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Fruit intake and cardiovascular disease mortality in the UK Women's Cohort Study

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Abstract

In observational studies, fruit intake is associated with a reduced risk of cardiovascular disease (CVD), though fruit type has been less frequently explored. The aim of the current study was to explore the association between total fruit and fruit subgroup intake according to polyphenol content and CVD mortality in the UK Women's Cohort Study. Total fruit intake (g/day) derived from a 217-item food frequency questionnaire, was obtained from 30,458 women (aged 35 to 69 years) at baseline from 1995–1998. Fruit intakes were sub-categorised according to similarities in polyphenol profile from Phenol Explorer, including berries, citrus, drupes, pomes and tropical fruits. Mortality events were derived from the NHS Central Register. During the mean follow-up period of 16.7 years, 286 fatal CVD deaths (138 coronary heart disease (CHD), 148 stroke) were observed. Survival analysis was conducted using participants free from history of CVD at baseline. Total fruit intake was associated with lower risk of CVD and CHD mortality, with a 6-7% reduction in risk for each 80 g/day portion consumed (99% CI 0.89, 1.00 and 0.85, 1.01 respectively). Concerning particular fruit types, the direction of the associations tended to be inverse, but point estimates and tests for trend were not generally statistically significant. However, women in the highest intake group of grapes and citrus experienced a significant reduction in risk of CVD and stroke respectively compared with non-consumers [HR 0.56 (99% CI 0.32, 0.98) and 0.34 (0.14, 0.82) respectively]. These findings support promoted guidelines encouraging fruit consumption for health in women, but do not provide strong evidence to suggest that fruit type is as important.

Keywords: Fruit Intake, Polyphenol, Epidemiology, Cardiovascular Disease, Stroke, Coronary Heart Disease

Introduction

Cardiovascular disease (CVD) is a major cause of death in Europe [1] and the United Kingdom (UK), being accountable for a third of all-cause mortality [2]. Observational epidemiological studies in older adults have indicated that higher fruit and vegetable intake may lower risk of CVD [3-7]. There is evidence in the literature that demonstrates high total fruit intakes have beneficial effects on coronary heart disease [8, 9] and stroke [10, 11], but null findings for coronary heart disease (CHD) have also been reported [12]. A protective association has also been observed for risk of CHD when investigating fruit intakes by subgroups (e.g. citrus fruits) and individual fruits (i.e. blueberries and strawberries) [8, 13], as well as for the risk of stroke with increased consumption of citrus fruits [4, 10]. However, evidence is limited for berries [11], and pomes [13], with no published evidence for drupes and tropical fruits to our knowledge.

Suggested properties of fruit that may contribute to a protective effect on CVD risk include dietary fibre [14, 15], potassium [16, 17], folate [18] and “antioxidants”, such as polyphenols. However, polyphenol profiles differ for each type of fruit. Citrus fruits are rich in flavanones specifically, and berries are rich in anthocyanins. In terms of polyphenol content, drupes are more complex than citrus as they are rich in flavanols and hydroxycinnamic acids, while pomes contain different proportions of flavonols, flavanols and hydroxycinnamic acids. Some observational studies have reported lower CVD mortality risk in individuals with a higher consumption of flavonoids (a subgroup of polyphenols) [13, 19, 20]. The main flavonoid in oranges is hesperidin, which is bioavailable [21], and exhibits favourable effects on hypertension [22-24]. Anthocyanins from berries have been associated with ‘healthy’ blood lipid profiles, [25] and are also anti-inflammatory [26]. However, there is little evidence from intervention studies to directly support the effect of flavonoids from pomes, drupes and tropical fruit intakes on CVD risk or CVD risk factors. Furthermore, very few studies have thoroughly and specifically investigated CVD risk and the relationship between consumption of fruit subgroups.

The aim of the current study was to explore the association between total fruit intake and subgroups of fruit intake according to similarities in polyphenol profile with reference to Phenol Explorer [27] and risk of CVD mortality using data from the UK Women’s Cohort Study (UKWCS).

Methods

Study Population

Baseline information from participants of the UKWCS was collected between 1995 and 1998. A 217-item food frequency questionnaire (FFQ), adapted from the EPIC-Oxford Cohort [28], was sent out to 61,000 potential participants, who had previously responded to a direct mail survey from the World Cancer Research Fund (WCRF) [29]. A total of 35,692 women completed and returned the FFQ and associated questions, providing information on about 600 diet, health and lifestyle variables. The FFQ was also validated using a semi-weighed 4-day food diary, and all correlation coefficients between nutrient intakes from the FFQ and food diary were highly significant ($p < 0.01$) and comparable to those observed in other studies [30].

Baseline Characteristics

Age, waist circumference, height, weight, medical history and smoking habits, were self-reported. Physical activity was recorded using a binary question in the FFQ which questioned if participants spent time on activities vigorous enough to cause sweating or a faster heartbeat, which indicated moderate physical activity. Supplement usage was identified by asking whether participants took any vitamins, minerals, fish oils, fibre or other food supplements. Participants also self-reported their status regarding adoption of vegetarian or vegan diets. Classification of socio-economic status was undertaken based on occupation, according to the United Kingdom National Statistics-Socio-Economic Classification (NS-SEC), where women are divided into three categories, 1) Managerial/professional, 2) Intermediate, or 3) Routine/manual [31]. Additional socio-demographic information such as marital status and high school education was determined by self-report questions asking for marital status (married or living as married, divorced, single, widowed, separated) and achieved qualifications (CSE, GCE ‘O’ Level, City & Guilds, ‘A’ Levels or Highers, Teaching diploma or HNC, Degree, None of these) respectively.

Dietary Information

Participants were required to choose their frequency of consumption for each food listed on the FFQ by answering the question ‘how often have you eaten these foods in the last 12 months?’ using one of ten response categories (ranging from never to 6+ portions per day). Nutrient intakes (including ethanol intake) were derived by applying a standard portion size to the relevant frequency category and calculating the nutrient intake by summing nutrients from all foods to generate intakes per day. Nutrient information for foods was obtained from McCance & Widdowson’s The Composition of Foods (5th Edition) [32]. Total vegetable intake was generated by combining multiple vegetable FFQ items; excluding potatoes, but including the vegetable components of composite dishes. Total fruit intake was similarly estimated, including fresh fruits, dried fruits, pure fruit juices and processed fruits (Table 1). These groups were also investigated separately. Fruits were then divided into sub-categories by botanical family on Phenol Explorer to characterise fruit types according to their polyphenol content. These sub-categories were berries, citrus, drupes, pomes and tropical fruits [27]. Consumption was expressed as grams of fruit per day (g/day). For the small amount of missing data on fruit consumption, non-response was taken to indicate non consumption.

Mortality Data

Mortality data were available for participants who had provided information at baseline to allow tracing of their records through the UK's NHS Central Register (98% of participants provided this). There were no important differences in characteristics of those who were traced versus those untraced (data not shown). Deaths of participants were classified using codes provided by International Classification of Disease (ICD) 9th and 10th editions. Deaths from CVD were classified as either fatal cerebrovascular cases (codes 430-438 or I60-I69.8) or fatal heart disease cases (codes 410-4149 or I20-I25.9).

Statistical Methods and Design

Survival analysis was conducted using the Cox proportional hazards models to calculate a hazard ratio (HR) and 99% confidence intervals (CI). Time of survival was determined by the date the questionnaire was received until death or censor date (18th December 2013). Participants were divided into five approximately equal groups based on fruit intake of the whole cohort. Risk of CVD mortality was determined by comparing each intake group with the reference group, which included the lowest consumers (non-consumers in the case of citrus fruit). Linear trend was tested by calculating increments of fruit intake according to a typical portion size of 80 g, with the exception of 250 g for orange juice and 125 g for other fruit juices, since these represent more commonly consumed portion sizes [33].

Selection of potential confounding variables for inclusion in models was determined using directed acyclic graphs (DAGs) [34], taking into account previously identified risk factors for CVD within the scientific literature and avoided exclusively statistical approaches such as stepwise procedures, although we were partly guided by implementation of likelihood ratio tests to indicate whether there were major changes in point estimates after adjusting for potential confounders. Analysis of variance, chi squared tests and correlation tests were performed to prevent over-inclusion of variables in the model. Likelihood ratio tests were also performed to provide statistical evidence for the inclusion or exclusion of variables for effect modification and multicollinearity in the model. The assumptions for proportional hazards were checked using hazard function plot and scaled Schoenfeld residuals test. Models presented in the results section were adjusted for 1) age or 2) additionally for BMI, ethanol intake (g/day), physical activity status (moderately active or not), socio-economic status (professional or managerial/intermediate/routine or manual), smoking status (smokers v. non-smokers) and total amount of vegetables consumed (g/day). Models that investigated subgroup fruit intakes were further adjusted for fruit intake not in that subgroup, for example citrus fruits were adjusted for the total amount of non-citrus fruit consumed (g/day). Sensitivity analysis was performed by including adjustment for energy intake (kcal/day) in the models stated above. However, since there was no significant difference between the model including and excluding energy, the latter approach was adopted in the results below. Effect modifications were explored by stratifying on certain variables selected a priori, and generating HRs per unit increment. Variables explored were BMI (obese v. non-obese), smoking (smoking v. non-smoking), menopausal status (pre-menopausal v. post-menopausal) and self-reported high blood pressure. However, due to inadequate numbers of fatal cases (<50), these analyses were ultimately restricted to postmenopausal women, women with and without self reported high blood pressure, non-smokers and non-obese women. Statistical significance was determined by 2-sided p-value of ≤ 0.01, to reflect 99% significance level and thus to lower the likelihood of type 1 error. Stata version 12.0 [35] was used for all statistical analyses.

Ethical Approval

Ethical approval was granted by 174 local research ethics committees, which represented all participants at the time of cohort establishment in 1993. Study ethical approval is now overseen by the National Research Ethics Committee-Yorkshire and the Humber, Leeds East and approval concerning follow-up work for the cohort was granted in December 2011.

Results

Baseline Characteristics

Cohort participants who did not provide sufficient information for linkage to the UK national death registry were excluded (n = 768). Those who had self-reported stroke, angina, heart attacks, cancer and type 2 diabetes at baseline were excluded from the current analysis due to risk of potential post-diagnosis changes in dietary behaviour (n = 3929), and those with extreme total energy intakes (outside 500 kcal – 6,000 kcal/day) were also excluded to minimise errors from under- and over-estimation of intakes (n = 49). Outliers were excluded by removing those who had extreme fruit intakes (>1500 g/day) (n = 241). This left a total of 30,458 eligible participants for inclusion in the analyses. During the follow-up period from 1995 to 2013 (mean = 16.7 years), there were 286 CVD fatalities, of which 138 were from CHD and 148 from stroke.

The baseline characteristics of all participants, cases and non-cases, are reported in Table 2. Fatal CVD cases tended to be older, with a higher BMI and larger waist circumference than non-cases. They reported higher smoking rates, lower vitamin/mineral supplement consumption, lower physical activity, and a lower proportion were vegetarians. Fatal CVD cases also had a higher percentage of participants with lower socio-economic status and were less likely to be married than non-cases. In addition, the percentage of self-reported medical conditions was twice as high in fatal CVD cases compared to non-cases. Minor differences between fatal CVD cases and non-cases were observed for energy intake, total fruit and vegetable consumption, where fatal cases were more likely to have lower intakes than non-cases. When distributed into fruit consumption quintiles (Table 3), with increasing total fruit intake, participants were older and slimmer with a lower BMI. Participants with a higher fruit intake also tended to report other healthy lifestyle habits, such as high vegetable consumption, lower alcohol consumption, lower smoking rates and higher levels of physical activity. In addition, participants with higher fruit intake were also more likely to be married and have a higher socio-economic status and higher energy intake.

Survival Analysis

In the fully-adjusted model (Table 4), HR and 99% CI for increasing quintiles of fruit intake are presented with analysis of linear association addressing dose response. Participants from the highest total fruit intake quintile, consuming >7 portions/day had a 43% lower risk of death from CVD (99% CI 0.34 to 0.95, p-value = 0.013) compared with women in the lowest quintile consuming <2.5 portions/day. When CVD outcomes were analysed separately, no association was found with fatal stroke. However, there was an association for fatal CHD in the highest quintile of total fruit intake, with risk lowered by 55% (95 % CI 0.21 to 0.97, p-value = 0.031) compared to the lowest quintile. When total fruit intake was examined in fully-adjusted dose-response models, a lower risk of fatal CVD of between 6 to 8% was seen for every additional 80 g/day of fresh fruit intake, the combined intake of fresh fruit & juice, as well as for combined fresh & dried fruit (Table 4). Negative associations for total fruit intake were also found for risk of fatal CHD alone. Risk of fatal CHD was halved in the highest total fruit intake quintile compared with the reference intake group, and borderline significantly reduced by 7% with every additional 80g portion of fruit consumed (99 % CI 0.85 to 0.1.01, p-value = 0.031). The risk of CHD was also 11% lower for every 80 g increase of fresh & dried fruit intake (excluding fruit juice). Total fruit intake was not statistically associated with risk of fatal stroke. Neither dried fruit intake nor fruit juice intake alone were associated with risk of fatal CVD, CHD or stroke.

With regard to fruit subgroups, the risk of fatal CVD in the highest quintile for total citrus intake (juice and fruit) was halved when compared to non-consumers [HR 0.49 (99 % CI 0.25 to 0.96)], and was found to be even lower for risk of fatal stroke [HR 0.34 (99 % CI 0.14 to 0.82)]. However, neither association was seen to have a significant dose response. Similarly, an inverse association was seen with citrus fruits and fatal CVD [HR 0.54 (99 % CI 0.31 to 0.95)] and fatal stroke [HR 0.49 (95 % CI 0.23 to 1.07)] when comparing the highest consuming quintile and non-consumers, but significant dose responses were not observed. No association was found with citrus fruit intake and fatal CHD. Orange juice intake was also not associated with fatal CVD risk. Risk of fatal CVD was 34% lower with each 80 g/day greater grape intake (99 % CI 0.43 to 1.02, p-value = 0.014) Intake of grapes was not associated with fatal CHD or stroke, and no association or dose response for fatal CVD was found in the analysis of subgroups of berries, pomes, drupes and tropical fruit.

When analyses were restricted to certain participants within the cohort (separate analyses on the non-obese, non-smokers, post-menopausal women, and women with or without high blood pressure), the HRs for CVD in relation to each 80 g/d increment for total, fresh, fresh and juice, and fresh and dried fruits combined remained inverse, and similar to those for the full cohort (data not shown). However, in participants that reported they had high blood pressure, these HR were close to unity and not statistically significant (e.g. for total fruit the CVD HR per 80 g/d was 0.99, 99% CI 0.91 to 1.09).

Discussion

The objective of this study was to investigate the association between total fruit intake and different subgroups of fruit and fatal CVD risk. Results from the present study indicated a lower risk of fatal CVD with higher intake of total fruit and grapes, and lower fatal CHD with higher intake of fresh fruit. These associations were restricted to women who did not report having high blood pressure, but this finding requires verification with larger sample sizes. In terms of the associations with fruit types, generally there was little evidence of association. Greater intake of total citrus was associated with a lower risk of fatal stroke. There was no indication that the risk of stroke was lower with higher intake of citrus fruit, due to the absence of a significant linear trend. No evidence of association was determined for total fruit juice, orange juice, dried fruit, berries, pomes, drupes and tropical fruit.

Previous meta-analyses of observational studies have indicated a significant, inverse association with risk of total CVD [36], CHD and greater consumption of fruit and vegetables [37]. This exposure also had a similar association with risk of stroke [38]. In addition, evidence from studies conducted on the effects of total fruit intake on CVD risk in different countries is generally consistent with the current study [39-41], as well as for CHD [4, 7, 8] and stroke. However, studies rarely investigate both CHD and stroke outcomes in the same cohort [41]. Stroke and CHD share some common aetiology, being mainly driven by the process of atherosclerosis, and were thus examined together to explore total CVD. However, there are distinct differences between these two conditions which warrant separate examination. For example, stroke manifests in the brain, while CHD occurs in the heart. These conditions could also be caused by different biological mechanisms (high blood cholesterol, weak endothelial function, capillary permeability, and occlusion or rupturing arteries) involving different risk factors [42, 43]. This approach was therefore adopted in the current study. There was a lack of association between fruit juices and CVD risk in this study, and there are a number of potential explanations. In the UKWCS, citrus juice consumption was higher than the broad fruit juice category. Citrus fruits also retain more flavanones after processing, although some studies report a higher content of flavanones in fruit, than in juice [44]. However, apple juice, as included in the broad fruit juice category, does not [45]. In addition, a randomized controlled trial (RCT) indicated that whole fruit had a more potent impact on reducing CVD risk factors than apple juice, suggesting that the fibre content might potentially be more important than the polyphenols delivered, or that disaggregation of the polyphenols may render them less biologically potent [46]. However, possibly more importantly, juice consumption levels are low in the cohort overall, and there are fewer consumers compared to whole fruit.

Other observational studies exploring fruit subgroups and CVD risk, have tended to focus on grape consumption, or wine and the polyphenols contained within, stemming from the so-called ‘French Paradox’ [47]. Evidence for polyphenols in grapes consumed fresh or as products that support health benefits has been fairly consistent, and reported attributes such as total antioxidant capacity (which is effectively a general estimate of total polyphenol content) [48] and vasoprotective effects [49] support the findings of the current study. There is also evidence relating to increased total citrus intake and lowered risk of CHD [4, 8]. Evidence from cohort studies of a protective association between citrus consumption and risk of CVD is suggestive of a lowering of risk [10], although there is some inconsistency between studies, possibly due to variation in consumption pattern between countries [10, 50]. In the analyses reported here, no dose response with increasing citrus consumption was observed, although, non-citrus consumers were found to be at greater risk of fatal CVD in comparison to citrus consumers overall (data not shown). This suggests a possible protective effect of citrus fruits independent of a dose response or may indicate the presence of residual confounding. High levels of vitamin C in citrus fruits were previously suggested as a possible mechanism for lowering risk of CVD through its biological activities including antioxidant action, but results from RCTs of vitamin C intake (not fruit) do not support this hypothesis [51, 52]. However, epidemiological studies have found significant associations between flavanone intake and CVD risk [13, 19], and hesperidin (a polyphenol in citrus fruit) was seen to significantly lower diastolic blood pressure in two human studies after a single dose of 500 mL commercial orange juice [23, 24]. Hesperidin also improved endothelial function [22], and reduced permeability and fragility of capillary walls [53], which were symptoms that manifests in hypertension, a major risk factor for stroke. Therefore, the current evidence is indicative of a potentially beneficial effect deriving from polyphenols rather than specifically from vitamin C intake.

Considering all the evidence given above, if beneficial effects of all polyphenols are responsible for lowered fatal CVD risk, then associations should also be seen for pomes, berries, drupes and tropical fruit intakes. However, no association was found between pomes and CVD risk in UKWCS, despite high levels of consumption, in contrast to other studies [13, 19, 50]. Further investigations into berries, drupes and tropical fruits in this cohort revealed relatively low intakes and this limited variation in consumption may somewhat explain the lack of association here, as the concentration of active compounds may not be high enough in vivo to have any mechanistic effects. Moreover, the UKWCS contains a higher proportion of vegetarians and well educated participants who tend to eat more healthily than the general population, thus results need to be carefully interpreted. In addition, fruit subgroups tend to contain a broad spectrum of different polyphenols, rather than being a concentrated source of one particular type (such as flavanones in citrus fruits), and so it is possible that in isolation, none of these fruit types provided sufficient amounts of the most potent types of polyphenol. It is also important to note that other components in fruits, such as dietary fibre, nitrates and carotenoids may also play a role in CVD prevention besides polyphenols. For example, one recent meta-analysis of cohort studies reported an inverse association between fruit fibre and CHD risk, although numbers of included studies were low and heterogeneity between studies was high [54]. Fibre from fruit may impact on CVD risk factors through multiple suggested mechanisms, including, but not restricted to, lowering blood cholesterol via alteration of bile acid synthesis and excretion [55]. Observational studies have also suggested that carotenoids (single and total) are associated with lower CHD risk [56]. Suggested mechanisms include free radial scavenging and protecting low-density lipoproteins against oxidation, however, RCTs have failed to show a reduction in CVD events with β-carotene supplementation [57].

In interpreting the results of these analyses, certain limitations of the study should be considered. The relatively low numbers of cases of CVD, incomplete follow-up of all participants and missing information on certain covariates may have lowered our ability to detect associations. Other limitations of the study include the fact that dietary intakes from one time point only were utilised in these analyses, which meant any changes in dietary pattern over time could not be taken into account. Self-reported fruit intakes in the UKWCS (400 g/day) are well above the national average value [58, 59] and other studies [11, 60], possibly due to over-reporting on FFQ in general [61], as observed in other cohort studies employing this method of dietary assessment [62]. In addition, results are more difficult to generalize to current diets, as assessment of diet was conducted more than two decades ago, and so the dietary patterns for the cohort then compared to the population now could be different. In the past two decades the variety and availability of previously seasonal fruit has expanded, and the range of processed foods containing exotic fruits with unquantified polyphenol content has also increased [63, 64]. Whilst inverse associations between fruit intake and risk of CVD have been observed, interpretation of the extent of causality should be undertaken with caution since with any observational study, there is substantial potential for biases caused by incomplete adjustment for confounding, measurement error in the exposure estimate, and other biases in participant selection or data collection. The bias could be large in size, and act in either direction, either towards or away from the null. In particular, results are not necessarily transferrable to men, as fruit intake [59] and CVD risks [2] differ between genders, although we do not have reason to suppose that the mechanism of action of fruit on CVD risk may differ by gender. Further intervention studies on subgroups of fruits divided by polyphenol profiles would be recommended to establish causal relationships. The current study also only investigated mortality data, which meant that any non-fatal events were unknown and misclassified as non-cases. This would reduce the number of fatal events available, especially for sensitivity analyses where case numbers were lower.

However, the analysis has certain strengths: the UKWCS is a large prospective cohort which has been followed up for a long period of time, and a wide diversity in dietary intakes and patterns in this health-conscious cohort facilitates the elucidation of associations between chronic disease and dietary intake.

Furthermore, to our knowledge, this is the first study that has extensively investigated the effects of subgroups of fruit according to polyphenol profiles on risk of CVD. The estimation of total fruit intake is also strengthened by the inclusion of other fruit sources such as dried fruit, juices or processed fruits. In addition, using Phenol Explorer as a reference database for sub-dividing fruit intake has certain advantages, due to the extensive method implemented to collect high-quality literature articles on polyphenol composition, the impacts of food processing on polyphenols and metabolite composition in the body, ensuring that the fruit groupings applied here were sensible with regard to the variety of polyphenols in each fruit group.

In conclusion, greater consumption of total fruit intake, fresh fruit intake and fresh grapes were seen to be protectively associated with fatal CVD risk in the UKWCS. This finding is aligned with widely promoted guidelines promoting fruit consumption for health. Further investigations are recommended for consumption of citrus fruits to assess its relationship with CVD risk in the population. Overall, the findings of this study do not provide strong evidence to suggest that fruit type is important. Until further knowledge is obtained from intervention studies, consumption of a wide variety of different types of fruit is recommended.

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Table 1: Baseline fruit variables grouped for survival analysis according to categorization in Phenol Explorer

Investigated Variable			**FFQ Variables**	**Major Polyphenol Composition**
Total Fruit Intake	Total Fruit Juice		Orange Juice (Pure Fruit) Other (100%) Pure Fruit Juices	Flavanones (orange juice); dependent on type of fruit juice for other fruit juices
	Total Dried Fruits		Dates Figs Prunes Mixed Dried Fruit e.g. Apricots, Apples, Pears, Mangoes Currants, Raisins, Sultanas	Varied depending on fruit type
	Processed Fruits*		Fruit Tarts, Pies, Crumbles	Dependent on fruit within the dish
	Total Fresh Fruit	Total Citrus	Oranges, Satsumas, Grapefruits etc Orange Juice (Pure Fruit)	Flavanones
		Berries	Raspberries Red currants/Black currants Strawberries	Anthocyanins, Flavonols, Hydroxybenzoic acids
		Pomes	Apples Pears	Flavanols, Hydroxycinnamic acids
		Drupes	Apricots Nectarines Peaches Plums	Flavanols, Flavonols, Hydroxycinnamic acids
		Tropical Fruits	Bananas Kiwi Fruit Mangoes Papaya Pineapple	Flavanols, Lignans
		Grapes	Grapes	Anthocyanins, Flavanols, Hydroxycinnamic acids

*Not investigated individually

Table 2: Baseline characteristics for CHD mortality, stroke mortality and non-fatal cases

	CHD Mortality Cases	**Stroke Mortality Cases**	**Non-cases**
No. of cases (n)	138	148	30172
Age, years (SD)	63.5 (8.0)	64.0 (8.3)	51.5 (9.0)
BMI, kg/m^2 (SD)	25.8 (4.7)	24.5 (4.2)	24.3 (4.2)
Waist Circumference, cm (SD)	77.2 (11.5)	75.8 (10.1)	73.1 (9.0)
Supplement Users (%, 95% C.I.)	53.0 (44.9, 61.1)	52.9 (44.9, 60.9)	57.7 (57.1, 58.3)
Non-Smokers (%, 95% C.I.)	82.2 (76.4, 88.0)	83.6 (78.1, 89.1)	89.4 (89.1, 89.8)
Moderately Active/Active (%, 95% C.I.)	38.5 (30.7, 46.2)	38.3 (30.9, 45.8)	59.7 (59.1, 60.2)
Vegetarian/Vegan (%, 95% C.I.)	21.9 (15.6, 28.2)	19.8 (13.8, 25.7)	28.5 (28.0, 29.0)
Socio-Economic Status (%, 95% C.I.)			
Professional/Managerial	55.6 (47.8, 63.4)	57.1 (49.6, 64.7)	63.8 (63.2, 64.3)
Intermediate	36.9 (29.3, 44.4)	31.5 (24.4, 38.6)	27.2 (26.7, 27.7)
Routine and Manual	7.5 (0.3, 11.6)	11.3 (0.6, 16.1)	9.0 (8.7, 9.3)
Married/Living as Married (%, 95% C.I.)	54.5 (46.9, 62.2)	54.6 (47.1, 62.1)	76.2 (75.7, 76.7)
Highest Educational Qualification (%, 95% C.I.)			
No Education	31.0 (23.3, 38.7)	36.5 (28.6, 44.5)	15.5 (15.1, 16.0)
O-Level	27.5 (20.3, 34.9)	20.0 (13.4, 26.6)	31.7 (31.1, 32.2)
A-Level	19.7 (13.1, 26.3)	23.4 (16.5, 30.4)	24.9 (24.4, 25.4)
Degree	21.8 (14.9, 28.7)	20.0 (13.4, 26.6)	27.8 (27.3, 28.4)
History of parental cancer/heart disease (%, 95% C.I.)	69.5 (62.4, 76.5)	63.5 (56.2, 70.8)	66.0 (65.5, 66.6)
Had/Have high blood pressure (%, 95% C.I.)	39.0 (31.3, 46.6)	37.3 (29.7, 45.0)	15.1 (14.7, 15.5)
Had/Have high cholesterol/hyperlipidaemia (%, 95% C.I.)	11.8 (0.6, 17.1)	14.0 (0.8, 19.6)	6.4 (6.1, 6.7)
Energy Intake, kcal/day (SD)	2250 (722)	2240 (689)	2337 (700)
Ethanol Intake, g/day (SD)	5.4 (8.8)	7.4 (9.6)	8.8 (10.5)
Total Vegetables, g/day (SD)	296 (188)	277 (162)	313 (173)
Total Fruits, g/day (SD)	362 (256)	363 (240)	400 (245)
Portions of Vegetables, no. of 80 g/day (SD)	4.8 (3.4)	4.5 (2.6)	5.2 (2.8)
Portions of Fruit, no. of 80 g/day (SD)	4.6 (3.6)	4.5 (3.0)	5.1 (3.6)

Table 3: Participant baseline characteristics by quintile of total fruit intake (expressed as mean and standard deviation for continuous variables, % and 95% C.I. for categorical variables)

	Total fruit consumption quintiles including fruit juice, dried and processed fruits (g/day)				
	0-200	**200 - 302**	**302-410**	**410-568**	**568-1498**
General					
Participants (n)	6092	6092	6091	6092	6091
Age, years (SD)	50.4 (9.0)	51.2 (9.1)	51.8 (9.1)	52.5 (9.1)	52.3 (9.1)
BMI, kg/m^2 (SD)	24.6 (4.6)	24.3 (4.1)	24.3 (4.1)	24.2 (3.9)	24.1 (4.3)
Waist Circumference, cm (SD)	73.4 (9.7)	73.4 (9.0)	73.2 (8.7)	73.0 (8.6)	72.8 (8.9)
Dietary Intake					
Energy, kcal/day (SD)	2018 (623)	2193 (609)	2314 (641)	2446 (653)	2710 (763)
Ethanol, g/day (SD)	9.9 (12.6)	9.0 (10.7)	8.7 (10.0)	8.5 (9.5)	7.8 (9.3)
Total vegetables, g/day (SD)	229 (140)	271 (135)	308 (148)	342 (159)	411 (212)
Portions of fruit, no. of 80 g/day (SD)	1.7 (1.0)	3.3 (1.2)	4.5 (1.4)	6.1 (2.0)	9.7 (4.6)
Portions of vegetables, no. of 80 g/day (SD)	3.7 (2.2)	4.5 (2.2)	5.1 (2.4)	5.7 (2.6)	6.8 (3.4)
Lifestyle Habits					
Supplement users (%, 95% C.I.)	50.7 (49.4, 52.0)	55.1 (53.8, 56.4)	57.8 (56.7, 59.3)	60.4 (59.1, 61.2)	64.4 (63.2, 65.7)
Non-smokers (%, 95% C.I.)	81.4 (80.5, 82.4)	89.7 (88.9, 90.43)	90.9 (90.2, 91.6)	92.1 (91.5, 92.8)	92.7 (92.0, 93.3)
Moderately Active/Active (%, 95% C.I.)	48.5 (47.2, 49.8)	56.9 (55.6, 58.1)	61.3 (60.1, 62.6)	63.5 (62.2, 64.7)	67.0 (65.8, 68.2)
Vegetarian/Vegan (%, 95% C.I.)	24.3 (23.2, 25.3)	26.5 (25.4, 27.6)	27.0 (25.9, 28.2)	29.6 (28.4, 30.7)	34.5 (33.3, 35.7)
Socio Economic Status					
High school education & above (%, 95% C.I.)	44.2 (43.0, 45.6)	52.5 (51.2, 53.8)	53.6 (52.3, 54.9)	55.8 (54.5, 57.1)	57.1 (55.8, 58.4)
Married/Living as Married (%, 95% C.I.)	73.9 (72.7, 75.0)	75.6 (74.5, 76.7)	77.2 (76.1, 78.2)	76.8 (75.7, 77.9)	76.3 (75.2, 77.3)
Professional & Managerial job holders (%, 95% C.I.)	58.3 (57.1, 59.6)	62.5 (61.3, 63.8)	63.4 (62.2, 64.6)	65.7 (64.5, 66.9)	68.6 (62.5, 64.9)
Medical History					
History of parental cancer/heart disease (%, 95% C.I.)	65.6 (64.4, 66.8)	65.4 (64.2, 66.6)	66.0 (64.8, 67.2)	66.3 (65.1, 67.5)	67.0 (65.8, 68.1)
Had/Have high blood pressure (%, 95% C.I.)	15.2 (14.2, 16.1)	14.9 (14.0, 15.8)	15.7 (14.8, 16.6)	16.0 (15.0, 16.9)	15.2 (14.3, 16.1)
Had/Have high cholesterol/hyperlipidaemia (%, 95% C.I.)	5.8 (5.2, 6.4)	6.0 (5.4, 6.6)	6.4 (5.8, 7.0)	7.0 (6.3, 7.7)	7.2 (6.5, 7.9)

Table 4: Total fruit intake, fruit subgroup intake and cardiovascular mortality risk (expressed as hazard ratio and 99% C.I.)

	Intake (g/day)	CHD			Stroke			Total CVD		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Fruit Intake										
Q1	0 – 200	37	1	1	41	1	1	78	1	1
Q2	200 – 302	31	0.72 (0.41, 1.27)	0.76 (0.40, 1.43)	26	0.47 (0.25, 0.85)	0.60 (0.31, 1.15),	57	0.59 (0.39, 0.88)	0.67 (0.43, 1.06)
Q3	302 – 410	22	0.49 (0.26, 0.93)	0.53 (0.26, 1.08)	31	0.56 (0.32, 0.99)	0.74 (0.39, 1.39),	53	0.53 (0.35, 0.81)	0.64 (0.40, 1.02)
Q4	410 – 568	31	0.54 (0.30, 0.98)	0.68 (0.35, 1.32)	26	0.44 (0.25, 0.80)	0.59 (0.30, 1.16)	57	0.49 (0.32, 0.74)	0.64 (0.40, 1.02)
Q5	568 – 1498	21	0.41 (0.22, 0.79)	0.45 (0.21, 0.97)	28	0.46 (0.26, 0.83)	0.70 (0.35, 1.40)	49	0.44 (0.29, 0.68)	0.57 (0.34, 0.95)
p trend			0.002	0.031		0.002	0.171		<0.001	0.013
HR per 80 g/day			0.91 (0.85, 0.99)	0.93 (0.85, 1.01)		0.91 (0.85, 0.98)	0.96 (0.88, 1.04)		0.91 (0.87, 0.96)	0.94 (0.89, 1.00)
Fresh Fruit Intake										
Q1	0 – 133	36	1	1	35	1	1	71	1	1
Q2	133 – 210	24	0.49 (0.26, 0.91)	0.55 (0.28, 1.10)	34	0.67 (0.38, 1.19)	0.87 (0.47, 1.64)	58	0.58 (0.38, 0.88)	0.71 (0.44, 1.12)
Q3	210 – 292	33	0.65 (0.37, 1.14)	0.73 (0.38, 1.38)	29	0.54 (0.30, 0.98)	0.74 (0.38, 1.45)	62	0.59 (0.39, 0.90)	0.74 (0.46, 1.17)
Q4	292 – 415	29	0.52 (0.29, 0.93)	0.63 (0.32, 1.24)	26	0.44 (0.24, 0.83)	0.68 (0.34, 1.37)	55	0.48 (0.31, 0.74)	0.65 (0.40, 1.06)
Q5	415 – 1484	20	0.35 (0.18, 0.67)	0.39 (0.18, 0.87)	28	0.53 (0.30, 0.96)	0.78 (0.38, 1.59)	48	0.44 (0.28, 0.68)	0.56 (0.33, 0.96)
p trend			0.002	0.009		0.004	0.250		<0.001	0.008
HR per 80 g/day			0.89 (0.80, 0.98)	0.89 (0.79, 1.00)		0.90 (0.82, 0.99)	0.95 (0.86, 1.06)		0.89 (0.83, 0.96)	0.92 (0.85, 1.00)
Fresh Fruit and Juice Intake										
Q1	0 – 190	40	1	1	43	1	1	83	1	1
Q2	190 – 291	27	0.59 (0.33, 1.05)	0.60 (0.31, 1.16)	26	0.44 (0.24, 0.81)	0.56 (0.29, 1.07)	53	0.51 (0.34, 0.78)	0.58 (0.37, 0.92)
Q3	291 – 395	22	0.43 (0.23, 0.81)	0.49 (0.24, 0.98)	31	0.53 (0.30, 0.94)	0.69 (0.37, 1.30)	53	0.48 (0.32, 0.74)	0.59 (0.37, 0.94)
Q4	396 – 550	30	0.49 (0.27, 0.87)	0.61 (0.32, 1.18)	24	0.40 (0.22, 0.73)	0.51 (0.26, 1.02)	54	0.44 (0.29, 0.67)	0.56 (0.35, 0.90)
Q5	550 – 1497	23	0.42 (0.23, 0.78)	0.47 (0.22, 0.98)	28	0.45 (0.25, 0.81)	0.68 (0.34, 1.34)	51	0.44 (0.29, 0.67)	0.57 (0.34, 0.94)
p trend			0.003	0.039		0.002	0.182		<0.001	0.017
HR per 80 g/day			0.92 (0.85, 0.99)	0.93 (0.85, 1.02)		0.91 (0.85, 0.98)	0.96 (0.88, 1.04)		0.91 (0.87, 0.96)	0.94 (0.89, 1.00)
Fresh and Dried Fruit Intake										
Q1	0 – 142	36	1	1	35	1	1	71	1	1
Q2	142 – 221	25	0.50 (0.27, 0.93)	0.59 (0.30, 1.16)	34	0.67 (0.38, 1.18)	0.88 (0.47, 1.65)	59	0.58 (0.39, 0.89)	0.72 (0.46, 1.15)
Q3	221 – 305	31	0.60 (0.34, 1.06)	0.67 (0.35, 1.29)	28	0.51 (0.28, 0.93)	0.70 (0.36, 1.37)	59	0.55 (0.36, 0.84)	0.69 (0.43, 1.10)
Q4	305 – 433	29	0.50 (0.28, 0.91)	0.61 (0.31, 1.21)	28	0.46 (0.25, 0.85)	0.72 (0.36, 1.43)	57	0.48 (0.32, 0.74)	0.66 (0.41, 1.08)
Q5	433 – 1485	21	0.35 (0.18, 0.68)	0.41 (0.19, 0.89)	27	0.50 (0.28, 0.91)	0.73 (0.35, 1.51)	48	0.43 (0.28, 0.66)	0.55 (0.32, 0.94)
p trend			0.001	0.007		0.003	0.232		<0.001	0.006
HR per 80 g/day			0.89 (0.80, 0.97)	0.89 (0.79, 0.99)		0.90 (0.82, 0.98)	0.95 (0.86, 1.06)		0.89 (0.84, 0.95)	0.92 (0.85, 0.99)
Total Dried Fruit Intake										
Q1	0 – 3	32	1	1	31	1	1	63	1	1
Q2	3 – 6	18	0.53 (0.26, 1.07)	0.56 (0.26, 1.21)	19	0.66 (0.34, 1.30)	0.63 (0.29, 1.33)	37	0.60 (0.37, 0.97)	0.59 (0.35, 1.01)
Q3	6 – 10	25	0.74 (0.40, 1.37)	0.72 (0.36, 1.44)	33	0.94 (0.52, 1.71)	1.01 (0.53, 1.94)	58	0.84 (0.55, 1.29)	0.86 (0.53, 1.38)
Q4	10 – 19	34	0.74 (0.41, 1.34)	0.90 (0.47, 1.73)	33	0.77 (0.42, 1.41)	0.96 (0.50, 1.86)	67	0.75 (0.49, 1.15)	0.93 (0.58, 1.48)
Q5	19 – 460	33	0.67 (0.37, 1.20)	0.79 (0.40, 1.54)	36	0.69 (0.38, 1.25)	0.93 (0.48, 1.81)	69	0.68 (0.44, 1.03)	0.85 (0.53, 1.37)
p trend			0.061	0.241		0.063	0.557		0.008	0.217
HR per 25 g/day			0.78 (0.56, 1.09)	0.86 (0.61, 1.20)		0.79 (0.58, 1.09)	0.93 (0.70, 1.25)		0.79 (0.63, 0.99)	0.90 (0.72, 1.12)

(Table 4 continued)

	Intake (g/day)	CHD			Stroke			Total CVD		
		Cases ^{a}	Age Adjusted	Fully-Adjusted ^{b}	Cases ^{a}	Age Adjusted	Fully-Adjusted ^{b}	Cases ^{a}	Age Adjusted	Fully-Adjusted ^{b}
Fruit Juice Intake										
Q1	0 – 10	45	1	1	55	1	1	100	1	1
Q2	13 – 30	18	0.77 (0.41, 1.45)	0.74 (0.36, 1.52)	25	0.72 (0.40, 1.31)	0.82 (0.44, 1.54)	43	0.74 (0.48, 1.15)	0.78 (0.49, 1.26)
Q3	41 – 116	28	0.72 (0.41, 1.27)	0.77 (0.41, 1.44)	31	0.65 (0.38, 1.12)	0.72 (0.40, 1.30)	59	0.68 (0.46, 1.01)	0.74 (0.48, 1.14)
Q4	119 – 148	22	0.64 (0.34, 1.20)	0.79 (0.40, 1.55)	18	0.56 (0.31, 1.03)	0.52 (0.26, 1.07)	40	0.60 (0.39, 0.93)	0.64 (0.39, 1.04)
Q5	155 – 1015	29	0.82 (0.46, 1.45)	0.99 (0.53, 1.85)	23	0.57 (0.31, 1.03)	0.67 (0.35, 1.29)	52	0.68 (0.45, 1.03)	0.81 (0.52, 1.27)
p trend			0.449	0.931		0.128	0.430		0.106	0.611
HR per 125 g/day			0.93 (0.73, 1.18)	1.01 (0.79, 1.28)		0.86 (0.67, 1.11)	0.92 (0.71, 1.20)		0.90 (0.75, 1.07)	0.96 (0.81, 1.15)
Total Citrus Intake										
Non-Consumers	0	8	1	1	19	1	1	27	1	1
Q1	2 – 22	38	0.93 (0.40, 2.16)	1.13 (0.41, 3.09)	34	0.52 (0.26, 1.06)	0.36 (0.17, 0.77)	72	0.67 (0.39, 1.15)	0.59 (0.33, 1.06)
Q2	23 – 60	27	0.81 (0.34, 1.94)	1.01 (0.36, 2.85)	25	0.45 (0.21, 0.95)	0.40 (0.18, 0.86)	52	0.59 (0.33, 1.03)	0.58 (0.31, 1.06)
Q3	64 – 102	22	0.62 (0.25, 1.53)	0.76 (0.26, 2.22)	29	0.46 (0.22, 0.96)	0.39 (0.18, 0.85)	51	0.52 (0.30, 0.92)	0.50 (0.27, 0.93)
Q4	112 – 182	29	0.65 (0.27, 1.56)	0.91 (0.32, 2.55)	27	0.42 (0.20, 0.87)	0.33 (0.15, 0.71)	56	0.51 (0.29, 0.88)	0.50 (0.27, 0.91)
Q5	190 – 1422	19	0.59 (0.23, 1.50)	0.86 (0.28, 2.60)	19	0.34 (0.15, 0.77)	0.34 (0.14, 0.82)	38	0.43 (0.24, 0.80)	0.49 (0.25, 0.96)
p trend			0.015	0.168		0.054	0.301		0.002	0.086
HR per 80 g/day			0.84 (0.70, 1.01)	0.90 (0.74, 1.10)		0.88 (0.74, 1.04)	0.93 (0.77, 1.12)		0.86 (0.76, 0.97)	0.91 (0.80, 1.05)
Citrus Fruit Intake										
Non-Consumers	0	20	1	1	24	1	1	44	1	1
Q1	2 – 6	39	0.58 (0.31, 1.07)	0.65 (0.32, 1.33)	33	0.63 (0.33, 1.19)	0.44 (0.22, 0.89)	72	0.60 (0.38, 0.94)	0.54 (0.33, 0.88)
Q2	13	20	0.54 (0.26, 1.11)	0.62 (0.27, 1.40)	22	0.62 (0.30, 1.28)	0.56 (0.26, 1.19)	42	0.58 (0.35, 0.97)	0.58 (0.33, 1.02)
Q3	37	29	0.46 (0.23, 0.90)	0.58 (0.27, 1.25)	34	0.57 (0.29, 1.11)	0.60 (0.30, 1.19)	63	0.51 (0.32, 0.82)	0.59 (0.35, 0.98)
Q4	74	12	0.44 (0.19, 1.05)	0.64 (0.25, 1.67)	16	0.74 (0.34, 1.60)	0.70 (0.30, 1.64)	28	0.59 (0.33, 1.04)	0.67 (0.36, 1.26)
Q5	92 – 552	23	0.45 (0.23, 0.90)	0.61 (0.27, 1.37)	24	0.47 (0.23, 0.95)	0.49 (0.23, 1.07)	47	0.46 (0.28, 0.75)	0.54 (0.31, 0.95)
p trend			0.009	0.086		0.175	0.701		0.005	0.139
HR per 80 g/day			0.66 (0.43, 0.99)	0.74 (0.46, 1.16)		0.83 (0.59, 1.18)	0.95 (0.65, 1.37)		0.75 (0.57, 0.98)	0.85 (0.63, 1.13)
Orange Juice Intake										
Non-Consumers	0	30	1	1	40	1	1	70	1	1
Q1	3 – 10	41	0.76 (0.44, 1.34)	0.86 (0.46, 1.60)	43	0.64 (0.38, 1.09)	0.66 (0.37, 1.16)	84	0.70 (0.47, 1.02)	0.74 (0.49, 1.13)
Q2	20	11	0.62 (0.27, 1.42)	0.71 (0.28, 1.77)	12	0.60 (0.28, 1.29)	0.56 (0.24, 1.33)	23	0.61 (0.35, 1.07)	0.62 (0.33, 1.17)
Q3	58	19	0.68 (0.34, 1.36)	0.75 (0.35, 1.62)	24	0.62 (0.32, 1.18)	0.71 (0.36, 1.39)	43	0.65 (0.40, 1.04)	0.72 (0.43, 1.20)
Q4	116 – 145	39	0.74 (0.42, 1.30)	0.91 (0.48, 1.72)	30	0.51 (0.29, 0.90)	0.51 (0.27, 0.97)	69	0.61 (0.41, 0.91)	0.68 (0.44, 1.06)
Q5	363 – 870	3	0.32 (0.05, 2.06)	0.43 (0.06, 2.83)	4	0.53 (0.14, 2.02)	0.66 (0.17, 2.57)	7	0.43 (0.14, 1.28)	0.56 (0.19, 1.68)
p trend			0.167	0.510		0.122	0.312		0.038	0.231
HR per 250 g/day			0.69 (0.35, 1.37)	0.83 (0.41, 1.69)		0.66 (0.34, 1.31)	0.75 (0.37, 1.54)		0.68 (0.42, 1.10)	0.79 (0.48, 1.31)
Berries Intake										
Q1	0 – 1.6	42	1	1	34	1	1	73	1	1
Q2	1.7 – 4.0	23	0.56 (0.30, 1.02)	0.58 (0.30, 1.14)	24	0.71 (0.38, 1.34)	0.76 (0.38, 1.51)	46	0.63 (0.40, 0.97)	0.66 (0.41, 1.06)
Q3	4.0 – 7.7	12	0.31 (0.15, 0.65)	0.32 (0.13, 0.74)	26	0.82 (0.45, 1.51)	0.86 (0.44, 1.70)	40	0.54 (0.34, 0.85)	0.56 (0.33, 0.93)
Q4	7.8 – 15.3	37	0.60 (0.35, 1.04)	0.82 (0.45, 1.50)	36	0.82 (0.46, 1.45)	1.00 (0.53, 1.89)	68	0.70 (0.47, 1.03)	0.90 (0.58, 1.39)
Q5	15.4 – 365	28	0.55 (0.31, 0.98)	0.75 (0.38, 1.49)	32	0.70 (0.38, 1.28)	1.08 (0.55, 2.14)	60	0.62 (0.41, 0.93)	0.89 (0.55, 1.44)
p trend			0.944	0.124		0.109	0.765		0.248	0.393
HR per 80 g/day			0.98 (0.48, 2.00)	1.39 (0.80, 2.44)		0.48 (0.15, 1.56)	0.89 (0.34, 2.33)		0.75 (0.39, 1.43)	1.18 (0.72, 1.93)

(Table 4 continued)

	Intake (g/day)	CHD			Stroke			Total CVD		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Pomes Intake										
Q1	0 – 19	29	1	1	41	1	1	70	1	1
Q2	24 – 55	36	1.07 (0.60, 1.92)	1.39 (0.73, 2.67)	29	0.61 (0.34, 1.09)	0.79 (0.42, 1.49)	65	0.80 (0.54, 1.21)	1.03 (0.66, 1.62)
Q3	62 – 102	23	0.73 (0.38, 1.40)	0.99 (0.47, 2.06)	29	0.61 (0.34, 1.09)	0.91 (0.48, 1.74)	52	0.66 (0.43, 1.02)	0.94 (0.58, 1.52)
Q4	108 – 133	27	0.83 (0.44, 1.57)	1.29 (0.63, 2.65)	20	0.44 (0.23, 0.85)	0.68 (0.33, 1.42)	47	0.60 (0.38, 0.95)	0.94 (0.56, 1.55)
Q5	139 - 1392	27	0.75 (0.40, 1.40)	1.19 (0.56, 2.53)	33	0.68 (0.39, 1.17)	1.13 (0.58, 2.21)	60	0.71 (0.47, 1.07)	1.14 (0.69, 1.89)
p trend			0.060	0.693		0.326	0.210		0.044	0.540
HR per 80 g/day			0.86 (0.70, 1.05)	0.97 (0.77, 1.20)		0.93 (0.78, 1.12)	1.10 (0.91, 1.33)		0.90 (0.79, 1.03)	1.03 (0.89, 1.20)
Tropical Intake										
Q1	0 – 18	42	1	1	41	1	1	83	1	1
Q2	18 – 45	31	0.68 (0.38, 1.20)	0.73 (0.39, 1.34)	34	0.83 (0.47, 1.45)	0.82 (0.45, 1.50)	65	0.75 (0.50, 1.12)	0.77 (0.50, 1.18)
Q3	45 – 76	13	0.44 (0.21, 0.89)	0.41 (0.18, 0.94)	18	0.55 (0.28, 1.08)	0.62 (0.30, 1.30)	31	0.49 (0.30, 0.80)	0.51 (0.29, 0.88)
Q4	76 – 107	33	0.69 (0.40, 1.20)	0.76 (0.41, 1.40)	31	0.69 (0.39, 1.23)	0.78 (0.42, 1.46)	64	0.69 (0.46, 1.03)	0.77 (0.49, 1.19)
Q5	107 – 717	23	0.58 (0.32, 1.07)	0.70 (0.34, 1.45)	28	0.76 (0.43, 1.36)	0.99 (0.50, 1.97)	51	0.67 (0.44, 1.02)	0.84 (0.51, 1.38)
p trend			0.054	0.195		0.126	0.571		0.015	0.186
HR per 80 g/day			0.79 (0.58, 1.08)	0.83 (0.58, 1.19)		0.84 (0.63, 1.12)	0.93 (0.66, 1.30)		0.82 (0.66, 1.01)	0.88 (0.69, 1.13)
Drupes Intake										
Q1	0 – 1	50	1	1	41	1	1	91	1	1
Q2	1 – 3	25	0.56 (0.32, 0.99)	0.56 (0.30, 1.06)	36	0.90 (0.52, 1.55)	0.97 (0.53, 1.75)	61	0.72 (0.48, 1.06)	0.74 (0.48, 1.14)
Q3	3 – 6	17	0.34 (0.17, 0.66)	0.38 (0.18, 0.79)	28	0.65 (0.36, 1.18)	0.75 (0.39, 1.43)	45	0.48 (0.31, 0.74)	0.54 (0.34, 0.88)
Q4	6 – 10	25	0.52 (0.29, 0.94)	0.66 (0.34, 1.28)	25	0.63 (0.34, 1.17)	0.81 (0.41, 1.60)	50	0.57 (0.37, 0.87)	0.72 (0.45, 1.16)
Q5	10 – 165	25	0.53 (0.29, 0.95)	0.72 (0.35, 1.49)	22	0.58 (0.31, 1.08)	0.78 (0.36, 1.69)	47	0.55 (0.36, 0.85)	0.74 (0.44, 1.26)
p trend			0.015	0.279		0.071	0.433		0.003	0.186
HR per 80g/day			0.07 (0.00, 1.15)	0.27 (0.01, 6.17)		0.18 (0.01, 2.09)	0.41 (0.02, 7.62)		0.11 (0.02, 0.74)	0.33 (0.04, 2.84)
Grapes Intake										
Q1	0 – 2	49	1	1	53	1	1	102	1	1
Q2	7	33	0.56 (0.32, 0.97)	0.66 (0.37, 1.19)	34	0.56 (0.33, 0.95)	0.63 (0.36, 1.12)	67	0.56 (0.38, 0.82)	0.64 (0.43, 0.97)
Q3	14	23	0.55 (0.30, 1.02)	0.65 (0.34, 1.26)	27	0.58 (0.33, 1.02)	0.70 (0.38, 1.31)	50	0.57 (0.37, 0.86)	0.67 (0.43, 1.06)
Q4	40	22	0.52 (0.28, 0.95)	0.59 (0.30, 1.16)	23	0.46 (0.25, 0.84)	0.58 (0.30, 1.12)	45	0.49 (0.32, 0.75)	0.58 (0.36, 0.93)
Q5	80 – 600	15	0.59 (0.31, 1.13)	0.57 (0.26, 1.28)	15	0.38 (0.19, 0.78)	0.54 (0.25, 1.19)	30	0.48 (0.30, 0.77)	0.56 (0.32, 0.98)
p trend			0.139	0.130		0.001	0.046		0.001	0.014
HR per 80 g/day			0.77 (0.49, 1.21)	0.70 (0.39, 1.28)		0.46 (0.24, 0.86)	0.61 (0.33, 1.15)		0.61 (0.42, 0.90)	0.66 (0.43, 1.02)

[a] Case numbers apply to fully-adjusted models

[b] Adjusted for age, BMI, physical activity, smoking status, socio-economic status, alcohol intake, total vegetable intake, and mutual adjustments for fruits that are not in the exposure category