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Esta es la **versión de autor** del artículo publicado en:
This is an **author produced version** of a paper published in:

Clinical Nutrition 40.1 (2021): 277-285

DOI: <https://doi.org/10.1016/j.clnu.2020.05.018>

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El acceso a la versión del editor puede requerir la suscripción del recurso

Access to the published version may require subscription

TITLE PAGE

Title: Consumption of food fried in olive oil and unhealthy aging in a Mediterranean country.

Authors' names and affiliations:

Adrián Carballo-Casla,¹ Esther García-Esquinas,^{1,2} Esther López-García,^{1,2,3} Mercedes Sotos-Prieto,^{1,4} Ellen A. Struijk,^{1,2} Francisco Félix Caballero,^{1,2} Fernando Rodríguez-Artalejo,^{1,2,3*} Rosario Ortolá.^{1,2*}

¹ Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid/Idipaz. Madrid, Spain.

² CIBER of Epidemiology and Public Health (CIBERESP). Madrid, Spain.

³ IMDEA Food Institute. CEI UAM+CSIC. Madrid, Spain.

⁴ Department of Environmental Health, Harvard T.H. Chan School of Public Health. Boston, MA, USA.

***Corresponding authors:**

Rosario Ortolá, MD, or Fernando Rodríguez Artalejo, MD

Department of Preventive Medicine and Public Health

School of Medicine, Universidad Autónoma de Madrid

Calle del Arzobispo Morcillo 4, 28029 Madrid (SPAIN)

Telephone: (+34) 914975441

E-mail: ortolarosario@gmail.com or fernando.artalejo@uam.es

Authors' email addresses:

Adrián Carballo-Casla: adrian.carballo@uam.es

Esther García-Esquinas: esthergge@gmail.com

Esther López-García: esther.lopez@uam.es

Mercedes Sotos-Prieto: mercedes.sotos@uam.es

Ellen A Struijk: ellen.struijk@uam.es

Francisco F. Caballero: felix.caballero@uam.es

Fernando Rodríguez-Artalejo: fernando.artalejo@uam.es

Rosario Ortolá: ortolarosario@gmail.com

ABSTRACT

Background: Fried food has usually shown neutral or detrimental effects on many chronic diseases, possibly depending on the type of food fried and the frying oil, but their relationship with unhealthy aging is unknown.

Methods: Prospective cohort study in Spain with 2043 individuals aged ≥ 60 years, recruited in 2008-2010 (wave 0) and followed-up to 2012 (wave 1) and 2015 (wave 2). Fried food consumption was ascertained with a validated diet history, and unhealthy aging was measured with a 52-item health deficit accumulation index. We examined through linear regression how changes in total and group-specific fried food consumption over a 3-year period (wave 0 to wave 1) were linked to unhealthy aging over 3 (wave 0 to wave 1) and 6 years (wave 0 to wave 2).

Results: Compared with participants who reduced fried food consumption from wave 0 to wave 1, those who increased it showed less health deficit accumulation over 3 years (multivariable β [95% CI]: -1.45 [-2.30, -0.61]), but not over 6 years of follow-up. Results were similar for analyses restricted to food fried with olive oil. More deficit accumulation over 3 years was observed when replacing 100 g/day of fried food with an equal amount of non-fried food (1.48 [0.59, 2.37]); corresponding values in substitution analyses were 2.03 [1.03, 3.03] for fried protein-rich food, 10.76 [5.20, 16.33] for fried eggs, and 2.06 [0.68, 3.43] for fried fish. Also, increased olive oil intake was significantly associated with less 3-year deficit accumulation (olive oil as part of fried and non-fried food: -1.14 [-2.07, -0.21], and olive oil within non-fried food: -0.99 [-1.89, -0.08]).

Conclusions: In a Mediterranean country, where olive oil is the most common frying medium, increased fried food consumption was associated with short-term delayed unhealthy aging; consumption of olive oil, as well as fried protein-rich food (especially eggs and fish), were the main drivers of this association.

Keywords: fried food, olive oil, unhealthy aging, cohort study, older adults.

BACKGROUND

Frying with oil is a cooking technique traditionally used in Mediterranean countries. Frying changes food properties, creating a crust and replacing part of its water content with fat [1, 2]. This process makes food more appetizing through both crunchiness and unctuousness [3]. However, potentially harmful oxidation and hydrogenation compounds could be produced during frying [2, 4]; also, the increased energy density of fried food may lead to weight gain and obesity [5, 6]. With regard to chronic disease, recent evidence, mostly from Anglo-Saxon countries, has shown that frequent consumption of fried food is associated with a higher risk of type 2 diabetes, hypertension and heart failure [7], prostate cancer [8], and cardiovascular and overall mortality [9]. By contrast, similar studies in Mediterranean countries have not usually found an excess risk of coronary heart disease [7, 10] or cancer [11] associated with frequent consumption of fried food. Given that olive oil is the main frying medium in Mediterranean countries but not Anglo-Saxon countries [6, 12, 13], this heterogeneity in results could be partly due to the type of oil used for frying.

There are still major gaps in knowledge of the effects of fried food, as some studies do not report the type of oils used for frying or the specific groups of fried food consumed, or do not consider the overall dietary pattern of fried food consumers [7]. Moreover, to our knowledge, no previous research has investigated the relationship between fried food consumption and healthy aging. This investigation is important because of the progressive aging of the world population [14] and the limited understanding of the dietary determinants of healthy aging [15–18], which precludes the design of interventions to palliate the expected increase in age-associated health and social needs in the coming decades.

Therefore, we examined if changes in fried food consumption are associated with unhealthy aging, in a cohort of community-dwelling older adults in Spain with a detailed assessment of food consumption and food preparation techniques [19, 20]. Our data allowed us to conduct analyses for specific types of food and oils used for frying, and to account for the overall dietary pattern [21]. As a measure of unhealthy aging, we used a multi-

domain health deficit accumulation index (DAI) that has shown to predict adverse health outcomes, including death, institutionalization or hospitalization in older adults [22, 23].

METHODS

Study design and population

Data were taken from the Seniors-ENRICA cohort, whose methods have been reported elsewhere [19, 23]. In brief, study participants were selected between June 2008 and October 2010 by stratified cluster sampling of the non-institutionalized population of Spain aged 60 years or older. At baseline (wave 0), participants' socio-demographic, lifestyle, and morbidity data were collected by a computer-assisted telephone interview. In addition, trained professionals carried out two home visits to collect blood and urine samples, perform a physical examination, gather data on prescribed medications and functional limitations, and obtain a diet history [19, 20]. To update the study information, two subsequent follow-ups were performed in 2012 (wave 1) and 2015 (wave 2). The study participants gave written informed consent, and the Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the research protocol.

Study variables

Fried and non-fried food consumption.

At waves 0 and 1, the usual consumption of food in the preceding year was estimated with a validated computerized diet history developed from the one used in the EPIC cohort study in Spain [19, 20]. This diet history collected data on 861 foods that could be cooked in 29 different ways (including mixed forms of cooking and food preservation methods). It also allowed us to record the consumption of 184 recipes for dishes commonly eaten in Spain or those typical of each region; the recipes were converted into simple food based on the proportions and combinations reported by the respondent or according to standard compositions. The mentioned diet history also included 127 sets of digitized photographs to estimate the size of food portions; specifically, for each individual food or food mixture, the respondent was given photos of three portion sizes

(small, large and medium), which allowed seven different sizes of portion classification. When no photo of a particular food was available, the amount consumed was estimated with natural units or household measures; specifically, this diet history included 122 household measures (e.g., a carton of yogurt=125 g) [20].

For the purpose of this work, fried food was defined as that food for which the only cooking method used was frying (either deep-frying or pan-frying, with or without battering or breading) [10]. They belonged to the following food groups: 1) potatoes; 2) meat; 3) eggs; and 4) fish. An additional group of protein-rich food was built as the sum of meat, eggs, and fish. For comparison, non-fried food was defined as that which had been cooked with methods other than frying alone, and that belonged to any of the food groups habitually consumed fried. Changes in fried and non-fried food consumption (g/day) from wave 0 to wave 1 were calculated. Study participants were assigned to one of three categories of changes in food consumption: decrease, maintenance (little or no change) or increase. These groups were calculated roughly as the lowest, intermediate and highest tertiles of food consumption change, respectively (see Table 2, Table 3 and Additional file 1 for corresponding cut-off values).

Unhealthy aging

To assess unhealthy aging at waves 0, 1 and 2, we calculated a 52-item DAI with four dimensions or domains: 1) physical and cognitive functional impairments (22 items); 2) self-reported health/vitality (7 items); 3) mental health (6 items); and 4) morbidity/use of health services (17 items) [23]. The complete list of health deficits and associated scores is shown in Additional file 2. The overall DAI score was 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).

We calculated changes in the overall DAI score from wave 0 to wave 1 (median follow-up: 3.2 years; range: 1.7-4.6 years) and from wave 0 to wave 2 (median follow-up: 6.0 years; range: 4.6-7.0 years). Negative changes indicate health improvement, whereas positive changes indicate health deterioration.

Potential confounders of the study association

We used baseline data on self-reported sociodemographic and lifestyle characteristics, including sex, age, education (primary or less, secondary, or university), tobacco smoking (never, former, or current), alcohol consumption (never, former, moderate [<24 g/day in women and <40 g/day in men], or heavy), leisure-time physical activity expressed as metabolic equivalents of task-hour/week [24], and time (hours/day) spent watching TV as a proxy for sedentary behavior [25]. Energy intake (kcal/day) was calculated from food consumption recorded in the diet history, by using composition tables for Spanish food[20]. Diet quality was assessed with the Alternative Healthy Eating Index-2010 (AHEI-2010) since it does not rely on olive oil consumption, as other indices do [26]. It ranges from 0 to 110, with higher scores indicating better adherence to a dietary pattern associated with a lower risk of chronic disease [21]. Also, weight and height were measured in standardized conditions [27], and body mass index (BMI) was calculated as weight (in kg) divided by squared height (in m).

Statistical analysis

From the initial 3289 participants at wave 0, 108 (5.3%) had died and 662 (32.4%) had been lost to follow-up at wave 1. From the remaining 2519 individuals, we excluded 449 without valid food records at wave 0 or wave 1, 7 without data on the DAI score at wave 0 or wave 1, and 20 lacking information on potential confounders at wave 0. Thus, we used data of 2043 individuals for analyses of change in the DAI over 3 years of follow-up. From these 2043 subjects at wave 1, 62 (3.0%) had died and 367 (18.0%) had been lost to follow-up at wave 2. From the remaining 1614 participants, we excluded 15 without information on the DAI score at wave 2. Thus, we finally used data on 1599 individuals for analyses of DAI changes over 6 years of follow-up (Additional file 3).

The association of changes in fried food consumption from wave 0 to wave 1 with changes in the DAI over 3 and 6 years was summarized with β coefficients and their 95% confidence intervals (CIs), obtained from linear regression; the lowest category of food consumption change was used as the reference in the analyses. Two

models were fitted: model 1 was adjusted for age, sex, education, the consumption of the corresponding type of fried or non-fried food and the DAI at wave 0; and model 2 was further adjusted for smoking status, alcohol consumption, leisure-time physical activity, time watching TV, BMI, AHEI-2010, and energy intake at wave 0. Dose-response relationships were evaluated by modeling food consumption change as 1-SD increments, and by restricted cubic spline regression plots. Similar analyses were conducted for specific groups of fried food.

To better understand if the effects of fried food on unhealthy aging were due to frying *per se* or to the specific food that was fried, we replicated the above-described analyses using, as main exposure, the changes in non-fried food consumption, overall and by the same groups of food that are consumed fried. In addition, since olive oil is the main frying medium in Spain, we conducted similar analyses to examine the association between changes in olive oil consumption (total or with non-fried food) and changes in the DAI.

We also examined the association between the replacement of 100 g/day of total and group-specific fried food with an equal amount of the corresponding non-fried food and 3-year changes in the DAI; in these substitution analyses, the β coefficient was calculated by subtracting the coefficient for fried food from the coefficient for the corresponding type of non-fried food.

Lastly, we assessed if sex, age, education, physical activity, BMI, AHEI-2010 score, baseline fried and non-fried food consumption, the DAI score, or the main chronic diseases at baseline modified the study associations. Since no consistent interactions were found, results are presented for the total sample.

Statistical significance was set at two-sided $p < 0.05$; statistical tests were based on *a priori* hypotheses for the effect of fried food consumption; therefore, no adjustment was made for multiple testing. Analyses were performed with Stata[®] (StataCorp LLC), version 14.0.

RESULTS

Study participants consumed an average of 47.7 g/day of fried food and 196.2 g/day of non-fried food at baseline. Among fried food, 37.8% was fish, 29.6% potatoes, 19.1% meat, and 13.4% eggs. Among non-fried

food, 51.1% was meat, 21.5% fish, 17.7% potatoes, and 9.7% eggs (Additional file 4). A total of 80% of the subjects used olive oil for frying (56% refined olive oil and 24% virgin olive oil), while 20% used other oils.

Compared to individuals who reduced fried food consumption (>14 g/day from wave 0 to wave 1), those who increased it (>14 g/day) were slightly older, more often were never drinkers, and had lower baseline energy intake. As regards non-fried food, those who increased its consumption were less often current smokers, did more physical activity, and spent less time watching TV, and had a slightly higher BMI, better diet quality and less energy intake at baseline than those who reduced consumption (Table 1).

Compared with participants with a >14 g/day decrease in fried food consumption over 3 years (roughly >1 serving/week decrease [28]), those with an increase >14 g/day showed less deficit accumulation over 3 years (model 2 β [95% CI]: -1.45 [-2.30, -0.61]), with a clear dose-response relationship (p-trend <0.001 ; model 2 β per 1-SD increment: -0.73 [-1.08, -0.38]) (Table 2 and Figure 1). Consistent associations were obtained for fried protein-rich food (-1.37 [-2.21, -0.53]), fried meat (-1.65 [-2.58, -0.73]), fried eggs (-1.63 [-2.49, -0.76]) and fried fish (-1.20 [-2.05, -0.35]) (Table 3), as well as for fried poultry and fried white fish (Additional file 1). However, no significant association was found for fried potatoes (-0.19 [-1.05, 0.67]) (Table 2 and Figure 1). Similar results were observed when analyses were restricted to food fried with olive oil (Additional file 5). Changes in consumption of total and group-specific fried food were not associated with DAI changes over 6 years (Tables 2 and 3).

As regards non-fried food, when using as reference those individuals who decreased its consumption from wave 0 to wave 1, those who maintained it experienced less deficit accumulation over 3 years (model 2 β [95% CI]: -1.13 [-1.93, -0.32] for total food, and -0.82 [-1.64, -0.01] for protein-rich food), but not over 6 years. No dose-response relationships were found (Table 2 and Figure 1). Within specific non-fried food, we observed more deficit accumulation over 3 years in participants who increased vs. those who decreased eggs consumption (1.12 [0.23, 2.00]) (Table 3 and Figure 2); further subgroup analyses revealed a 3-year DAI decrease in subjects

who elevated red meat consumption, as well as a 6-year DAI increase in those who maintained or increased processed meat consumption (Additional file 1).

Replacement of total fried food, protein-rich fried food, fried eggs or fried fish with their non-fried equivalents led to more 3-year deficit accumulation (model 2 β [95% CI]: 1.48 [0.59, 2.37] for the replacement of 100 g/day of fried for non-fried food; 2.03 [1.03, 3.03] for protein-rich food; 10.76 [5.20, 16.33] for eggs; and 2.06 [0.68, 3.43] for fish) (Table 4). Also, the replacement of fried with non-fried white fish was linked to less deficit accumulation over 3 and 6 years (Table 4).

Lastly, compared to the individuals who decreased total olive oil consumption (as part of both fried and non-fried food), those who increased it showed less 3-year deficit accumulation (model 2 β [95% CI]: -1.19 [-2.11, -0.27]); this association was somewhat more marked for extra-virgin olive oil (-1.27 [-2.23, -0.30]). Corresponding values for increased consumption of olive oil with non-fried food were -0.99 [-1.89, -0.08] and -1.09 [-2.03, -0.15] (Additional file 6).

DISCUSSION

In this cohort of older adults in Spain, increasing fried food consumption over 3 years was associated with delayed unhealthy aging over the same period; increased consumption of olive oil and of fried protein-rich food (especially fried eggs and fried fish) seemed to be the main drivers of this association. Also, the replacement of 100 g/day of fried food, particularly protein-rich food, with the same amount of equivalent non-fried food led to more deficit accumulation over 3 years. However, these associations did not generally remain after 6 years.

This study is important for several reasons. First, this investigation has been the first to assess the association between fried food and unhealthy aging. Thus, this study makes a unique contribution to the little existing knowledge about the health effects of fried food consumption in older adults. In US postmenopausal women aged 50-79 years, frequent consumption of fried food, especially fried chicken and fried fish/shellfish, has been associated with higher all-cause and cardiovascular mortality during 18 years of follow-up; however, total or

individual fried food consumption was not generally associated with cancer mortality [9]. Then again, increased fried food consumption was linked to incident heart failure during an average follow-up of 10 years in middle-aged and older men in the US [29]. In both studies, the associations were independent of the type of oils used for frying and diet quality. Moreover, in a cross-sectional study in the US, higher fried food consumption was associated with a more rapid progression of Parkinson's disease, whereas non-fried fish was associated with a reduced rate of progression [30]. Also, 2-hydroxyoctanoate, a metabolite associated with fried potatoes consumption, was linked to estrogen receptor-positive breast cancer risk in postmenopausal women [31]. Nevertheless, these latter investigations did not account for the type of frying oils or diet quality.

Second, this study focused on a single population, with well-characterized dietary patterns and frying oils. The health effects of fried food consumption should be assessed in different settings and cultures, because the results in one setting may not apply to others that use different oils and techniques for frying. The above-mentioned studies were conducted in the US, where partially hydrogenated and highly unsaturated oils -such as corn oil- are a common frying medium [7, 32]. Both the hydrogenation process and the degree of oil unsaturation increase the formation of trans fatty acids during frying, which have adverse health effects [33, 34]. By contrast, in Spain and in other Mediterranean countries, olive oil is the fat habitually used for frying [6, 12]. Moreover, in the US and many Anglo-Saxon countries, fried food is usually deep-fried, whilst in Mediterranean countries both pan-frying and deep-frying are commonly used [35]. Though the type of frying technique may lead to different changes in food properties [36–38], contributing to distinct health effects of fried food consumption in Mediterranean versus other countries, olive oil has been found to be highly stable under both deep-frying [39–41] and pan-frying [40] conditions. Our results on the association between fried food and delayed unhealthy aging in older adults are in line with those of previous research in Mediterranean countries that found no excess risk of chronic diseases associated with fried food [10, 11]. Specifically, in a study with the EPIC-cohort in Spain, higher consumption of fried food was not associated with a greater risk of coronary heart disease or all-cause death [10]. Also, a large case-control study in Italy and Switzerland found no relevant role of fried food on colorectal cancer, although it reported a possible favorable effect of fried olive oil on the risk of colon -but

not of rectal- cancer [11]. In addition, our results are consistent with the existing robust evidence that olive oil has important anti-inflammatory and metabolic effects [42–44] and lowers the risk of chronic diseases [45, 46] and death [45, 47].

Third, we have gone farther than most previous research, separating the health effect of a specific food that is fried from the effect of frying *per se*. Specifically, we have assessed the effect of fried food, the equivalent non-fried food, and the frying (olive) oil, separately. As a result, we have found a favorable association of DAI changes with fried food consumption, and with olive oil consumption (both within and without fried food), as well as a distinct association for fried versus non-fried eggs, poultry, and white fish. While increased consumption of fried eggs, fried poultry, and fried white fish were associated with less health deficit accumulation, an increase in non-fried eggs consumption was linked to a worsening DAI, and no association was observed for non-fried poultry and non-fried white fish consumption. These results, when taken together, suggest that olive oil plays a key role in the relationship between fried food consumption and delayed healthy aging. Possible mechanisms for the beneficial effect of frying with olive oil are the production of angiotensin-converting enzyme inhibitory peptides in eggs [48], as well as the improvement of fat quality in fried lean food. While lean food is enriched with healthy monounsaturated fatty acids from olive oil during frying, fatty food's oil uptake is not as substantial, although some lipid exchange between the food and the frying medium might occur [2, 49]. Interestingly, in our study participants, while consumption of fried poultry and white fish –but not their non-fried equivalents– was associated with less health deficit accumulation, fried and non-fried red meat, processed meat, and oily fish showed a similar association with the DAI. Moreover, olive oil has beneficial phenolic compounds that remain after several frying sessions [36, 50] and it is less prone to oxidative deterioration during frying than other oils [39]; this is true also for refined olive oil [40], which was used by more than half of our study participants.

An important strength of our study is the detailed diet history that was used to ascertain fried and non-fried food consumption, and which has shown to be valid against seven 24-h recalls obtained over one year; the mean correlation coefficient was 0.48 for all 4 food groups considered, and 0.47 for oils [20]. A further strength is the

study design, as using changes in food consumption instead of baseline values mimics dietary intervention in clinical trials. Also, we used a proper instrument to assess unhealthy aging, because the DAI includes various validated measures of physical function (i.e. grip strength, balance, gait speed) and chronic conditions (i.e. diabetes, obesity, hypertension), it is based on standardized scales and validated assessments, and it has demonstrated to predict several adverse health outcomes in older adults [22, 51]. To place the strength of the observed study associations into context, it is worth noting that, in our cohort, annual increments of 0.74 points in the DAI have been associated with a 2% increase in all-cause mortality; thus, the magnitude of the association (a 1-2-point decrease of the DAI over 3 years in those increasing fried food consumption) observed in our study is of substantial clinical relevance.

Among the study limitations are that diet was self-reported, so we cannot exclude some recall or social desirability bias. Also, as in other aging cohorts, participants have probably been lost to follow-up due to ill health, disability, institutionalization or death; however, because study participants were younger and had better habits at baseline than those lost to follow-up, our results may underestimate the actual study associations. Moreover, the associations between fried food consumption and unhealthy aging were generally short-term, so they may partly result from reverse causation (health problems leading to changes in fried food intake). Nevertheless, it is not likely that our results are entirely explained by reverse causation because 1) The association between increased fried food consumption and 3-year lower deficit accumulation was maintained when adjusting for 3-year changes in diet quality (model 2 β [95% CI] per 1-SD increment in fried food consumption: -0.71 [-1.07,-0.36]), 2) It endured through the 6-year follow-up when restricting the analyses to participants without chronic diseases at wave 0 (-0.61 [-1.19,-0.03]), and 3) A significant association between higher fried food consumption at baseline and 3-year improvement in the DAI was also found (-0.38 [-0.71,-0.05]). Finally, there may be a number of reasons underlying participants' increased fried food consumption, so, as in any observational study, we cannot completely rule out residual confounding, despite adjusting for many sociodemographic and lifestyle variables, including the overall dietary pattern.

Conclusions

In a Mediterranean country, where olive oil is the most common frying medium, increased fried food consumption was associated with short-term delayed unhealthy aging in older adults. Increased consumption of olive oil as part of fried food seemed to play a key role in this association. The replacement of fried food with its equivalent non-fried food may not be warranted in older adults, as it might result in a greater health deficit accumulation.

List of abbreviations

DAI: deficit accumulation index.

AHEI-2010: Alternative Healthy Eating Index-2010.

BMI: body mass index.

DECLARATIONS

Ethics approval and consent to participate

Study participants provided written informed consent, and the Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by FIS grants 16/609,16/1512, 18/287 and 19/319 (Instituto de Salud Carlos III, State Secretary of R+D+I and FEDER/FSE), the Salamander Project (JPI-A Healthy Diet for a Healthy Life, State Secretary of R+D+I PCIN-2016-145), and the Cátedra de Epidemiología y Control del Riesgo Cardiovascular at UAM (#820024). AC-C has an FPI contract from the Universidad Autónoma de Madrid. 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.

Authors' contributions

FRA and RO conceived the study. ACC and RO performed statistical analyses. ACC, ELG, EAS, FRA, and RO contributed to results interpretation. ACC, FRA, and RO drafted the manuscript. All authors substantively reviewed the manuscript.

All authors have approved the submitted version, read and approved the final manuscript.

All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Acknowledgments

Not applicable.

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Table 1. Baseline characteristics of study participants, by categories of change in food consumption over 3 years.

	Change in fried food consumption (g/day)			Change in non-fried food consumption (g/day)		
	< -14 (n=629)	-14 to 14 (n=652)	> 14 (n=762)	< -35 (n=700)	-35 to 35 (n=690)	> 35 (n=653)
Sex – Men, %	50.9	40.3	52.6*	51.0	45.2	48.2
Age	68.2 (6.3)	68.5 (6.3)	69.1 (6.6)*	68.6 (6.4)	68.5 (6.3)	68.7 (6.3)
Educational level, %						
≤ Primary	53.3	52.0	54.7	52.4	53.8	54.1
Secondary	25.3	25.6	23.5	26.1	23.9	24.0
University	21.5	22.4	21.8	21.4	22.3	21.9
Tobacco smoking, %						
Never	59.1	60.6	55.2	55.6	61.7	57.1*
Former	31.3	28.4	32.0	32.4	25.8	33.8
Current	9.5	11.0	12.7	12.0	12.5	9.0
Alcohol consumption, %						
Never	24.6	34.5	31.4*	28.4	32.6	29.9
Moderate ^a	50.9	43.6	46.6	46.9	48.6	45.3
Heavy	10.3	7.4	8.5	9.1	6.8	10.3
Former	14.1	14.6	13.5	15.6	12.0	14.5
Leisure-time physical activity (Metabolic Equivalent of Task-h /week)	22.0 (15.2)	22.1 (15.2)	21.3 (15.4)	21.2 (15.4)	21.5 (15.3)	22.7 (15.1)*
Time watching TV (h/day)	2.56 (1.57)	2.49 (1.58)	2.57 (1.62)	2.68 (1.61)	2.54 (1.62)	2.40 (1.52)*
Body mass index (kg/m ²)	28.7(4.5)	28.2 (4.3)	28.5 (4.2)	28.4 (4.4)	28.2 (4.2)	28.9 (4.4)*
AHEI-2010 score ^b	60.9 (9.8)	61.7 (10.0)	61.0 (10.0)	60.1 (10.2)	61.5 (10.0)	62.0 (9.5)*
Energy intake (kcal/day)	2180 (573)	1970 (566)	1959 (555)*	2184 (585)	1979 (542)	1921 (556)*
Fried food consumption (g/day)	84.2 (53.8)	34.2 (42.4)	29.1 (35.0)*	41.7 (44.6)	46.2 (47.5)	55.7 (57.1)*
Non-fried food consumption (g/day)	191 (88)	197 (90)	199 (92)	263 (85.5)	177 (67)	145 (72.0)*
DAI ^c	15.9 (10.4)	15.8 (10.4)	16.0 (10.1)	15.8 (10.6)	15.9 (10.3)	16.1 (9.9)

Values are means (standard deviations) unless otherwise indicated.

*P value<0.05 for differences in means or proportions.

^aModerate drinking: ≤24 g/day in women and ≤40 g/day in men. ^bAlternative Healthy Eating Index-2010, ranging from 0 to 110 (highest adherence).

^cDeficit Accumulation Index, as a percentage of age-related health deficits out of those considered, ranging from 0 to 100.

Table 2. β coefficients (95% CI) for the association of changes in food consumption with 3 and 6-year changes in the DAI.

	Change in fried food consumption (g/day)				Change in non-fried food consumption (g/day)			
	< -14	-14 to 14	> 14	Per 1-SD increment	< -35	-35 to 35	> 35	Per 1-SD increment
3-year change in the DAI								
No.	629	652	762	2043	700	690	653	2043
Model 1	Ref.	-0.54 (-1.39, 0.32)	-1.42 (-2.27, -0.58)**	-0.71 (-1.07, -0.36)***	Ref.	-1.10 (-1.93, -0.27)**	-0.54 (-1.44, 0.37)	-†
Model 2	Ref.	-0.47 (-1.32, 0.38)	-1.45 (-2.30, -0.61)***	-0.73 (-1.08, -0.38)***	Ref.	-1.11 (-1.94, -0.29)**	-0.58 (-1.50, 0.34)	-
6-year change in the DAI								
No.	499	521	579	1599	542	542	515	1599
Model 1	Ref.	0.14 (-0.97, 1.25)	-0.03 (-1.14, 1.08)	-0.22 (-0.69, 0.24)	Ref.	0.04 (-1.05, 1.13)	0.89 (-0.31, 2.09)	0.20 (-0.32, 0.71)
Model 2	Ref.	0.29 (-0.81, 1.40)	0.01 (-1.10, 1.12)	-0.22 (-0.68, 0.24)	Ref.	-0.10 (-1.19, 0.98)	0.64 (-0.57, 1.86)	0.03 (-0.50, 0.55)
	Change in fried protein-rich food consumption (g/day)				Change in non-fried protein-rich food consumption (g/day)			
	< -11	-11 to 11	> 11	Per 1-SD increment	< -30	-30 to 30	> 30	Per 1-SD increment
3-year change in the DAI								
No.	652	677	714	2043	693	706	644	2043
Model 1	Ref.	-0.20 (-1.05, 0.65)	-1.36 (-2.20, -0.51)**	-0.83 (-1.19, -0.48)***	Ref.	-0.79 (-1.61, 0.02)	0.08 (-0.97, 0.81)	-†
Model 2	Ref.	-0.10 (-0.95, 0.75)	-1.37 (-2.21, -0.53)**	-0.83 (-1.18, -0.47)***	Ref.	-0.82 (-1.64, -0.01)*	-0.15 (-1.05, 0.76)	-
6-year change in the DAI								
No.	514	533	552	1599	534	557	508	1599
Model 1	Ref.	0.88 (-0.23, 2.00)	-0.05 (-1.15, 1.05)	-0.44 (-0.90, 0.03)	Ref.	0.29 (-0.77, 1.36)	1.32 (0.14, 2.50)*	0.37 (-0.13, 0.87)
Model 2	Ref.	1.05 (-0.05, 2.16)	-0.01 (-1.10, 1.09)	-0.40 (-0.86, 0.06)	Ref.	0.08 (-0.98, 1.15)	1.00 (-0.20, 2.20)	0.20 (-0.31, 0.70)
	Change in fried potatoes consumption (g/day)				Change in non-fried potatoes consumption (g/day)			
	< -3	-3 to 3	> 3	Per 1-SD increment	< -11	-11 to 11	> 11	Per 1-SD increment
3-year change in the DAI								
No.	587	650	806	2043	682	670	691	2043
Model 1	Ref.	0.02 (-0.88, 0.91)	-0.11 (-0.97, 0.74)	0.01 (-0.35, 0.36)	Ref.	-0.69 (-1.53, 0.16)	-0.55 (-1.43, 0.33)	-0.27 (-0.67, 0.13)
Model 2	Ref.	0.07 (-0.83, 0.96)	-0.19 (-1.05, 0.67)	-0.04 (-0.40, 0.32)	Ref.	-0.71 (-1.55, 0.14)	-0.53 (-1.42, 0.35)	-0.28 (-0.68, 0.12)
6-year change in the DAI								
No.	470	515	614	1599	535	514	550	1599
Model 1	Ref.	0.62 (-0.53, 1.78)	0.52 (-0.59, 1.63)	0.35 (-0.12, 0.82)	Ref.	-0.54 (-1.65, 0.57)	-0.84 (-2.00, 0.31)	-0.41 (-0.94, 0.12)
Model 2	Ref.	0.60 (-0.56, 1.75)	0.34 (-0.77, 1.44)	0.29 (-0.18, 0.76)	Ref.	-0.46 (-1.56, 0.65)	-0.80 (-1.95, 0.35)	-0.41 (-0.94, 0.12)

*P value<0.05; **P value<0.01; ***P value<0.001. † Analyses per 1-SD increment of DAI were not performed because tests for non-linearity were significant. DAI = deficit accumulation index.

Model 1: Linear regression model adjusted for sex, educational level (primary or less, secondary, or university), age (years), and the corresponding type of food (g/day) and the DAI at wave 0.

Model 2: As Model 1 and further adjusted for smoking status (never, former, or current), alcohol consumption (never, former, moderate [24 g/day in women and <40 g/day in men], or heavy drinker), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m²), diet quality (AHEI-2010 score), and energy intake (kcal/day) at wave 0.

Table 3. β coefficients (95% confidence intervals) for the association of 3-year changes in fried and non-fried group-specific protein-rich food consumption with changes in unhealthy aging, measured with the DAI, over 3 and 6 years.

		Change in fried meat consumption (g/day)				Change in non-fried meat consumption (g/day)			
		< -0	0	> 0	Per 1-SD increment	< -25	-25 to 25	> 25	Per 1-SD increment
3-year change in the DAI									
No.	596	892	555	2043	688	711	644	2043	
Model 1	Ref.	-0.97 (-1.86, -0.08)*	-1.62 (-2.55, -0.70)***	-0.46 (-0.84, -0.07)*	Ref.	-0.57 (-1.40, 0.25)	0.09 (-0.82, 1.00)	-†	
Model 2	Ref.	-1.03 (-1.92, -0.13)*	-1.65 (-2.58, -0.73)***	-0.43 (-0.82, -0.05)*	Ref.	-0.62 (-1.45, 0.20)	-0.03 (-0.94, 0.89)	-	
6-year change in the DAI									
No.	477	686	436	1599	534	559	506	1599	
Model 1	Ref.	0.23 (-0.92, 1.38)	-0.19 (-1.38, 1.01)	0.18 (-0.31, 0.68)	Ref.	0.30 (-0.78, 1.38)	1.04 (-0.15, 2.23)	0.49 (-0.03, 1.01)	
Model 2	Ref.	0.14 (-1.02, 1.30)	-0.23 (-1.43, 0.97)	0.21 (-0.28, 0.70)	Ref.	0.07 (-1.02, 1.15)	0.68 (-0.52, 1.87)	0.30 (-0.22, 0.83)	
		Change in fried eggs consumption (g/day)				Change in non-fried eggs consumption (g/day)			
		< -1	-1 to 1	> 1	Per 1-SD increment	< -6	-6 to 6	> 6	Per 1-SD increment
3-year change in the DAI									
No.	615	763	665	2043	647	663	733	2043	
Model 1	Ref.	-0.73 (-1.57, 0.11)	-1.54 (-2.41, -0.68)***	-0.69 (-1.06, -0.31)***	Ref.	0.70 (-0.15, 1.56)	1.14 (0.25, 2.02)*	0.38 (-0.02, 0.79)	
Model 2	Ref.	-0.85 (-1.69, 0.00)	-1.63 (-2.49, -0.76)***	-0.69 (-1.06, -0.31)***	Ref.	0.73 (-0.13, 1.59)	1.12 (0.23, 2.00)*	0.34 (-0.07, 0.74)	
6-year change in the DAI									
No.	493	592	514	1599	504	510	585	1599	
Model 1	Ref.	0.73 (-0.36, 1.82)	-0.73 (-1.85, 0.39)	-0.35 (-0.83, 0.12)	Ref.	0.47 (-0.66, 1.59)	0.45 (-0.70, 1.61)	0.13 (-0.38, 0.65)	
Model 2	Ref.	0.50 (-0.59, 1.60)	-0.82 (-1.94, 0.30)	-0.32 (-0.79, 0.15)	Ref.	0.48 (-0.64, 1.60)	0.37 (-0.79, 1.52)	0.05 (-0.47, 0.56)	
		Change in fried fish consumption (g/day)				Change in non-fried fish consumption (g/day)			
		< -7	-7 to 7	> 7	Per 1-SD increment	< -14	-14 to 14	> 14	Per 1-SD increment
3-year change in the DAI									
No.	569	676	798	2043	679	681	683	2043	
Model 1	Ref.	-0.36 (-1.24, 0.52)	-1.17 (-2.02, -0.31)**	-0.63 (-0.97, -0.28)***	Ref.	-0.24 (-1.07, 0.60)	0.26 (-0.58, 1.11)	-0.00 (-0.36, 0.36)	
Model 2	Ref.	-0.36 (-1.25, 0.53)	-1.20 (-2.05, -0.35)**	-0.64 (-0.98, -0.29)***	Ref.	-0.21 (-1.04, 0.62)	0.24 (-0.61, 1.09)	0.00 (-0.36, 0.37)	
6-year change in the DAI									
No.	487	518	624	1599	530	530	539	1599	
Model 1	Ref.	0.19 (-0.96, 1.34)	-0.79 (-1.90, 0.31)	-0.58 (-1.04, -0.13)*	Ref.	0.55 (-0.54, 1.64)	0.19 (-0.92, 1.30)	-0.02 (-0.50, 0.45)	
Model 2	Ref.	0.31 (-0.84, 1.45)	-0.67 (-1.78, 0.43)	-0.55 (-1.00, -0.10)*	Ref.	0.60 (-0.49, 1.69)	0.09 (-1.02, 1.20)	-0.07 (-0.54, 0.41)	

*P value<0.05; **P value<0.01; ***P value<0.001. † Analyses per 1-SD increment of DAI were not performed because tests for non-linearity were significant. DAI = deficit accumulation index.

Model 1: Linear regression model adjusted for sex, educational level (primary or less, secondary, or university), age (years), and the corresponding type of food (g/day) and the DAI at wave 0.

Model 2: As Model 1 and further adjusted for smoking status (never, former, or current), alcohol consumption (never, former, moderate [24 g/day in women and <40 g/day in men], or heavy drinker), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m²), diet quality (AHEI-2010 score), and energy intake (kcal/day) at wave 0.

Table 4. β coefficients (95% CI) for the association between the replacement of fried with non-fried food, and 3 and 6-year changes in the DAI.

	3-year change in the DAI	6-year change in the DAI
	n=2043	n=1599
Replacement of 100 g/day^a of fried with non-fried food		
Total food	1.48 (0.59, 2.37)**	0.53 (-0.65, 1.71)
Protein-rich food	2.03 (1.03, 3.03)***	1.21 (-0.10, 2.52)
Potatoes	- 0.61 (-2.84, 1.61)	-2.75 (-5.65, 0.16)
Total meat	1.83 (-0.13, 3.78)	-0.67 (-3.17, 1.83)
Poultry	1.77 (-1.51, 5.06)	-2.19 (-6.36, 1.99)
Red meat	1.79 (-1.22, 4.80)	-0.90 (-4.72, 2.92)
Processed meat	3.99 (-3.26, 11.24)	-0.32 (-9.55, 8.91)
Eggs	10.76 (5.20, 16.33)***	4.73 (-2.31, 11.77)
Total fish	2.06 (0.68, 3.43)**	1.71 (-0.09, 3.52)
Oily fish	0.75 (-2.13, 3.64)	0.90 (-2.79, 4.59)
White fish	2.74 (0.97, 4.51)**	2.62 (0.29, 4.94)*

*P value<0.05; **P value<0.01; ***P value<0.001. DAI = deficit accumulation index.

Substitution models are linear regression models including both fried and non-fried food for each type of food and adjusted as Model 2 in Tables 2 and 3: sex, educational level (primary or less, secondary, or university), age (years), the corresponding type of food (g/day), the DAI, smoking status (never, former, or current), alcohol consumption (never, former, moderate [24 g/day in women and <40 g/day in men], or heavy drinker), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m²), diet quality (AHEI-2010 score), and energy intake (kcal/day) at wave 0.

Substitution coefficients are calculated by subtracting the coefficient for the corresponding type of fried food from that for the corresponding type of non-fried food. Negative values favor non-fried food, whereas positive values favor fried food.

^a One serving comprises 150-200 g of potatoes, 100-125 g of meat, 60 g of eggs, and 125-150 g of fish [28].

Figure 1. Association of changes in fried and non-fried food consumption with 3-year changes in the DAI.

DAI = deficit accumulation index.

Plotted values are β coefficients (95% confidence intervals) from a linear regression model adjusted as Model 2 in Table 2: sex, educational level (primary or less, secondary, or university), age (years), the corresponding type of food (g/day), the DAI, smoking status (never, former, or current), alcohol consumption (never, former, moderate [24 g/day in women and <40 g/day in men], or heavy drinker), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m²), diet quality (AHEI-2010 score), and energy intake (kcal/day) at wave 0.

Figure 2. Association of changes in group-specific fried and non-fried food consumption with 3-year changes in the DAI.

DAI = deficit accumulation index.

Plotted values are β coefficients (95% confidence intervals) from a linear regression model adjusted as Model 2 in Table 3: sex, educational level (primary or less, secondary, or university), age (years), the corresponding type of food (g/day), the DAI, smoking status (never, former, or current), alcohol consumption (never, former, moderate [24 g/day in women and <40 g/day in men], or heavy drinker), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m²), diet quality (AHEI-2010 score), and energy intake (kcal/day) at wave 0.

