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Fruit and vegetable intake and risk of acute coronary syndrome

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Prospective epidemiological studies have reported that a higher fruit and vegetable intake is associated with a lower risk of CHD. The aim of the present study was to examine associations between fruit and vegetable consumption, in particular the subgroupings citrus fruits, apples and cruciferous vegetables, and the risk of acute coronary syndrome (ACS). During a median follow-up of 7·7 years, 1075 incident ACS cases were identified among 53 383 men and women, aged 50–64 years at recruitment into the Diet, Cancer and Health cohort study in 1993–7. Fruit and vegetable intake was estimated from a validated FFQ, and ACS incidence rate ratios (IRR) were estimated using Cox proportional hazards models. Overall, a tendency towards a lower risk of ACS was observed for both men and women with higher fruit and vegetable consumption. For men, we found an inverse association for apple intake (IRR per 25 g/d: 0·97; 95 % CI 0·94, 0·99). This association was also seen among women, albeit borderline significant. However, a higher risk was seen among women with higher fruit juice intake (IRR per 25 g/d: 1·04; 95 % CI 1·00, 1·08). The present results provide some support for previously observed inverse associations between fresh fruit intake, particularly apples, and ACS risk.

Fruits: Vegetables: CHD

A higher consumption of fruits and vegetables has been associated with a lower risk of CHD in several epidemiological studies[1–5]. Furthermore, two recent meta-analyses have reported an inverse association between fruit and vegetable consumption and the risk of CHD[6,7].

Several mechanisms may explain the possible cardioprotective qualities of fruit and vegetables, including those concerning antioxidants, dietary fibre and cholesterol-lowering effects[8]. The biological mechanisms behind these effects are not entirely clear and are likely to be both multi-fold and interconnected. Most studies have not examined the effects of specific types of fruits and vegetables; in addition, studies frequently examine proxies of fruit and vegetable intake, such as antioxidant intake[2]. Furthermore, CVD has often been investigated without discriminating between CHD and cerebrovascular disease.

In the present study, we focused solely on CHD events. Thus, we investigated the associations between total fruit and vegetable intake and of specific fruit and vegetable groupings in relation to the risk of acute coronary syndrome (ACS), which is the composite of unstable angina pectoris, myocardial infarction and cardiac arrest. Investigated food items were selected *a priori*, and two fruit groupings of particular interest were citrus fruits, as lowered risk for citrus fruits was seen in the PRIME (Prospective Epidemiological Study of Myocardial Infarction) study[1] as well as apples due to their possible cholesterol-lowering properties[9]. Furthermore, fruit juices were examined separately, as they lack fibre, are less satiating and have a high sugar content. Juice has in the Nurses' Health Study been linked to a higher risk of diabetes mellitus, which is an important risk factor for CHD[10]. Cruciferous vegetables were also of particular interest, as they have been found to be inversely associated with the risk of CHD[2,11], presumably due to their content of isothiocyanates.

Methods

The present study is based on data from the prospective Danish Diet, Cancer and Health cohort study. A total of 57 053 men and women were enrolled into the cohort in 1993–7 and were included if they fulfilled the following criteria: aged between 50–64 years, born in Denmark and no previous cancer diagnosis in the Danish Cancer Registry.

A detailed FFQ and lifestyle questionnaire were filled in by each participant. Development and validation of the FFQ are

Abbreviations: ACS, acute coronary syndrome; IRR, incidence rate ratio.

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described elsewhere[12,13]. The FFQ contained questions regarding 192 food and beverage items and was developed to obtain information on the participants' habitual diet during the preceding year. Biological and anthropometric measurements were taken including height (m) and weight (kg), from which BMI was calculated (kg/m^2). A thorough description of data collection has been published previously[14].

Participant exclusions

The present cohort was originally established to investigate cancer; thus, individuals with a prevalent diagnosis of cancer at study enrolment (*n* 564) were excluded from the present study. While the present study concerns heart disease, these individuals are always removed from studies done in the cohort. Furthermore, a previous diagnosis of ACS at baseline was cause for exclusion (*n* 1013). Also, individuals with a diagnosis of diabetes mellitus at baseline as determined from the National Diabetes Register were excluded due to potential effect modification, which could not be explored due to low numbers, as well as potential dietary changes after diagnosis and treatment (*n* 1106). After exclusion due to ACS or diabetes mellitus, 54 370 individuals remained in the study. Further reasons for exclusions included missing medical information (*n* 123), an incomplete lifestyle questionnaire (*n* 42) and missing information on potential confounders (*n* 759) or dietary variables (*n* 63). A total of 53 383 individuals were ultimately included in the study.

Follow-up and ascertainment of acute coronary syndrome cases

The participants in the cohort were linked to the Central Population Registry for information on vital status and emigration. Information on ACS incidence was obtained by linkage of the Central Population Registry number of each participant to the National Patient Registry and the Cause of Death Registry. Each individual was followed for primary ACS occurrence from date of entry until censoring, which included date of event (fatal or non-fatal ACS), death of another cause, migration or 31 December 2003. Incident cases of fatal or non-fatal ACS in the cohort were identified and defined according to the International Classification of Diseases (ICD) eighth revision (ICD-8 diagnosis codes 410–410·99 and 427·27) until 31 December 1993 and subsequently by ICD tenth revision (ICD-10 diagnosis codes I20·0, I21·0–I21·9 and I46·0–I46·9). There have been considerable changes in the definition of myocardial infarction since 2000 and therefore since the beginning of the Danish Diet, Cancer and Health study, and in order to minimise potential discrepancies in ACS ascertainment, each case was individually validated through review of medical records. In fact, more than 80 % of the cases were diagnosed using very sensitive biomarkers (troponins and creatine kinase MB (CK-MB)). When cases ascertained before or after 2000 were compared, no significant differences in positive predictive value were seen, thus ensuring correct ACS diagnoses[15]. During a median follow-up of 7·7 years, 1075 cases were identified.

Dietary assessment

Intake of fruits and vegetables was estimated based on the FFQ completed at baseline. Daily intake was calculated for each participant using the software program FoodCalc[16] and specifically developed standardised recipes and portion sizes. For fruit, only intake of fresh fruit (as indicated on the FFQ) was examined, while vegetable intake also included estimated contributions from recipes. This was done to ensure maximal validity of the fruit groupings, since contributions from recipes for fruit intake are likely to be minimal. The groupings used for fruit were: total fruits, citrus fruits (consisting of oranges, mandarins, grapefruits), other fruits (pears, bananas, nectarines/peaches, strawberries, kiwis, melons), apples (all sorts) and fruit juice (orange, grape). For vegetables, groupings were: total vegetables, cruciferous vegetables (broccoli, cauliflower, Brussels sprouts, kale, cabbages, pointed cabbages) and other vegetables (including types of leafy vegetables, fruiting vegetables, root vegetables, mushrooms, onions and stalk vegetables/sprouts).

Statistical analyses

Analyses of the associations between fruit and vegetable intake and the incidence rate ratios (IRR) of ACS were based on Cox proportional hazards models (including time-dependent variables) using age as the time axis to ensure that the estimation procedure was based on comparisons of individuals at the same age. Time-under-study was included as the time-dependent variable and was modelled by a linear spline with a boundary at 1, 2 and 3 years after entry into the cohort study to allow the rate to change with time. The proportional hazards assumption was for each categorical variable evaluated graphically using a Kaplan–Meier plot. Two-sided 95 % CI for the IRR were calculated on the basis of Wald's test of the Cox regression parameter, i.e. on the log rate ratio scale. Analyses were performed separately for men and women.

All quantitative variables were entered linearly into Cox models after linear spline testing, as this is biologically more plausible than the step functions corresponding to categorisation; furthermore, this approach increases the power of the analysis[17]. The exposure variables were included as a linear variable in a specific unit (g/d), which was determined based on the interquartile range and a realistic difference in consumption. Therefore, 100 g/d for total fruits and total vegetables and 25 g/d for subgroups of fruits and vegetables were used (25 g corresponds approximately to a quarter of a medium-sized apple). Quartile analyses were also performed, although tertiles were used for apples to account for the categories provided by the questionnaire. Categories were based on the baseline intake in the cohort for men and women, respectively.

Age-adjusted IRR (presented as crude) were examined along with two multivariable models. In the first multivariable model, intake was mutually adjusted as well as adjusted for baseline values of potential risk factors for ACS: BMI (linear), length of school education (≤ 7 years, 8–10 years and >10 years), smoking (never, former, current (1–14, 15–25 or >25 g tobacco per d)), alcohol intake (linear spline with a boundary at 10 g/d), alcohol abstainers and physical activity (≤ or > 3·5 h per week and non-active), intake of saturated fats (g/d) and of whole grains (g/d). The second multivariable model was additionally adjusted for total serum cholesterol levels (mmol/l) and systolic blood pressure (mmHg).

The PHREG procedure in SAS (release 9.1; SAS Institute Inc., Cary, NC, USA) on a TextPad platform was used for the statistical analyses on incidence, while the LIFETEST procedure in SAS was used to test the proportional hazards assumption.

Results

The study population consisted of 53 % (*n* 28 318) women. However, a substantially larger proportion of the cases occurred in men (*n* 820; 76 %). Table 1 shows selected CHD risk factors by quartile of total fruit and vegetable intake for men and women. Men with the highest intakes of fruits and vegetables were more likely to have a higher education, to be physically active and to have slightly lower total cholesterol levels. Also, they had a lower alcohol and tobacco consumption, higher whole-grain consumption, but also slightly higher consumption of saturated fats than those with the lowest intakes of fruits and vegetables. Overall, the same distribution pattern was seen for women.

Intakes of total fruits and vegetables and of citrus fruits, other fruits, fruit juice, apples, other vegetables and cruciferous vegetables are presented in Table 2. In general, men had a lower intake of fruits and vegetables than women. Male cases had a lower intake of all groupings of fruits and vegetables than the cohort. Fruit juice intake, however, was identical among cases and the cohort. The same pattern was evident for women except for apples, where female cases and the cohort had the same median apple intake of 54 g/d.

Intake of fruits and vegetables combined per 100 g/d was borderline significantly associated with a lower risk of ACS for both men and women in the continuous analyses (results not shown in a Table). For men, the crude IRR was 0·91 (95 % CI 0·87, 0·95), while for women the estimate was 0·88 (95 % CI 0·82, 0·94). However, the estimates were attenuated after multivariable adjustment and were borderline significant (for men, IRR 0·97 (95 % CI 0·93, 1·01) and for women, IRR 0·95 (95 % CI 0·89, 1·01)).

Table 3 presents the association between fruit consumption and the risk of ACS for both men and women. Overall, the crude models indicated inverse associations between intake of total fruits as well as of the various groupings in relation to ACS risk. However, after multivariable adjustment, only few associations persisted. Higher total fruit intake was associated with a non-significant 4 % lower risk of ACS for men (IRR per 100 g/d: 0·96; 95 % CI 0·91, 1·02). Apple intake was likewise associated with a lower risk of ACS (IRR per 25 g/d: 0·97; 95 % CI 0·94, 0·99). The categorical estimates showed lower risk for those in the top tertile of apple intake; the IRR for the top tertile was 0·78 (95 % CI 0·64, 0·95) in the multivariable-adjusted analyses. No associations were seen for intake of citrus or other fruits.

Similar results were seen among women (Table 3). Crude models indicated inverse associations between fruit groupings and ACS risk, but most associations did not persist after adjustment. However, intake of total fruits was borderline significantly associated with a lower risk of ACS (IRR per 100 g/d: 0·93; 95 % CI 0·85, 1·01), and apple intake was associated with a 3 % lower risk of ACS (IRR per 25 g/d: 0·97; 95 % CI 0·93, 1·01). No associations were seen for intake of citrus or other fruits. Intake of fruit juice was associated with a 4 % higher risk of ACS (IRR per 25 g/d: 1·04; 95 % CI 1·00, 1·09). No fruit groupings were associated with statistically significant results in the adjusted models when examined categorically.

Table 4 presents the associations between total vegetable intake and ACS risk for both men and women. For total and cruciferous vegetable intake among men, significantly lower risks were seen in the crude models, but these did not persist after adjustment (IRR per 100 g/d for total vegetables: 0·98; 95 % CI 0·90, 1·07; IRR per 25 g/d for cruciferous vegetables: 1·05; 95 % CI 0·91, 1·22). When the associations were examined categorically, intake of total vegetables was associated with lower risk in the top quartile of intake, but this estimate was no longer significant after adjustment (IRR 0·93; 95 % CI 0·75, 1·16). Among women, total and cruciferous vegetable intakes were both associated with significantly lower risk in the crude estimates, but, again, these results were attenuated and non-significant in the adjusted models (IRR per 100 g/d for total vegetables: 0·97; 95 % CI 0·84, 1·13; IRR per 25 g/d for cruciferous vegetables: 0·99; 95 % CI 0·76, 1·29). No associations were seen for intake of other vegetables for either men or women.

Discussion

We observed an inverse association between apple intake and risk of ACS for both men and women. Furthermore, fruit juice consumption was associated with a higher ACS risk among women. Total fruit intake also indicated a protective association with ACS, but the associations were borderline significant. For intake of vegetables no consistent associations were observed.

The nearly complete follow-up (99·6 %) of this population-based prospective study, as well as the large number of cases, are among the strengths of the present study. Exposure information was obtained before diagnosis of ACS, and the detailed information regarding fruit and vegetable intake made it possible to look at groupings of fruits and vegetables of interest; this was done using both linear and categorical estimates. It was possible to examine apples as a separate group, which is highly relevant, as this fruit is a major contributor to fruit intake in Denmark. Apple intake was specified in the FFQ, and intake is thus based on fresh fruit intake and not estimated from recipes. Furthermore, the individual validation of all ACS cases ensured that only those diagnoses that truly were an ACS event were included; thus, information bias is not likely to have affected the study results. A limitation of the present study is potential over-reporting of fruits and vegetables. It is conceivable that intake of fruits and vegetables were over-reported, as they are often perceived to be health-promoting, but it seems unlikely that some groupings were over-reported in the FFQ to a higher degree than others. Information on all fruit and vegetable types was collected using identical questions with the same twelve possible answer categories. It is, however, possible that intake data on fruit are more valid than those of vegetables, as only intake from

Table 1. Baseline characteristics for the Diet, Cancer and Health cohort (men and women) for selected CHD risk factors according to quartiles (Q) of total fruit and vegetable intake
(Median values and 5th and 95th percentiles within each category or percentages)

	Men										Women									
	Cohort (*n* 25 065)		Q1		Q2		Q3		Q4		Cohort (*n* 28 318)		Q1		Q2		Q3		Q4	
Range of intake (g/d)			>0 to ≤ 180		>180 to ≤ 273		>273 to ≤ 392		>392				>0 to ≤ 237		>237 to ≤ 350		>350 to ≤ 497		>497	
Variable	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %
Age (years)	55	50–64	56	50–64	55	50–64	55	50–64	55	50–64	56	50–64	56	50–64	56	50–64	56	50–64	56	50–64
Education (%)																				
≤ 7 years	34		44		34		30		29		31		38		32		27		27	
8–10 years	42		41		45		42		39		50		50		51		51		50	
> 10 years	24		15		21		28		32		19		12		17		22		23	
BMI (kg/m^2)	26	21–33	26	21–33	26	21–33	26	22–33	26	22–33	25	20–34	25	20–34	25	20–33	25	20–34	25	20–34
Smoking status (%)																				
Never	26		19		27		28		31		44		35		45		47		49	
Former	34		27		32		38		41		23		18		24		25		28	
Current																				
1–14 g tobacco/d	11		10		11		11		10		15		17		15		15		13	
15–24 g tobacco/d	17		25		19		15		11		15		25		14		12		9	
25+g tobacco/d	11		19		11		8		7		3		5		2		1		1	
Alcohol intake (g/d)*	20	2–81	22	2–91	20	3–82	20	3–70	18	2–67	10	1–42	10	1–53	10	1–43	10	1–40	8	1–37
Abstainers (%)	1·7		2·2		1·5		1·3		1·9		2·6		3·6		2·1		1·9		2·9	
Physical activity (%)																				
Not physically active	21		31		22		17		14		16		23		16		13		11	
≤ 3·5 h per week	44		44		46		47		41		47		50		50		47		41	
>3·5 h per week	35		25		32		36		45		37		27		34		40		48	
Total cholesterol (mmol/l)	5·9	4·3–7·9	6·0	4·4–8·0	5·9	4·3–7·9	5·9	4·3–7·9	5·8	4·2–7·8	6·2	4·5–8·4	6·3	4·6–8·5	6·2	4·5–8·5	6·1	4·5–8·3	6·1	4·5–8·3
Systolic blood pressure (mmHg)	140	114–176	141	115–179	140	113–176	139	114–176	140	114–176	136	106–175	136	107–176	135	106–176	135	106–172	135	106–174
Saturated fat intake (g/d)	36	20–61	34	19–57	36	20–59	37	20–61	38	20–65	28	15–48	26	14–48	27	15–46	28	15–49	29	14–52
Whole-grain intake (g/d)	130	41–267	112	22–242	130	42–263	144	58–267	163	61–300	113	31–221	98	25–213	110	33–214	116	42–234	124	42–252

* Alcohol intake among drinkers.

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Table 2. Baseline intake of fruits and vegetables for the Diet, Cancer and Health cohort (men and women) and acute coronary syndrome cases
(Median values with 5th and 95th percentiles within each category)

	Men				Women			
	Cohort (*n* 25 065)		Cases (*n* 820)		Cohort (*n* 28 318)		Cases (*n* 255)	
Variable (g/d)	Median	5–95 %	Median	5–95 %	Median	5–95 %	Median	5–95 %
Total fruit and vegetables (excluding juice)	273	84–646	247	65–598	350	114–789	305	84–710
Total fruit (excluding juice)	112	15–411	97	12–401	168	28–506	149	19–439
Apples	54	2–313	18	2–125	54	2–313	54	2–125
Citrus fruit	11	2–101	9	2–101	20	3–118	17	2–111
Other fruit	35	7–162	32	6–167	61	11–240	51	9–223
Fruit juice*	8	0–100	8	0–100	9	0–101	8	0–250
Total vegetables (excluding juice)	148	47–328	129	37–314	167	50–371	139	42–331
Cruciferous vegetables	14	2–43	13	2–42	16	3–45	13	2–38
Other vegetables	131	41–296	115	33–287	149	45–340	121	37–296

* The range of fruit juice intake is among consumers but has been rounded off to the nearest whole number. Minimum intake for both sexes was 0·01 g fruit juice/d.

fresh fruits and juice (i.e. what was actually reported in the FFQ) was included for analysis, whereas for vegetables, intake estimated from recipes was also included.

The associations were examined separately by sex, as men have a higher risk of CHD, and risk factors differ to some extent between the sexes. Furthermore, a range of potential confounders, primarily chosen based on literature review, were adjusted for in multivariable models. Estimates changed markedly, when the analyses were mutually and multivariable adjusted. Specifically, we adjusted for various known risk factors of CHD as well as dietary factors possibly associated with fruit and vegetable intake. Residual confounding can thus not be excluded, and more detailed control may further attenuate the observed associations. In a second multivariable model, we adjusted for total cholesterol and systolic blood pressure, as both are risk factors for CHD but are also possible intermediate factors in the causal pathway between fruit and vegetable intake and ACS risk. As mentioned earlier, it is hypothesised that an effect on ACS risk from, for example, apples might be due to a cholesterol-lowering effect. However, the association between intake of apples and risk of ACS was also present after control for the potential intermediate variables, indicating that other mechanisms may be important in explaining the observed association.

Overall, the present results indicate associations that are consistent with those observed in similar cohort studies. Two recent meta-analyses have summarised the current evidence from all eligible cohort studies on risk of CHD and fruit and vegetable intake, and both reported an inverse association. In the meta-analysis by Dauchet *et al.* [6], a relative risk of 0·96 (95 % CI 0·93, 0·99) per portion per d for fruit and vegetable intake overall was found, and a more marked decrease for fruit consumption alone was seen (relative risk 0·93; 95 % CI 0·89, 0·96). Similarly, He *et al.* [7] found a pooled relative risk of 0·83 (95 % CI 0·77, 0·89) for an intake of fruit and vegetables more than five servings/d.

In the present study, apples were found to be associated with a lower risk of ACS. Likewise, a lower risk of CHD mortality in association with apple intake was seen in a Finnish cohort study by Knekt *et al.* [18] where the relative risks between the highest and lowest quartiles of apple intake were 0·57 (95 % CI 0·36, 0·91) and 0·81 (95 % CI 0·61, 1·09) for women and men, respectively[18]. An American cohort study including 35 000 women further found that the phytochemicals catechin and epicatechin from apples and tea were strongly inversely related to CHD mortality[19]. The results seen for apples in the present study could potentially be due to a lowering of cholesterol, as apples have been found to have serum cholesterol-lowering properties in several rodent studies[20–22]. Human intervention studies are sparse; however, one study investigating the effects of fresh apple consumption on cholesterol levels found reduced total plasma cholesterol and increased HDL-cholesterol. On average, a reduction exceeding 10 % of their starting plasma cholesterol level was observed among the study participants[23]. Furthermore, a Japanese intervention study on intake of supplements containing apple polyphenols found lowered levels of total and LDL-cholesterol[9].

The other groupings that were investigated separately in the present study were cruciferous vegetables and citrus fruits. Cruciferous vegetables have a high content of isothiocyanates and have been found in other studies to be inversely associated with CHD[2,11]. In the present study, no consistent associations were observed, which may in part be due to the rather low intake of cruciferous vegetables in the cohort. Citrus fruits have in the PRIME (Prospective Epidemiological Study of Myocardial Infarction) study been found to be associated with a reduced CHD risk for two populations in France and Northern Ireland[1]. An inverse association was likewise seen in the present study for both men and women with the highest intake of citrus fruits; however, in the adjusted models, the results were no longer statistically significant.

Juice intake was found to be associated with a 4 % higher risk of ACS among women. As mentioned previously, juice intake was in the Nurses' Health Study associated with a higher risk of diabetes mellitus, which is a strong risk factor for CHD. We excluded participants with prevalent diabetes mellitus, thus presumably eliminating this as an effect modifier. However, the possibility remains that undiagnosed, preclinical diabetes mellitus in the cohort could account for the observed risk increase among women. The higher risk of diabetes mellitus seen in the Nurses' Health Study was in fact seen among women[10]. In contrast, juice intake was not associated with diabetes risk in the Nurses' Health Study II; however, the authors found that increasing intake was associated with larger weight gain, which is also a risk

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Table 3. Risk of acute coronary syndrome among men and women in the Diet, Cancer and Health cohort according to daily intake of total fruit (per 100 g/d), apples, citrus fruits, other fruits or juice (per 25 g/d) or by quartile (Q)*

(Incidence rate ratios (IRR) and 95 % confidence intervals)

	Men								Women							
	Q2		Q3		Q4		Linear		Q2		Q3		Q4		Linear	
Variable (g/d)	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI
Total fruit																
Range (g/d)	> 50 to ≤ 112		> 112 to ≤ 188		> 188		Per 100 g/d		> 95 to ≤ 168		> 168 to ≤ 272		> 272		Per 100 g/d	
Crude model†	0·85	0·70, 1·02	0·72	0·60, 0·88	0·75	0·62, 0·91	0·92	0·86, 0·97	0·76	0·55, 1·05	0·70	0·50, 0·99	0·60	0·42, 0·85	0·87	0·80, 0·96
Multivariable model 1‡	0·96	0·80, 1·16	0·88	0·72, 1·08	0·93	0·75, 1·14	0·96	0·90, 1·02	0·95	0·68, 1·33	0·93	0·65, 1·32	0·81	0·55, 1·18	0·93	0·85, 1·01
Multivariable model 2§	0·98	0·81, 1·18	0·89	0·73, 1·09	0·93	0·75, 1·14	0·96	0·91, 1·02	0·94	0·67, 1·32	0·92	0·65, 1·30	0·80	0·54, 1·17	0·93	0·85, 1·01
Apples																
Range (g/d)	> 18 to ≤ 98		> 98		–		Per 25 g/d		> 18 to ≤ 54		> 54		–		Per 25 g/d	
Crude model†	0·80	0·67, 0·94	0·69	0·58, 0·83	–	–	0·95	0·93, 0·98	0·91	0·67, 1·23	0·68	0·50, 0·92	–	–	0·94	0·90, 0·98
Multivariable model 1‡	0·89	0·75, 1·05	0·78	0·64, 0·94	–	–	0·97	0·94, 0·99	1·17	0·86, 1·60	0·94	0·67, 1·30	–	–	0·97	0·93, 1·01
Multivariable model 2§	0·89	0·75, 1·06	0·78	0·64, 0·95	–	–	0·97	0·94, 0·99	1·16	0·85, 1·59	0·93	0·67, 1·29	–	–	0·97	0·93, 1·01
Citrus fruits																
Range (g/d)	> 5 to ≤ 11		> 11 to ≤ 43		> 43		Per 25 g/d		> 9 to ≤ 19		> 19 to ≤ 54		> 54		Per 25 g/d	
Crude model†	0·86	0·71, 1·04	0·75	0·62, 0·92	0·82	0·68, 1·00	0·97	0·93, 1·02	0·57	0·40, 0·82	0·73	0·52, 1·01	0·63	0·44, 0·89	0·95	0·89, 1·01
Multivariable model 1‡	0·94	0·77, 1·14	0·86	0·70, 1·06	1·02	0·82, 1·26	1·00	0·95, 1·05	0·73	0·51, 1·05	1·00	0·71, 1·41	0·89	0·61, 1·31	0·98	0·92, 1·05
Multivariable model 2§	0·96	0·79, 1·16	0·87	0·71, 1·07	1·00	0·81, 1·24	0·99	0·95, 1·04	0·71	0·49, 1·02	0·98	0·70, 1·38	0·85	0·58, 1·25	0·98	0·92, 1·04
Other fruits																
Range (g/d)	> 18 to ≤ 34		> 34 to ≤ 72		> 72		Per 25 g/d		> 29 to ≤ 61		> 61 to ≤ 117		> 117		Per 25 g/d	
Crude model†	0·76	0·63, 0·93	0·74	0·61, 0·90	0·82	0·68, 0·99	0·99	0·96, 1·02	0·85	0·61, 1·18	0·77	0·64, 0·91	0·80	0·67, 0·96	0·97	0·93, 1·01
Multivariable model 1‡	0·88	0·72, 1·07	0·89	0·73, 1·09	1·05	0·85, 1·29	1·02	0·99, 1·05	0·96	0·68, 1·34	0·83	0·58, 1·19	1·03	0·71, 1·48	0·99	0·95, 1·04
Multivariable model 2§	0·89	0·73, 1·08	0·90	0·74, 1·10	1·07	0·87, 1·32	1·02	0·99, 1·05	0·97	0·70, 1·36	0·84	0·58, 1·20	1·05	0·73, 1·51	0·99	0·95, 1·04
Fruit juice																
Range (g/d)	> 2 to ≤ 8		> 8 to ≤ 43		> 43		Per 25 g/d		> 2 to ≤ 8		> 8 to ≤ 43		> 43		Per 25 g/d	
Crude model†	0·85	0·68, 1·06	0·77	0·64, 0·91	0·80	0·67, 0·96	0·99	0·96, 1·03	0·68	0·44, 1·04	0·73	0·53, 1·00	0·76	0·56, 1·04	1·03	0·99, 1·08
Multivariable model 1‡	1·02	0·81, 1·28	0·93	0·78, 1·12	1·03	0·85, 1·24	1·01	0·98, 1·05	0·89	0·57, 1·36	0·92	0·66, 1·27	1·01	0·73, 1·40	1·04	1·00, 1·09
Multivariable model 2§	1·01	0·81, 1·27	0·92	0·77, 1·10	1·03	0·85, 1·24	1·01	0·98, 1·04	0·87	0·56, 1·34	0·90	0·65, 1·24	1·01	0·73, 1·41	1·04	1·00, 1·08

* Q1 is the reference group (IRR = 1) and is not shown. Tertiles were used for apples.

† Crude model: IRR among consumers.

‡ Multivariable model 1: mutually adjusted and adjusted for potential confounders – BMI, length of school education (low, medium, high), smoking (never, former, current (1–14, 15–25, > 25 g tobacco per d)), alcohol intake (linear spline with a boundary at 10 g/d), alcohol abstainers and physical activity (≤ or > 3·5 h per week and non-active), intake of saturated fats (g/d) and whole grains (g/d).

§ Multivariable model 2: as model 1 and further adjusted for total cholesterol and systolic blood pressure.

Table 4. Risk of acute coronary syndrome among men and women in the Diet, Cancer and Health cohort according to daily intake of total vegetables (per 100 g/d), cruciferous or other vegetables (per 25 g/d) or by quartile (Q)*

(Incidence rate ratios (IRR) and 95 % confidence intervals)

	Men								Women							
	Q2		Q3		Q4		Linear		Q2		Q3		Q4		Linear	
	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI
Total vegetables																
Range (g/d)	> 96 to ≤ 148		> 148 to ≤ 211		> 211		Per 100 g/d		> 110 to ≤ 167		> 167 to ≤ 237		> 237		Per 100 g/d	
Crude model†	0·90	0·75, 1·08	0·77	0·64, 0·93	0·64	0·52, 0·78	0·83	0·76, 0·90	0·87	0·64, 1·19	0·57	0·40, 0·82	0·60	0·42, 0·85	0·77	0·67, 0·89
Multivariable model 1‡	1·06	0·88, 1·27	1·01	0·83, 1·23	0·91	0·73, 1·13	0·97	0·88, 1·06	1·15	0·84, 1·58	0·88	0·61, 1·28	1·05	0·71, 1·55	0·96	0·83, 1·11
Multivariable model 2§	1·06	0·88, 1·28	1·03	0·85, 1·26	0·93	0·75, 1·16	0·98	0·90, 1·07	1·15	0·84, 1·58	0·88	0·61, 1·28	1·09	0·74, 1·61	0·97	0·84, 1·13
Cruciferous vegetables																
Range (g/d)	> 7 to ≤ 14		> 14 to ≤ 24		> 24		Per 25 g/d		> 8 to ≤ 16		> 16 to ≤ 25		> 25		Per 25 g/d	
Crude model†	0·81	0·67, 0·98	0·79	0·66, 0·96	0·78	0·64, 0·94	0·86	0·75, 0·98	0·83	0·60, 1·16	0·80	0·58, 1·11	0·68	0·48, 0·97	0·73	0·57, 0·94
Multivariable model 1‡	0·97	0·80, 1·19	1·03	0·84, 1·26	1·09	0·87, 1·36	1·06	0·92, 1·23	1·08	0·76, 1·52	1·14	0·80, 1·62	1·10	0·74, 1·66	0·98	0·75, 1·28
Multivariable model 2§	0·98	0·81, 1·19	1·03	0·84, 1·26	1·08	0·87, 1·35	1·05	0·91, 1·22	1·09	0·77, 1·54	1·15	0·80, 1·64	1·12	0·75, 1·68	0·99	0·76, 1·29
Other vegetables																
Range (g/d)	> 84 to ≤ 131		> 131 to ≤ 188		> 188		Per 25 g/d		> 97 to ≤ 149		> 149 to ≤ 215		> 215		Per 25 g/d	
Crude model†	0·86	0·72, 1·03	0·77	0·64, 0·92	0·62	0·51, 0·76	0·98	0·97, 0·99	0·86	0·63, 1·17	0·54	0·38, 0·78	0·58	0·40, 0·82	0·97	0·96, 0·99
Multivariable model 1‡	0·99	0·82, 1·19	0·97	0·79, 1·19	0·84	0·66, 1·07	0·99	0·98, 1·00	1·13	0·82, 1·56	0·84	0·57, 1·25	1·02	0·67, 1·56	0·99	0·98, 1·01
Multivariable model 2§	0·99	0·82, 1·20	0·99	0·81, 1·22	0·87	0·68, 1·10	1·00	0·99, 1·01	1·12	0·81, 1·54	0·85	0·57, 1·25	1·04	0·68, 1·60	1·00	0·98, 1·02

* Q1 is the reference group (IRR = 1) and is not shown.
† Crude model: IRR among consumers.
‡ Multivariable model 1: mutually adjusted and adjusted for potential confounders – BMI, length of school education (low, medium, high), smoking (never, former, current (1–14, 15–25, > 25 g tobacco per d)), alcohol intake (linear spline with a boundary at 10 g/d), alcohol abstainers and physical activity (≤ or > 3·5 h per week and non-active), intake of saturated fats (g/d) and whole grains (g/d).
§ Multivariable model 2: as model 1 and further adjusted for total cholesterol and systolic blood pressure.

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factor of CHD[24]. Furthermore, it might be that juice intake is associated with intake of other dietary factors that we did not correct for and thus represents an association with some other lifestyle or dietary factor.

In conclusion, the present study provides some support for an inverse association between a higher intake of fruit, specifically apples, and reduced risk of ACS. However, more research is needed to examine the biological mechanisms behind this association. Biomarker studies, such as metabolomics, would provide a novel and more accurate way of assessing disease risk in association with dietary intakes.

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The contributions of the authors were as follows: A. T. and K. O. collected the data; L. H. was the principal investigator and performed data analysis, wrote the manuscript and is the guarantor; L. O. D., A. O., J. C., A. T., E. B. S. and K. O. contributed to data analysis and to the writing of the manuscript.

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