; SD = standard deviation.

Supplemental Table 3 Mean (SD) of macronutrient intake (% en) by categories of change in animal or vegetable protein intake from wave 0 to wave 1.

	Change in animal protein intake (% en)							
	<−2% n=562		−2% to <0% n=400		0% to 2% n=422		>2% n=567	
	Wave 0	Wave 1	Wave 0	Wave 1	Wave 0	Wave 1	Wave 0	Wave 1
Animal protein	15.5 (3.5)	10.9 (2.9)	12.6 (2.5)	11.6 (2.4)	11.3 (2.7)	12.3 (2.7)	9.8 (2.6)	13.9 (2.8)
Vegetable protein	5.6 (1.3)	6.2 (1.2)	6.1 (1.3)	6.2 (1.3)	6.4 (1.4)	6.2 (1.3)	6.5 (1.3)	5.9 (1.1)
Fats	36.5 (6.6)	36.8 (6.4)	35.8 (6.3)	36.4 (5.6)	35.7 (6.2)	36.3 (5.6)	35.8 (6.5)	36.5 (5.8)
Carbohydrates	39.6 (7.1)	43.1 (6.8)	42.2 (6.6)	42.7 (6.7)	43.5 (6.7)	42.6 (6.1)	44.5 (6.9)	40.9 (6.3)
Alcohol	2.8 (4.7)	3.0 (4.2)	3.3 (5.0)	3.1 (4.3)	3.2 (4.8)	2.6 (3.6)	3.5 (5.4)	2.8 (4.2)
	Change in vegetable protein intake (% en)							
	<−1% n=449		**−1% to <0%** n=531		**0% to 1%** n=519		**>1%** n=452	
	Wave 0	Wave 1	Wave 0	Wave 1	Wave 0	Wave 1	Wave 0	Wave 1
Animal protein	11.5 (3.5)	13.1 (3.1)	12.0 (3.4)	12.3 (2.7)	12.3 (3.4)	11.5 (3.1)	13.6 (3.9)	11.5 (3.1)
Vegetable protein	7.3 (1.2)	5.5 (1.0)	6.3 (1.1)	5.8 (1.0)	5.8 (1.1)	6.9 (1.2)	5.1 (1.2)	6.9 (1.2)
Fats	33.7 (6.1)	37.5 (5.7)	35.2 (6.0)	36.9 (5.6)	37.0 (6.2)	35.2 (6.5)	38.0 (6.7)	35.2 (6.5)
Carbohydrates	45.2 (6.6)	41.0 (6.8)	43.3 (6.2)	42.0 (6.2)	41.2 (6.9)	43.9 (6.5)	39.9 (7.8)	43.9 (6.5)
Alcohol	2.3 (3.9)	2.9 (4.2)	3.2 (5.1)	2.9 (4.2)	3.7 (5.4)	2.5 (3.7)	3.4 (5.3)	2.5 (3.7)

% en = percentage of energy intake; SD = standard deviation.

METHODOLOGICAL APPENDIX

CONSTRUCTION OF THE DEFICIT ACCUMULATION INDEX DIMENSIONS

Functional impairments dimension. The overall dimension on functional impairments was calculated using the following 22 health deficits:

- *Self-care disability*: Assessed with five questions from the Katz index:[1] 1) "Do you experience any difficulty in bathing yourself without assistance?", 2) "Do you experience any difficulty eating without assistance?", 3) "Do you experience any difficulty dressing yourself without assistance?", 4) "Do you experience any difficulty getting to or using the toilet?", and 5) Do you lose urine involuntarily/accidentally?
- *Disability in instrumental activities of daily living:* Measured using five questions from the Lawton and Broady´s Scale:[2] 1) "Can you go shopping for groceries or clothes?", 2) "Can you prepare your own meals?", 3) "Can you do your housework?", 4) "Can you take your own medication?", and 5) "Can you handle your own money?
- *Agility disability*: Ascertained with the following question from the Rosow and Breslau scale[3]: "Do you experience any difficulty in bending or kneeling?"
- *Mobility disability:* Evaluated with the following questions from the Rosow and Breslau scale[3] and the 12-Item Short-Form Health Survey (SF-12):[4] 1) "Do you experience any difficulty in picking up or carrying a shopping bag?", 2) "Do you experience any difficulty in climbing one flight of stairs?", 3) "Do you experience any difficulty in walking several city blocks (a few hundred meters)?", and 4) "Does your health limit you in moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf?" Decreased life-space mobility was measured using the mobility question from the Mini-Nutritional Assessment.[5]
- *Limitation in lower-extremity physical performance:* Evaluated with three components of the Short Physical Performance Battery (SPPB):[6] balance, walking speed and ability to rise from a chair. For balance, participants were asked to remain standing with their feet as close together as possible, and hold that position for 10 seconds. For gait speed, the time required to travel 3 m at a usual pace was measured. The test was performed twice and the fastest time was used for analyses. Slow walking speed was defined as the lowest quintile in the study sample, taking into account the distribution of sex and height in the study sample. For the standing test, participants were asked to stand and sit in a chair five times as quickly as possible with arms crossed over the chest.
- *Low grip strength:* Assessed in the dominant hand with a Jamar dynamometer; the highest value in two consecutive measures was used in the analyses. Low strength was defined as the lowest quintile in the study sample taking into account the distribution of sex and BMI in the study sample.
- *Low physical activity:* Defined as walking 2.5 h/week in men and 2 h/week in women.[7,8]
- *Cognitive impairment:* Assessed using the score in the Mini-Mental State Examination (MMSE).[9]

Self-rated health and vitality dimension. This dimension was evaluated with 7 items: a self-reported question on unintentional weight loss of 4.5 kg of body weight in the preceding year, and 6 questions from the SF-12:[4] 1) "In general, would you say your health is excellent, very good, good, fair, or poor?", 2) "Thinking about the past four weeks, have you accomplished less than you would like as a result of your physical health?", 3) "During the past four weeks, were you limited in the kind of work or other activities you could do as a result of your physical health?", 4) "During the last four weeks, how much of the time has your physical health or emotional problems interfered with your social activities, like visiting with friends, relatives etc.?", 5) "During the past four weeks, how much did pain interfere with your normal work including both work outside the home and housework?", and 6) "How much of the time during the past four weeks did you have a lot of energy?".

Mental health dimension. This was assessed using the following questions: 1) "In the past four weeks, did you accomplish less than you would like as a result of an emotional problem, such as feeling depressed or anxious?" from the 12-item version of the General Health Questionnaire (GHQ-12); [10] 2) "During the last four weeks, did you have trouble doing work or other activities as carefully as usual as a result of an emotional problem, such as feeling depressed or anxious?" from the Geriatric Depression Scale (GDS);[11] and 3) The following four questions from the SF-12: [4] 1) "How much of the time during the past four weeks have you felt calm and peaceful?", 2) "How much of the time during the past four weeks have you felt downhearted and blue?", 3) "Have you recently been able to face up to problems?," and 4) "Do you often feel helpless?"

Morbidities and health care use dimension. This last dimension was constructed using self-reported information, laboratory and physical measurements. It included 17 items (14 morbidities, 1 question on polymedication, and 2 questions regarding hospitalization and use of outpatient and inpatient services in the previous 12 months). At baseline and follow-up, participants reported the following physician-diagnosed diseases: *cardiovascular disease* (heart attack, heart failure, or stroke), *cancer*, *respiratory disease* (asthma, chronic bronchitis), *osteomuscular disease* (arthritis, osteoarthritis, or hip fracture), *Parkinson's disease* and *periodontal disease*. Glucose was measured using the oxidase glucose technique (ADVIS 2400 Chemistry System analyzer, Siemens), and participants were considered *diabetic* if they reported a physician-diagnosis of diabetes, were prescribed diabetes medications, or had fasting serum glucose 126 mg/dl. *Depression* was defined as a physician-diagnosis of depression or as being on antidepressant medication. *Weight and height* were measured using electronic scales (model Seca 841, precision to 0.1 kg) and portable extendable stadiometers (model Ka We 44 444Seca), respectively, by trained staff under standardized conditions.[12] Mean values of 2 consecutive measurements were used for analyses. *Body mass index* (BMI) was calculated as weight in kg divided by square height in m, and an *unhealthy BMI* was defined as BMI <18.5 or 25. Finally, blood pressure was measured with standardized procedures using validated automatic devices (Omron model M6) and 3 cuff sizes according to arm circumference. Two sets of blood pressure readings were made separated by 90 minutes. In each set, blood pressure was measured 3 times at 1-2 minute intervals, after resting 3 to 5 minutes in a seated position. Blood pressure was calculated as the mean of 3 of the last 5 readings. *Hypertension* was defined as a systolic blood pressure 140 mmHg, a diastolic blood pressure 90 mmHg, or the current use of antihypertensive drugs. Participants also reported any prescribed drugs (including antidepressants, antihypertensive, and glucose lowering drugs), which were checked by the study staff against drug packages at home.

Bibliography methodological appendix

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