

Original Research

The Contribution of Dietary Fatty Acids to Prediction of All-Cause Mortality in a Cohort of Middle-Aged Men Followed-Up for 61 Years Until Extinction

Alessandro Menotti¹, Paolo Emilio Puddu^{1, 2, *}

1. Association for Cardiac Research, Rome, Italy; E-Mails: amenotti2@gmail.com; puddu.pe@gmail.com
2. EA 4650, Signalisation, électrophysiologie et imagerie des lésions d'ischémie reperfusion myocardique, Normandie Université, UNICAEN, 14000 Caen, France

* **Correspondence:** Paolo Emilio Puddu; E-Mail: puddu.pe@gmail.com

Academic Editor: Cristiano Capurso

Recent Progress in Nutrition
2025, volume 5, issue 2
doi:10.21926/rpn.2502011

Received: November 09, 2024

Accepted: May 08, 2025

Published: May 19, 2025

Abstract

To describe the contribution of three classes of dietary fatty acids to all-cause mortality and age at death among middle-aged men followed up for 61 years until extinction. The cohort comprised 1712 men aged 40-59 years at entry examination in 1960, belonging to the Italian Rural Areas of the Seven Countries Study of Cardiovascular Diseases. A dietary survey allowed to estimate dietary fatty acids [saturated (SAFA), mono-unsaturated (MUFA), poly-unsaturated (PUFA) and their ratios (M/S, P/S)] that were fed as possible predictors in a series of Cox models and a multiple linear regression model (MLR) with all-cause mortality and age at death as end-points, respectively, together with 17 possible confounders. Cox multivariate coefficients of SAFA and MUFA were significantly predictive of the end-point (all-cause mortality) in a direct and inverse way, respectively, for the first 31 years and then for the final 61 years of follow-up while P/S and M/S ratios had a minor role. Prediction of the isolated events occurring between years 31 and 61 of follow-up did not show a significant association with the same fatty acids. In an MLR model with age at death as the endpoint, 1 standard deviation over SAFA was associated with the loss of 1 year. In comparison, 1 standard deviation over PUFA was associated with a gain of 0.61 years. Intake of butter, milk, cheese,



© 2025 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

meat, and pastry was significantly larger in high levels of SAFA and in low levels of P/S ratio. In a long-term follow-up, all-cause mortality and age at death are associated considerably with SAFA, MUFA, and partly PUFA using different predictive models, all adjusted for 17 possible confounding variables.

Keywords

Dietary fatty acids; dietary score; food groups; all-cause mortality; age at death

1. Introduction

In a previous contribution, we described the predictive power of major dietary fatty acids versus cardiovascular mortality in a cohort of middle-aged men followed up for 61 years until extinction [1]. Here we intend to investigate the contribution of the same dietary fatty acids to all-cause mortality (and separately to age at death) of the same cohort, which reached extinction, in the presence of some other baseline risk factors and characteristics.

The relationship of fatty acids with all-cause mortality is a debated issue, although less frequently than the parallel problem dealing with cardiovascular diseases (CVD). As for CVD, contributions are documenting a role of fatty acids [2-22] while others tend to negate it [23-26]. The approaches and arguments are somewhat variegated and, time by time, they used the three major classes of fatty acids [2, 3, 5, 10, 13, 15, 20, 23-27], or some of them or particular subtypes. Several studies adopted the theoretical “replacement” procedure of one fatty acid with another to estimate the possible effects on the end-point of such exchange [10, 11, 21]. On the other hand, other studies tended to insist more on dietary scores describing “healthy” versus “not healthy” diets for their association with all-cause mortality [4, 6, 7, 12, 14] where the contribution of fatty acids was not always explicitly indicated and frequently hidden in the choice of the diet type usually based on food groups. Finally, some narrative papers were summarizing others’ data or proposing preventive approaches [10, 13]. All this means that not all the discussed reports may directly compare with our analysis, whose details are below.

2. Materials and Methods

2.1 Population and Measurements

The study cohort was made by the Italian Rural Areas (IRA) of the Seven Countries Study enrolled in 1960 when the baseline examination was made on 1712 middle-aged men (aged 40-59) out of 1735 listed in the roster of two rural municipalities, with an entry participation rate of 98.7% [28].

The entry examination included the collection of family and social data, lifestyle behaviors including smoking, motion, and dietary habits, a series of anthropometric measurements, a few biochemical and biophysical measurements, diagnoses of major prevalent diseases obtained with a complex medical examination, and other diagnostic procedures [28]. All measurement techniques underwent strict standardization procedures.

The dietary survey was based on the dietary history [29] using an ad-hoc questionnaire administered by trained and supervised nutritionists [1]. These data allowed us to identify 18 food

groups and to estimate the amount of several nutrients based on local food tables [30]. The fatty acids used in this analysis were saturated (SAFA), monounsaturated (MUFA), and polyunsaturated (PUFA). Moreover, the following ratios were computed: MUFA/SAFA (M/S) and PUFA/SAFA (P/S) [1].

The intake of oligosaccharides, polysaccharides, and protein was also estimated, together with energy intake.

At year 31 of follow-up, in connection with a periodical re-examination of the survivors, the dietary survey was repeated with the same procedures, thus allowing comparison of nutritional habits time trends and posing the basis for further estimating subsequent all-cause mortality.

The three main fatty acids were the principal variables of analysis. In contrast, several potential confounders for multivariate analysis were considered, choosing only those measured in both the year 0 and year 31 examinations. These variables, listed in Table 1, were measured following the procedures suggested in the WHO Cardiovascular Survey Method manual [31] except serum cholesterol, which was measured following the Anderson-Keys technique [32].

Table 1 List of study variables, confounding variables and demographic data.

Study variables					
	Year 0, N = 1712		Year 31, N = 390		P of difference
	mean	SD	mean	SD	
SAFA, g/day	28.7	11.7	20.6	8.8	<0.0001
MUFA, g/day	49.3	16.3	47.3	15.3	0.0270
PUFA, g/day	11.4	6.8	8.1	5.4	<0.0001
P/S ratio	0.40	0.25	0.39	0.27	0.1604
M/S ratio	1.72	0.64	2.29	1.36	<0.0001
Confounding variables					
Age, years	49.1	5.1	77.4	4.1	<0.0001
Never smokers, %	25.4	1.1	22.3	2.1	0.2000
Ex smokers, %	13.6	0.8	61.8	2.5	<0.0001
Smokers, %	61.1	1.2	15.9	1.9	<0.0001
Body mass index, kg/m ²	25.2	3.7	26.1	3.5	<0.0001
Subscapular skinfold	11.8	5.9	19.3	6.4	<0.0001
Systolic blood pressure, mmHg	143.6	21.0	160.5	19.6	<0.0001
Heart rate, beats/min	71.3	12.9	70.3	13.5	0.1900
Serum cholesterol, mg/dl	201.6	40.8	208.2	41.0	0.0040
Proteins, g/day	76.5	24.5	76.1	20.9	0.7700
Oligosaccharides, g/day	57.9	35.5	74.2	31.3	<0.0001
Polysaccharides, g/day	254.7	90.8	200.3	67.4	<0.0001
Cardiovascular diseases, %	4.4	0.5	39.5	2.5	<0.0001
Cancer, %	0.3	0.1	6.7	1.3	<0.0001
Diabetes, %	4.7	0.5	13.6	1.7	<0.0001
Chronic bronchitis, %	6.3	0.6	41.3	2.5	<0.0001
Energy intake, calories	2941	642	2388	584	<0.0001
Demographic data					
	Age-range	alive	deaths	examined	
Year 0	40-59	1712	--	1712	
Year 31	71-90	631	1081	390	
Year 61	--	4	1708	--	

Discrete variables are reported in proportion and standard error.

P-value of differences from the T-test for continuous variables and the test of proportions for discrete variables.

Collection and coding of mortality data were performed up to year 61 of follow-up when the cohort was practically extinct. Among 1712 men examined at entry, there were 1708 deaths (99.8%), three survivors, and 1 lost to follow-up after 50 years.

For analytical purposes, we used all-cause mortality and also, but marginally, age at death (AD), an old demographic metric that has been recently re-evaluated [33-35], whose use in cohort studies is proper only if the cohort is extinct or nearly extinct.

2.2 Statistical Analysis

Variables used for analysis were preliminarily treated descriptively.

A series of Cox proportional hazards models were computed with the three fatty acids (altogether) and separately the P/S and M/S ratios as independent variables and all-cause mortality as the dependent variable, all adjusted for a series of 17 possibly confounding variables. This operation was repeated 3 times, that is, for measurements taken at year 0 and follow-up mortality from year 0 to 31, from year 0 to 61, and from year 31 to 61. Then, another model was computed using measurements taken at year 31 for a follow-up from year 31 to 61.

Separately, a single multiple linear regression model (MLR) was computed for age at death after 61 years as the dependent variable, using baseline measurements of fatty acids and the usual confounding variables as covariates.

Finally, some food groups possibly related to high levels of SAFA were distributed in 2 classes of SAFA and separately of the P/S ratio.

2.3 Ethics Statement

The Board of Directors of the various institutions of the Seven Countries Study involved in data collections were de facto playing the role of ethical committee approving the execution of the study on the basis of the local existing legislation by the date this investigation started. Baseline measurements were taken before the era of the Helsinki Declaration and approval was implied in participation, while verbal or written consent was obtained for the collection of follow-up data.

3. Results

In Table 1, a descriptive presentation was made of variables distributed into 3 categories, i.e., study variables, confounding variables, and demographic data. Baseline means values of nutrients, suggested relatively low amounts of SAFA (8.8% of energy) and relatively high amounts of MUFA (15.0%) as expected from a population of the Mediterranean area, plus the relatively high contribution of carbohydrates (43% of energy).

Among the risk factors, there were relatively high levels of blood pressure and smoking habits, as well as relatively low levels of serum cholesterol. There were significant differences in the characteristics of men examined at entry with those still alive and examined after 31 years. Despite the reduction of total energy intake, some small, probably beneficial changes in the fatty acids profile and the drastic decrease in smoking habits, there were systematic increases in the mean level of major cardiovascular risk factors and of significant disease prevalence.

A low participation rate hampered the evaluation of personal characteristics at year 31 in the examination performed on the survivors, with 631 alive and 390 examined (62%). Comparing some entry characteristics between two groups (390 examined versus 241 not reviewed), we found a few significant differences, i.e., the non-examined subjects had a higher age by 1.5 years, slightly higher levels of serum cholesterol, and a lower prevalence of chronic bronchitis. However, in the long run, the distribution of 26 groups of causes of death was not different between the two groups, but the non-examined had an age at death 1 year lower.

Cox models of Tables 2 to 5 provide much information that can be summarized as follows considering all p values of coefficients reported in the Tables: A) Baseline SAFA predicted in a

significant and direct way fatal events occurred during the first 31 years of follow-up and during the whole period of 61 years, with hazards ratios (for 1 standard deviation difference) of 1.15 and 1.10 respectively; B) Baseline MUFA predicted in a significant and inverse way fatal events occurred during the first 31 years of follow-up and during the whole period of 61 years, with hazards ratios (for 1 standard deviation difference) of 0.92 and 0.94; C) Baseline PUFA predicted in a significant and inverse way only fatal events occurred during the whole period of 61 years with a hazard ratio of 0.94; D) Baseline P/S ratio was inversely and significantly related to events only for the 0 to 61 years period with a hazard ratio of 0.95; E) Baseline M/S ratio was inversely and significantly related only to events occurring during the first 31 years with a hazard ratio of 0.94; F) All models having as end-point the events of the period 31 to 61 did not produce significant associations, both with fatty acid measured at baseline and at 31-year examination. All estimates were adjusted for the 17 confounding variables reported in Table 1. Simulating a replacement procedure derived from the first model of Table 2, replacing 1 standard deviation of SAFA (12 g) with 1 standard deviation of MUFA (16 g), all-cause mortality within 31 years would decrease by 23%.

Table 2 Cox models with 31-year all-cause mortality as end-point and fatty acids measured at baseline as independent variables, adjusted for the other 17 covariates (including 1 reference).

Variables	Coefficient	P value	Delta	Hazard ratio	95% CI	
Model SAFA-MUFA-PUFA						
SAFA	0.0116	0.0126	+12	1.15	1.03	1.28
MUFA	-0.0049	0.0500	+16	0.92	0.85	0.99
PUFA	-0.0067	0.1808	+7	0.95	0.89	1.02
MODEL P/S						
P/S	-0.1863	0.1462	+0.25	0.95	0.90	1.02
MODEL M/S						
M/S	-0.1074	0.0479	+0.64	0.94	0.87	1.00

Delta = levels of variables used for the estimate of end-point changes, roughly corresponding to 1 standard deviation difference. CI = confidence intervals.

Table 3 Cox models with 61-year all-cause mortality as end-point and fatty acids measured at baseline as independent variables, adjusted for the other 17 covariates (including 1 reference).

Variables	Coefficient	P value	Delta	Hazard ratio	95% CI	
Model SAFA-MUFA-PUFA						
SAFA	0.0080	0.0303	+12	1.10	1.01	1.20
MUFA	-0.0040	0.0455	+16	0.94	0.88	1.00
PUFA	-0.0094	0.0172	+7	0.94	0.89	0.99
MODEL P/S						
P/S	-0.2248	0.0218	+0.25	0.95	0.90	0.99
MODEL M/S						
M/S	-0.0161	0.7194	+0.64	0.99	0.94	1.05

Delta = levels of variables used for the estimate of end-point changes, roughly corresponding to 1 standard deviation difference. CI = confidence intervals.

Table 4 Cox models with 31-61-year all-cause mortality as end-point and fatty acids measured at baseline as independent variables, adjusted for the other 17 covariates (including 1 reference).

Variables	Coefficient	P value	Delta	Hazard ratio	95% CI	
Model SAFA-MUFA-PUFA						
SAFA	0.0080	0.2174	+12	1.10	0.94	1.28
MUFA	-0.0033	0.3433	+16	0.96	0.85	1.06
PUFA	-0.0053	0.4414	+7	0.96	0.88	1.06
MODEL P/S						
P/S	-0.1523	0.3301	+0.25	0.96	0.89	1.04
MODEL M/S						
M/S	0.0318	0.6909	+0.64	1.02	0.92	1.13

Delta = levels of variables used for the estimate of end-point changes, roughly corresponding to 1 standard deviation difference. CI = confidence intervals.

Table 5 Cox models with 31-61-year all-cause mortality as end-point and fatty acids measured at year 31 as independent variables, adjusted for the other 17 covariates (including 1 reference).

Variables	Coefficient	P value	Delta	Hazard ratio	95% CI	
Model SAFA-MUFA-PUFA						
SAFA	0.0068	0.5433	+9	1.06	0.87	1.30
MUFA	0.0009	0.8747	+15	1.01	0.86	1.19
PUFA	-0.0054	0.5825	+5	0.97	0.88	1.07
MODEL P/S						
P/S	-0.0429	0.8276	+0.27	1.01	0.91	1.12
MODEL M/S						
M/S	-0.0185	0.7156	+1.36	0.97	0.85	1.12

Delta = levels of variables used to estimate end-point changes, roughly corresponding to a 1 standard deviation difference. CI = confidence intervals.

An alternative way to look at the same problem derives from the inspection of the MLR of Table 6 where age at death at year 61 of follow-up represented the end-point. At the same time, the three major fatty acids and the 17 confounding covariates were the independent variables. In this case, the magnitude of the coefficients represents the gained (if positive) or lost (if negative) years of life for a difference of 1 unit of measurement of the variable. The so-called “effect” represents the exact estimate adjusted for the variable difference of 1 standard deviation in the case of the continuous variables. It appears that 1 standard deviation in excess for SAFA corresponds to 1 year lost in age at death, roughly the same finding derived from 40 mg/dl increase of serum cholesterol. Simulating a replacement process, if SAFA is reduced by 1 standard deviation while PUFA is increased by 1 standard deviation, the net result will be a gain of $1 + 0.63$ years of life. On the other hand, there is

a heavy contribution to prediction from the 4 major prevalent diseases that may interfere with the role of the other covariates. The advantage of this approach is that gains and losses are additive and, in theory, can be combined in an infinite number of associations.

Table 6 MLR model with age at death after 61 years of follow-up as dependent variable, three dietary fatty acids as predictors and 17 other confounding variables (including 1 reference).

Variable	Coefficient	Standardized Coefficient	P value	Delta	Effect	95% CI	
Intercept	101.1461	----	----	----	----	----	
SAFA	-0.0831	-0.0840	0.0325	12	-1.00	-1.91	-0.08
MUFA	0.0381	0.0535	0.0796	16	0.61	-0.07	1.29
PUFA	0.0905	0.0531	0.0321	7	0.63	0.05	1.21
Age	0.0411	0.0181	0.4522	5	0.21	-0.33	0.74
Never smoker	reference	----	----	----	----	----	
Ex smoker	-1.6473	-0.0488	0.0648	1	-1.65	-3.39	0.10
Smoker	-3.3355	-0.1407	<0.0001	1	-3.34	-4.58	-2.09
Body mass index	0.0446	0.0143	0.6955	4	0.18	-0.71	1.07
Subscapular skinfold	0.0977	0.0489	0.1808	6	0.59	-0.27	1.44
Systolic blood pressure	-0.1208	-0.2190	<0.0001	21	-2.54	-3.13	-1.94
Heart rate	-0.0664	-0.0740	0.0025	13	-0.86	-1.42	-0.30
Serum cholesterol	-0.0267	-0.0941	0.0001	40	-1.07	-1.60	-0.53
Cardiovascular diseases	-4.3645	-0.0778	0.0008	1	-4.36	-6.92	-1.81
Cancer	-19.2506	-0.0899	0.0001	1	-19.25	-28.86	-9.64
Diabetes	-2.7561	-0.0506	0.0290	1	-2.76	-5.23	-0.28
Chronic bronchitis	-3.3243	-0.0696	0.0026	1	-3.32	-5.49	-1.16
Proteins	-0.0056	-0.0118	0.7584	25	-0.14	-1.03	0.75
Oligosaccharides	0.0161	0.0480	0.0974	35	0.56	-0.10	1.23
Polysaccharides	-0.0012	-0.0090	0.7647	90	-0.10	-0.78	0.57
Energy	-0.0004	-0.0238	0.3007	640	-0.27	-0.79	0.24

Units of measurement from Table 1. Standardized coefficients allow for comparing the strength of coefficient predictive power despite the difference in units of measurement.

Delta (roughly corresponding to 1 standard deviation for continuous variables) is the difference in the covariates' levels used to compute the Effect. The effect is the number of years gained (if positive) or lost (if negative) for increasing the delta in the covariate level.

An entirely different approach consisted of exploring the intake of food groups typically associated with high levels of SAFA, defined by its median value. All food groups involved were associated with SAFA, showing highly significant p-values of the T-test (Table 7). The parallel analysis involving low and high P/S ratios, again defined by the median value, provided inverted findings compared to those of SAFA, although significant only in two cases out of five. In summary, a high intake of butter, milk, cheese, meat, and pastry is associated with high levels of SAFA and low levels of the P/S ratio.

Table 7 Intake of some food groups versus SAFA and P/S ratio expressed as mean (and standard deviation) in grams per day.

Panel 1: 856 men with Low SAFA [20.0 (9.7)] versus 856 men with High SAFA [37.4 (9.7)].			
	Low SAFA	High SAFA	P of difference
Butter, g	7.9 (13.1)	15.3 (15.4)	<0.0001
Milk, g	78.7 (127.1)	138.9 (156.4)	<0.0001
Cheese, g	12.7 (15.1)	14.6 (18.0)	0.0181
Meat, g	104.4 (61.1)	129.9 (62.7)	<0.0001
Pastry, g	9.9 (17.9)	15.1 (25.0)	<0.0001
Panel 2: 856 men with High P/S [0.58 (0.28)] versus 856 men with Low P/S [0.27 (0.06)].			
	High P/S	Low P/S	P of difference
Butter, g	10.3 (13.9)	13.0 (15.6)	0.0002
Milk, g	98.0 (134.5)	120.0 (155.2)	0.0017
Cheese, g	14.0 (17.3)	13.4 (15.5)	0.4499
Meat, g	113.0 (61.6)	116.3 (63.8)	0.2764
Pastry, g	10.7 (16.8)	14.3 (25.9)	0.1364

4. Discussion

This analysis has shown that dietary fatty acids have a role in predicting all-cause mortality in an extinct cohort of middle-aged men. This was particularly true for the adverse role of SAFA and the beneficial role of MUFA, while the roles of PUFA and P/S or M/S ratios were less consistent. These findings were limited to the periods 0-31 and 0-61 years while no significant coefficients were produced for the isolated 31 to 61 years interval.

Findings with the follow-up of 61 should be considered with caution due to the possible influence of changing dietary habits and food composition during the extended follow-up. However, if this is true, the projection of prediction to 61 years can be only somewhat impaired and the conclusion can be simply conservative. Moreover, we can suppose that the predictive role of fatty acids, say after 31 years, may have relatively limited influence considering that it applies only to about one third of the original population size that has reached an age range of 71 to 90 years.

If we treat the hazard ratios of SAFA for the 0-31 years and the 31-61 periods as parts of a partitioned analysis, (that is combining the estimates of the two time-periods instead of using a single more extended period), the final crude hazard ratio for the whole 0-61 period is about 2% smaller than the one derived from the partitioned analysis. Something similar happens considering the role of MUFA, with an inverse outcome due to the different algebraic sign of the coefficients. All this is reassuring about the value of the prediction from year 0 to year 61.

Similar considerations are partly valid for the absence of significant coefficients related to fatty acids measured at year 31, a finding likely hampered by the reduced denominator of people still alive and partly re-examined, with the addition of the overwhelming role of the four major prevalent diseases.

Incidentally, the baseline levels of some traditional cardiovascular risk factors, such as serum cholesterol and blood pressure, have been shown in this population to maintain the same strength of predictive role for at least 40 years in dedicated partitioned analyses [36].

In the previous analysis of dietary fatty acids versus 61-year cardiovascular mortality of the same population, the adverse role of SAFA and the beneficial role of MUFA showed somewhat similar findings to those of the present analysis. Still, this outcome was confined to coronary heart disease and absent for other major cardiovascular disease groups [1].

An advantage of this analysis was the availability of age at death, thanks to the extinction of the cohort. This allowed us to compute an MLR model with age at death as the endpoint and the three fatty acids plus 17 confounding variables as covariates. In this case, the adverse role of SAFA and the beneficial ones of MUFA and PUFA were again clearly shown, still in the presence of 17 confounding variables. In this MLR analysis, the contribution of the single covariates, either basic (fatty acids) and confounding (all the others), to prediction seems relatively small except those of prevalent major diseases. This is mainly due to the presence of many confounding variables and the consequent fact that each variable is adjusted with all the others with a substantial loss of predictive power compared with that obtained by analyzing the risk factors singularly, one by one. In similar analyses run on the same population, involving around 30 predictive covariates and with age at death as endpoint, it was shown that arbitrary combinations of coefficients dealing with various covariates ends up with significant gains (or losses) in the overall age at death showing to be important determinants of the length of life [33].

A partial, indirect validation of our analysis is provided by the direct relationship between a few food groups (chosen because supposedly connected with SAFA intake) in high and low levels of SAFA and the inverse relationship with the P/S ratio.

This analysis has limitations due to the small size of the study population, the absence of the women component of the population (excluded at that time due to the need to enroll a much larger cohort producing fewer cardiovascular events), and the use of only the three major groups of dietary fatty acids. All this is probably, at least partially, compensated by the extreme length of the follow-up, which lasted 61 years with the reach of the cohort extinction.

Another problem may be related to the limited value of the technique used in the dietary survey. It should be considered that in the early 1960, the dietary history [29] was one of the rare tools available to describe dietary habits, and at that time, probably a better alternative was not available. If that is unreliable, then most nutritional surveys conducted during the last century should be discarded together with all the knowledge piled up in those years. Moreover, in the previous few decades, many studies were performed using questionnaires that describe only the frequency of food groups intake [37], which is probably not better than the dietary history.

The selection of a few references from the literature was based on identifying titles and abstracts that promised to be relatively similar to the characteristics of our analysis, thus allowing some comparisons. Several papers had some interesting similarities with our analysis. A Spanish population study compared all-cause mortality of the highest with the lowest quintile of some dietary fatty acids, and found a direct association for SAFA and an inverse association for MUFA and PUFA [3]. In an analysis of the NHANES data, all-cause mortality was inversely associated with PUFA and directly with SAFA [13]. In another study of the NHANES data dealing with adult and older adults, the highest quintile of the low-fat diet was associated with a 18% lower all-cause mortality and a 3% lower SAFA intake was also associated with lower all-cause mortality [19]. In a Chinese study covering over 1.5 million person-years, the SAFA intake had a positive and significant association with all-cause mortality, with a relative risk of 1.13, while the corresponding relative risk for PUFA was 0.79 [15].

Recently, the research group of the Seven Countries Study produced new contributions confirming and expanding the early findings of the last century, using, as tradition dictates, the ecological comparison across 16 cohorts of middle-aged men. The correlation of SAFA intake was significantly predictive of 50-year all-cause mortality with an R of 0.66, when the estimate was adjusted for high socio-economic status [22]. Moreover, indices of atherogenicity and thrombogenicity computed using 11 measured dietary fatty acids were associated with all-cause mortality with significant R values of 0.55 and 0.62, respectively [27].

A giant evaluation of the problem was produced by the US Department of Agriculture in 2020 [14] that included, among other sources, 141 observational studies of diet versus all-cause mortality using several different approaches. Diets like the Mediterranean and other similar ones, characterized by high P/S or M/S ratios, were associated with lower all-cause mortality rates.

Several papers dealt with a single fatty acid or a single primary class of them. Two papers showed lower all-cause mortality for high intake of MUFA [5, 16], one the same outcome for high intake of alpha-linolenic acid [17], and two for high intake of PUFA [18, 19], the first of the last two mainly based on high fish consumption.

Other papers studied the effect of replacing SAFA with similar amounts of PUFA or other fatty acids. In a Spanish population study [10], the isocaloric replacement of MUFA or carbohydrates with SAFA was associated with a significant increase in all-cause mortality. In a US study, the equi-energetic substitution of 10% of energy from SAFA to an equal amount of energy from MUFA or PUFA resulted in a significant reduction of all-cause mortality risk ranging from 4 to 8% [11]. In a large meta-analysis, replacing 5% of energy from SAFA and Trans fatty acids with the equivalent amount of PUFA, MUFA and plant-PUFA lowered the relative risk for all-cause mortality to ranges of relative risk between 0.75 to 0.91 [21]. A review of several sources showed that the reduction in SAFA intake does not affect all-cause mortality [25]. In an extensive US study involving half a million adults [2], replacement of carbohydrates with major fatty acids, produced for all-cause mortality hazards ratios ranging from 1.29 (for SAFA) to 0.92 (for PUFA).

A small group of contributions reported the experience of studies focused on dietary scores or other special diets potentially valid to be related with mortality outcome. A paper described the role of the vegetarian diet, naturally almost free from saturated fat, that was associated with smaller all-cause mortality rates, compared with standard diets [7]. The EPIC project run in half million subjects in 12 European countries showed that a complex dietary score characterized among other things by low SAFA and high PUFA and designed for the purpose, was associated, with its high levels (corresponding to an unhealthy diet), to an excess of 7% in all-cause mortality [12]. A similar study conducted in Singapore [6], employing more than one different dietary score, showed a relative risk ranging from 0.82 to 0.88 for diets rich in plant foods and PUFA. In a Spanish study, the adherence to the Mediterranean Diet, including higher M/S ratio and evaluated by different methods, was associated with lower all-cause mortality [4].

A couple of papers had a narrative shape, one reporting the conclusions of a Presidential (USA) committee that recommended the reduction of SAFA intake and other potentially dangerous nutrients [9], the other negating the role of saturated fat on health and disease based on generic review of literature [24].

We found other contributions with negative conclusions towards the role of dietary fatty acids in health and disease. One was already commented on in the paragraph of studies with replacement of fatty acids [25]. The review and re-analysis of unpublished data from an old dietary experiment,

showed that substituting SAFA with seed oil was associated with a 13% reduction of serum cholesterol, but at the same time with an increase of total mortality of 22% for each 30 mg/dl reduction of cholesterol [23]. An extensive review and metanalysis of many studies suggested that high fat intake was associated with reduced all-cause mortality (relative risk of 0.92). At the same time, SAFA were irrelevant in relation with the same end-point.

This short and limited review of some contributions from the recent literature suggests, unexpectedly, that a majority of studies tend to attribute a role of dietary fatty acids in relation to all-cause mortality, in particular the favorable effect of unsaturated fatty acids and the deleterious impact of SAFA. However, considering the existence of opposite conclusions, more research is probably needed.

5. Conclusions

Our analysis seems to confirm the conclusions of the majority of the literature findings, consisting of the opposite contributions of SAFA and PUFA versus all-cause mortality.

This accomplishment was obtained in a small cohort, but had the advantage to have used also age at death end-point beyond of all-cause mortality due to the extinction of the cohort and to have estimated the role of SAFA and PUFA after the adjustment for a large number of risk factors and personal characteristics measured at baseline including other nutrients.

Acknowledgments

The authors acknowledge Ms Giovina Catasta for her contribution in data collection.

Author Contributions

A.M. and P.E.P. contributed to the conception, design, work analysis, interpretation of data, draft of the manuscript, final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

For the initiation of the Italian Section of Seven Countries Study of Cardiovascular Diseases, funds were received from Prof Ancel Keys, University of Minnesota, USA, obtained as research grants from the National Heart Institute (later NHLBI) and the American Heart Association. Other funds obtained at national level came from the: Association for Cardiac Research, Rome; Centre of Cardiovascular Disease, S. Camillo Hospital, Rome; City of Naples; National Institute of Public Health (ISS); National Research Council (CNR); European Union; Centre for the Fight against Infarction, Rome. Analysis and writing of this manuscript were not covered by the above funds.

Competing Interests

None declared.

References

1. Menotti A, Puddu PE. Dietary fatty acids predicting long term cardiovascular mortality in a cohort of middle-aged men followed-up until extinction. *Hearts*. 2024; 5: 196-210.
2. Zhuang P, Zhang Y, He W, Chen X, Chen J, He L, et al. Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521 120 individuals with 16 years of follow-up. *Circ Res*. 2019; 124: 757-768.
3. Guasch-Ferré M, Babio N, Martinez-Gonzalez MA, Corella D, Ros E, Martin-Pelaez S, et al. Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease¹. *Am J Clin Nutr*. 2015; 102: 1563-1573.
4. Dominguez LJ, Bes-Rastrollo M, De la Fuente-Arrillaga C, Toledo E, Beunza JJ, Barbagallo M, et al. Similar prediction of total mortality, diabetes incidence and cardiovascular events using relative-and absolute-component mediterranean diet score: The SUN cohort. *Nutr Metab Cardiovasc Dis*. 2013; 23: 451-458.
5. Schwingshackl L, Hoffmann G. Monounsaturated fatty acids, olive oil and health status: A systematic review and meta-analysis of cohort studies. *Lipids Health Dis*. 2014; 13: 154.
6. Neelakantan N, Koh WP, Yuan JM, van Dam RM. Diet-quality indexes are associated with a lower risk of cardiovascular, respiratory, and all-cause mortality among Chinese adults. *J Nutr*. 2018; 148: 1323-1332.
7. Li D. Effect of the vegetarian diet on non-communicable diseases. *J Sci Food Agric*. 2014; 9: 169-173.
8. Marklund M, Leander K, Vikström M, Laguzzi F, Gigante B, Sjögren P, et al. Polyunsaturated fat intake estimated by circulating biomarkers and risk of cardiovascular disease and all-cause mortality in a population-based cohort of 60-year-old men and women. *Circulation*. 2015; 132: 586-594.
9. Sacks FM, Lichtenstein AH, Wu JH, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary fats and cardiovascular disease: A presidential advisory from the American heart association. *Circulation*. 2017; 136: e1-e23.
10. Dominguez LJ, Bes-Rastrollo M, Basterra-Gortari FJ, Gea A, Barbagallo M, Martínez-González MA. Should we recommend reductions in saturated fat intake or in red/processed meat consumption? The SUN prospective cohort study. *Clin Nutr*. 2018; 37: 1389-1398.
11. Ricci C, Baumgartner J, Zec M, Kruger HS, Smuts CM. Type of dietary fat intakes in relation to all-cause and cause-specific mortality in US adults: An iso-energetic substitution analysis from the American national health and nutrition examination survey linked to the US mortality registry. *Br J Nutr*. 2018; 119: 456-463.
12. Deschasaux M, Huybrechts I, Julia C, Hercberg S, Egnell M, Srouf B, et al. Association between nutritional profiles of foods underlying Nutri-score front-of-pack labels and mortality: EPIC cohort study in 10 European countries. *BMJ*. 2020; 370. doi: 10.1136/bmj.m3173.
13. Mazidi M, Mikhailidis DP, Sattar N, Toth PP, Judd S, Blaha MJ, et al. Association of types of dietary fats and all-cause and cause-specific mortality: A prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants. *Clin Nutr*. 2020; 39: 3677-3686.
14. Boushey C, Ard J, Bazzano L, Heymsfield S, Mayer-Davis E, Sabaté J, et al. Dietary patterns and all-cause mortality: A systematic review [Internet]. Alexandria, VA: USDA Nutrition Evidence Systematic Review; 2020. Available from: <https://nesr.usda.gov/2020-dietary->

[guidelines-advisory-committee-systematic-reviews/dietary-patterns-subcommittee/dietary-patterns-all-cause-mortality.](#)

15. Yao X, Xu X, Wang S, Xia D. Associations of dietary fat intake with mortality from all causes, cardiovascular disease, and Cancer: A prospective study. *Front Nutr.* 2021; 8: 701430.
16. Lotfi K, Salari-Moghaddam A, Yousefinia M, Larijani B, Esmailzadeh A. Dietary intakes of monounsaturated fatty acids and risk of mortality from all causes, cardiovascular disease and cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. *Ageing Res Rev.* 2021; 72: 101467.
17. Naghshi S, Aune D, Beyene J, Mobarak S, Asadi M, Sadeghi O. Dietary intake and biomarkers of alpha linolenic acid and risk of all cause, cardiovascular, and cancer mortality: Systematic review and dose-response meta-analysis of cohort studies. *BMJ.* 2021; 375. doi: 10.1136/bmj.n2213.
18. Jurek J, Owczarek M, Godos J, La Vignera S, Condorelli RA, Marventano S, et al. Fish and human health: An umbrella review of observational studies. *Int J Food Sci Nutr.* 2022; 73: 851-860.
19. Zhong N, Han P, Wang Y, Zheng C. Associations of polyunsaturated fatty acids with cardiovascular disease and mortality: A study of NHANES database in 2003-2018. *BMC Endocr Disord.* 2023; 23: 185.
20. Zhao Y, Li Y, Wang W, Song Z, Zhuang Z, Li D, et al. Low-carbohydrate diets, low-fat diets, and mortality in middle-aged and older people: A prospective cohort study. *J Intern Med.* 2023; 294: 203-215.
21. Wallerer S, Papakonstantinou T, Morze J, Stadelmaier J, Kiesswetter E, Gorenflo L, et al. Association between substituting macronutrients and all-cause mortality: A network meta-analysis of prospective observational studies. *EClinicalMedicine.* 2024; 75: 102807.
22. Menotti A, Kromhout D, Puddu PE, Alberti-Fidanza A, Hollman P, Kafatos A, et al. Baseline fatty acids, food groups, a diet score and 50-year all-cause mortality rates. An ecological analysis of the seven countries study. *Ann Med.* 2017; 49: 718-727.
23. Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, Broste SK, Frantz RP, et al. Re-evaluation of the traditional diet-heart hypothesis: Analysis of recovered data from Minnesota Coronary Experiment (1968-73). *BMJ.* 2016; 353. doi: 10.1136/bmj.i1246.
24. Gershuni VM. Saturated fat: Part of a healthy diet. *Curr Nutr Rep.* 2018; 7: 85-96.
25. Aramburu A, Dolores-Maldonado G, Curi-Quinto K, Cueva K, Alvarado-Gamarra G, Alcalá-Marcos K, et al. Effect of reducing saturated fat intake on cardiovascular disease in adults: An umbrella review. *Front Public Health.* 2024; 12: 1396576.
26. Ma Y, Zheng Z, Zhuang L, Wang H, Li A, Chen L, et al. Dietary macronutrient intake and cardiovascular disease risk and mortality: A systematic review and dose-response meta-analysis of prospective cohort studies. *Nutrients.* 2024; 16: 152.
27. Menotti A, Puddu PE, Geleijnse JM, Kafatos A, Tolonen H. Dietary atherogenicity and thrombogenicity indexes predicting cardiovascular mortality: 50-year follow-up of the seven countries study. *Nutr Metab Cardiovasc Dis.* 2024; 34: 2107-2114.
28. Menotti A, Puddu PE. How the seven countries study contributed to the launch and development of cardiovascular epidemiology in Italy. A historical perspective. *Nutr Metab Cardiovasc Dis.* 2020; 30: 368-383.
29. Burke BS. The dietary history as a tool in research. *J Am Diet Assoc.* 1947; 23: 1014-1046.
30. Fidanza F, Versiglioni N. Tabelle di composizione degli alimenti. Napoli, Italy: Idelson; 1981.

31. Rose GA, Blackburn H. Cardiovascular survey methods. Geneva, Switzerland: World Health Organization; 1965.
32. Anderson JT, Keys A. Cholesterol in serum and lipoprotein fractions: Its measurement and stability. *Clin Chem.* 1956; 2: 145-159.
33. Menotti A, Puddu PE, Catasta G. Determinants of longevity and age at death in a practically extinct cohort of middle-aged men followed-up for 61 years. *Aging Clin Exp Res.* 2022; 34: 1247-1258.
34. Robine JM. Age at death, the return of an old metric whose importance is growing. *Aging Clin Exp Res.* 2018; 30: 1147-1149.
35. Menotti A, Puddu PE. Focus on age at death in field epidemiology. *Aging Clin Exp Res.* 2023; 35: 1187-1194.
36. Menotti A, Puddu PE. Risk factors measured in middle-aged men predicting coronary events in geriatric age. *Int J Cardiol.* 2016; 222: 1116-1121.
37. Wirfält AE, Jeffery RW, Elmer PJ. Comparison of food frequency questionnaires: The reduced block and Willett questionnaires differ in ranking on nutrient intakes. *Am J Epidemiol.* 1998; 148: 1148-1156.