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Fruit and Vegetable Consumption With Risk of Abdominal Aortic Aneurysm

Otto Stackelberg, MD; Martin Björck, MD, PhD; Susanna C. Larsson, PhD; Nicola Orsini, PhD; Alicja Wolk, DMSc

Background—Dietary factors affecting the risk of developing abdominal aortic aneurysm (AAA) are scarcely investigated.

The aim of this study was to investigate the associations of fruit and vegetable consumption with the risk to develop AAA.

Methods and Results—The prospective Cohort of Swedish Men and the Swedish Mammography Cohort, consisting of 44 317 men and 36 109 women, 46 to 84 years of age at the start of the 13-year follow-up (1998–2010), were used. Fruit and vegetable consumption was assessed at baseline with a 96-item food-frequency questionnaire. By linkage to the Swedish Inpatient Register and the Swedish Vascular Registry (Swedvasc), 1086 primary cases of AAA (222 ruptured) were identified. Cox proportional hazards models were used to estimate hazard ratios with 95% confidence intervals (CIs). Those in the highest quartile of fruit consumption (>2.0 servings/d), in comparison with those in the lowest quartile (<0.7 servings/d), had a 25% (95% CI, 9%–38%) lower risk of AAA, and a 43% (95% CI, 11%–64%) lower risk of ruptured AAA, specifically. Consumption of 2 fruits per day was associated with 31% (95% CI, 11%–47%) lower risk of nonruptured AAA, and 39% (95% CI, 1%–63%) lower risk of ruptured AAA, in comparison with no consumption of fruit. No association was observed between vegetable consumption and AAA risk.

Conclusions—We observed an inverse association between consumption of fruit, but not vegetables, and the risk of AAA, with a more pronounced association with ruptured AAA. (*Circulation*. 2013;128:795-802.)

Key Words: aortic aneurysm, abdominal ■ antioxidants ■ diet ■ epidemiology ■ risk factors

The often asymptomatic disease abdominal aortic aneurysm (AAA) occurs in 1.7% to 4.5% of men above the age of 65,^{1–3} and in 0.5% to 1.3% of women in the same age group.^{4,5} Ultrasound-based screening and preventive surgery has been shown to be the most effective strategy to prevent rupture,^{6,7} a highly lethal event with an overall mortality risk of 70% before surgery and of 35% after surgery, according to contemporary data.^{8,9} The most established risk factors for AAA are advanced age, male sex, and smoking,^{1,10} and smoking cessation intervention has been reported as the most effective way of decreasing expansion rate.¹¹ Other modifiable risk factors for AAA development, such as diet, have scarcely been investigated.

Clinical Perspective on p 802

Growing evidence indicates that inflammation and oxidative stress may play an important role in AAA pathophysiology,^{12–17} and the redox balance facilitated by antioxidants has made them subject to speculation of having protective effects against AAA development.¹⁸ Fruits and vegetables are rich in antioxidants and thus could potentially reduce the risk to develop AAA. However, only 1 previous study has investigated the association between fruit and vegetable consumption and the risk of AAA.¹⁹ Although a combined consumption of fruits and vegetables was found to be inversely associated

with AAA, that screening study did not report associations of fruits or vegetables separately, nor did they investigate the risk of rupture.

We evaluated the hypothesis that a high consumption of fruits and vegetables reduces the risk of AAA by examining the associations in 2 large population-based prospective cohorts of men and women from central Sweden. We further evaluated whether an association between fruit and vegetable consumption and risk of AAA differed by rupture status, or by specific fruits and vegetables.

Methods

Study Population

The study population consisted of women from the Swedish Mammography Cohort and men from the Cohort of Swedish Men. In brief, the Swedish Mammography Cohort was established between 1987 and 1990 when 74% of all women (90 303), born 1914–1948, residing in central Sweden (Västmanland and Uppsala counties) responded to a questionnaire on diet, anthropometrics, and education. In the fall of 1997, 70% of all surviving participants (56 030) who still lived in the study area responded to an expanded questionnaire with 96 food items accompanied by other lifestyle-related factors.

Simultaneously in 1997, the Cohort of Swedish Men was initiated when 49% of all men (100 303), born 1918–1952, residing in central Sweden (Västmanland and Örebro counties) responded to a questionnaire identical (except for some sex-specific questions) to the Swedish Mammography Cohort 1997 questionnaire. Written

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information to participants and a returned completed questionnaire was considered to imply informed consent.

Of the eligible 48 850 men and 39 227 women, we excluded those with the following characteristics: incorrect Personal Identity Number (a unique number identifying all Swedish citizens used for linkage of registers), previous diagnosis of AAA or cancer (except for nonmelanoma skin cancer; to avoid possible misclassification of exposure), implausible energy intake (± 3 standard deviations [SDs] of the mean log-transformed energy), or missing data on fruit or vegetable consumption. For final analyses, 44 317 men and 36 109 women remained. The study was approved by the regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden).

Ascertainment of AAA Cases and Follow-Up of the Cohorts

By linkage to the Swedish Inpatient Register and the Swedish National Cause of Death register, all individual discharges, or deaths, attributable to nonruptured (*International Classification of Diseases, Tenth Revision: I71.4*) and ruptured (*International Classification of Diseases, Tenth Revision: I71.3*) AAA were identified through December 2010. AAA repair was identified by using the Nordic Classification of Surgical Procedures (Nomesco). Although no specific validity assessment of AAA diagnosis or repair in the Swedish Inpatient Register has been performed, the national coverage has been nearly 100% since 1987²⁰ with a high validity in general.²¹ Surgical codes have been reported as incorrect in 2%, and missing in 5.3%, of the records.²¹ To classify aneurysmal localization and rupture status of AAA repairs, we linked the cohorts to the Swedish National Registry for Vascular Surgery (the Swedvasc, founded in 1987, covering all Swedish hospitals with a vascular service since 1994 and 93.1% of all AAA repairs in Sweden).²² A localization in the infra- or suprarenal abdominal aorta and the common or internal iliac arteries was considered as abdominal.

Hence, cases were defined by first-time events of either a discharge diagnosis code of, or repair attributable to, nonruptured and ruptured AAA; thus, all cases were identified by clinical events, not by general screening of the 2 cohorts.

Assessment of Fruit and Vegetable Consumption

Fruit and vegetable consumption was assessed by a 96-item food-frequency questionnaire at baseline, 1997. The average frequency of consumption during the previous year was reported by the use of 8 predefined frequency consumption categories, ranging from never to ≥ 3 times per day. After converting the responses to average daily consumption of each item, we summed the daily average consumption of all individual fruits ($n=5$) and vegetables ($n=12$) to estimate the average daily consumption of total fruits and total vegetables. The Spearman correlation coefficients between the food-frequency questionnaire and four 1-week weighted diet records ranged from 0.6 (apples, pears) to 0.7 (oranges, other citrus fruits) for fruits and from 0.4 (tomatoes) to 0.6 (spinach) for vegetables (A. Wolk, unpublished data, 1992).

Assessment of Covariates

The 1997 questionnaire solicited information on education, alcohol consumption, diet, physical activity, waist circumference, and smoking status, duration and number of cigarettes smoked per day during different periods in life, as well. Energy intake was calculated by the use of food composition data from the Swedish National Food Administration.²³ History of cardiovascular disease, diabetes mellitus, hypertension, and hypercholesterolemia was obtained from the Swedish Inpatient Register and the Swedish National Diabetes Register and supplemented with self-reported data from the questionnaire.

Statistical Analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the

associations of daily fruit and vegetable consumption with the risk of AAA. Participants accrued follow-up time from January 1, 1998 until the date of diagnosis or repair of AAA, death, or December 31, 2010, whichever occurred first.

Fruit and vegetable consumption was categorized according to the quartile distribution of daily consumption in the study population and included simultaneously in all models. Probability values for linear trends were obtained by treating fruit and vegetable consumption as continuous variables after assigning each quartile of consumption its median value. Because the rate of AAA increased with age in a nonlinear fashion, we flexibly modeled age by using restricted cubic splines. As a proxy for central adiposity, owing to previous findings in these cohorts,²⁴ we adjusted for waist circumference (World Health Organization classification,²⁵ <80 , 80 to <88 , or ≥ 88 cm for women; <94 , 94 to <102 , or ≥ 102 cm for men), and not for body mass index. Further adjustments were made for education (primary school, high school, university), smoking status (current or past smokers with <20 or ≥ 20 pack-years smoked; never smokers), sex-specific quartiles of alcohol consumption (g/wk) and total energy intake (kcal/d), physical activity (<20 ; 20 – 40 ; >40 minutes of walking or bicycling per day), fish consumption (<1 ; 1 – 2 ; 2 – 3 ; >3 servings/wk), quartiles of meat (servings/d) and whole grains (servings/d) consumption, whereas diabetes mellitus, hypertension, hypercholesterolemia, and cardiovascular diseases (angina, myocardial infarction, ischemic stroke, or heart failure) were modeled as binary variables. Indicator variables were used to identify missing data; however, results did not change when complete case analyses were performed. Furthermore, subanalyses by AAA rupture status, and by specific fruits and vegetables (servings/wk, continuously), were performed. The assumption of proportional hazard for fruit or vegetable consumption was not violated when scaled Schoenfeld residuals were regressed against survival time.

Dose–response relationships between fruit and vegetable consumption and risk of nonruptured and ruptured AAA were investigated by modeling the quantitative exposure with restricted cubic splines with 3 knots at fixed percentiles (10th, 50th, and 90th) of the distribution.²⁶ The coefficients of the second spline transformation equal to zero were tested to obtain probability values for nonlinearity. Furthermore, because cigarette smoking increases oxidative stress,²⁷ we stratified our results on smoking status, additionally adjusting for numbers of pack-years smoked (continuously) among past and current smokers.

We used the likelihood ratio test to test statistical significance of the interaction between fruit and vegetable consumption and history of cardiovascular disease (CVD), sex, and smoking status as potential effect modifiers. Sensitivity analyses were performed by restricting the outcome to repair of nonruptured AAA, which is most commonly performed electively (occasionally emergent if impending rupture is suspected) because of the diameter exceeding 55 mm in men and 50 mm in women. Furthermore, because CVD diagnoses are more prevalent, potentially increasing the likelihood of undergoing examinations that detect AAA, among low consumers of fruit and vegetables, we conducted sensitivity analyses by restricting the analyses to individuals without CVD at baseline, and further by censoring those who developed CVD during follow-up. In addition, a sensitivity analysis was performed by excluding the first 3 years of follow-up to account for dietary consumption being secondary to preclinical or chronic disease. To account for a potentially decreased longevity among low consumers of fruits and vegetables, reducing the time at risk of AAA, a competing risk analysis was performed with all-cause mortality as the competing risk. Statistical analyses were performed with Stata version 12.1 (StataCorp, TX). All statistical tests were 2-sided, and P values of <0.05 were considered statistically significant.

Results

During 13 years of follow-up (1998–2010; 960 024 person-years), 1086 primary cases (899 in men, 82.8%) of AAA (222 ruptured [181 in men, 81.5%]) were identified. Mean age for nonruptured AAA was 73.9 (SD 7.0) among men and 76.2 (SD 7.1) among women; corresponding mean age for ruptured

AAA was 75.9 (SD 8.1) and 78.5 (SD 6.9) among men and women, respectively.

The sex-specific distribution of baseline characteristics according to quartiles of daily fruit and vegetable consumption are presented in Tables 1 and 2. Men and women with a high consumption of fruit and vegetables had higher educational level, consumed more fish, meat, and whole grains, were more likely to be leaner and physically active, and were less likely to be current smokers. Moreover, high consumers of fruits tended to consume less alcohol, whereas the inverse applied for high consumers of vegetables. The most commonly consumed fruits and vegetables were apples and pears, bananas, oranges and other citrus fruits, tomatoes and tomato juice, lettuce and leafy greens, carrots, and onions (see footnotes to Tables 1 and 2).

Total and sex-specific associations of quartiles of fruit and vegetable consumption with risk of AAA are shown in Table 3. The risk of AAA decreased with increasing consumption of fruit (P for linear trend=0.003), whereas no significant association was observed for vegetable consumption. Among women and men combined, in comparison with those in the lowest quartile of fruit consumption (<0.7 servings/d), those in the highest quartile (>2.0 servings/d) had a 42% (95% CI, 30%–52%) lower risk of AAA when adjusting for age and sex only. After adjustments for other potential confounders, there was a 25% (95% CI, 9%–38%) lower risk of AAA for those in the highest than in those in the lowest quartile of fruit consumption. The main confounder was smoking. Removing

smoking from the multivariable model resulted in an HR of 0.60 (95% CI, 0.49–0.73), for the highest versus the lowest quartile of fruit consumption. There was no evidence of interaction between sex and consumption of fruits (P for interaction=0.79) or vegetables (P for interaction=0.98) with risk of AAA. The HR of AAA comparing the highest quartile of fruit consumption with the lowest was decreased by 21% (95% CI, 1%–36%) among men, and 29% (95% CI, –11% to 55%) among women. In subanalyses of specific fruits and vegetables, no item was significantly associated with AAA risk. For example, the HRs of AAA for every 3 additional servings per week were 0.93 (95% CI, 0.85–1.00) for apples and pears, and 0.90 (95% CI, 0.80–1.01) for bananas.

Subanalyses by rupture status for the associations of quartiles of fruit consumption with AAA risk are presented in Table 4. Among those in the highest compared with the lowest quartile of fruit consumption, the HR of nonruptured AAA was nonsignificantly decreased by 19% (95% CI, –1% to 35%), and the risk of ruptured AAA was decreased by 43% (95% CI, 11%–64%). There was no evidence of an interaction between fruit consumption and sex with risk of nonruptured (P for interaction=0.28) or ruptured (P for interaction=0.54) AAA. Vegetable consumption was not associated with risk of nonruptured or ruptured AAA (data not shown).

We next modeled fruit consumption with risk of nonruptured (Figure, A) and ruptured (Figure, B) AAA with the use of restricted cubic splines. The rate of change in the risk of nonruptured AAA seemed to decrease with fruit consumption

Table 1. Sex-Specific Distribution of Baseline Characteristics by Quartiles of Fruit Consumption

Characteristics	Quartiles of Fruit Consumption, servings/d*							
	Cohort of Swedish Men				Swedish Mammography Cohort			
	<0.7	0.7–1.2	1.3–2.0	>2.0	<0.7	0.7–1.2	1.3–2.0	>2.0
No. of subjects	14 314	12 248	9 850	7 905	6 144	8 076	9 891	11 998
Age, y (SD)	59.4 (9.7)	59.9 (9.7)	60.6 (9.6)	61.4 (9.6)	62.3 (9.6)	61.9 (9.3)	61.7 (9.1)	61.4 (9.0)
Educational level: university, %	13.5	16.5	18.3	19.5	14.1	17.5	19.6	22.1
Waist circumference, cm	96.6	95.9	95.7	95.6	84.2	84.0	83.4	83.1
Current smokers, %	32.1	23.6	18.8	17.6	31.7	20.8	16.1	13.2
Pack-years of smoking	23.5	20.3	18.9	18.2	18.0	15.1	14.2	13.3
Alcohol consumption, g/wk	109.5	93.9	89.7	86.8	38.3	36.4	36.0	34.1
Physical activity (>40 min/d), %	25.4	29.7	31.8	35.8	26.7	30.2	33.1	37.9
Energy intake, kcal/d	2442	2633	2777	3017	1519	1627	1746	1926
Fish consumption, † servings/wk	1.7	1.9	2.1	2.3	1.9	2.0	2.2	2.4
Meat consumption, ‡ servings/d	1.2	1.3	1.3	1.4	1.0	1.1	1.1	1.1
Wholegrain consumption, § servings/d	3.8	4.2	4.6	5.0	3.2	3.5	3.8	4.1
Diabetes mellitus, %	10.0	9.4	9.9	9.8	5.2	5.2	4.5	4.8
Hypertension, %	26.0	25.6	24.2	25.1	22.4	21.7	22.0	22.0
Hypercholesterolemia, %	16.8	16.6	16.3	16.1	8.2	8.4	8.7	9.2
Cardiovascular diseases, %	12.4	11.7	11.7	12.1	6.8	6.3	6.3	5.9

Values are means unless otherwise indicated. All values (except age) were age-standardized according to the sex-specific distribution of age in seven 5-year categories of the study population. SD indicates standard deviation.

*Fruits (mean, servings/wk) include oranges and other citrus fruits (2.0), apples and pears (3.9), bananas (2.6), berries (1.3), and other fruits (1.7).

†Fish includes herring, salmon, and codfish.

‡Meat includes sausage, black pudding, liver paste, ham, meatballs, pork, veal, and kidney.

§Whole grains include hard bread, whole meal, oatmeal, gruel, flakes, and wheat bran.

||History of cardiovascular diseases includes angina pectoris, myocardial infarction, ischemic stroke, and heart failure.

Table 2. Sex-Specific Distribution of Baseline Characteristics by Quartiles of Vegetable Consumption

Characteristics	Quartiles of Vegetable Consumption, servings/d*							
	Cohort of Swedish Men				Swedish Mammography Cohort			
	<1.4	1.4–2.2	2.3–3.3	>3.3	<1.4	1.4–2.2	2.3–3.3	>3.3
No. of subjects	13 736	11 994	10 258	8 329	6 426	8 232	9 734	11 717
Age, y (SD)	61.5 (9.8)	59.7 (9.6)	59.4 (9.5)	59.5 (9.6)	64.8 (9.6)	62.4 (9.2)	61.0 (8.9)	60.2 (8.8)
Educational level: university, %	9.8	15.1	20.0	24.3	9.7	15.9	20.2	24.3
Waist circumference, cm	96.7	95.8	95.7	95.6	84.6	83.7	83.3	83.0
Current smokers, %	29.8	23.6	21.2	19.9	25.7	20.2	17.6	15.8
Pack-years of smoking	22.7	20.5	19.8	19.6	16.8	15.3	14.7	14.0
Alcohol consumption, g/wk	91.1	96.3	99.5	103.9	27.6	33.9	37.6	39.9
Physical activity (>40 min/d), %	25.9	30.5	32.2	33.6	27.8	30.2	34.0	37.5
Energy intake, kcal/d	2480	2638	2739	2961	1521	1659	1748	1919
Fish consumption, † servings/wk	1.6	1.9	2.1	2.6	1.6	1.9	2.2	2.7
Meat consumption, ‡ servings/d	1.1	1.3	1.3	1.5	0.9	1.0	1.1	1.2
Whole grain consumption, § servings/d	3.8	4.3	4.5	4.8	3.2	3.5	3.8	4.1
Diabetes mellitus, %	10.4	8.8	9.1	10.5	4.9	4.4	4.5	5.5
Hypertension, %	26.5	24.7	24.0	25.4	21.4	22.2	22.1	22.0
Hypercholesterolemia, %	16.5	16.3	16.7	16.3	8.7	8.5	8.9	8.9
Cardiovascular diseases, %	12.2	11.7	12.1	12.2	6.6	6.3	5.8	6.2

Values are means unless otherwise indicated. All values (except age) were age-standardized according to the sex-specific distribution of age in seven 5-year categories of the study population. SD indicates standard deviation.

*Vegetables (mean, servings/wk) include carrots (2.6), beets (0.8), lettuce and leafy greens (2.9), cabbage (1.5), cauliflower (0.7), broccoli and Brussels sprouts (0.7), tomatoes and tomato juice (3.5), peppers (1.8), spinach (0.5), onions and leek (2.4), garlic (1.2), and green peas (1.1).

†Fish includes herring, salmon, and codfish.

‡Meat includes sausage, black pudding, liver paste, ham, meatballs, pork, veal, and kidney.

§Whole grains include hard bread, whole meal, oatmeal, gruel, flakes, and wheat bran.

||History of cardiovascular diseases includes angina pectoris, myocardial infarction, ischemic stroke, and heart failure.

up to ≈ 2 daily servings of fruit, after which no further decrease was observed (P for nonlinearity=0.004). The risk of ruptured AAA seemed to decrease in a linear fashion (P for nonlinearity=0.36) by 17% (95% CI, 3%–30%) for every additional daily serving of fruit. For 1, 2, and 3 daily servings of fruit, in comparison with no consumption, the HR of nonruptured AAA was decreased by 24% (95% CI, 9%–37%), 31% (95% CI, 11%–47%), and 27% (95% CI, 6%–43%), respectively. Corresponding risk reduction of ruptured AAA was 27% (95% CI, –5% to 49%), 39% (95% CI, 1%–63%), and 44% (95% CI, 7%–66%), respectively.

We observed no evidence of an interaction between fruit consumption and smoking status (never, past, or current smoker) in relation to risk of nonruptured or ruptured AAA (P for interaction=0.34 and 0.24, respectively) in a model in which pack-years smoked was added as a continuous covariate. In stratified analysis, the HRs of ruptured AAA in the highest versus the lowest quartile of fruit consumption was 1.02 (95% CI, 0.39–2.70) among never smokers, 0.42 (95% CI, 0.19–0.94) among past smokers, and 0.39 (95% CI, 0.17–0.94) among current smokers. The crude incidence of ruptured AAA among never, past, and current smokers was 10, 30, and 40 events per 100 000 person-years, respectively.

In a sensitivity analysis with repair of nonruptured AAA as outcome ($n=271$), the HR of AAA for the highest in comparison with the lowest quartile of fruit consumption was 0.60 (95% CI, 0.39–0.91), which is similar to the subanalyses of

ruptured AAA. When restricting the analyses to individuals without CVD at baseline, results did not change and the HR of AAA was 0.74 (95% CI, 0.58–0.93) for the highest in comparison with the lowest quartile of fruit consumption. Furthermore, there was no evidence of an interaction with CVD (P for interaction=0.50). The associations of AAA risk in the highest in comparison with the lowest quartile of fruit consumption did not change substantially when restricting the analysis to individuals without CVD at baseline and censoring those who developed CVD during follow-up (HR, 0.67; 95% CI, 0.51–0.90). The multivariable HRs of AAA for the highest in comparison with the lowest quartile of fruit consumption was not affected when excluding the first 3 years of follow-up (HR, 0.74; 95% CI, 0.60–0.91). Finally, competing risk analyses with all-cause mortality as competing risk did not yield any changes of acquired results, and the HR of AAA was 0.76 (95% CI, 0.62–0.92) for the highest versus the lowest quartile of fruit consumption.

Discussion

In this prospective population-based cohort study, consumption of fruit but not vegetables was inversely associated with risk of AAA. The reduction in risk associated with AAA was more pronounced for ruptured than nonruptured AAA. This is the first prospective study to report associations of fruit and vegetable consumption separately with risk of nonruptured and ruptured AAA.

Table 3. Associations of Fruit and Vegetable Consumption With Risk of Abdominal Aortic Aneurysm

	Quartiles of Consumption				P for Trend
	1	2	3	4	
Fruit, servings/d (median)	<0.7 (0.4)	0.7–1.2 (1.0)	1.3–2.0 (1.6)	>2.0 (2.8)	
Total					
Cases/person-years	401/240 443	287/242 147	215/237 143	183/240 291	
Model 1, HR (95% CI)*	1 (Reference)	0.76 (0.65–0.89)	0.62 (0.52–0.74)	0.58 (0.48–0.70)	<0.001
Model 2, HR (95% CI)†	1 (Reference)	0.88 (0.75–1.03)	0.79 (0.67–0.95)	0.75 (0.62–0.91)	0.003
Men					
Cases/person-years	351/167 272	241/144 442	169/116 509	138/92 694	
Model 1, HR (95% CI)*	1 (Reference)	0.77 (0.65–0.91)	0.64 (0.53–0.77)	0.62 (0.50–0.77)	<0.001
Model 2, HR (95% CI)†	1 (Reference)	0.88 (0.74–1.04)	0.80 (0.65–0.97)	0.79 (0.64–0.99)	0.026
Women					
Cases/person-years	50/73 171	46/97 705	46/120 633	45/147 597	
Model 1, HR (95% CI)*	1 (Reference)	0.69 (0.46–1.04)	0.55 (0.36–0.84)	0.44 (0.28–0.68)	<0.001
Model 2, HR (95% CI)†	1 (Reference)	0.93 (0.62–1.40)	0.85 (0.56–1.31)	0.71 (0.45–1.11)	0.12
Vegetables, servings/d (median)	<1.4 (1.0)	1.4–2.2 (1.8)	2.3–3.3 (2.8)	>3.3 (4.3)	
Total					
Cases/person-years	384/232 152	273/241 770	222/242 403	207/243 698	
Model 1, HR (95% CI)*	1 (Reference)	0.90 (0.77–1.05)	0.87 (0.74–1.04)	0.99 (0.82–1.19)	0.51
Model 2, HR (95% CI)†	1 (Reference)	0.96 (0.81–1.12)	0.98 (0.82–1.17)	1.11 (0.92–1.35)	0.39
Men					
Cases/person-years	339/157 239	230/142 005	175/122 650	155/99 024	
Model 1, HR (95% CI)*	1 (Reference)	0.89 (0.75–1.06)	0.84 (0.70–1.02)	0.97 (0.79–1.20)	0.33
Model 2, HR (95% CI)†	1 (Reference)	0.93 (0.78–1.10)	0.92 (0.76–1.12)	1.07 (0.86–1.32)	0.84
Women					
Cases/person-years	45/74 913	43/99 765	47/119 753	52/144 675	
Model 1, HR (95% CI)*	1 (Reference)	0.94 (0.62–1.44)	1.06 (0.69–1.63)	1.14 (0.74–1.77)	0.51
Model 2, HR (95% CI)†	1 (Reference)	1.12 (0.72–1.72)	1.33 (0.85–2.07)	1.44 (0.91–2.26)	0.09

AAA indicates abdominal aortic aneurysm; CI, confidence interval; and HR, hazard ratio.

*Stratified by sex and adjusted for age by the use of restricted cubic splines. Fruit and vegetables were included simultaneously in the model.

†As in model 1 and additionally adjusted for educational level (primary school, high school, university), waist circumference (<80 cm, 80 to <88 cm, or ≥88 cm for women; and <94 cm, 94 to <102 cm, or ≥102 cm for men), smoking (current/past smokers with </≥20 pack-years, never smokers), sex-specific quartiles of alcohol consumption (g/wk) and energy intake (kcal/d), physical activity (<20; 20–40; >40 min/d), fish consumption (<1; 1–2; 2–3; >3 servings/wk), quartiles of meat and whole grain consumption (servings/d), and dichotomous for diabetes mellitus, hypertension, hypercholesterolemia, and cardiovascular diseases (history of angina pectoris, myocardial infarction, ischemic stroke, or heart failure).

Oxidative stress, an imbalance in the production and reduction of reactive oxygen species and reactive nitrogen species has been observed to promote inflammation, a fundamental process in AAA pathophysiology.^{12,28} Furthermore, reactive oxygen species and reactive nitrogen species have been found to be increased in human AAA tissue¹³ and suggested to contribute to AAA formation through smooth muscle cell apoptosis,^{14–16} matrix proteolysis,¹⁷ increased mechanical forces attributable to hypertension,²⁹ and the recruitment of cytokines and other proinflammatory cells.^{30,31}

Antioxidants have the potential to reduce oxidative stress, and, although no randomized trials have investigated the effect of such treatment on AAA development,¹⁸ it is biologically plausible that an antioxidant regimen through dietary intake could reduce the risk of developing AAA.

The absence of an inverse association between vegetables and AAA risk in the present study was therefore somewhat unexpected, because both fruit and vegetables are rich in

antioxidants. A possible explanation may be the different types of antioxidants found in fruits and vegetables that could have more or less effect on oxidative stress in the aortic wall. For instance, fruits are rich in flavonoids such as procyanidins, of which vegetables contain barely any.^{32,33} Procyanidins have recently been shown to inhibit the reactive oxygen species-generating enzyme NADPH oxidase activity in human endothelial cells of in vitro and ex vivo models.³⁴

Indeed, NADPH oxidase has been suggested to play a role in the pathogenesis of AAA in animal models,³⁵ possibly in humans,¹³ and as a potential target for AAA treatment.¹⁸

Smoking increases oxidative stress,²⁷ which could explain a possibly stronger association of fruit consumption with ruptured AAA among past and current smokers, whereas the more optimal redox balance among never smokers might explain the absence of significant findings in this group. It has also been suggested that the hemodynamic forces present in infrarenal AAA alone might further increase reactive oxygen

Table 4. Associations of Fruit Consumption With Risk of Abdominal Aortic Aneurysm by Rupture Status

	Quartiles of Consumption				P for Trend
	1	2	3	4	
Fruit, servings/d (median)	<0.7 (0.4)	0.7–1.2 (1.0)	1.3–2.0 (1.6)	>2.0 (2.8)	
Nonruptured AAA					
Cases/person-years	312/240 443	224/242 147	176/237 143	152/240 291	
Model 1, HR (95% CI)*	1 (Reference)	0.76 (0.64–0.90)	0.65 (0.53–0.78)	0.60 (0.49–0.75)	<0.001
Model 2, HR (95% CI)†	1 (Reference)	0.88 (0.74–1.05)	0.84 (0.69–1.02)	0.81 (0.65–1.01)	0.060
Ruptured AAA					
Cases/person-years	89/240 443	63/242 147	39/237 143	31/240 291	
Model 1, HR (95% CI)*	1 (Reference)	0.77 (0.56–1.08)	0.54 (0.36–0.80)	0.48 (0.31–0.74)	<0.001
Model 2, HR (95% CI)†	1 (Reference)	0.87 (0.63–1.22)	0.65 (0.44–0.97)	0.57 (0.36–0.89)	0.007

AAA indicates abdominal aortic aneurysm; CI, confidence interval; and HR, hazard ratio.

*Stratified by sex and adjusted for age by the use of restricted cubic splines.

†As in model 1 and additionally adjusted for educational level (primary school, high school, university), waist circumference (<80 cm, 80 to <88 cm, or ≥88 cm for women; and <94 cm, 94 to <102 cm, or ≥102 cm for men), smoking (current/past smokers with </≥ 20 pack-years, never smokers), sex-specific quartiles of alcohol consumption (g/wk) and energy intake (kcal/d), physical activity (<20; 20–40; >40 min/d), fish consumption (<1; 1–2; 2–3; >3 servings/wk), quartiles of vegetable, meat, and whole grain consumption (servings/d), and dichotomous for diabetes mellitus, hypertension, hypercholesterolemia, and cardiovascular diseases (history of angina pectoris, myocardial infarction, ischemic stroke, or heart failure).

species production,³⁶ serving as a possible explanation for the additional benefits of increased fruit consumption observed on the risk of ruptured AAA and repair of nonruptured AAA. However, the observational nature of this study does just allow for speculative explanations to observed results, and the assemblage of bioactive phytochemicals contained in fruits and vegetables probably could have many more effects on vascular disease than just oxidative stress.

Although the null findings of total vegetable consumption with risk of AAA in this study may seem surprising, the results are highly consistent with previous research on cardiovascular-related morbidity such as CVD,³⁷ stroke,^{38,39} and peripheral artery disease,⁴⁰ which has shown none to small inverse associations with vegetable consumption. No previous

study has reported results separately for fruit and vegetable consumption in relation to AAA risk; however, 1 study has investigated the association with a combined consumption of fruit and vegetables.¹⁹ In that study, estimates for several categories of consumption (daily, 4–5 and 2–3 servings/wk, and 2–4 servings/mo) were only age-adjusted, whereas, in the multivariable adjusted model, combined fruit and vegetable consumption was dichotomized into >3 or <3 times per week. In this study population, however, only 543 participants had a combined consumption less than that level. Although the study by Kent et al¹⁹ is unique in being performed on a very large number of participants (3.1 million from the Life Line Screening), its value for etiologic research is somewhat limited by the fact that it has a cross-sectional design.

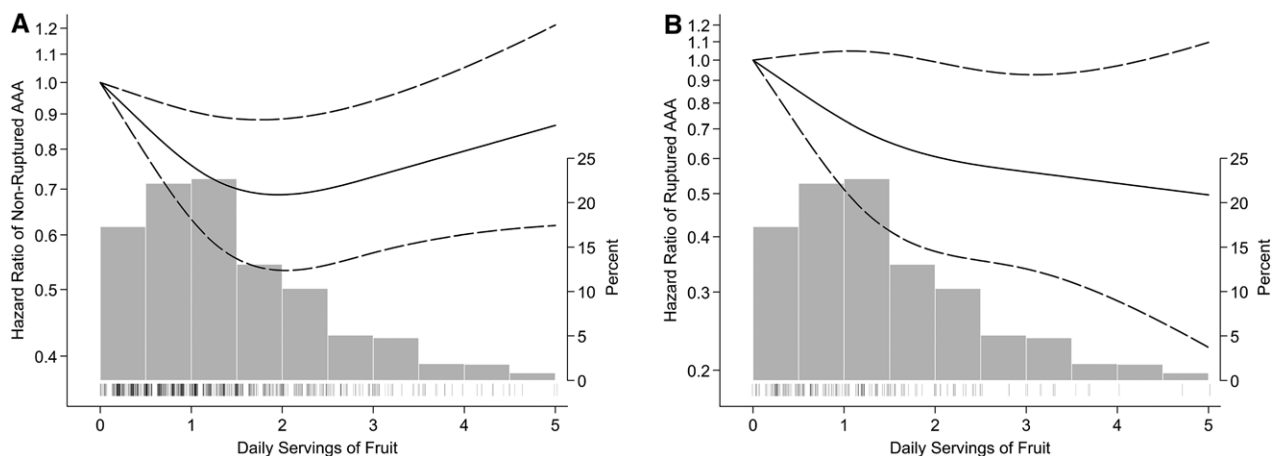


Figure. Adjusted hazard ratio of nonruptured (A) and ruptured (B) abdominal aortic aneurysm (AAA), associated with daily consumption of fruit among 44 317 men in the Cohort of Swedish Men and 36 109 women in the Swedish Mammography Cohort, 1998–2010. Data were fitted by the use of a Cox proportional hazards model with restricted cubic splines with 3 knots (0.35, 1.2, and 3.0 servings/d) of the distribution of fruit consumption. Estimates were adjusted for the same variables as model 2 in Table 4. Probability values for nonlinearity were 0.004 and 0.36 for nonruptured and ruptured AAA, respectively. Dashed lines represent 95% confidence limits. Zero daily servings served as reference. The vertical axis is on a log scale. Tick marks represent the positions of nonruptured (A) and ruptured (B) AAA cases. The histogram represents the percentage distribution of daily fruit servings (by steps of 0.5 daily servings) in the study population.

The strengths of the present study are the prospective design, its population-based large sample size, the completeness in register-based case ascertainment, and the detailed information on diet and potential confounders. Furthermore, there were no appreciable changes of results when conducting sensitivity analyses confined to CVD-free individuals, censoring of CVD during follow-up, exclusion of the first 3 years of follow-up, or in competing risk analyses. Additionally, limiting the possible influence of genetic variance in AAA development, the studied population was ethnically rather homogenous.

There are also limitations to this study. Data on fruit and vegetable consumption were collected by the use of a self-administered food-frequency questionnaire, which is likely to be affected by some degree of misclassification and may, furthermore, have changed during the follow-up time. Because of the prospective design, such potential sources of bias would, however, be nondifferential according to outcome status and most likely dilute any true associations. Moreover, a routine investigation of the aorta in these cohorts was not performed. Hence, the presence of asymptomatic AAA among participants not classified as cases cannot be ruled out. Contemporary screening studies have reported a prevalence of AAA among 65-year-old men in the study area of 2.2%.¹ However, the prevalence of AAA over 55 mm, requiring surgery, was only 0.1%, and even less among women.⁵ Such marginal underdetection of asymptomatic, clinically relevant AAA would most likely not affect HR estimates substantially. Furthermore, sub-analyses of rupture as outcome are most likely not affected by underdetection.

In conclusion, these results showed that a consumption of fruit, but not vegetables, was associated with a decreased risk of AAA, and that this reduction in risk was even more pronounced for the risk of ruptured AAA. A diet high in fruits may help to prevent many vascular diseases, and this study provides evidence that a lower risk of AAA will be among the benefits.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Abdominal aortic aneurysm (AAA) is an understudied vascular entity, and there is a need to identify modifiable factors associated with the disease. Smoking is a crucial risk factor, and smoking cessation has been shown to be the most important intervention to reduce rupture risk and to postpone surgical intervention among AAA patients. In this prospective cohort of 80 000 men and women, a high consumption of fruit, but not vegetables, was found to be associated with a decreased risk of developing AAA, especially ruptured AAA. Although the AAA cases were identified through high-quality registers, and not with general ultrasound screening of all participants, the pathophysiology is likely to be similar regardless the manner of detection. Further studies are needed to see whether a healthy diet could also decrease AAA growth rate among patients with screening-detected disease. In the meantime, “some apples a day seems to keep the surgeon away.”