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Original Contribution

Fruit and Vegetable Consumption and Mortality

European Prospective Investigation Into Cancer and Nutrition

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In this study, the relation between fruit and vegetable consumption and mortality was investigated within the European Prospective Investigation Into Cancer and Nutrition. Survival analyses were performed, including 451,151 participants from 10 European countries, recruited between 1992 and 2000 and followed until 2010. Hazard ratios, rate advancement periods, and preventable proportions to respectively compare risk of death between quartiles of consumption, to estimate the period by which the risk of death was postponed among high consumers, and to estimate proportions of deaths that could be prevented if all participants would shift their consumption 1 quartile upward. Consumption of fruits and vegetables was inversely associated with all-cause mortality (for the highest quartile, hazard ratio = 0.90, 95% confidence interval (CI): 0.86, 0.94), with a rate advancement period of 1.12 years (95% CI: 0.70, 1.54), and with a preventable proportion of 2.95%. This association was driven mainly by cardiovascular disease mortality (for the highest quartile, hazard ratio = 0.85, 95% CI: 0.77, 0.93). Stronger inverse associations were observed for participants with high alcohol consumption or high body mass index and suggested in smokers. Inverse associations were stronger for raw than for cooked vegetable consumption. These results support the evidence that fruit and vegetable consumption is associated with a lower risk of death.

fruit; mortality; prospective studies; survival analysis; vegetables

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation Into Cancer and Nutrition; HR, hazard ratio.

A healthy diet, including a daily consumption of 400–500 g of fruits and vegetables, is known to play an important role in prevention of chronic diseases (1). Most prospective studies have consistently shown an approximately 10%–25% lower all-cause mortality when comparing people with high and low fruit and vegetable consumption (2–9). When separating mortality Into cancer and cardiovascular disease mortality, evidence is more convincing that fruit and vegetable consumption protects against cardiovascular disease (10, 11) than against cancer (12). However, according to the 2007 expert report of the World Cancer Research Fund and the American Institute for Cancer Research (13), some types of vegetables and fruits possibly protect against certain types of cancer.

Only a few studies examined whether the effect of fruit and vegetable consumption on all-cause mortality varied by smoking status, body size/adiposity, or gender, and these did not observe significant differences (7–9). In addition, very few studies have quantified the number of years of life that can be gained by increasing fruit and vegetable consumption. Gundgaard et al. (14) estimated an increase in cancer-free life expectancy by 1 year or more for those consuming 400 g/day or more when compared with 250 g/day, but this was based solely on cancer mortality reductions taken mainly from case-control studies (15).

This study aimed to investigate the association of fruit and vegetable consumption with mortality of all causes, cancer, and cardiovascular disease within the European Prospective Investigation Into Cancer and Nutrition (EPIC) and to estimate the time period by which the risk of death was postponed among participants with a high consumption of fruits and vegetables. Additionally, associations with mortality for vegetables will be compared according to preparation (i.e., cooked vs. raw). Preparation of vegetables is known to affect availability of nutrients, but its association with mortality has been rarely studied. The large size of this cohort combined with its long follow-up, the large number of deaths, and wide range of fruit and vegetable consumption provides an ideal setting to study these associations and allows identification of subgroups of the population that may benefit more from consumption of fruits and vegetables.

MATERIALS AND METHODS

Study population

The EPIC cohort included 521,448 participants, mostly aged between 25 and 70 years, recruited in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) between 1992 and 2000 (16, 17). Most participants were recruited from the general population, except for the French (a teacher's organization health insurance program), Italian (except Florence and Varese), and Spanish (mostly blood donors) cohorts; the Florence (Italy) and Utrecht (the Netherlands) cohorts (women attending mammographic screening programs); and the Oxford (United Kingdom) cohort (vegetarian and health-conscious participants). At recruitment, anthropometric measurements were obtained, and participants were asked to complete dietary and lifestyle questionnaires. All participants gave written informed consent, and the study was approved by the relevant ethics committees in participating countries and the internal review board of the International Agency for Research on Cancer.

Participants with missing data or incomplete follow-up information were excluded ($n = 9{,}739$). To minimize misreporting and to exclude implausible values, we excluded participants in the lowest or highest 1% of the distribution of the ratio of reported energy intake to energy requirement, the lowest or highest 0.5% of the distribution of body mass index, or the highest 0.5% of the distribution of fruit and/or vegetable consumption ($n = 19{,}450$). Participants with a history of cancer ($n = 14{,}459$), myocardial infarction ($n = 3{,}678$), stroke ($n = 2{,}762$), angina ($n = 4{,}857$), diabetes ($n = 10{,}645$), or any combination of these ($n = 4{,}707$) were excluded because these participants were exposed to an increased risk of death and possibly changed their diet prior to recruitment. The analyses included 129,882 men and 321,269 women.

Exposure assessment

At baseline, the diet of participants reflecting the past 12 months was assessed by country-specific dietary questionnaires designed to reflect local dietary patterns (17, 18). A dietary questionnaire was combined with a 7-day record in the United Kingdom and Malmö (Sweden) cohorts. Information on the validity of the dietary questionnaire has been published previously (19, 20). In brief, the EPIC validation study calculated correlations between measures of the dietary questionnaire and the individuals' average of twelve 24-hour recalls. Correlations, averaged over subgroups by country and gender, were 0.45 for fruit and 0.56 for vegetable consumption (20). Baseline information on lifestyle was obtained by using lifestyle questionnaires with questions on smoking habits, alcohol consumption, physical activity, education, and medical history.

This study focuses on consumption of total fruits (mainly fresh fruits, but also including dried or canned fruits), total vegetables, and fruits and vegetables combined. Legumes, potatoes, and other tubers were not included as vegetables. Consumption of fruit and vegetable juices was excluded because these differ nutritionally (e.g., added sugars and vitamins) and were quantified in liquid form. Subgroups of fruits (citrus fruits, hard fruits (apples, pears), stone fruits (cherries, mirabelles, plums, apricots, peaches, nectarines), grapes, berries) and vegetables (leafy vegetables, fruiting vegetables, root vegetables, cabbage, mushrooms, grain and pod vegetables, onion and garlic, stalk vegetables, mixed salads/vegetables) and olives, nuts and seeds, legumes, and potatoes and other tubers were analyzed separately. Information on consumption of some subgroups of fruits and vegetables was missing for a few centers. Details of the food items included in fruit and vegetable subgroups have been reported elsewhere (21).

Outcome assessment

Follow-up information was obtained by using record linkage with cancer registries, boards of health, and death indices in Denmark, Italy (except Naples), the Netherlands, Norway, Spain, Sweden, and the United Kingdom. In France, Germany, Greece, and Naples (Italy), this information was obtained by active follow-up consisting of a combination of methods including health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next of kin. The end of follow-up varied among centers, ranging between 2006 and 2010. A total of 25,682 participants (55.7% women) were reported as deceased among all 451,151 participants. The underlying cause of death was assigned to cancer (codes C00–C97, excluding C44 for nonmelanoma skin cancer, $n = 10{,}438$) or

cardiovascular disease (consisting of ischemic heart disease (codes I20–I25, $n = 2{,}139$), cerebrovascular disease (codes I60–I69, $n = 1{,}291$), other forms of heart disease (codes I30–I52, $n = 793$), diseases of the arteries, arterioles, and capillaries (codes I70–I79, $n = 424$), and other cardiovascular diseases (codes I00–I15, I26–I28, I80–I99, $n = 478$)) according to the *International Classification of Diseases, 10th Revision,* thereby covering more than 75% of all deaths with a reported cause ($n = 20{,}737$).

Statistical analysis

Hazard ratios with 95% confidence intervals were calculated by using Cox proportional hazards models, using age as the underlying time variable. Gender, center, and age at recruitment were used as stratification variables to minimize departure from proportionality (confirmed by using log-log plots).

Consumption of fruits and vegetables was modeled by using EPIC-wide quartiles and continuous increments of 100 g/day for separate fruit and vegetable consumptions and 200 g/day for the consumptions combined. Tests for trend were performed by using quartile medians modeled continuously. Restricted cubic splines with 4 knots (at the 5th, 35th, 65th, and 95th percentiles) were modeled by using continuous variables of fruit and vegetable consumptions to examine the shape of the relation between consumption and all-cause mortality. Fruit and vegetable subgroups were analyzed by using a category for nonconsumers and EPIC-wide tertiles, using the lowest tertile as a reference group, and continuously, using increments of subgroup-specific standard deviations. Consumers were compared with nonconsumers if more than 25% of the population were nonconsumers. Analysis of total vegetable consumption was additionally stratified by mode of preparation (raw or cooked).

Analyses were adjusted for physical activity according to the Cambridge Physical Activity Index (inactive, moderately inactive, moderately active, active) (22), level of education (no education/primary school, technical/professional school, secondary school, university), smoking status at baseline (never, former, current), and processed meat consumption (g/day). The preventable proportion with 4 knots each was fitted for number of cigarettes smoked per day, lifetime duration of smoking in years, years since stopped smoking, alcohol consumption (g/day), and body mass index (weight (kg)/height $(m)^2$) to model nonlinear relations between covariates and mortality. Because of a moderate correlation ($r = 0.28$), models for vegetable and fruit consumptions were mutually adjusted. Models for subgroups were adjusted for all other fruit and vegetable consumptions. Red meat consumption was not included as a covariate, because it was not associated with all-cause mortality in the multivariable-adjusted model. Missing indicator variables were used for categorical variables, as exclusion of these participants ($n = 62{,}549$, including the entire Norway cohort for which the Cambridge Physical Activity Index was missing) did not materially change the results. A substitution model was created by additionally adjusting for total energy intake (kcal/day). In this model, an increased consumption of fruits and vegetables comes at the expense of other energy-containing nutrition, with exception of dietary variables that were also included in the model.

To examine if associations differ among participants who are at different risks of death a priori, we performed joint analyses by using quartiles of fruit and vegetable consumption and categories of smoking status (current, former, never smokers); alcohol consumption (low: <3 g/day of ethanol in women and <6 g/day in men; moderately low: 3–<12 g/day in women and 6–<24 g/day in men; moderately high: 12–30 g/day in women and 24–60 g/day in men; and high: >30 g/day in women and >60 g/day in men); and body mass index (<25, 25–30, >30) calculated as weight (kg)/height $(m)^2$. Multiplicative interaction was assessed by using a likelihood ratio test for cross-product terms. Heterogeneity in the association of fruits and vegetables between countries was examined by using a cross-product term as well.

To correct diet-outcome associations for random and systematic measurement errors in estimates of intake from the dietary questionnaire, associations were calibrated by using a fixed-effects linear model (23) in which gender- and center-specific 24-hour dietary recall data from a random sample of the cohort (24) were regressed on questionnaire intakes controlling for covariates included in the mortality model. Nonconsumers were kept in the regression, and negative values occurring after regression were set to 0. Continuous models were based on both observed and calibrated values.

Rate advancement periods were calculated by using similar Cox models, with follow-up as the time variable and age at recruitment as the covariate. The rate advancement period equals the ratio of risk estimates for age (in years) and the highest quartile of exposure (compared with the lowest) and is defined as the time period by which the risk of death is postponed among participants in the highest quartile when compared with the lowest (25, 26). Preventable proportions were calculated to estimate the preventable proportion of deaths if all participants in the lowest 3 quartiles of consumption of fruits and vegetables would shift their intake 1 quartile upward (27). Preventable proportions (PPs) were calculated by the following formula, where p is the original proportion of all controls in quartile i (e.g., 0.25 in quartile 4 for the adjusted association between fruit and vegetable consumption and all-cause mortality), p^* is the proportion after the shift (e.g., 0.50), and r is its corresponding hazard ratio (e.g., 0.90):

$$\mathrm{PP} = 1 - \frac{\sum_{i=1}^{4} p_i r_i}{\sum_{i=1}^{4} p_i^* r_i}.$$

RESULTS

The observed median value consumption of fruits and vegetables combined in the total study population was 387.9 g/day and seemed to increase according to a North-to-South gradient (Table 1). Parallel to a high consumption

Table 1. Number of Participants and Deaths, Age at Recruitment, Follow-up Time, and Consumption of Vegetables, Fruits, and the Combined Consumption as Measured by the Dietary Questionnaire According to Country,[a] the European Prospective Investigation Into Cancer and Nutrition, 1992–2010

Country	No. of Participants		Median Age at Recruitment, years	Median Follow-up Time, years	No. of Deaths	Median Observed Consumption, g/day		
	Men	Women				Vegetables	Fruits	Fruits and Vegetables
Norway		35,523	48.0 (42.3–54.1)[b]	11.1 (11.0–11.1)	899	126.5 (58.3–242.0)	136.8 (32.9–322.6)	273.7 (127.0–515.0)
Sweden	20,991	27,089	50.6 (39.8–64.9)	14.2 (12.3–16.3)	4,323	102.3 (25.5–238.4)	148.8 (40.5–339.5)	268.2 (94.9–535.4)
Denmark	23,862	27,098	56.0 (51.2–63.1)	12.0 (11.0–13.2)	4,306	162.0 (65.4–306.4)	143.0 (74.5–373.8)	318.4 (136.0–619.2)
United Kingdom	20,768	50,250	48.8 (29.1–67.9)	13.1 (11.2–15.0)	5,529	244.0 (126.0–430.8)	205.1 (63.3–448.4)	464.3 (238.0–818.8)
The Netherlands	9,229	25,569	50.9 (29.7–63.0)	13.3 (11.4–15.2)	1,819	123.3 (72.3–198.4)	166.7 (48.7–370.6)	301.3 (153.9–527.5)
Germany	19,234	26,286	49.7 (38.6–61.7)	11.5 (10.3–12.6)	1,840	112.3 (63.6–193.0)	108.5 (45.7–267.0)	237.6 (131.5–427.6)
France		64,406	51.3 (44.9–62.6)	15.6 (13.5–15.7)	2,773	263.1 (131.0–455.6)	233.5 (77.2–461.1)	507.9 (273.5–835.3)
Italy	13,274	29,136	50.4 (39.9–60.9)	12.3 (10.2–14.6)	1,381	155.9 (70.1–297.6)	313.7 (137.0–575.6)	484.6 (254.5–812.4)
Spain	13,732	22,918	48.1 (38.6–60.5)	13.7 (12.2–15.3)	1,527	221.7 (87.1–434.7)	271.5 (51.9–580.2)	520.1 (224.9–909.6)
Greece	8,792	12,994	51.5 (35.6–69.1)	10.6 (4.2–12.9)	1,285	421.5 (252.7–625.2)	334.6 (159.4–554.8)	767.6 (479.2–1,104.4)
Overall	129,882	321,269	51.2 (38.6–63.0)	12.8 (10.7–15.6)	25,682	172.9 (69.4–388.2)	193.7 (52.3–446.2)	387.9 (162.4–772.8)

[a] Sorted by Geographical Location from north to south.
[b] Numbers in parentheses, 10%–90% range.

of fruits and vegetables, the proportions of older participants, women, and never smokers increased, and participants seemed to consume less processed meat and alcohol (Table 2). The median follow-up was almost 13 years.

A higher consumption of fruits and vegetables combined was inversely associated with all-cause mortality (Table 3). Differences in the risk of death over the upper quartiles were weaker than over the first 2 quartiles, indicating a nonlinear relation. Results were similar for models with and without correction for energy intake. In the adjusted model, a hazard ratio of 0.90 (95% confidence interval (CI): 0.86, 0.94) and a corresponding rate advancement period of 1.12 (95% CI: 0.70, 1.54) were observed for participants in the highest (>568.8 g/day) versus the lowest (<249.1 g/day) quartile. For every 200-g/day higher intake of fruits and vegetables combined, the risk of death was 3%–6% lower (observed hazard ratio (HR) = 0.97, 95% CI: 0.96, 0.98; calibrated HR = 0.94, 95% CI: 0.91, 0.96). If participants in the 3 lowest quartiles shifted their consumption 1 quartile upward, the preventable proportion of deaths was 2.68%. The fully adjusted model with spline terms for combined consumption of vegetables and fruits showed a threshold around 400 g/day of consumption, after which the risk of death did not decrease further (Figure 1). Separate splines for fruits and vegetables are given in Web Figure 1 available at http://aje.oxfordjournals.org/.

Participants with a high fruit consumption had a slightly lower risk of death when analyzed overall, but after stratification by gender, the association was observed only in women. When comparing the highest versus the lowest quartiles (>312.1 vs. <106.8 g/day), the hazard ratio for women was 0.92 (95% CI: 0.87, 0.97) with a rate advancement period of 1.19 (95% CI: 0.65, 1.72), and the hazard ratio for men was 1.03 (95% CI: 0.97, 1.10). The preventable proportion for women was 2.13%. When fruit was modeled as a continuous variable, no significant association with mortality was observed for each 100-g/day higher intake of fruit. The risk of death was inversely associated with vegetable consumption, with a hazard ratio of 0.90 (95% CI: 0.86, 0.94) and a rate advancement period of 1.17 (95% CI: 0.74, 1.60) for participants in the highest versus the lowest quartile (>312.1 vs. <106.8 g/day). No notable differences between gender were observed. The overall preventable proportion was 2.69%. Mortality was 3%–5% lower for every 100-g/day higher intake of vegetables (observed HR = 0.97, 95% CI: 0.96, 0.98; calibrated HR = 0.93, 95% CI: 0.90, 0.97). When stratifying vegetable consumption by mode of preparation, we observed stronger inverse associations for raw vegetables (in the highest quartile, HR = 0.84, 95% CI: 0.80, 0.88) than for cooked vegetables (in the highest quartile, HR = 0.93, 95% CI: 0.89, 0.98). Additionally, no threshold appeared in the inverse association between raw vegetables and all-cause mortality.

Fruit and vegetable consumptions were inversely associated with cardiovascular disease mortality, with a hazard ratio in the highest quartile of 0.85 (95% CI: 0.77, 0.93), rate advancement period of 1.37 (95% CI: 0.65, 2.09), and preventable proportion of 4.24%. However, no clear inverse association with cancer mortality was observed with a hazard ratio in the highest quartile of 0.96 (95% CI: 0.90,

Table 2. Baseline Characteristics According to Quartiles of the Consumption of Fruits and Vegetables Combined as Measured by the Dietary Questionnaire in the Total Study Population, the European Prospective Investigation Into Cancer and Nutrition, 1992–2010

Characteristic	Total Cohort ($n = 451,151$)		Observed Combined Fruit and Vegetable Consumption by Quartiles[a]							
			Quartile 1 ($n = 112,788$)		Quartile 2 ($n = 112,788$)		Quartile 3 ($n = 112,788$)		Quartile 4 ($n = 112,787$)	
	%	Median (10%–90%)	%	Median (10%–90%)	%	Median (10%–90%)	%	Median (10%–90%)	%	Median (10%–90%)
Deaths	5.7		6.6		5.8		5.3		5.1	
Female	71.2		59.2		71.4		77.5		76.8	
Age at recruitment, years		51.2 (38.6–63.0)		50.4 (37.8–61.7)		51.3 (38.8–62.9)		51.5 (39.3–63.5)		51.4 (38.5–64.0)
Total energy intake, kcal/day		1,993 (1,349–2,891)		1,828 (1,211–2,731)		1,938 (1,333–2,812)		2,021 (1,406–2,882)		2,171 (1,520–3,076)
Observed vegetable consumption, g/day		172.9 (69.4–388.2)		91.1 (37.1–151.1)		151.6 (82.0–238.2)		215.6 (113.0–333.1)		339.4 (170.3–548.4)
Observed fruit consumption, g/day		193.7 (52.3–446.2)		74.6 (19.3–136.3)		159.9 (79.4–245.0)		250.1 (139.0–364.1)		403.0 (237.6–646.9)
Observed fruit and vegetable consumption, g/day		387.9 (162.4–772.8)		178.8 (90.3–235.7)		316.8 (262.4–373.2)		468.4 (403.1–546.0)		725.3 (593.8–1032.7)
Red meat consumption, g/day		34.3 (3.7–90.1)		30.2 (7.2–88.9)		34.3 (4.9–90.6)		36.0 (2.9–90.0)		37.8 (1.4–90.1)
Processed meat consumption, g/day		24.5 (2.0–67.6)		33.1 (8.6–80.4)		27.6 (4.5–70.4)		22.1 (2.0–61.7)		15.2 (0.2–54.1)
Body mass index[b]		24.7 (20.6–30.6)		24.8 (20.7–30.4)		24.5 (20.6–30.2)		24.5 (20.5–30.4)		25.0 (20.7–31.4)
Alcohol status										
Consumption, g/day		5.7 (0.0–32.5)		6.1 (0.1–38.7)		6.2 (0.1–33.1)		5.8 (0.0–30.4)		4.8 (0.0–29.3)
Nonconsumers	5.4		6.2		5.3		5.0		5.4	
Smoking status										
Never smokers	49.0		39.3		47.3		53.2		56.4	
Former smokers	26.2		26.3		27.7		26.4		24.5	
Time since stopped smoking, years		14 (2.5–29)		14 (2–28.5)		14.5 (2.5–29.5)		14.5 (3–29.5)		13.5 (2.5–29)
Smoking duration, years		17 (4–33)		17 (4–33)		17 (4–33)		16.5 (4–33)		17 (5–33)
Current smokers	22.6		33.0		23.1		18.1		16.4	
Cigarettes/day, no.		13 (3–25)		15 (5–25)		12 (3–21)		11 (2.5–23)		12 (2.5–30)
Smoking duration, years		30 (16.5–42.5)		31.5 (18.5–43)		31 (17.5–42.5)		30 (16.5–42)		27.5 (14–41)
Missing/unknown	2.1		1.5		1.9		2.3		2.7	
Physical activity										
(Moderately) active	39.7		38.2		39.9		40.3		40.3	
Missing/unknown	9.4		15.6		12.2		6.9		2.7	

Table continues

Table 2. Continued

Characteristic	Total Cohort ($n = 451,151$)		Observed Combined Fruit and Vegetable Consumption by Quartiles[a]							
			Quartile 1 ($n = 112,788$)		Quartile 2 ($n = 112,788$)		Quartile 3 ($n = 112,788$)		Quartile 4 ($n = 112,787$)	
	%	Median (10%–90%)	%	Median (10%–90%)	%	Median (10%–90%)	%	Median (10%–90%)	%	Median (10%–90%)
Education completed										
None/primary school	29.0		29.7		26.1		27.2		33.1	
Technical/professional school	22.6		30.3		25.8		20.0		14.3	
Secondary school	20.8		17.4		20.1		23.0		22.7	
University	24.2		20.2		24.9		25.6		25.1	
Missing/unknown	3.5		1.7		3.1		4.3		4.7	

[a] Quartile ranges by restricted cubic splines with 4 knots: 0–249.1, 249.1–387.9, 387.9–568.8, and 568.8–1,548.6 g of fruits and vegetables per day.
[b] Body mass index: weight (kg)/height (m)^2.

1.03), rate advancement period of 0.55 (95% CI: −0.27, 1.37), and preventable proportion of 1.04%. Approximately similar associations were observed for vegetable consumption with cardiovascular disease (in the highest quartile, HR = 0.79, 95% CI: 0.71, 0.87) and cancer (in the highest quartile, HR = 0.95, 95% CI: 0.89, 1.02) mortality. Stronger inverse associations with both cancer and cardiovascular disease mortality were seen for raw vegetables than for cooked vegetables. Fruit consumption showed no clear association with either cause of death (Table 4; Web Table 1).

The association of a higher fruit and vegetable consumption with mortality seemed stronger for participants with a high consumption of alcohol ($P_{\text{interaction}} < 0.0001$) and participants with a body mass index over 30 ($P_{\text{interaction}} = 0.0042$) (Table 5). Although the test for interaction was not statistically significant ($P_{\text{interaction}} = 0.06$), a higher fruit and vegetable consumption seemed to have a stronger association in smokers. A significant heterogeneity in the association of fruits and vegetables with all-cause mortality was observed among countries ($P_{\text{interaction}} = 0.0019$) (Web Figure 2). In general, stronger inverse associations were observed for southern countries than for northern countries.

For subgroups of fruits and vegetables, nonconsumers generally showed a significantly higher risk of death when compared with the lowest tertile of consumers (Web Table 2). The risk of death for subgroups of fruit did not seem lower with an increase in consumption, whereas for vegetable subgroups the highest tertile showed 5%–10% lower risks of death. Continuous modeling of subgroups showed weak positive associations for a higher consumption of grapes and legumes, whereas leafy, fruiting, root, and mixed vegetables showed inverse associations.

DISCUSSION

In this large prospective study, lower mortality was observed with large consumption of fruits and vegetables. An 11% lower risk of death was found in this study for the highest quartile of fruit and vegetable consumption (>569 g/day) when compared with the lowest (<249 g/day). This association is slightly weaker than in previous studies, which indicated a 10%–25% lower mortality (2–9). This difference might be explained by our larger study population (most previous studies included between 1,000 and 70,000 subjects) causing the overall estimates to be less prone to error. However, considering its sampling frame, the included population may have a healthier diet than the general population, causing smaller differences between lower and higher quartiles. Additionally, using the preventable proportion to estimate flexible exposure-risk associations instead of categorical adjustments potentially reduced residual confounding (28). Most previous studies that corrected for baseline smoking status or alcohol consumption did so categorically (2, 4, 6–9) or using metabolites (5), representing a recent exposure only and ignoring increased risks from lifetime exposure (29). Adjustment for energy intake did not change the results, indicating that a higher consumption of fruits and vegetables is beneficial, regardless of whether they are consumed instead of or in addition to other products.

Table 3. Hazard Ratios for the Consumption of Vegetables, Fruits, and Combined With All-Cause Mortality According to Quartiles and Observed and Calibrated Continuous Increase of Consumption, the European Prospective Investigation Into Cancer and Nutrition, 1992–2010

	Quartiles								P_{trend}[a]	Continuous[b]				Q4 vs. Q1		Preventable Proportion Shift in Quartile, %
	1		2		3		4			Observed		Calibrated				
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	RAP, years[c]	95% CI	
Fruit and vegetable consumption[d]																
Model 1 (crude)	1.00	Referent	0.81	0.78, 0.84	0.73	0.70, 0.75	0.70	0.68, 0.73	0.00	0.90	0.89, 0.91	0.72	0.66, 0.78	3.52	3.11, 3.92	9.07
Model 2[e] (adjusted)	1.00	Referent	0.93	0.90, 0.97	0.90	0.86, 0.93	0.90	0.86, 0.94	0.00	0.97	0.96, 0.98	0.94	0.91, 0.96	1.12	0.70, 1.54	2.68
Model 2[e] (men)	1.00	Referent	0.93	0.89, 0.98	0.90	0.85, 0.95	0.93	0.87, 1.00	0.02	0.97	0.95, 0.99	0.93	0.89, 0.98	0.67	0.02, 1.32	1.86
Model 2[e] (women)	1.00	Referent	0.94	0.89, 0.98	0.89	0.85, 0.94	0.89	0.84, 0.94	0.00	0.97	0.96, 0.99	0.94	0.91, 0.97	1.35	0.78, 1.91	2.96
Fruit consumption[f]																
Model 1 (crude)	1.00	Referent	0.81	0.78, 0.84	0.76	0.73, 0.78	0.75	0.72, 0.78	0.00	0.94	0.93, 0.95	0.84	0.80, 0.87	2.99	2.61, 3.36	7.53
Model 2[e] (adjusted)	1.00	Referent	0.95	0.92, 0.98	0.94	0.91, 0.98	0.97	0.93, 1.01	0.21	1.00	0.99, 1.01	0.98	0.96, 1.00	0.72	0.33, 1.12	0.78
Model 2[e] (men)	1.00	Referent	0.98	0.93, 1.03	0.98	0.92, 1.03	1.03	0.97, 1.10	0.40	1.01	0.99, 1.02	1.00	0.97, 1.03	0.09	0.51, 0.68	-0.75
Model 2[e] (women)	1.00	Referent	0.92	0.88, 0.97	0.91	0.87, 0.96	0.92	0.87, 0.97	0.02	0.99	0.98, 1.00	0.97	0.95, 1.00	1.19	0.65, 1.72	2.13
Vegetable consumption[g]																
Model 1 (crude)	1.00	Referent	0.84	0.81, 0.87	0.77	0.74, 0.80	0.75	0.72, 0.78	0.00	0.92	0.91, 0.94	0.74	0.65, 0.85	2.87	2.45, 3.29	7.44
Model 2[e] (adjusted)	1.00	Referent	0.93	0.89, 0.96	0.89	0.86, 0.93	0.90	0.86, 0.94	0.00	0.97	0.96, 0.98	0.93	0.90, 0.97	1.17	0.74, 1.60	2.69
Model 2[e] (men)	1.00	Referent	0.94	0.90, 0.99	0.88	0.83, 0.93	0.88	0.83, 0.95	0.00	0.95	0.93, 0.97	0.89	0.85, 0.94	1.12	0.47, 1.77	3.24
Model 2[e] (women)	1.00	Referent	0.91	0.87, 0.96	0.90	0.86, 0.95	0.91	0.86, 0.96	0.02	0.98	0.97, 1.00	0.96	0.93, 1.00	1.20	0.62, 1.78	2.42

Table continues

Table 3. Continued

	Quartiles								P_{trend}[a]	Continuous[b]				Q4 vs. Q1		Preventable Proportion Shift in Quartile, %
	1		2		3		4			Observed		Calibrated				
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	RAP, years[c]	95% CI	
Raw vegetable consumption[h]																
Model 2[e] (adjusted)	1.00	Referent	0.92	0.89, 0.95	0.85	0.81, 0.88	0.84	0.80, 0.88	0.00	0.92	0.90, 0.94	0.85	0.80, 0.91	1.77	1.33, 2.21	4.44
Cooked vegetable consumption[i]																
Model 2[e] (adjusted)	1.00	Referent	0.96	0.92, 1.00	0.92	0.88, 0.96	0.93	0.89, 0.98	0.02	0.99	0.97, 1.01	0.94	0.88, 1.02	0.93	0.46, 1.41	1.84

Abbreviations: CI, confidence interval; HR, hazard ratio; Q1/Q4, quartile 1/quartile 4; RAP, rate advancement period.

[a] Trend was assessed by using quartile medians modeled continuously in the survival analysis.

[b] Continuous analyses used 200 g per day as the increment for the combined consumption of fruits and vegetables. All other models used 100 g per day as the increment.

[c] Rate advancement periods were calculated by using similar models as quartiles, but they were additionally adjusted for age at recruitment, by using follow-up time as the underlying time variable.

[d] Quartile ranges by restricted cubic splines with 4 knots: quartile 1, 0–249.1 g per day including 7,461 deaths; quartile 2, 249.1–387.9 g per day including 6,492 deaths; quartile 3, 387.9–568.8 g per day including 5,974 deaths; and quartile 4, 568.8–1,548.6 g per day including 5,755 deaths.

[e] Adjusted for smoking status, smoking duration, time since stopped smoking, number of cigarettes smoked per day, alcohol consumption, body mass index, physical activity, education, and processed meat consumption. The model for vegetables was additionally adjusted for fruit consumption and vice versa.

[f] Quartile ranges by restricted cubic splines with 4 knots: quartile 1, 0–106.8 g per day including 7,331 deaths; quartile 2, 106.8–193.7 g per day including 6,485 deaths; quartile 3, 193.7–312.1 g per day including 6,105 deaths; and quartile 4, 312.1–1,014.5 g per day including 5,761 deaths.

[g] Quartile ranges by restricted cubic splines with 4 knots: quartile 1, 0–108.8 g per day including 7,334 deaths; quartile 2, 108.8–172.9 g per day including 6,078 deaths; quartile 3, 172.9–271.1 g per day including 6,078 deaths; and quartile 4, 271.1–820.9 g per day including 6,060 deaths.

[h] Quartile ranges by restricted cubic splines with 4 knots: quartile 1, 0–22.9 g per day including 8,783 deaths; quartile 2, 22.9–50.1 g per day including 6,109 deaths; quartile 3, 50.1–100.0 g per day including 5,456 deaths; and quartile 4: 100.0–770.7 g per day including 5,334 deaths.

[i] Quartile ranges by restricted cubic splines with 4 knots: quartile 1, 0–49.9 g per day including 6,718 deaths; quartile 2, 49.9–90.8 g per day including 6,051 deaths; quartile 3, 90.8–157.8 g per day including 6,229 deaths; and quartile 4, 157.8–772.7 g per day including 6,684 deaths.

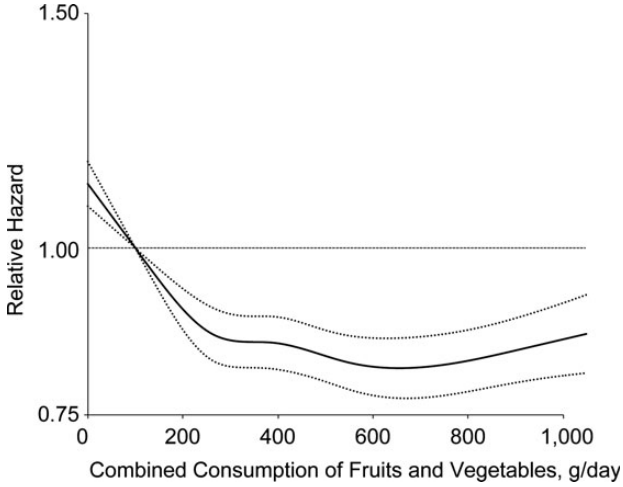

Figure 1. Restricted cubic spline and 95% confidence intervals of the nonlinear relation between fruit and vegetable consumption combined (in grams per day) and all-cause mortality, the European Prospective Investigation Into Cancer and Nutrition, 1992–2010.

Compared with participants who eat less than 249 g/day, participants who eat more than 569 g/day of fruits and vegetables have the risk of death postponed by 1.12 years. Moreover, if all participants shifted consumption 1 quartile upward, the preventable proportion of all-cause mortality is 2.68%.

Stronger inverse associations were observed for raw vegetables when compared with cooked vegetables. The relation between raw vegetables and a lower risk of death has been observed previously (30). Possible mechanisms by which cooking affects the association between vegetables and mortality include changes in the availability of nutrients, destruction of digestive enzymes, and alteration of the structure and digestibility of vegetables (31).

After separating the analyses for mortality from cancer or cardiovascular disease, we found that the overall inverse association seemed driven largely by a strong inverse association with cardiovascular disease mortality, whereas inverse associations were merely suggestive for cancer mortality. These observations seem consistent with the findings from previous studies Into the risk of developing cardiovascular disease or cancer (10–12). Our findings also correspond with previous studies within EPIC Into the overall risk of developing cancer (32) and risk of ischemic heart disease mortality (33). This agreement is caused partly by the overlap in cases, although Boffetta et al. (32) studied the risk of developing cancer instead of the corresponding mortality, and only 42% of the cardiovascular disease mortality in our study is accounted for by ischemic heart disease. It should be noted that the lack of significant inverse associations for cancer mortality may be explained by the longer induction periods that exist for cancers than for cardiovascular disease. It is possible that the follow-up period in this study was too short to identify small inverse associations for cancer mortality.

Most subgroups of fruits and vegetables showed higher risks of death for nonconsumers. No lower risk of death was observed for consumers of subgroups of fruit, whereas a higher consumption of subgroups of vegetables was associated with a 5%–10% lower risk of death when compared with the lowest tertile of consumers. Results for individual fruits and vegetables should be interpreted with caution because of multiple comparisons.

Fruit consumption associated inversely with risk of death among women, whereas no association was present among men. Previous studies found no clear differences between genders in the association of fruit consumption and mortality (11, 12). No obvious reason for the difference observed in our study was found. The estimated validity of measures for consumption of fruits and vegetables, as calculated by the EPIC validation study (20), did not differ clearly between genders. Confounding by alcohol consumption, body mass index, and lifetime exposure to tobacco smoking was limited by fitting the preventable proportion for these variables Into the model. The remaining possible explanations include residual confounding by a variable specific for women, a chance finding, or a true biological difference that remains to be explained.

The inverse association between fruit and vegetable consumption and mortality seemed stronger for participants with a body mass index over 30 and participants with high alcohol consumption (>30 g/day in women and >60 g/day in men) and was suggested for smokers. This seems consistent with the antioxidant properties of fruits and vegetables, as a higher alcohol consumption, a higher body mass index, and smoking all have been shown to increase oxidative stress (34–36). However, residual confounding cannot be excluded here, because participants that consume more fruits and vegetables may be healthier considering factors that were not included in the analysis.

Strengths of this study include the prospective design, large sample size, and great variance in fruit and vegetable consumption. Calibration of dietary intakes increased the validity of exposure estimates, and it should be noted that this had no major effects on the multivariable-adjusted risk estimates. However, measurement error may still remain as errors in the 24-hour dietary recall might be correlated to those in the food frequency questionnaire (37). Also, dietary assessment was based on a single measure of a yearly average, which may not fully reflect the relevant lifetime exposure and therefore result in an underestimation of the true association (38).

The results from this study further strengthen the evidence for an inverse association between fruit and vegetable consumption and all-cause mortality, driven largely by cardiovascular disease mortality. Consumption of raw vegetables seemed to show stronger associations with mortality than cooked vegetables, including cancer mortality as well, whereas associations of similar strength were found for nearly all subgroups of fruits and vegetables. The association of a higher fruit and vegetable consumption with mortality seemed stronger for participants with a high alcohol consumption and participants with a body mass index over 30 and was suggested for smokers.

Table 4. Hazard Ratios for the Consumption of Vegetables, Fruits, and Combined With Cancer and Cardiovascular Disease Mortality According to Quartiles of Consumption, the European Prospective Investigation Into Cancer and Nutrition, 1992–2010

	Quartiles								P_{trend}[a]	Q4 vs. Q1		Preventable Proportion Shift in Quartile, %
	1		2		3		4					
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		RAP, years[b]	95% CI	
Fruit and vegetable consumption[c]												
Model 2[d] (cancer)	1.00	Referent	0.97	0.92, 1.02	0.94	0.88, 0.99	0.96	0.90, 1.03	0.21	0.55	-0.27, 1.37	1.04
Model 2[d] (cardiovascular disease)	1.00	Referent	0.95	0.87, 1.02	0.89	0.82, 0.97	0.85	0.77, 0.93	0.00	1.37	0.65, 2.09	4.24
Fruit consumption[e]												
Model 2[d] (cancer)	1.00	Referent	0.98	0.93, 1.04	0.98	0.92, 1.04	0.98	0.92, 1.05	0.64	0.50	-0.28, 1.26	0.51
Model 2[d] (cardiovascular disease)	1.00	Referent	0.91	0.84, 0.98	0.95	0.87, 1.03	0.96	0.87, 1.05	0.70	0.84	0.18, 1.50	1.05
Vegetable consumption[f]												
Model 2[d] (cancer)	1.00	Referent	0.96	0.91, 1.02	0.96	0.90, 1.01	0.95	0.89, 1.02	0.22	0.62	-0.22, 1.47	1.30
Model 2[d] (cardiovascular disease)	1.00	Referent	0.91	0.84, 0.98	0.82	0.75, 0.90	0.79	0.71, 0.87	0.00	1.88	1.15, 2.62	6.34
Raw vegetable consumption[g]												
Model 2[d] (cancer)	1.00	Referent	0.96	0.91, 1.01	0.88	0.83, 0.93	0.90	0.84, 0.96	0.01	1.24	0.41, 2.08	2.74
Model 2[d] (cardiovascular disease)	1.00	Referent	0.90	0.84, 0.97	0.82	0.75, 0.90	0.74	0.67, 0.82	0.00	2.40	1.64, 3.16	8.12
Cooked vegetable consumption[h]												
Model 2[d] (cancer)	1.00	Referent	0.98	0.92, 1.04	0.97	0.91, 1.03	0.98	0.91, 1.06	0.65	0.48	-0.46, 1.41	0.51
Model 2[d] (cardiovascular disease)	1.00	Referent	0.99	0.91, 1.08	0.89	0.81, 0.98	0.88	0.79, 0.98	0.02	1.28	0.47, 2.09	3.30

Abbreviations: CI, confidence interval; HR, hazard ratio; Q1/Q4, quartile 1/quartile 4; RAP, rate advancement period.

[a] Trend was assessed by using quartile medians modeled continuously in the survival analysis.

[b] Rate advancement periods were calculated by using similar models as quartiles, but they were additionally adjusted for age at recruitment, using follow-up time as the underlying time variable.

[c] Number of cancer deaths in quartiles 1–4: 3,084, 2,701, 2,377, and 2,276. Number of cardiovascular disease deaths in quartiles 1–4: 1,534, 1,253, 1,142, and 1,196.

[d] Adjusted for smoking status, smoking duration, time since stopped smoking, number of cigarettes smoked per day, alcohol consumption, body mass index, physical activity, education, and processed meat consumption. The model for vegetables was additionally adjusted for fruit consumption and vice versa.

[e] Number of cancer deaths in quartiles 1–4: 2,972, 2,636, 2,478, and 2,352. Number of cardiovascular disease deaths in quartiles 1–4: 1,486, 1,230, 1,227, and 1,182.

[f] Number of cancer deaths in quartiles 1–4: 3,060, 2,673, 2,461, and 2,244. Number of cardiovascular disease deaths in quartiles 1–4: 1,571, 1,207, 1,103, and 1,244.

[g] Number of cancer deaths in quartiles 1–4: 3,233, 2,592, 2,291, and 2,322. Number of cardiovascular disease deaths in quartiles 1–4: 1,872, 1,247, 992, and 1,014.

[h] Number of cancer deaths in quartiles 1–4: 2,857, 2,675, 2,586, and 2,320. Number of cardiovascular disease deaths in quartiles 1–4: 1,370, 1,186, 1,196, and 1,373.

Table 5. Joint Analyses for Quartiles of Combined Consumption of Fruits and Vegetables as Measured by the Dietary Questionnaire in the Total Study Population and Categories of Smoking Status, Body Mass Index, and Alcohol Consumption, the European Prospective Investigation Into Cancer and Nutrition, 1992–2010[a]

	Observed Combined Intake of Fruits and Vegetables, g/day							
	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Smoking status								
Never smokers ($n = 221,244$)	0.44	0.42, 0.48	0.43	0.40, 0.45	0.42	0.39, 0.45	0.42	0.39, 0.45
Former smokers ($n = 118,342$)	0.51	0.48, 0.54	0.47	0.44, 0.50	0.44	0.41, 0.47	0.47	0.44, 0.51
Current smokers ($n = 102,121$)	1.00	Referent	0.94	0.89, 0.99	0.90	0.84, 0.96	0.83	0.77, 0.90
$P_{interaction}$[b]				0.06				
Body mass index[c]								
<25 ($n = 239,481$)	0.78	0.73, 0.84	0.75	0.70, 0.81	0.70	0.65, 0.75	0.71	0.65, 0.76
25–30 ($n = 156,642$)	0.76	0.71, 0.81	0.72	0.67, 0.77	0.71	0.66, 0.76	0.71	0.66, 0.77
>30 ($n = 55,028$)	1.00	Referent	0.82	0.75, 0.89	0.82	0.75, 0.90	0.81	0.74, 0.88
$P_{interaction}$[b]				0.0042				
Alcohol intake, g/day[d]								
Low ($n = 163,410$)	0.74	0.68, 0.80	0.72	0.66, 0.78	0.69	0.64, 0.75	0.69	0.63, 0.75
Moderately low ($n = 147,992$)	0.64	0.60, 0.70	0.62	0.57, 0.67	0.59	0.54, 0.64	0.60	0.55, 0.65
Moderately high ($n = 86,468$)	0.69	0.63, 0.75	0.64	0.59, 0.70	0.62	0.57, 0.68	0.66	0.60, 0.72
High ($n = 28,701$)	1.00	Referent	0.80	0.72, 0.89	0.76	0.68, 0.85	0.63	0.55, 0.72
$P_{interaction}$[b]				<0.0001				

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Analyses were adjusted for smoking status, smoking duration, time since stopped smoking, number of cigarettes smoked per day, alcohol intake, body mass index, physical activity, education, and processed meat intake.

[b] Interaction was assessed by using the likelihood ratio test for the multiplicative interaction term added to the fully adjusted model.

[c] Body mass index: weight (kg)/height $(m)^2$.

[d] Low alcohol intake: <3 g/day for women, <6 g/day for men; moderately low alcohol intake: 3–12 g/day for women, 6–24 g/day for men; moderately high alcohol intake: >12–30 g/day for women and >24–60 g/day in men; and high alcohol intake: >30 g/day in women and >60 g/day in men.

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