

# Plasma vitamin C predicts incident heart failure in men and women in European Prospective Investigation into Cancer and Nutrition–Norfolk prospective study

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**Background** Fruit and vegetable intake has been associated with lower risk for cardiovascular risk factors and disease, but data on heart failure are sparse and inconsistent. The association of plasma vitamin C, a biomarker reflecting fruit and vegetable intake, with heart failure has not been studied.

**Methods** We examined the prospective association of plasma vitamin C concentrations with incident fatal and nonfatal heart failure events in apparently healthy 9,187 men and 11,112 women aged 39 to 79 years participating in the “European Prospective Investigation into Cancer and Nutrition” study in Norfolk.

**Results** The risk of heart failure decreased with increasing plasma vitamin C; the hazard ratios comparing each quartile with the lowest were 0.76 (95% CI 0.65-0.88), 0.70 (95% CI 0.60-0.81), and 0.62 (95% CI 0.53-0.74) in age- and sex-adjusted analyses (*P* for trend <.0001). Every 20 μmol/L increase in plasma vitamin C concentration (1 SD) was associated with a 9% relative reduction in risk of heart failure after adjustment for age, sex, smoking, alcohol consumption, physical activity, occupational social class, educational level, systolic blood pressure, diabetes, cholesterol concentration, and body mass index, with similar result if adjusting for interim coronary heart disease.

**Conclusions** Plasma vitamin C, a biomarker reflecting fruit and vegetable intake, was inversely associated with the risk of heart failure in this healthy population. This observation should be regarded as hypothesis generating for further prospective trials aimed at examining the effect of a diet rich in fruit and vegetables for prevention of heart failure. (*Am Heart J* 2011;162:246-53.)

There is increasing emphasis on preventing early stages of heart failure, with a stage A in the new classification of the American Heart Association including “at-risk” patients without any structural or functional cardiac abnormalities.<sup>1</sup> Although several risk factors for heart failure such as hypertension, diabetes, and coronary heart disease are well recognized, these appear responsible for only half of the incident cases in the population.<sup>2</sup> There are only few data available on the effect on heart failure of lifestyle factors such as dietary habits, which could be modified. Consumption of fruit and vegetable ( $\geq 5$  portions a day) is one of the most

prominent dietary recommendations for prevention of chronic diseases, but data on the risk for heart failure are sparse and inconsistent. Djousse et al<sup>3</sup> described a reduced lifetime risk of heart failure for consumption of fruit and vegetable in the Physicians' Health Study, whereas Nettleton et al<sup>4</sup> found no association in the Atherosclerosis Risk in Communities study.

This inconsistency may, in part, be because of the impact of measurement error in the assessment of fruit and vegetable consumption.<sup>5</sup> Use of a biomarker would help to resolve this issue. Plasma vitamin C concentration is a good candidate to act as a biomarker for fruit and vegetable consumption because in Western diets, fruit and vegetable consumption is the main source of vitamin C.<sup>5</sup> Plasma vitamin C concentration is more strongly related to fruit and vegetable intake than that of plasma carotenoids or vitamin E.<sup>6</sup>

The aim of this study was to investigate the prospective association between plasma vitamin C concentration and the risk of developing heart failure in a population of apparently healthy men and women and to compare this with the association of self-reported dietary fruit and vegetable intake.

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**Table I.** Population characteristics at baseline by quartiles of plasma vitamin C: EPIC-Norfolk study, 1993 to 2009

	Plasma vitamin C quartiles				
	1	2	3	4	P*
Men (n)	2222	2249	2301	2415	
Vitamin C (μmol/L)					<.0001
Mean (SD)	22.9 (8.0)	41.5 (3.7)	52.9 (3.1)	69.9 (11.6)	
Range	3 to <35	35 to <48	48 to <59	59-175	
Age (y)	59.4 (9.4)	58.5 (9.1)	57.9 (9.1)	57.9 (9.1)	<.0001
BMI (kg/m <sup>2</sup> )	26.8 (3.6)	26.8 (3.3)	26.4 (3.0)	25.7 (2.9)	<.0001
Waist-hip ratio	0.94 (0.06)	0.94 (0.06)	0.92 (0.06)	0.91 (0.06)	<.0001
Systolic BP (mm Hg)	140 (18)	138 (17)	136 (17)	135 (17)	<.0001
Diastolic BP (mm Hg)	85.7 (11.7)	85.0 (11.0)	84.2 (10.6)	83.0 (10.5)	<.0001
Total cholesterol (mmol/L)	6.03 (1.13)	6.07 (1.07)	6.05 (1.11)	5.97 (1.05)	.046
LDL cholesterol (mmol/L)	3.88 (0.98)	3.92 (0.94)	3.95 (0.99)	3.90 (0.94)	.35
HDL cholesterol (mmol/L)	2.00 (0.32)	1.22 (0.32)	1.24 (0.32)	1.28 (0.35)	<.0001
Serum glucose (mmol/L)	4.47 (2.00)	4.37 (1.87)	4.25 (1.56)	4.18 (1.45)	<.0001
CRP (mg/L)	4.1 (8.9)	2.9 (4.6)	2.4 (3.5)	2.0 (3.3)	<.0001
Alcohol intake (g/d)	11.7 (17.5)	12.0 (15.3)	12.1 (15.4)	13.7 (16.0)	<.0001
Fruit and vegetable intake (g/d)	307 (178)	391 (201)	432 (214)	460 (234)	<.0001
Hypertension (%) <sup>†</sup>	53.4	48.7	46.7	41.6	<.0001
Diabetes (%)	4.5	4.3	2.7	2.0	<.0001
Smoking ever (%)	75.0	63.6	61.0	60.5	<.0001
Vitamin C supplement (%)	1.1	2.5	3.7	11.8	<.0001
Occupational social class (%) <sup>‡</sup>					<.0001
I	4.9	7.2	9.1	9.7	
II	30.6	36.7	41.4	44.1	
III, nonmanual	12.8	12.2	12.0	12.2	
III, manual	31.0	27.3	22.9	20.6	
IV	16.1	13.9	12.1	11.6	
V	4.6	2.8	2.6	1.8	
Education					<.0001
No qualification	38.5	30.3	27.3	23.4	
O level	8.1	9.7	8.8	8.6	
A level	43.7	44.7	46.3	46.9	
Degree/higher	9.7	15.3	17.6	21.2	
Physical activity					<.0001
Inactive	35.4	29.4	28.4	23.7	
Mod inactive	23.3	25.9	23.7	25.2	
Mod active	21.7	23.1	23.2	25.9	
Active	19.7	21.6	24.7	25.2	
Women (n)	2762	2596	2781	2973	
Vitamin C (μmol/L)					<.0001
Mean (SD)	33.7 (10.9)	53.3(3.2)	63.7 (3.1)	81.8 (13.4)	
Range	3 to <48	48 to <59	59 to <70	70-242	
Age (y)	59.0 (9.5)	57.5 (9.4)	57.4 (9.0)	57.8 (9.0)	<.0001
BMI (kg/m <sup>2</sup> )	27.1 (4.8)	26.4 (4.2)	25.9 (4.0)	25.1 (3.5)	<.0001
Waist-hip ratio	0.81 (0.07)	0.79 (0.06)	0.79 (0.06)	0.78 (0.06)	<.0001
Systolic BP (mm Hg)	136 (19)	133 (19)	133 (18)	131 (18)	<.0001
Diastolic BP (mm Hg)	82.1 (11.2)	80.6 (11.0)	80.4 (10.9)	79.7 (10.8)	<.0001
Total cholesterol (mmol/L)	6.40 (1.22)	6.26 (1.19)	6.29 (1.21)	6.21 (1.20)	<.0001
LDL cholesterol (mmol/L)	4.10 (1.09)	3.98 (1.06)	3.99 (1.09)	3.93 (1.08)	<.0001
HDL cholesterol (mmol/L)	1.49 (0.41)	1.55 (0.41)	1.59 (0.41)	1.64 (0.43)	<.0001
Serum glucose (mmol/L)	4.45 (1.99)	4.20 (1.58)	4.12 (1.39)	4.14 (1.30)	<.0001
CRP (mg/L)	4.6 (10.1)	3.0 (5.3)	2.7 (4.6)	2.1 (3.0)	<.0001
Alcohol intake (g/d)	4.4 (7.6)	5.4 (8.2)	5.9 (8.5)	6.6 (9.0)	<.0001
Fruit and vegetable intake (g/d)	411 (229)	493 (242)	534 (285)	546 (274)	<.0001
Hypertension (%) <sup>†</sup>	47.4	39.5	38.5	35.7	<.0001
Diabetes (%)	3.8	2.5	1.9	1.5	<.0001
Smoking ever (%)	48.7	41.9	39.9	39.9	<.0001
Vitamin C supplement (%)	2.9	5.5	6.7	17.2	<.0001
Occupational social class (%) <sup>‡</sup>					<.0001
I	4.6	6.0	6.9	8.2	

(continued on next page)

Table I (continued)

	Plasma vitamin C quartiles				P*
	1	2	3	4	
II	29.0	33.9	37.2	40.7	
III, nonmanual	20.0	21.0	19.5	18.7	
III, manual	24.0	22.4	20.8	18.1	
IV	16.7	13.0	12.1	11.8	
V	5.8	3.8	3.5	2.6	
Education					<.0001
No qualification	50.7	41.1	38.5	35.7	
O level	11.4	11.9	10.8	13.1	
A level	31.2	36.2	38.5	37.4	
Degree/higher	6.7	10.8	12.2	13.8	
Physical activity					<.0001
Inactive	36.5	28.9	25.3	25.2	
Mod inactive	31.0	31.4	33.8	32.4	
Mod active	20.6	23.8	23.2	23.9	
Active	12.0	15.9	17.7	18.5	

Data are expressed as mean (SD) unless indicated otherwise. *BMI*, Body mass index; *BP*, blood pressure; *CRP*, C-reactive protein; *Mod*, Moderately.

\* Linear regression was used for continuous variables, and a  $\chi^2$  test was used for categorical variables.

† Defined as history of hypertension or systolic/diastolic blood pressure  $\geq 140/90$  mm Hg.

‡ Social class I, professionals; social class II, managerial and technical occupations; social class III, subdivided into nonmanual skilled workers and manual skilled workers; social class IV, partly skilled workers; and social class V, unskilled manual workers.

## Methods

### Participants

The individuals in this analysis were part of European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk, a prospective population study of 25,639 men and women aged between 39 and 79 years, residents of Norfolk, UK.<sup>7</sup> The EPIC-Norfolk population is broadly similar to the UK population in terms of the distribution of anthropometric, smoking, and cardiovascular risk factors.<sup>7</sup> The EPIC-Norfolk study was approved by the Norfolk Local Research Ethics Committee, and participants gave signed informed consent at each contact.

### Study design

At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire and attended a clinical visit for anthropometric measurements and blood collection as described previously.<sup>7,8</sup> About a year after the start of the study, when funding became available, extra blood samples from participants were taken for ascorbic acid (vitamin C) assays (measurements available in 22,474 participants). Plasma vitamin C was measured from blood taken into citrate bottles, and plasma was stabilized in a standardized volume of metaphosphoric acid stored at  $-70^{\circ}\text{C}$ . We estimated plasma vitamin C concentration with a fluorometric assay within 1 week of sampling.<sup>9</sup> Serum concentrations of C-reactive protein (milligrams per liter) and glucose (millimoles per liter) were measured in 2010 from frozen baseline serum samples when additional funding became available using an Olympus AU640 clinical chemistry analyser (Olympus UK Ltd, Watford, UK).

At baseline, participants completed a 130-item semiquantitative food frequency questionnaire (FFQ), which was validated in a British sample against 16-day weighed food records.<sup>10</sup> The lists of foods included 11 questions related to fruit intake and 26

questions related to vegetable intake. Food and nutrient intakes (in grams per day) were estimated from the reported food intake and in-house databases.<sup>11</sup>

### Case ascertainment

We defined prevalent heart failure by self-reported intake of drugs that were recommended for treatment of heart failure in clinical practice at the time of the baseline survey.<sup>12</sup> Accordingly, heart failure was defined if loop diuretics were reported in combination with digitalis or angiotensin-converting enzyme inhibitors. A study in UK general practices from 1996 showed that 90% of patients received any of these treatment regimes within 6 months after diagnosis of heart failure.<sup>13</sup> Moreover, we had amino-terminal part of pro-brain natriuretic peptide (NT-pro-BNP) measures available in a random subgroup of 926 participants. Based on the NT-pro-BNP cutoff of 400 pg/mL recommended by the European Society of Cardiology to rule out diagnosis of heart failure, our definition of prevalent heart failure had a specificity of 99.8%.<sup>14</sup> Incident heart failure cases were ascertained by using death certificate data and hospital record linkage with virtually complete follow-up. Death certificates are coded by trained nosologists using *International Classification of Diseases, 10th Revision (ICD-10)*. Participants are also linked to National Health Service hospital information systems so that admissions anywhere in the United Kingdom are reported to EPIC-Norfolk through routine annual record linkage. *Heart failure death* was defined as *ICD-10* I50 anywhere on the death certificate. *Incident heart failure* was defined as heart failure death or hospital discharge code *ICD-10* I50, which is the most frequently used discharge code for heart failure and also was shown to be highly specific.<sup>15</sup> For secondary analyses, myocardial infarction was defined by hospital discharge code *ICD-10* I21-22; and ischemic heart disease, by hospital

**Table II.** Adjusted HRs (95% CI) for incident heart failure by quartiles of plasma vitamin C in men, women, and the total population: EPIC-Norfolk study, 1993 to 2009

	Plasma vitamin C quartiles				P trend	Per 1 SD*
	1	2	3	4		
Men (events)	n = 222	n = 198	n = 154	n = 150		
Model A	1.00	0.93 (0.76-1.12)	0.70 (0.57-0.86)	0.65 (0.53-0.80)	<.0001	0.83 (0.77-0.90)
Model B	1.00	0.98 (0.80-1.20)	0.80 (0.65-1.00)	0.71 (0.57-0.88)	.001	0.88 (0.81-0.95)
Model C	1.00	0.98 (0.80-1.20)	0.84 (0.68-1.05)	0.78 (0.62-0.97)	.01	0.90 (0.83-0.98)
Women (events)	n = 185	n = 112	n = 122	n = 115		
Model A	1.00	0.69 (0.55-0.88)	0.72 (0.57-0.90)	0.62 (0.49-0.78)	<.0001	0.83 (0.76-0.90)
Model B	1.00	0.79 (0.61-1.01)	0.82 (0.65-1.05)	0.75 (0.59-0.96)	.03	0.90 (0.82-0.99)
Model C	1.00	0.81 (0.63-1.04)	0.88 (0.69-1.12)	0.83 (0.64-1.07)	.19	0.93 (0.85-1.03)
Total (events)	n = 432	n = 307	n = 279	n = 240		
Model A	1.00	0.76 (0.65-0.88)	0.70 (0.60-0.81)	0.62 (0.53-0.74)	<.0001	0.83 (0.78-0.87)
Model B	1.00	0.83 (0.71-0.97)	0.79 (0.68-0.93)	0.72 (0.61-0.87)	<.0001	0.88 (0.83-0.94)
Model C	1.00	0.85 (0.73-0.99)	0.84 (0.71-0.99)	0.81 (0.68-0.97)	.02	0.91 (0.86-0.97)

Model A was adjusted for age and in sex combined analysis, for age and sex; model B was additionally adjusted for smoking (ever and never), current alcohol consumption (yes and no), physical activity, occupational social class, and educational level (categories as in Table I); model C was additionally adjusted for baseline systolic blood pressure, diabetes, cholesterol level, and body mass index.

\*Hazard ratios are per increase of 1 SD plasma vitamin C concentration (20 μmol/L in women and the total population and 19 μmol/L in men).

discharge code ICD-10 I20-25. The current study is based on follow-up through June 2009.

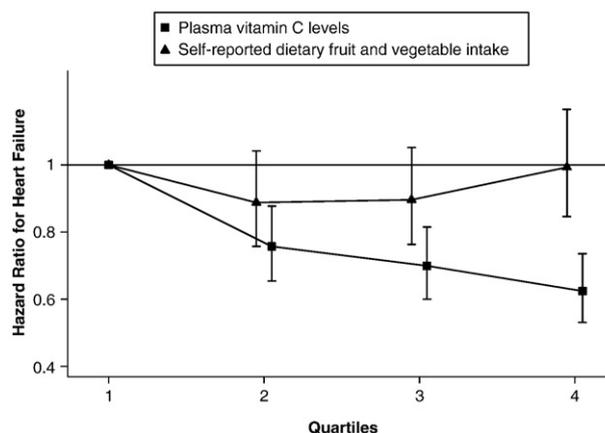
### Statistical analysis

We excluded 2,075 of 22,474 participants with available vitamin C measurement who reported a history of myocardial infarction, stroke, or any cancer and 100 participants with heart failure at the baseline clinic visit, which left 20,299 participants for analysis. Because women had higher vitamin C concentrations than men, we divided the individuals into 4 groups based on sex-specific quartiles of plasma vitamin C. We examined risk factors in vitamin C concentration categories and calculated age-adjusted hazard ratios (HRs) for combined fatal and nonfatal heart failure using Cox proportional hazards models. The HR per quartile of vitamin C increase was also estimated. A similar analytic approach was used to investigate the association of reported fruit and vegetable intake with heart failure risk. Multivariable Cox regression was used to determine the independent contribution of vitamin C for incident heart failure with different degrees of adjustment as indicated. We combined data for men and women because there was no evidence for an interaction between the exposure and sex and included vitamin C as a continuous variable in the model (per 20 μmol/L corresponding to 1 SD). To assess whether the association of vitamin C and heart failure was mediated by preceding myocardial infarction or coronary heart disease, we added hospitalization for myocardial infarction or ischemic heart disease as a time-dependent variable to the model.

All analyses were undertaken using Stata statistical software, version 11.1 (Stata Corporation, College Station, TX).

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**Figure 1**



Hazard ratios for incident heart failure by quartiles of plasma vitamin C concentrations and self-reported dietary fruit and vegetable intake, adjusted for age and sex: EPIC-Norfolk study, 1993 to 2009. Error bars indicate 95% CIs.

### Results

The mean (SD) age of the study population was 58.1 (9.2) years. Plasma vitamin C levels were higher in women (mean [SD] 58.7 [19.8] μmol/L) than in men (mean [SD] 47.3 [18.7] μmol/L). Table I shows characteristics of the participants according to sex-specific quartiles of plasma vitamin C concentration. Increasing vitamin C was associated with decreasing or less frequent cardiovascular risk factors, except for low-density lipoprotein (LDL) cholesterol in men. The proportion of

**Table III.** Adjusted HRs (95% CI) for incident heart failure by plasma vitamin C, stratified by age, body mass index, smoking status, systolic blood pressure, and C-reactive protein: EPIC-Norfolk study, 1993 to 2009

Subgroup	Categories	No. of events/n*	HR (95% CI)†	P	P for interaction
By age	<58 y	215/9461	0.87 (0.75-1.01)	.07	.89
	≥58 y	933/9430	0.92 (0.86-0.99)	.02	
By BMI	<27.5 kg/m <sup>2</sup>	677/12973	0.88 (0.81-0.96)	.002	.24
	≥27.5 kg/m <sup>2</sup>	471/5918	0.97 (0.88-1.08)	.58	
By smoking status	Ever	714/9976	0.88 (0.81-0.95)	.001	.05
	Never	434/8915	0.99 (0.89-1.09)	.81	
By systolic blood pressure	<140 mm Hg	511/12030	0.98 (0.90-1.08)	.69	.02
	≥140 mm Hg	637/6861	0.85 (0.78-0.93)	<.0001	
By C-reactive protein‡	<1.5 mg/L	312/7454	0.88 (0.78-1.00)	.04	.59
	≥1.5 mg/L	570/7619	0.90 (0.83-0.99)	.03	
Excluding prevalent diabetes		1064/18370	0.91 (0.85-0.97)	.004	
Excluding vitamin C-containing supplement		1096/17598	0.91 (0.86-0.98)	.008	
Excluding events within 2 y		1121/18864	0.91 (0.86-0.97)	.006	

Adjustment as in model C, Table II.

\*One thousand one hundred forty-eight events per 18,891 participants available for this analysis due to missing covariates.

†Hazard ratios are per increase of 1 SD (20 μmol/L) plasma vitamin C concentration.

‡Eight hundred eighty-two events per 15,073 participants available due to missing C-reactive protein concentration.

those who took vitamin C-containing supplements increased with increasing quartiles.

During a mean follow-up of 12.8 years, 1,258 (154 fatal and 1,104 nonfatal) incident cases of heart failure were identified in 724 men and 534 women (incidence 4.8 per 1000 person-years). With 1 exception, the covariates listed herein were also associated with heart failure in unadjusted Cox regression. Self-reported consumption of fruit and vegetable assessed by FFQ was not associated with heart failure.

Table II shows HRs for heart failure comparing each quartile of plasma vitamin C with the lowest quartile for men and women separately and combined. The risk of heart failure decreased with increasing quartiles of plasma vitamin C in both men and women, with no evidence for a sex × vitamin C interaction ( $P = .48$ ). Figure 1 compares the association of incident heart failure with quartiles of plasma vitamin C concentrations and self-reported fruit and vegetable intake, with suggestion of a dose-dependent association for plasma vitamin C but not for self-reported fruit and vegetable intake.

With increasing adjustments for covariates, the association between plasma vitamin C and heart failure risk was attenuated (Table II). In model C, every 20 μmol/L increase in plasma vitamin C concentration was associated with a 9% risk reduction for heart failure, independently of age, sex, smoking, alcohol consumption, physical activity, occupational-social class, educational level, prevalent diabetes, systolic blood pressure, cholesterol concentration, and body mass index. Replacing total cholesterol by LDL and high-density lipoprotein (HDL) cholesterol, replacing body mass index by waist-hip ratio, and further adjusting for serum glucose levels in addition to history of diabetes did not change the results (data not shown). The results were also similar after further adjusting for baseline C-reactive

protein concentrations (HR 0.91, 95% CI 0.85-0.98,  $P = .012$ ) and exclusion of participants with reported intake of vitamin C-containing supplements, those with baseline diabetes, and those with incident heart failure events occurring during the first 2 years of follow-up (Table III). When adjusting for myocardial infarction or ischemic heart disease in addition to covariates of model C, every 20 μmol/L difference in plasma vitamin C was associated with a 8% (95% CI 2%-13%,  $P = .01$ ) risk reduction for incident heart failure.

Table III shows results of stratified analyses categorized by baseline risk factors. There was a consistent trend for reduced heart failure risk with increasing concentrations of plasma vitamin C in all stratified analyses. The association seemed to be attenuated in those who never smoked and those with normal systolic blood pressure, with significant interaction term for systolic blood pressure.

## Discussion

In a prospective population-based study, we demonstrated an inverse association between plasma vitamin C concentrations and risk for incident heart failure in apparently healthy middle-aged men and women. Every increase of 20 μmol/L (1 SD) in plasma vitamin C concentration was associated with a 17% relative decrease in risk for heart failure, and the significant relation with heart failure risk remained after multivariate adjustment. We did not observe a significant association between self-reported dietary fruit and vegetable intake and heart failure.

Humans can obtain vitamin C only exogenously, and 90% of vitamin C is thought to be obtained from fruit and vegetables in a Western population.<sup>5</sup> Plasma vitamin C concentration is strongly correlated with dietary fruit and

vegetable intake ( $r = 0.35-0.64$ ).<sup>6,16</sup> In a previous analysis on the correlation of plasma vitamin C with food intake estimated from 7-day diaries, we found that plasma vitamin C correlated consistently and more substantially with fruit and vegetable intake than with other food.<sup>16</sup> Moreover, increased consumption of fruit and vegetables was shown to be associated with a significant increase in plasma vitamin C concentration under randomized controlled conditions.<sup>17</sup>

This and earlier studies addressing the association between fruit and vegetable intake and heart failure used FFQs to assess diet,<sup>3,4</sup> which have well-recognized limitations in ranking individuals as well as in estimating effect size.<sup>5</sup> A previous analysis in this population showed a poor correlation between plasma vitamin C and the high range of FFQ-reported fruit and vegetable intake,<sup>18</sup> which corresponds to our divergent findings for heart failure risk between the high range of plasma vitamin C and fruit and vegetable intake. Taken together, this strongly suggests that fruit and vegetable intake indeed is inversely associated with heart failure risk; and measurement error of the dietary assessment is the reason for previous inconsistent and negative results.

Our findings might have 2 major implications: first, plasma vitamin C is a new marker that indicates increased risk for heart failure, independent of established risk factors. As mentioned earlier, there is increasing effort to characterize high-risk subgroups for implementation of preventive strategies. Second, the use of this biomarker contributes to the evidence for the beneficial association between intake of fruit and vegetable and risk for heart failure, which might have implication for clinical and public health recommendations. The beneficial association of plasma vitamin C and heart failure risk was observed throughout the whole reference range; and thus, small shifts such as 1 additional serving (corresponding to 20  $\mu\text{mol/L}$  difference in plasma vitamin C)<sup>16</sup> in the population intake might have substantial and progressively increasing effects. The 9% risk reduction observed for every 20  $\mu\text{mol/L}$  change in plasma vitamin C is comparable with the effect of a 4-mm Hg decrement in systolic blood pressure or 1.4- to 2-U decrement in body mass index.<sup>19,20</sup>

Trials on vitamin C supplementation failed to show beneficial clinical effects so far.<sup>21</sup> Several potential explanations have been discussed for the discrepancy between trial results and epidemiological studies such as patient selection, short follow-up time, and vitamin doses used in trials and confounding of the vitamin C associations in observational studies by social and behavioral factors.<sup>22</sup> Hence, it is important to acknowledge that plasma vitamin C should be interpreted rather to be a biomarker reflecting a healthy lifestyle, most probably a diet rich in fruit and vegetable, than a causal pathway preventing cardiovascular disease or heart failure.

There are several plausible mechanisms explaining the beneficial association of fruit and vegetable consumption on heart failure, both by mitigating traditional intermediate-risk factors and by directly influencing cardiac contractility.

A substantial body of epidemiological evidence indicates an inverse association between plasma vitamin C or fruit and vegetable intake and cardiovascular disease.<sup>23,24</sup> Our findings indicate that the association between plasma vitamin C and heart failure was not mediated by interim coronary heart disease. However, as only coronary events leading to hospitalization were considered in our analysis, we might have underestimated our adjustment. There is also observational evidence indicating a plausible link between plasma vitamin C or fruit and vegetable intake and nonischemic heart failure such as diabetic and hypertensive heart disease.<sup>18,25</sup> Importantly, a diet rich in fruit and vegetable was associated with a significant reduction in blood pressure in a strictly controlled randomized trial.<sup>26</sup> Fruit and vegetable intake is also inversely associated with systemic inflammation and oxidative stress,<sup>27,28</sup> both of which are shown to affect cardiac contractility.<sup>29</sup> Adjustment for C-reactive protein, which did not attenuate the association between plasma vitamin C and heart failure in our analysis, might not be sufficient to fully account for confounding by inflammation. Furthermore, there is experimental evidence that distinct nutrients found particularly in fruit and vegetables have direct positive effects on myocardial contractility.<sup>30</sup> Finally, fruit and vegetables are rich in minerals such as potassium and magnesium, deficiency of which is associated with decreased cardiac contractility and increased risk for ventricular arrhythmias, which might lead to an earlier clinical exacerbation of ventricular dysfunction.

We observed a trend for beneficial association between plasma vitamin C and heart failure risk consistently in all subgroups of established risk factors with a somehow attenuated association for those participants who never smoked or had normal baseline blood pressure. Adjustment for smoking and hypertension did not substantially attenuate the association in the total population, indicating only minor relevance for mediating the association of fruit and vegetable intake. Given the borderline significance of the interactions and the overlap in CIs, these results should be interpreted cautiously and need further exploration.

There are some limitations to our study. First, observational studies cannot establish causality of an association. We addressed issues of confounding and reverse causality by (1) adjusting for a variety of traditional cardiovascular risk factors, lifestyle factors, and socioeducational status; (2) excluding prevalent chronic disease including medically treated heart failure, vitamin supplement use, and events in the first 2 years; and (3) stratifying analysis by important heart failure risk

factors with consistent results. Nonetheless, specifically designed trials are needed to further confirm a causal link. Second, we defined prevalent heart failure by drug treatment only, which might be less sensitive. However, community surveillance reports have indicated that 74% of outpatient heart failure cases are hospitalized within 1.7 years.<sup>31</sup> Excluding events of the first 2 years as potential preexisting heart failure cases did not change results. Third, the approach of ascertaining cases through hospital records will tend to result in the detection of more severe cases and, thus, is a specific approach to finding heart failure but is likely to be relatively insensitive. This limits the generalizability of our conclusions to less severe heart failure; however, heart failure is a progressive disease; and it is likely that many participants with less severe heart failure in early years of follow-up were eventually hospitalized by the end of the almost 13 years of follow-up. Finally, we have no information on the etiology of the incident heart failure cases, for example, echocardiography to distinguish diastolic and systolic heart failure. The pathogenesis of distinct heart failure entities varies; however, even if the plasma vitamin C association is only with a subset of these, this would only attenuate the overall vitamin C association with heart failure as general group.

In conclusion, we observed an inverse association between plasma vitamin C and the risk of heart failure. These epidemiological findings suggest that intake of food, most plausibly fruit and vegetables, associated with high plasma vitamin C concentrations might be preventive for heart failure and should be regarded as hypothesis generating for further prospective randomized trials aimed at examining the effect of a diet rich in fruit and vegetables for prevention of heart failure.

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