Clinical Nutrition 37 (2018) 1389–1398

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Should we recommend reductions in saturated fat intake or in red/processed meat consumption? The SUN prospective cohort study

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ARTICLE INFO

Article history:
Received 11 December 2016
Accepted 8 June 2017

Keywords:
Mortality
Red meat
Total meat
Diet
Cohort
Prospective

SUMMARY

Background & aims: While most studies have shown increased mortality associated with excessive red/processed meat consumption, the association of saturated fatty acids (SFA) intake with mortality is less homogeneous. We aimed to prospectively assess the association of both, meat consumption (red, processed, red + processed, and total) and SFA intake, with the risk of all-cause death.
Methods: We assessed 18,540 participants of the SUN (Seguimiento Universidad de Navarra) cohort, followed-up for a mean of 9.5 years. A validated 136-item FFQ was administered at baseline. We used Cox models adjusted for potential confounders.
Results: We observed 255 deaths during 176,916 person-years of follow-up. Age modified the association between meat consumption and all-cause mortality (p for interaction = 0.027, 0.075, and 0.013, for red, total, and processed meat, respectively). Among participants aged >45 years the fully-adjusted HRs (95% CIs) for one additional serving/d of red, total, and red + processed meat consumption were 1.47 (1.06, 2.04), 1.23 (1.05, 1.45), and 1.32 (1.05, 1.65), respectively, with significant linear trends (P for trend 0.022, 0.012, and 0.018, respectively). In these participants, SFA intake was non-significantly associated with mortality. However, isocaloric replacement of monounsaturated fat or carbohydrates by SFA resulted in significantly higher mortality risk. Likewise, replacing 100 g of vegetables, fruits & nuts or cereals by 100 g of red meat resulted in higher mortality risk. No association of meat consumption or SFA with all-cause mortality was observed in participants younger than 46 years.
Conclusions: Among highly educated persons, aged >45 years, a high consumption of red, total, and red + processed meat was related to increased all-cause mortality, compared with those with low consumption, whereas no significant associations were found for SFA intake. Dietary guidelines should specifically limit meat consumption and not relying only in limiting SFA intake.

1. Introduction

In recent decades, meat consumption has increased markedly. Data from the Food Agriculture Organization show that meat consumption has increased from ~30 kg/person/year in the 80's to ~43.4 kg/person/year in 2015 worldwide [1], with values as high as ~125 kg/person/year in the USA [2]. After World War II, meat consumption expansion was mainly observed in industrialized nations. However, most of the global increases in animal-source foods, comprising meat, take place in low- and middle-income countries [3].

Though there is evidence of the drawbacks linked to excessive meat consumption [4–18], its nutritional value as an optimal source of protein, iron, zinc, B- and A vitamins is established. For example, iron and folate contained in meat are crucial in the prevention of anaemia. Yet, a high intake of haem-iron from meat may

Abbreviations: DGA, Dietary Guidelines for Americans; FAO, Food Agriculture Organization; IARC, International Agency for Research on Cancer; SUN, Seguimiento Universidad de Navarra.

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http://dx.doi.org/10.1016/j.clnu.2017.06.013
0261-5614/

lead to endogenous formation of n-nitroso compounds, which have been linked to the development of colon cancer [4]. In October 2015, the International Agency for Research on Cancer of the World Health Organization (IARC/WHO) classified red meat as "probably carcinogenic to humans" and processed meat, as "carcinogenic to humans" [5]. Numerous [6–18], but not all [19–22] epidemiological studies have reported an association of red and/or processed meat consumption with all-cause mortality or cause-specific mortality. Meta-analyses on this association confirmed a significant positive relationship [23–26], although they also showed between-study heterogeneity. None has specifically compared young and old groups.

Increased cardiovascular (CV) risk related to high consumption of red and processed meat has been linked to their high content of saturated fatty acids (SFA) [27]. However, considering SFA intake as a whole may be misleading because diverse food sources of SFA have shown different impact on CV outcomes and mortality risk [26–29]. The potential controversies are mainly explained by the macronutrient that is substituted for SFA [30,31]. Based on this knowledge acquired in nutritional research, the current 2015–2020 Dietary Guidelines for Americans (DGA) recommend limiting SFA intake to less than 10% of calories but they give almost no specific recommendation on limiting meat consumption [32]. As it happened with some other dietary guidelines, when the recommendation for optimal health is to increase the consumption, the message is straightforward, but the language is not so clear when foods should be reduced.

In light of recent research in this area and of the possible implications for dietary recommendations, we aimed to prospectively assess both, the associations of meat consumption (red, processed, red + processed, and total) as well as of SFA intake with the risk of death in the SUN ("Seguimiento Universidad de Navarra") longitudinal study and to asses if age was an effect modifier of this association.

2. Subjects and methods

2.1. Study design and population

The SUN project is a permanently open dynamic cohort with prospective design, recruiting university graduates. The cohort started in 1999 with follow-up obtaining biennial updated information. Details of the design and methods of the SUN project can be found elsewhere [33,34], which has been performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University of Navarra. Once a university graduate is invited to participate with a mailed questionnaire, his/her initial response is regarded as informed consent to participate. After the initial assessment, participants receive follow-up questionnaires every two years on diet, risk factors, medical conditions, and other lifestyle parameters. For those participants who do not respond to a follow-up questionnaire, five additional letters are mailed.

The present analyses were performed by examining the last available database as of the 1st of December 2015, corresponding to 22,476 participants. We recruited participants who had spent enough time in the study as to be able to complete and return at least the 2-year follow-up questionnaire (>2 years and additional 9 months to account for the lag time in returning the questionnaires) and we excluded 798 participants for this reason. Participants were also excluded from the analyses if they reported total energy intake out of pre-defined limits (800–6000 kcal/d for men and 500–5500 kcal/d for women) or if they left 20 or more items in blank from the FFQ ($n = 1512$) [35] or they were lost to follow up ($n = 1626$). The final analytic population included 18,540 participants. Overall retention was 91% (91% of participants recruited at least 2 years and 9 months ago returned ≥1 of the follow-up questionnaires).

2.2. Dietary assessment

Dietary habits were assessed in the first questionnaire by a semi-quantitative 136-item FFQ formerly described in detail [36]. The questionnaire has been repeatedly validated [36,37] and its reproducibility has been assessed [38]. Nutrient scores were calculated as previously reported in detail [36–38] utilizing information on the latest available Spanish food composition tables [39,40]. In the semi-quantitative FFQ we explicitly included serving sizes (in grams) according to the typical serving size of each food in the Spanish population, corresponding to 125 g of red meat, 125 g of white meat, 50 g of processed meat, and 100 g of total meat. The meat variables included consumption of white meat (chicken, turkey, and rabbit), red meat (veal, pork, lamb, liver, viscera (offal), hamburger), and processed meat (dry cured ham [Serrano ham type], cooked ham [York ham type], sausages [salami, mortadella, blood sausage, spicy pork sausage, würstel], bacon, pancetta, paté), as well as total meat considering together all types of meat. Sources of SFA in our cohort are shown in Table 7 (supplemental files). We adjusted SFA intake for total energy intake by using the residual method separately for men and women [41]. We adjusted meat consumption for total energy intake as an independent variable in the main analyses and by using the residual method in sensitivity analyses.

2.3. Other covariates

We also included in the analyses other covariates assessed in the initial questionnaire, such as anthropometric measurements (weight, body mass index [BMI]), socio-demographic parameters (age, sex, marital status, years of university education), clinical variables (personal history of depression, hypertension and/or hypercholesterolemia at baseline, history of cardiovascular disease, cancer and/or diabetes), health-related habits (physical activity, smoking status, alcohol use, following special diets, snacking, and hours of television watching), and year of entering the cohort. Body weight and BMI were self-reported and have been formerly validated in a sub-sample of this cohort [42]. Physical activity was assessed using a previously validated questionnaire with a Spearman correlation coefficient of 0.51 ($p < 0.001$) with objective measurements [43]. Physical activity was expressed in metabolic equivalent tasks (METs-h/week) as calculated from the time spent at each activity in hours/week multiplied by its typical energy expenditure [44]. We used the score proposed by Trichopoulou et al. [45] to assessed the adherence to the Mediterranean food pattern.

2.4. Ascertainment of mortality

We identified the occurrence of each new death by means of a uninterrupted and dynamic follow-up of all participants in the cohort. All participants were contacted on several occasions every year, asking for information on eventual changes of postal address. For each cohort member, we have 3 updated alternative postal addresses in order to facilitate the contacts during the follow-up period. Alternatively, we used the participants' emails and phone numbers to contact them when postal contact failed. In addition, we contacted regularly with the alumni associations and other professional associations to request information about participants who did not return the follow-up questionnaires. Most of deceases in our cohort (>85%) were reported by next of kin, professional associations, or by the postal system. We also checked the National Death Index every six months to confirm the vital status of our participants and to request and complete the data regarding mortality, including the cause of death in our cohort.

2.5. Statistical analysis

We calculated means and SDs for normally distributed variables, median (p10, p90) for non-normally distributed variables, or proportions of baseline characteristics for descriptive purposes, across levels of red meat, total meat, processed meat, and red + processed meat consumption. Red + processed meat category was included in order to isolate them from white meats. We calculated follow-up time for each participant taking into consideration the date of returning the initial questionnaire up to the date of death or up to the date of returning the last follow-up questionnaire. Death rates were calculated across baseline categories of meat consumption (less than 3 servings per week, 3–6 servings per week, 7 servings per week [once a day], and more than 7 servings per week). We calculated HR and 95% CI by means of Cox proportional hazards models using the lowest category of consumption as the reference category. Age was the underlying time variable, and different degrees of adjustment were used: 1) adjusted for sex and age (in 10 categories); 2) additional adjustments for year of entering the cohort (4 categories), BMI (continuous), years of university education (continuous), alcohol use (in 5 categories), smoking (in 3 categories), physical activity (MET-h/week) (continuous), hours per day spent watching television (continuous), history of hypercholesterolemia, hypertension, and/or depression, CV disease, cancer, and/or diabetes, following special diets at baseline, snacking between meals, and total energy intake (continuous). We also performed all the analyses using as exposure a 1-serving per day increment (as a continuous variable) in the different types of meat consumption. Trend tests were calculated using meat consumption as a continuous variable. Multivariable-adjusted estimates for restricted cubic splines were used to calculate dose–response association between SFA intake or red meat consumption and total mortality. We assessed interactions with age using likelihood ratio tests in fully adjusted Cox models. We introduced a product-term with both age and meat servings/d (or SFA intake) as continuous variable in this term.

We also performed multivariable analyses to examine the HRs for mortality when we did isocaloric replacements of MUFA, PUFA, and carbohydrates by SFA, and replaced 100 g of fish, potatoes, poultry, eggs, vegetables, fruits and nuts, and cereals by 100 g of red meat. These variables were incorporated in the same fully-adjusted model as continuous variables, and the differences in their beta-coefficients, variances and covariance were used to calculate the beta-coefficient ± SE for the substitution effect. Subsequently, we used these parameters to estimate the HRs and 95% CIs.

We performed diverse sensitivity analyses by estimating the fully adjusted HR for a 1-serving increment in red meat consumption and total meat consumption after changing several assumptions: 1) including only men or women; 2) considering different allowed limits for total energy intake; 3) adopting allowed limits for total energy intake from percentile 1 to 99; 4) excluding participants with history of diabetes at baseline; 5) Excluding prevalent cancer, CVD, and diabetes; 6) excluding participants with diagnosis of hypertension and hypercholesterolemia at baseline; 7) censoring the follow-up time of participants at 6 or 8 years; 8) excluding early deaths (within the first 2 years of follow-up); 89) adjusting for the Mediterranean diet score calculated as proposed by Trichopoulou et al. [45], excluding meat and alcohol to avoid redundancy (maximum score = 7 points); 10) including only deaths occurring at 60 years of age and over; 11) including only cancer deaths; 12) including only CV deaths. The analyses were performed with Stata software package version 12 (Stata Corp). Statistical significance was set at 2-tailed P values < 0.05. Values in the text are means ± SDs unless otherwise specified.

3. Results

During 176,916 person-years follow-up from 1999 to 2015 (mean follow-up: 9.5 years; range: 0.06–15.8 years), we observed 255 deaths in the SUN cohort, after exclusions. The mean age at death was 56.4 ± 15.7 years (range: 20–91 years); 73% of participants were aged ≤45 years at recruitment. As expected, because of higher prevalence of hypertension, hypercholesterolemia, diabetes, and cancer, crude death rates were higher among participants older than 45 years. We found a statistically significant interaction between age and red meat consumption on all-cause mortality (p for interaction = 0.027) with a positive association between red meat consumption and all-cause death only present in participants older than 45 years (Fig. 1). This significant interaction was also present for processed meat consumption (p for interaction = 0.013), and for total meat consumption, which was marginally significant (p for interaction = 0.075) (Fig. 2). Therefore, we analysed separately participants over and under 45 years of age.

Table 1 shows baseline characteristics of participants older than 45 years according to extreme categories (<3 and >7 servings/week) of total, red, and processed meat consumption. Participants in the highest category of consumption (>7 servings/week) of total, red and processed meat vs. those with the lowest consumption (<3 servings/week) were more likely to be men, married, current smokers, have a higher (though moderate) alcohol consumption, history of diabetes, and a higher total energy intake. These participants had lower levels of leisure-time physical activity and were less likely to be on special diets. Participants with a previous history of depression, hypertension, and CV disease at baseline tended to have lower consumption of all types of meat, possibly related to lower total energy intake in the former, and to previous medical advice of limiting excessive meat consumption for those with a

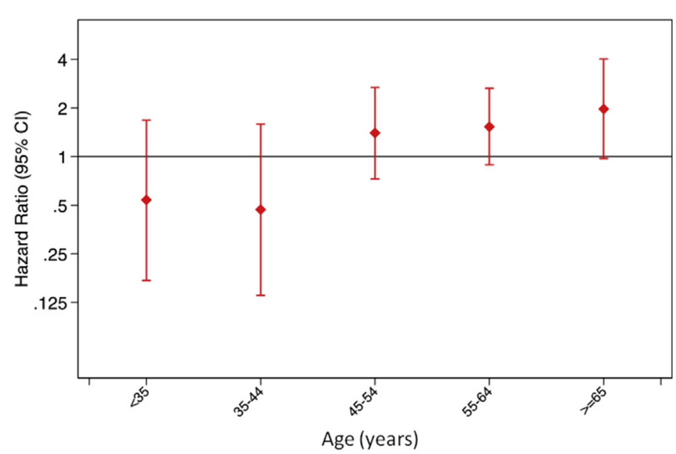

Fig. 1. Multivariable-adjusted Hazard Ratios for all-cause death by each additional serving of red meat, by categories of age. We observed a significant interaction between age and red meat consumption on all-cause mortality (p for interaction = 0.0268, both as continuous, 1 df). The model was adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university education, BMI, smoking (3 categories), alcohol (5 categories), physical activity (MET-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, and total energy intake.

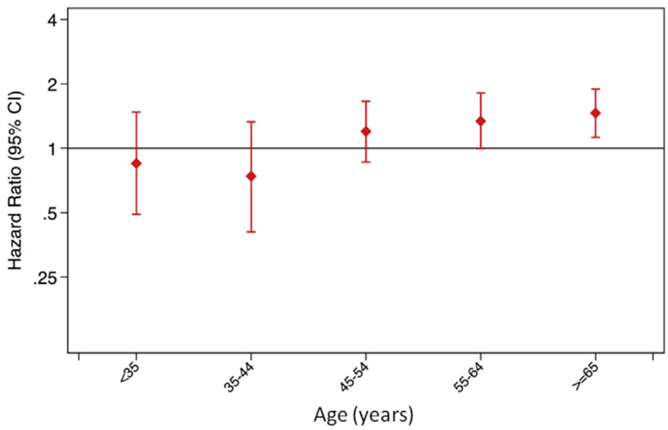

Fig. 2. Multivariable-adjusted Hazard Ratios for all-cause death by each additional serving of total meat, by categories of age. We observed a marginally significant interaction between age and total meat consumption on all-cause mortality (p for interaction = 0.0746). The model was adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university education, BMI, smoking (3 categories), alcohol (5 categories), physical activity (MET-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, and total energy intake.

history of hypertension and CV disease. Persons with higher consumption of processed meat had a higher frequency of between-meal snacking.

Participants with higher consumption of total, red and processed meat were more likely to eat less fruit, but more likely to consume more fish, cereals, and whole dairy products. Unsurprisingly, participants with higher intake of total, red and processed meat had higher mean intake of total fat, SFA, and iron from haem sources.

A significantly positive linear trend in the Cox model was observed for the associations of red meat consumption, total meat consumption, and red + processed meat consumption with all-cause mortality after adjustment for sex and age (Table 2). An additional serving/d of red meat consumption, total meat consumption, or red + processed meat consumption was significantly associated with higher all-cause mortality in the fully-adjusted model (Table 2). White meat consumption was not associated with mortality (Table 8, supplemental files).

An additional serving/d of processed meat was significantly associated with all-cause mortality after adjustment for sex and age, while it did not remain significant in the fully-adjusted model (Table 2). It is noteworthy that most participants aged over 45 years belonged to the lowest consumption category (<3 servings/week) (n = 3276) with very few of them belonging to the highest consumption (7 servings/week, n = 96; >7 servings/week, n = 195). The small number of observed fatalities in these categories may explain the lack of statistical significance for the positive linear trend. Notwithstanding, when processed meat was combined with red meat, the models reached statistical significance regardless of the potential confounders included as covariates.

For SFA, among participants older than 45 years, a positive trend in the Cox models for energy-adjusted quintiles of SFA intake was apparent, but it did not reach statistical significance, both, after adjustment for sex and age and in the fully-adjusted model (Table 3). No significant association with mortality was observed when participants older than 45 years in extreme quintiles of SFA were compared or comparing SFA intake >10% vs ≤10% of total calories in all participants, young and old (data not shown).

In substitution models, isocaloric substitution of SFA for MUFA or carbohydrates resulted in significant higher mortality risk. Likewise, replacing 100 g of vegetables, fruits & nuts, and cereals by 100 g of red meat resulted in higher mortality risk (Table 4).

Figure 3 shows the dose–response association between SFA intake (panel A), red meat consumption (panel B) or processed meat consumption (panel C) and total mortality in participants aged 45 years and over. A clear positive association between increasing g/day of red meat and all-cause mortality was found, starting with a dose of 190 g/day. Conversely, the relationship was not linear and non-significant for SFA intake with wide confidence intervals in the highest levels of intake. In our spline analyses, the steepest slope for the point estimate of the positive association between consumption and mortality was observed for processed meats, however, the confidence intervals were wide and included the null value across all the range of consumption, and the overall consumption was lower for processed meats than for red meats (Fig. 3 panel C).

Several sensitivity analyses were carried out in order to appraise the robustness of our findings (Tables 5 and 6). When we assessed red meat consumption as a continuous variable in the main analysis, for each additional serving/day, the mortality relative risk increment was 47%. This association remained significant in most sensitivity analyses after considering only men, allowing for energy limits between percentiles 1 and 99, censoring follow-up at 6 years, excluding early deaths (those occurring during the first 2 years of follow-up), excluding external causes of death, or adjusting for an overall healthy dietary pattern (i.e., the Mediterranean diet score). The analyses showed a positive association but they did not remain statistically significant when considering only women, in which case the number of events was very low, excluding participants with hypertension and hypercholesterolemia at baseline, excluding participants with cancer, CVD, and diabetes at baseline, censoring follow-up at 8 years, or including only CV deaths. They were marginally significant when adopting different allowed limits for total energy intake, after excluding prevalent diabetes, including only deaths occurring at ≥60 years of age, or including only cancer deaths.

When we assessed total meat consumption as a continuous variable in the main analysis, for each additional serving per day, the mortality relative risk increment was 23%. This association remained significant when considering only men, excluding prevalent diabetes, early deaths, or external causes of death, adjusting for Mediterranean diet score, and including only deaths occurring after 60 years of age. The relationship was marginally significant when allowing for energy limits between percentiles 1 and 99.

Analyses on participants aged 45 years or younger were not statistically significant and are shown in the Supplemental files (Tables 9 and 10).

4. Discussion

Using data from a prospective, large, well-characterized cohort of Spanish university graduates, we found: 1) that age modified the relation between meat consumption and all-cause mortality; 2) a significant, independent, and strong association between red, total, and red + processed meat consumption and all-cause mortality among participants aged >45 years, which remained significant in most sensitivity analyses; 3) a non-significant and even not linear association between SFA intake and all-cause mortality. Our findings, derived from analyses in the same prospective cohort, strengthen the importance of limiting meat consumption and to include more explicitly this advice in dietary guidelines addressed to the general public. This could have implications for national dietary policies and guidelines of dietary recommendations.

The effects of meat consumption on human health outcomes have been extensively examined [6–22]. Most studies [6–18] have shown a significant association of red and processed meat consumption with all-cause, cancer, and CV mortality. Fewer reports

Table 1
Baseline characteristics of participants according to extreme categories of total meat, red meat, and processed meat consumption among participants older than 45 years in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999–2015.

	Total meat		Red meat		Processed meat	
	Low <3 servings/week	High >7 servings/week	Low <3 servings/week	High >7 servings/week	Low <3 servings/week	High >7 servings/week
N	239	3798	1704	708	3276	195
Women, %	46	41	45	33	45	35
Age, y[a]	55.0 ± 8.0	53.6 ± 7.0	53.9 ± 7.0	53.8 ± 7.2	54.3 ± 7.3	52.4 ± 6.3
Married, %	68	80	74	79	77	82
University education, y[a]	5.2 ± 1.8	5.3 ± 1.7	5.3 ± 1.7	5.3 ± 1.8	5.3 ± 1.7	5.1 ± 1.4
BMI, kg/m^2 [a]	24.6 ± 3.2	25.4 ± 3.5	25.1 ± 3.5	25.8 ± 3.7	25.1 ± 3.4	25.8 ± 3.9
Smoking						
Current, %	13	19	16	20	17	20
Former smoker, %	46	48	50	49	48	55
Alcohol (g/d)[b]	1.2 (0, 13.9)	2.1 (0, 15.3)	1.8 (0, 13.9)	3.3 (0, 18)	1.8 (0, 13.3)	5.4 (0, 28.0)
Leisure-time physical activity, METs-h/wk[b]	19.6 (3.3, 49.5)	16.5 (2.5, 46.5)	17.1 (2.9, 48.2)	16.3 (2.2, 46.4)	16.8 (2.8, 46.7)	16.3 (0.8, 49.2)
Television watching, h/d[b]	1.2 (0.3, 3.0)	1.3 (0.4, 3.0)	1.3 (0.4, 3.0)	1.4 (0.4, 3.3)	1.3 (0.4, 3.0)	1.3 (0.4, 3.3)
History of depression at baseline, %	2.5	1.2	1.8	1.3	2.0	1.0
Hypertension at baseline, %	22	18	20	18	20	17
Hypercholesterolemia at baseline, %	34	33	34	30	35	27
History of cardiovascular disease, %	6.3	2.8	3.9	2.8	3.5	2.1
History of cancer, %	8.0	5.3	6.0	6.4	6.1	5.6
History of diabetes, %	2.1	4.5	3.8	5.7	4.7	6.2
Total energy intake, kcal/d	1990 ± 759	2521 ± 761	2206 ± 728	2795 ± 813	2257 ± 712	3233 ± 817
Adoption of special diets, %	17	10	13	9.9	13	5.6
Between-meal snacking, %	26	25	25	27	23	37
Dietary consumption						
Vegetables (g/d)[b]	537 (202, 1102)	520 (245, 992)	525 (219, 1040)	508 (236, 985)	523 (231, 1006)	524 (230, 1202)
Fruit (g/d)[b]	340 (128, 961)	331 (119, 755)	343 (119, 878)	297 (112, 732)	342 (125, 802)	331 (103, 847)
Legumes (g/d)[b]	16 (4, 38)	21 (12, 38)	21 (8, 34)	21 (12, 47)	21 (8, 34)	25 (12, 51)
Cereals (g/d)[b]	81 (15, 193)	92 (26, 206)	81 (21, 199)	94 (27, 214)	81 (21, 201)	107 (30, 214)
Whole bread (g/d)[b]	0 (0, 60)	0 (0, 60)	0 (0, 60)	0 (0, 28)	0 (0, 60)	0 (0, 28)
Nuts (g/d)[b]	3 (0, 50)	3 (0, 21)	3 (0, 39)	3 (0, 21)	3 (0, 21)	3 (0, 21)
Olive oil (g/d)[b]	13 (4, 35)	14 (5, 35)	13 (5, 35)	15 (6, 42)	14 (5, 35)	18 (8, 43)
Eggs (g/d)[b]	9 (0, 26)	26 (9, 47)	26 (4, 26)	26 (9, 47)	26 (4, 26)	26 (7, 47)
Fish and other seafood (g/d)[b]	86 (20, 190)	106 (48, 182)	100 (41, 183)	116 (49, 212)	105 (43, 182)	120 (55, 244)
Whole dairy products (g/d)[b]	51 (3, 329)	102 (19, 385)	75 (10, 354)	123 (21, 398)	75 (12, 346)	162 (33, 542)
Low-fat dairy products (g/d)[b]	157 (0, 539)	200 (0, 554)	200 (0, 575)	161 (0, 541)	203 (0, 575)	157 (0, 508)
Coffee (cups/d)[b]	5 (0, 6)	5 (0, 6)	5 (0, 6)	5 (0, 6)	5 (0, 6)	5 (0, 6)
Dietary intakes						
Carbohydrate (% of energy)	51 ± 9.3	43 ± 7.4	47 ± 8.1	40 ± 7.2	46 ± 8.0	39 ± 7.0
Protein (% of energy)	16 ± 3.6	19 ± 3.3	18 ± 3.6	20 ± 3.4	19 ± 3.6	19 ± 3.1
Total fat (% of energy)	31 ± 8.2	36 ± 6.3	33 ± 7.1	38 ± 5.9	34 ± 6.7	40 ± 5.4
MUFAs (% of energy)	14 ± 4.9	16 ± 3.7	15 ± 4.1	17 ± 3.5	15 ± 3.9	17 ± 3.2
SFAs (% of energy)	9.0 ± 3.6	12 ± 3.1	10 ± 3.2	14 ± 2.9	11 ± 3.2	14 ± 2.9
PUFAs (% of energy)	4.7 ± 1.9	5.2 ± 1.5	5.0 ± 1.6	5.3 ± 1.5	5.0 ± 1.6	5.5 ± 1.4
Vitamin C (mg/d)[b]	286 (122, 640)	275 (141, 520)	288 (132, 561)	263 (134, 480)	280 (136, 530)	295 (128, 609)
Vitamin D (mcg/d)[b]	2.6 (1.1, 6.6)	3.0 (1.5, 6.9)	2.8 (1.3, 6.8)	3.3 (1.6, 7.0)	2.8 (1.4, 6.7)	3.7 (2.0, 9.2)
Iron from haem sources (mg/d)[a]	16 ± 7.1	19 ± 6.3	17 ± 6.4	20 ± 6.3	17 ± 6.2	23 ± 7.0
Folate (mcg/d)[a]	466 ± 230	459 ± 212	458 ± 216	457 ± 202	456 ± 215	500 ± 229
Dietary fibre (g/d)[b]	30 (16, 62)	29 (17, 50)	30 (16, 54)	29 (17, 50)	29 (17, 51)	32 (19, 55)

MET: metabolic equivalent task; MUFA: monounsaturated fatty acid; SFA: saturated fatty acid; PUFA: polyunsaturated fatty acid.
[a] Values are mean ± SD for normally distributed variables, unless otherwise stated.
[b] Values are median (p10, p90) for non-normally distributed variables.

showing null results on this association [19–22] involved populations with moderate meat consumption and different ethnicity, i.e., Japanese [20,22], or were not extensive enough to omit small/moderate differences for specific causes of death [21]. In studies comparing non-vegetarians with vegetarians [13,14,16,18], the association of meat consumption and mortality may also be ascribed to other lifestyle components. Likewise, dietary patterns linked to a healthy lifestyle, such as the Mediterranean diet [11], may have other beneficial aspects in addition to low-meat consumption. Our results remained significant regardless of adjustments for multiple lifestyle confounders, and for the adherence to Mediterranean diet, underscoring the independent detrimental effect of an excessive consumption of meat.

Our assessment of participants older than 45 years is supported by two facts. First, most causes of death before 45 years are less likely to be related to major chronic disease. Second, most previous cohorts included participants older than those in the SUN cohort. Therefore, this decision provides a stronger basis for assessing consistency with the results of previously published cohorts. One of our novel findings is the evidence for an interaction with age, that should be replicated in other cohorts also including participants with a wide range of ages. Red/processed meat consumption was significantly associated with mortality in participants >45 years, while it was not significant for younger participants. As expected, younger participants had few deaths, being age the main risk factor for CV disease [46] and cancer [47]. The interaction with age is also plausible because of the time lag needed for the pathophysiologic development of these conditions.

Our results in participants older than 45 years are consistent with most previous studies. In large US and European cohorts, meat-associated increased mortality risk was independent of smoking, obesity and other lifestyle confounders [7,9,10]. Four meta-analyses

Table 2
Association between meat consumption and mortality among participants older than 45 years in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999–2015.[a]

Red meat	Categories of red meat consumption				Red meat consumption as a continuous variable	
	<3 servings/wk	3–6 servings/wk	7 servings/wk	>7 servings/wk	For 1 additional serving/d	*P*-trend
n	1704	2290	176	708		
Deaths	55	92	7	44		
Person-years	15,832	21,252	1563	6390		
Crude mortality rate ($\times 10^{-3}$)	3.47	4.33	4.48	6.89		
Age-, sex-adjusted HR	1 (ref.)	1.20 (0.86, 1.68)	1.28 (0.58, 2.83)	1.83 (1.23, 2.73)	1.38 (1.07, 1.77)	0.012
Multivariate-adjusted HR[b]	1 (ref.)	1.28 (0.89, 1.84)	1.19 (0.52, 2.74)	1.86 (1.19, 2.93)	1.47 (1.06, 2.04)	0.022
Processed meat	Categories of processed meat consumption				Processed meat consumption as a continuous variable	
	<3 servings/wk	3–6 servings/wk	7 servings/wk	>7 servings/wk	For 1 additional serving/d	*P*-trend
n	3276	1311	96	195		
Deaths	130	49	10	9		
Person-years	30,109	12,233	858	1836		
Crude mortality rate ($\times 10^{-3}$)	4.32	4.01	11.66	4.90		
Age-, sex-adjusted HR	1 (ref.)	1.06 (0.76, 1.49)	1.70 (1.39, 5.22)	1.52 (0.77, 3.02)	1.37 (1.00, 1.87)	0.047
Multivariate-adjusted HR[b]	1 (ref.)	1.08 (0.75, 1.56)	2.21 (1.06, 4.60)	1.57 (0.76, 3.24)	1.35 (0.96, 1.91)	0.082
Total meat	Categories of total meat consumption				Total meat consumption as a continuous variable	
	<3 servings/wk	3–6 servings/wk	7 servings/wk	>7 servings/wk	For 1 additional serving/d	*P*-trend
n	239	527	324	3788		
Deaths	11	17	10	160		
Person-years	2087	5011	3020	34,917		
Crude mortality rate ($\times 10^{-3}$)	5.27	3.39	3.31	4.58		
Age-, sex-adjusted HR	1 (ref.)	0.73 (0.34, 1.57)	1.00 (0.42, 2.41)	1.18 (0.63, 2.21)	1.23 (1.08, 1.40)	0.002
Multivariate-adjusted HR[b]	1 (ref.)	0.65 (0.29, 1.44)	0.66 (0.26, 1.66)	1.04 (0.53, 2.02)	1.23 (1.05, 1.45)	0.012
Red + Processed meat	Categories of red + processed meat consumption				Red + processed meat consumption as a continuous variable	
	<3 servings/wk	3–6 servings/wk	7 servings/wk	>7 servings/wk	For 1 additional serving/d	*P*-trend
n	392	1293	485	2708		
Deaths	17	44	16	121		
Person-years	3528	11,996	4579	24,933		
Crude mortality rate ($\times 10^{-3}$)	4.82	3.67	3.49	4.85		
Age-, sex-adjusted HR	1 (ref.)	0.93 (0.53, 1.64)	0.81 (0.41, 1.62)	1.26 (0.75, 2.10)	1.28 (1.08, 1.52)	0.005
Multivariate-adjusted HR[b]	1 (ref.)	1.03 (0.57, 1.88)	0.86 (0.41, 1.78)	1.31 (0.75, 2.30)	1.32 (1.05, 1.65)	0.018

SUN, Seguimiento Universidad de Navarra.
[a] Values are HR estimated with Cox regression and 95% confidence intervals (CI). If the CI includes 1.00, the results are not significant, $P > 0.05$ (2-tailed).
[b] HR adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university education, body mass index, smoking (3 categories), alcohol (5 categories), physical activity (METs-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, and total energy intake.

available [23–26] showed a significant relationship despite high between-study heterogeneity and substantial variability in types of meat and mortality outcomes assessed. Overall, the relationship was more significant for processed meat consumption attributed to its higher content of cholesterol, SFA, salt, nitrite, hem-iron, polycyclic aromatic hydrocarbons, and heterocyclic amines [48,49]. We found a significant positive trend for the association of processed meat consumption with all-cause mortality, adjusting for sex and age.

Table 3
Association between SFA intake and mortality among participants older than 45 years in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999–2015.[a]

SFA	Quintiles of energy-adjusted SFA intake[b]					SFA intake as a continuous variable	
	Q1	Q2	Q3	Q4	Q5	For additional 5% of energy from SFA	*P*-trend
n	983	983	983	983	983		
Median intake (% calories from SFA)	21	27	31	35	41		
Deaths	43	28	37	47	43		
Person-years	9038	8941	9005	8973	9079		
Crude mortality rate ($\times 10^{-3}$)	4.76	3.13	4.11	5.24	4.74		
Age-, sex-adjusted HR	1 (ref.)	1.03 (0.63, 1.68)	1.11 (0.71, 1.74)	1.61 (1.05, 2.48)	1.23 (0.79, 1.90)	1.15 (0.94, 1.39)	0.171
Multivariate-adjusted HR[c]	1 (ref.)	0.96 (0.57, 1.63)	1.16 (0.71, 1.88)	1.60 (1.01, 2.55)	1.21 (0.74, 1.97)	1.20 (0.96, 1.49)	0.106

[a] Values are HR estimated with Cox regression and 95% CI. If the CI includes 1.00, the results are not significant, $P > 0.05$ (2-tailed). SUN, Seguimiento Universidad de Navarra.
[b] The residual method was used to adjust for total energy intake.
[c] HR adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university education, BMI, smoking (3 categories), alcohol (5 categories), physical activity (MET-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, and total energy intake.

Table 4
Substitution models of meat consumption, SFA intake and mortality in participants older than 45 years in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999–2015.[a]

	For each 5% of total energy intake	*P*-value
Isocaloric replacement		
SFA replaces MUFA		
Age-, sex-adjusted HR	1.28 (0.95, 1.73)	0.103
Multivariate-adjusted HR[b]	1.41 (1.03–1.93)	0.034
SFA replaces PUFA		
Age-, sex-adjusted HR	1.09 (0.82–1.45)	0.552
Multivariate-adjusted HR[b]	1.17 (0.87–1.58)	0.288
SFA replaces CHO		
Age-, sex-adjusted HR	1.28 (1.00–1.66)	0.054
Multivariate-adjusted HR[b]	1.34 (1.02–1.75)	0.037
Non-isocaloric replacement		
Red meat (100 g) replaces 100 g of fish		
Age-, sex-adjusted HR	1.14 (0.76–1.71)	0.523
Multivariate-adjusted HR[b]	1.14 (0.76–1.71)	0.533
Red meat (100 g) replaces 100 g of potatoes		
Age-, sex-adjusted HR	1.14 (0.80–1.61)	0.467
Multivariate-adjusted HR[b]	1.04 (0.71–1.53)	0.823
Red meat (100 g) replaces 100 g of poultry		
Age-, sex-adjusted HR	1.02 (0.67–1.54)	0.944
Multivariate-adjusted HR[b]	1.07 (0.71–1.62)	0.739
Red meat (100 g) replaces 100 g of eggs		
Age-, sex-adjusted HR	3.43 (1.19–9.90)	0.023
Multivariate-adjusted HR[b]	3.01 (0.99–9.16)	0.053
Red meat (100 g) replaces a serving of vegetables		
Age-, sex-adjusted HR	1.57 (1.25–1.98)	<0.001
Multivariate-adjusted HR[b]	1.51 (1.15–1.97)	0.003
Red meat (100 g) replaces 100 g of fruits & nuts		
Age-, sex-adjusted HR	1.39 (1.12–1.72)	0.002
Multivariate-adjusted HR[b]	1.37 (1.07–1.75)	0.013
Red meat (100 g) replaces 100 g of cereals		
Age-, sex-adjusted HR	1.43 (1.11–1.84)	0.005
Multivariate-adjusted HR[b]	1.41 (1.04–1.87)	0.024

[a] Values are HR estimated with Cox regression and 95% CI. If the CI includes 1.00, the results are not significant, $P > 0.05$ (2-tailed). SUN, Seguimiento Universidad de Navarra.

[b] HR adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university of education, BMI, smoking (3 categories), physical activity (MET-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, prescription of special diets at baseline and snacking between meals.

However, the statistical significance was lost in the fully-adjusted model. In our Mediterranean cohort, the consumption of high amounts of processed meat (≥1 servings per day) was infrequent, probably as a result of a cultural tradition of moderate consumption of this type of food, or to consume it in small amount as part of dishes prepared with other components. We included analyses combining red and processed meat to isolate their effect from that of white and other types of meat. In these analyses, where participants in the higher categories of consumption and the number of events increased, we found a significant relationship of red + processed meat consumption with mortality risk. White meat consumption alone was not associated with mortality. In a recent Danish study replacing meat by vegetables or potatoes was associated with a reduced risk of myocardial infarction [50], similarly, we found that substituting vegetables, fruits & nuts, and cereals for red meat resulted in higher mortality risk.

Our observed significant interaction between age and red/processed meat consumption on all-cause mortality has some public health implications. Messages of prevention may not be easily followed by younger persons who are asymptomatic and unaware of the later negative consequences of lifestyle. Our results suggest that the general public should become aware of the long-term harmful consequences of excessive meat consumption, and messages should be explicit and plain.

Concerning SFA intake, our analyses suggested an association with all-cause mortality that was non-linear. The dose–response analysis was clearly non-significant with wide variability probably reflecting the various dietary sources of SFA and the lack of specificity of this parameter, confirming the results of previous studies [26–29] and the controversial and doubtful nature of considering SFA intake a predictor of mortality. Similarly to what is found in the literature, the sources of SFA are very varied. For example, components that have shown benefit such as olive oil, in addition to its high content of MUFA, also contains SFA. Such SFA sources may not be associated with increased mortality. On the contrary, not all the variability in SFA intake comes from meats. As shown in Table 7 (supplemental files), sausages, pork, and lamb have a small contribution to the variability of SFA intake in our study population. As in other dietary guidelines, the 2015–2020 DGA advise limiting SFA [32], probably generating an unclear message about which type of food people might choose or avoid, instead of giving clear food-based recommendations to reduce red/processed meat. There is a need for rendering food-based guidelines more practical, scientifically sound, and easily understandable. When we considered isocaloric replacement of MUFA by SFA we observed a higher mortality risk, in accordance with results from previous studies [26,30], denoting the importance of not considering all fats as detrimental.

Diet structure has changed since the 70's towards an increased consumption of animal-source foods including meat and processed foods, together with increased sedentary lifestyles. Dietary modifications were not recognized until the rise in hypertension, diabetes, and obesity was clearly apparent worldwide. Dietary changes were probably linked to relative food price variations since World War II, which may have been purposeful and relate to agricultural policies [3,51]. The worrying consequences of excessive meat consumption may be perpetuated if dietary recommendations are not explicitly delivered, while the opportunity to change the current alarming trends of otherwise preventable diseases and related mortality will continue to be missed.

Certainly, meat consumption cannot be considered in isolation because people eat combinations of foods. Our results, after multiple adjustments including the overall food pattern, indicate an independent effect of excessive meat consumption on mortality. Nevertheless, it is essential to consider the context in which meat consumption is evaluated. For example, the effects seem to differ in Asian populations [20,22,26]; in low-income countries small amounts of added meat may significantly improve micronutrient deficits [3]. The novelty of our results relies on three points: 1) We compared in the same cohort the rates of all-cause mortality associated with red/processed meat and with SFA. This is relevant because recommendations in some dietary guidelines are not clear or straightforward. This is crucial because the detrimental effects of red/processed meat should not be hidden behind a generic recommendation of limiting SFA. 2) We found that age modified the relationship between meat consumption and all-cause mortality, with a more detrimental effect at advanced ages. Our cohort allows this type of analysis because it comprises a wide range of age. 3) No previous longitudinal study has reported these findings in a Mediterranean country.

Our study has several strengths, such as a large sample size, prospective design, long-lasting follow-up, high retention rate, possibility to control for a wide array of confounding factors, including demographic confounders, diverse lifestyle parameters, and several sensitivity analyses where the results remained robust or indicating a positive association (though confidence intervals in some cases were wide due to sample size reduction by splitting the sample).

There are also some potential limitations of our study, including the use of self-reported information, even if parameters such as self-reported weight and BMI have been previously validated [40]. Our cohort is composed of highly educated persons, with low

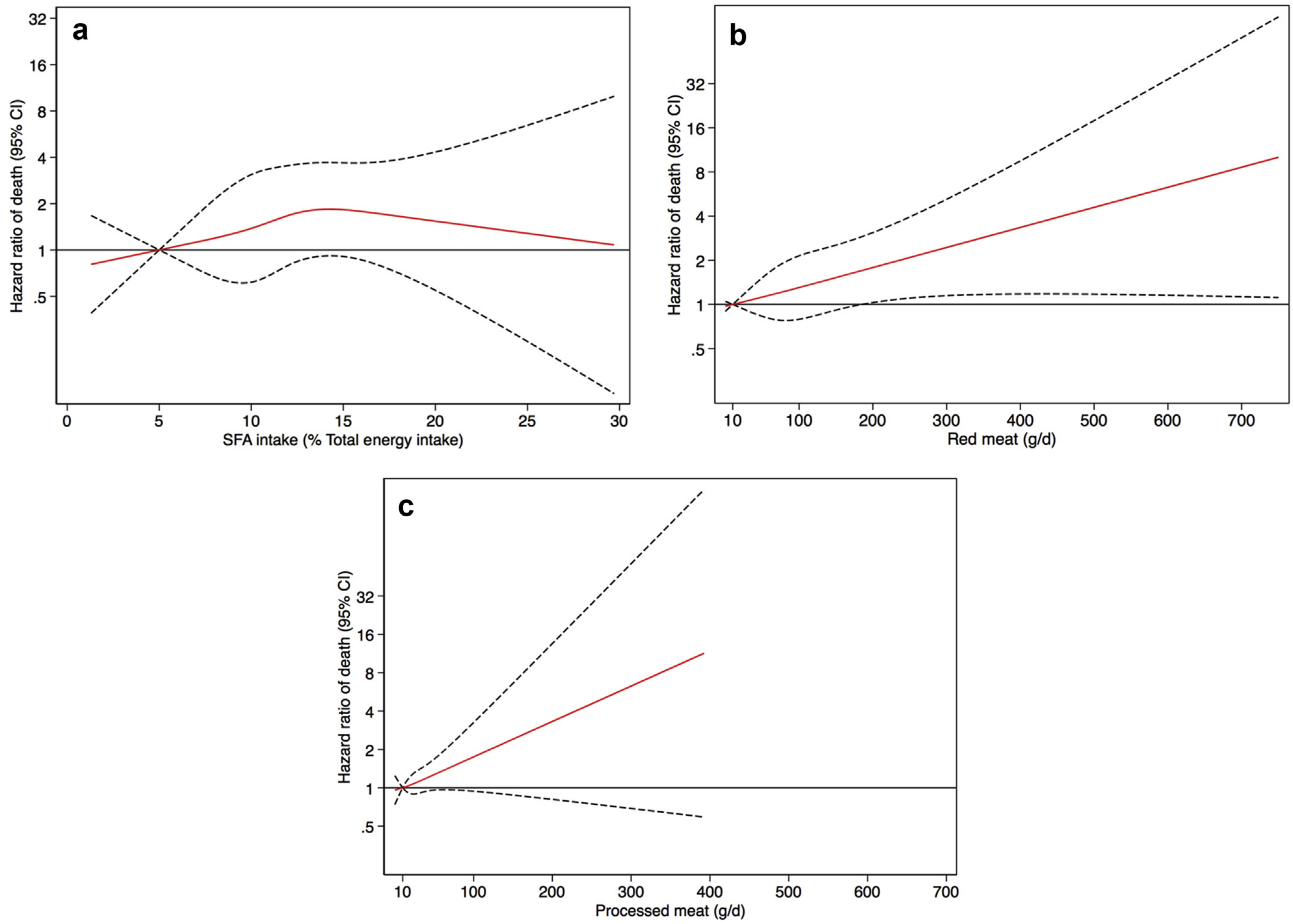

Fig. 3. Dose–response association between SFA intake (panel A), red meat consumption (panel B), or processed meat consumption (panel C) and total mortality in participants aged >45 years in the SUN cohort. Multivariable-adjusted estimates, restricted cubic splines.

Table 5
Sensitivity analyses: Multivariable-adjusted Hazard Ratios of all-cause mortality associated with 1 additional serving/d of red meat (among participants older than 45 years in the SUN Project, 1999–2015).[a]

	n	Deaths, n	HR (95% CI)[b]	*P*-trend[b]
All participants >45 years (main analysis)	4878	198	1.47 (1.06, 2.04)	0.022
Including only men	2862	168	1.50 (1.06, 2.12)	0.023
Including only women	2016	30	1.49 (0.47, 4.74)	0.502
Energy limits: percentiles 1–99[d]	5339	242	1.43 (1.05, 1.95)	0.025
Energy limits: 500–3500 (women) & 800–4000 kcal/d (men)[d]	5186	234	1.43 (0.99, 2.06)	0.054
Excluding prevalent diabetes	4666	177	1.42 (0.99, 2.03)	0.058
Excluding prevalent cancer, CVD, and diabetes	4284	132	1.14 (0.71, 1.84)	0.578
Excluding hypertension and hypercholesterolemia at baseline	2795	92	1.42 (0.91, 2.23)	0.123
Censoring follow-up at 8 y	4878	123	1.25 (0.81, 1.92)	0.318
Censoring follow-up at 6 y	4878	90	1.70 (1.05, 2.77)	0.031
Excluding early deaths (first 2 y)	4847	167	1.42 (1.02, 1.99)	0.040
Excluding external causes of death	4866	186	1.52 (1.10, 2.10)	0.010
Adjusting for Mediterranean diet score[c]	4878	198	1.45 (1.04, 2.02)	0.027
Including only deaths occurring ≥60 y[e]	2971	103	1.46 (0.96, 2.24)	0.080
Including only cancer deaths	4775	95	1.51 (1.00, 2.30)	0.052
Including only cardiovascular deaths	4725	45	1.11 (0.46, 2.68)	0.825

SUN, Seguimiento Universidad de Navarra.
[a] Values are HR estimated with Cox regression and 95% CI. If the CI includes 1.00, the results are not significant, $P > 0.05$ (2-tailed).
[b] HR adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university education, BMI, smoking (3 categories), alcohol (5 categories), physical activity (MET-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, and total energy intake.
[c] The Mediterranean score was calculated as proposed by Trichopoulou et al. [45], excluding meat and alcohol to avoid redundancy (maximum score = 7 points).
[d] The criteria for exclusion here were only based on energy intake, but not on the number of blank items. This is the reason why the number of participants was higher in this ancillary analysis.
[e] Participants who did not attain the age of 60 years during follow-up were excluded.

Table 6
Sensitivity analyses: Multivariable-adjusted Hazard Ratios of all-cause mortality associated with 1 additional serving/d of total meat (among participants older than 45 years in the SUN Project, 1999–2015).[a]

	n	Deaths, n	HR (95% CI)[b]	*P*-trend[b]
All participants >45 years (main analysis)	4878	198	1.23 (1.05, 1.45)	0.012
Including only men	2862	168	1.21 (1.02, 1.45)	0.030
Including only women	2016	30	1.40 (0.85, 2.31)	0.190
Energy limits: percentiles 1–99[d]	5339	242	1.16 (1.00, 1.35)	0.053
Energy limits: 500–3500 (women) & 800–4000 kcal/d (men)[d]	5186	234	1.16 (0.96, 1.39)	0.128
Excluding prevalent diabetes	4666	177	1.22 (1.02, 1.45)	0.031
Excluding prevalent cancer, CVD, and diabetes	4284	132	1.13 (0.89, 1.44)	0.311
Excluding hypertension and hypercholesterolemia at baseline	2795	92	1.17 (0.89, 1.54)	0.271
Censoring follow-up at 8 y	4878	123	1.19 (0.95, 1.49)	0.135
Censoring follow-up at 6 y	4878	90	1.24 (0.96, 1.59)	0.098
Excluding early deaths (first 2 y)	4847	167	1.24 (1.06, 1.47)	0.009
Excluding external causes of death	4866	186	1.25 (1.06, 1.47)	0.007
Adjusting for Mediterranean diet score[c]	4878	198	1.22 (1.04, 1.44)	0.015
Including only deaths occurring ≥60 y[e]	2971	103	1.30 (1.06, 1.58)	0.011
Including only cancer deaths	4775	95	1.22 (0.95, 1.55)	0.119
Including only cardiovascular deaths	4725	45	1.22 (0.89, 1.66)	0.217

SUN, Seguimiento Universidad de Navarra.
[a] Values are HR estimated with Cox regression and 95% CI. If the CI includes 1.00, the results are not significant, $P > 0.05$ (2-tailed).
[b] HR adjusted for age (10 categories), sex, year of entering the cohort (4 categories), years of university education, BMI, smoking (3 categories), alcohol (5 categories), physical activity (MET-h/wk), hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, and total energy intake.
[c] The Mediterranean score was calculated as proposed by Trichopoulou et al. [45], excluding meat and alcohol to avoid redundancy (maximum score = 7 points).
[d] The criteria for exclusion here were only based on energy intake, but not on the number of blank items. This is the reason why the number of participants was higher in this ancillary analysis.
[e] Participants who did not attain the age of 60 years during follow-up were excluded.

frequency of overweight or obese participants and with high levels of leisure-time physical activity. This may help to explain the relatively low number of deaths and the consequent width of some confidence intervals. However, in these participants we found strong significant positive associations between meat consumption and mortality risk. Regardless of the fact that the SUN cohort is composed of highly educated participants, the possible validity of our results in other populations must be based on plausible biological mechanisms instead of on mere statistical “representativeness”. We used restriction in order to reduce potential confounding by education, socioeconomic status, presence of disease, and alleged access to health care. Nonetheless, forthcoming studies are warranted in order to assess the external validity of our results in other populations. Data originating from FFQ could contain measurement errors that may bias analytical results. However, they are probably not differential and therefore should any bias have occurred, it probably would go towards the null. We used an FFQ that has been repeatedly validated [34–36]; moreover, it is challenging to find a better affordable procedure to characterize food habits of large samples, surveyed prospectively for long periods of time, with the intention of assessing their associations with incident clinical end-points [33].

5. Conclusions

High consumption of red, total, and red + processed meat was significantly, independently, and strongly associated with increased all-cause mortality among highly educated persons older than 45 years compared with those with low consumption. In the same cohort, the association between SFA intake and all-cause mortality was non-significant.

Our results are important in the context of an increasing meat consumption worldwide, particularly in the USA [2]. Regrettably, as with other dietary guidelines, the recently released 2015–2020 DGA [32] do not specifically limit red or total meat consumption, disregarding the compelling evidence of detrimental effects linked to an excessive meat consumption [6–18,23–26], and the recent report of IARC/WHO indicating carcinogenesis of red/processed meat [5].

The unfavourable effects of excessive red/processed meat consumption may continue if dietary recommendations do not explicitly include and reinforce the advice to avoid excessive meat consumption instead of relying in the only and unclear recommendation of limiting SFA.

Authorship statement

LJD and MAM-G designed research; MAM-G, MB-R, FJB-G, and AG conducted research; MAM-G, LJD, MB-R, and AG analysed data, performed statistical analysis or interpret the data; LJD and MAM-G draft the article; LJD, MAM-G, MB-R, AG, MB, and FJB-G revised the article critically for important intellectual content. All authors read and approved the final version of the manuscript to be submitted.

Conflict of interest

None of the authors has any conflict of interest to declare.

Funding sources

The SUN Project has received funding from the Spanish Government-Instituto de Salud Carlos III, and the European Regional Development Fund (FEDER) (RD 06/0045, CIBER-OBN, Grants PI10/02658, PI10/02293, PI13/00615, PI14/01668, PI14/01798, PI14/01764, and G03/140), the Navarra Regional Government (45/2011, 122/2014), and the University of Navarra. Funding sources had no role in study design, data collection, analysis and interpretation of data, writing the report, and decision to submit the article for publication.

Acknowledgements

The authors thank the participants of the SUN Project for their enthusiastic collaboration.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.06.013.

References

[1] Food and Agricultural Organization of the United Nations. Food outlook. Biannual report on global food markets. October 2015. http://www.fao.org/giews/ [accessed 20.05.16].

[2] Daniel CR, Cross AJ, Koebnick C, Sinha R. Trends in meat consumption in the USA. Public Health Nutr 2011;14:575–83.

[3] Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev 2012;70:3–21.

[4] Hebels DG, Sveje KM, de Kok MC, van Herwijnen MH, Kuhnle GG, Engels LG, et al. N-nitroso compound exposure-associated transcriptomic profiles are indicative of an increased risk for colorectal cancer. Cancer Lett 2011;309:1–10.

[5] Bouvard V, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015;16:1599–600.

[6] Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Differences in survival associated with processed and with nonprocessed red meat consumption. Am J Clin Nutr 2014;100:924–9.

[7] Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjonneland A, et al. Meat consumption and mortality – results from the European Prospective Investigation into cancer and nutrition. BMC Med 2013;11:63.

[8] Takata Y, Shu XO, Gao YT, Li H, Zhang X, Gao J, et al. Red meat and poultry intakes and risk of total and cause-specific mortality: results from cohort studies of Chinese adults in Shanghai. PLoS One 2013;8:e56963.

[9] Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Stampfer MJ, et al. Red meat consumption and mortality: results from 2 prospective cohort studies. Arch Intern Med 2012;172:555–63.

[10] Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A. Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med 2009;169:562–71.

[11] Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek epic prospective cohort study. BMJ 2009;338:b2337.

[12] Kelemen LE, Kushi LH, Jacobs Jr DR, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. Am J Epidemiol 2005;161:239–49.

[13] Chang-Claude J, Hermann S, Eilber U, Steindorf K. Lifestyle determinants and mortality in German vegetarians and health-conscious persons: results of a 21-year follow-up. Cancer Epidemiol Biomarkers Prev 2005;14:963–8.

[14] Appleby PN, Key TJ, Thorogood M, Burr ML, Mann J. Mortality in British vegetarians. Public Health Nutr 2002;5:29–36.

[15] Fortes C, Forastiere F, Farchi S, Rapiti E, Pastori G, Perucci CA. Diet and overall survival in a cohort of very elderly people. Epidemiology 2000;11:440–5.

[16] Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-hispanic white California seventh-day adventists. Am J Clin Nutr 1999;70:532S–8S.

[17] Whiteman D, Muir J, Jones L, Murphy M, Key T. Dietary questions as determinants of mortality: the oxcheck experience. Public Health Nutr 1999;2:477–87.

[18] Kahn HA, Phillips RL, Snowdon DA, Choi W. Association between reported diet and all-cause mortality. Twenty-one-year follow-up on 27,530 adult seventh-day adventists. Am J Epidemiol 1984;119:775–87.

[19] Kappeler R, Eichholzer M, Rohrmann S. Meat consumption and diet quality and mortality in NHANES III. Eur J Clin Nutr 2013;67:598–606.

[20] Nagao M, Iso H, Yamagishi K, Date C, Tamakoshi A. Meat consumption in relation to mortality from cardiovascular disease among Japanese men and women. Eur J Clin Nutr 2012;66:687–93.

[21] Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Mortality in british vegetarians: results from the European Prospective Investigation into cancer and nutrition (EPIC-Oxford). Am J Clin Nutr 2009;89:1613S–9S.

[22] Sauvaget C, Nagano J, Allen N, Grant EJ, Beral V. Intake of animal products and stroke mortality in the Hiroshima/Nagasaki life span study. Int J Epidemiol 2003;32:536–43.

[23] Wang X, Lin X, Ouyang YY, Liu J, Zhao G, Pan A, et al. Red and processed meat consumption and mortality: dose-response meta-analysis of prospective cohort studies. Public Health Nutr 2016;19:893–905.

[24] Abete I, Romaguera D, Vieira AR, Lopez de Munain A, Norat T. Association between total, processed, red and white meat consumption and all-cause, CVD and IHD mortality: a meta-analysis of cohort studies. Br J Nutr 2014;112:762–75.

[25] Larsson SC, Orsini N. Red meat and processed meat consumption and all-cause mortality: a meta-analysis. Am J Epidemiol 2014;179:282–9.

[26] O'Sullivan TA, Hafekost K, Mitrou F, Lawrence D. Food sources of saturated fat and the association with mortality: a meta-analysis. Am J Public Health 2013;103:e31–42.

[27] Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010;7:e1000252.

[28] Praagman J, Beulens JW, Alssema M, Zock PL, Wanders AJ, Sluijs I, et al. The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and nutrition-Netherlands cohort. Am J Clin Nutr 2016;103:356–65.

[29] Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 2014;160:398–406.

[30] Guasch-Ferré M, Babio N, Martínez-González MA, Corella D, Ros E, Martín-Peláez S, et al. PREDIMED Study Investigators. Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease. Am J Clin Nutr 2015;102:1563–73.

[31] Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. J Am Coll Cardiol 2015;66:1538–48.

[32] US Department of Health and Human Services; US Department of Agriculture. 2015-2020 dietary guidelines for Americans. 8th ed. Washington, DC: US Dept of Health and Human Services; December 2015. http://www.health.gov/DietaryGuidelines [accessed 21.11.16].

[33] Martinez-Gonzalez MA, Sanchez-Villegas A, De Irala J, Marti A, Martinez JA. Mediterranean diet and stroke: objectives and design of the SUN project. Seguimiento Universidad de Navarra. Nutr Neurosci 2002;5:65–73.

[34] Segui-Gomez M, de la Fuente C, Vazquez Z, de Irala J, Martinez-Gonzalez MA. Cohort profile: the 'Seguimiento Universidad de Navarra' (SUN) study. Int J Epidemiol 2006;35:1417–22.

[35] Willett W. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998.

[36] Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol 1993;22:512–9.

[37] Fernandez-Ballart JD, Pinol JL, Zazpe I, Corella D, Carrasco P, Toledo E, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly mediterranean population of Spain. Br J Nutr 2010;103:1808–16.

[38] de la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, Sampson L, Martinez-Gonzalez MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr 2010;13:1364–72.

[39] Moreiras O, Carbajal A, Cabrera L, Cuadrado C. Food composition tables [Tablas de composición de alimentos]. 16th ed. Madrid: Piramide; 2013.

[40] Mataix Verdu J. Food composition tables [Tabla de composición de alimentos]. 5th ed. Granada: Universidad de Granada; 2009.

[41] Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.

[42] Bes-Rastrollo M, Perez Valdivieso JR, Sanchez-Villegas A, Alonso A, Martinez-Gonzalez MA. Validation of self-reported weight and body mass index of participants in a cohort of university graduates [Validación del peso e índice de masa corporal auto-declarados de los participantes de una cohorte de graduados universitarios]. Rev Esp Obes 2005;3:183–9.

[43] Martinez-Gonzalez MA, Lopez-Fontana C, Varo JJ, Sanchez-Villegas A, Martinez JA. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study. Public Health Nutr 2005;8:920–7.

[44] Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–504.

[45] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–608.

[46] Chantler PD, Lakatta EG. Arterial-ventricular coupling with aging and disease. Front Physiol 2012;3:90.

[47] Hoffe S, Balducci L. Cancer and age: general considerations. Clin Geriatr Med 2012;28:1–18.

[48] Bingham SA, Hughes R, Cross AJ. Effect of white versus red meat on endogenous n-nitrosation in the human colon and further evidence of a dose response. J Nutr 2002;132:3522s–5s.

[49] Behsnilian D, Butz P, Greiner R, Lautenschlaeger R. Process-induced undesirable compounds: chances of non-thermal approaches. Meat Sci 2014;98:392–403.

[50] Würtz AM, Hansen MD, Tjønneland A, Rimm EB, Schmidt EB, Overkad K, et al. Substitution of meat and fish with vegetables or potatoes and risk of myocardial infarction. Br J Nutr 2016;116:1602–10.

[51] Anand SS, Hawkes C, de Souza RJ, Mente A, Dehghan M, Nugent R, et al. Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the World Heart Federation. J Am Coll Cardiol 2015;66:1590–614.