High red meat intake and all-cause cardiovascular and cancer mortality: is the risk modified by fruit and vegetable intake?[1,2]

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ABSTRACT

Background: High red meat consumption is associated with a shorter survival and higher risk of cardiovascular disease (CVD), cancer, and all-cause mortality. Fruit and vegetable (FV) consumption is associated with a longer survival and lower mortality risk. Whether high FV consumption can counterbalance the negative impact of high red meat consumption is unknown.

Objective: We evaluated 2 large prospective cohorts of Swedish men and women (the Swedish Mammography Cohort and the Cohort of Swedish Men) to determine whether the association between red meat consumption and the risk of all-cause, CVD, and cancer-specific mortality differs across amounts of FV intake.

Design: The study population included 74,645 Swedish men and women. Red meat and FV consumption were assessed through a self-administered questionnaire. We estimated HRs of all-cause, CVD, and cancer mortality according to quintiles of total red meat consumption. We next investigated possible interactions between red meat and FV consumption and evaluated the dose-response associations at low, medium, and high FV intake.

Results: Compared with participants in the lowest quintile of total red meat consumption, those in the highest quintile had a 21% increased risk of all-cause mortality (HR: 1.21; 95% CI: 1.13, 1.29), a 29% increased risk of CVD mortality (HR: 1.29; 95% CI: 1.14, 1.46), and no increase in the risk of cancer mortality (HR: 1.00; 95% CI: 0.88, 1.43). Results were remarkably similar across amounts of FV consumption, and no interaction between red meat and FV consumption was detected.

Conclusion: High intakes of red meat were associated with a higher risk of all-cause and CVD mortality. The increased risks were consistently observed in participants with low, medium, and high FV consumption. The Swedish Mammography Cohort and the Cohort of Swedish Men were registered at clinicaltrials.gov as NCT01127698 and NCT01127711, respectively. *Am J Clin Nutr* 2016;104:1137–43.

Keywords: fruit, red meat, vegetables, interaction, effect modification

INTRODUCTION

Observational studies have consistently shown that high intakes of red meat are progressively associated with a higher risk of all-cause mortality (1), cardiovascular disease (CVD)[3] (2), certain cancers (3, 4), diabetes (5), and shorter survival (6). These harmful effects are more pronounced when evaluating the consumption of processed red meat, and some studies have not observed any significant association when restricting analyses to nonprocessed red meat (6–8).

Little is known, however, about the relation between red meat intake and other lifestyle and dietary factors (9). It has been suggested, for example, that the link between high red meat intake and mortality and chronic diseases could be partly explained by the association between red meat consumption and a lower-quality diet (10). Fruit and vegetables (FVs), in particular, have been linked to various health benefits such as a lower risk of major chronic diseases and longer survival (11–13) and may be inversely associated with high red meat intake (10). It has been hypothesized that high concentrations of FVs may partly counterbalance the potential harmful effects of red meat (9). To our knowledge, no study has explored the association between red meat consumption and mortality over different subpopulations defined by their intake of FVs, thus limiting the reliability of the current epidemiologic evidence on red meat (9, 10). Evaluating the role of different dietary components and their interaction is crucial for understanding their public health implications and planning and introducing dietary recommendations (14). We therefore evaluated whether the association between red meat consumption and the risk of all-cause, CVD, and cancer-specific mortality differed across FV amounts in a large prospective cohort of Swedish men and women.

METHODS

Study population

The population investigated in this study included participants from the Cohort of Swedish Men (COSM) (NCT01127711) and

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[2] Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[3] Abbreviations used: COSM, Cohort of Swedish Men; CVD, cardiovascular disease; FV, fruit and vegetable; SMC, Swedish Mammography Cohort.

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the Swedish Mammography Cohort (SMC) (NCT01127698) (15). SMC started between 1987 and 1990 when a questionnaire and invitation to participate in the study were sent to all women born between 1914 and 1948 and residing in 2 counties of central Sweden (Västmanland and Uppsala). The questionnaire included questions on anthropometric measures, (e.g., body weight and height), sociodemographic information (e.g., educational status), and a 96-item food-frequency section. A second questionnaire was sent in the late fall of 1997 to participants who were still alive and residing in the study area. The aim of this second questionnaire was to update all previous items and to collect additional information such as smoking status, physical activity, and other lifestyle factors. This second self-reported questionnaire was returned by a total of 39,227 women (70%) aged 48–83 y who were included in this analysis.

COSM was established in 1997 when all men aged 45–79 y residing in 2 regions of central Sweden (Västmanland and Örebro) were asked to reply to a questionnaire that included the same questions about food consumption as the one received by SMC participants. A total of 48,850 (49%) men returned the questionnaire.

For our analyses, we excluded participants who reported an incorrect national personal identification number or who did not report their personal number (n = 540), those who died before the start of follow-up (n = 97), and those with any history of CVD (n = 6994) or cancer (n = 4390). We further excluded participants with an unlikely extreme value of total energy intake (3 SDs from the log-transformed mean energy intake; n = 709) and those with unlikely high daily red meat consumption (>300 g/d; n = 305) or missing information on red meat consumption (n = 397). In total, 74,645 participants (40,089 men and 34,556 women) were included (**Supplemental Figure 1**). This study was approved by the Regional Research Ethics Board at Karolinska Institutet, and all participants gave their informed consent.

Red meat and FV assessment

All items related to red meat and FV intake were assessed by means of a food-frequency questionnaire. The total intake of red meat, assessed in g/d, was calculated by combining information on the amount and frequency of the consumption of different types of red meat. Participants had to report the mean frequency of consumption of different types of processed and nonprocessed red meat with the use of 8 predefined frequency categories ranging from never to ≥3 times/d. Nonprocessed red meat included fresh and minced pork, beef, and veal. Processed red meat included sausages, hot dogs, salami, ham, processed meat cuts, liver pate, and blood sausage. All reported information was combined to derive continuous variables of total, processed, and nonprocessed meat intake. The age of the participants was taken into account when translating frequency and portion sizes into the total information of red meat intake. Total, processed, and nonprocessed red meat intakes were then categorized into quintiles and investigated as categorical covariates.

Information on daily FV intake was obtained with the use of 14 questions on vegetable consumption (carrots, beetroots, lettuce, cabbage, cauliflower, broccoli, tomatoes, peppers, spinach, green peas, onion, garlic, pea soup, other vegetables), 5 on fruit (oranges, apples, bananas, berries, other fruits), and 1 on orange juice. Total FV consumption was summarized into a single variable, expressed as servings/d, that was obtained by converting the questionnaire responses to a mean daily intake of each item and adding the intake of all items together. A total of 46% of the participants completed all 20 questions on FV consumption, and ∼80% had <2 missing values. When aggregating items, it was assumed that missing values for an individual food meant no intake for that particular item (16). To assess the association between red meat consumption and mortality across levels of FV consumption, the main variable of FV consumption was categorized into 3 predefined levels (low FV intake: <2 servings/d; medium FV intake: 2–4 servings/d; and high FV intake: >4 servings/d). This predefined categorization was preferred over the classic quantile approach to be able to detect risk differences at very low levels of FV consumption, where a large part of the effects are generally observed (13).

All dietary variables recorded from the COSM and SMC food-frequency questionnaires underwent internal validation studies that were conducted by assessing detailed weekly records in a subsample of the original population. For food items included in this article, the Spearman correlation coefficients between the mean of four 1-wk diet records and the dietary questionnaire ranged from 0.4 to 0.8, showing relatively high validity.

Case ascertainment and follow-up

During 16 y of follow-up (1 January 1998 through 31 December 2013), 17,909 deaths occurred in the cohort (7486 women and 10,423 men). Mortality resulting from CVD-related causes accounted for 5495 cases, whereas 4426 deaths were attributed to cancer. Information on death and cause of death was ascertained with the use of the Swedish National Register of Death Causes at the National Board of Health and Welfare (17).

Statistical analysis

Cox proportional hazard regression with attained age at the event as the primary time scale was used to assess the association between red meat and FV consumption and the risk of total, CVD, and cancer-specific mortality. The assumption of proportionality of the hazards was tested by calculating Schoenfeld residuals, regressed against survival time, and tested for a nonzero slope. No evidence of departure from this assumption was observed in all the reported models. The lowest quintile of either total, processed, and nonprocessed meat was used as reference category.

All multivariable models were adjusted for sex, pack-years of smoking, physical activity, educational status, BMI (in kg/m^2), alcohol consumption, diabetes, fish consumption, and total energy.

We first assessed the association between quintiles of total red meat consumption and overall mortality, estimating HRs of death in the overall population and across amounts of FV consumption. The statistical interaction between red meat and FVs was assessed by testing the product terms of the categorical indicators jointly equal to 0. This main analysis was replicated in 3 sensitivity analyses. First, we assessed whether there was any difference in the results between women and men. Second, to assess the possible influence of reverse causation, we excluded participants who died in the first 3 y of follow-up. Third, we further adjusted the main model for whole grain intake and soft drink and soda consumption.

We next replicated the main analysis over levels of fruit consumption and vegetable consumption, investigated as 2 independent

covariates. Both fruit and vegetable consumption were categorized into 3 predefined groups to reflect low, medium, and high intakes.

We also evaluated processed and nonprocessed red meat consumption as 2 distinct exposures in a mutually adjusted model. HRs of death were estimated in the overall population and across levels of FV consumption, testing for the presence of an interaction between processed and nonprocessed meat and FVs in predicting mortality.

Last, we considered the endpoints of CVD and cancer-specific mortality and estimated HRs of cause-specific mortality in the entire population and over the strata of FV consumption. The presence of statistical interactions between the 2 exposures was also investigated.

Analyses were carried out with the use of Stata version 14 (StataCorp LP). All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 displays the age-standardized baseline characteristics of the study population by quintiles of total red meat consumption. Red meat intake was considerably higher in men, and the prevalence of diabetes increased together with the consumption of red meat. Participants with lower red meat consumption were generally older and had lower fish consumption and lower energy intakes. FV consumption was not correlated with processed, nonprocessed, or total red meat consumption.

Higher concentrations of total red meat were associated with a progressively higher mortality risk (**Table 2**), ≤21% when comparing the lowest and highest quintiles of the distribution (HR: 1.21; 95% CI: 1.13, 1.29). The dose-response association did not change when restricted to men or women, when excluding cases that occurred in the first 3 y of follow-up, or when further adjusted for the consumption of additional food items such as whole grain and soft drinks and soda. We did not observe any evidence of interaction between total red meat and FV consumption in predicting mortality ($P = 0.29$). The association between red meat and all-cause mortality was similar across levels of FV consumption, with high concentrations of red meat intake associated with the highest mortality (Table 2).

Higher mortality at high intakes of red meat was also observed across the entire distribution of vegetable consumption alone (**Table 3**) and fruit consumption (**Table 4**). In both situations, we did not find any evidence of a statistical interaction between red meat and fruit ($P = 0.22$) or vegetables ($P = 0.14$).

We next evaluated the consumption of processed and nonprocessed red meat in a mutually adjusted model (**Supplemental Tables 1** and **2**). High consumption of processed red meat was associated with a progressively higher mortality [HR = 1.13 (95% CI: 1.06, 1.20) when comparing the lowest and highest quintiles]. Increased intakes of nonprocessed meat were not associated with higher mortality, and a negligible association was only observed at the highest amounts (HR: 1.06; 95% CI: 0.99, 1.14). When stratifying for levels of FV intake, the dose-response associations between processed and nonprocessed red meat and overall mortality were remarkably similar (Supplemental Tables 1 and 2). We did not observe any interaction between processed meat and FV consumption ($P = 0.51$), and nonprocessed meat and FV consumption ($P = 0.73$).

We then assessed the association between total red meat consumption and CVD and cancer-specific mortality risks (**Table 5**). Compared with participants in the lowest level of intake, those with the highest level of consumption had a 29% increased risk of CVD mortality (HR: 1.29; 95% CI: 1.14, 1.46). We did

TABLE 1
Age-standardized baseline characteristics by quintiles of red meat consumption in Swedish men aged 45–79 y and Swedish women aged 48–83 y[1]

	Quintiles of red meat consumption, g/d (median)				
Characteristics	<46 (31)	46–67.0 (57)	67.1–88.0 (77)	88.1–117 (101)	>117 (140)
Subjects, *n*	14,932	14,928	14,928	14,944	14,913
Women, %	70	66	55	29	12
Age at baseline, y	63.6 ± 9.5[2]	62.1 ± 9.2	60.2 ± 9.2	58.5 ± 9.1	57.0 ± 8.4
BMI, kg/m^2	25.0 ± 3.7	25.2 ± 3.7	25.3 ± 3.6	25.5 ± 3.5	25.7 ± 3.5
Total physical activity, MET[3]	42.3 ± 4.8	42.2 ± 4.7	42.0 ± 4.8	41.8 ± 4.9	41.8 ± 5.1
Smoking status, %					
Current	24	23	22	24	25
Former	27	29	30	33	36
Never	49	48	48	43	39
Alcohol consumption, %					
Current	82	86	87	89	89
Former	6	4	4	3	3
Never	12	10	9	8	8
Education, %					
≥High school or university	29	27	27	28	28
Diabetes, %	4	4	5	5	7
Fruit and vegetable consumption, servings/d	4 ± 3	5 ± 2	5 ± 2	4 ± 2	5 ± 2
Fish consumption, g/d	17 ± 30	19 ± 21	21 ± 21	22 ± 20	25 ± 25
Energy intake, kcal/d	1745 ± 653	1929 ± 636	2155 ± 684	2471 ± 743	2873 ± 837

[1]All factors except age were directly standardized to the age distribution of the entire study cohort, *n* = 74,645.
[2]Mean ± SD (all such values).
[3]MET, metabolic equivalent.

TABLE 2
HRs of death according to quintiles of total red meat consumption, overall and stratified by categories of FV consumption, in Swedish men aged 45–79 y and Swedish women aged 48–83 y[1]

	Quintiles of red meat consumption, g/d (median)				
	<46 (31)	46–67 (57)	67.1–87 (77)	87.1–117 (101)	117.1–300 (140)
Overall					
Cases/total, *n*	4545/14,932	3804/14,928	3443/14,928	3139/14,944	2973/14,913
HR (95% CI)	Ref	1.01 (0.95, 1.06)	1.06 (1.00, 1.13)	1.07 (1.00, 1.13)	1.21 (1.13, 1.29)
Low FV					
Cases/total, *n*	1194/2636	557/1417	404/1242	352/1269	334/1104
HR (95% CI)	Ref	0.97 (0.84, 1.13)	0.90 (0.77, 1.07)	0.91 (0.76, 1.08)	1.14 (0.95, 1.37)
Medium FV					
Cases/total, *n*	1775/5559	1700/6182	1602/6138	1493/6562	1243/6283
HR (95% CI)	Ref	1.01 (0.93, 1.10)	1.11 (1.02, 1.21)	1.14 (1.04, 1.26)	1.23 (1.11, 1.37)
High FV					
Cases/total, *n*	1576/6737	1547/7329	1437/7548	1294/7113	1396/7526
HR (95% CI)	Ref	1.02 (0.94, 1.11)	1.07 (0.98, 1.17)	1.03 (0.93, 1.13)	1.22 (1.10, 1.35)

[1]HRs estimated with multivariable Cox regressions and adjusted for sex, pack-years of smoking, physical activity, educational status, BMI (in kg/m^2), alcohol consumption, diabetes, fish consumption, and total energy. Low FV consumption was defined as <2 servings/d, medium FV consumption as 2–4 servings/d, and high FV consumption as >4 servings/d. Age was chosen as the primary time scale. FV, fruit and vegetable; ref, reference.

not observe a significant association between total red meat and cancer-specific mortality (Table 5). An interaction between total red meat and FV consumption was not observed either for CVD mortality ($P = 0.93$) nor cancer-specific mortality ($P = 0.81$). In analyses stratified by levels of FV intake, we observed a moderate variation in the dose responses (Table 5). However, significant increases or decreases in the risk of CVD or cancer-specific mortality were not detected either in the overall population or at a specific amount of FV consumption.

DISCUSSION

In this prospective population-based study of Swedish men and women, we evaluated whether the association between red meat consumption and all-cause, CVD, and cancer-specific mortality differed across levels of FV consumption. We found that the shape of the dose-response associations between red meat and all investigated outcomes were consistent over all FV concentrations. Higher intakes of total red meat intake were progressively associated with an increased risk of overall and CVD mortality, and these negative associations were largely reduced when restricting the analyses to nonprocessed red meat.

Although an association between high red meat consumption and mortality is recognized (1, 2, 5), little is known about the interaction between red meat and other lifestyle and dietary factors. High red meat consumption may be associated with a low-quality diet (9, 10), and it has been suggested that this relation between meat and other dietary factors may partly explain the link between high red meat intake and the increased risk of mortality and chronic diseases (9, 10, 18). The interaction between red meat intake and other lifestyle and dietary factors has not been thoroughly investigated, thus limiting the reliability of this epidemiologic evidence on the role of red meat consumption in health. FVs are an important dietary component that

TABLE 3
HRs of death according to quintiles of total red meat consumption, stratified by categories of vegetable consumption, in Swedish men aged 45–79 y and Swedish women aged 48–83 y[1]

	Quintiles of total read meat consumption, g/d (median)				
	<46 (31)	46–67 (57)	67.1–87 (77)	87.1–117 (101)	117.1–300 (140)
Low vegetables					
Cases/total, *n*	1604/3634	842/2244	622/1913	503/1852	462/1637
HR (95% CI)	Ref	0.98 (0.87, 1.10)	0.96 (0.84, 1.10)	0.90 (0.78, 1.04)	1.17 (1.00, 1.36)
Medium vegetables					
Cases/total, *n*	1849/6493	1938/7616	1840/7715	1744/8023	1481/7662
HR (95% CI)	Ref	1.05 (0.96, 1.13)	1.13 (1.04, 1.23)	1.16 (1.06, 1.27)	1.28 (1.16, 1.41)
High vegetables					
Cases/total, *n*	1066/4692	1012/5011	969/5247	879/5023	1009/5521
HR (95% CI)	Ref	0.98 (0.88, 1.09)	1.04 (0.94, 1.16)	1.03 (0.92, 1.15)	1.17 (1.04, 1.32)

[1]HRs estimated with multivariable Cox regressions and adjusted for sex, pack-years of smoking, physical activity, educational status, BMI (in kg/m^2), alcohol consumption, diabetes, fish consumption, total energy, and fruit consumption. Low vegetable consumption was defined as ≤1 serving/d, medium vegetable consumption as 1.5–2 servings/d, and high vegetable consumption as >2 servings/d. Age was chosen as the primary time scale. Ref, reference.

TABLE 4
HRs of death according to quintiles of total red meat consumption, stratified by categories of fruit consumption, in Swedish men aged 45–79 y and Swedish women aged 48–83 y[1]

	Quintiles of total red meat consumption, g/d (median)				
	<46 (31)	46–67 (57)	67.1–87 (77)	87.1–117 (101)	117.1–300 (140)
Low fruit					
Cases/total, *n*	2375/6621	1780/6006	1570/5896	1482/6571	1344/6511
HR (95% CI)	Ref	1.02 (0.94, 1.11)	1.05 (0.96, 1.15)	1.10 (1.00, 1.21)	1.19 (1.08, 1.32)
Medium fruit					
Cases/total, *n*	1136/4093	1115/4737	1098/4922	996/4835	908/4923
HR (95% CI)	Ref	0.94 (0.85, 1.05)	1.06 (0.96, 1.18)	1.06 (0.94, 1.18)	1.13 (1.00, 1.28)
High fruit					
Cases/total, *n*	1007/4096	899/4124	767/4066	650/3491	707/3410
HR (95% CI)	Ref	1.03 (0.92, 1.14)	1.03 (0.91, 1.15)	0.95 (0.84, 1.08)	1.27 (1.11, 1.45)

[1]HRs estimated with multivariable Cox regressions and adjusted for sex, pack-years of smoking, physical activity, educational status, BMI (in kg/m^2), alcohol consumption, diabetes, fish consumption, total energy, and vegetable consumption. Low fruit consumption was defined as ≤1 serving/d, medium fruit consumption as 1.5–4 servings/d, and high fruit consumption as >4 servings/d. Age was chosen as the primary time scale. Ref, reference.

provide various health benefits (11–13). A recent study from COSM and SMC observed a longer survival and lower mortality risk at high concentrations of FVs (13). Moreover, FVs may be inversely associated with the consumption of red meat in some populations (9). However, it is unclear whether the potential harmful effects of red meat can be counterbalanced by a high consumption of healthy foods such as FVs (10).

There are several reasons why an interaction between meat consumption and FVs could be expected. For example, meats are a major source of highly bioavailable heme iron, which may

TABLE 5
HRs of CVD and cancer-related mortality according to quintiles of total red meat consumption, overall and stratified by categories of FV consumption, in Swedish men aged 45–79 y and Swedish women aged 48–83 y[1]

	Categories of total red meat consumption, g/d (median)				
	<46 (31)	46–67 (57)	67.1–87 (77)	87.1–117 (101)	117.1–300 (140)
CVD					
Overall					
Cases, *n*	1458	1190	1038	922	887
HR (95% CI)	Ref	1.06 (0.96, 1.17)	1.10 (0.99, 1.23)	1.05 (0.93, 1.17)	1.29 (1.14, 1.46)
Low FV					
Cases, *n*	411	202	148	119	101
HR (95% CI)	Ref	1.07 (0.82, 1.39)	1.18 (0.89, 1.56)	0.95 (0.70, 1.30)	1.11 (0.80, 1.56)
Medium FV					
Cases, *n*	573	539	471	427	379
HR (95% CI)	Ref	1.05 (0.90, 1.23)	1.04 (0.89, 1.23)	1.07 (0.90, 1.28)	1.28 (1.06, 1.54)
High FV					
Cases, *n*	474	449	419	376	407
HR (95% CI)	Ref	1.05 (0.89, 1.23)	1.15 (0.97, 1.35)	1.01 (0.84, 1.22)	1.35 (1.12, 1.63)
Cancer					
Overall					
Cases, *n*	986	934	888	814	804
HR (95% CI)	Ref	0.99 (0.89, 1.11)	1.05 (0.93, 1.17)	0.94 (0.83, 1.06)	1.00 (0.88, 1.43)
Low FV					
Cases, *n*	221	125	83	88	88
HR (95% CI)	Ref	1.16 (0.85, 1.57)	1.01 (0.71, 1.43)	0.93 (0.65, 1.34)	1.24 (0.86, 1.79)
Medium FV					
Cases, *n*	393	414	409	404	341
HR (95% CI)	Ref	0.99 (0.83, 1.17)	1.08 (0.91, 1.29)	1.00 (0.83, 1.21)	1.00 (0.82, 1.23)
High FV					
Cases, *n*	372	395	396	322	375
HR (95% CI)	Ref	0.97 (0.82, 1.14)	1.02 (0.86, 1.21)	0.86 (0.72, 1.04)	0.95 (0.78, 1.15)

[1]HRs estimated with multivariable Cox regressions and adjusted for sex, pack-years of smoking, physical activity, educational status, BMI (in kg/m^2), alcohol consumption, diabetes, fish consumption, and total energy. Low FV consumption was defined as <2 servings/d, medium FV consumption as 2–4 servings/d, and high FV consumption as >4 servings/d. Age was chosen as the primary time scale. CVD, cardiovascular disease; FV, fruit and vegetable; ref, reference.

contribute to excessive iron stores. Iron can act as a catalyst in the production of reactive oxygen species, which contribute to the development of several diseases, including CVD (19). FVs contain nutrients and phytochemicals with antioxidant capabilities and could therefore be especially important for maintaining a favorable redox balance in the context of a high meat diet. Processed meat also contains high concentrations of sodium, which may contribute to a higher sodium:potassium ratio. The sodium:potassium ratio may be an important determinant of blood pressure (20), which is a major risk factor for CVD and stroke. FVs are important sources of potassium and may therefore attenuate the negative effects of a diet high in processed meat. Processed meat contains *N*-nitroso compounds, which have been shown to be carcinogenic in several animal species. Furthermore, meat consumption increases the endogenous production of *N*-nitroso compounds (21). Studies in rodents suggest that phytochemicals in FVs may inhibit the carcinogenic effects of *N*-nitroso compounds (22). Therefore, it is plausible that high FV consumption could protect against the increased risk of cancers associated with high meat consumption.

This study is the first to our knowledge to investigate the relation between red meat and FVs in predicting mortality. We did not observe a direct relation between high red meat consumption and low FV intake, and our results seem to exclude that the harmful association between high red meat intake and mortality could be counterbalanced by including a large consumption of protective dietary items such as FVs. Our study also reinforces the evidence that processed and nonprocessed types of red meat might have different consequences on health, differences that should be taken into account when planning dietary recommendations.

Evaluating associations of health status with combined food components is critical for fully understanding the health implications of diet and for promoting healthy dietary guidelines that take into account the entire diet rather than the consumption of single items (9, 10, 14). Red meat consumption is an intensely discussed topic, and no agreement has been reached on the health effects of regular red meat consumption (1, 23). Studies that investigated red meat as a single exposure have generally observed negative associations at high concentrations, especially when focusing on CVD (5) and colorectal cancers (3). On the other hand, dietary patterns that include a moderate consumption of fresh red meat, such as the Mediterranean diet, have generally shown a longer survival (24) and lower risk of chronic diseases (25–27). Evaluating the interplay between red meat and other food components is crucial for clarifying the effects of this popular and largely debated dietary factor (9, 10).

Strengths of our study include the large size of the cohort, the large number of cases, the completeness of case ascertainment through the Swedish National Register of Death Causes, and its population-based and prospective design. A main limitation of the study is the self-reported nature of the main exposure, which can increase the level of measurement error and risk of misclassification. Nevertheless, misclassifying the exposure is expected to be nondifferential with regard to the outcome and would most likely lead to an attenuation of the estimates. Moreover, additional red meat items that could increase the precision of our main exposures, such as lamb and game, were not collected in the questionnaire. We mainly focused herein on all-cause mortality, evaluating cancer and CVD mortality as secondary analyses. Future studies that focus on specific cancers such as colorectal and pancreatic cancers are warranted. To simplify the presentation of the exposure-outcome association over levels of another exposure, we chose to categorize both covariates of red meat and FVs. To avoid common limitations of categorical approaches, such as the limit for detecting within-category associations (28), we preferred the use of predefined categories to the common approach of categorizing by quintiles. FV categories were chosen based on a previous article that flexibly investigated the exposure as a continuous covariate (13). Another limitation of our study is the lack of a comparison group composed by only vegans or vegetarians. Studies that compared meat consumers with vegans or vegetarians, while confirming an increased mortality at higher concentrations of meat, also reported no increased mortality at higher meat intakes when FV intake was comparable to that of vegetarians (29, 30).

In conclusion, we documented that high intakes of red meat were associated with a higher risk of all-cause and CVD mortality. The increased risks were consistently observed among participants with low, medium, and high FV consumption.

The authors' responsibilities were as follows—AB: analyzed the data and participated in writing the manuscript; AB and AW: designed the study; FS and AW: interpreted the results; AW: collected the data, participated in writing the manuscript, and critically reviewed the manuscript; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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