Association of frequency of fruit and vegetable consumption with cardiovascular disease among smokers and non smoker men

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Association between the frequency of fruit and vegetable consumption and cardiovascular disease in male smokers and non-smokers

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Abstract

Background. Consumption of fruit and vegetables (F&V) is associated with a lower cardiovascular (CVD) risk. Smoking may affect the strength of this association.

Objective. To compare the relationship between the frequency of F&V intake and CVD risk in male current, former and never smokers.

Design. A prospective study in men (n=8060) aged 50-59 years and recruited in France and Northern Ireland. The frequency of F&V intake was assessed by using a food frequency questionnaire. The outcome criteria were incident cases of acute coronary syndrome (ACS) and total CVD (coronary heart disease and stroke) over 10 years.

Results. A total of 367 ACS and 612 CVD events occurred during the follow-up period. A multivariate analysis revealed a statistically significant interaction between smoking status and F&V intake for ACS and for CVD (both $p< 0.05$). In current smokers, the relative risks for ACS were 0.78 [0.54–1.13] and 0.49 [0.30-0.81] in the 2nd and 3rd tertiles of F&V intake, respectively (p trend<0.001); for CVD, the values were 0.80 [0.59–1.08] and 0.64 [0.44-0.93], respectively (p trend<0.001). In contrast, no statistically significant associations were observed for never and former smokers. Similar statistical interactions for ACS were observed for fruit intake ($p=0.07$) and vegetable intake ($p <0.05$) taken separately.

Conclusion. These results suggest that high fruit and vegetable intake is associated with a lower risk of CVD in male smokers.

Keywords. Fruit, vegetable, smoking, coronary heart diseases, cohort

Introduction

Smoking is a major risk factor for cardiovascular disease (CVD) events (Chouraki *et al.,* 2008; US Departement of Health and Human Service, 2004). More than 40% of myocardial infarctions in men aged 50-54 are related to tobacco exposure (Mahonen *et al.*, 2004). Tobacco affects coronary risk in humans by promoting systemic inflammation, increasing oxidative stress and altering haemostasis and coagulation (Yanbaeva *et al.*, 2007).

In observational cohort studies, fruit and vegetable (F&V) consumption has been consistently associated with lower CVD risk in both men and women (Dauchet *et al.,* 2005; Dauchet *et al.*, 2006; He *et al.*, 2006; He *et al.*, 2007). In meta-analyses of prospective studies, each additional portion of F&V is associated with a 4% reduction in the risk of coronary heart disease (Dauchet *et al.*, 2006) and a 5% reduction in the risk of stroke (Dauchet *et al.*, 2005). The mechanisms by which F&V may reduce CVD are unclear (Dauchet *et al.*, 2009). In humans, F&V consumption has been associated with lower systemic inflammation (Esmaillzadeh *et al.*, 2006), reduced oxidative stress (Kris-Etherton *et al.*, 2002) and decreased platelet aggregation (Vita, 2005). These properties may partially counteract the systemic effects of smoking.

Previous investigations have sought to establish the possible influence of smoking exposure on the relationship between F&V intake and CVD occurrence. However, the results have been divergent; some studies have reported favourable associations in smokers only (Hung *et al.*, 2004), whereas others presented incomplete data or lacked formal statistical tests (Bazzano *et al.,* 2002; Johnsen *et al.*, 2003; Liu *et al.*, 2001; Nakamura *et al.*, 2008; Takachi *et al.*, 2008). Hence, the goal of the present study was to assess the relationship between the frequency of F&V intake and the occurrence of CVD in male never, former and current smokers. Our working hypothesis was that smokers benefit more from the consumption of F&V than non-smokers.

Methods

The methods have been described in detail in the 5-year follow-up report on the PRIME study (Dauchet *et al.*, 2004).

Population recruitment.

Briefly, the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study was established in 1991 in the populations of four WHO-MONICA centres in Belfast (United Kingdom), Lille (northern France), Strasbourg (eastern France) and Toulouse (south-western France). The target was to recruit 2500 men aged 50-59 in each centre. The PRIME study was approved by the appropriate local independent ethics committees and was performed in accordance with the current legislation in France and Northern Ireland.

Questionnaire

Self-administered questionnaires related to demographic and socioeconomic factors and diet were completed at home by the participants and then checked in the latter's presence by survey staff at the investigating centre. Data on educational level, employment status, personal and family medical histories, tobacco and alcohol consumption, drug intake and physical activity were also collected. Smoking habits were determined from the answers to questions on present and past habits. Subjects were classified into 3 categories: never smokers, former smokers and current smokers. For current smokers, information on the number and type of cigarettes, cigars or pipes smoked per day over the previous five years was collected. Alcohol consumption was assessed via a questionnaire in which the subject reported his mean consumption (in units) of wine, beer, cider and spirits on each day of the week. The personal history of cardiovascular risk factors was assessed by asking the subject to state whether a medical doctor had ever reported a given risk factor, followed by a question on past and present medical treatments. Anthropometric parameters and blood pressure were measured using standardized methods. A venous blood sample was collected once at inclusion and assayed for total cholesterol and HDL-cholesterol levels.

Subjects with evidence of cardiovascular disease at baseline (total 891, including 823 with coronary heart disease and 77 with cerebrovascular disease) were not included in the analysis. In addition, 1343 men who reported that they were on a diet for hypertension, hypercholesterolemia or diabetes were excluded from the analyses. Lastly, 309 subjects were excluded because of missing data on the frequency of fruit and/or vegetable intake and/or adjustment variables, leaving a total of 8060 included participants. The follow-up duration was 10 years.

In addition, plasma vitamin levels were assayed at inclusion in 99 randomly selected men (24 in Lille and 25 in each of the other centres). Liposoluble plasma vitamins were assayed by HPLC (Hess *et al.*, 1991) at the Swiss Reference Laboratory (Basel, Switzerland; appointed by the National Institute of Standards and Technology, Gaithersburg, MD, USA). Vitamin C levels (as the sum of ascorbic acid and dehydroascorbic acid) were measured by automated fluorimetry (Brubacher *et al.*, 1974). The test laboratory was always blinded to the origin of the samples. The coefficient of variation for all parameters was ≤3%; periodic, parallel analyses of reference samples were checked for systematic errors.

Dietary assessment

Dietary information on the frequency of F&V intake was obtained for 4 categories of F&V ("fresh citrus fruit", "other fresh fruit", "raw vegetables" and "cooked vegetables" – excluding potatoes and legumes). In a face-to-face interview at their home, subjects were asked to indicate their usual frequency of consumption of a standard portion of fruit or vegetables. The frequencies of "fruit", "vegetable" and "fruit and vegetable" intake was calculated as the sum of number of servings per day of fruit and/or vegetables. In a previous analysis, the frequency of fruit and vegetable consumption measured with this questionnaire was seen to be associated with plasma vitamin concentrations. The frequency of fruit intake was correlated with beta-cryptoxanthin ($r=0.32$, $p<0.005$) and vitamin C ($r=0.33$, $p<0.004$) levels. Likewise, the frequency of citrus fruit intake was correlated with beta-cryptoxanthin ($r=0.34$, $p<0.002$) and vitamin C ($r=0.37$, $p<0.0007$). Similarly, the frequency of vegetable intake was correlated with alpha-

carotene (r=0.26, p<0.03), beta-carotene (r=0.29, p<0.02), beta-cryptoxanthin (r=0.32, p<0.04) and vitamin C (r=0.24, p<0.04) (Dauchet *et al.*, 2004).

Follow up and outcomes.

During the 10-year follow-up period, each subject was contacted every year by letter and asked to complete a clinical event questionnaire and return it to the investigating centre in a prepaid envelope. For all subjects reporting a possible event, clinical information was requested directly from the hospital or family doctor. Death certificates were checked for supporting clinical and post-mortem information on the cause of death. A Medical Committee was established in order to independently validate incident coronary events in the PRIME Study (Ducimetiere *et al.*, 2001). The Committee comprised one member from each PRIME centre plus several independent cardiologists (from France and the UK). Two endpoints were analysed: (i) acute coronary syndrome (ACS, including incident myocardial infarction, coronary death and unstable angina) and (ii) all-cause CVD (including ACS, angina pectoris, ischemic and haemorrhagic strokes) (Ducimetiere *et al.*, 2001). Acute coronary syndromes are thought to be representative of plaque rupture and subsequent thrombosis formation (Empana *et al.*, 2008), whereas CVD includes a larger number of cardiovascular events.

Statistical analysis

Baseline characteristics were described by smoking status and tertiles of F&V intake frequency. Kruskal-Wallis and chi-squared tests were used to compare never, former and current smokers in terms of the study endpoints. General linear models, logistic and polytomic regressions were used to assess the association between a subject's characteristics or risk factors on one hand and F&V intake (considered as a continuous variable in the statistical model) on the other.

The Kaplan-Meier method and the log-rank test were used to compare unadjusted survival curves according to the tertile of F&V intake. Cox's proportional hazard regression models were used to assess the relationship between F&V intake (again as a continuous variable) and the time-to-endpoint events. The interaction between F&V intake frequency and smoking status was used to test possible differences between smoking categories. Next, analyses stratified by

smoking status were performed using a separate slope design (Hill *et al.*, 2006). For the sake of presentation the results are presented by tertiles of F&V distribution.

Three different models were used, adjusted for: (1) age and centre, (2) age, centre and possible confounding variables (alcohol consumption, vitamin supplement intake, physical activity, educational level and employment status), (3) the variables in the second model plus potential mediating variables (systolic blood pressure, total cholesterol, HDL-cholesterol, BMI and treatment for hypertension, diabetes or dyslipidaemia).

For these latter analyses, age, BMI, blood pressure and total & HDL-cholesterol levels were treated as continuous variables. Other variables were defined as follows: centre (Belfast, Lille, Strasbourg or Toulouse), educational level (elementary school or below, high school, university), smoking status (never, former, current), physical activity (less than once a week, light exercise most weeks, more than 20 min of vigorous exercise once or twice a week, at least 20 min of vigorous exercise three or more times per week), employment status (employed/unemployed), weekly alcohol consumption (teetotal, <177 ml, 177.0 ml-367.2 ml and >367.2 ml), vitamin supplementation (yes/no) and treatment for hypertension, diabetes or dyslipidaemia (yes/no).

The interactions between country (France/Northern Ireland) and frequency of fruit and/or vegetable intake (as continuous variables) were also tested. The two-tailed cut-off value for statistical significance was set to $p<0.05$. Statistical analyses were performed using version 9.1 of SAS software (SAS Institute Inc., Cary, NC, USA).

Results

At baseline (**Table 1**), current smokers reported less frequent intakes of F&V than never and former smokers (23.9% vs. 37.2% and 36.0%, respectively; all $p<0.0001$). The same was true for fruit intake (25.0% vs. 33.2% and 34.8%, respectively), and vegetable intake (26.6% vs. 39.6% and 38.2%, respectively) (all $p<0.0001$). Overall, the smokers were slightly younger than

never and former smokers (54.5y vs. 54.8y and 54.9y, respectively; p<0.0001), had a lower education level (34.9% vs. 28.9 and 31.0%; p<0.0003), performed less physical activity (16.5% vs. 10.7% and 12.7%; p<0.0001) and consumed more alcohol (38.7% vs. 16.1% and 27.9%; p<0.0001). Current smokers had lower levels of plasma of beta-cryptoxanthin (p<0.05), beta-carotene (p<0.02) and alpha-tocopherol (p<0.002).

Table 2 reports on the associations between the frequency of F&V intake and possible confounders, according to smoking status. When comparing smoking exposure strata, the relationships with F&V intake were homogeneous for all variables other than centre (p<0.03), BMI (p<0.0001) and HDL (p<0.02). Mean age and systolic blood pressure did not differ as a function of the F&V tertiles (all p>0.05). Moving from low to high F&V tertiles, the educational level and exercise level increased, whereas alcohol intake and plasma cholesterol levels decreased. In contrast, the difference in F&V intake between the Belfast centre on one hand and the French centres on the other was more pronounced in current smokers than in never and former smokers. The BMI increased in current smokers and decreased in never smokers across F&V intake tertiles. The HDL-cholesterol levels increased in never smokers only. Lastly, for current smokers, the number of cigarettes smoked per day decreased across F&V tertiles.

Over the 10-year follow-up period, 400 (5.0%) subjects were lost to follow-up (median duration of follow-up of 6.4 years in these cases). Compared with subjects who remained in the cohort, the subjects lost to follow-up were more likely to be smokers (39% vs. 51%; p<0.0001), have a lower level of education (university graduate 11% vs. 15%; p<0.03), perform less regular physical activity (21% vs. 28 %; p<0.002) and have a higher BMI (26.9 vs. 26.5 kg/m^2; p<0.02) and lower plasma cholesterol levels (2.16 vs. 2.21 g/l; p<0.0033).

During the 10-year follow-up period, 367 ACS events and 612 CVD events were recorded. **Figure 1** shows the Kaplan-Meier curve for the ACS events by tertile of F&V intake in never, former and current smokers. Low F&V intake was associated with more ACSs in current smokers (p<0.0002). In both never smokers and former smokers, these associations were not statistically significant.

In a multivariate model adjusted for age, centre, alcohol consumption, vitamin supplement intake, physical activity, educational level, employment status, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI and treatment for hypertension, diabetes or dyslipidaemia, we found a statistically significant interaction between smoking status and F&V intake for ACS ($p<0.02$) and CVD ($p<0.03$) (**Table 3**). In stratified analyses, the risks of ACS and CVD decreased across F&V intake tertiles in current smokers. No statistically significant relationships between F&V intake and ACS or CVD were observed in never or former smokers. Similar interactions between the frequency of fruit intake alone or vegetable intake alone and tobacco exposure were observed for ACS ($p=0.07$ and $p<0.05$, respectively). Partial and full adjustments had little influence on the relative risk (RR) values, when compared in the age- and centre-adjusted model (**Supplementary Tables 1 and 2, Table 3)**.

For current smokers, further analyses were performed by adjusting for the number of cigarettes, cigars, cigarillo or pipes smoked per day over the previous five years. The corresponding RRs for ACS were 0.84 [0.57-1.22] and 0.53 [0.31-0.90] for the 2^{nd} and 3^{rd} tertiles vs. the 1^{st} tertile of F&V intake frequency, respectively (p trend < 0.005). The RRs for CVD were 0.85 [0.63-1.16] and 0.68 [0.45-1.01], respectively (p trend = 0.06).

Discussion

Tobacco is a major risk factor for cardiovascular disease. Earlier studies have reported inconsistent associations between F&V intake and the occurrence of CVD in current, former and never smokers. In the present prospective study of middle-aged men of European descent, we found a statistically significant relationship between F&V intake frequency and lower ACS and CVD rates in current smokers but not in former or never smokers.

In agreement with our present results, fruit and/or vegetable intake were more strongly associated with a reduction of CVD in current smokers than in never or former smokers in

American cohorts of male and female health professionals (Hung *et al.,* 2004; Liu *et al.*, 2001). In a cohort of Danish men and women, F&V intake was also associated with a greater lowering of ischemic stroke risk in smokers than in non-smokers (a difference which, however, did not achieve statistical significance) (Johnsen *et al.*, 2003). In contrast, there was no interaction between tobacco exposure and F&V intake for the CVD risk in a number of other prospective studies (Bazzano *et al.,* 2002; Genkinger *et al.*, 2004; Johnsen *et al.*, 2003; Nakamura *et al.*, 2008) . A strong, favourable association between F&V intake and CVD was reported (but not tested statistically) in a Japanese cohort (Takachi *et al.*, 2008). Our results suggest that the relationship between the frequency of F&V intake and the occurrence of CVD is different in smokers and non-smokers. Additional studies are needed to confirm these findings.

There are several possible explanations for the observed association. Firstly, the high antioxidant vitamin content of some F&Vs may reduce or prevent the oxidative damage caused by toxic tobacco products. Oxidative damage may be more intense in smokers because smoking products lower the levels of antioxidant micronutrients in the bloodstream (Bruno *et al.,* 2006; Dietrich *et al.*, 2003; Yanbaeva *et al.*, 2007). Furthermore, pharmacological studies in humans have shown that antioxidants improve biological markers of oxidation and endothelial function (Bruno *et al.,* 2005; Bruno *et al.*, 2006; Heitzer *et al.*, 1996; Karatzi *et al.*, 2007; Stadler *et al.*, 2007), which could counter the harmful effects of tobacco. However, clinical trials have not confirmed a protective effect of antioxidant vitamins in terms of CVD outcomes (Steinhubl, 2008). Secondly, flavonoids from F&V inhibit platelet aggregation (Vita, 2005), which may partially counteract the effects of tobacco on blood viscosity (Yanbaeva *et al.*, 2007). Thirdly and lastly, F&V consumption is associated with lower plasma C-reactive protein (CRP) concentrations (Chun *et al.,* 2008; Esmaillzadeh *et al.*, 2006), which might attenuate smoking's intensifying effects on inflammatory reactions (Yanbaeva *et al.*, 2007) and related atherosclerosis (Ross, 1999).

Alternatively, a residual confounding effect of unmeasured factors could also explain the more pronounced association between F&V and CVD events in smokers than in non-smokers. Firstly, smokers who frequently consume F&V might be more health conscious and smoke less than

less frequent consumers of F&V. This hypothesis is supported by the observation that the frequency of F&V intake is inversely associated with the number of cigarettes smoked per day, which may contribute to the lower risk. Adjustment for the number of cigarettes does not substantially attenuate the RRs. However, some degree of measurement error may still be present and would thus result in residual confounding (Skuladottir *et al.*, 2004). We suggest that better modelling and use of biomarkers (such as cotinine) should be employed in future studies, in order to better assess smoke exposure (Twardella *et al.*, 2004). Secondly, consumers of F&V may quit smoking more often or more rapidly than non-consumers. This hypothesis is supported by data from 2 of our centres showing that smoking cessation tended to be more frequent among frequent F&V consumers than among non-consumers. Thirdly and lastly, the frequency of F&V intake may be associated with other healthy habits and practices which were not measured in this study but which could have confounded the results.

It is known that F&V intake decreases blood pressure (Appel *et al.*, 1997)**.** In the present study F&V intake was not correlated with the blood pressure values at baseline; this may be explained by our study's cross-sectional design. Furthermore, some subjects with high normal hypertension or untreated hypertension may have increased their F&V consumption, which would also have confounded the association. Conversely, F&V intake was inversely associated with plasma LDL cholesterol, as reported in some (Djousse *et al.*, 2004) (but not other) studies (Dauchet *et al.*, 2009)

Our study had a number of limitations. Firstly, the present study was performed in men only. Thus, it may not be appropriate to extrapolate the results to women, given the gender differences in the prevalence and characteristics of smoking habits (Dedobbeleer *et al.,* 2004; Escobedo *et al.*, 1996; Hill, 1998; Osler *et al.*, 1999). Indeed, studies in Japan have reported more pronounced associations between F&V intake and CVD in men than in women (Nakamura *et al.,* 2008; Takachi *et al.*, 2008). In contrast, the associations were similar in both genders in Caucasian cohorts (Joshipura *et al.*, 1999). Secondly, the food frequency questionnaire is too simple a tool for the quantitative assessment of food intake. Therefore, the results of the present study should be interpreted as an analysis of the relationship between smoking and the

frequency of F&V intake and not the absolute amount consumed. In this respect, Thompson et al (Thompson *et al.*, 2002) showed that questionnaires with a restricted number of items and lacking a quantitative assessment of portion size do not very much affect the ability to rank subjects according to F&V intake. Furthermore, it was recently reported that a 19-item F&V screener and a single question on overall F&V had similar correlations with multiple 24-hour dietary recall interviews (Peterson *et al.*, 2008). Moreover, the correlation analysis between frequency of F&V intake and plasma vitamin concentrations observed in the present study suggests that our assessment of the frequency of F&V intake was reasonably accurate (Dauchet *et al.*, 2004). Furthermore, since the food frequency questionnaire had a limited number of items, it was not possible to adjust for other nutritional factors (such as total energy intake, saturated and polyunsaturated fats), or to compare the F&V intake to current nutritional guidelines. Therefore, the observed associations between CVD events and fruit and/or vegetable intake might be partly explained by compensatory changes in other nutrients or food items. Thirdly, food intake was assessed only on entry into the present study; changes in dietary habit over time might weaken the associations. However, earlier reports in Dutch men aged 55 to 68 have shown that food habits were fairly stable over 5 years (Goldbohm *et al.*, 1995). Fourthly, changes in smoking habits could have affected the association between F&V intake and CVD events in different smoking exposure strata. However, additional analyses have shown that very few quitters resumed smoking during the follow-up and suggest that classification errors were unlikely in this group. In contrast and as mentioned above, smoking F&V consumers tended to quit more frequently than non-consumers, which may have amplified the strength of the association.

In conclusion, the results of the PRIME Study showed a stronger relationship between the frequency of F&V consumption and lowered CVD risk in current male smokers than in former and never smokers. These data highlight the need for more in-depth analysis of the interaction between smoking exposure and diet and its impact on health outcomes in future cohort or interventional studies.

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Supplementary information is available at The European Journal of Clinical Nutrition's website.

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Figure 1**. Kaplan-Meier estimates of acute coronary syndrom by smoking status for the three tertil of F&V consumption**

Table 1 : Demographic, lifestyle characteristics and plasma vitamins by smoking status

	Never smokers	Former smokers	Current smokers	*p**
n	2410	3353	2297	
End-points				
Acute Coronary Syndrome (n)	79	140	148	
Cardiovascular disease (n)	145	237	230	
Fruit and vegetable intake				
Fruit and vegetable (%)				*<0.0001*
≤1.57 (time/d)	28.8	30.3	44.4	
1.6-2.57 (time/d)	33.9	33.7	31.7	
≥2.6 (time/d)	37.2	36.0	23.9	
Fruit (%)				*<0.0001*
≤0.57 (time/d)	35.3	34.7	43.6	
0.64-1.14 (time/d)	31.5	30.6	31.4	
≥1.29 (time/d)	33.2	34.8	25.0	
Vegetable (%)				*<0.0001*
≤0.79 (time/d)	30.3	32.5	46.8	
1-1.29 (time/d)	30.1	29.3	26.6	
≥1.5 (time/d)	39.6	38.2	26.6	
Characterisctic of the subjects				
Center (%)				*<0.0001*
Belfast	30.9	20.1	29.6	
Lille	18.9	26.0	21.4	
Strasbourg	25.2	27.7	25.7	
Toulouse	25.1	26.2	23.3	
Age (years)	54.8 (2.9)	54.9 (2.9)	54.5 (2.8)	*<0.0001*
Currently employed (%)	83.4	80.5	78.7	*<0.0003*
Education level (%)				*<0.0003*
University graduated	15.7	15.9	13.8	
High school	55.4	53.1	51.4	
Elementary school or less	28.9	31	34.9	
Physical activity (%)				*<0.0001*
No	10.7	12.7	16.5	
Light	59.4	57.4	62.0	
Vigourous	22.0	22.7	17.3	
Intense	8.0	7.1	4.3	
Vitamin supplements ≥ 1/week (%)	15.7	14.7	13.8	*0.18*
Alcohol consumption (%)				*<0.0001*
Non-consumer	24.6	14.1	13.0	
≤171.1 ml/week	33.1	28.5	21.1	
171.1 to 374.1 ml/week	26.2	29.4	27.3	
≥ 374.1 ml/week	16.1	27.9	38.7	
Body Mass Index (kg/m^2)	26.3 (3.2)	27.0 (3.3)	26.0 (3.6)	*<0.0001*
Plasma vitamins †				
n	33	39	27	
Beta-Cryptoxanthin (µmol/ l)	0.16	0.18	0.11	*<0.05*
Lycopene (µmol/ l)	0.39	0.41	0.2	*<0.06*
Alpha-Carotene (µmol/ l)	0.12	0.1	0.07	*<0.07*
Total Beta-Carotene (µmol/ l)	0.52	0.46	0.3	*<0.02*
Alpha-Tocopherol (µmol/ l)	32.7	34.8	29.7	*<0.002*
Ascorbic acid (µmol/ l)	39.8	46.3	31.2	*<0.07*

* Chi-square for qualitative variables. Kruskal-Wallis for quanlitative variables. Standard deviations are in brackects.
† Analyses performed in a random sample of 99 subjects.

Table 2. Mean values and distribution of major cardiovascular risk factors by fruit and vegetable tertiles of intake and smoking status

Frequency of fruit and vegetable intake	Never smokers				Former smokers				Current smokers				*p for interation†*
(range)	≤ 1.57	1.6 - 2.57	≥2.6	*p for trend* *	≤ 1.57	1.6 - 2.57	≥2.6	*p for trend* *	≤ 1.57	1.6 - 2.57	≥2.6	*p for trend* *	
(median)	1.14	2.07	3.50		1.14	2.07	3.50		1.14	2.07	3.50		
n	695	818	897		1016	1130	1207		1020	727	550		
Age (years)	54.7 (2.9)	54.9 (2.9)	54.9 (2.9)	*0.50*	54.9 (2.9)	54.8 (2.9)	55 (2.8)	*<0.06*	54.5 (2.9)	54.5 (2.8)	54.6 (2.9)	*0.56*	*0.68*
Center (%)				*<0.0001*				*<0.0001*				*<0.0001*	*<0.03*
Belfast	41.4	32.6	21.2		26.6	22.4	12.6		41.6	25.6	12.5		
Lille	14.2	19.6	21.9		26.9	23.7	27.3		17.4	23.1	26.7		
Strasbourg	30.4	26.4	20.0		32.4	30.6	21.1		26.5	28.9	20.2		
Toulouse	14.0	21.4	37.0		14.2	23.3	38.9		14.6	22.4	40.5		
Currently employed (%)	39.1	36.8	36	*0.38*	40.9	39.3	38.8	*0.350*	42.3	40.8	38.5	*<0.03*	*0.47*
Education level (%)				*<0.0002*				*<.0001*				*<0.0001*	*0.11*
University graduated	32.9	28.0	26.6		34.3	28.7	30.4		40.4	30.3	30.7		
High school	56.1	56.5	53.8		55.2	55.2	49.3		50.2	54.5	49.5		
Elementary school or less	10.9	15.5	19.5		10.5	16.1	20.3		9.4	15.3	19.8		
Physical activity (%)				*<0.0001*				*<0.0001*				*<0.0001*	*0.07*
No	0.128	0.099	0.098		0.16	0.127	0.1		0.178	0.165	0.138		
Light	0.642	0.611	0.541		0.599	0.59	0.539		0.674	0.6	0.545		
Vigourous	0.186	0.211	0.253		0.201	0.21	0.265		0.114	0.194	0.256		
Intense	0.045	0.078	0.108		0.039	0.073	0.096		0.034	0.041	0.06		
Vitamin supplements ≥ 1/week	15.1	15.6	16.3	*0.81*	11.7	15.5	16.5	*<0.005*	12.2	15.3	14.7	*0.15*	*0.75*
Alcohol consumption (%)				*<0.0001*				*<0.0001*				*<0.0001*	*0.63*
Non-consumer	27.8	24.2	22.4		16.4	13.4	12.9		14.4	12.4	11.1		
≤171.1 (ml/week)	27.1	34.0	36.9		22.1	29.4	33.0		17.5	24.1	23.8		
171.1 to 374.1 (ml/week)	23.3	26.7	28.1		28.5	30.0	29.7		24.9	26.3	32.9		
≥ 374.1 (ml/week)	21.9	15.2	12.6		32.9	27.3	24.4		43.2	37.3	32.2		
BMI (kg/m2)	26.7 (3.3)	26.2 (3.1)	26 (3.2)	*<0.0002*	27.1 (3.4)	26.9 (3.2)	26.9 (3.3)	*0.72*	25.7 (3.6)	26.1 (3.5)	26.3 (3.9)	*<0.008*	*<0.0001*
Systolic BP (mmHg)	134.1 (19.3)	131.8 (16.8)	131.9 (17.5)	*0.84*	136.1 (19.7)	134.3 (18.6)	133.2 (18.2)	*0.16*	132.5 (19.7)	132.1 (18.6)	129.8 (18.4)	*0.38*	*0.33*
Total cholesterol (g/L)	2.24 (0.37)	2.18 (0.34)	2.15 (0.35)	*<0.02*	2.26 (0.38)	2.24 (0.38)	2.19 (0.35)	*<0.0001*	2.24 (0.41)	2.22 (0.42)	2.16 (0.37)	*<0.003*	*0.8*
HDL cholesterol (g/L)	0.48 (0.13)	0.49 (0.12)	0.50 (0.13)	*<0.03*	0.49 (0.13)	0.49 (0.13)	0.50 (0.12)	*0.330*	0.49 (0.14)	0.48 (0.14)	0.48 (0.12)	*0.07*	*<0.02*
Treatement (%)													
hypertension	10.40	7.00	7.50	*0.43*	9.20	11.10	11.20	*0.150*	5.50	8.30	7.10	*0.58*	*0.35*
diabetes	0.60	0.60	0.20	*0.11*	0.40	0.50	0.50	*0.130*	0.30	0.30	0.40	*0.77*	*0.11*
dyslipidemia	2.40	4.00	3.90	*0.61*	4.20	4.20	4.90	*0.920*	3.10	3.40	2.50	*0.68*	*0.92*
Cigarettes smoked (n)	na	na	na		na	na	na		16.1 (10.7)	13.6 (11.0)	11.7 (10.1)	*<0.0001*	

* General linear, logistic and polytomic regressions adjusted on age and centre with F&V intake as continuous variable were used to compare characteristics across F&V tertiles. † Interaction between smoking status and F&V intake. Standard deviations are in brackects. na : not applicable

Table 3. Fully adjusted (model 3) mutivariate relative risk (RR) for cardiovascular events according to frequency of fruit and vegetable intake stratified by smoking status

		Acute Coronary Syndrome					Cardiovascular disease				
	n	No. of cases	RR*	95% CI	P for trend *	P for interaction †	No. of cases	RR*	95% CI	P for trend *	P for interaction †
Fruit and vegetables											
Never smokers											
≤1.57 (time/d)	695	24	1				40	1			
1.6-2.57 (time/d)	818	28	1.13	[0.65 ; 1.95]	*0.85*		53	1.32	[0.87 ; 1.99]	*0.26*	
≥2.6 (time/d)	897	27	1.06	[0.60 ; 1.84]			52	1.27	[0.84 ; 1.93]		
Fomer smokers											
≤1.57 (time/d)	1016	48	1				83	1.00			
1.6-2.57 (time/d)	1130	41	0.80	[0.53 ; 1.22]	*0.80*	*<0.02*	74	0.85	[0.62 ; 1.17]	*0.54*	*<0.04*
≥2.6 (time/d)	1207	51	0.98	[0.66 ; 1.47]			80	0.93	[0.68 ; 1.27]		
Current smokers											
≤1.57 (time/d)	1020	84	1				124	1.00			
1.6-2.57 (time/d)	727	44	0.78	[0.54 ; 1.13]	*<0.001*		67	0.80	[0.59 ; 1.08]	*<0.02*	
≥2.6 (time/d)	550	20	0.49	[0.30 ; 0.81]			39	0.64	[0.44 ; 0.93]		
Fruit											
Never smokers											
≤0.57 (time/d)	731	18	1				36	1			
0.64-1.14 (time/d)	725	32	1.93	[1.08 ; 3.46]	*0.96*		50	1.55	[1.00 ; 2.39]	*0.30*	
≥1.29 (time/d)	954	29	1.33	[0.72 ; 2.45]			59	1.45	[0.94 ; 2.23]		
Fomer smokers											
≤0.57 (time/d)	1090	54	1				81	1			
0.64-1.14 (time/d)	982	32	0.66	[0.42 ; 1.02]	*0.40*	*0.07*	64	0.92	[0.66 ; 1.28]	*0.52*	*0.09*
≥1.29 (time/d)	1281	54	0.83	[0.56 ; 1.23]			92	1.06	[0.77 ; 1.45]		
Current smokers											
≤0.57 (time/d)	1076	81	1				117	1			
0.64-1.14 (time/d)	611	43	1.00	[0.68 ; 1.45]	*<0.02*		66	1.05	[0.77 ; 1.43]	*0.15*	
≥1.29 (time/d)	610	24	0.61	[0.38 ; 0.99]			47	0.82	[0.57 ; 1.16]		
Vegetables											
Never smokers											
≤0.79 (time/d)	850	30	1				54	1			
1-1.29 (time/d)	760	19	0.71	[0.40 ; 1.26]	*0.75*		41	0.86	[0.57 ; 1.30]	*0.77*	
≥1.5 (time/d)	800	30	1.25	[0.74 ; 2.13]			50	1.14	[0.77 ; 1.71]		
Fomer smokers											
≤0.79 (time/d)	1162	49	1				86	1			
1-1.29 (time/d)	1025	40	0.95	[0.62 ; 1.45]	*0.50*	*<0.05*	74	0.98	[0.71 ; 1.34]	*0.92*	*0.15*
≥1.5 (time/d)	1166	51	1.29	[0.85 ; 1.95]			77	1.04	[0.76 ; 1.44]		
Current smokers											
≤0.79 (time/d)	1002	84	1				121	1			
1-1.29 (time/d)	720	38	0.65	[0.44 ; 0.96]	*0.07*		67	0.77	[0.57 ; 1.05]	*0.10*	
≥1.5 (time/d)	575	26	0.72	[0.45 ; 1.14]			42	0.74	[0.51 ; 1.07]		

* Cox proportional hazard model adjusted for centre, age, alcohol consumption, physical activity, education level, employment status, supplement vitamin intake, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, treatment for hypertension, diabetes and dyslipidemia. P values are for trends (using fruit and vegetable intake as a continuous variable) in stratified analyses using a separate slope design.

† P values for interaction between fruit and vegatable intake (continuous variable) and smoking (3 strata) were assessed with Cox regression

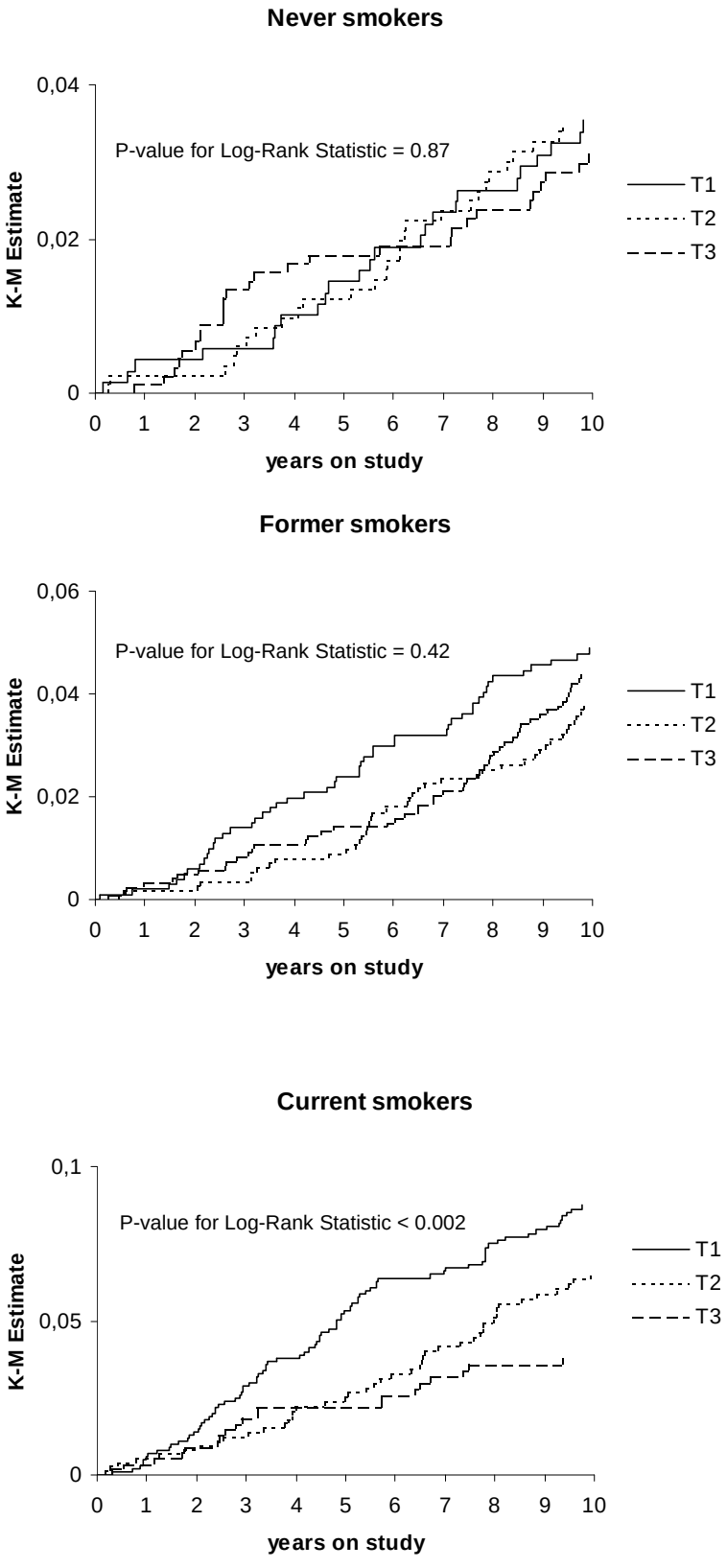
Never smokers
P-value for Log-Rank Statistic = 0.87
K-M Estimate
0,04
0,02
0
0 1 2 3 4 5 6 7 8 9 10
years on study
T1
T2
T3
Former smokers
P-value for Log-Rank Statistic = 0.42
K-M Estimate
0,06
0,04
0,02
0
0 1 2 3 4 5 6 7 8 9 10
years on study
T1
T2
T3
Current smokers
P-value for Log-Rank Statistic < 0.002
K-M Estimate
0,1
0,05
0
0 1 2 3 4 5 6 7 8 9 10
years on study
T1
T2
T3

Figure 1.