Dietary sources of (poly)phenols and the risk of cardiovascular disease in the United Kingdom

Heidi Tsz Mung Lai

Submitted in accordance with the requirements for the degree of
Doctor of Philosophy

The University of Leeds
School of Food Science and Nutrition

April 2016

Intellectual property and publication statement

I hereby confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 3 entitled 'Fruit and vegetable intake and cardiovascular disease in the UK Women's Cohort Study' incorporates the majority of a conference proceeding and a journal article:

Lai, H. T., Threapleton, D. E., Day, A. J., Williamson, G., Cade, J. E. and Burley, V. J. (2014) Total fruit intake and cardiovascular disease mortality in the UK Women's Cohort Study (UKWCS) *Journal of Epidemiology and Community Health*; 68(Suppl 1): A9

Lai, H. T., Threapleton, D. E., Day, A. J., Williamson, G., Cade, J. E. and Burley, V. J. (2015) Fruit intake and cardiovascular disease mortality in the UK Women's Cohort Study *European Journal of Epidemiology*; 30(9): p. 1035-48

I was jointly responsible for the design of the analysis with Andrea Day, Victoria Burley and Gary Williamson. Diane Threapleton provided the database with case ascertainment for the analysis. I then undertook all the analysis and the interpretation of the results. I was also the lead author for authoring the manuscript, incorporating comments from all co-authors above, and Victoria Burley submitted the manuscript.

The analysis conducted in **Chapter 9**, relating to the analysis of (poly)phenol content in fruit based beverages was completed in collaboration with Hanis Matsura Yahya, where part of the shared results was published in her thesis. We were jointly responsible for the design of the methodology, subsequent analyses and the interpretation of the results.

A small proportion of results from **Chapter 10**, which involved the analysis of fruit and vegetable intake and blood pressure in the National Diet and Nutrition Survey Rolling Programme was published in a conference proceeding for Nutrition Society Summer

Meeting 2015, as well as in an abstract booklet for the International Conference on Polyphenols and Health, 2015:

Lai, H. T., Holmes, M., Williamson, G, and Burley, V. J. (2015) Fruit and vegetable intakes and the association with blood pressure within adults in the United Kingdom's National Diet and Nutrition Survey Rolling Programme (2008/09-2011/12) *Proceedings of the Nutrition Society*; 74(OCE5): E318

Lai, H. T., Holmes, M., Williamson, G, and Burley, V. J. (2015) Fruit intake was associated with a lower blood pressure within adults in the United Kingdom's National Diet & Nutrition Survey Rolling Programme (2008/09-2011/12) International Conference on Polyphenols and Health; P405, p.185

I was jointly responsible for the design of the analysis with Melvin Holmes, Victoria Burley and Gary Williamson. Melvin Holmes recoded the dietary exposures of interest based on criteria derived with all the co-authors above. I then undertook all the analysis and the interpretation of the results.

Acknowledgements

First and foremost, I thank God for His blessings, strength, perseverance and wisdom to help me to complete my thesis. May the work completed here glorify His name.

My deepest gratitude to my panel of supervisors, Dr. Andrea Day, Dr. Melvin Holmes, Dr. Victoria Burley and Prof. Gary Williamson. Thank you, Andrea, for believing that I have the potential. Your enthusiasm, supportiveness, and encouragement during my B.Sc. and the early years of my Ph.D. inspired me greatly and granted me confidence, lifting my spirits to tackle the toughest challenges. To Gary, my sincerest thanks for your dedicated mentorship over the years. The support, guidance and advice you have given me are unparalleled, enabling me to become an independent researcher. I am grateful to Victoria, who opened my eyes and mind to the wonderful world of epidemiology. Your patience, attention to detail (contrary to my occasional carelessness) and persistent guidance is deeply appreciated, especially when my grammar did not make sense most of the time. To Mel, I am ever so grateful for your support in statistics, especially working throughout Christmas to help me with my analyses.

To my mentor, Prof. Simon Capewell, I am in your debt for your tireless support and encouragement during the final year of my Ph.D. Your advice and guidance are invaluable, helping me to find my confidence and develop my character.

To all my colleagues and friends in the School of Food Science and Nutrition, in particular, the Functional Food, and Nutritional Epidemiology groups. Thank you all for the encouragement, the laughs, hugs and especially the support for when I am down. I cherish the company you have provided in the labs repeating experiments for the umpteenth time, furiously programming on Stata and of course, all the coffee, tea and fun we also had together.

To the academic and administrative staff in the School of Food Science and Nutrition, thank you for your support and advice throughout the years that I have been here.

Not forgetting, my dearest friends, relatives, and extended family in the UK and overseas for your prayers, support and faith that I can complete this thesis when I had nearly lost faith myself.

Lastly, I would like to dedicate this thesis to my parents (Frederick and Laura) and my brother (Joel). There are no words fitting to express your unwavering support and unconditional love, which have kept me strong throughout this journey through nearly impossible odds.

Abstract

Higher total fruit and vegetable intake (FV) is associated with a lower CVD risk, however, the relative importance of particular fruits or vegetables (subgroups) is unknown. The association between coffee, tea intakes, and CVD risk is also inconsistent. FV, coffee, and tea are (poly)phenol-rich foods commonly consumed in the UK. This thesis studied the association between these food groups, their respective subgroups and CVD mortality, incidence, and blood pressure (BP) in the UK Women's Cohort Study (UKWCS) and the National Diet and Nutritional Survey Rolling Programme (NDNS RP).

Survival analysis was applied to calculate the risk of CVD mortality, and CVD incidence with increasing FV, coffee and tea intake in the UKWCS. The odds of being hypertensive were assessed using logistic regression in the UKWCS (self-reported) and the NDNS RP (measured). Measured BP levels were also investigated in the NDNS RP using multivariate regression. Aspects of methodology were explored between dietary assessments in the UKWCS using the Kappa statistic.

Overall, CVD risk was lower with higher intakes of FV, especially for total fruit, berries, citrus and grapes, but not for total vegetable. Greater intakes of total vegetables, fruit vegetables, and pomes were associated with a lower incidence of self-reported BP. Systolic BP was lower with increasing FV intake while diastolic BP lowered with a greater pome consumption. Attenuated associations in subpopulations with CVD risk factors suggest that protective effects are more apparent in healthy subpopulations. Coffee and tea intakes were not associated with the risk of CVD in either UK populations.

The FFQ in the UKWCS was able to rank the participants by low and high intakes, providing evidence for significant and null associations detected above. Novel findings from the total phenolic content within fruit juices and concentrates from the UK highlights the importance of updating Phenol Explorer, to accurately estimate (poly)phenol intake in the future. Implementation of RCTs based on hypotheses generated here would aid the determination of causal links between FV subgroups such as berries, citrus, pomes, grapes, and fruit vegetables and CVD risk.

Contents

List of figures

List of tables

Abbreviations

ACS	Acute coronary syndrome
ANOVA	Analysis of variance
BMI	Body mass index
BP	Blood pressure
CAPI	Computer assisted personal interview
CBG	Cyctosolic β-glucoside
CCE	Chronic coronary event
CE	Capillary zone electrophoresis
CHD	Coronary heart disease
CI	Confidence interval
COMT	Catechol-*O*-methyltransferase
COX-2	Cyclo-oxygenase
CVD	Cardiovascular disease
CY3RUT	Cyanidin-3-*O*-rutinoside
DAG	Directed acyclic graph
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DF	Dried fruit (UKWCS)
DINO	Diet in Nutrients Out
DP3RUT	Delphinidin-3-*O*-rutinoside
eNOS	Endothelial nitric oxide
EPIC	European Prospective Investigation into Cancer and Nutrition
FDF	Fresh and dried fruit (UKWCS)
FF	Fresh fruit (UKWCS)
FFJ	Fresh fruit and juice (UWKCS)
FFQ	Food frequency questionnaire
FJ	Fruit juice (UKWCS)
FSA	Food Standards Agency
FV	Fruit and vegetable
GAE	Gallic acid equivalents
HBP	High blood pressure
HDL-C	High-density lipoprotein cholesterol
HES	Hospital Episode Statistics
HNR	Human Nutrition Research
HPLC	High-performance liquid chromatography
HR	Hazard ratio
HS	Haemorrhagic stroke
ICD	International Classification of Diseases
iNOS	Inducible nitric oxide synthase
IS	Ischaemic stroke
K	Kappa statistic
K_w	Weighted Kappa statistic
LDL-C	Low-density lipoprotein cholesterol
LPH	Lactase phloridizin hydrolase
MA	Meta-analysis
MFP	Main food provider
MI	Myocardial infarction
MINAP	Myocardial Ischaemia Nutritional Audit Project

MRC	Medical Research Council
MY3RNS	Myricetin-3-*O*-rhamnoside
NDNS RP	National Diet and Nutritional Survey Rolling Programme
NHS	National Health Service
NO	Nitric oxide
NS-SEC	National Statistics Socio-Economic Classification
OR	Odds ratio
PAF	Postcode address file
PAR	Population attributable risk
PSU	Primary sampling unit
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SES	Socio-economic status
SR	Systematic review
TF	Total fruit (UKWCS)
TPC	Total phenolic content
UK	United Kingdom
UKWCS	UK Women's Cohort Study
US	United States
USDA	United States Agricultural Database
USt	Unclassified stroke

Chapter 1
Introduction and Objectives

1.1 Cardiovascular disease overview

Cardiovascular disease (CVD) is a collection of diseases that includes coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease (Figure 1.1). CHD and cerebrovascular disease are conditions caused by narrowing and occlusion of blood vessels supplying the heart and brain respectively [1]. These are caused by the continuous development of atheromatous plaques in blood vessels during the life course, which progress on towards atherosclerosis with increasing severity. Atherosclerosis is a chronic condition and is the major cause leading to CVD (described below). Despite the decreasing trends in the recent decade, CVD is still the leading cause of mortality in Europe, United Kingdom and other developing countries. It is also accountable for >80% of CVD mortality worldwide [2].

1.1.1 Cardiovascular disease types and pathogenesis

1.1.1.1 Overview

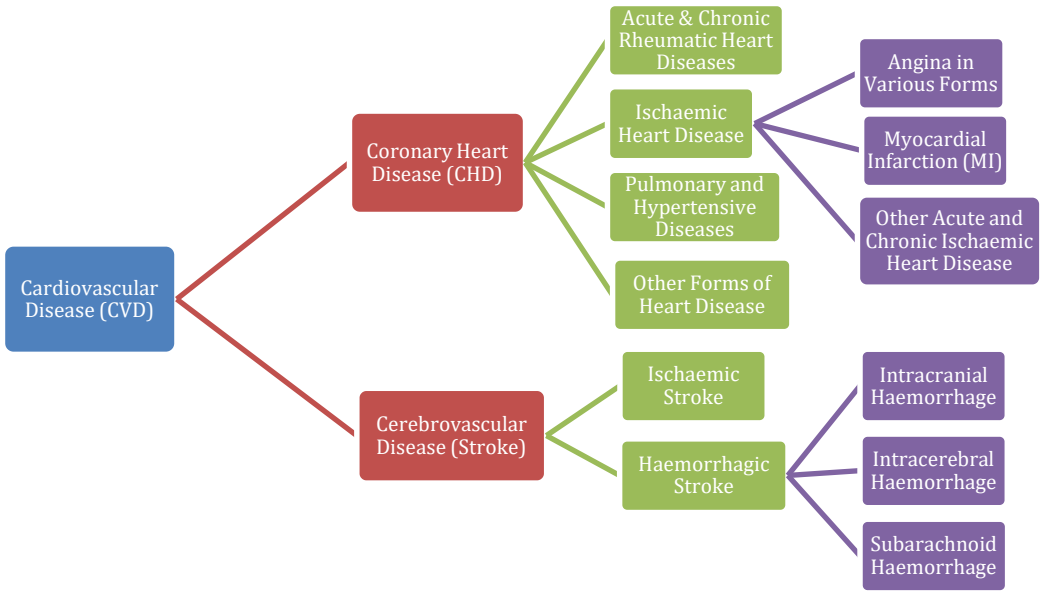


Figure 1.1 Summary of cardiovascular disease types

As mentioned above, atherosclerosis is the underlying disease which causes CHD and stroke events. It is a condition for the development of lesions or plaques on the arterial wall, and is responsible for the majority of CVD cases. Development could begin in young adulthood as atheroma due to natural lipid accumulation (such as fatty deposits and cholesterol) in the blood vessels, or endothelial injury and inflammation [3]. Macrophages react by engulfing up the lipids and become foam cell macrophages, which results in the formation of lesions termed 'fatty streaks' [4]. In the later stages, accumulation of 'fatty streaks' leads to the formation of fibrous plaques with a necrotic core, caused by dying macrophages that are engorged with lipids [4, 5]. A plaque with a large necrotic core occludes the blood vessels, causing a disruption in blood flow and eventually ruptures when it becomes unstable, triggering the formation of a blood clot or thrombus [4, 6].

1.1.1.2 Coronary heart disease

Acute coronary and cerebrovascular events occur when blood flow is obstructed in the blood vessels located in the myocardial or cerebral tissues, causing significant amount of damage to the heart or brain. CHD consists of angina, silent ischaemia, unstable angina, myocardial infarction (MI), arrhythmias, heart failures and sudden death [5]. These conditions are almost always due to atheromatous narrowing and occlusion of the arterial vessel. Angina occurs when plaques formed through atherosclerosis cause the arterial wall to thicken, and restrict or slow down blood supply to the heart muscles, while MI is caused by a thrombus occluding the flow of blood within the heart after it reaches a certain size [5].

1.1.1.3 Cerebrovascular Disease

Cerebrovascular disease, commonly known as stroke, manifests as ischaemic stroke and haemorrhagic stroke. The majority of strokes are identified by ischaemic stroke. Ischaemic strokes are caused by occlusion of the cerebral arteries by formation of atherosclerosis (as mentioned previously), or by thromboembolism, where the occlusion is caused by a thrombus from a cardiac origin such as a recent MI. This form of stroke is also known as cardioembolic stroke. Cardioembolic stroke may also be accelerated by the formation of atherosclerotic plaque in intracerebral arteries [7] and is accountable for 20% of strokes [3]. The cerebral damage caused is irreversible, and stroke in this form is more common in Western countries. Haemorrhagic stroke is the rupturing of blood vessels in the brain, causing the release of blood directly into the brain and is thought to be less common [7].

1.1.2 Cardiovascular disease in the UK

In the last few decades, the rates of CVD mortality and incidence in developed countries have declined [6, 8-11]. The overall CVD mortality rates for under 75s in the UK has fallen from 155,000 in 1961, to 45,000 in 2009 [12]. Overall age standardized death rates for CHD (under 65 years) have also declined in men from 143/100,000 in 1980 to 33/100,000 in 2010, and in women from 36/100,000 in 1980 to 8/100,000 in 2010 [10]. However, CHD mortality rates in the UK have not been decreasing as quickly as other developing countries [13], and may be stabilising, especially in younger adults of both sexes [9, 14]. Incidence rates are reported to have continuously declined in both men and women across all age groups since 1979 [12]. However, prevalence rates have not followed the same decline as mortality and incidence rates, and have increased over the last few decades. Prevalence of CVD for men reached its peak in the mid-2000s at 11.9%, remaining rather stable. The prevalence rate for women also peaked in the mid-2000s, but has declined since then [15]. Despite the positive outlook in decreasing mortality and incidence rates, cardiovascular disease is still the leading cause of death in the UK today, where 1 in 3 deaths are accounted for. Approximately 1.6 million men and 1 million women were living in the UK with CVD in 2010. Furthermore, it is also a main cause of premature mortality (over 25,000 cases), and a financial burden on the country, costing £19 billion a year in the UK [15]. Socioeconomic inequality gradients have also persisted among CHD mortality rates, and worsened, where the most deprived areas in the UK have the highest rates of CHD hospital admissions [15].

1.1.3 Cardiovascular disease risk factors

Several modifiable risk factors are known to be strongly associated with CVD. Hypertension, diabetes, physical activity, high alcohol use, abnormal lipid profiles, current smoking, abdominal obesity, high risk diet and psychosocial stress were reported in the INTERHEART study to account for more than 90% of population attributable risk (PAR) globally for the risk of MI [16]. The INTERSTROKE study also observed a similar set of risk factors mentioned previously for ischaemic stroke. In particular, significant risk factors for intracerebral haemorrhagic stroke were hypertension, smoking, waist-to-hip ratio, diet and alcohol intake [17]. Thus, unmodifiable CVD risk factors such as age, sex, ethnicity/race and family history of CVD, only contribute a minor component, making CVD a largely modifiable disease.

1.1.1.4 Overview of unmodifiable CVD risk factors

It is well known that increased age leads to a higher fatal CVD risk. There are also marked differences between sex. Figure 1.2 depicts a sharp increase in the number of fatal CVD deaths past 65 years, where 74% of total CVD deaths occur in the 75+ age group compared to other age groups in the UK [15]. Men are also more likely to encounter CVD before 65 years than women. However, the total number of deaths drastically increases in women, and overtakes men after 65 years of age exponentially [15]. A Finnish cohort clearly demonstrated the same concept [18], where difference in rates of CHD incidence were the largest between sexes at 25 to 49 years, and narrowed as age increased. Both CHD mortality and incidence also increased with age.

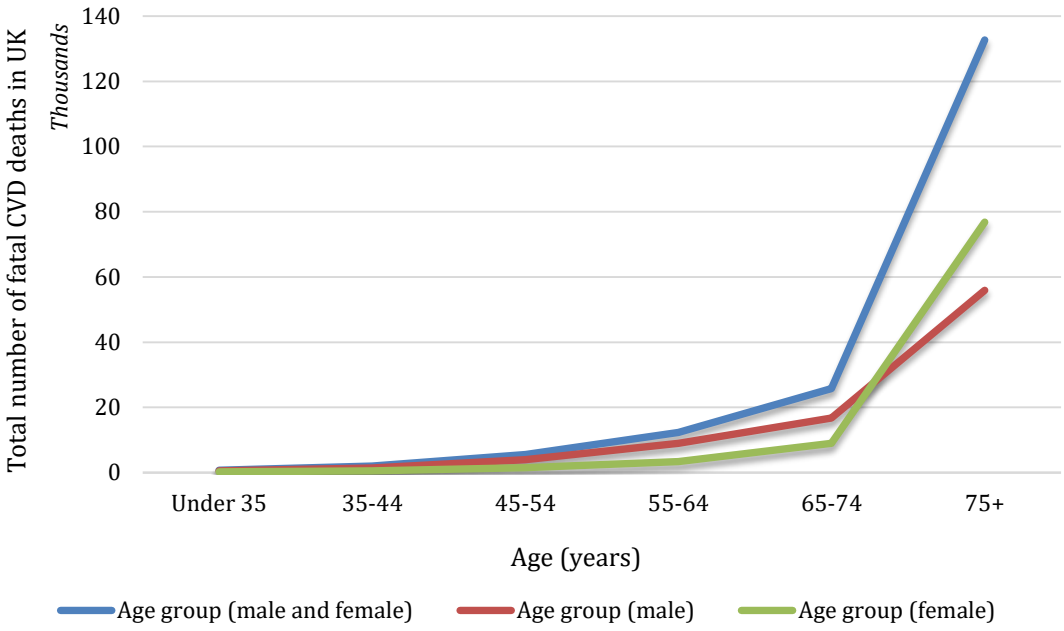


Figure 1.2 Total number of fatal CVD deaths in men and women within various age groups in the UK, 2010 [15]

Aging is clearly unmodifiable, unavoidable, and is associated with a natural progressive deterioration of the cardiac system and its functions. These age-associated changes include (but are not limited to), an increase in vascular intimal thickness (the thickness of innermost two layers of the artery, tunica intima and tunica media) and vascular stiffness [19], which may be associated with the development of atherosclerosis and increased systolic blood pressure (SBP), as well as stroke risk respectively [20]. Deterioration of the cardiac structure (left ventricle wall thickness and left atrial size) also increases the likelihood of heart failure, arrhythmia and reduces diastolic and systolic function [21].

In terms of sex, previous studies have focused on studying the association between men and CVD risk more than in women [22], as it was considered to be a 'man's disease' in the past [23]. However, this is no longer the case as women are equally, if not, possibly more likely to be susceptible to CVD [23]. In addition, the population of elderly women is increasing [13, 24]. The absolute number of women who develop CVD is also higher than men in the UK (91,500 and 87,528 respectively) [15], as well as in other countries [23, 25]. As the burden of CVD shifts towards women, there is a call to investigate sex differences and CVD risk in addition to the underrepresentation of women in randomized controlled trials (RCTs) [26]. Fundamental differences between sex involve factors such as hormonal changes which stem from pregnancy and the menopause [27]. Oestrogen supplementation was formerly proposed as a candidate for primary or secondary prevention of CHD in postmenopausal women, due to plausible mechanisms to raise 'good cholesterol' levels (high density lipoprotein), improve arterial compliance and coronary flow reserve [25]. However, RCTs propose that ingestion of oestrogen (alone or with progestin) may not be beneficial, and might even be harmful [28, 29]. On the other hand, recent observational studies showed no differences between menopausal status and risk of CVD [30]. Alternatively, a review suggests it is more likely that post-menopausal women experience a delayed onset of CHD rather than acceleration of CHD at the age of menopause compared to men, whose decreasing androgen levels cause a deceleration of CVD deaths [31]. Thus men are exposed to the disadvantage of premature CVD, while women suffer approximately 10 years later. This is also demonstrated in a modelling study that reached a similar conclusion [32]. In fact, the study reported a steady increase in mortality throughout all ages in women, instead of a sudden increase at menopausal age. Summarizing the evidence above, it would seem the role of menopausal status in women changed drastically over the last decade, and perhaps might not play such an important role in the development of CVD throughout the life course. Emphasis should be placed across all age groups, especially when mortality rates seem to be equalizing, and maybe even increasing over the past decade within young adults aged 35 to 44 years [13].

Other unmodifiable risk factors for CVD include race/ethnicity and family history of diseases. Prior studies as well as the INTERHEART study have established that parental history of CHD is associated with higher risk of developing CHD [33]. The odds of CVD was also 45% greater for participants with a sibling history of CVD in the Framingham Offspring study [34]. Observed differences are most likely due to the higher likelihood of sharing similarities in genetic traits. This is because approximately 50% of the genetic variation is shared between biologically related first-degree relatives (parents, siblings and offspring).

Likewise, subpopulations living within the same geographical region are also more likely to share genetic similarities [35], and are thus more susceptible to certain modifiable CVD risk factors than others from a different geographical region (Table 1.1).

Table 1.1 CVD risk factors in the order of severity (the top being the most severe risk) in various regions around the world [36]

East Asia Pacific	Eastern Europe and Central Asia	Latin America	Middle East and North Africa	South Asia	Sub-Saharan Africa
Hypertension	Smoking	Smoking	Obesity	Hypertension	Hypertension
Smoking	Obesity	Obesity	Low fruit and vegetable intake	Diabetes	Low fruit and vegetable intake
Obesity	Hypertension	Abdominal obesity	Physical inactivity	Smoking	Physical inactivity
Hyperlipidaemia	Hypercholestero-lemia	Hypertension	Hypertension	Overweight/ Obesity	Overweight/ Obesity
Diabetes	Low fruit and vegetable intake	Diabetes	Hypercholestero-lemia	High waist-to-hip ratios	Smoking
	Physical inactivity	Hypercholestero-lemia	Diabetes	Abdominal obesity	
	Stress		Smoking	Lipids (Hyperlipidaemia)	
	Diabetes			Physical inactivity	
				Low fruit and vegetable intake	

Different ethnic groups could also live in the same region, where prevalence of CVD risks, such as hypertension, diabetes and obesity varies with racial/ethnic groups [37]. Blacks (African-Americans, African/Caribbean in UK) have exhibited higher prevalence of hypertension [37] and stroke [38] in contrast to the White ethnic groups. In comparison to European women, Chinese women (by race) have higher BP, and Chinese people in general exhibit higher rates of stroke. However, rate of CHD in Chinese was similar to, or lower than Caucasians [39]. South Asians (Indians, Sri Lankans, Bangladeshis, Nepalese and Pakistanis) are more prone to a higher prevalence of diabetes, CHD (especially MI) and CVD in general compared to non-South Asians or White Europeans. [38, 39]. As before, genetic factors are likely to contribute to the differences between South Asians (which were most widely studied compared to other ethnic groups) and Europeans, in terms of the distribution of body fat, amount of muscle and fat mass, and waist-to-hip ratio. Specifically, South Asians may have a smaller frame and thinner limbs, but the waist-to-hip ratio is greater than their UK counterparts [39]. Healthy South Asians also have higher levels of pro-thrombotic factors, homocysteine and fibrinogen compared to Europeans, which may raise the likelihood of developing risk factors such as diabetes, or initiating atherogenesis [39].

Genome-wide association techniques have provided evidence for the genotype-phenotype relationship in association to CVD risk, however discovered genetic markers do not improve CVD prediction in comparison to parental history [35]. Other factors such as early life stress and nutrition, environmental factors, perhaps unmeasured factors that

parental/sibling history have accounted for, could also explain the differences observed for parental/siblings history, as well as racial/ethnic groups [33, 39].

1.1.1.5 Modifiable CVD risk factors

1.1.1.5.1 High blood pressure or hypertension

Hypertension is a clinical condition when BP is elevated beyond 140/90 mmHg. It is a major risk factor that relates directly to an increased risk of CVD [15]. High blood pressure (HBP) is also associated with the highest percent of attributable deaths (13%) to CVD mortality compared to other risk factors [6]. In a Korean cohort, women had a hazard ratio of 1.88 (95% CI 1.35, 2.61) and 2.26 (95% CI 1.49, 3.41) for CVD and stroke respectively if they had hypertension, in comparison to normotensives [40]. Women from the INTERHEART study experienced almost three-fold the odds of acute MI when compared to normotensives. In addition, 22% of men and women from Western Europe and 25% of men and women from Central and Eastern Europe had acute MI with history of hypertension [41].

Hypertension is also associated with age. The prevalence of hypertension increases with age [15]. A meta-analysis (MA) of one million adults showed that for adults aged from 40 – 69 years old, a 20 mmHg increase in SBP or a 10 mmHg increase in diastolic blood pressure (DBP) is equivalent to a two-fold increase in CVD risk [42]. The prevalence of hypertension varies with geographical locations. Prevalence of hypertension on average in United Kingdom is 13.6%, where the highest prevalence is in the West Midlands at 14.6%. London has the lowest prevalence of hypertension at 11%, suggesting hypertension may also be related to some variables related to social economic status.

1.1.1.5.2 Diabetes

Type 2 diabetes is a condition when insulin produced in an individual is unable to maintain and regulate normal blood glucose levels due to insulin resistance. Long term insulin resistance leads to increased insulin secretion to counter insensitive insulin receptors, and could eventually result in a total loss of insulin secretion and pancreatic β-cell function. It is an independent risk factor for CVD risk, and often co-exists together with other conditions, such as hypertension [43]. The Framingham Study reported a two-fold increase in CVD incidence in male subjects with diabetes after 20 years of follow up, in comparison to non-diabetic male subjects, while the increase in CVD incidence in female subjects was three-fold, compared to non-diabetic female subjects [44]. However, a Finnish cohort found no statistically significant difference between the two groups for risk of

myocardial infarction [45]. A Dutch cohort also demonstrated that male and female subjects with diabetes, but without previous CVD events has the same risk as women without diabetes, but with previous CVD events [46]. In the INTERHEART case-control study, odds ratio of acute myocardial infarction was 4.26 (95% CI 3.51, 5.18) in female subjects, and 2.67 (95% CI 2.36, 3.02) in male subjects [41]. This indicates females are at higher risk than males if they are diabetic. A recent study conducted in Scotland also reported an increased risk of all-cause and CVD mortality in diabetic subjects as compared to non-diabetic subjects [47]. The prevalence of type 2 diabetes increases with age, and is more common in female than male subjects. Prevalence also varies with geographical locations in UK. Wales has the highest prevalence at 7% for men and 6% for women [15]. Type 2 diabetes is also associated with social economic status. Areas with more deprivation tend to have higher rates of diabetes [48].

1.1.1.5.3 Hypercholesterolemia/Lipid profile

Hypercholesterolemia is a condition where there are high levels of cholesterol in the blood. It can be hereditary, known as familial hypercholesterolemia. Hypercholesterolemia accelerates the formation of atherosclerosis, which can lead to MI. A Swedish study also reported an increased risk of CVD mortality within male subjects with hypercholesterolemia [49]. In addition, a Dutch cross-sectional study also determined that elevated LDL-cholesterol (LDL-C) levels and lowered HDL-cholesterol (HDL-C) levels can contribute to an increased risk of familial hypercholesterolemia [50]. In a MA of cohort studies, lower total cholesterol was also associated with lower risk of ischaemic heart disease mortality [51]. Prevalence of hypercholesterolemia increases with age, and manifestation of this disease is higher in male subjects. It also varies with geographical location, as female subjects in East Midlands had the highest prevalence of hypercholesterolemia. Income seems to be related to prevalence of hypercholesterolemia, where a higher income is associated with lower levels of HDL-C [15].

1.1.1.5.4 Obesity

Overweight and obesity, particularly abdominal obesity are established independent risk factors for the risk of CVD, hypertension, high blood cholesterol and diabetes [15]. Results from the 26-year follow up from the Framingham Heart study demonstrated that obesity was a long-term predictor for CVD incidence [52]. Relative to men, the strength of obesity as a risk factor was higher in women, as only age and BP were more powerful predictors. However, authors pointed out that more women were extremely overweight in

comparison to men, and apparent excess weight in men is more likely to be a result of muscularity [52]. A 44-year follow up of the Framingham study also revealed a higher relative risk between 1.13 to 1.38 for total CVD in overweight and obese participants [53]. In particular, women from the Nurses' Health Study who were overweight or obese had a relative risk of 1.3 (95% CI 0.9, 1.9) and 3.3 (95% CI 2.3, 4.5) for CHD compared to the reference [Body mass index, (BMI) <21] [54]. In addition, controlling for history of medical conditions such as diabetes, hypertension and hypercholesterolemia attenuated the strength of association, indicating that a combination of being overweight/obese and one of the former conditions could result in a several-fold increase in relative risk of CHD [54].

When adipose tissue is concentrated in the abdomen (abdominal obesity), the adverse effect of obesity increases further [15]. The INTERHEART study reported a significant adverse association between waist-to-hip ratio and risk of MI globally, and this association was stronger than the relationship between BMI and MI risk [55]. The PAR for the top two quantiles of greater waist-to-hip ratio (24%) was also higher than BMI (7.7%) [55]. The authors proposed various hormonal and biochemical factors which may lead to higher visceral fat, lower skeletal mass and insulin resistance (risk factor for diabetes) [55].

Obesity may also increase with age in general, and susceptibility of obesity is partly hereditary (40% to 70%), but influenced by diet and the environment [15, 56]. The obesity epidemic is global, but especially serious in disadvantaged groups in high-income countries, and among wealthy middle-aged women in low-income countries [56]. Within the UK, two-thirds of men are obese or overweight, while obesity rates vary in women depending on income. Men from West Midlands were most likely to be obese/overweight (72%), while women from East and East Midlands have the highest prevalence (63%) in comparison to other regions [15]. Obesity may also vary by ethnic groups, where Chinese men had lowest prevalence of obesity by BMI relative to the general population. However, when using waist-to-hip ratio as comparison, differences were removed entirely due to the natural variation of body shapes within ethnic groups, related to storage of fat in different places in the body [15].

1.1.1.5.5 Smoking

Cigarette smoking is known to be a major risk factor for CVD. Proposed mechanisms by which smoking affects health include the promotion of atherosclerosis [57], thrombosis and elevation of serum total cholesterol [58]. Smoking may also cause an increase in lipid peroxidation, and increase the uptake of LDL-C by macrophages [59]. These macrophages turn into foam cells that contribute to the development of lesions and plaques, leading to

possibility of atherosclerosis. Other possible mechanisms include oxidative stress, mitochondrial damage [58], and increased risk in other diseases, such as type 2 diabetes [43] and hypertension. Prevalence of smoking the UK had remain relatively stable since 2003 among adults aged 16 years and above, where one in five are currently smokers [60]. Smoking prevalence within men (22%) is higher than women (17%) in the UK. The amount of risk contributing to the development of CVD is also dependant on when smoking was initiated, when cessation occurred and how long did cessation last for. According to Shields *et. al* [61], men were more likely to be smokers than women in a Canadian cohort. There were also more male smokers in a Korean cohort [40]. However, within developed countries, the proportion of female smokers has increased, reflected in higher rates of lung cancer in women compared to previous years [62]. Nevertheless, both studies suggested a reduction in the risk of cardiovascular mortality if smoking ceases or the number of cigarettes smoked per day decreased. This concept is also supported by a systematic review (SR) by Critchley *et. al* [63], which indicated that quitting smoking is strongly associated with a reduced CVD mortality.

1.1.1.5.6 Physical activity

From observational studies, higher physical activity is reported in multiple studies from various countries to be associated with a lower risk of CVD, where 150 min/week or 75 min/week of moderate aerobic exercise and vigorous aerobic exercise is strongly associated with a reduced risk respectively [64]. Further evidence from the 40-year follow up of the Framingham Heart study observed that long-term physical activity is protective against CVD mortality relative to long-term physical inactivity. This is also seen in men for CVD incidence, but not for women [65]. Physical activity levels are relatively low in the UK for both men and women. Nutritional surveys indicate Scottish men and women report the most exercise, at 45% and 33% respectively above recommended levels of physical activity [15]. However, using objective accelerometer data, only 6% of men and 4% women met the recommended levels, relative to previous reported averages of 39% and 29% for men and women respectively. By ethnic group, British South Asians are less likely to be physically active in comparison to White counterparts, contributing to >20% excess of CHD mortality [66].

1.1.1.5.7 Other potential risk factors

The effects of residence can already be seen in previous sections discussing the prevalence of biological risks in different areas of UK. Education seems to also be associated

with modification of behavioural risks, where lower educational level is linked to higher risk of CVD. Increased level of intelligence and influencing lifestyle behaviours were some of the possible explanations offered [67]. Occupation is also suggested to have an inverse association with CVD risk. In Marmot *et. al* [68], male subjects who had clerical and office-support jobs had an odds ratio of 1.50 (95% CI 0.98, 2.29)as compared to subjects who had administrative jobs. However, a statistically significant relationship was not observed in the former publication. Social economic status can also influence other risk factors, as shown in Lawlor *et. al* [69]. It can affect behaviours such as smoking and physical activity, which in turn influences obesity levels. In Lawlor *et. al* [69] involving analyses of three age cohorts of Australian women, the most advantageous social economic status was seen to have an inverse relation with physical activity, obesity and physical activity [69]. However, relationships between smoking and socio-economic status (SES) varied between the three cohorts. This is indicative that there is no definite positive or negative association between social economic factors and other behavioural risks. Therefore, the adjustment of these variables has to be considered carefully.

1.1.1.5.8 Dietary components and patterns

Research on dietary intake and CVD mortality was initiated in the late 1950s in the Seven Countries Study, focusing on fat and cholesterol intake, giving way to the 'diet-heart hypothesis' [70]. Other nutrients such as vitamin B (B6, B12, folate), C, E and carotenoids were also investigated over time, however, evidence for the supplementation or increased intake of these single nutrients was either inconclusive, or not recommended for the prevention of CVD [70].

While single nutrients could possibly play a mechanistic role *in vivo*, it is consumed as a complex food matrix with other nutrients, and may interact with or act synergistically with other food components. Thus, leading to investigation of whole foods, dietary patterns and CVD risk. Food components such as fatty fish (high in mono- and poly-saturated fats), fruits and vegetables (FVs) [fibre, 'antioxidants', (poly)phenols] whole grain (fibre) and moderate amounts of alcohol in the form of wine [(poly)phenols] are shown to be inversely associated with CVD risk [70]. In contrast, foods such as meat, milk and butter tend to have an adverse association with CVD mortality. [71]. When the former foods are studied in combination as the Mediterranean diet, multiple studies report an inverse relationship with CVD mortality [72-75]. Results from MA [76] and SR [77] also support the former findings stated. In addition, evidence from RCTs was provided by the PREDIMED trial in Estruch *et. al* [78] and Estruch *et. al* [79], where diets supplemented with olive oil or nuts as compared to low-fat

diet, has beneficial effects for risk of CVD. However, the effects seen are not as prominent, as the trial was based on a population residing in the Mediterranean area to begin with, and therefore potentially following a Mediterranean diet. Alternatively, the Dietary Approaches to Stop Hypertension (DASH) diet, rich in fruits, vegetables and low-fat dairy products was successful at lowering CVD risk by lowering BP [70, 80]. In addition, a recent RCT reported reduced risk by a third in healthy middle-aged and older participants with adherence to the following recommendations promoted to lower or prevent CVD [81, 82]:

- High intake of vegetables, fruits, whole grains, low- or non-fat dairy, seafood (oily fish), legumes and nuts
- Moderate consumption of alcohol
- Low intake of sodium, red and processed meat, sugar-sweetened foods, drinks, refined grains

FVs are rich in a variety of nutrients which may be protective against CVD risk. Proposed components which may exert benefits within FVs in general include fibre, carotenoids, vitamin C, magnesium and potassium [70]. Multiple SR and MA have reported a significant, inverse association between greater intake of FVs and risk of CVD, CHD and stroke [83-85]. The EPIC-HEART study observed that every additional portion of FV (80 g) consumed per day leads to a 4% lower risk of CVD mortality [86]. In addition, Scarborough and colleagues estimated that 15,000 deaths could also be avoided in UK if adherence to five-a-day portions of FVs was achieved [87]. This is consistent with the study from the World Health Organisation (WHO), which reports an inadequacy of FV intake worldwide [88]. However, FVs are also (poly)phenol-rich foods, and there are few studies to support if specific fruits or fruit subgroups are more important than others, and associated with lower risk of CVD.

In addition to FVs, coffee and tea are also rich in (poly)phenols, and play a significant role in the habitual diet within UK. Coffee was previously associated with an increased risk of CVD [89-91]. However, results overall are inconsistent. Recent MAs contradicts the former findings [92, 93]. The latter MAs included recent studies, and reported no positive relationship with greater consumption of coffee. There was also a non-linear response, where three cups of coffee was associated with the greatest risk reduction [93]. Furthermore, moderate coffee consumption (1 to 3 cups/day in US or 3 to 4 cups in Europe) significantly lowered CHD risk by 18% (95% CI 0.73 to 0.92) and 13% (95% CI 0.80 to 0.86) in men and women followed for more than ten years [92]. Wu and colleagues also did not observe a positive association with higher habitual coffee intake [92].

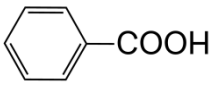
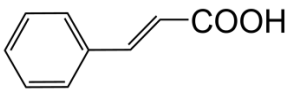
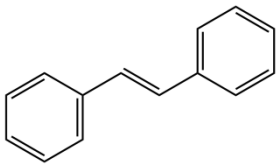
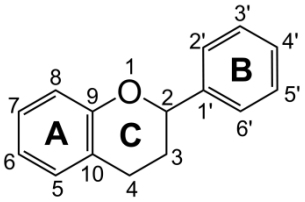
As for evidence on tea consumption, green tea seems to only show a positive effect of lowering the risk of CVD in case-control studies and male subjects, but not for cohort studies or female subjects in case-control studies [94]. The evidence for beneficial health effects of consumption of black tea is inconclusive. A MA on RCTs reported that the consumption of black tea had no effects on BP and cholesterol levels, but it improved flow-mediated dilation [95]. However, another MA of cohort and case-control studies states that incidence of myocardial infarction reduced by 11% if consumption of tea was increased to 3 cups/day [89]. Despite multiple findings that act in either direction, a review of meta-analyses proposed that evidence for tea consumption (black and green) and stroke was the strongest out of all CVD outcomes [96]. Thus, further investigation is warranted for coffee and tea outcomes.

1.2 (Poly)phenols overview

(Poly)phenols represent a group of secondary plant metabolites that exists in plant based foods. Their functions within the plant includes assisting with growth, reproduction, defense and provision of colour characteristics [97]. They also play an important role in the prevention of diseases, such as cancer, stroke and CHD [98], through effects such as gene, enzyme and cell receptor modulations [99]. They are readily consumed in large quantities, from sources such as fruits, vegetables, red wine, tea, coffee and cocoa [100]. The estimated daily intake is known to be about 1 g/day [101].

All (poly)phenols have an aromatic ring and a minimum of one hydroxyl group, and are divided into different classes according to their skeleton structures (Table 1.2). The largest groups of dietary (poly)phenols are phenolic acids and flavonoids. Flavonoids are further classified into subclasses: anthocyanidins, flavones, flavanols (catechins), flavonols, flavanones and isoflavones (Figure 1.3), which are found in large quantities at various concentrations within different plant-based foods [100]. Other classes include phenylacetic acids, napthoquinones, xanthones, lignans and condensed tannins (proanthocyanidin), which are present in limited food sources at various concentrations [102]. (Poly)phenols within each subclass are often metabolized in a similar manner, the general biological process is described in the following section.

Table 1.2 The classification and skeletal structure of (poly)phenols

Classification	Skeleton	Structure
Phenolics		
Hydroxybenzoic acid	C_6-C_1	
Hydroxycinnamic acid	C_6-C_3	
(Poly)phenolics		
Stillbenes	C_6-C_2-C_6	
Flavonoids	C_6-C_3-C_6	
Lignans	$(C_6$-$C_3)_2$	*Not shown here as skeletal structure not consistent*

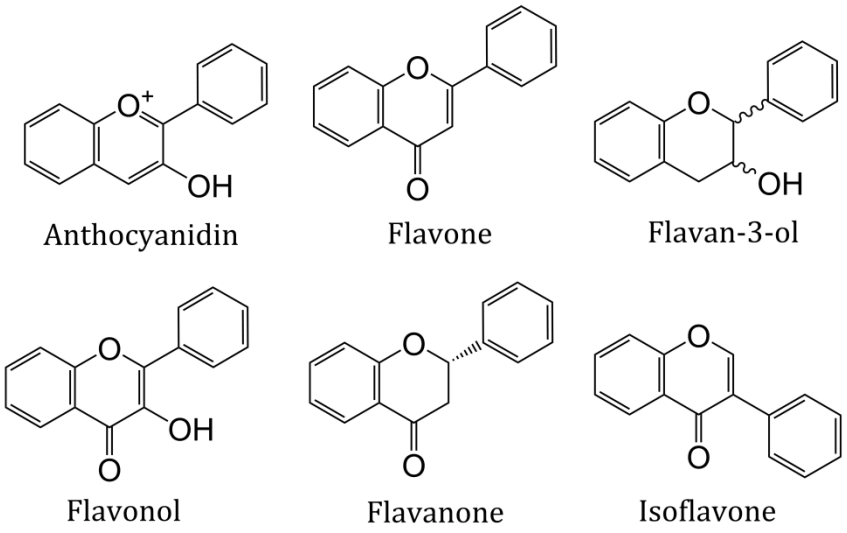


Figure 1.3 The skeletal structure of flavonoid subclasses

1.2.1 Absorption and bioavailability of (poly)phenols

(Poly)phenols are present in large quantities within plant-based dietary sources, and extensively metabolized in the body, leading to the formation of various (poly)phenol metabolites. During ingestion, chewing releases (poly)phenols from the food matrix [103]. Some (poly)phenols are absorbed in the stomach and small intestine, where hydrolysis of the glycoside moiety to form aglycone is essential to facilitate absorption [104]. There are two proposed mechanisms concerning (poly)phenol absorption that have been reviewed. The first mechanism involves the enzyme lactase phloridizin hydrolase (LPH) which is capable of deglycolysation and hydrolysis of lactose. LPH is located in the brush-border of the small intestine epithelial cells. The specificity of this enzyme is very broad, and it readily converts flavonoid glucosides to aglycones. This increases the lipophilicity and proximity of (poly)phenols to the cellular membrane, resulting in passive diffusion into epithelial cells [105]. The alternative mechanism invovles an enzyme, cytosolic β-glucoside (CBG) located in epithelial cells. Polar glucosides are transported by active sodium-independent glucose transporter SGLT1 into the cell to be hydrolysed, catalysed by CBG [106]. Before passage into the bloodstream, the (poly)phenols now in the form of aglycones are conjugated via three possible mechanisms, including methylation, sulfation and glucuronidation, by action of catechol-*O*-methyltransferases (COMT), sulfotransferases and uridine-5'-diphosphate glucuronosyltransferases respectively [107]. These metabolites are carried via the portal bloodstream to the liver, where (poly)phenol metabolites are subjected to phase II metabolism and further conversions [107]. (Poly)phenols which are not metabolised and absorbed in the small intestine move on to the colon, where the microflora cleaves the remaining (poly)phenols glucosides into aglycones, possibly leading to the production of phenolic acids and hydroxycinnamic acids. [107]. (Poly)phenols in the colon could be absorbed to reach the liver, and undergo phase II metabolism before being excreted in the urine [107].

Bioavailability refers to the the quantity and effectiveness of (poly)phenols absorption from the gut into the bloodstream via the two possible mechanisms as explained above, and its metabolites are quantified in blood plasma and urine in human studies. The chemical structure of the (poly)phenol affects the rate of absorption into the blood, where levels in plasma rarely exceed 1μM when the ingested doses are in line with amounts normally consumed in the diet [98] (Table 1.3). Examples of relatively well-absorbed (poly)phenols include gallic acid and isoflavones [108] (Table 1.4). This is followed by

catechins (flavan-3-ols), flavanones and quercetin glucosides. Proanthocyanidins, galloylated tea catechins and anthocyanins are the least well absorbed [108].

Table 1.3 Pharmacokinetics on major (poly)phenol classes summarised from Manach *et. al* [108]

(Poly)phenol subclass	Range of dosage[1]	T_{max} in plasma[2] (hr)	Plasma concentration	Elimination half-life (hr)	Urinary excretion (% of intake)
Anthocyanins	150 mg to 2 g	0.75 – 4	10 – 50 nmol/L	-	0.004 – 0.1
Flavonols	1.6 mg to 4 g	0.5 – 7.5	0.15 – 7.6 µmol/L	10.9 – 28.1	1 – 6.4
Flavanones	7.2 to 500 mg	2 – 5.8	0.06 – 5.99 µmol/L	1.3 – 2.9	1.1 – 30.2
Flavan-3-ols	32 mg to 1.6 g	0.5 – 2.9	0.21 – 7.4 µmol/L	1 – 8.6	0.1 – 55
Isoflavones	12.5 to 389 mg	2 – 9.5	0.17 – 3.7 µmol/L	3.4 – 10.8	4 – 63

[1]From various sources, including pure compound, supplements and foods
[2]Time to maximum concentration (C_{max}) in plasma

Table 1.4 Summary of the biological activities of (poly)phenol subclasses from Manach *et. al* [108] and Del Rio *et. al* [109]

(Poly)phenol subclass	Metabolism	Absorption
Anthocyanins	**Limited** – Often found as unchanged glycosides, sometimes as glucuronidated and/or sulfated derivatives. The gut microflora also converts limited amounts of anthocyanins to phenolic acid derivatives and aldehyde constituents. Anthocyanins are highly unstable, subjected to degradation through physiological changes (pH).	**Rapidly absorbed and eliminated, but with poor efficiency (low bioavailability)** - Mostly absorbed in the stomach and small intestine, partially in the large intestine.
Flavonols	**Extensively metabolised** and conjugated in small and large intestine, not present as an aglycone, and undergoes substantial phase II metabolism.	**Efficiently absorbed** as conjugates, where the bioavailability is dependent on the type of glycoside and food source. Relatively high urinary excretion and elimination half-life, indicating good chemical stability (see Table 1.3)
Flavanones	**Extensively metabolised** and conjugated especially in the large intestine, undergoing substantial phase II metabolism.	**Rapidly absorbed** in the large intestine as glucoronidated forms and phenolic acid derivatives, and especially in the form of an aglycone after deglycosylation through gut microflora.
Flavan-3-ols	Catechins are **metabolised and conjugated** as methylated forms (epigallocatechin) or glucoronidated and/or sulfated forms (other catechins). Theaflavins and thearubigins are not expected to be metabolised differently to catechins.	Catechins are **well absorbed** in the small and large intestine, but **rapidly eliminated**. Rarely absorbed as unmetabolised forms. Theaflavins and thearubigins are absorbed in the large intestine after microflora catabolism. Their mode of absorption is not expected to be largely different to catechins.
Isoflavones	**Rapidly metabolised** into deglycosylated glucoronides and sulfates from glycosides.	**Absorption occurs simultaneously in both the small and large intestine over a long period of time (see half-life in Table 1.3)**, where the bioavailability is relatively highest in comparison to other flavonoid subclasses.

1.2.2 Measuring (poly)phenol intake

There are currently two leading (poly)phenol databases: the United States Department of Agriculture (USDA) flavonoid database [110] and the Phenol Explorer [111]. The USDA flavonoid database contain values for 506 foods on flavones, flavonols, flavan-3-nols, flavanones and anthocyanidins. A wide range of analytical procedures that separate

flavonoid compounds effectively were accepted for the development of this database, such as (and not limited to) high-performance liquid chromatography (HPLC) and capillary zone electrophoresis (CE). However, spectrophotometric and pH differential methods were not accepted due to the lack of specificity. This database only reports values in aglycone form, conversion factors were applied to glycosylated forms (except for catechins and epicatechins). On the other hand, Phenol Explorer reports nine classes and 67 subclasses of (poly)phenols in 458 foods, including metabolites from intervention studies. In addition, retention factors for food processing were also recently published on 35 processes and 155 foods [112]. Phenol Explorer also accepts values from a wider range of analytical methods for various purposes. Spectrophotometric methods such as Folin-Ciocalteu method and pH differential method are accepted as a global assay to estimate total phenolic content (TPC) and total anthocyanin content respectively, while HPLC, gas chromatography and CE before and after hydrolysis are accepted as main procedures for quantification of (poly)phenol glycosides and aglycones. Most studies derive their (poly)phenol intake estimates by incorporating either one of the two databases above, or a combination of both, sometimes in addition to supplementary data from literature, and are currently limited to US or European cohorts using food records or 24-hour recalls, with no standalone UK cohorts estimating (poly)phenol intake [113-115]. Unlike the previous studies, no total polyphenol score or intake is generated in this thesis, due to the following reasons. Firstly, (poly)phenol contents reported in databases are often the average of multiple samples. Natural variations exist within food samples, dependent on cultivar, species, growing, processing and storage conditions. Therefore, importing values from (poly)phenol databases and estimating (poly)phenol intake within individuals is subject to a large measurement error. Furthermore, as (poly)phenol databases are still under development, (poly)phenol content within less commonly consumed or processed foods, as well as foods with complex food matrices are limited, thus potentially under- or over-estimating (poly)phenol intake.

1.2.3 Major (poly)phenol profiles in foods

(Poly)phenol profiles in foods are hugely complex, and mostly contain multiple classes of (poly)phenols in a single plant. Few studies have examined the association of classes of (poly)phenols in relation to chronic disease outcomes [116-118], however, (poly)phenols are not consumed by class or sub-class. Estimation is also subject to limitations described above. (Poly)phenols are consumed as a mixture in different types of plant-based foods by culinary or botanical categories instead. Thus, before investigating the

association between (poly)phenols and CVD risk, the relationship between (poly)phenol-rich foods and CVD risk itself should be investigated first.

There are multiple methods to classify FVs, demonstrated within Pennington *et. al* [119], where groupings are available by botanic family, colour, plant part and total antioxidant capacity. However, in order to study the association of (poly)phenol rich foods and CVD in an applicable manner, the botanical, culinary and (poly)phenol systems must be taken into account altogether. In the interest of taking the (poly)phenol classes into account, as well as to address the lack of existing research on for FV subgroups and CVD risk in this thesis, FV subgroups were loosely based on the Phenol Explorer categorisation. Thus, fruits were divided into five subgroups: berries, citrus, drupes, pomes and tropical fruits, while vegetables were divided into: *Allium*, *Brassicaceae*, fruit vegetables, pod vegetables and 'stalk and root' vegetables.

1.2.3.1 Fruits

The definition of fruit in botany refers to "the pericarp which derives from the ovary (or ovaries) of the flower, usually containing seeds for dispersal". In common parlance and by culinary definitions, fruits are edible fleshy structures of plants which are usually sweet or sour, often consumed raw, which includes apples, bananas, oranges, strawberries, melons and grapes. The thesis follows the latter definition of fruits.

1.2.3.1.1 Berries

In botanical terms, the definition of a 'true berry' is "a fleshy fruit without a stone, consisting of a potentially edible pericarp, formed from a ripened simple or compound ovary". This definition includes bananas and tomatoes, but excludes fruits commonly recognised as 'berries', such as blackberries, raspberries, blueberries and strawberries. The special term 'hesperidium' is also given to citrus fruits such as oranges and lemons which are botanically similar to 'true berries', while the term 'pepo' includes plants from the pumpkin family, such as pumpkin, melons and watermelon.

Berries defined in this thesis is based on the term 'berry' in common parlance, associating more closely with the culinary applications, as well as in accordance with Phenol Explorer definitions [111]. Thus, consisting of fruits that are brightly coloured, juicy, sweet or sour without a stone or pit, but may contain pips or seeds, such as (but not limited to) the more commonly consumed blackberries (*Rubus fruticosus*), blackcurrants (*Ribes nigrum*), blueberries (*Vaccinium cyanococcus*), cranberry (*Vaccinium oxycoccus*), grapes (*Vitis*

vinifera), raspberries (*Rubus idaeus*), redcurrants (*Ribes rubrum*) and strawberries (*Fragaria × ananassa*).

Berries are naturally rich in moisture, fibre, vitamin C and E, folic acid, calcium, selenium, and carotenoids such as α-, β-carotene and lutein [120]. They also contain high proportions of anthocyanins. Anthocyanins are the glycoside form (i.e. bonded to a sugar moiety) of anthocyanidins (Figure 1.4), and are pre-dominantly responsible for the bright colours (e.g. purple, blue, red, orange, pink) within berries. Cyanidin is the most widely distributed anthocyanidin within foods, followed by delphinidin, pelargonidin, peonidin, petunidin and malvidin [121] (Table 1.5). Berries also contain other (poly)phenols such as phenolic acids, flavanols and flavonols, but their contribution towards total anthocyanin intake is the greatest [122, 123]. The distribution of anthocyanins varies greatly across different fruits, where some fruits contain high levels of a particular anthocyanin, and others contain moderate levels of few (Table 1.6).

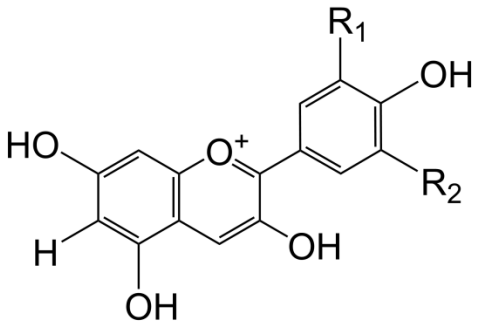


Figure 1.4 The skeletal structure of anthocyanidin and substitution sites

Table 1.5 Substitution pattern and approximate distribution of major anthocyanidins across food sources [121]

Name	R_1	R_2	Distribution (%)
Cyanidin	OH	H	50
Delphinidin	OH	OH	12
Pelargonidin	H	H	12
Peonidin	OMe	H	12
Petunidin	OMe	OH	7
Malvidin	OMe	OMe	7

Table 1.6 Distribution of major anthocyanins across commonly consumed berries, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major anthocyanins	Total (poly)phenol content mg/100g FW
Blackberry	Cyanidin-3-*O*-glucoside	569 (226)
Blackcurrant	Delphinidin-3-*O*-rutinoside, cyanidin-3-*O*-rutinoside, delphinidin-3-*O*-glucoside	821 (230)
Blueberries (Highbush)	Delphinidin-3-*O*-galactoside, malvidin-3-*O*-galactoside, delphinidin-3-O-arabinoside, malvidin-3-O-arabinoside, petunidin-3-*O*-galactoside, malvidin-3-*O*-glucoside	223 (173)
Blueberries (Lowbush)	Malvidin-3-*O*-glucoside, malvidin-3-*O*-galactoside, delphinidin-3-*O*-galactoside, delphinidin-3-*O*-glucoside, malvidin-3-*O*-(6''-acetyl-glucoside), petunidin-3-*O*-glucoside	-
Cranberry (American)	Peonidin-3-*O*-galactoside, cyanidin-3-*O*-galactoside	315 (0)
Grapes (Black)	Malvidin-3-*O*-glucoside, cyanidin-3-*O*-glucoside, delphinidin-3-*O*-glucoside	185 (18)
Raspberry	Cyanidin-3-*O*-glucoside	155 (91)
Redcurrant	Cyanidin-3-*O*-xylosyl-rutinoside, cyanidin-3-*O*-sambubioside	448 (85)
Strawberry	Pelargonidin-3-*O*-glucoside, pelargonidin-3-*O*-(6''-succinyl-glucoside)	289 (95)

The estimated consumption of anthocyanins vary greatly across regions, influenced by methodological differences and variation in diet composition. Previous estimation of mean anthocyanin intake in the US was 12.5 mg/day, where the consumption of berries contributed approximately 56% of total anthocyanin intake [122]. Within the NHANES 2007-2010 study, mean estimated anthocyanin intake was 11.7 mg/day, where berry fruits contributed ~39% towards total anthocyanin intake [115]. Within the EPIC-cohort, berries were estimated to provide ~25% (~50%, inclusive of wine) of all anthocyanidins within the European region, with Italian men and French women having the highest anthocyanidin intake of 44 to 64 mg/day and 32 to 40 mg/day respectively. Estimated anthocyanidin intake in a UK general population was between 22-24 mg/day, and 28 to 31 mg/day within a health-conscious cohort [123]. More recently, estimates performed on the European region using dietary data collected from 1997 onwards reported a lower estimate of 19 mg/day overall. Finland and Italy consumed the highest amount of anthocyanidins (28 mg/day), while the UK estimate was 16 mg/day [113].

Berries are often processed into food products, such as jams and juices. During the production of these foods, anthocyanins are subjected to temperature and pH changes, which may affect the stability of the compounds. Thermal treatment is known to reduce

anthocyanin content in jams by up to 80%, and long storage periods (60 days) could also result in at least ~50% loss from blueberry puree and juice [124].

1.2.3.1.2 Citrus

As mentioned above, hesperidia are botanically similar to 'true berries' with a tough, leathery rind, fluid-filled sacs known as carpels, and varying number of seeds, consisting of fruits from the *Rutaceae* family, *Citrus* genus. The same term is also consistent with culinary definitions. Commonly consumed citrus fruits include sweet orange (*Citrus × sinensis*), bitter/sour orange, (*Citrus × aurantium*), grapefruit (*Citrus × paradisi*), lemon (*Citrus × limon*), lime (*Citrus aurantifolia*), mandarin (*Citrus reticulata*), clementines (*Citrus × clementina*), tangerines (*Citrus tangerina*) and pomelos (*Citrus maxima*). Citrus fruit are naturally rich in moisture, fibre, vitamin C, sugars (sucrose, glucose and fructose), potassium, carotenes, vitamin B and E, and low in sodium.

Citrus fruits are especially rich in flavanones (Figure 1.5) and were reported to contribute at least 90% towards total flavanone intake in the US [115]. The dominant form exists as hesperidin (hesperitin-7-*O*-rutinoside), present pre-dominantly in sweet orange, lemon, lime and mandarin. Bitter/sour orange is rich in neohesperidin (hesperitin-7-*O*-neohesperidoside) and grapefruit contains a high concentration of naringin (naringin-7-*O*-neohesperidoside) (Table 1.7), both known to be bitter flavoured compounds [100]. Flavanones are present in both the tissue and juice of the fruit, but are not evenly distributed. Citrus peel has the highest concentration of flavanones, while the juice, albedo and segment/sac membranes contain significantly less in comparison [125]. Citrus fruits are also consumed as juices, however, the amount of flavanones present in juices is lower in comparison (~50%), as the albedo and segments (which contain a higher concentration of flavanones) are not present [125, 126]. The stability of flavanones is high in comparison to anthocyanins, as temperature and storage result in minimal losses [127]. Quantification of flavanones is subjected to variation, dependent on the amount of albedo tissue remaining on the segment after peeling the fruit [100]. In addition, the natural variation of flavanones produced within different cultivars of the same species also introduces quantification issues [128, 129].

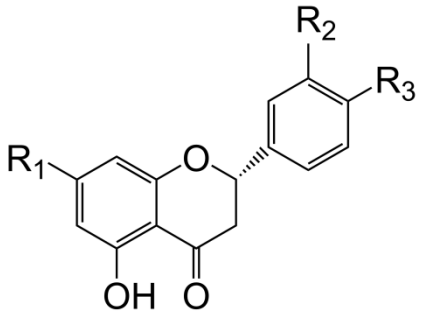


Figure 1.5 The skeletal structure of flavanone and respective substitution sites

Table 1.7 The substitution pattern of major flavanones and its glycosides

Name	R_1	R_2	R_3
Hesperitin	OH	OH	OCH_3
Naringenin	OH	H	OH
Hesperidin	rutinoside	OH	OCH_3
Narirutin	rutinoside	H	OH
Neohesperidin	neohesperidose	OH	OCH_3
Naringin	neohesperidose	H	OH

An earlier assessment on average flavanone intake within Europe was conducted using the EPIC-cohort [130]. Within men, highest consumers were from Spain and health-conscious UK, with an intake of ~69 mg/day, while women from Netherlands had an average intake of ~49 mg/day. Women from UK consumed between 40 to 43 mg/day of flavanones. However, estimates from US, NHANES were much lower at ~14 mg/day [131], in agreement with Vogiatzoglou *et. al* [113]. Intakes for UK population from Vogiatzoglou *et. al* [113] was 9 mg/day, where the highest flavanone consuming country was Finland (30 mg/day).

1.2.3.1.3 Drupes

By botanical definition, drupes (or stone fruits) are fruits with a fleshy mesocarp, surrounding a single seed, known as the pit, including fruits from the *Prunus* genus, mangoes and olives. However, the term 'drupes' here refer to only fruits from the *Prunus* genus, such as (and not limited to) apricots (*Prunus armeniaca*), sour cherries (*Prunus cerasus*) and sweet cherries (*Prunus avium*), nectarines (*Prunus persica var. nucipersica*), peaches (*Prunus persica*), plums (*Prunus domestica*) and prunes (*Prunus domestica*). Drupes are rich in potassium, sugars and contain some vitamin C and malic acid.

The (poly)phenol profile of drupes is complex, and not dominantly rich in any particular flavonoid class like berries and citrus. Instead, they contain varying levels of hydroxycinnamic acids, flavanols and anthocyanins (Table 1.8). For this reason, estimation intakes are not available. Distribution of (poly)phenols also seem to be uneven, due to differences between peeled and whole nectarines and peaches, suggesting at least half of the total (poly)phenols are located within the skin. Thus, it is important to make note of the way drupes are consumed to accurately estimate (poly)phenol intakes.

Table 1.8 Distribution of major (poly)phenol classes across commonly consumed drupes, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [100, 111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Apricots	**Hydroxycinnamic acids** (3-caffeoylquinic acid), **flava-3-nols** [(-)-epicatechin]	133 (0)
Cherries	**Anthocyanins** (cyanidin-3-*O*-rutinoside), **hydroxycinnamic acids** (3-caffeoylquinic acid)	Sweet: 174 (77) Sour: 352 (62)
Nectarines	**Hydroxycinnamic acids** (5-caffeoylquinic acid), **flava-3-nols** (proanthocyanidins), **anthocyanins** (cyanidin-3-*O*-glucoside)	Peeled: 47 (13) Whole: 55 (12)
Peaches	**Hydroxycinnamic acids** (5-caffeoylquinic acid), **flavanols** [(-)-epicatechin], **anthocyanins** (cyanidin-3-*O*-glucoside)	Peeled: 107 (69) Whole: 279 (196)
Plums	**Hydroxycinnamic acids** (3-caffeoylquinic acid), **anthocyanins** (cyanidin-3-*O*-rutinoside), **flava-3-nols** (proanthocyanidins)	410 (276)

1.2.3.1.4 Pomes

Pomes in botany are accessory fruits with a fleshy receptacle, and a core consisting of a few seeds surrounded by a shell. It also specifically refers to fruits from the *Rosaceae* family and *Malinae* subtribe. Apples (*Malus domestica*) and pears (*Pyrus communis*) belong in this subgroup, and are widely consumed. Pomes are a rich source of fibre, potassium, sugars, and contain varying amounts of vitamin C (3 to 14 mg/100 g) [132]. Apples are one of the main sources of proanthocyanidins (polymers of flavan-3-ols) after tea,

hydroxycinnamic acids and flavonols [100, 113, 115]. The (poly)phenol profile for pear is also very similar to apples (Table 1.9). Apples and pears also contribute 3.9 to 11.2% towards total (poly)phenol intake within Europe, and provide between 24.6% to 45.3% of selected proanthocyanidins in the diet [114]. Apples are often consumed fresh, or as apple juice, but in contrast to the stability of flavanones in orange juice, (poly)phenol content in apple juice is significantly lower in comparison to the unprocessed counterpart [133].

Table 1.9 Distribution of major (poly)phenol classes for apples and pears, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean and standard deviation in mg/100 g fresh weight [100, 111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Apple (Dessert)	**Flavan-3-nols** (procyanidin dimer B2), **Hydroxycinnamic acid** (5-caffeoylquinic acid), **Flavonols** (quercetin-3-*O*-glucoside)	Peeled: 132 (119) Whole: 201 (105)
Apple (Cider)	**Hydroxycinnamic acid** (5-caffeoylquinic acid), **Flavan-3-ols** [(-)-epicatechin, procyanidin dimer B2]	Peeled: 251 (126) Whole: -
Pear	**Hydroxycinnamic acid** (5-caffeoylquinic acid), **Flavan-3-ols** [(-)-epicatechin]	Peeled: 126 (102) Whole: 108 (47)

1.2.3.1.5 Tropical fruits

Tropical fruits consist of fruits from multiple botanical families, commonly consumed examples include bananas (*Musa acuminta, Musa balbisiana*), kiwifruit (*Actinidia deliciosa*), mango (*Mangifera indica*), passion fruit (*Passiflora edulis*), papaya (*Carica papaya*) and pineapple (*Ananas comosus*). These fruits are mostly cultivated in the tropics and subtropics, and are thus more widely consumed there. Data on (poly)phenol content within these fruits are limited, but current evidence suggest that tropical fruits do not seem to contribute greatly towards (poly)phenol intake in general, with the exception of bananas (Table 1.10). However, they do provide nutrients such as vitamin C, and are often particularly rich in both starch and sugars.

Table 1.10 Distribution of major (poly)phenol classes across commonly consumed tropical fruits, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Banana[1]	**Flava-3-nols** [(+)-catechin]	155 (79)
Kiwifruit[1]	**Flavones** (luteolin), **flavan-3-ols** [(-)-epicatechin]	180 (112)
Mango[1]	**Flava-3-nols** [(+)-catechin]	145 (109)
Passion fruit	*Data not available*	57 (0)
Papaya[2]	**Flavonols** (myricetin), **flavones** (luteolin)	58 (0)
Pineapple[2]	**Flavonols** (quercetin)	148 (61)

[1]Major flavonols from Phenol Explorer, [2]major flavonol aglycone from USDA flavonoid database

1.2.3.2 Vegetables

The definition of vegetables is largely driven by culinary tradition, referring to plant parts (usually not sweet) commonly consumed with various meats in savoury dishes. Vegetables could also be consumed raw as a salad. With the exception of the *Allium* genus, (poly)phenol profiles of vegetables are largely similar, consisting of mostly lignans. Thus, vegetables were firstly grouped by taking into account the genus, followed by plant parts and usual methods of consumption.

1.2.3.2.1 Allium

Allium vegetables here literally refer to vegetables from the *Allium* genus, such as onion (*Allium cepa*), shallot (*Allium cepa var. aggregatum*), chive (*Allium schoenoprasum*), garlic (*Allium sativum*) and leek (*Allium ampeloprasum*). These vegetables are more commonly consumed after cooking, although onion, garlic and chives can also be consumed raw. *Allium* vegetables pre-dominantly consist of flavonols (Figure 1.6), where the most abundant form is quercetin (Table 1.11) and its glycosides. Red onions are rich in quercetin-3,4'-*O*-diglucoside and quercetin-4'-*O*-glucoside. They also contain some anthocyanins which contribute to the red pigment. White onions in contrast have a lower (poly)phenol content. The (poly)phenol composition of shallots is similar to red onions, while data on other *Allium* vegetables are limited due to lack of evidence (Table 1.12). Cooking methods such as frying, boiling or microwaving may decrease flavonol content within onions by 21%, 75% and 64% in comparison to uncooked onions, though some (poly)phenols are leached into cooking water [134]. Even so, failure to account for retention factors may lead to bias in estimation of flavonol intakes. In addition to (poly)phenols, *Allium* vegetables are also rich in potassium and vitamin C.

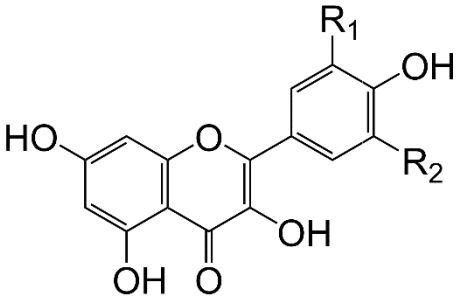


Figure 1.6 The skeletal structure of flavonol and respective substitution sites

Table 1.11 The substitution pattern of major flavonols

Name	R_1	R_2
Quercetin	OH	H
Myricetin	OH	OH
Kaempferol	H	H
Isorhamnetin	OCH_3	H

Table 1.12 Distribution of major flavonols in *Allium* vegetables, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major flavonols	Total (poly)phenols mg/100g FW
Onions[1]	Quercetin-3,4'-*O*-diglucoside, quercetin-4'-*O*-glucoside	Red: 45 White: 103 (22)
Shallot[1]	Quercetin-3,4'-*O*-diglucoside, quercetin-4'-*O*-glucoside	Pink shallot: 115
Garlic[2]	Quercetin, myricetin	87 (52)
Leek[2]	Kaempferol	-
Chives[2]	Kaempferol, quercetin	81 (21)

[1]Major flavonols from Phenol Explorer, [2]major flavonol aglycone from USDA flavonoid database

Flavonols are also present in a wide range of other foods, such as tea, alcoholic beverages, dark green vegetables and apples [115]. Sources of flavonols within the UK health-conscious EPIC cohort originate from tea (45.5%), soups (15.0%), pomes (6.0%), onions and garlic (6.0%), and is among the highest in the European region (42 to 54 mg/day) [130]. Ireland and the UK were also reported to have the highest intake of flavonols reported by Vogiatzoglou *et. al* [113], at 38 and 28 mg/day respectively. In contrast, flavonol intake in United States was estimated to be lower (16 mg/day) [115].

1.2.3.2.2 Brassicaceae

As above, *Brassicaceae* refers to vegetables belonging to the *Brassicaceae* family by classification. This includes commonly consumed examples, broccoli (*Brassica oleracea* Italica Group), Brussel sprouts (*Brassica oleracea* Gemmifera Group), cabbage (*Brassica oleracea* Capitata Group), cauliflower (*Brassica oleracea* Botrytis Group), radish (*Raphanus sativus*), swede (*Brassica napus* Napobrassica Group), turnip (*Brassica rapa* Rapifera Group)

and watercress (*Nasturtium officinale*). *Brassicaceae* vegetables are rich in fibre, carotenes, as well as glucosinolates. Table 1.13 provides the overview of major (poly)phenols in *Brassicaceae* vegetables. Unlike *Allium* vegetables, *Brassicaceae* vegetables do not specifically provide any particular class of (poly)phenols in abundance, with the exception of lignans. Lignans are polymers of hydroxycinnamic acids present in most vegetables. They are not to be confused with lignins (classed as insoluble fibre), though they share similar chemical characteristics.

Table 1.13 Distribution of major flavonols in *Brassicaceae* vegetables, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Broccoli	**Flavonols** (kaempferol-3-*O*-sophoroside), **hydroxycinnamic acid** (3-caffeoylquinic acid)	199 (120)
Brussel sprouts	**Flavonols** (kaempferol), **lignans** (lariciresinol)	221 (183)
Cabbage	**Flavonols** (quercetin), **lignans** (pinoresinol, lariciresinol)	White: 15 (0) Green: 89 (89) Red: 451 (173) Savoy: 120 (52)
Cauliflower	**Hydroxycinnamic acid** (sinapic acid), **hydroxybenzoic acid** (syringic acid)	82 (106)
Radish	**Flavonols** (kaempferol)	44 (15)
Swede	**Flavones** (apigenin), **flavonols** (myricetin)	-
Turnip	**Lignans** (lariciresinol)	55 (0)
Watercress	**Flavonols** (quercetin), **lignans** (lariciresinol)	-

1.2.3.2.3 Fruit vegetables

Fruit vegetables consist of vegetables from multiple botanical families, including those previously identified as 'pepo'. They are also botanically identified as fruits. Commonly consumed examples are aubergine (*Solanum melongena*), butternut squash (*Cucurbita moschata*), courgette (*Cucurbita pepo*), cucumber (*Cucumis sativus*), marrow (*Cucurbita pepo*), tomatoes (*Solanum lycopersicum*), olives (*Olea europaea*), sweet pepper (*Capsicum annuum* Longum Group) and pumpkin (*Cucurbita pepo*). These vegetables as a whole are rich in potassium, vitamin C and carotenes. In terms of (poly)phenol profile, fruit vegetables mostly contain low to moderate levels of hydroxybenzoic acids, hydroxycinnamic acids and lignans (Table 1.14). Olives and tomatoes are the most well quantified, while (poly)phenol data on butternut squash, marrow and sweet peppers are lacking. Processing can alter the levels of (poly)phenol within vegetables, such as tomatoes, leading it to decrease by mechanical or thermal treatment, or to increase by 'reconstitution' (addition of a sauce rich in tomato seeds and peels) [135]. Cooking processes such as frying, boiling and microwaving could also decrease the level of (poly)phenols by 35%, 82% and

65% [134], reinforcing the importance of retention factors in the estimation of (poly)phenol intake.

Table 1.14 Distribution of major (poly)phenols in fruit vegetables, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Aubergine	**Hydroxybenzoic acid** (protocatechuic acid)	61 (5)
Butternut squash	*Data not available*	-
Courgette	**Flavonols** (quercetin-3-*O*-rutinoside), **lignans** (lariciresinol)	30 (6)
Cucumber	**Lignans** (lariciresinol)	20 (4)
Marrow	*Data not available*	-
Tomato	**Hydroxycinnamic acid** (5-caffeoylquinic acid), **flavonols** (quercetin-3-*O*-rutinoside)	45 (16)
Olive	Green: Tyrosols (oleuropein), **hydroxycinnamic acid** (sinapic acid) Black: **Tyrosols** (oleuropein), **anthocyanins** (cyanidin-3-*O*-rutinoside), **hydroxycinnamic acid** (verbascoside), **flavonols** (quercetin-3-*O*-rutinoside)	Green: 161 (187) Black: 117 (64)
Sweet pepper	**Lignans** (lariciresinol)	Red: 229 (206) Yellow: 214 (218) Green: 181 (118)
Pumpkin	**Flavones** (luteolin)	110 (81)

1.2.3.2.4 Pod vegetables

Pod vegetables grouped here include legumes which are usually consumed fresh with the pod. Examples include (and are not limited to) French beans (*Phaseolus vulgaris*), green beans (*Phaseolus vulgaris*), peas (*Pisum sativum*) and runner beans (*Phaseolus coccineus*). As described below (Table 1.15), there is a lack of data for the quantification of (poly)phenols in pod vegetables, but current evidence suggests low amounts of (poly)phenols in general.

Table 1.15 Distribution of major (poly)phenols in pod vegetables, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Green beans	**Flavonols** (quercetin-3-O-rutinoside), **flavanols** [(-)-epicatechin], **lignans** (lariciresinol)	32 (23)
Peas	**Lignans** (pinoresinol)	-
Runner beans	*Data not available*	-

1.2.3.2.5 Stalk and root vegetables

Lastly, stalk and root vegetables as the name suggests, consist of plant stalks and roots consumed as vegetables. Common examples include beetroot (*Beta vulgaris*), carrot (*Daucus carota*), celery (*Apium graveolens*), parsnip (*Pastinaca sativa*) and sweet potato (*Ipomoea batatas*). Stalk and root vegetables are rich in fibre, sodium and potassium, along with a modest amount of nutrients and minerals. Carrots in particular are rich in β-carotene, which provides the characteristic orange colour. Stalk and root vegetables are not major sources of (poly)phenols (Table 1.16).

Table 1.16 Distribution of major (poly)phenols in stalk and root vegetables, and estimated total phenolic content using Folin-Ciocalteu assay, expressed as mean (standard deviation) in mg/100 g fresh weight [111]

Name	Major (poly)phenol class (dominant compound)	Total (poly)phenols mg/100g FW
Beetroot	**Flavones** (luteolin), **flavonols** (quercetin)	164 (0)
Carrot	**Hydroxycinnamic acid** (5-caffeoylquinic acid)	58 (52)
Celery	**Flavones** (apigenin)	14 (1)
Parsnip	**Flavonols** (quercetin)	-
Sweet potato	**Lignans** (matairesinol)	74 (0)

1.2.3.3 Coffee

Coffee is one of the most widely consumed beverages globally, processed from coffee cherry seeds. There are two varieties of coffee dominating the commercial market, known as Arabica coffee (*Coffea Arabica*), originally from Ethopia, and robusta coffee (*Coffea canephora*) which is cultivated in Africa. Coffee contains caffeine (1% to 2.5% of fresh weight) [132], but can also be consumed as decaffeinated coffee after caffeine removal using supercritical carbon dioxide or solvents [136]. Green coffee beans are rich in chlorogenic acids (between 6% to 10% by dry weight) [100], which are conjugates of hydroxycinnamic acids (Figure 1.7, Table 1.17) with tartaric or quinic acid. However, coffee beans undergo roasting, which destroys between 8 to 10% of chlorogenic acids for every 1% of dry weight lost [100]. Nonetheless, substantial amounts remain in the coffee beverage, where the most abundant compounds are 5-caffeoylquinic acid, 4- caffeoylquinic acid and 3-caffeoylquinic acid [111]. Regular coffee drinkers could consume up to 1 g/day of phenolic acids [100].

Coffee also contains other bioactive components such as caffeine (30 to 300 mg/cup depending on type of brew) and diterpenes (cafestol, kahweol) [137], where the latter is known to exhibit cholesterol-raising effects. Likewise, caffeine is also reported to cause an acute pressor effect. However, it has been recently reported that caffeine does not cause

adverse effects when caffeine from coffee or tea is consumed *ad libitum* [138]. Coffee may be consumed black, or with the addition of milk and sugar. The addition of milk does not seem to affect the absorption of chlorogenic acids [139].

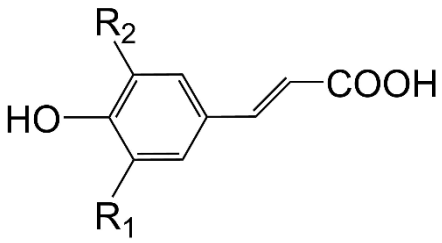


Figure 1.7 The skeletal structure of hydroxycinnamic acid and respective substitution sites

Table 1.17 The substitution pattern of major hydroxycinnamic acids

Name	R_1	R_2
Caffeic acid	H	OH
Ferulic acid	H	OCH_3
p-Coumaric acid	H	H
Sinapic acid	OCH_3	OCH_3

1.2.3.4 Tea

Tea is also a globally popular beverage produced from the leaves of the plant *Camellia spp.*. The leaves of the plant may contain between 3% to 4% of caffeine, and up to 30% (poly)phenols by dry weight, thus it is an extremely rich source of flavan-3-ols [100]. Tea is consumed as green, oolong or black, where black tea is subjected to the most processing. In the preparation of green tea, the leaves are steamed or subjected to firing (dry heat) to inhibit enzymes such as (poly)phenol oxidase. Black tea undergoes mechanical processes to disrupt the cell structure, releasing and activating enzymes. During the fermentation stage, (poly)phenols are transformed, before the leaves are dried, graded and sorted. Oolong tea is partly fermented, while other minor teas such as Pu-erh tea is additionally fermented by microorganisms [140].

Green tea is rich in flavan-3-ols, specifically (-)-epigallocatechin-3-*O*-gallate, (-)-epigallocatechin, (-)-epicatechin and (-)-epicatechin-3-*O*-gallate. It also contains minor amounts of (poly)phenols such as hydroxycinnamic acids and flavonols [111]. The major (poly)phenol composition in black tea is also flavan-3-ols, but up to 90% of flavan-3-ols are destroyed during fermentation, and what remains are partly transformed into theaflavins [141], such as theaflavin-3'-*O*-gallate [111]. There are also still some uncharacterised (poly)phenols after transformation.

Black tea is habitually consumed with milk in UK, and multiple studies have investigated the antioxidant activity of flavan-3-ols with and without milk [142]. However, the evidence presented consists of mostly *in vitro* experiments using antioxidant assays, that do not reflect conditions *in vivo*. Where *in vivo* evidence is available, an increase in total catechins within plasma is not significantly affected by the addition of milk within a human study [143]. An *in vitro* digestion experiment was also supportive of the former conclusions, presenting no significant changes that would suggest impairment for catechin bioaccessibility when green or black tea was digested together with skimmed, semi-skimmed and whole milk [144]. Thus the current evidence suggest that (poly)phenol bioavailability is not affected by the addition of milk in tea.

Flavan-3-ol (monomers) intake varies greatly in the European region, where Ireland and UK have the highest intake at 156 and 110 mg/day, in comparison to Spain and Italy (5 and 12 mg/day) [113]. Average daily flavan-3-ol (monomers) intake in United States (158 mg/day) and UK health-conscious cohort from EPIC study (148 to 156 mg/day) was also similar to the estimation above [115, 145]. Daily consumption of theaflavins and thearubigins were also higher for countries with high consumption of flavan-3-ol monomers [113, 145], as the main contributor to flavan-3-ol intake is tea (95%) [115].

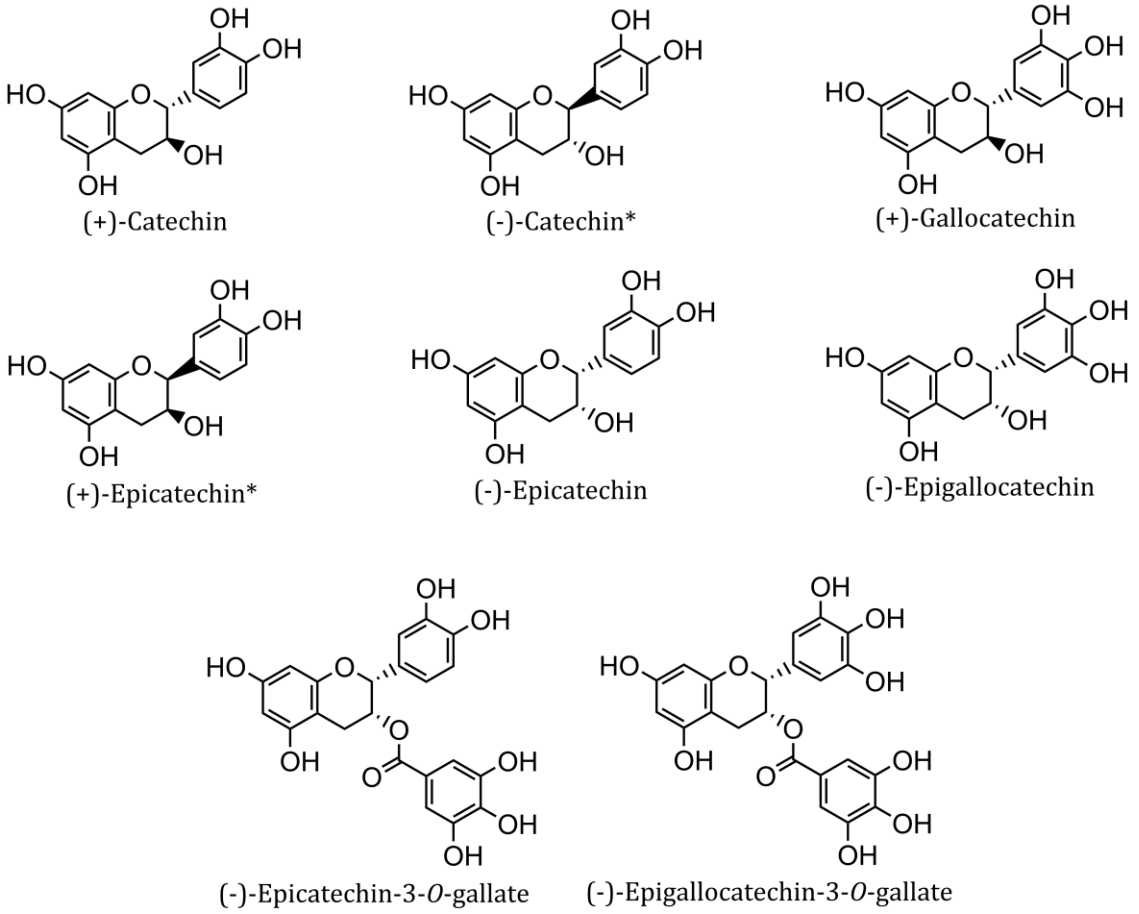


Figure 1.8 Flavan-3-ol monomers [(+)-catechin and (-)-epicatechin], where * are rare forms of flavan-3-ol monomers, its hydroxylated forms [(+)-gallocatechin and (-)-epigallocatechin] and subsequent forms after esterification [(-)-epicatechin-3-*O*-gallate and (-)-epigallocatechin-3-*O*-gallate] [100]

1.2.4 (Poly)phenol mechanisms and its impact on CVD risk factors

(Poly)phenols were believed to exhibit non-specific mechanisms, such as anti-oxidant activity [146]. However, this is now considered to be a quantity measurement rather than *in vivo* mechanistic function. More specifically, (poly)phenols can modulate metabolic enzymes, nuclear receptors, multiple signalling pathways and alter gene expression [104]. The potential mechanisms for each CVD risk factor and function is summarised briefly below. The literature surrounding each dietary source of (poly)phenols will be summarised and discussed within relevant results chapters.

1.2.4.1 Endothelial function and blood pressure

Endothelial function is the functional capacity of the monolayer of endothelial cells in the blood vessel lumen, known as the endothelium. Adequate nitric oxide (NO) output is an important feature of a healthy endothelium, as well as regulating vasodilation. The enzyme

endothelial nitric oxide synthase (eNOS) is responsible for its production. Simply put, endothelial dysfunction occurs when endothelium-dependent vasodilation decreases, causing an imbalance between vasodilation and vasoconstriction [147]. Endothelial dysfunction is also one of the main contributors to hypertension [57].

Red wine (poly)phenols have been demonstrated in cell culture studies to increase production of endothelial NO by inducing eNOS protein expression [147]. Animal studies also proposed that ferulic acid enhances bioavailability of nitric oxide (NO), improving endothelial-dependent vasodilation [148], and 5-caffeoylquinic acid improved endothelial function in hypertensive rats [147]. In human trials, a decrease in BP has been observed after consumption of cranberry juice and berry supplementation [120], and also an increase in NO production, as well as endothelium-dependent vasodilation [147]. Tea intake, specifically epigallocatechin gallate, improved endothelial function and flow-mediated dilation within CHD patients. However, this effect was not observed within healthy participants [147]. In particular, hesperidin (previously identified as vitamin P) is known to reduce permeability and fragility of capillary walls, a symptom which manifests in hypertension [149]. Its anti-hypertensive effect was also demonstrated in human studies, where BP was lowered in healthy subjects after consumption of orange juice [150, 151]. SRs and MAs of RCTs have reported favourable effects of chlorogenic acids, green tea catechins and black tea on BP [152-154].

1.2.4.2 Blood lipid profile

Human intervention studies using various berries (blackcurrants, blueberries, cranberries, raspberries, strawberries, and the less commonly consumed acai berries, bilberries, boysenberries, chokeberries, lingonberries and wolfberries) which are rich in anthocyanins, revealed a decrease in total cholesterol, LDL-oxidation, lipid peroxidation, increase in HDL-C, as well as increased urinary or plasma antioxidant capacity after intervention [120]. The evidence for grape (poly)phenols from red wine is also fairly well established. It was proposed that anthocyanins could either reduce cholesterol absorption by increasing fecal bile acids, or by up-regulating the expression of LDL receptor [155].

Within animal and cell culture studies, catechins from green tea exhibit cholesterol-lowering effects in animal plasma, and favourable cholesterol metabolism in cells [155]. Mechanisms are not fully understood, however, it was suggested that catechins could increase LDL-receptor activity, leading to lower plasma cholesterol [155]. There is mixed evidence from human interventions for the cholesterol-lowering effect, where some studies

report reduced levels of total cholesterol and LDL-C. However, other studies reported no significant change after administration of green or black tea to healthy volunteers [155].

1.2.4.3 Type 2 Diabetes

From *in vitro* studies [104, 156], it is suggested that (poly)phenols may exert multiple anti-diabetic effects by:

1) Reducing the absorption of simple sugars through:

a) Inhibition of α-amylase and α-glucosidase within the intestinal lumen – Most (poly)phenols such as flavones, flavonols, catechins, anthocyanins, isoflavones, flavanones, phenolic acids have demonstrated this effect.

b) Inibition of glucose transporters, sodium dependent glucose transporter, SGLT1 – chlorogenic acid, ferulic acid, caffeic acid, and sodium-independent glucose transporter, GLUT2 – quercetin, myricetin, apigenin and catechins.

2) Improving uptake of glucose in muscle, skeletal and adipose tissues – Epigallocatechin gallate, quercetin, kaempferol, ferulic acid.

3) Promote storage of glucose as glycogen by increasing activity of hepatic glucokinase – Epigallocatechin gallate, naringin, hesperidin, ferulic acid.

4) Suppressing hepatic gluconeogenesis – Epigallocatechin gallate, naringin, hesperidin, genistein, daidzein.

5) Protecting integrity of β-cells (preventing glucotoxicity) and increasing insulin production – catechins and flavonols.

Evidence from human intervention trials also indicate a reduction in postprandial glucose after consumption of red wine, coffee, berries and apple juice, supporting mechanisms related to the reduction of glucose absorption [156].

1.2.4.4 Obesity

Studies *in vitro* have demonstrated that (poly)phenols may exert various mechanistic functions which may impact on body weight control. Catechins, especially epigallocatechin gallate from green tea is suggested to have several mechanisms, such as supressing adipocyte differentiation and proliferation, inducing apoptosis in mature adipocytes, inhibiting fat absorption in the gut, and inhibiting COMT, which inhibits oxidation of fatty acids in brown adipose tissue [157]. However, studies performed *in vivo* for the consumption of green tea catechins were inconclusive, possibly due to the heterogeneity of

study design parameters [158]. Blueberries, rich in anthocyanins were able to attenuate parameters which affects obesity [157]. *In vitro*, other (poly)phenols such as resveratrol from grapes and red wine, also exhibited effects to induce apoptosis in mature adipocytes and decrease adipocyte proliferation, with limited supporting evidence *in vivo* [158].

1.2.4.5 Inflammation

Inflammation is a highly complex process the body employs as an immune defence mechanism. Specific to CVD, multiple *in vitro* studies have been reviewed to demonstrate the anti-inflammatory action of flavonoids by modulating signal transduction pathways and gene expression, such as the downregulation of inducible NO synthase (iNOS) (produced during when immune defence is activated) and cyclo-oxygenase (COX-2) expression [159]. Luteolin and apigenin were also reported to inhibit pro-inflammatory cytokine expression, while epigallocatechin-3-gallate, epigallocatechin and epicatechin-3-gallate from tea enhanced anti-inflammatory cytokines [159]. (Poly)phenols were also demonstrated *in vitro* to attenuate the expression of adhesion molecules (apigenin, kaempferol, quercetin), inhibit monocyte-endothelial cell adhesion (isoflavones) and stabilizing atheroma plaques (quercetin) [160]. *In vivo*, the adherence and consumption of a high flavonoid FV diet (>four portions/day) lowered C-reactive.protein levels and vascular cell adhesion molecules within men at risk of CVD [161]. A seven-day supplementation of red orange juice (500 mL) within nondiabetic subjects with high risk of CVD significantly lowered C-reactive protein level, an inflammatory marker [162]. Berries supplied in various forms (fresh or extracts) can also reduce inflammatory stress by inhibiting pro-inflammatory markers or increasing anti-inflammatory molecules. Evidence for commonly consumed berries such as blueberries, cranberries and strawberries require further research to verify current findings. The evidence for less commonly consumed berries (bilberries, chokeberries etc.) in comparison, are overall more consistent [163].

1.3 Aims and objectives

1.3.1 Thesis aims

Based on the evidence presented above on (poly)phenol mechanisms and CVD risk factors, the primary aim of the thesis is to investigate the association between (poly)phenol-rich foods in the UK and CVD risk, in particular:

1. The direct association between (poly)phenol-rich foods and CVD risk.
2. The indirect association between (poly)phenol-rich foods and CVD through the major CVD risk factor, HBP.
3. To identify individual relationships between four groups of (poly)phenol-rich foods (FVs, tea and coffee) and CVD risk and BP.
4. To explore if associations exist between FV subgroups by (poly)phenol content and CVD risk or BP to provide supporting evidence for hypotheses reported in literature, or generate further hypotheses for future investigation.

1.3.2 Thesis objectives

Table 1.18 summarises the objectives of the current thesis.

Table 1.18 Objectives of the thesis matching the aims met in the stated chapters

	Objective	Chapter	Aim
1	Explore and describe the study population and dietary assessment methods in two UK cohorts, the United Kingdom Women's Cohort Study (UKWCS) (1995 – 1998) and the National Diet and Nutrition Survey Rolling Programme (NDNS RP) (2008 – 2012).	2	-
2	Explore and report consumption levels of (poly)phenol-rich foods in both study populations	2	-
3	Sub-categorise (poly)phenol-rich foods into groups which can be representative of major flavonoid subclasses, taking into account methods and habit of consumption, as proposed in the introduction	2	-
4	Define appropriate statistical methods to be used to analyse the relationship between (poly)phenol rich-foods and CVD	2	-
5	Assess if a direct association exists between four groups of (poly)phenol-rich foods (FVs, tea and coffee) and CVD mortality in the UKWCS	3, 5	1, 3, 4
6	Explore associations between fruit and CVD incidence in the UKWCS	4	1, 3, 4
7	Investigate associations between the incidence of HBP (self-reported) in the UKWCS and (poly)phenol-rich foods	6, 7	2, 3, 4
8	Validate strength, weakness and agreement of dietary assessment tools used in the UKWCS to assess accuracy and precision of diet captured at baseline	8	-
9	Undertake (poly)phenol analysis of selected fruit beverages for where current evidence is limited, and explore variation in (poly)phenol content with selected fruit beverages	9	-
10	Explore associations between BP and FV intakes in the NDNS	10	2, 3, 4
11	Discuss and conclude evidence generated by the research, and propose recommendations for further investigations	11	4

1.3.3 Thesis overview

The overview of the thesis is illustrated below in Figure 1.9:

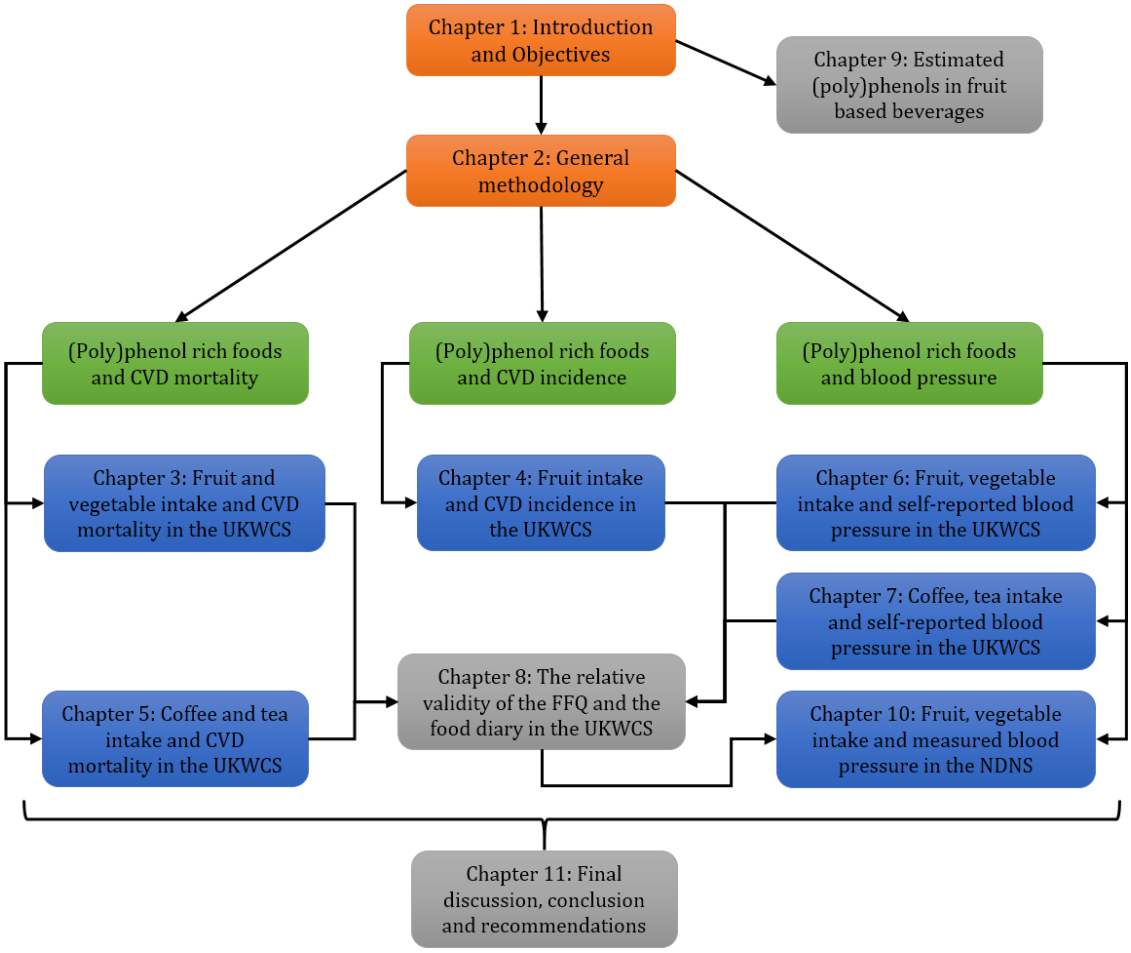


Figure 1.9 Thesis flowchart

Chapter 2
General methodology

2.1 Abstract

This chapter contains three sections, detailing the description of the UK Women's Cohort Study (UKWCS) and the National Diet and Nutrition Survey Rolling Programme (NDNS RP), followed by model building strategies undertaken throughout the thesis. In the following sections, the methodology for data collection in the UKWCS and the NDNS RP was described. Justification was provided for each potential confounder for inclusion, and statistical models were proposed for adaptation in each results chapter. In order to correctly assess the association between (poly)phenol-rich foods and CVD, directed acyclic graphs (DAG) were additionally applied to help visualise the relationships between potential confounders, exposure, and outcome. The exploration of dietary variables (fruit, vegetable, coffee and tea) and the corresponding baseline characteristics prior to exclusions were then provided and discussed.

2.2 UK Women's Cohort Study: Study design

2.2.1 Sample design

The UK Women's cohort study was initially funded by the World Cancer Research Fund. Participants living in England, Wales and Scotland were recruited by direct mail survey in 1995 to 1998. There were half a million respondents (17% response rate), of which 16,000 were self-reported vegetarians and non-red meat eaters (aged 35 – 69 years). Women who expressed interest for further contact were eligible for inclusion [164]. Self-reported vegetarians and non-red meat eaters from the respondents were matched with a non-vegetarian by age (no larger than 10 years). This recruitment design maximises power to detect statistically significant associations between diet and disease outcome through generating a cohort with high degree of dietary heterogeneity [165]. Further recruitment was also accomplished by inviting friends and relatives of initial respondents from a similar age group [164].

2.2.2 Survey design

Baseline information from participants of the UKWCS was initially collected between 1995 and 1998, using a food frequency questionnaire (FFQ). A subsequent phase of data collection included a questionnaire, four-day food diary and physical activity diary (Figure 2.1). However, only the baseline FFQ, phase 2 questionnaire and four-day food diary are explained in detail as data from the physical activity diary were not used in this thesis.

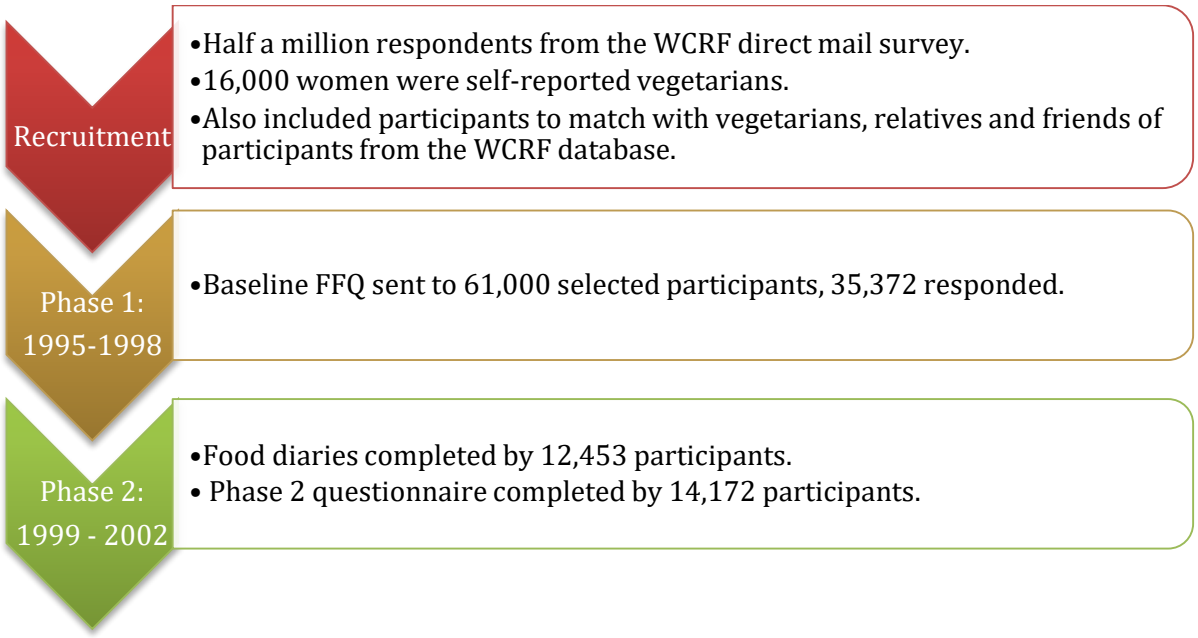


Figure 2.1 Study design for the UKWCS

2.2.2.1 Food frequency questionnaire

The 217-item FFQ was adapted and modified from the EPIC-Oxford Cohort [166], after a pilot study with a subsample of vegetarian women [164]. Additional vegetable composite dish items and portion sizes were also added into the FFQ from the same pilot study. The FFQ was designed to capture yearlong dietary intake, health and lifestyle habits. Participants were required to report the frequency of consumption of listed foods by answering the question, "How often have you eaten those foods in the last 12 months?" using one of ten response categories ranging from "Never" to "More than 6+ portions a day" (Figure 2.2). Foods were presented as individual items in categories, but could also represent multiple types of the same food. For example, "Apples" could include a variety of types including cooking apples, dessert apples, and could be consumed raw or stewed with sugar. This ensures all variations were accounted for. Nine of 17 fruit items were classed under 'seasonal', and participants had to report the frequency of consumption when it was

seasonally available. The number of months the fruits were in season was taken into account when calculating daily intakes [167].

Please estimate how often you eat the following foods, and please answer every question.

PLEASE PUT A TICK(✓) ON EVERY LINE

FOODS AND AMOUNTS	HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS?									
	NEVER	Less than once a month	1-3 per month	once a week	2-4 per week	5-6 per week	once per day	2-3 per day	4-5 per day	6+ per day
SEASONAL FRUIT **How often have you eaten these fruits, when they are in season?**										
Apricots	0	1	2	3	4	5	6	7	8	9
Melon	0	1	2	3	4	5	6	7	8	9
Nectarines	0	1	2	3	4	5	6	7	8	9
Peaches	0	1	2	3	4	5	6	7	8	9
Plums	0	1	2	3	4	5	6	7	8	9
Raspberries	0	1	2	3	4	5	6	7	8	9
Red currants/Black currants	0	1	2	3	4	5	6	7	8	9
Rhubarb	0	1	2	3	4	5	6	7	8	9
Strawberries	0	1	2	3	4	5	6	7	8	9

Figure 2.2 An extract from the FFQ showing the categories on the frequency of consumption

Each food has nutrient composition data derived from *McCance & Widdowson's The Composition of Foods* (5th Edition) [168]. Average nutrient intakes such as energy, macronutrient and micronutrient intakes are calculated by multiplying the frequency of consumption for each food with an estimated portion size. Portion sizes were an estimated average based on three sources [167], 1) a pilot study on food diaries [169], 2) women's food portion sizes from the National Diet and Nutrition Survey [170], and 3) other published values [171]. The FFQ was also validated using a semi-weighed four-day food diary [172], where all correlation co-efficients between nutrient intakes from the FFQ and the food diary were highly significant ($p < 0.01$). With regard to health, lifestyle habits and personal information, participants had to answer questions relating to age (as date of birth), anthropometrics (height, weight, waist circumference), smoking habits, physical activity levels, self-reported illnesses (including treatments and past surgeries, if applicable), education, employment, parity, as well as dietary habits (including portion size, cooking methods, alcohol consumption, the usage of milk, salt, fats, supplements, vegetarian/special diet status).

2.2.2.2 Four-day food diary

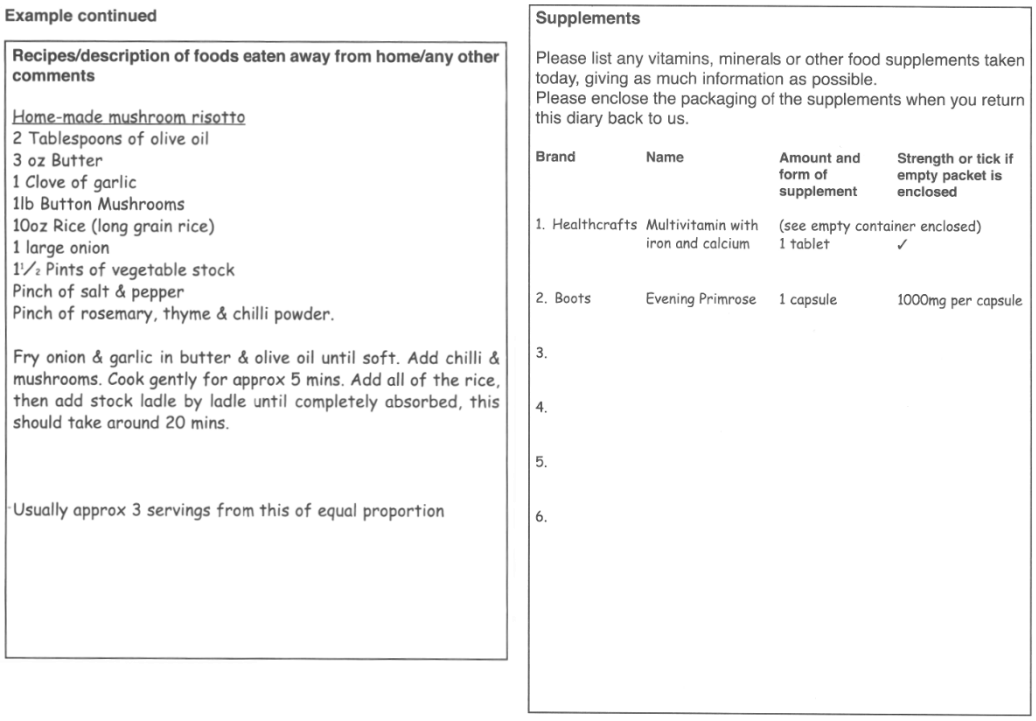
There were 12,453 four-day semi-weighed food diaries collected in total during Phase 2 of the study between 1999 to 2002. Participants were requested to list all the drinks and foods, as well as estimate the portion size or weigh foods consumed, following the example in Figure 2.3. They were also requested to start on a particular day (Friday, Saturday or Sunday). However, this meant that Thursday was never represented, and weekends were over-represented.

EXAMPLE DAY - UP TO LUNCH

Date: 14 October 1998 Day of the week Friday		
Time of food or drink	**Description of food or drink consumed (include brandname where possible)**	**amount**
7.15 am	Filter Coffee	1 cup (200ml)
	semi-skimmed milk	3 tablespoons
7.30 am	Sainsbury's orange juice, un-sweetened	1 glass (150ml)
	Sainsbury's Bran flakes	40g
	semi-skimmed milk	180ml
10.30am	Plain chocolate digestives (large biscuits)	2
	Earl Grey tea (weak) no milk	1 cup
11 am	banana (medium sized)	95g
11.30 am	London herb company Lemon Zester tea	1
12.10 pm	Local bakery's wholemeal bread un-sliced loaf (cut thickly)	1 slice 47g
	Tesco sunflower margarine	thinly spread
	home-made mushroom risotto (see recipe)	About 1/3 of recipe
	green seedless grapes	32g
	Cox's Orange Pippin apple (medium)	82g
	Sainsbury's wholemilk fruit yoghurt (150g)	1 pot
	London herb company sweet berry tea	1
2pm	Warburton's Carrot cake – with cream cheese topping (see nutritional information)	1 slice – 75g (on packet)

Figure 2.3 An example from the UKWCS four-day food diary on recording food items and portion sizes

Participants were also asked to include homemade recipes of foods made at home, consumed away from home or from takeaways, as well as supplement intake, following the example given in Figure 2.4.



Example continued

Recipes/description of foods eaten away from home/any other comments

Home-made mushroom risotto
2 Tablespoons of olive oil
3 oz Butter
1 Clove of garlic
1lb Button Mushrooms
10oz Rice (long grain rice)
1 large onion
1½ Pints of vegetable stock
Pinch of salt & pepper
Pinch of rosemary, thyme & chilli powder.

Fry onion & garlic in butter & olive oil until soft. Add chilli & mushrooms. Cook gently for approx 5 mins. Add all of the rice, then add stock ladle by ladle until completely absorbed, this should take around 20 mins.

Usually approx 3 servings from this of equal proportion

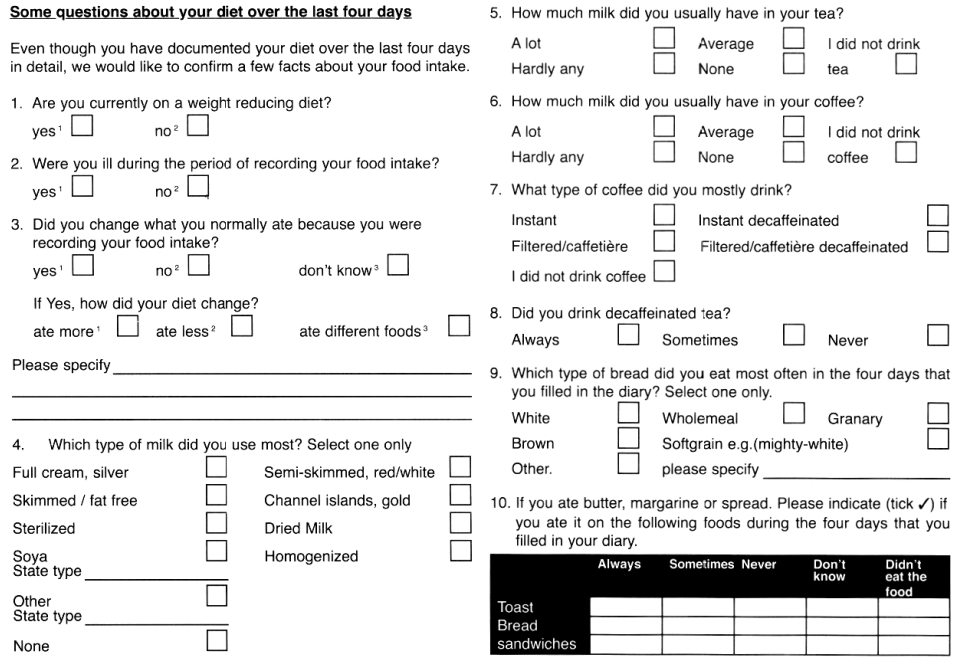
Supplements

Please list any vitamins, minerals or other food supplements taken today, giving as much information as possible.
Please enclose the packaging of the supplements when you return this diary back to us.

Brand	Name	Amount and form of supplement	Strength or tick if empty packet is enclosed
1. Healthcrafts	Multivitamin with iron and calcium	(see empty container enclosed) 1 tablet	✓
2. Boots	Evening Primrose	1 capsule	1000mg per capsule
3.			
4.			
5.			
6.			

Figure 2.4 An example from the UKWCS four-day food diary entry on recording homemade recipes and supplements

In addition, participants had to fill in a short questionnaire on eating habits within the food diary during the period of food recording, shown in Figure 2.5 & Figure 2.6. The questions aided coders in the decision-making process when participants did not provide adequate information in their records, e.g. recording consumption of 'milk' but not specifying whether it is whole, semi-skimmed or skimmed milk.



Some questions about your diet over the last four days

Even though you have documented your diet over the last four days in detail, we would like to confirm a few facts about your food intake.

1. Are you currently on a weight reducing diet?
   yes[1] ☐ no[2] ☐
2. Were you ill during the period of recording your food intake?
   yes[1] ☐ no[2] ☐
3. Did you change what you normally ate because you were recording your food intake?
   yes[1] ☐ no[2] ☐ don't know[3] ☐
   If Yes, how did your diet change?
   ate more[1] ☐ ate less[2] ☐ ate different foods[3] ☐
   Please specify _____

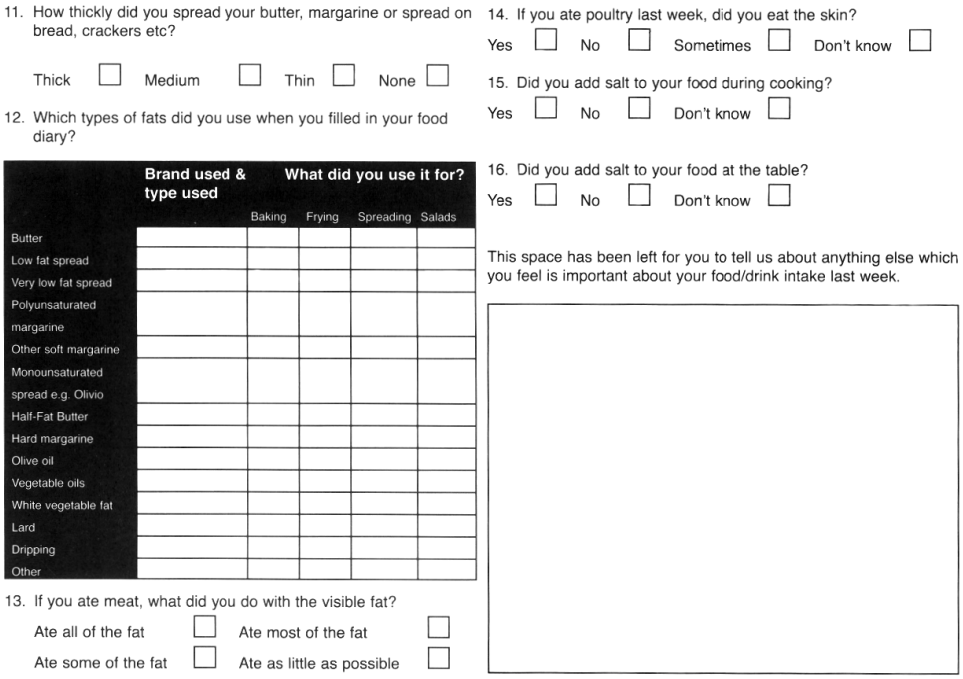
4. Which type of milk did you use most? Select one only

Full cream, silver	☐	Semi-skimmed, red/white	☐
Skimmed / fat free	☐	Channel islands, gold	☐
Sterilized	☐	Dried Milk	☐
Soya State type _____	☐	Homogenized	☐
Other State type _____	☐		
None	☐		

5. How much milk did you usually have in your tea?
   A lot ☐ Average ☐ I did not drink
   Hardly any ☐ None ☐ tea ☐
6. How much milk did you usually have in your coffee?
   A lot ☐ Average ☐ I did not drink
   Hardly any ☐ None ☐ coffee ☐
7. What type of coffee did you mostly drink?
   Instant ☐ Instant decaffeinated ☐
   Filtered/caffetière ☐ Filtered/caffetière decaffeinated ☐
   I did not drink coffee ☐
8. Did you drink decaffeinated tea?
   Always ☐ Sometimes ☐ Never ☐
9. Which type of bread did you eat most often in the four days that you filled in the diary? Select one only.
   White ☐ Wholemeal ☐ Granary ☐
   Brown ☐ Softgrain e.g.(mighty-white) ☐
   Other. ☐ please specify _____
10. If you ate butter, margarine or spread. Please indicate (tick ✓) if you ate it on the following foods during the four days that you filled in your diary.

	Always	Sometimes	Never	Don't know	Didn't eat the food
Toast					
Bread					
sandwiches					

Figure 2.5 Questions from the UKWCS four-day food diary on dietary preferences



11. How thickly did you spread your butter, margarine or spread on bread, crackers etc?
    Thick ☐ Medium ☐ Thin ☐ None ☐
12. Which types of fats did you use when you filled in your food diary?

	Brand used & type used	What did you use it for?			
		Baking	Frying	Spreading	Salads
Butter					
Low fat spread					
Very low fat spread					
Polyunsaturated margarine					
Other soft margarine					
Monounsaturated spread e.g. Olivio					
Half-Fat Butter					
Hard margarine					
Olive oil					
Vegetable oils					
White vegetable fat					
Lard					
Dripping					
Other					

13. If you ate meat, what did you do with the visible fat?
    Ate all of the fat ☐ Ate most of the fat ☐
    Ate some of the fat ☐ Ate as little as possible ☐
14. If you ate poultry last week, did you eat the skin?
    Yes ☐ No ☐ Sometimes ☐ Don't know ☐
15. Did you add salt to your food during cooking?
    Yes ☐ No ☐ Don't know ☐
16. Did you add salt to your food at the table?
    Yes ☐ No ☐ Don't know ☐

This space has been left for you to tell us about anything else which you feel is important about your food/drink intake last week.

Figure 2.6 Questions from the UKWCS four-day food diary on dietary preferences (continued)

Lastly, participants were also able to record dietary information from food labels if they consumed ready-made or packaged foods. A prompt was provided at the end of the recording day for any foods that the participants might have left out (Figure 2.7).

Nutritional Information for Ready Made / Packaged foods
Please state, if the information is for a serving or for per 100g

Food	Serving size	per 100g	Energy kcal	Protein	Carbohydrate	Fat	Fibre

Any extras not already recorded, e.g. sweets/snacks/drinks?

Figure 2.7 A table in the UKWCS food diary for ready-made/packaged foods

An in-house tool developed in the University of Leeds using Microsoft Access known as 'DANTE' contained standard nutrient intakes from *McCance & Widdowson's The Composition of Foods* (5th Edition) [168], supplementary information from food manufacturers, food labels and homemade recipes. DANTE also contained typical portion sizes for each food derived from *Food Portion Sizes* [171]. Typical portion sizes would be chosen when a portion size was not reported in the food diary for an entry. If no match was found for the reported food item, coders substituted the reported item with another item by matching nutrient information. When homemade recipes were provided, exact serving proportions were calculated by coders, and foods were coded by appropriate cooking methods.

As food diary coding can be labour intensive, there were only 2136 food diaries which were coded and available for further study applications. However, since there were too few cases within this subpopulation to conduct a sensible statistical analysis on dietary exposure and outcome, the information was applied to validate the FFQ instead, which would be evaluated in Chapter 8.

2.2.2.3 Phase two questionnaire

All women were invited to partake in the second FFQ approximately five years after the completion of the baseline FFQ. There were 14,245 women who responded to the phase 2 questionnaire. This questionnaire contained similar health, lifestyle habits and personal information questions from the baseline FFQ in Section 2.2.2.1, but was structured differently. Some questions also provided more detail compared to the baseline FFQ, e.g. on self-reported illnesses (Figure 2.8). The questionnaire also provided additional information relative to the baseline FFQ on cooking methods and preferences.

ILLNESSES

32. Has a doctor ever told you that you have, or have had, any of the following conditions? (Please exclude conditions relating to pregnancy only).

Condition	Yes	year of diagnosis	No
Heart attack, coronary thrombosis, myocardial infarction	1		2
Angina	1		2
Stroke	1		2
High Blood Pressure (Hypertension)	1		2
High Blood Cholesterol, Hyperlipidaemia	1		2
Diabetes	1		2
Gallstones	1		2
Polyps in the large intestine	1		2
Cancer	1		2
Diabetes	1		2
Stomach (e.g. ulcer or gastritis)	1		2
Irritable bowel syndrome	1		2
Haemorrhoids	1		2
Diverticular disease	1		2
Anal fissure	1		2
Ulcerative colitis	1		2
Arthritis	1		2
Anorexia Nervosa	1		2
Bulimia Nervosa	1		2

Figure 2.8 An extract from the phase 2 questionnaire on self-reported illnesses

2.2.3 Ethical Approval

Ethical approval was granted by 174 local research ethics committees, which represented all participants at the time of cohort establishment in 1993 [173]. Study ethical approval is now overseen by the National Research Ethics Committee-Yorkshire and the Humber, Leeds East. Approval concerning follow-up work for the cohort was granted in December 2011.

2.3 National Diet and Nutrition Survey Rolling Programme: Study design

2.3.1 Study background and design

The National Diet and Nutrition Survey Rolling Programme (NDNS RP) is a nation-wide research collaboration between NatCen Social Research, Medical Research Council (MRC) Human Nutrition Research (HNR) and the University College London Medical School, funded by Public Health England (Department of Health) and the UK Food Standards Agency (FSA). The project focuses on the dietary assessment of food, nutrient intakes and nutritional status of people aged 1.5 years and above from private households. The survey is also designed to be representative of the UK population, and has collected data from 6,828 participants in the past four years. In brief, the methods of assessment include a four-day food diary, background interview using computer assisted personal interview (CAPI) programme, anthropometric and BP measurements, self-completion questionnaires on smoking, drinking and physical activity, as well as the collection of information on prescribed medicines, 24-hour urine collection and blood sample. A detailed description of the full methodology is reported elsewhere [174]. The sections below will provide a brief summary of the study procedures.

2.3.2 Sample design

The NDNS RP survey aims to collect information from at least 1,000 participants (500 adults, 500 children) who are representative of the general UK population. The study sample was drawn from the Postcode Address File (PAF), which contained all the addresses in UK. From April 2008 to March 2011, a random sample of 21,573 addresses from 799 postcode sectors were drawn. These addresses were clustered into Primary Sampling Units (PSU) to improve cost effectiveness. There were 27 random addresses in each PSU, and selected addresses were subsequently allocated into two groups known as 'adult (19 years+) and child (1.5 to 18 years)', or 'child only', also known as child boost. On average each year, 10 to 11 addresses were allocated into the 'adult and child' group, while 16 to 17 addresses were in the child boost group to ensure the target goal of 500 children was achieved. The interviewer would select one household at random for each address, and either one adult and child, or one child were randomly selected for participation. Information describing the purpose of the study was posted to selected addresses, followed by a face-to-face visit to recruit eligible participants [174].

In Years 1 to 4 combined, 46% of 21,573 addresses were eligible for household selection. The remaining 54% consist of vacant and derelict properties and institutions, which were ineligible. If addresses selected for child boost did not contain any children in the eligible age range, they were also excluded. [174]. 91% of selected addresses were eligible for household selection, while 9% refused before household selection was conducted. 58% of eligible households were productive, indicating at least one participant completed three or four food diary recording days [174].

2.3.3 Survey design

The survey was conducted in two stages, with a total of five visits from the interviewer or nurse. Types of dietary and lifestyle information collected at each stage are listed in Figure 2.9. Stages which collect relevant data for the current study are elaborated in sections below.

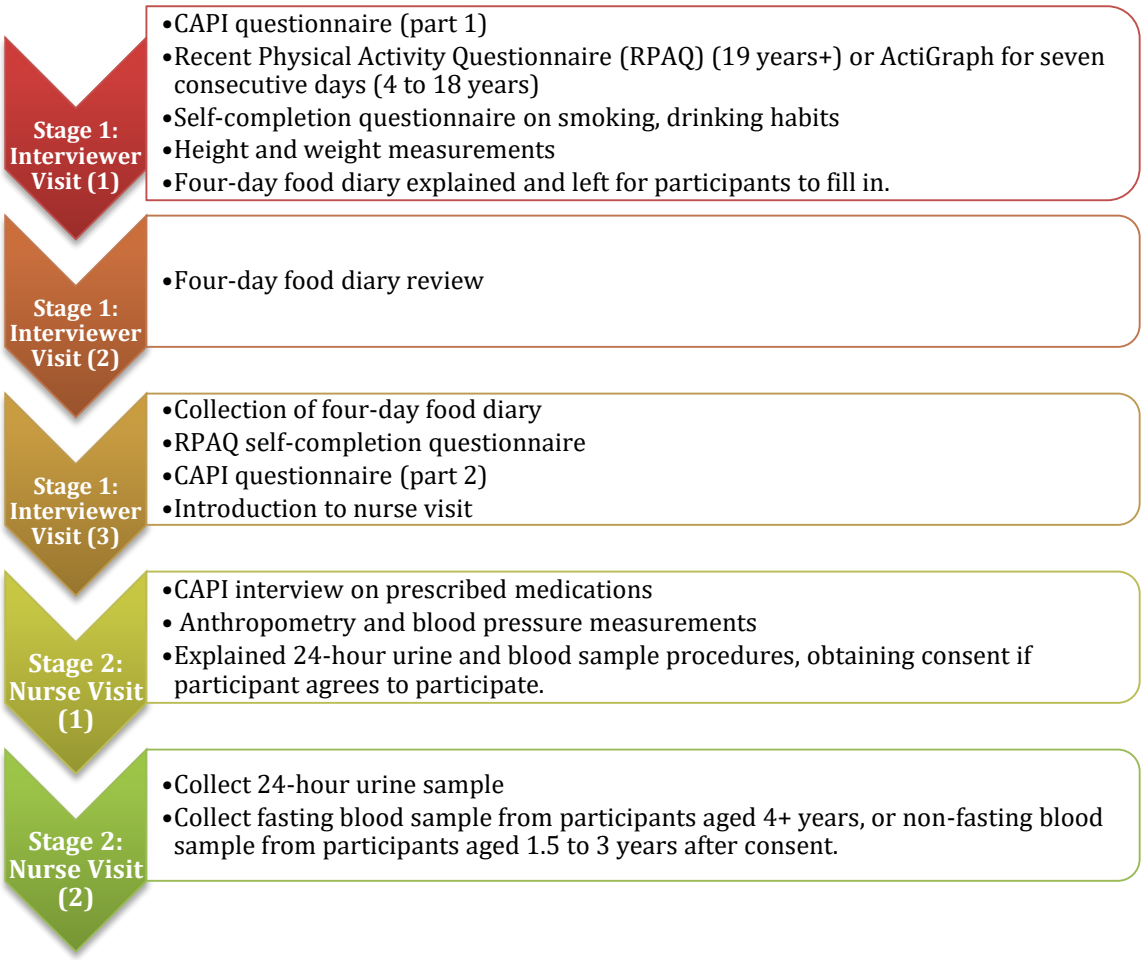


Figure 2.9 Main survey design framework for the NDNS RP

2.3.3.1 Computer Assisted Personal Interview (CAPI) programme

The CAPI interview required the interviewer to read out questions from the laptop screen, followed by entering the participant's answers in designated fields. There were three main sections in the CAPI questionnaire, (1) household composition/structure interview, (2) Main Food Provider (MFP) interview and (3) individual interview (which was divided into two parts). The household composition/structure section contained questions about housing tenure and employment to aid determination of the socio-economic classification, and was answered by the 'Household Reference Person' in each household. Information on food shopping, preparation practices and facilities in the MFP interview was answered by the MFP who was not a selected participant. Lastly, the selected participant answered the individual interview in two parts during the first and third interviewer visit.

2.3.3.2 Four-day food diary

Selected participants were required to complete a four-day food diary on four consecutive days, beginning on the day selected at random by the interviewer's laptop program. Participants could also request to start on an alternative date of their choice if they found the CAPI program's assigned date unsuitable for them. This was because previously in Year 1, food diary records always started on Thursday, Friday or Saturday. Thus, both weekend days were always included, and Wednesdays were never included. To address this issue of over-representing weekend days, food diary records could start during any day of the week from Year 2, so that all days were equally represented [174].

Participants had to keep a detailed record of everything they ate and drunk, both in and outside home (Figure 2.11), and declare whether they ate or drank more food and drink than usual, stating the reasons why. Similarly to the UKWCS food diary reported in Section 2.2.2.2, intake of supplements were asked to be recorded in detail (Figure 2.10), and prompts were provided to include leftovers and snacks. Participants were also asked to provide recipes for made-up dishes and takeaway (Figure 2.12). The interviewer would contact the participant on either the second or third day face-to-face, or over the telephone to conduct a food diary check. The purpose of this visit/call was to collect any missing details for food records, and to improve recording for the remaining days. Interviewers would also provide encouragement to participants to complete their food diary. The food diary was subsequently collected no later than three days after completion date during the third interviewer visit.

If yes, **please describe the supplements you took below**

Brand	Name (in full) including strength	Number of pills, capsules, teaspoons
Healthspan	*Omega3 fish oil with vitamin A, C, D & E*	*2 capsules*
Boots	*Calcium (1000mg) with vitamin D*	*1 tablet*
Holland & Barrett	*Vitamin C 60mg*	*1 tablet*

Figure 2.10 An example of recording supplement intake from the NDNS RP [174]

Day: *Thurs*		**Date:** *31st March*		
Time	**Where? With Whom? TV on? At table?**	**Food/Drink description & preparation**	**Brand Name**	**Portion size or quantity eaten**
How to describe what you had and how much you had can be found on pages 16 - 21				
		6am to 9am		
6.30 am	*Kitchen* *Alone* *No TV* *Not at table*	*Filter coffee, decaffeinated* *milk (fresh, semi-skimmed)* *Sugar white*	*Douwe Egberts* *Silverspoon*	*Mug* *A little* *1 level tsp*
7.30 am	*Kitchen* *Partner* *TV on* *At table*	*Filter coffee with milk and sugar* *Cornflakes* *Milk (fresh, semi-skimmed)* *Toast, granary medium sliced* *Light spread* *Marmalade*	*As above* *Tesco's own* *Hovis* *Flora* *Hartleys*	*As above* *1b* *drowned* *1 slice* *med spread* *1 heaped tsp*
		9am to 12 noon		
10.15 am	*Office desk* *Alone* *No TV* *Not at table*	*Instant coffee, not decaffeinated* *Milk (fresh, whole)* *Sugar brown*	*Kenco*	*Mug* *A little* *1 level tsp*
11 am	*Office desk* *Alone* *No TV* *Not at table*	*Digestive biscuit – chocolate coated on one side*	*McVities*	*2*

Figure 2.11 An example of the four-day food diary entry from the NDNS RP [174]

Write in recipes or ingredients of made up dishes or take-away dishes			
NAME OF DISH: *Bolognese sauce*		***SERVES:*** *4*	
Ingredients	***Amount***	***Ingredients***	***Amount***
Co-op low fat beef mince	*500g*	*Lea & Perrins worcester sauce*	*dash*
garlic	*3 cloves*		
onion	*1 medium*		
sweet red pepper	*1 medium*		
Napoli chopped tomatoes	*400g tin*		
Tesco tomato puree	*1 tablespoon*		
Tesco olive oil	*1 tablespoon*		
mixed herbs	*1 dessertspoon*		
Brief description of cooking method			
Fry onion & garlic in oil, add mince and fry till brown.			
Add pepper, tomatoes, puree, Worcester sauce & herbs. Simmer for 30 mins			

Figure 2.12 An example of recording a homemade dish recipe from the NDNS RP [174]

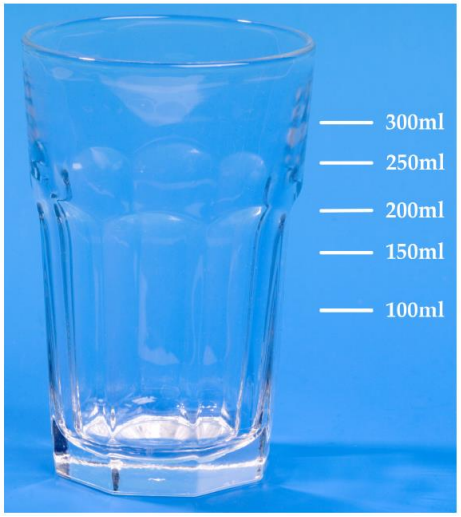
As the diary was not weighed, participants estimated food portion sizes using household measures (e.g. a glass of orange juice or a slice of bread) or food product labels (330 ml can of coke or 400 g tin of soup) (Figure 2.13 & Figure 2.14). Photographs of ten frequently consumed foods were also included in the diary to help those aged 16 and over to describe their portion size (Figure 2.15).

Food/Drink	*Description & Preparation*	*Portion size or quantity*
Fish cakes & fish fingers	Type of fish; plain or battered or in breadcrumbs; fried, grilled, baked or microwaved; economy	Size, number, packet weight
Fruit - fresh	What sort; eaten with or without skin	Small, medium or large
Fruit - stewed/canned	What sort; sweetened or unsweetened; in fruit juice or syrup; juice or syrup eaten	Spoons, weight of can
Fruit – juice (pure)	What sort e.g. apple, orange; sweetened or unsweetened; pasteurised or UHT/Longlife; freshly squeezed; added vitamins/minerals, omega 3	Glass (size or volume) or carton size
Ice cream	Flavour; dairy or non-dairy alternatives e.g. soya; luxury/premium	Spoons/ scoops
Jam, honey	What sort; low-sugar/diabetic; shop bought/brand or homemade	Spoons, heaped or level, or thin or thick spread
Marmalade	Type; low-sugar; thick cut; shop bought/brand or homemade	Spoons, heaped or level, or thin or thick spread
Meat (see also bacon, burgers & sausages)	What sort; cut of meat e.g. chop, breast, minced; lean or fatty; fat removed or eaten; skin removed or eaten; how cooked; with or without gravy	Large/small/medium, spoons, or picture 6 for stew portion
Milk	What sort; whole, semi-skimmed, skimmed or 1% fat; fresh, sterilized, UHT, dried; soya milk (sweetened/unsweetened), goats' milk, rice milk, oat milk; flavoured; fortified with added vitamins and/or minerals	Pints, glass (size or volume) or cup. On cereal: *damp/normal/ drowned*. In tea/coffee: *a little/some/a lot*

Figure 2.13 A portion size estimation guide provided in the four-day food diary in the NDNS RP

Typical quantities of drinks in various containers measured in millilitres (ml)

	Small glass	Average glass	Large glass	Vending cup	Cup	Mug
Soft drinks	150	200	300			
Wine	125	175	250			
Hot drinks				170	190	260



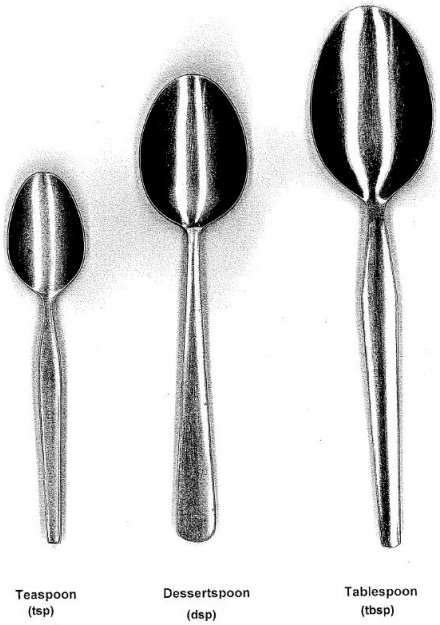


Figure 2.14 'Life size' glass, spoon and typical drink sizes in mL within the four-day food diary in the NDNS RP (not life-sized here)

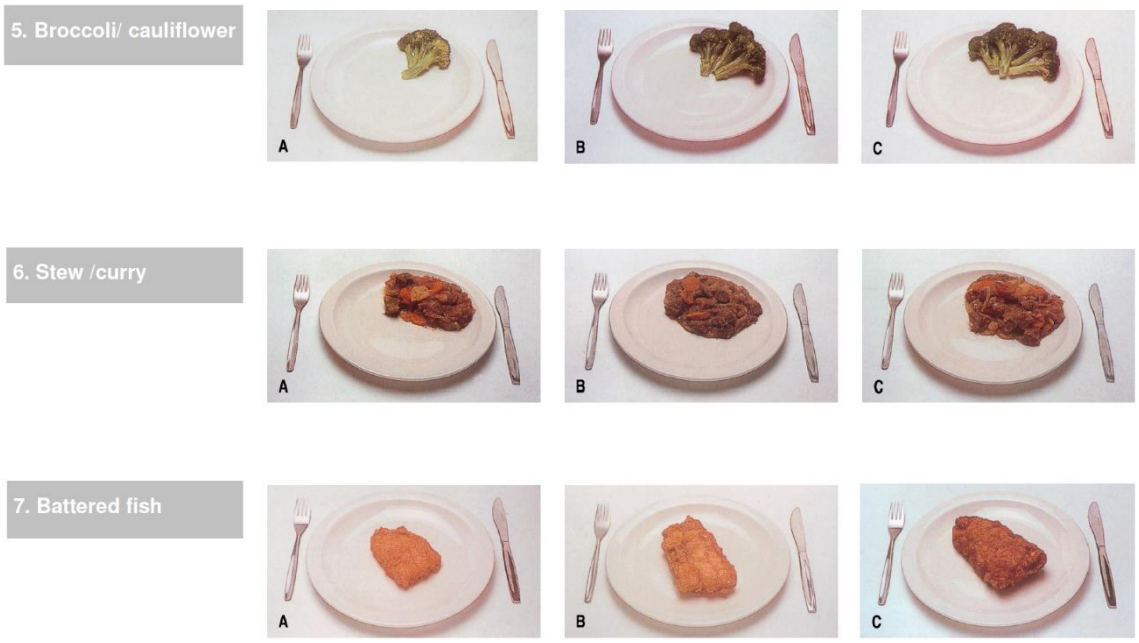


Figure 2.15 Photographs of typical portion sizes of commonly consumed foods within the NDNS RP food diary [174]

Parents were asked to help with keeping the food diary on behalf of participants aged 11 years and younger. Carers were also able to contribute information where possible in addition to the child's own contribution. In addition, three age-appropriate versions of 'Young person's food photograph atlas' [175] were used during the food diary check. The atlases contained 44 commonly consumed foods with a range of served and leftover portion sizes which were difficult to estimate. During the food diary check, the interviewer would use the atlases to ask the participant to select the appropriate portion size for all food entries in the diary. Overall response rate for fully productive participants (completing three or four food diary days) was between 53% to 57% for four years, providing a total of 6,828 participants [174].

Food diaries were coded by trained coders and editors, using an in-house tool known as Diet In Nutrients Out (DINO), which was developed at MRC HNR using Microsoft Access. The food composition data used was from the Department of Health's NDNS Nutrient Databank, which was based on *McCance and Widdowson's Composition of Foods* [168], FSA *Food Portion Sizes* [176] and manufacturer labels when applicable. The Nutrient Databank was also updated regularly with new food products and relevant nutrient outputs every year, old food items that were outdated or unavailable were also removed [177]. In order to capture dietary data more accurately from composite dishes made of two or more ingredients, they were systematically disaggregated into various components and added into the Nutrient Databank. The main components that were disaggregated include fruits,

vegetables, meats, fish and cheese. These components were further divided into subgroups. Detailed description of method for disaggregation can be found elsewhere [178].

2.3.3.3 Blood pressure measurements

BP measurements were taken according to a standard protocol [174]. In brief, the nurse gathered information on whether participants had exercised, ate, smoke or drunk alcohol in the past half an hour, indicating if the BP measurement was valid. Participants were required to sit still for five minutes, before BP measurements were taken thrice using an Omron HEM 907 BP monitor and an appropriate cuff size, with a minute interval in between each measurement. An average of the three measurements was also calculated and reported.

24-hour urine and blood sample procedures were reported in detail elsewhere [174], and would not be discussed in the chapter as the data was not used.

2.3.4 Ethical approval

The current study was conducted according to guidelines laid down in the Declaration of Helsinki. Ethical approval was obtained from the Oxfordshire A Research Ethics Committee, and written informed consent was also obtained from all participants [174].

2.4 Statistical methodology

2.4.1 Confounding

When examining the association between any dietary exposure (e.g. fruit intake) and disease outcome (e.g. CVD risk), it is important to note that in addition to covariates which are fitted into the model, there may be other extraneous variables which associate with both the exposure and outcome, known as confounders. Failure to adjust for confounding would usually lead to confounding bias, or misinterpretation of the association between the exposure and outcome, which may distort relative risk estimates in different directions, either towards or away from the null [179].

In this thesis, the selection of potential confounding variables for inclusion in models was determined using directed acyclic graphs (DAGs) [180, 181]. DAGs are diagrams designed to aid in the determination of causal relationships between variables in epidemiological studies using a graphical approach. They may be combined with traditional methods such as stratification, univariate and multivariate analysis [182]. A DAG consist of a series of arrows depicting causal relationships between variables along a timeline. Since

time cannot go backwards, the arrows must not form a cycle, therefore termed acyclic [181]. When a variable has an arrow pointing towards the exposure and outcome as illustrated in Figure 2.16 through pathways 'fruit intake←A→F→CVD' and 'fruit intake←B→C→CVD', it is identified as an unblocked backdoor path. Thus any association discovered may be due to the independent effects of the confounder on the exposure and outcome, and may not directly reflect the true association between them. If the confounder is adjusted, the true association may then be defined [180, 181]. However, bias might also be introduced when adjustments are made for 'confounders'. Causal relationships may exist between 'fruit intake←A→D', as well as 'D←E→CVD'. If the collider (D) were adjusted for, it would introduce a bias, since there is no true relationship between variables 'A' and 'E' [181].

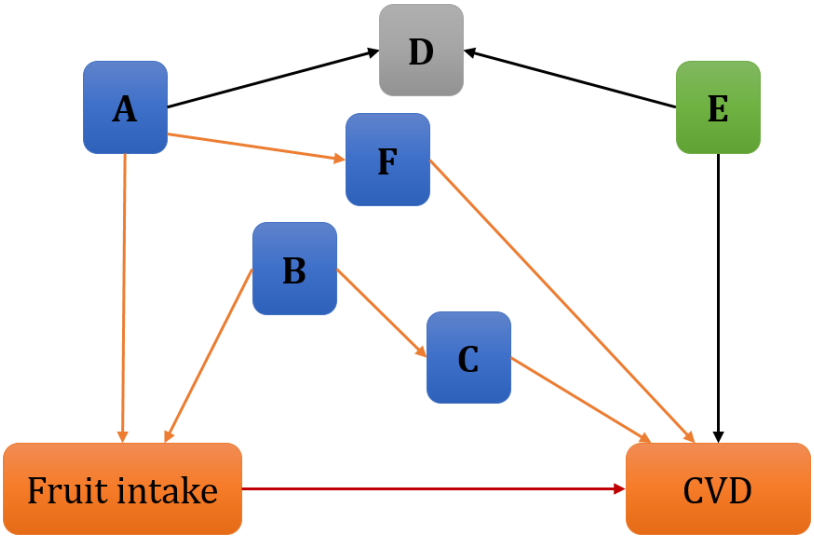


Figure 2.16 Example of a direct acyclic graph containing confounders (blue) and a collider (grey)

Variables that populate the DAG can be defined *a priori* according to the information from previous studies which investigate specific variables as predictors of a disease outcome. Some variables modify the effect of an exposure on the outcome, causing different subpopulations (strata) to have different relative risk estimates. This is known as effect modification. A DAG was generated to guide the selection of several potential confounders or effect modifiers with the potential relationship between exposure and outcome.

2.4.2 Testing for statistical assumptions

Throughout the thesis, various statistical methods have been applied to explore associations between diet and health. Namely, multivariate regression, logistic regression and survival analysis. Correct application of these methods relies on fulfilling certain statistical assumptions. The methods to check for these statistical assumptions are described below.

2.4.2.1 Multiple Linear Regression

In a multivariate model, residuals are the differences between the observed value and the predicted value by the model [182]. One of the assumptions requires the assumption of normality to be fulfilled for residuals of exposure variables. To check the residuals fulfil this assumption, a histogram of residuals was plotted for every model throughout the analysis. An inverse normal plot, commonly known as a Q-Q plot was also applied as an alternative graphical method to assess normality. This plot compares values from the observed distribution and compares it with points on the normal distribution. Observations are ranked and assigned a quantile via the formula *n/(n+1)*, a probit (value of standard normal distribution corresponding to the quantile) was then calculated for each observed value. The inverse normal plot points are then calculated by the formula, *mean+probit*S.D.* [182]. The original observations are then compared to the inverse normal plot points. If the plot is linear, it fulfils the assumption of normality.

In addition, Shapiro-Wilk test could also be performed to assess the normality of residuals by looking at the *p-value* outcome, this provides an objective test in addition to the graphical approach. However, the Shapiro-Wilk test can be extremely sensitive to large datasets, such as the current study, so generating a graphical representation would be more useful to double-check results from Shapiro-Wilk test [182]. This method was therefore not used. Scatter plots of residuals v.s. fitted or predicted values are also used to assess normality. If patterns exist in the scatter plot, it indicates the violation of assumptions. In other words, a scatter plot with no strong patterns (shaped like a cloud), would fulfil the model assumptions. The histogram of residuals, inverse normal plot, scatter plot of residuals v.s. fitted and predicted values were applied in Chapter 10.

2.4.2.2 Logistic Regression

Logistic regression was applied in Chapter 6, Chapter 7 and Chapter 10. This method does not have the model assumptions that are required in multiple regression. However, the model needs to be fitted correctly. The Hosmer-Lemeshow goodness of fit test was chosen to assess whether the model was fitted well. This test ranks participants by computed predicted risks and ranks them from largest to smallest values. It then divides the ordered predicted risks into percentile groupings, usually into deciles. This is followed by computing the observed, expected cases, as well as non-cases. The Hosmer-Lemeshow statistic is calculated by summing the percentile grouping values of cases and non-cases, followed by testing for significance against the percentage point of chi-square with the number of percentile groupings minus 2 degrees of freedom [183].

2.4.2.3 Survival Analysis

The survival analysis was applied in Chapter 3, Chapter 4 and Chapter 5. To use the Cox proportional hazards model correctly, the assumption that the HR is constant over time needs to be met. This meant that the survivor function has to be constant over time, and the hazard function needs to be proportional between different quintiles. To check that the model fulfils this assumption, proportional hazards were assessed using graphical approaches, such as the log-minus-log plot [184]. The log-minus-log plot expresses the survival probability (-ln[-ln](S)) against (ln)time. Exposure quantiles were plotted to assess whether survival probability for total CVD mortality was parallel between different intake quintiles over time. The roughly parallel lines in the graph indicate that the assumptions of proportional hazards have been met. Fulfilling the assumption meant that one HR could be generated for the whole duration of the study, as the hazards are proportional throughout time. The same method was also used for assessing if hazards are proportional for all exposures with CHD, stroke and CVD outcomes. Schoenfeld residuals test were used as an objective approach to validate the goodness of fit of the model, in addition to graphical approaches. If the assumption of proportional hazards is true, Schoenfeld residuals for the covariates in the model would not be correlated with survival time. For example, physical activity assessed as a binary variable reported a borderline significant *p-value* in Chapter 3, which suggests a degree of violation of assumption, indicating that the variable residuals may be correlated with survival time. However, none of the other covariates nor the global result rejected the null hypothesis, so the model is said to have fulfilled the assumption objectively.

2.5 Model building

2.5.1 Selection of variables for adjustment

To provide evidence for the inclusion of potential confounders objectively, analysis of variance (ANOVA), chi-squared tests and correlation tests were performed to prevent over-inclusion of variables in the model. Table 2.1 reports no correlation between the variables, suggesting minimal likelihood of multicollinearity. Likelihood ratio tests were also implemented to provide objective statistical evidence for the inclusion or exclusion of variables for effect modification and multicollinearity in the model. Energy intake was explored as one of the variables considered for inclusion or exclusion. Univariate analysis was also conducted to explore associations between potential confounders and CVD risk (Table 2.2). Results show a statistically significant elevated CVD risk with higher age, no

moderate physical activity, SES classification as intermediate and smoking, while a small increment of alcohol intake (g/day) was associated with lower CVD risk.

Table 2.1 Correlation between variables included in the model

Correlation	Age	BMI	Physical Activity	SES	Smoking	Alcohol	Total Vegetables
Age	1.00						
BMI	0.13	1.00					
Physical Activity	0.16	0.10	1.00				
SES	0.09	0.04	0.07	1.00			
Smoking	0.07	0.03	0.04	0.02	1.00		
Alcohol	0.11	0.06	0.06	0.07	0.11	1.00	
Total Vegetables	<0.01	0.02	0.11	0.04	0.03	0.03	1.00

Table 2.2 Univariate analyses of potential confounders and CHD, stroke and cardiovascular disease outcome [HR (95% CI)]

Variable of Interest	CHD	Stroke	Total CVD
Age (years)	1.17 (1.15, 1.19)	1.18 (1.60, 1.21)	1.18 (1.16, 1.19)
BMI (kg/m^2)	1.04 (1.03, 1.06)	1.01 (0.98, 1.05)	1.03 (1.02, 1.05)
Moderate Physical Activity			
Moderate Physical Activity -Yes	1	1	1
Moderate Physical Activity -No	2.42 (1.75, 3.34)	2.44 (1.78, 3.33)	2.43 (1.94, 3.04)
Socioeconomic Status (SES)			
Professional/Managerial	1	1	1
Intermediate	1.58 (1.14, 2.20)	1.32 (0.94, 1.84)	1.44 (1.14, 1.82)
Routine/Manual	0.98 (0.53, 1.79)	1.43 (0.88, 2.35)	1.21 (0.83, 1.78)
Smoking Status			
Smoking Status - No	1	1	1
Smoking Status - Yes	1.88 (1.27, 2.79)	1.71 (1.15, 2.54)	1.79 (1.35, 2.37)
Alcohol Intake (g/day)	0.95 (0.93, 0.97)	0.98 (0.97, 1.00)	0.97 (0.96, 0.98)
Total fruit (80g portion)	0.94 (0.89, 1.00)	0.94 (0.89, 1.00)	0.94 (0.91, 0.98)
Total vegetables (80g portion)	0.95 (0.88, 1.02)	0.89 (0.82, 0.96)	0.92 (0.87, 0.97)
Total coffee (250g portion)	0.96 (0.86, 1.07)	0.89 (0.79, 0.99)	0.92 (0.85, 1.00)
Total tea (250g portion)	1.03 (0.96, 1.11)	1.02 (0.95, 1.09)	1.02 (0.97, 1.08)

Rationale for adjustment and effect modification for listed potential confounders above are provided in the following sections.

2.5.1.1 BMI, physical activity and total energy intake

The implications of adjustment for total energy intake in epidemiological analysis had been well documented by Willett [185]. In general, three factors are known to cause variation in energy intake, namely body size (height, weight, BMI etc.), physical activity and metabolic efficiency (thermogenesis). The latter has the least amount of evidence for application in nutritional epidemiology. In addition, thermogenesis is only known to contribute ≈10% of individual energy expenditure, whereas ≈60% originates from resting metabolic rate. This is in turn dependent on body mass and composition, thus BMI is usually the primary determinant of energy intake. Physical activity can vary between individuals, it

contributes ≈30% to total energy expenditure, and is considered to be a major determinant of energy intake [185].

In this case, it is possible to adjust for all three variants, but this would lead to over-adjustment. Therefore, likelihood ratio tests were conducted to give an objective reasoning if energy intake should be adjusted additionally. High BMI, or obesity is an independent and major risk factor for CVD [186], while high physical activity is also independently associated with a lower risk of CVD (and *vice versa*) [187], as elaborated in Chapter 1 Section 1.1.1.5. Furthermore, participants in the cohort with a higher fruit intake tend to have a statistically significant lower BMI and higher physical activity. Therefore, adjustments are warranted for BMI and physical activity. As described previously, BMI and physical activity also account for the majority of energy intake, thus it is likely that adjustment for energy intake is not necessary. However, a higher fruit intake may be accompanied by higher energy intake. This is because high fruit consumers might be eating more of everything in general by proportion. To objectively support the additional adjustment of energy after adjustment for BMI and physical activity, likelihood ratio tests were applied. Results show no significant differences between the fully adjusted model with energy and a fully adjusted model without energy adjustment. Thus, energy intake was only adjusted for with a fully adjusted model as part of the sensitivity analysis.

In the cohort, there were various variables that describes body size. BMI (consisting of height and weight) was highly correlated with waist circumference and weight. It was chosen to be adjusted as this variable had the smallest amount of missing data. Physical activity was adjusted as a binary variable, where participants were required to answer if they were moderately active or not. A continuous variable using physical activity level would seem more ideal, however, there was a proportion of missing data (5.4%), and thus the binary variable was favoured instead to include the maximum number of cases.

2.5.1.2 Smoking

Smoking was described as a major CVD risk factor in Chapter 1 Section 1.1.1.5. There were multiple variables describing smoking habits in the cohort, however, smoking was chosen to be adjusted for as a binary variable (smokers vs. non-smokers) as there were fewer missing cases within this variable. It was also investigated as a potential effect modifier, due to the elevated CVD risk in smokers compared to non-smokers when conducting univariate analysis reported in Table 2.2.

2.5.1.3 Socio-economic status

Chapter 1 Section 1.1.1.5 reported SES as one of the modifiable CVD risk factors. SES was chosen to be adjusted for in favour of education status, because there were fewer missing cases. SES was also able to represent a multitude of variables, such as income and occupation in addition to education which may influence the consumption levels of various dietary intakes or lifestyle behaviours. In addition, SES was also correlated with education, thus education was not adjusted for to prevent multicollinearity. Alternatively, deprivation scores could also be used to represent socio-economic status, however, this is not available within the cohort.

2.5.1.4 Alcohol

Excessive alcohol consumption is known to increase CVD risk. However, moderate alcohol intake was reported in Chapter 1 Section 1.1.1.5 to be associated with lower CVD risk, and this also applies to small amounts of alcohol consumption [188]. This is shown in Table 2.2. and is therefore adjusted for in the model.

2.5.1.5 High blood pressure

HBP was explored as an effect modifier in analysis that investigate CVD risk, as it is a major risk factor for CVD [189], described in Chapter 1 Section 1.1.1.5. Participants with HBP have a higher risk of fatal CVD than participants without HBP. The relationship between HBP and (poly)phenol-rich foods was also specifically explored in Chapter 6, Chapter 7 and Chapter 10.

2.5.1.6 Menopausal status

Menopausal status is strongly correlated with age. As age is included in all models. It was investigated as an effect modifier only.

Variables that were not adjusted or considered to be included as part of the model included ethnicity. Ethnicity of the cohort is 99% white, and consist of only women, thus the proportion of non-white ethnic group was too small to warrant inclusion of ethnicity as a variable in the model.

With reference to the justifications above, unless stated otherwise, models employed in the analysis were:

1. Age (years)
2. Age (years), BMI (kg/m^2), moderate physical activity (Yes/No), smoking status (smoker v.s. non-smoker), alcohol intake (ethanol g/day) and socio-economic status (professional/managerial, intermediate or routine/manual).
3. In addition to model 2, energy intake (kcal/day) was also included for the reasons stated above.

In general, models that investigated subgroup fruit or vegetable 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). To maximise power in the model, variables with some missing data for body mass index (BMI) and smoking were updated using data collected via a questionnaire in a later stage of the study. This second phase of data collection has been previously reported in the current chapter as well as in published literature [190].

2.5.2 Directed acyclic graph

A DAG was generated for the variables which are associated with fruit, vegetable, coffee and tea intake and CVD mortality risk in Figure 2.17, HBP in Figure 2.18. According to the diagram based on the analyses above, the possible confounders are SES, physical activity, BMI, alcohol intake and smoking, as they are the variables that lie within the unblocked backdoor paths. However, adjusting only for the possible confounders as mentioned above would over-simplify the relationship between the dietary intakes and CVD. Thus, it is also important to adjust for variables which are known to influence risk of CVD from established literature evidence.

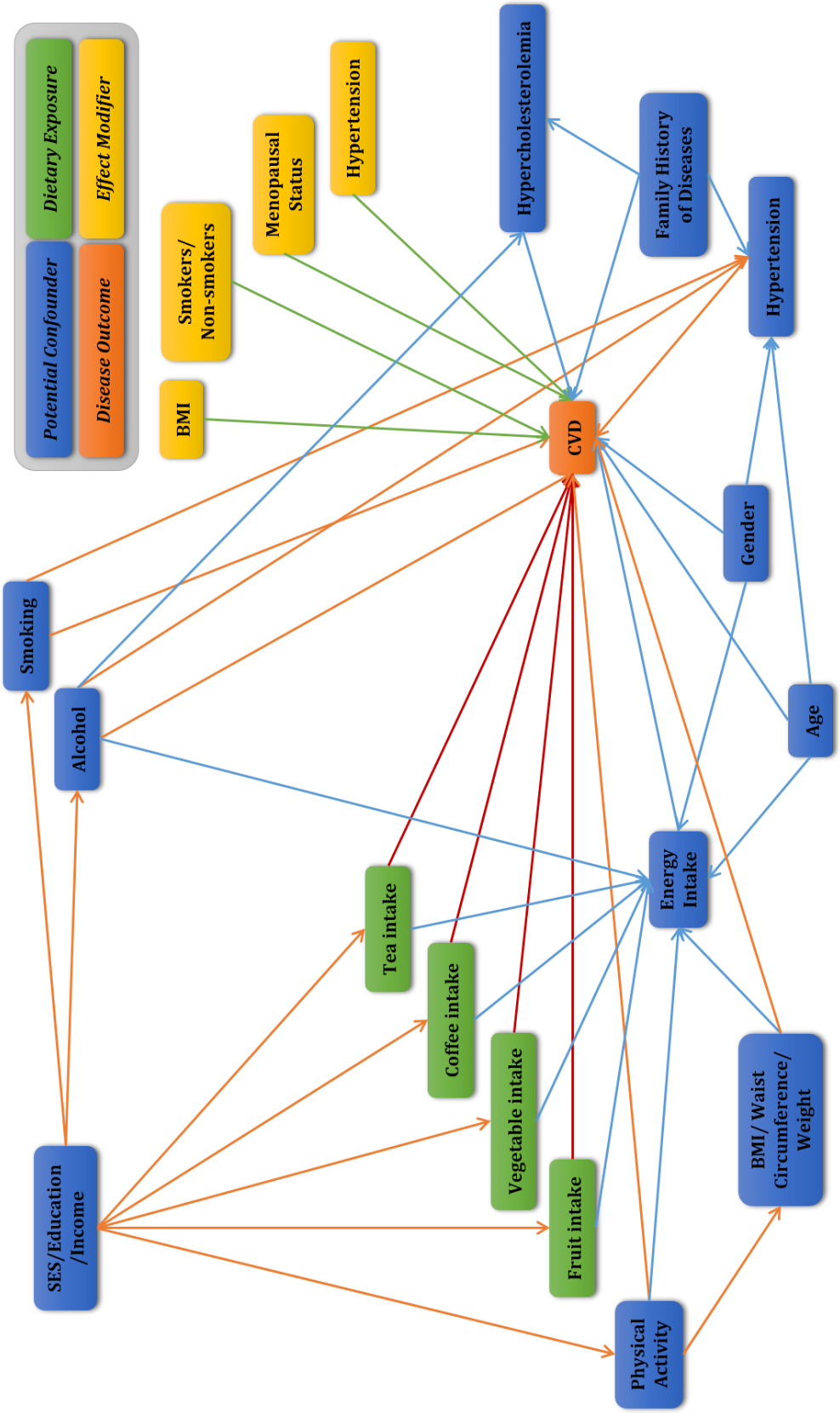


Figure 2.17 Causal diagram showing associations between potential confounders between fruit, vegetable, coffee and tea intake and CVD outcome

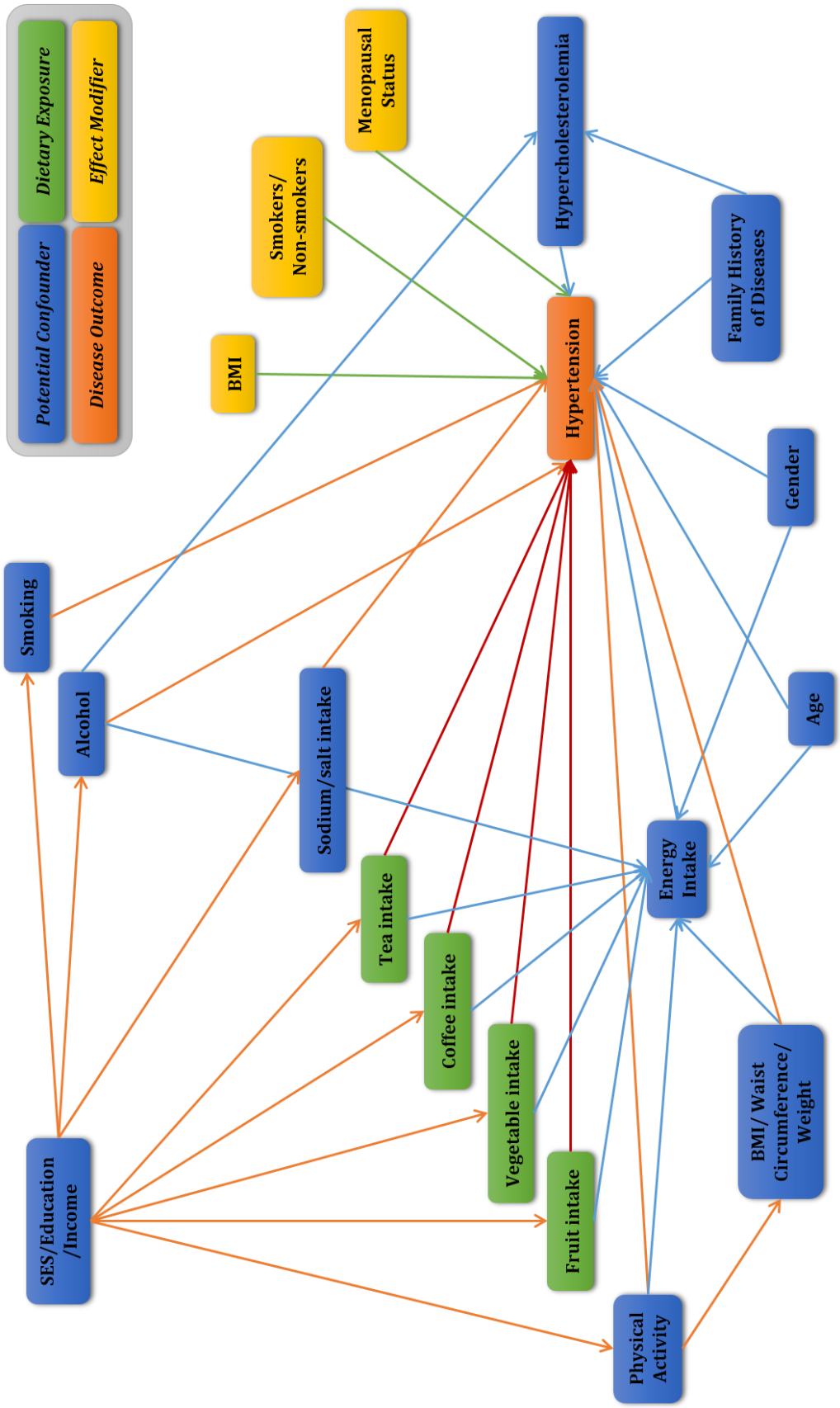


Figure 2.18 Causal diagram showing associations between potential confounders between fruit, vegetable, coffee and tea intake and hypertension

2.6 UK Women's Cohort Study: Dietary intakes of (poly)phenol-rich foods and participant characteristics

2.6.1 Dietary exposures

Four main (poly)phenol-rich sources were explored in the thesis, namely fruit, vegetables, coffee and tea as they are the main sources of (poly)phenols in the UK diet. Alcoholic beverages such as wine, and chocolate were not explored in this thesis due to time constraint, but should also be noted as a rich source of dietary (poly)phenols. Total fruit intake was derived by combining multiple variables from the FFQ, including intakes of fresh fruits, dried fruits, pure fruit juices and processed fruits (Table 2.3). Cooking and food processing techniques (heating, freezing, canning etc.) are thought to affect stability of (poly)phenols by increasing or decreasing levels of (poly)phenols within fruits or vegetables [191, 192]. Therefore, fruit subgroups were also investigated individually, except for processed fruits, due to low intake levels. Fresh fruits were divided into subgroups by culinary/botanical family on Phenol Explorer to characterise fruit types according to their similarities in (poly)phenol profiles. These subgroups were berries, citrus, drupes, pomes and tropical fruits, with the exception of grapes [111]. Grapes was categorised under 'berries' within Phenol Explorer. However, due to differences in botanical families, (poly)phenol content [111] and the frequency of consumption, it was defined as an individual category. Likewise, total vegetable intake, total coffee and total tea was also derived from multiple FFQ variables in a similar manner described above. However, starchy vegetables such as potatoes, as well as pulses, grains, nuts and seeds were excluded from this variable, as they have a different (poly)phenol profile, and for public health implications, are also not included as a part of 'five-a-day' in the UK.

The range of reported intakes shown in Table 2.3 tend to be very wide. The most consumed fruit on average is apples, followed by orange juice, bananas, citrus fruits, other forms of pure juices and grapes. The remaining types of fruit are consumed less frequently compared to the fruits listed formerly. As for vegetables, tomatoes were the most commonly consumed fruits, followed by 'broccoli, spring greens and kale', carrots, cauliflower and 'green beans, runner beans'. Cabbage and Brussel sprouts are also consumed in decent amounts compared to other fresh vegetables, while stir-fry vegetables is the most popularly consumed item within the vegetable dish group.

Consumption of tea is almost two-fold higher than coffee in general. In comparison to black tea, average intake of herbal tea is nearly six times less, while intake of decaffeinated coffee is three times less than regular coffee.

Major composition of flavonoid subgroups are reported in Table 2.3 and Table 2.4.

Table 2.3 Baseline total fruit, fruit subgroups, coffee, tea and respective subgroups from the FFQ grouped according to suggested categorisation in the Phenol Explorer prior to the application of exclusion criteria

Investigated variables			FFQ variables	Mean (SD) (g/day)	Median (g/day)	Intake range (g/day)	Major Flavonoid Composition
Total fruit intake (TF), n = 34,677	**Total fruit juice (FJ), n = 35,372**		Orange Juice (Pure Fruit)	66 (89)	20	0 – 870	Flavanones (orange juice); dependent on type of fruit juice for other fruit juices
			Other (100%) Pure Fruit Juices	34 (67)	10	0 – 870	
	Total dried fruits (DF), n = 35,372		Dates	2 (6)	0.5	0 – 150	Varied depending on fruit type
			Figs	2 (10)	0	0 – 330	
			Prunes	1 (5)	0.4	0 – 120	
			Mixed Dried Fruit e.g. Apricots, Apples, Pears, Mangoes	2 (6)	0.5	0 – 150	
			Currants, Raisins, Sultanas	2 (5)	1.1	0 – 90	
	*Processed Fruits**		Fruit Tarts, Pies, Crumbles	8 (14)	2.2	0 – 500	Dependent on fruit(s) within the dish
	Total fresh fruit (FF), n = 34, 677	**Total citrus, n = 35,372**	Oranges, Satsumas, Grapefruits etc.	40 (54)	13	0 – 552	Flavanones
			Orange Juice (Pure Fruit)	65 (89)	20	0 – 870	
		Total berries, n = 34,878	Raspberries	4 (10)	1.2	0 – 102	Anthocyanins, Flavonols, Hydroxybenzoic acids
			Red currants/Black currants	4 (14)	0.7	0 – 210	
			Strawberries	3 (6)	1.2	0 – 53	
		Total pomes, n = 35,372	Apples	75 (80)	47	0 – 702	Flavanols, Hydroxycinnamic acids
			Pears	24 (42)	8	0 – 690	
		Total drupes, n = 34,792	Apricots	1 (2)	0.1	0 – 39	Flavanols, Flavonols, Hydroxycinnamic acids
			Nectarines	3 (5)	1.5	0 – 64	
			Peaches	2 (3)	1	0 – 42	
			Plums	1 (2)	0.5	0 – 20	
		Total tropical fruits, n = 35,372	Bananas	55 (56)	40	0 – 600	Flavanols, Lignans
			Kiwi Fruit	7 (15)	1.2	0 – 360	
			Mangoes	4 (14)	2.6	0 – 780	
			Papaya	2 (12)	0	0 – 840	
			Pineapple	4 (9)	1.3	0 – 384	
		Grapes, n = 35,372	Grapes	27 (51)	14	0 – 600	Anthocyanins, Flavanols, Hydroxycinnamic acids
Total Coffee, n = 35,372			Coffee	281 (316)	190	0 – 1140	Hydroxycinnamic acids
			Decaffeinated Coffee	98 (212)	0	0 – 1140	
			Black Tea	679 (511)	650	0 – 1560	Flavanols, Hydroxybenzoic acids
			*Herbal Tea**	100 (231)	5	0 – 1560	Dependent on herb(s) within the dish

**Not investigated individually*

Table 2.4 Baseline total vegetable and vegetable subgroups from the FFQ grouped according to suggested categorisation in the Phenol Explorer prior to the application of exclusion criteria

Investigated variables			FFQ variables	Mean (SD) (g/day)	Median (g/day)	Intake range (g/day)	Major Flavonoid Composition
Total vegetable intake, n = 35,372	Vegetable Dishes*		Quorn	1.1 (3.4)	0	0 – 37.7	Dependent on vegetable(s) within the dish
			Textured vegetable protein/Sosmix/burger mix/soya sausages	0	0	0	
			Vegetarian chilli /Vegetable curry	3 (7)	0	0 – 380	
			Mixed bean casserole /Ratatouille	4 (7)	2	0 – 459	
			Stir-fry vegetables	22 (35)	19	0 – 1600	
			Vegetable – Lasagne/Moussaka/Ravioli/ filled pasta with sauce	7 (12)	3	0 – 641	
			Vegetable pizza	2 (4)	1	0 – 260	
	Total fresh vegetable intake, n = 35,372	***Allium*, n = 35,372**	Garlic	1 (1)	0.4	0 – 18	Flavonols, Lignans
			Leeks	10 (13)	5	0 – 337	
		***Brassicaceae*, n = 35,372**	Broccoli, Spring greens, Kale	25 (26)	13	0 – 540	Flavones, Flavonols, Lignans
			Brussel sprouts	13 (19)	6	0 – 540	
			Cabbage	17 (22)	13	0 – 570	
			Cauliflower	19 921)	13	0 – 540	
			Swede	7 (11)	5	0 – 342	
			Turnip	4 (8)	1	0 – 456	
			Watercress, Mustard & Cress	1 (2)	0.2	0 – 60	
		Fruit vegetables, n = 35,372	Courgettes, Marrow, Squash	9 (13)	6	0 – 382	Hydroxybenzoic acids, Hydroxycinnamic acids, Lignans
			Cucumber	6 (7)	3	0 – 138	
			Aubergine	2 (4)	1	0 – 175	
			Olives	1 (3)	0	0 – 120	
			Peppers (Red, green, yellow, black etc.)	10 (12)	6	0 – 270	
			Tomatoes (raw/canned/sauce)	46 (43)	33	0 – 498	
		Pod vegetables, n = 35,372	Green beans, Runner beans	19 (22)	12	0 – 528	Lignans
			Okra/Lady's Fingers	1 (2)	0.5	0 – 117	
			Peas, Mushy peas, Mange-tout	12 (13)	9	0 – 372	
		Stalk/Root vegetables, n = 35,372	Beetroot	3 (6)	1	0 – 240	Flavones, Hydroxycinnamic acids, Lignans
			Carrot	24 (23)	25	0 – 372	
			Celery	7 (10)	3	0 – 240	
			Parsnip	7 (11)	5	0 – 456	

**Not investigated individually*

Figure 2.19 demonstrates the distribution of total fruit, vegetable, coffee and tea which were investigated. Most distributions here do not conform to normality, and were positively skewed with a long tail. Distributions of total coffee and tea were not normal at all. This may be due to the application of fixed portion sizes of typical cups (190 g) and mugs (250 g) when translating frequency into g/day.

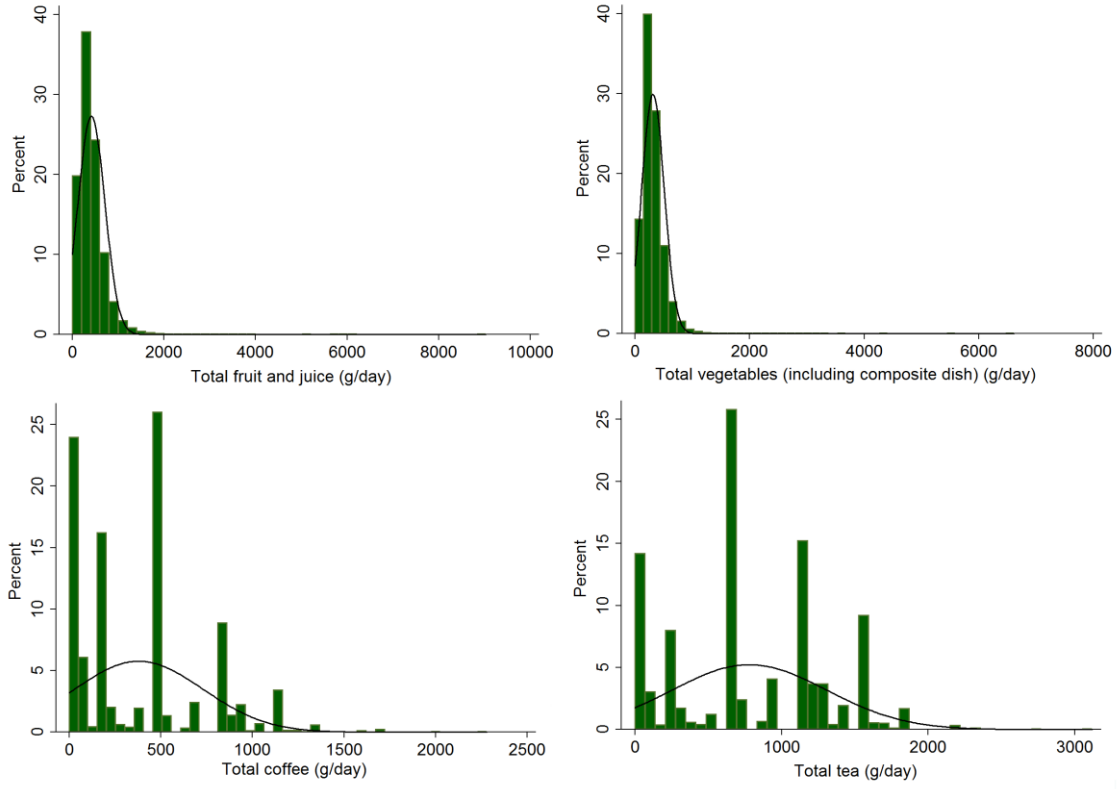


Figure 2.19 Distribution of total fruit, vegetable, coffee and tea intakes in histograms prior to the application of exclusion criteria

Correlations between fruit and fruit subgroup variables are presented in Table 2.5. Total fruit, fresh fruit, 'fresh fruit & juice' and 'fresh and dried fruit' were all highly correlated with each other (0.90 to 0.99). Total citrus was also highly correlated with citrus fruit (0.60, 95% CI 0.59 to 0.60) and orange juice (0.87, 95% CI 0.87 to 0.88). However, citrus fruit and orange juice were weakly correlated (0.13, 95% CI 0.12 to 0.14). In general, fruit subgroups were moderately correlated with total fruit, fresh fruit, 'fresh fruit & juice' and 'fresh and dried fruit' groups. Correlation between fruit subgroups tend to be weak, ranging between 0.05 to 0.49. With regard to vegetable and vegetable subgroups, total vegetables are highly correlated with fresh vegetables, while the correlation of vegetable subgroups ranged from weak to moderate (0.25 to 0.61).

Table 2.5 Correlations between total fruit and fruit subgroups intake assessed from the baseline FFQ prior to the application of exclusion criteria

	Total fruit	Fresh fruit	Fresh fruit and juice	Fresh and dried fruit	Total fruit juice	Dried fruits	Berries	Total citrus	Citrus fruit	Orange juice	Drupes	Pomes	Tropical fruit
Total fruit	1												
Fresh fruit	0.90	1											
Fresh fruit and juice	0.99	0.90	1										
Fresh and dried fruit	0.91	0.99	0.90	1									
Total fruit juice	0.58	0.18	0.58	0.19	1								
Dried fruits	0.33	0.26	0.26	0.34	0.10	1							
Berries	0.43	0.46	0.42	0.47	0.10	0.19	1						
Total citrus	0.64	0.39	0.65	0.39	0.75	0.10	0.14	1					
Citrus fruit	0.53	0.57	0.53	0.57	0.14	0.11	0.18	0.60	1				
Orange juice	0.48	0.14	0.48	0.14	0.85	0.05	0.06	0.87	0.13	1			
Drupes	0.52	0.57	0.52	0.57	0.12	0.21	0.49	0.23	0.31	0.09	1		
Pomes	0.65	0.4	0.65	0.74	0.08	0.16	0.18	0.20	0.33	0.05	0.32	1	
Tropical fruit	0.63	0.69	0.63	0.69	0.14	0.17	0.18	0.21	0.27	0.10	0.29	0.37	1

Table 2.6 Correlations between vegetable and vegetable subgroups intake assessed from the baseline FFQ prior to the application of exclusion criteria

	Total vegetables	Fresh vegetables	*Allium*	*Brassicaceae*	Fruit vegetables	Pod vegetables	Stalk/Root vegetables
Total vegetables	1						
Fresh vegetables	0.97	1					
Allium	0.54	0.54	1				
Brassicaceae	0.77	0.81	0.36	1			
Fruit vegetables	0.68	0.69	0.31	0.25	1		
Pod vegetables	0.63	0.65	0.44	0.42	0.36	1	
Stalk/Root vegetables	0.73	0.76	0.37	0.61	0.37	0.39	1

2.6.2 Baseline characteristics of participants

Table 2.7 to Table 2.10 report the baseline characteristics of all participants by dietary intakes prior to the application of exclusion criteria. When possible, participants were divided into approximately five equal groups for each dietary intake. Participants who consumed more total fruit tend to be older and slightly slimmer with a lower BMI (Table 2.7). Energy intake, total vegetable consumption, portions of FV tend to be higher across the quintiles as intake of total fruit increases. However, ethanol intake tends to be lower with increasing total fruit intake. Participants who consumed more total fruit also tended to consume supplements, be moderately active, report being vegetarian or vegan, and not smoke. In terms of socioeconomic status, they tend to be well educated, and were more likely to hold a professional/managerial job as consumption of total fruit increases. There were no significant differences in the history of parental heart disease, heart attack, high BP and diabetes when compared across quintiles. However, there was a significant difference between percentage of participants with parental history of cancer/heart disease, high cholesterol/hyperlipidaemia by total fruit quintiles, though the trend may not necessarily be linear. Participants were also more likely to have had a stroke or angina by increasing total fruit quintiles, where participants consuming 202 to 306 g of fruits reporting the least angina.

The baseline characteristics of participants by total vegetable intake was largely similar to what was reported above, except for a few differences (Table 2.8). Contrary to ethanol intake levels by total fruit quintile, the consumption of ethanol increased with increasing vegetable intake. In terms of medical history, participants who consumed moderate amount of vegetables tend to have the lowest history of heart attack, stroke and angina compared to lowest and highest consumers. There were no obvious trends by history of parental cancer/heart disease and heart disease alone. In addition, participants who consumed more total vegetables were less likely to have history of diabetes.

When participants were divided by coffee consumption quintiles (Table 2.9), the fourth quintile contained the least number of participants, while the third quintile had the highest number. On average, participants from the second quintile were the oldest with the largest waist circumference, while the highest coffee consumers were the youngest. Lowest coffee consumers also had the smallest waist circumference. BMI remained stable by increasing coffee intake, but increased sharply in the fifth quintile. Energy and ethanol intake tend to be higher across coffee intake quintiles, while total tea intake tend to be lower when coffee consumption is higher. Portions of FV did not differ between coffee quintiles.

High coffee consumers were also less likely to be supplement users, non-smokers, moderately active or vegetarian/vegan. Participants in the fourth quintile tend to be more well-educated, and more likely to hold a professional/managerial job compared to other quintiles. Trends do not follow a linear pattern in terms of medical history, however, lower coffee consumers tend to have higher proportion of participants who had history of cardiovascular diseases and cancer, and vice versa for higher coffee consumers.

Baseline characteristics by black tea intake quartiles are shown in Table 2.10. General characteristics of participants were similar across quartiles. Higher tea consumers had a higher energy intake, but lower intakes of ethanol, coffee and portions of FV. They were also less likely to be supplement users, non-smokers, moderately active, be well-educated and hold a professional/managerial status. With regard to medical history, higher tea consumers were more likely to hold a history of parental cancer/heart disease, had a heart attack, stroke, angina, HBP, diabetes, high cholesterol and cancer.

Table 2.7 Baseline characteristics of all UKWCS participants by quintiles of total fruit intake prior to the application of exclusion criteria (expressed as mean and SD for continuous variables, % and 95% CI for categorical variables)

	Total fruit intake including fruit juice, dried and processed fruits (g/day)				
	0 – 202	**202 – 306**	**306 – 416**	**416 – 581**	**581 – 9039**
General					
Participants (n)	7075	7074	7075	7074	7074
Age, years (SD)	51.1 (9.3)	51.9 (9.4)	52.5 (9.3)	53.1 (9.3)	53.0 (9.3)
BMI, kg/m^2 (SD)	24.8 (4.9)	24.4 (4.2)	24.4 (4.1)	24.4 (4.1)	24.3 (4.4)
Waist Circumference, cm (SD)	73.8 (10.0)	73.8 (9.3)	73.6 (9.1)	73.4 (9.0)	73.1 (9.3)
Dietary Intake					
Energy, kcal/day (SD)	2012 (634)	2199 (632)	2309 (644)	2449 (681)	2794 (1077)
Ethanol, g/day (SD)	9.7 (12.5)	8.9 (10.5)	8.5 (9.8)	8.4 (10.2)	7.6 (9.3)
Total vegetables, g/day (SD)	229 (143)	273 (138)	310 (152)	345 (163)	430 (272)
Portions of fruit, no. of 80 g/day (SD)	1.7 (1.0)	3.4 (1.2)	4.6 (1.4)	6.2 (2.0)	10.5 (6.0)
Portions of vegetables, no. of 80 g/day (SD)	3.7 (2.3)	4.5 (2.3)	5.1 (2.5)	5.7 (2.6)	7.1 (3.9)
Lifestyle Habits					
Supplement users (%, 95% CI)	50.8 (49.6, 52.0)	55.2 (54.0, 56.5)	58.0 (56.8, 59.2)	60.7 (59.5, 61.9)	64.4 (63.2, 65.5)
Non-smokers (%, 95% CI)	81.2 (80.3, 82.1)	89.6 (88.9, 90.3)	90.9 (90.2, 91.5)	92.2 (91.6, 92.8)	92.2 (91.5, 92.8)
Moderately Active/Active (%, 95% CI)	47.7 (46.5, 48.9)	56.0 (54.8, 57.2)	59.9 (58.7, 61.1)	62.8 (61.6, 63.9)	65.4 (64.2, 66.5)
Vegetarian/Vegan (%, 95% CI)	23.7 (22.8, 24.7)	25.9 (24.9, 26.9)	26.0 (25.0, 27.0)	28.9 (27.9, 30.0)	33.9 (32.8, 35.0)
Socio Economic Status					
High school education & above (%, 95% CI)	43.5 (41.6, 45.6)	51.1 (49.1, 53.3)	52.9 (50.8, 55.1)	55.3 (53.1, 57.5)	55.8 (53.7, 58.1)
Professional & Managerial job holders (%, 95% CI)	57.8 (56.6, 59.0)	61.7 (60.6, 62.8)	62.9 (61.8, 64.1)	65.7 (64.5, 66.8)	67.9 (66.8, 69.0)
Medical History					
History of parental cancer/heart disease (%, 95% CI)	65.9 (64.8, 67.0)	66.1 (65.0, 67.2)	66.4 (65.2, 67.4)	67.2 (66.1, 68.3)	67.3 (66.2, 68.4)
History of parental heart disease (%, 95% CI)	39.5 (38.4, 40.6)	39.4 (38.3, 40.5)	39.7 (38.5, 40.8)	41.3 (40.1, 42.4)	40.8 (39.7, 41.9)
Had/Have heart attack (%, 95% CI)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.5 (1.2, 1.8)	1.6 (1.3, 1.9)	1.9 (1.5, 2.2)
Had/Have stroke (%, 95% CI)	0.8 (0.6, 1.0)	0.7 (0.5, 0.9)	0.6 (0.4, 0.8)	0.8 (0.6, 1.1)	1.2 (0.9, 1.5)
Had/Have angina (%, 95% CI)	2.0 (1.7, 2.4)	1.8 (1.5, 2.1)	2.1 (1.8, 2.5)	2.3 (2.0, 2.7)	2.7 (2.4, 3.1)
Had/Have high blood pressure (%, 95% CI)	16.5 (15.7, 17.4)	16.8 (15.9, 17.7)	17.4 (16.5, 18.3)	18.0 (17.1, 19.0)	17.5 (16.6, 18.5)
Had/Have diabetes (%, 95% CI)	1.7 (1.4, 2.0)	2.1 (1.7, 2.4)	1.9 (1.6, 2.2)	2.3 (1.9, 2.7)	2.0 (1.7, 2.4)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	6.8 (6.2, 7.5)	6.9 (6.3, 7.6)	7.6 (7.0, 8.2)	7.9 (7.3, 8.6)	9.0 (8.3, 9.7)
Had/Have cancer (%, 95% CI)	7.1 (6.5, 7.7)	6.9 (6.3, 7.5)	7.5 (6.9, 8.1)	7.6 (7.0, 8.3)	8.2 (7.6, 8.9)

Table 2.8 Baseline characteristics of all UKWCS participants by quintiles of total vegetable intake prior to the application of exclusion criteria (expressed as mean and SD for continuous variables, % and 95% CI for categorical variables)

	Total vegetable intake including vegetables from composite dishes (g/day)				
	0 – 177	**177 – 246**	**246 – 320**	**320 – 427**	**427 – 6620**
General					
Participants (n)	7075	7074	7075	7074	7074
Age, years (SD)	52.6 (9.7)	52.2 (9.4)	52.1 (9.2)	52.3 (9.3)	52.4 (9.1)
BMI, kg/m^2 (SD)	24.7 (4.5)	24.5 (4.2)	24.4 (4.2)	24.3 (4.3)	24.3 (4.5)
Waist Circumference, cm (SD)	74.0 (10.0)	73.6 (9.2)	73.6 (9.1)	73.3 (8.9)	73.2 (9.5)
Dietary Intake					
Energy, kcal/day (SD)	1975 (632)	2188 (613)	2324 (463)	2470 (678)	2804 (1076)
Ethanol, g/day (SD)	7.5 (10.4)	8.5 (10.1)	9.1 (11.1)	9.1 (10.5)	9.0 (10.6)
Total fruit and juice, g/day (SD)	283 (212)	356 (229)	398 (243)	455 (259)	587 (395)
Portions of fruit, no. of 80 g/day (SD)	3.4 (2.9)	4.4 (3.3)	5.0 (3.5)	5.9 (4.0)	7.7 (5.6)
Portions of vegetables, no. of 80 g/day (SD)	2.1 (0.7)	3.5 (0.6)	4.7 (0.7)	6.2 (0.9)	9.5 (3.3)
Lifestyle Habits					
Supplement users (%, 95% CI)	52.7 (51.5, 54.0)	55.1 (53.9, 56.3)	57.4 (56.1, 58.6)	60.4 (59.2, 61.6)	63.4 (62.6, 64.6)
Non-smokers (%, 95% CI)	85.5 (84.7, 86.3)	89.6 (88.9, 90.3)	89.6 (88.9, 90.3)	91.0 (90.3, 91.7)	90.3 (89.6, 91.0)
Moderately Active/Active (%, 95% CI)	47.4 (46.2, 48.6)	56.2 (55.0, 57.3)	59.3 (58.1, 60.4)	63.4 (62.3, 64.5)	65.4 (64.3, 66.5)
Vegetarian/Vegan (%, 95% CI)	16.7 (15.9, 17.6)	22.9 (21.9, 23.9)	26.0 (25.0, 27.0)	33.2 (32.1, 34.3)	39.6 (38.4, 40.7)
Socio Economic Status					
High school education & above (%, 95% CI)	46.2 (44.2, 48.3)	51.8 (49.6, 53.9)	54.4 (52.3, 56.7)	53.5 (51.5, 55.7)	52.7 (50.7, 54.9)
Professional & Managerial job holders (%, 95% CI)	58.9 (57.7, 60.1)	62.1 (61.0, 63.3)	64.0 (62.9, 65.1)	65.0 (63.8, 66.1)	66.0 (64.9, 67.1)
Medical History					
History of parental cancer/heart disease (%, 95% CI)	66.2 (65.0, 67.3)	65.4 (64.3, 66.5)	67.3 (66.2, 68.4)	66.8 (65.7, 67.9)	67.3 (66.2, 68.4)
History of parental heart disease (%, 95% CI)	39.1 (38.0, 40.3)	38.3 (37.2, 39.4)	41.0 (39.9, 42.2)	40.9 (39.8, 42.1)	41.2 (40.1, 42.4)
Had/Have heart attack (%, 95% CI)	1.9 (1.6, 2.3)	1.5 (1.2, 1.8)	1.1 (0.9, 1.4)	1.4 (1.1, 1.7)	1.8 (1.5, 2.1)
Had/Have stroke (%, 95% CI)	0.9 (0.7, 1.2)	0.7 (0.5, 0.9)	0.6 (0.5, 0.8)	0.7 (0.6, 1.0)	1.1 (0.8, 1.3)
Had/Have angina (%, 95% CI)	2.3 (1.9, 2.7)	2.0 (1.7, 2.4)	1.9 (1.6, 2.3)	2.1 (1.7, 2.4)	2.7 (2.3, 3.1)
Had/Have high blood pressure (%, 95% CI)	18.1 (17.2, 19.0)	17.2 (16.3, 18.1)	17.4 (16.5, 18.3)	16.9 (16.0, 17.8)	16.8 (16.0, 17.8)
Had/Have diabetes (%, 95% CI)	2.5 (2.2, 2.9)	2.0 (1.7, 2.4)	1.8 (1.5, 2.1)	1.8 (1.5, 2.1)	1.8 (1.5, 2.2)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	7.4 (6.8, 8.1)	6.9 (6.3, 7.5)	8.1 (7.5, 8.8)	7.8 (7.2, 8.5)	7.9 (7.3, 8.6)
Had/Have cancer (%, 95% CI)	7.4 (6.8, 8.1)	7.2 (6.6, 7.9)	7.6 (7.0, 8.2)	7.1 (6.5, 7.7)	8.0 (7.3, 8.6)

Table 2.9 Baseline characteristics of all UKWCS participants by quintiles of total coffee intake prior to the application of exclusion criteria (expressed as mean and SD for continuous variables, % and 95% CI for categorical variables)

	Total coffee and decaffeinated coffee intake (g/day)				
	0 – 27	**30 – 190**	**194 – 475**	**479 – 665**	**855 – 2280**
General					
Participants (n)	8149	7403	8765	4613	6442
Age, years (SD)	51.4 (9.3)	53.5 (9.8)	53.3 (9.5)	51.8 (9.1)	51.2 (8.5)
BMI, kg/m^2 (SD)	24.3 (4.4)	24.3 (4.2)	24.4 (4.2)	24.3 (4.0)	25.0 (4.7)
Waist Circumference, cm (SD)	73.2 (9.6)	73.8 (9.3)	73.7 (9.3)	73.3 (8.7)	73.7 (9.4)
Dietary Intake					
Energy, kcal/day (SD)	2258 (754)	2350 (763)	2364 (747)	2425 (698)	2406 (991)
Ethanol, g/day (SD)	6.6 (9.7)	8.4 (10.6)	9.2 (10.9)	9.5 (9.6)	10.0 (11.4)
Total tea, g/day (SD)	961 (553)	936 (486)	762 (472)	708 (455)	447 (493)
Portions of fruit, no. of 80 g/day (SD)	5.3 (4.5)	5.3 (4.0)	5.3 (4.0)	5.4 (4.0)	5.2 (4.5)
Portions of vegetables, no. of 80 g/day (SD)	5.3 (3.2)	5.2 (2.9)	5.2 (2.8)	5.2 (2.7)	5.2 (3.2)
Lifestyle Habits					
Supplement users (%, 95% CI)	61.3 (60.1, 62.4)	61.0 (59.8, 62.2)	56.4 (55.3, 57.4)	59.0 (57.6, 60.5)	50.9 (49.6, 52.2)
Non-smokers (%, 95% CI)	91.2 (90.6, 91.8)	90.3 (89.6, 91.0)	90.2 (89.5, 90.8)	91.8 (90.9, 92.5)	82.3 (81.3, 83.2)
Moderately Active/Active (%, 95% CI)	57.8 (56.7, 58.9)	57.3 (56.2, 58.5)	59.3 (58.2, 60.3)	62.0 (60.5, 63.4)	56.3 (55.0, 57.5)
Vegetarian/Vegan (%, 95% CI)	34.7 (33.6, 35.7)	27.5 (26.5, 28.6)	24.4 (23.5, 25.3)	25.2 (23.9, 26.5)	25.2 (24.1, 26.3)
Socio Economic Status					
High school education & above (%, 95% CI)	50.4 (48.4, 52.3)	49.6 (47.4, 51.6)	52.2 (50.3, 54.1)	58.3 (55.6, 61.1)	50.9 (48.7, 53.1)
Professional & Managerial job holders (%, 95% CI)	62.7 (61.6, 63.8)	61.7 (60.5, 62.8)	62.0 (61.0, 63.0)	66.8 (65.4, 68.2)	64.7 (63.5, 65.8)
Medical History					
History of parental cancer/heart disease (%, 95% CI)	65.3 (64.2, 66.3)	67.0 (65.9, 68.1)	67.5 (66.5, 68.5)	66.1 (64.7, 67.5)	66.9 (65.7, 68.1)
History of parental heart disease (%, 95% CI)	39.7 (38.7, 40.8)	39.4 (38.3, 40.6)	40.2 (39.2, 41.2)	39.8 (38.4, 41.2)	41.5 (40.3, 42.7)
Had/Have heart attack (%, 95% CI)	1.9 (1.7, 2.3)	1.9 (1.6, 2.2)	1.5 (1.3, 1.8)	0.7 (0.5, 1.0)	1.2 (0.9, 1.5)
Had/Have stroke (%, 95% CI)	1.1 (0.8, 1.4)	0.9 (0.7, 1.1)	0.7 (0.5, 0.9)	0.3 (0.1, 0.5)	0.9 (0.7, 1.2)
Had/Have angina (%, 95% CI)	2.7 (2.4, 3.1)	2.4 (2.1, 2.8)	2.3 (2.0, 2.7)	1.6 (1.2, 2.0)	1.5 (1.3, 1.9)
Had/Have high blood pressure (%, 95% CI)	17.1 (16.3, 18.0)	18.7 (17.8, 19.7)	17.6 (16.8, 18.4)	17.0 (15.9, 18.2)	15.5 (14.7, 16.5)
Had/Have diabetes (%, 95% CI)	2.2 (1.8, 2.5)	2.1 (1.8, 2.4)	2.0 (1.7, 2.4)	1.3 (1.0, 1.7)	2.0 (1.7, 2.4)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	6.9 (6.4, 7.5)	8.3 (7.7, 9.0)	8.3 (7.7, 8.9)	7.3 (6.6, 8.1)	7.1 (6.5, 7.8)
Had/Have cancer (%, 95% CI)	7.3 (6.7, 7.9)	8.4 (7.8, 9.1)	7.5 (7.0, 8.1)	7.3 (6.5, 8.1)	6.6 (6.0, 7.2)

Table 2.10 Baseline characteristics of all UKWCS participants by quintiles of black tea intake prior to the application of exclusion criteria (expressed as mean and SD for continuous variables, % and 95% CI for categorical variables)

	Black tea (g/day)			
	0 – 104	**208 – 650**	**1170**	**1560**
General				
Participants (n)	8207	15261	7970	3934
Age, years (SD)	51.1 (8.8)	52.6 (9.4)	52.9 (9.5)	52.6 (9.6)
BMI, kg/m² (SD)	24.6 (4.8)	24.3 (4.2)	24.5 (4.2)	24.7 (4.4)
Waist Circumference, cm (SD)	73.63 (9.7)	73.4 (9.1)	73.7 (9.0)	74.2 (10.0)
Dietary Intake				
Energy, kcal/day (SD)	2237 (891)	2345 (723)	2436 (764)	2522 (909)
Ethanol, g/day (SD)	8.7 (11.7)	9.5 (10.6)	7.8 (9.2)	7.0 (10.2)
Total coffee, g/day (SD)	524 (421)	393 (312)	280 (291)	220 (305)
Portions of fruit, no. of 80 g/day (SD)	5.4 (4.4)	5.3 (4.1)	5.2 (4.0)	5.1 (4.6)
Portions of vegetables, no. of 80 g/day (SD)	5.4 (3.2)	5.2 (2.8)	5.1 (2.9)	5.1 (3.3)
Lifestyle Habits				
Supplement users (%, 95% CI)	58.9 (57.8, 60.0)	57.5 (56.7, 58.3)	57.6 (56.5, 58.8)	57.0 (55.3, 58.6)
Non-smokers (%, 95% CI)	87.3 (86.5, 88.0)	90.4 (90.0, 90.8)	90.8 (90.1, 91.4)	85.6 (84.5, 86.7)
Moderately Active/Active (%, 95% CI)	59.2 (58.1, 60.2)	59.6 (58.8, 60.4)	57.2 (56.1, 58.3)	54.0 (52.4, 55.6)
Vegetarian/Vegan (%, 95% CI)	34.0 (32.9, 35.0)	25.5 (24.8, 26.2)	25.5 (24.6, 26.5)	27.2 (25.9, 28.6)
Socio Economic Status				
High school education & above (%, 95% CI)	54.1 (52.1, 56.1)	54.0 (52.6, 55.5)	48.2 (46.3, 50.2)	45.2 (42.6, 48.1)
Professional & Managerial job holders (%, 95% CI)	65.7 (64.6, 66.7)	63.7 (62.9, 64.5)	61.1 (60.0, 62.1)	60.4 (58.8, 61.9)
Medical History				
History of parental cancer/heart disease (%, 95% CI)	65.7 (64.7, 66.7)	66.5 (65.7, 67.2)	67.5 (66.4, 68.5)	67.2 (65.7, 68.6)
History of parental heart disease (%, 95% CI)	39.8 (38.8, 40.9)	39.4 (38.6, 40.2)	41.8 (40.7, 42.9)	40.1 (38.6, 41.7)
Had/Have heart attack (%, 95% CI)	1.5 (1.2, 1.7)	1.3 (1.2, 1.5)	1.6 (1.4, 2.0)	2.1 (1.7, 2.6)
Had/Have stroke (%, 95% CI)	0.8 (0.7, 1.1)	0.7 (0.5, 0.8)	0.8 (0.7, 1.1)	1.2 (0.9, 1.6)
Had/Have angina (%, 95% CI)	2.1 (1.8, 2.5)	2.0 (1.8, 2.2)	2.4 (2.1, 2.8)	2.7 (2.2, 3.3)
Had/Have high blood pressure (%, 95% CI)	15.9 (15.1, 16.7)	17.0 (16.4, 17.6)	18.7 (17.8, 19.6)	18.3 (17.1, 19.6)
Had/Have diabetes (%, 95% CI)	1.9 (1.6, 2.3)	1.8 (1.6, 2.0)	2.1 (1.8, 2.4)	2.7 (2.2, 3.3)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	6.5 (6.0, 7.1)	7.8 (7.4, 8.3)	8.2 (7.6, 8.8)	8.3 (7.4, 9.2)
Had/Have cancer (%, 95% CI)	7.2 (6.7, 7.8)	7.4 (7.0, 7.8)	7.5 (6.9, 8.1)	8.1 (7.2, 9.0)

Table 2.11 reported the baseline characteristics of all participants, and by completion of phase 2 questionnaire. There was approximately one third of all participants who completed the phase 2 questionnaire. Overall, phase 2 participants displayed more health-conscious behaviours than non-participants. By age and waist circumference, there were no significant differences between the two groups. However, participants who completed phase 2 questionnaire tend to have a slightly lower BMI than those who did not. In general, participants who completed the phase 2 questionnaire were more likely to be supplement users, non-smokers, moderately active and vegetarian/vegan. They were also more likely to hold professional/managerial status, more educated. In terms of medical history, participants who completed phase 2 questionnaire were more likely to have parents who had a history of cancer and/or heart disease and a personal history of high cholesterol. However, they were less likely to have a history of heart attack, stroke, angina, HBP, diabetes and cancer compared to participant who did not complete the phase 2 questionnaire. With regard to dietary intakes, participants who completed the phase 2 questionnaire were more likely to have a higher energy, total fruit, vegetable and tea intake, while participants who did not complete the phase 2 questionnaire tend to consume more alcohol. There were no significant differences between coffee consumption by completion of phase 2 questionnaire.

Table 2.11 Baseline characteristics of all UKWCS participants by completion of phase 2 questionnaire prior to the application of exclusion criteria (expressed as mean and SD for continuous variables, % and 95% CI for categorical variables)

	Participants who completed Phase 2 Questionnaire	Participants who did not complete Phase 2 Questionnaire	*p-value*	Full Cohort
Participants (n)	14172	21200		35372
Age, years (SD)	52.4 (9.1)	52.3 (9.5)	0.150	52.3 (9.3)
BMI, kg/m^2 (SD)	24.1 (4.3)	24.7 (4.4)	*<0.001*	24.5 (4.4)
Waist Circumference, cm (SD)	73.5 (9.0)	73.6 (9.5)	0.284	73.5 (9.3)
Supplement Users (%, 95% CI)	60.2 (59.3, 61.0)	56.2 (55.5, 56.9)	*<0.001*	57.8 (57.3, 58.3)
Non-Smokers (%, 95% CI)	91.6 (91.2, 92.1)	87.6 (87.1, 88.0)	*<0.001*	89.2 (88.9, 89.5)
Moderately Active/Active (%, 95% CI)	61.8 (61.0, 62.6)	56.0 (55.3, 56.7)	*<0.001*	58.3 (57.8, 58.9)
Vegetarian/Vegan (%, 95% CI)	32.0 (31.3, 32.8)	24.8 (24.2, 25.3)	*<0.001*	27.7 (27.2, 28.1)
Socio-Economic Status (%, 95% CI)				
Professional/Managerial	66.1 (65.3, 66.9)	61.3 (60.6, 61.9)		63.2 (62.7, 63.7)
Intermediate	25.9 (25.2, 26.6)	28.6 (28.0, 29.2)	*<0.001*	27.5 (27.0, 28.0)
Routine and Manual	8.0 (7.6, 8.5)	10.1 (9.7, 10.5)		9.3 (9.0, 9.6)
Highest Educational Qualification (%, 95% CI)				
No Education	13.6 (13.0, 14.2)	19.4 (18.9, 20.0)		17.1 (16.7, 17.5)
O-Level	29.8 (29.0, 30.6)	32.0 (31.3, 32.7)	*<0.001*	31.1 (30.6, 31.6)
A-Level	25.9 (25.2, 26.7)	23.7 (23.1, 24.3)		24.6 (24.1, 25.1)
Degree	30.6 (29.8, 31.4)	24.9 (24.3, 25.5)		27.2 (26.7, 27.7)
History of parental cancer/heart disease (%, 95% CI)	67.7 (66.9, 68.5)	65.9 (65.2, 66.5)	*<0.001*	
History of parental heart disease (%, 95% CI)	41.3 (40.5, 42.1)	39.3 (38.7, 40.0)	*<0.001*	40.1 (39.6, 40.6)
Had/Have heart attack (%, 95% CI)	1.2 (1.0, 1.4)	1.7 (1.6, 1.9)	*<0.001*	1.5 (1.4, 1.7)
Had/Have stroke (%, 95% CI)	0.6 (0.5, 0.8)	0.9 (0.8, 1.1)	*0.004*	0.8 (0.7, 0.9)
Had/Have angina (%, 95% CI)	1.8 (1.5, 2.0)	2.5 (2.3, 2.7)	*<0.001*	2.2 (2.0, 2.4)
Had/Have high blood pressure (%, 95% CI)	16.1 (15.5, 16.7)	18.1 (17.6, 18.6)	*<0.001*	17.3 (16.9, 17.7)
Had/Have diabetes (%, 95% CI)	1.4 (1.2, 1.6)	2.4 (2.2, 2.6)	*<0.001*	2.0 (1.8, 2.1)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	7.8 (7.4, 8.3)	7.5 (7.1, 7.9)	0.285	7.6 (7.4, 7.9)
Had/Have cancer (%, 95% CI)	7.0 (6.5, 7.4)	7.8 (7.4, 8.2)	*0.007*	7.4 (7.2, 7.7)
Energy Intake, kcal/day (SD)	2365 (764)	2344 (820)	*0.012*	2352 (798)
Alcohol Intake, g/day (SD)	8.4 (10.5)	8.8 (10.6)	*<0.001*	8.6 (10.6)
Total Fruits, g/day (SD)	426 (289)	409 (297)	*<0.001*	416 (294)
Total Vegetables, g/day (SD)	328 (197)	310 (190)	*<0.001*	317 (193)
Portions of Fruits, no. of 80 g/day (SD)	5.5 (4.3)	5.1 (4.2)	*<0.001*	5.3 (4.2)
Portions of Vegetables, no. of 80 g/day (SD)	5.4 (3.0)	5.1 (3.0)	*<0.001*	5.2 (3.0)
Total Coffee, g/day (SD)	379 (346)	379 (353)	0.896	379 (350)
Total Tea, g/day (SD)	785 (528)	776 (530)	0.102	780 (529)

2.7 National Diet and Nutrition Survey: Dietary intakes of (poly)phenol rich foods and participant characteristics

2.7.1 Dietary exposures

Two main (poly)phenol-rich sources were explored in this study, namely FVs. Total fruit intake (excluding juice) was derived by NatCen, by combining all food diary entries relating to fruit, including intakes of fresh fruits, dried fruits, and processed fruits. Mean fruit intake (excluding juice) is 108 g/day, while mean fruit juice intake is 61 g/day. Total vegetable was also derived by the NDNS RP, and the mean intake is 184 g/day.

Food items coded in the Nutrient Databank main food groups "Salads and other raw vegetables", "Vegetables (not raw), "Fruit" and "Fruit Juice" were listed for inclusion. Fruit subgroups by processing methods (juice, dried fruits) and (poly)phenol profiles were also investigated for similar reasons stated in Section 2.6.1. Likewise, total vegetable intake was also derived in a similar manner described above. A flowchart was subsequently used to decide whether food items were eligible for inclusion (Figure 2.20).

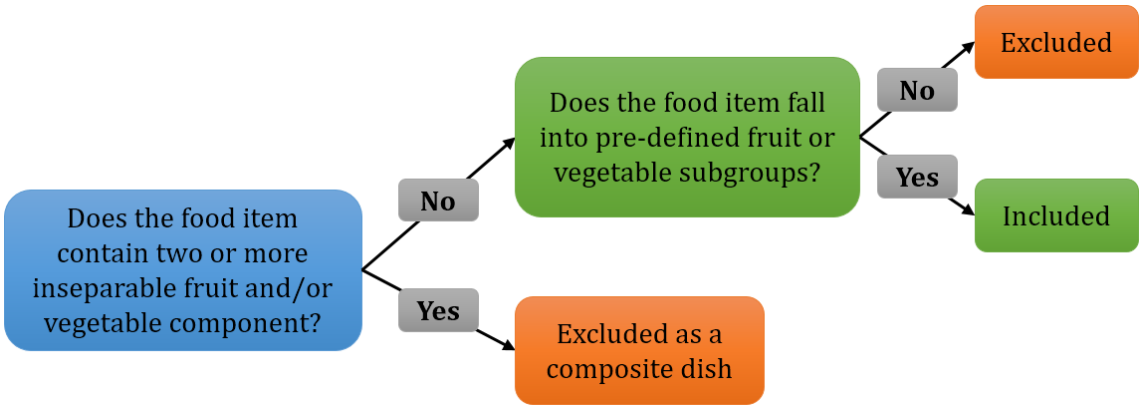


Figure 2.20 Decision flowchart for the inclusion of food items from the NDNS Nutrient Databank for division into FV subgroups

The intake range of fruits tend to be varied (Table 2.12). The most popularly consumed fruits were apple, pears, oranges and bananas, while the remaining fruits were consumed in small or insignificant amounts. Citrus and pomes fruits were the most popular groups with the highest total number of consumers, while tropical, drupes and berries were less frequently consumed. Bananas, apples and oranges were the most frequently consumed, followed by grapes, pears, tangerine, clementine and strawberries. By intake levels, apples were consumed the most, 114 g/day equivalent to a small apple a day. With regard to vegetables, in terms of quantity, tomatoes, carrots and onions were the most

abundantly consumed, followed by peas, broccoli, cucumber and peppers. Tomatoes, carrots and onions were also the most frequently consumed, followed by lettuce, cucumber, peas and peppers. The major (poly)phenol composition for each subgroup was previously reported in Table 2.3 and Table 2.4.

Table 2.12 Fruit subgroup intakes within adults (aged >19 years) in the NDNS RP grouped according to derived categories of fruit prior to the application of exclusion criteria (n = 2073)

Fruit subgroups	Individual Fruit	Mean (SD) (g/day)	Median (g/day)	Intake range (g/day)	Consumers (n)
Berries	Bilberries	1.0 (6.5)	0	0 – 100	93
	Blackberries	0.3 (4.3)	0	0 – 142	28
	Blackcurrants	0.04 (1.0)	0	0 – 33	8
	Cranberries	0.04 (1.0)	0	0 – 33.5	6
	Goji berries/Wolfberries	0.008 (0.23)	0	0 – 8.2	3
	Gooseberries	0.1 (2.0)	0	0 – 70	10
	Grapes	6.0 (24)	0	0 – 515	386
	Mulberries	0.007 (0.3)	0	0 – 15	1
	Physalis	0.004 (0.2)	0	0 – 7.5	1
	Pomegranate	0.9 (11.6)	0	0 – 284	22
	Raspberries	1.3 (7.1)	0	0 – 106	123
	Redcurrants	0.02 (0.6)	0	0 – 25	3
	Sharonfruit	0.04 (1.3)	0	0 – 55	2
	Strawberries	4.3 (15)	0	0 – 232	266
Citrus	Orange	38.8 (88.9)	0	0 – 1420	703
	Grapefruit	2.7 (24)	0	0 – 800	76
	Lemon	0.5 (3.8)	0	0 – 98	205
	Lime	0.03 (0.32)	0	0 – 5.7	29
	Mandarin	0.4 (5.5)	0	0 – 200	22
	Tangerines, Clementines	5.7 (18.7)	0	0 – 227	285
Drupes	Apricots	0.65 (5.0)	0	0 – 94	58
	Cherries	0.6 (6.1)	0	0 – 147	55
	Dates	0.10 (1.8)	0	0 – 50	8
	Greengages	0.03 (1.13)	0	0 – 50	2
	Nectarines	1.6 (8.9)	0	0 – 135	83
	Peaches	1.5 (9.4)	0	0 – 165	86
	Plums	1.9 (11)	0	0 – 246	117
	Prunes	0.77 (8.3)	0	0 – 187	40
Pomes	Apples	114 (198)	0	0 – 1750	978
	Pears	39.6 (124)	0	0 – 2074	307
	Quinces	0.001 (0.05)	0	0 – 2.3	1
Tropical	Bananas (Green, yellow)	25.3 (35.5)	0	0 – 250	986
	Kiwi	1.2 (6.1)	0	0 – 120	125
	Mango	1.1 (7.9)	0	0 – 187	77
	Passion fruit	0.01 (0.4)	0	0 – 15	5
	Paw-paw, Papaya	0.16 (2.7)	0	0 – 75	10
	Pineapple	3.1 (15.5)	0	0 – 212	157
Total fruit		108 (109)	81.1	0 – 1022	2073
Total fruit juice		61 (110)	9.1	0 – 1529	2073

Table 2.13 Vegetable subgroups within adults (aged >19 years) in the NDNS RP grouped according to derived categories of vegetables prior to the application of exclusion criteria (n = 2073)

Vegetable subgroups	Individual Vegetables	Mean (SD) (g/day)	Median (g/day)	Intake range (g/day)	Consumers (n)
Allium	Chives	0.008 (0.1)	0	0 – 3.7	20
	Garlic	0.3 (0.9)	0	0 – 17.5	457
	Leeks	1.7 (7.4)	0	0 – 80	187
	Onion	14.7 (19.0)	8.1	0 – 176	1367
***Brassicaceae* and leaves**	Broccoli/Broccoli Spears	7.4 (14.5)	0	0 – 110	596
	Brussel Sprouts	1.6 (6.5)	0	0 – 75	161
	Cabbage (Red, Savoy, Spring, Summer, White, Winter Kale)	4.1 (11.0)	0	0 – 135	385
	Cauliflower	3.9 (11.3)	0	0 – 112	331
	Chinese Leaves	0.1 (2.1)	0	0 – 66	10
	Lettuce (Butterhead, Cos, Iceberg, Webb)	4.8 (8.7)	0	0 – 94	927
	Mustard Cress	0.02 (0.3)	0	0 – 10	26
	Raddiccio	0.02 (0.6)	0	0 – 25	3
	Radish (Red, white)	0.23 (1.5)	0	0 – 28	67
	Sauerkraut	0.03 (0.8)	0	0 – 31	4
	Swede	1.3 (6.1)	0	0 – 80	137
	Turnip	0.46 (3.1)	0	0 – 45	80
	Watercress	0.2 (1.7)	0	0 – 30	64
Fruit vegetables	Aubergine	0.28 (2.9)	0	0 – 65	31
	Avocado	0.9 (5.9)	0	0 – 109	71
	Butternut squash	0.9 (8.5)	0	0 – 250	54
	Cho cho	0.02 (0.6)	0	0 – 27	2
	Courgette	1.3 (6.6)	0	0 – 145	154
	Cucumber	5.9 (12.3)	0	0 – 120	800
	Gherkins	0.09 (1.12)	0	0 – 31	24
	Gourd, bitter	0.01 (0.5)	0	0 – 15	2
	Gourd, bottle	0.005 (0.2)	0	0 – 7.5	2
	Marrow	0.08 (1.5)	0	0 – 51	9
	Tomatoes	31 (41)	20	0 – 623	1449
	Peppers (Red, Yellow, Green)	5.8 (13.4)	0	0 – 122	674
	Pumpkin	0.05 (1.7)	0	0 – 65	3
	Olives	0.5 (2.5)	0	0 – 35	122
Pod vegetables	Beansprouts	0.4 (2.6)	0	0 – 32	54
	Capers	0.01 (0.2)	0	0 – 8	13
	Cluster guar beans	0.006 (0.29)	0	0 – 13	1
	French beans	2.1 (7.8)	0	0 – 112	213
	Green beans	0.007 (0.3)	0	0 – 15	1
	Mange Tout	0.44 (3.0)	0	0 – 42.5	68
	Okra	0.07 (1.2)	0	0 – 34.5	9
	Peas	8.1 (15.2)	0	0 – 201	775
	Petit Pois	0.4 (3.4)	0	0 – 67	47
	Runner beans	1.5 (6.9)	0	0 – 105	152
Root vegetables	Beetroot	1.5 (5.9)	0	0 – 104	192
	Carrot	16.2 (22.1)	10	0 – 180	1210
	Cassava	0.07 (1.75)	0	0 – 72	5
	Celery	1.3 (5.3)	0	0 – 86	221
	Celeriac	0.06 (1.5)	0	0 – 64	8
	Fennel	0.1 (1.9)	0	0 – 62	15
	Ginger root	0.09 (0.6)	0	0 – 14	99
	Parsnip	2.1 (8.2)	0	0 – 100	204
	Sweet potato	0.6 (3.9)	0	0 – 50	64
	Water chestnut	0.02 (0.4)	0	0 – 11	9
	Yam	0.08 (1.6)	0	0 – 52	8
Total vegetables		184 (106)	168	0 – 1168	2073

Correlations between fruit and fruit subgroup variables are presented in Table 2.14. 'Total fruit and juice' was strongly correlated with total fruit intake and 'fruit juice & smoothies' (0.74 and 0.75 respectively). The two latter categories were also strongly correlated with citrus intake. The intake of pomes were moderately correlated with total fruit and 'total fruit and juice', while tropical fruit was moderately correlated with total fruit.

In general, correlation between the remaining fruit subgroups tend to be weak, ranging between 0.03 to 0.39. With regard to vegetable and vegetable subgroups, total vegetables were highly correlated with fruit vegetables, and moderately correlated with *Allium*, *Brassicaceae* and 'stalk and root vegetables'. Total vegetables were the least correlated with pod vegetables, while the correlation of vegetable subgroups ranged from weak to moderate (0.02 to 0.38).

Table 2.14 Correlations between total fruit and fruit subgroups intake assessed from the food diary prior to the application of exclusion criteria

	Total fruit	Fruit juice & smoothies	Total fruit and juice	Dried fruit	Berries	Citrus	Drupes	Pomes	Tropical fruit
Total fruit	1								
Fruit juice & smoothies	0.12	1							
Total fruit and juice	0.74	0.75	1						
Dried fruit	0.32	0.03	0.23	1					
Berries	0.39	0.18	0.38	0.12	1				
Citrus	0.25	0.80	0.70	0.05	0.05	1			
Drupes	0.36	0.07	0.29	0.17	0.12	0.04	1		
Pomes	0.55	0.28	0.56	0.13	0.08	0.12	0.09	1	
Tropical fruit	0.63	0.07	0.47	0.12	0.13	0.09	0.10	0.25	1

Table 2.15 Correlations between total vegetables and vegetable subgroups intake assessed from the food diary prior to the application of exclusion criteria

	Total vegetables	*Allium*	*Brassicaceae*	Fruit vegetables	Pod vegetables	Stalk/Root vegetables
Total vegetables	1					
Allium	0.51	1				
Brassicaceae and leaves	0.46	0.12	1			
Fruit vegetables	0.70	0.33	0.17	1		
Pod vegetables	0.25	0.02	0.10	0.02	1	
Stalk/Root vegetables	0.51	0.23	0.38	0.19	0.17	1

Table 2.16 Correlation between total fruit and total vegetable intake assessed from the food diary prior to the application of exclusion criteria

	Total fruit	Total vegetables
Total fruit	1	
Total vegetables	0.29	1

2.7.2 Baseline characteristics of participants

Adults (aged 19 and above) within the NDNS RP study were divided into approximately equal tertiles by intakes of FV prior to the application of exclusion criteria (Table 2.17). Mean age increased with higher FV intakes, with a greater proportion of adults aged 65 years and above. There was no particular trend by BMI, and no significant differences between the proportion of obese and non-obese participants by tertiles. Waist circumference was also not significantly different with higher FV intake. However, there was a higher proportion of hypertensive participants with increasing FV intake. In terms of lifestyle habits, participants in the third tertile were more likely to be vegetarian or vegan, non-smokers and supplement users. There were no significant trend for the usage of statins (without prescription) and moderate/vigorous physical activity levels. Participants were also more likely to hold a professional/managerial job in comparison with intermediate or manual job with increasing FV intake. With regard to dietary intakes, energy intake increased across the tertiles, while intake of alcohol remained stable. Higher intake of carbohydrates, fats and proteins, as well as the percentage of energy from these nutrients were also greater with a higher intake of FVs, with the exception of percentage of energy from total fat. Consumption of sodium, total fruit, total vegetables and portions of FVs was also increased across the tertiles.

Table 2.17 Baseline characteristics of participants by tertiles of total FV intakes prior to the application of exclusion criteria, expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables

	Total fruit and vegetable intake (g/day)			ANOVA/Chi-Squared Test
	0 - 201	**202 - 339**	**339 – 1554**	***p-value***
General				
Participants (n)	695	694	694	
Age (years) (SD)	45.2 (17.9)	49.4 (16.7)	52.9 (16.0)	*<0.001*
19 – 64 years (%, 95% CI)	83.4 (80.5, 86.0)	79.7 (76.5, 82.5)	75.2 (71.9, 78.3)	*0.001*
65 + years (%, 95% CI)	16.5 (14.0, 19.5)	20.3 (17.5, 23.5)	24.8 (21.7, 28.1)	
BMI (kg/m^2) (SD)	27.6 (5.5)	28.1 (5.5)	27.3 (5.1)	*0.047*
<29.9 kg/m^2 (%, 95% CI)	71.4 (67.8, 74.9)	68.5 (64.8, 72.0)	74.4 (70.9, 77.6)	0.063
30+ kg/m^2 (%, 95% CI)	28.5 (25.1, 32.2)	31.5 (28.0, 35.2)	25.6 (22.3, 29.1)	
Waist Circumference (cm) (SD)	93.5 (14.8)	94.6 (14.7)	93.0 (14.6)	0.211
Systolic Blood Pressure (mmHg) (SD)	127 (16)	127 (17)	127 (17)	*<0.001*
Diastolic Blood Pressure (mmHg) (SD)	75 (11)	75 (11)	73 (10)	*<0.001*
Hypertensive (140/90 mmHg) (%, 95% CI)	14.7 (12.2, 17.5)	18.7 (16.0, 21.8)	19.0 (16.3, 22.1)	*<0.001*
Dietary Intake				
Total Energy (kcal/d) (SD)	1680 (571)	1804 (571)	1924 (558)	*<0.001*
Total Energy –no alcohol (kcal/d) (SD)	1586 (514)	1709 (517)	1829 (519)	*<0.001*
Alcohol (g/d) (SD)	13.5 (25.1)	13.5 (24.2)	13.6 (19.6)	0.992
Carbohydrates (g/d) (SD)	200 (72)	215 (66)	235 (71)	*<0.001*
% Energy from Carbohydrates (%) (SD)	47.4 (6.9)	47.5 (6.6)	48.3 (6.7)	*0.014*
Protein (g/d) (SD)	64.3 (21.3)	74.1 (27.4)	80.2 (23.7)	*<0.001*
% Energy from Protein (%) (SD)	16.5 (3.8)	17.6 (3.8)	17.9 (4.0)	*<0.001*
Total Fat (g/d) (SD)	64.3 (24.8)	67.5 (26.4)	69.7 (26.5)	*<0.001*
% Energy from Total Fat (%) (SD)	36.1 (6.1)	34.9 (6.0)	33.7 (6.6)	*<0.001*
Sodium (mg/d) (SD)	2092 (802)	2241 (807)	2306 (867)	*<0.001*
Portions of Fruits & Vegetables (no./d) (SD)	2.0 (0.8)	3.9 (0.8)	6.8 (1.9)	*<0.001*
Total fruit (excluding juice) (g/day) (SD)	28.4 (31.3)	87.5 (55.0)	209 (121)	*<0.001*
Total vegetables (g/day) (SD)	95.7 (46.7)	176 (55)	280 (108)	*<0.001*
Lifestyle Habits				
Vegetarian/Vegan Status (%, 95% CI)	0.7 (0.3, 1.7)	2.4 (1.5, 3.9)	3.4 (2.2, 5.9)	*0.009*
Non-smokers (%, 95% CI)	42.3 (38.7, 46.0)	55.2 (51.5, 58.8)	65.6 (61.9, 69.0)	
Ex-regular smoker (%, 95% CI)	19.3 (16.5, 22.4)	26.4 (23.2, 29.8)	25.8 (22.7, 29.2)	*<0.001*
Current smokers (%, 95% CI)	38.4 (34.9, 42.1)	18.4 (15.7, 21.5)	8.6 (6.8, 11.0)	
Cigarettes smoked (if smokers) (no./d) (SD)	5.1 (8.4)	2.1 (5.5)	1.0 (4.1)	*<0.001*
Supplement users (%, 95% CI)	25.2 (22.1, 28.5)	34.9 (31.4, 38.5)	41.9 (38.3, 45.6)	*<0.001*
Statin users (%, 95% CI)	4.3 (3.0, 6.1)	3.4 (2.3, 5.1)	5.5 (4.0, 7.4)	0.065
Moderately/Vigorously Active (hr/d) (SD)	1.4 (2.3)	1.5 (2.2)	1.7 (2.2)	0.221
Socio Economic Status				
Professional & Managerial (%, 95% CI)	30.8 (27.5, 34.3)	43.4 (39.7, 47.1)	50.0 (46.3, 53.7)	*<0.001*
Intermediate (%, 95% CI)	19.3 (16.5, 22.4)	18.7 (16.0, 21.8)	21.5 (18.6, 24.7)	
Routine/Manual (%, 95% CI)	45.7 (42.1, 49.5)	34.6 (31.1, 38.2)	24.3 (21.3, 27.7)	
Unemployed (%, 95% CI)	2.7 (1.7, 4.2)	1.4 (0.8, 2.6)	2.0 (1.2, 3.4)	

2.8 Discussion

2.8.1 Comparison of FV intakes in the UKWCS and other studies

The mean intake of fruits (excluding juice) and vegetables (including composite dishes) assessed by the baseline FFQ in UKWCS was 302 g/day and 317 g/day respectively, while the median intake was 252 g/day and 282 g/day respectively. These intakes were higher compared to other studies, elaborated as follows. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reported a median consumption of 205 g/day of fruit and 244 g/day of vegetables within the UK [193], while the EPIC-Heart study reported a mean intake of 328 g/day and 384 g/day of FVs for men and women respectively in the UK [86]. Within cohorts from other countries, the Nurses' Health Study observed a median intake of 186 g/day of fruit, 230 g/day of vegetables, and participants in the Health Professionals' Study consumed a median intake of 170 g/day of fruits and 235 g/day of vegetables [194]. Intakes from the Women's Health Study were nearly half for fruits at 176 g/day, but similar for vegetables at 312 g/day, while a Swedish cohort reported mean intakes of 216 g/day for fruits and 376 g/day for vegetables.

The consumption of FV in the UKWCS is relatively high in comparison to other cohorts. This could be explained by the higher proportion of vegetarians in the study, or because they were relatively more health-conscious, consisting of women only. In addition, there are also methodological limitations to account for. For example, higher consumption of FVs could be attributed to a higher number of FFQ items [195]. The current study has 17 fruit items and 22 vegetable items. This is less than the number of FFQ items in the Nurses' Health Study, Health Professionals' Follow-up Study and the Women's Health Study from US with lower FV intakes [194, 196], while the Swedish cohort, [197] reports a higher consumption of FV intakes compared to UKWCS, with a lower number of FFQ items. However, these studies measure diet from different countries, thus it would not be fair to compare across studies. An objective way to assess if over-reporting exist is through the assessment of biochemical markers (biomarkers), as well as relative validity using 24-hour recalls (single or multiple) and food diaries. Mean β-carotene intakes derived from FFQ were higher than β-carotene intakes derived from a seven-day food diary within the UK arm of the EPIC-study, due to the higher vegetable intake in FFQ by 120 g/day, attributed to the higher number of FFQ vegetable items [198]. Similarly, the FFQ also overestimated vitamin C, α-, β-carotene and folate when compared to a 7-day food diary in the Whitehall II Study for the same reason [199]. In terms of fruit intake, overestimation also occurred within the Shanghai Women's Health Study, due to severe overestimation of watermelon consumption

despite adjustments for seasonality. In addition, the authors partly attributed this to participants with a social desirability bias, who may report food consumption based on social desirability, e.g. underreporting fat and energy intake [200]. This is most likely a possible limitation of the UKWCS due to the large proportion of 'health-conscious' women within the study. To address whether the UKWCS FFQ is relatively valid, a comparison must be made against the food diary from the UKWCS instead of other studies. This will be assessed in Chapter 8, along with strengths and limitations of both dietary assessments.

2.8.2 Comparison of FV intakes in the NDNS RP and other studies

With regard to intakes from food diaries in the NDNS RP [174, 201], mean intakes reported from publications (with weighting factors applied) for FVs were 108 g/day (104 g/day for men, 112 g/day for women) and 184 g/day (187 g/day for men, 181 g/day for women) respectively, while median intakes were 81 g/day (75 g/day for men, 86 g/day for women) and 167 g/day (167 g/day for both men and women) respectively. In the NDNS conducted in 2001 before NDNS RP which used a seven-day weighed food diary, the consumption of fruits had remained relatively similar, and even decreased a little for women (104 g/day for men, 120 g/day for women). However, intakes of vegetables had improved from 112 g/day for men and women [202]. When intakes were compared with other studies, the North/South Ireland Consumption Survey reported a slightly higher intake at 136 g/day for fruits (133 g/day in men, 140 g/day in women) and a slightly lower intake for vegetables at 140 g/day (149 g/day in men, 132 g/day in women) [203]. Within the EPIC-Norfolk cohort, mean total fruit intake was higher than NDNS (158 g/day in men, 183 g/day in women) while vegetable intakes were lower (151 g/day in men, 150 g/day in women) [204]. In summary, intakes of FVs do not vary as much between studies as the observed intakes measured by FFQ, possibly due to nature of the participants. However, there are also other methodological concerns within the food diary which may affect reported intakes. Firstly, the definition of 'total fruits' and 'total vegetables' may vary between studies [204]. For example, fruits are more likely consumed fresh, thus less likely to be part of a composite dish, while vegetables are *vice versa*. An Irish cohort demonstrated that only 5% of fruit intake was from composite dishes, while the proportion of vegetables from composite dishes were 26% [203]. Thus the exclusion of vegetables from composite dishes could introduce bias in intake estimates or misclassification when ranking individuals by consumption. Within the NDNS RP, FV intakes were disaggregated to minimize bias in this manner. It was also reported in the EPIC-Norfolk cohort that differences between crude and disaggregated intakes ranged from 0.5 to 1 portion of fruit

or vegetable, which could affect which category participants belonged to, thus affecting the outcome estimates [204].

2.8.3 Comparison of FV intakes between the UKWCS and NDNS RP

In terms of which foods are consumed most frequently, dietary intakes captured by the FFQ in the late 1990s within the UKWCS and by the food diary in the NDNS RP a decade later do not show substantial differences in patterns of intakes for FV intakes. In both studies, apples, bananas and citrus fruits (both fruit and juice) were reported to be consumed in the largest quantities relative to the other fruits, while tomatoes, carrots and broccoli were consumed in the largest quantities relative to other vegetables within these two studies. Onion consumption was also very high (14.7 g/day) in the NDNS RP study, however, intake of onions was not available in the UKWCS baseline FFQ. An Irish study, O'Brien *et. al* [203] reports similar preferences for FV intakes, where apples, bananas and citrus fruits (including juice) were the most frequently consumed, while tomatoes, carrots and onions had the highest mean intakes.

2.9 Summary

This chapter provided the relevant methodology for the UKWCS and the NDNS RP to support the following result chapters. The study design of both studies were described, along with the descriptive statistics and exploration of FV intakes from both studies, coffee and tea intakes from the UKWCS, using correlations and histograms. Participant characteristics were also presented by FV, coffee and tea intake quantiles when appropriate. Consumption of these foods were discussed and compared with other studies. Further investigation on the relative validity of the FFQ and the food diary within the UKWCS will be addressed in Chapter 8 including the strengths and limitations of both dietary assessment methods. The following chapters will be using the dietary data and the methods of analyses presented here to examine the risk between CVD, HBP and fruit, vegetable, coffee and tea intake.

Chapter 3
Fruit and vegetable intake and cardiovascular disease mortality in the UK Women's Cohort Study

3.1 Abstract

FV intake is associated with a reduced risk of cardiovascular disease (CVD) in observational studies, though fruit or vegetable type has been less frequently explored. The aim of the current study was to explore the association between total fruit, total vegetable and respective FV subgroup intake according to (poly)phenol content and CVD mortality in the UK Women's Cohort Study. Total FV 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 to 1998. FV intakes were sub-categorised according to similarities in (poly)phenol profile from Phenol Explorer, including berries, citrus, drupes, pomes and tropical fruits, as well as *Allium*, *Brassicaceae*, fruit vegetables, pod vegetables and stalk & root vegetables. 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 a 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). The direction of the associations tended to be inverse for some fruit subgroups, 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]. Total vegetable intake was associated with a lower risk of stroke mortality, with a 9% reduction in risk for each 80 g/day portion consumed (95% CI 0.82 to 1.00). Fresh vegetables and vegetable subgroups were not associated with a lower risk of CVD. Overall, the findings of this study do not provide strong evidence to suggest that FV type is important. Until further knowledge is obtained from intervention studies, consumption of a wide variety of different types of fruit is recommended.

3.2 Background

CVD is a major cause of death in Europe [10] and the UK, being accountable for a third of all-cause mortality [15]. Observational epidemiological studies in older adults have indicated that higher FV intake may lower risk of CVD [86, 196, 205-209]. Evidence in the literature that demonstrates high total FV intakes individually have beneficial effects on CHD [205, 210-212] and stroke [197, 213, 214], but null findings for CHD have also been previously reported for fruit intake [212], as well as vegetable intake [86, 194, 196, 215, 216].

There are also protective associations observed for CHD risk when investigating fruit intakes by subgroups (e.g. citrus fruits) and individual fruits (i.e. blueberries and strawberries) [117, 210], as well as for stroke risk with increased consumption of citrus fruits [205, 213]. However, evidence is limited for berries [197], and pomes [117], with no published evidence for drupes and tropical fruits to our knowledge. In studies which investigated types of vegetables, a high consumption of green leafy vegetables was associated with a lower risk of CVD [194], CHD [205] and total stroke [197], while higher intakes of cruciferous vegetables (*Brassicaceae*) was associated with lower CHD risk [205]. Higher intake of carrots was also associated with a lower risk of CVD and stroke mortality, while greater intake of peas was associated with a lower risk of CHD mortality [217]. Similarly, studies also reported null associations with higher intakes of vegetable subgroups and CVD risk [197, 214, 216, 218], leading to inconclusive findings, thus further research in this area is warranted.

Dietary fibre [219-221], potassium [222-224], folate [225] and "antioxidants", such as carotenoids [226] and (poly)phenols are suggested properties of FV which may be protective against CVD. However, (poly)phenol profiles differ for each type of FV. Citrus fruits are rich in flavanones specifically, and berries are rich in anthocyanins. In terms of (poly)phenol 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. On the other hand, all vegetables contain various concentration of lignans in general, onions (especially red) from the *Allium* genus are rich in flavonols, especially quercetin. Other vegetables contain complex (poly)phenol profiles. The *Brassicaceae* family pre-dominantly consist of flavones and flavonols. Fruit vegetables are rich in phenolic acids such as hydroxybenzoic and hydroxycinnamic acids, while stalk and root vegetables contain different proportions of hydroxycinnamic acids and flavones.

Some observational studies have reported lower CVD mortality risk in individuals with a higher consumption of flavonoids (a subgroup of (poly)phenols) [116, 117, 227]. The main flavonoid in oranges is hesperidin, which is bioavailable [228], and exhibits favourable effects on hypertension [126, 150, 151]. Anthocyanins from berries have been associated with 'healthy' blood lipid profiles, [120] and are also anti-inflammatory [163]. High quercetin consumption was also associated with lower ischemic heart disease risk [116]. Quercetin is known to exhibit *in vitro* various protective effects on endothelial function, as well as anti-hypertensive and anti-atherogenic functions [229]. However, there are limited evidence *in vivo* within human trials [229]. Evidence from intervention studies are also lacking to directly support the effect of flavonoids from pomes, drupes, tropical fruit and various vegetable subgroups on CVD risk or CVD risk factors. Furthermore, very few studies have thoroughly and specifically investigated CVD risk and the relationship between consumption of FV subgroups.

The aim of the current study was to explore the association between total FV intake and subgroups of FV intake according to similarities in (poly)phenol profile with reference to Phenol Explorer [111] and the risk of CVD mortality using data from the UK Women's Cohort Study (UKWCS).

3.3 Method

3.3.1 Dietary exposure

Total FV intake was individually generated by combining multiple variables from the FFQ which recorded intakes of fresh fruits, dried fruits, pure fruit juices, processed fruits, fresh vegetables and vegetables from composite dishes reported in Chapter 2 Section 2.6.1. Non-response was taken to indicate non consumption for the small amount of missing data on fruit intake. There were no missing data in vegetable intakes. Consumption was expressed as grams of fruit per day (g/day).

3.3.2 Mortality outcomes

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). Deaths of participants were classified using codes provided by the International Classification of Disease (ICD) 9th edition 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). There were no important differences in the characteristics of those who were traced versus those untraced (data not shown).

3.3.3 Statistical method and design

3.3.3.1 Outliers and exclusions

Prior to analysis, various methods were applied to detect outliers within the distribution. Normality of the distribution was evaluated by histograms, while boxplots were used to detect outliers in continuous variables. Scatter graphs and correlations were useful for identifying patterns and interactions between variables, demonstrated in Chapter 2. It is important to detect for outliers as they would lead to estimation bias. Outliers can occur due to over or misreporting in the case of FFQs, such as values outside of expected normal variation within the population. Analyses for FV intakes were conducted separately. Participants who met the following criteria were excluded from the analysis:

1. No, or incorrect NHS number provided at baseline FFQ, (n = 695)
    - Without the appropriate follow-up data, participants are unable to be traced for cancer or mortality outcomes, and are therefore excluded from the analysis.
2. Extreme energy intakes (<500 kcal/day & >6000 kcal/day) (n = 86)

- Implausible intakes of energy could be generated due to under, or over reporting within the FFQ or recall bias, and were excluded.

3. Extreme total fruit and juice intakes (> 1500 g/day) (n = 970) or extreme total vegetable intake (>1500 g/day) (n = 59)
    - Implausible intakes of FV could be generated due to participant error, over reporting within the FFQ or recall bias, and were excluded. The cut-off point was decided by plotting a boxplot shown below, where most outliers are excluded (Figure 3.1). The cut-off point for total vegetables was also based on Figure 3.1.
4. Previous self-reported heart attacks, angina, cancer, diabetes and stroke at baseline (n = 4,014).
    - Participants with self-reported diseases mentioned above were likely to be subjected to post-diagnosis changes in dietary behaviour. The current analysis also intended to study a healthy population. Where information was missing for prior history of disease, participants were assumed to have no prior history.

There were 30,643 participants eligible for inclusion after the application of the exclusion criteria above.

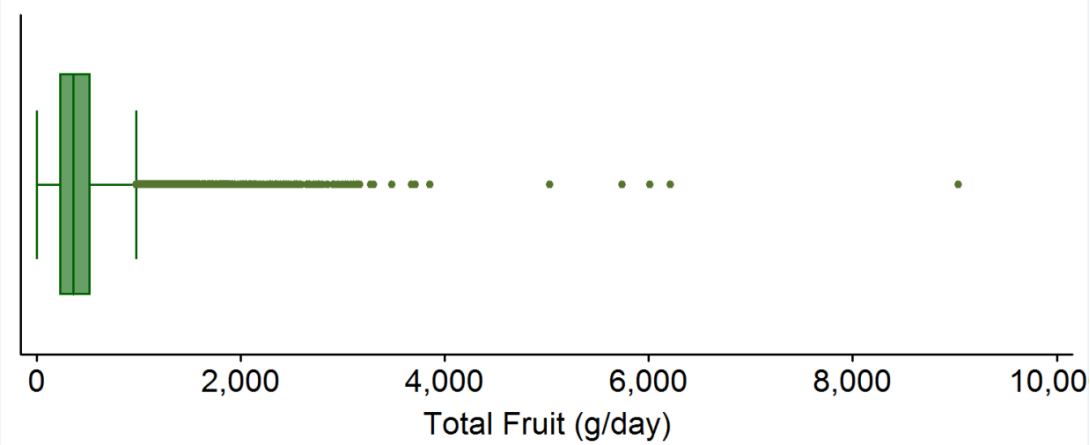


Figure 3.1 Boxplot of total fruit intake, including dried fruits and fruit juice, prior to exclusion criteria application

3.3.3.2 Confounding

The current analysis is based on the DAG from Chapter 2, Section 2.5.2 to provide evidence for inclusion of previously identified risk factors for CVD within the scientific literature. Exclusively statistical approaches such as stepwise procedures were avoided, but likelihood ratio tests were implemented as objective evidence to indicate whether there were major changes in point estimates after adjusting for potential confounders. These

confounders were also previously explored as a correlation matrix in Chapter 2. Results show that none of the potential confounders are correlated to each other, thus multicollinearity is unlikely. Univariate analysis was also conducted to explore the relationship between the variable of interest and outcome. Models for the presented results in this chapter were adjusted for:

1. Age (years)
2. Age (years), BMI (kg/m^2), moderate physical activity (Yes/No), smoking status (smoker v.s. non-smoker), alcohol intake (ethanol g/day) and socio-economic status (professional/managerial, intermediate or routine/manual), additionally fruit intake when investigating vegetable intake
3. In addition to model 2, energy intake (kcal/day) was also included for the reasons stated above (data not shown).

Models that investigated subgroup fruit or vegetable intakes were further adjusted for fruit or vegetables not in that subgroup. For example, citrus fruits were adjusted for the total amount of non-citrus fruit consumed (g/day). To maximise power in the model, variables with some missing data for BMI and smoking were updated using data collected via a questionnaire in a later stage of the study. This second phase of data collection has been previously reported [190] and elaborated in Chapter 2 Section 2.2.2.3.

3.3.3.3 Descriptive statistics

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 the adoption of vegetarian or vegan diets. Classification of socio-economic status was undertaken based on occupation, according to the UK National Statistics-Socio-Economic Classification (NS-SEC), where women are divided into three categories, 1) Managerial/professional, 2) Intermediate, or 3) Routine/manual [230]. 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.

3.3.3.4 Survival analysis

Survival analysis was conducted using the Cox proportional hazards models to calculate a hazard ratio (HR) and 99% CI [231]. Time of survival was determined by the date the questionnaire was received until death or censor date. The censor date applied to patients who had died of a different disease, or for surviving patients. The last censor date in the current analysis for surviving patients was at 18th December 2013. 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 association was tested by calculating increments of FV 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 [176].

Sensitivity analysis was performed by including adjustment for energy intake (kcal/day) in the models stated above. Effect modification was explored by stratification of subgroups of participants selected *a priori*. Variables investigated included BMI (obese v. non-obese), smoking (smoking v. non-smoking), menopausal status (pre-menopausal v. post-menopausal) and self-reported HBP. However, due to inadequate numbers of fatal cases (<50), these analyses were ultimately restricted to postmenopausal women, women with and without self-reported HBP, non-smokers and non-obese women. A summary of exclusion criteria and analysis plan is provided in Figure 3.2 and Figure 3.3.

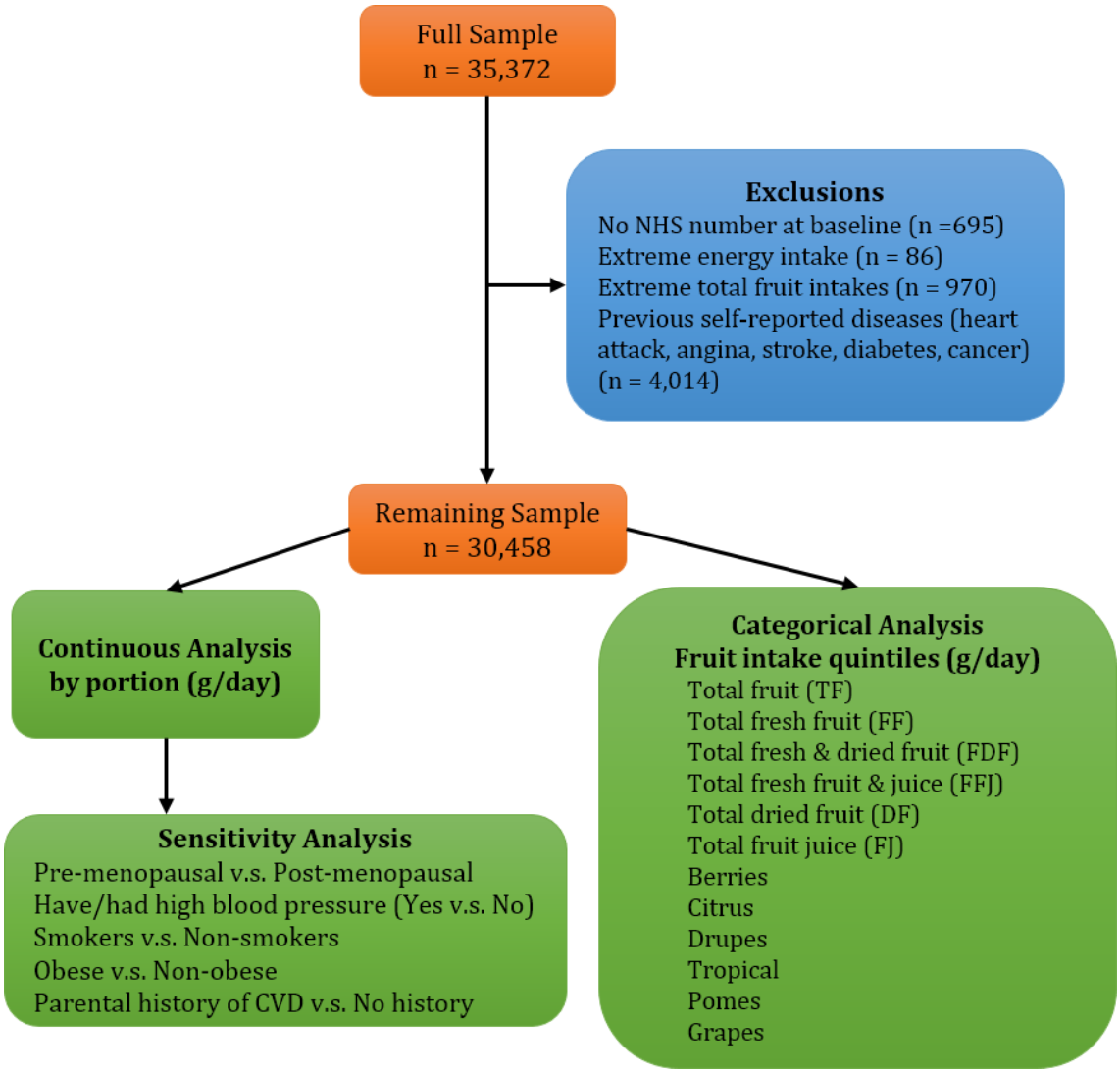


Figure 3.2 Summary flowchart of the current study exclusion criteria and analysis plan

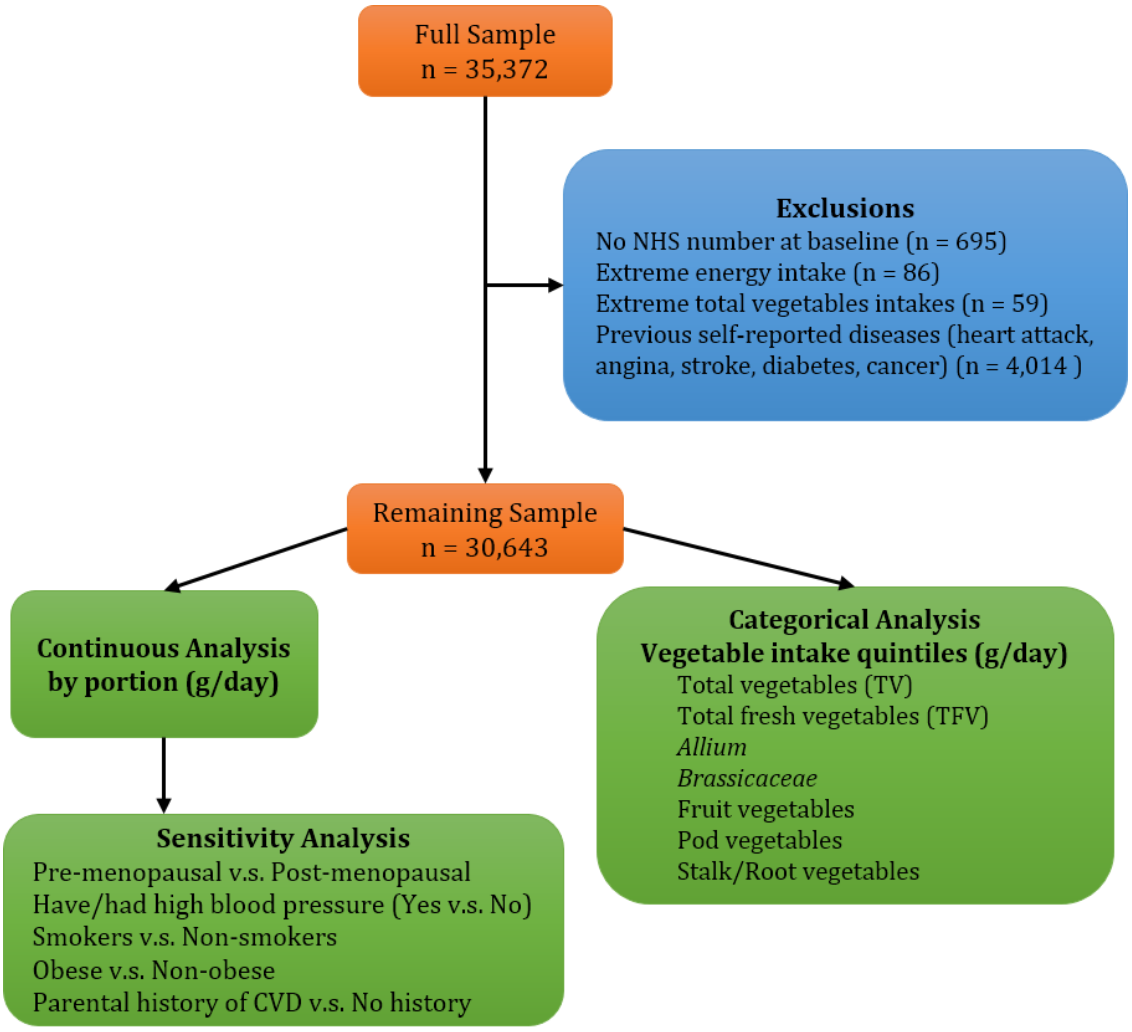


Figure 3.3 Summary flowchart of the current study exclusion criteria and analysis plan

3.3.3.5 Testing for statistical assumptions

Statistical assumptions were tested according to the procedure reported in Chapter 2 Section 2.4.2. Table 3.1 lists the Schoenfeld residuals for fully-adjusted model on total fruit intake. Most *p-values* were not significant, indicating covariates in the model were not correlated with survival time. Although physical activity was borderline significant, the overall global test is not. Figure 3.4 displays the log-minus-lot plot for total fruit analysis. The lines in the graph are roughly parallel to each other, thus statistical assumptions were fulfilled. Statistical significance was determined by 2-sided *p-value* of ≤0.01 for 99% CI. Stata version 12.0 [232] was used for all statistical analysis.

Table 3.1 Schoenfeld residuals of covariates in the full-adjusted model for total fruit intake on total CVD mortality.

Covariates	*p-value*
1st Quintile (Total fruit)	-
2nd Quintile	0.97
3rd Quintile	0.46
4th Quintile	0.86
5th Quintile	0.40
Age	0.12
BMI	0.34
Moderate physical activity	0.05
Socio-economic Status	
Professional/Managerial	-
Intermediate	0.29
Routine/Manual	0.94
Smoking Status	
Non-smoker	-
Smoker	0.13
Alcohol	0.84
Total vegetables	0.12
Global Test	0.26

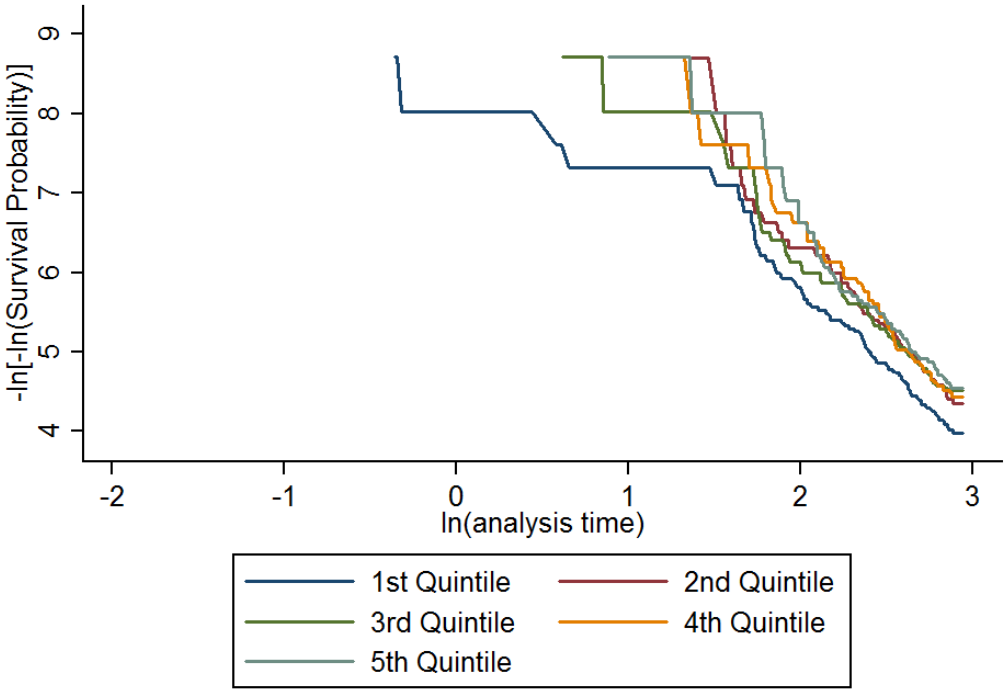


Figure 3.4 Survival probability for quintiles of total fruit intake on total CVD mortality plotted over time

3.4 Results

3.4.1 Baseline Characteristics

After the exclusion criteria was applied, 30,458 eligible participants were left for inclusion in the analysis. The baseline characteristics of participants by case status, are reported in Table 3.2 and Table 3.4. During the follow-up period from 1995 to 2013, there were 286 cases of CVD mortality, of which 138 were CHD deaths and 148 were stroke mortality cases. In summary, fatal CVD cases tend to be older, with a higher BMI and larger waist circumference than non-cases. Fatal CVD cases also report higher rates of 'unhealthy lifestyle habits', such as higher smoking rates, lower vitamin/mineral supplement consumption, lower physical activity, and a lower proportion of vegetarians. Fatal CVD cases also tend to be from a lower socio-economic class and are 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 FV consumption, where fatal cases were more likely to have lower intakes than non-cases. Participant characteristics reported here after the application of exclusion criteria by fruit or vegetable consumption quintile (Table 3.3 and Table 3.5) were not largely different from what was described in Chapter 2 (Table 2.8).

Table 3.2 Baseline characteristics for CHD mortality, stroke mortality and non-fatal cases, expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables

	CHD Mortality Cases	Stroke Mortality Cases	Non-cases
No. of cases (n)	138	148	30172
Age[a], 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% CI)	53.0 (44.9, 61.1)	52.9 (44.9, 60.9)	57.7 (57.1, 58.3)
Non-smokers (%, 95% CI)	82.2 (76.4, 88.0)	83.6 (78.1, 89.1)	89.4 (89.1, 89.8)
Moderately active/active (%, 95% CI)	38.5 (30.7, 46.2)	38.3 (30.9, 45.8)	59.7 (59.1, 60.2)
Vegetarian/vegan (%, 95% CI)	21.9 (15.6, 28.2)	19.8 (13.8, 25.7)	28.5 (28.0, 29.0)
Socio-economic status (%, 95% CI)			
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% CI)	54.5 (46.9, 62.2)	54.6 (47.1, 62.1)	76.2 (75.7, 76.7)
Highest educational qualification (%, 95% CI)			
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% CI)	69.5 (62.4, 76.5)	63.5 (56.2, 70.8)	66.0 (65.5, 66.6)
Had/Have high blood pressure (%, 95% CI)	39.0 (31.3, 46.6)	37.3 (29.7, 45.0)	15.1 (14.7, 15.5)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	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)
Alcohol 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 3.3 Baseline characteristics of total fruit intake expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables, for participants in UKWCS including dietary habit, lifestyle habits, socio economic status and medical history

	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)
Alcohol, 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% CI)	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% CI)	81.4 (80.5, 82.4)	89.7 (88.9, 90.43)	90.9 (90.2, 91.6)	92.1 (91.5, 92.8)	92.69 (92.0, 93.3)
Moderately active/active (%, 95% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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 3.4 Baseline characteristics for CHD mortality, stroke mortality and non-fatal cases for the analysis of vegetable consumption, expressed as mean and standard deviation for continuous variables, % and 95% CI for categorical variables

	CHD Mortality Cases	Stroke Mortality Cases	Non-cases
No. of cases (n)	138	148	30172
Age[a], 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% CI)	53.0 (44.9, 61.1)	52.9 (44.9, 60.9)	57.7 (57.1, 58.3)
Non-smokers (%, 95% CI)	82.2 (76.4, 88.0)	83.6 (78.1, 89.1)	89.4 (89.1, 89.8)
Moderately active/active (%, 95% CI)	38.5 (30.7, 46.2)	38.3 (30.9, 45.8)	59.7 (59.1, 60.2)
Vegetarian/vegan (%, 95% CI)	21.9 (15.6, 28.2)	19.8 (13.8, 25.7)	28.5 (28.0, 29.0)
Socio-economic status (%, 95% CI)			
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% CI)	54.5 (46.9, 62.2)	54.6 (47.1, 62.1)	76.2 (75.7, 76.7)
Highest educational qualification (%, 95% CI)			
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% CI)	69.5 (62.4, 76.5)	63.5 (56.2, 70.8)	66.0 (65.5, 66.6)
Had/Have high blood pressure (%, 95% CI)	39.0 (31.3, 46.6)	37.3 (29.7, 45.0)	15.1 (14.7, 15.5)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	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)
Alcohol 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 3.5 Baseline characteristics of participants in UKWCS by quantiles of total vegetable intake, expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables, including dietary habits, lifestyle habits, socio-economic status and medical history

	Vegetable consumption quintiles including vegetables from composite dishes (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)
Alcohol, 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% CI)	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% CI)	81.4 (80.5, 82.4)	89.7 (88.9, 90.43)	90.9 (90.2, 91.6)	92.1 (91.5, 92.8)	92.69 (92.0, 93.3)
Moderately active/active (%, 95% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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)

3.4.2 Survival Analysis

3.4.2.1 Full Cohort

In the fully-adjusted model (Table 3.6), HR and 99% CI for increasing quintiles of fruit intake are presented with analysis of linear association addressing dose response. Participants from the highest TF intake quintile, consuming >7 portions/day had a 43% lower risk of death from CVD (95% CI 0.34 to 0.95) 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 TF intake, with risk lowered by 55% (95 % CI 0.21 to 0.97) 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 FF, FFJ intake, as well as for FDF intake consumed (Table 3.6). Significant associations for TF intake were also found when analysing CHD individually. Risk of fatal CHD was halved in the highest TF intake quintile compared with the reference intake group, and reduced by 7% with every additional 80g portion of fruit consumed (95 % CI 0.85 to 1.01). The risk of CHD was also 11% lower for every 80 g increase of FFJ intake (excluding dried fruits), and FDF intake (excluding fruit juice). TF intake was not statistically associated with the risk of fatal stroke, although point estimates tended to be lower with increasing consumption. Neither total DF intake nor FJ intake alone were associated with risk of fatal CVD, CHD or stroke.

Total vegetable intake was not associated with CHD and stroke mortality by quintiles, however, the risk of fatal stroke was lowered by 9% (95% CI 0.82 to 1.00) for every additional 80 g portion of total vegetables in the dose response analysis (Table 3.7). The risk of fatal CVD was also significantly lowered by 38% (95% CI 0.42 to 0.92) when participants consumed between four to five portions of total vegetables (fourth quintile), compared with women from the first quintile. However, the association was no longer significant when participants consumed five or more portions. In the age-adjusted model for fresh vegetable intake and fatal stroke and CVD, there was a significant inverse association, but the association was attenuated in the fully-adjusted model.

With regard to FV subgroups, the risk of fatal CVD in the highest quintile for total citrus intake (fruit and juice) 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 (99 % 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 is 34% lower with each 80 g/day greater grape intake (99 % CI 0.43 to 1.02). Intake of grapes was not associated with fatal CHD or stroke. Participants who consumed between 11 to 13 g of *Allium* vegetables had a 71% (99% CI 0.12 to 0.70) lower risk of fatal CHD and 54% (99% CI 0.26 to 0.80) lower risk of fatal CVD compared to the lowest consumers. However, the linear association was not significant. No association or dose response for fatal CVD was found in the analysis of subgroups of berries, pomes, drupes, tropical fruit, *Brassicaceae* species, fruit vegetables, pod vegetables and stalk & root vegetable.

3.4.2.2 Sensitivity Analysis

Further analysis addressed dose response through establishing linear associations for age-adjusted and fully adjusted models restricted to certain participants (separate analyses on the non-obese, non-smokers, post-menopausal women, women with or without HBP, and women with or without parental history of CVD). These are subsequently reported in Appendix A. Due to the limited number of CVD cases, analysis by increasing quintiles were not investigated in subgroups as meaningful conclusions cannot be drawn.

No significant associations were found for stratified populations of non-smoking women, non-obese women, and in women with or without parental history of fruit and CVD (Table A.1). There was an 8 to 14% lower fatal CVD risk with every additional portion of TF, FF, FFJ and FDF intakes within women with no self-reported HBP (Table A.1). Similar associations were detected between fatal risk of CHD and FF, FDF intakes, where every 80 g/day portion lowered risk by 16%. However, these associations were not seen in women with self-reported HBP (Table A.1). In addition, there is double the risk of fatal CHD for every additional portion of berries consumed among women with self-reported HBP. Within postmenopausal women, previous associations between TF, FF, FFJ, FDF intakes and CVD were not significant, however, every 80 g portion of grapes lowered CVD risk by 38% (Table A.1). No significant associations for vegetable intake and CVD were found for the stratified subpopulations of non-obese, non-smokers, self-reported HBP, postmenopausal and parental history of CVD (Table A.2).

Table 3.6 Total fruit intake, fruit subgroup intake and cardiovascular mortality risk (expressed as HR and 99% CI)

	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										
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										
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										
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										
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)

(Table 3.6 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]
Dried fruit										
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)
Fruit juice										
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 – 16	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										
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 80g/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										
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)

(Table 3.6 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]
Orange juice										
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										
Q1	0 – 1.6	41	1	1	34	1	1	73	1	1
Q2	1.7 – 4.0	22	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 – 8.0	13	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	8.1 – 15.3	36	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	27	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)
Pomes										
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	28	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 fruit										
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 – 78	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	78 – 108	36	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	108 – 1235	21	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)

(Table 3.6 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]
Drupes										
Q1	0 – 1	49	1	1	41	1	1	91	1	1
Q2	1 – 3	26	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	16	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	24	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										
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	23	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 80g/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] Cases 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

Table 3.7 Total vegetable, and vegetable subgroup intake and cardiovascular mortality risk (expressed as HR and 95% or 99% CI)

	Intake (g/day)	CHD (HR, 95% or 99% CI)			Stroke (HR, 95% or 99% CI)			Total CVD (HR, 95% or 99% CI)		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total vegetable										
Q1	0 – 177	37	1	1	45	1	1	82	1	1
Q2	178 – 246	29	0.77 (0.49, 1.21)	0.91 (0.56, 1.49)	33	0.71 (0.47, 1.08)	0.81 (0.51, 1.27)	62	0.74 (0.54, 1.00)	0.85 (0.61, 1.19)
Q3	246 – 282	27	0.77 (0.49, 1.21)	0.90 (0.54, 1.49)	30	0.65 (0.43, 1.00)	0.78 (0.49, 1.25)	57	0.71 (0.52, 0.97)	0.83 (0.59, 1.17)
Q4	319 – 424	18	0.46 (0.27, 0.78)	0.64 (0.36, 1.14)	23	0.45 (0.28, 0.74)	0.61 (0.36, 1.02)	41	0.46 (0.32, 0.65)	0.62 (0.42, 0.92)
Q5	424 – 1490	32	0.88 (0.57, 1.36)	1.21 (0.72 ,2.02)	22	0.55 (0.35, 0.87)	0.62 (0.36, 1.06)	54	0.70 (0.51, 0.96)	0.87 (0.60, 1.26)
p trend			0.267	0.523		0.005	0.043		0.006	0.308
HR per 80 g/day			0.96 (0.89 ,1.03)	1.03 (0.94, 1.12)		0.89 (0.82, 0.97)	0.91 (0.82, 1.00)		0.92 (0.87, 0.98)	0.97 (0.91, 1.03)
Fresh vegetable										
Q1	0 – 150	32	1	1	40	1	1	72	1	1
Q2	151 – 210	27	0.75 (0.41, 1.40)	0.98 (0.50, 1.94)	35	0.87 (0.50, 1.49)	0.95 (0.52, 1.73)	62	0.81 (0.54, 1.23)	0.96 (0.61 ,1.51)
Q3	210 – 274	24	0.70 (0.37, 1.30)	0.90 (0.45, 1.83)	22	0.46 (0.24, 0.89)	0.61 (0.30, 1.22)	46	0.57 (0.36, 0.89)	0.74 (0.45, 1.21)
Q4	274 – 365	26	0.60 (0.32, 1.14)	0.95 (0.47, 1.93)	33	0.67 (0.38, 1.17)	0.87 (0.46 ,1.64)	59	0.64 (0.42, 0.97)	0.91 (0.57 ,1.45)
Q5	365 – 1478	34	0.87 (0.49, 1.53)	1.39 (0.69, 2.80)	23	0.51 (0.28, 0.94)	0.64 (0.31, 1.33)	57	0.67 (0.45, 1.01)	0.95 (0.58, 1.57)
p trend			0.512	0.155		0.005	0.111		0.014	0.871
HR per 80 g/day			0.97 (0.87, 1.08)	1.07 (0.94, 1.21)		0.88 (0.78, 0.99)	0.91 (0.79, 1.05)		0.93 (0.85, 1.00)	0.99 (0.90, 1.09)
Allium*										
Q1	0 – 2	53	1	1	43	1	1	96	1	1
Q2	2 – 6	28	0.53 (0.31, 0.93)	0.59 (0.32, 1.08)	39	0.88 (0.52, 1.51)	1.00 (0.56, 1.78)	67	0.69 (0.47, 1.01)	0.77 (0.51, 1.17)
Q3	6 – 10	20	0.50 (0.27, 0.95)	0.61 (0.30, 1.22)	27	0.99 (0.56, 1.75)	1.05 (0.55, 2.01)	47	0.72 (0.47, 1.09)	0.80 (0.50, 1.28)
Q4	11 – 13	11	0.32 (0.15, 0.65)	0.29 (0.12, 0.70)	20	0.53 (0.27, 1.04)	0.68 (0.33, 1.41)	31	0.41 (0.25, 0.67)	0.46 (0.26, 0.80)
Q5	13 – 195	31	0.61 (0.35, 1.05)	0.73 (0.37, 1.43)	24	0.67 (0.37, 1.22)	0.84 (0.40, 1.76)	55	0.64 (0.43, 0.95)	0.78 (0.48, 1.28)
p trend			0.033	0.188		0.238	0.778		0.020	0.242
HR per 80 g/day			0.29 (0.07, 1.29)	0.42 (0.08, 2.27)		0.55 (0.15, 2.01)	0.84 (0.16, 4.24)		0.41 (0.16, 1.10)	0.59 (0.18, 1.89)
Brassicaceae*										
Q1	0 – 34	25	1	1	25	1	1	50	1	1
Q2	34 – 54	26	0.98 (0.50, 1.89)	0.96 (0.47, 1.99)	35	1.15 (0.61, 2.15)	1.36 (0.69, 2.67)	61	1.06 (0.68, 1.68)	1.15 (0.70, 1.88)
Q3	54 – 80	30	0.97 (0.51, 1.86)	1.05 (0.52, 2.13)	29	0.96 (0.51, 1.83)	1.11 (0.54, 2.26)	59	0.97 (0.61, 1.53)	1.07 (0.65, 1.77)
Q4	80 – 125	27	0.84 (0.44, 1.61)	0.85 (0.41, 1.79)	35	0.94 (0.50, 1.75)	1.24 (0.62, 2.50)	62	0.89 (0.57, 1.39)	1.03 (0.62, 1.71)
Q5	125 – 934	35	0.87 (0.46, 1.62)	1.01 (0.48, 2.12)	29	0.72 (0.38, 1.37)	1.03 (0.48, 2.22)	64	0.79 (0.50, 1.24)	1.02 (0.60, 1.74)
p trend			0.871	0.346		0.073	0.364		0.240	0.986
HR per 80 g/day			1.01 (0.81, 1.27)	1.10 (0.84, 1.43)		0.84 (0.65, 1.08)	0.90 (0.66, 1.22)		0.93 (0.78, 1.09)	1.00 (0.82, 1.23)

(Table 3.7 continued)

	Intake (g/day)	CHD (HR, 95% or 99% CI)			Stroke (HR, 95% or 99% CI)			Total CVD (HR, 95% or 99% CI)		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Fruit vegetable*										
Q1	0 – 33	35	1	1	45	1	1	80	1	1
Q2	33 – 51	40	0.86 (0.50, 1.49)	1.20 (0.66, 2.18)	31	0.65 (0.37, 1.13)	0.75 (0.41, 1.38)	71	0.75 (0.51, 1.10)	0.95 (0.62, 1.45)
Q3	51 – 76	18	0.55 (0.28, 1.08)	0.71 (0.33, 1.53)	23	0.63 (0.34, 1.15)	0.77 (0.39, 1.51)	41	0.59 (0.38, 0.93)	0.74 (0.44, 1.22)
Q4	76 – 106	27	0.68 (0.37, 1.23)	0.94 (0.47,1.87)	36	0.78 (0.45, 1.33)	1.05 (0.57, 1.94)	63	0.73 (0.49, 1.09)	0.99 (0.63, 1.57)
Q5	106 – 802	23	0.70 (0.38, 1.29)	0.96 (0.44, 2.09)	18	0.49 (0.25, 0.93)	0.70 (0.32, 1.55)	41	0.59 (0.38, 0.92)	0.82 (0.47, 1.42)
p trend			0.224	0.975		0.037	0.965		0.019	0.968
HR per 80 g/day			0.86 (0.62, 1.18)	1.00 (0.70, 1.44)		0.76 (0.55, 1.06)	1.01 (0.69, 1.46)		0.81 (0.64, 1.02)	1.00 (0.77, 1.30)
Pod vegetable*										
Q1	0 – 11	43	1	1	33	1	1	76	1	1
Q2	11 – 20	11	0.32 (0.15, 0.70)	0.31 (0.13, 0.74)	29	0.87 (0.48, 1.59)	1.14 (0.59, 2.21)	40	0.57 (0.36, 0.91)	0.65 (0.39, 1.09)
Q3	21 – 35	19	0.63 (0.33, 1.19)	0.59 (0.29, 1.21)	27	0.93 (0.50, 1.72)	1.16 (0.59, 2.29)	46	0.77 (0.49, 1.19)	0.83 (0.51, 1.35)
Q4	35 – 46	36	0.71 (0.41 ,1.24)	0.84 (0.45, 1.55)	38	0.96 (0.55, 1.67)	1.35 (0.71, 2.56)	74	0.82 (0.56, 1.22)	1.04 (0.67, 1.63)
Q5	47 – 590	34	0.89 (0.52, 1.52)	0.95 (0.49, 1.86)	26	0.72 (0.39, 1.33)	1.21 (0.57, 2.54)	60	0.81 (0.54, 1.22)	1.06 (0.65, 1.75)
p trend			0.279	0.030		0.164	0.712		0.805	0.085
HR per 80 g/day			1.26 (0.72, 2.21)	1.65 (0.91, 2.99)		0.71 (0.37, 1.34)	1.11 (0.52, 2.40)		0.96 (0.62, 1.47)	1.39 (0.85, 2.27)
Stalk & root vegetable*										
Q1	0 – 16	34	1	1	40	1	1	74	1	1
Q2	16 – 29	24	0.71 (0.38, 1.32)	0.69 (0.34, 1.37)	34	0.80 (0.46, 1.41)	0.88 (0.48, 1.61)	58	0.76 (0.50, 1.15)	0.78 (0.50, 1.24)
Q3	29 – 41	24	0.71 (0.39, 1.32)	0.66 (0.32, 1.33)	23	0.54 (0.29, 1.01)	0.61 (0.31, 1.23)	47	0.62 (0.40, 0.96)	0.63 (0.38, 1.03)
Q4	41 – 61	32	0.69 (0.37, 1.27)	0.83 (0.42, 1.63)	21	0.43 (0.22, 0.83)	0.57 (0.27, 1.18)	53	0.55 (0.35, 0.86)	0.69 (0.42, 1.13)
Q5	62 – 470	29	0.60 (0.33, 1.10)	0.61 (0.28, 1.33)	35	0.64 (0.37, 1.10)	0.89 (0.43 ,1.81)	64	0.62 (0.42, 0.93)	0.74 (0.43, 1.25)
p trend			0.214	0.680		0.031	0.617		0.016	0.510
HR per 80 g/day			0.78 (0.46, 1.31)	0.90 (0.46 ,1.75)		0.64 (0.37, 1.09)	0.88 (0.44, 1.73)		0.70 (0.49, 1.02)	0.88 (0.55, 1.43)

[a] Cases apply to fully-adjusted models

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

3.5 Discussion

3.5.1 Summary of Results

The objective of this study was to investigate the association between different subgroups of FV and fatal CVD risk. Results from the present study indicated a lower risk of fatal CVD with higher intake of TF and grape, and lower fatal CHD with higher intake of FF. A lower risk of fatal stroke for every 80 g portion of total vegetables was also present, but not with risk of fatal CVD or CHD. In terms of FV subgroups, greater intake of total citrus and grapes were associated with a lower risk of fatal stroke, however, due to the absence of a significant linear trend, the association for lower fatal stroke risk and increasing citrus intake could not be confirmed. Point estimates also indicate a lower risk of fatal CHD and CVD for participants consuming between 11 to 13 g/day of *Allium* species, but a significant linear trend was absent. No evidence of association was determined for FJ, orange juice, dried fruit, and the remaining FV subgroups in the full cohort.

Within subgroup analyses, significant associations reported above were restricted to women with no self-reported HBP for fruit intake, while no associations were significant for vegetable intakes. These findings require further verification with larger sample sizes. Consumption of berries were also associated with two-fold increase in fatal CHD. However, CI were particularly wide, thus this finding also need to be further verified and carefully interpreted.

3.5.2 General comparison with literature

Previous MAs of observational studies have indicated a significant, inverse association with risk of total CVD [83], CHD and greater consumption of FVs [84]. This exposure also had a similar association with risk of stroke [85]. 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 [215, 218, 233], as well as for CHD [86, 205, 210] and stroke. Findings for total vegetables are also consistent with other studies based in Northern Europe [197, 214]. However, the association between total vegetable and fatal CVD or CHD was not significant, contrary to the conclusions from the EPIC-Diabetic cohort, US and Japan [205, 208, 209, 212]. Northern European studies also tend to report an inverse association between stroke and total vegetable intake in comparison to other countries, where the Nordic diet [234] recently demonstrated to improve blood lipid profile and lower BP in hypercholesterolaemic participants [235].

Studies rarely investigate both CHD and stroke outcomes in the same cohort [215]. 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 [3, 5]. This approach was therefore adopted in the current study. There was also 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 [125]. However, apple juice, as included in the broad fruit juice category, does not [133]. In addition, a 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 (poly)phenols delivered, or that disaggregation of the (poly)phenols may render them less biologically potent [236]. However, possibly and more importantly, juice consumption levels are low in the cohort overall, and there are fewer consumers compared to whole fruit.

3.5.3 Relevance with (poly)phenol mechanisms

The vegetable subgroups proposed within this chapter have been studied similarly within other observational studies [194, 197, 205, 214, 216, 218, 237]. Furthermore, these proposed categories were also loosely based on a botanical and culinary criteria proposed by the American Institute for Cancer Research [238]. While the intention was to divide groups according to (poly)phenol profiles, vegetable subgroups, unlike fruits tend to contain a broad spectrum of different (poly)phenols, rather than being a concentrated source of one particular type. Therefore the best approach was to group them using a botanical and culinary criteria, and then hypothesise if (poly)phenols could possibly play a role in any significant associations detected within the study.

Observational studies exploring fruit subgroups and CVD risk, have tended to focus on grape consumption, or wine and the (poly)phenols contained within, stemming from the so-called 'French Paradox' [239]. Evidence for (poly)phenols 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

(poly)phenol content] [240] and vasoprotective effects [241] support the findings of the current study. There is also evidence relating to increased total citrus intake and lowered risk of CHD [205, 210]. Evidence from cohort studies of a protective association between citrus consumption and risk of CVD is suggestive of a lowering of risk [213], although there is some inconsistency between studies, possibly due to variation in consumption pattern between countries [213, 242]. 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 [243, 244]. However, epidemiological studies have found significant associations between flavanone intake and CVD risk [116, 117], and hesperidin [a (poly)phenol in citrus fruit] was seen to significantly lower DBP in two human studies after a single dose of 500 mL commercial orange juice [150, 151]. Hesperidin also improved endothelial function [126], and reduced permeability and fragility of capillary walls [149], 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 (poly)phenols rather than specifically from vitamin C intake.

Allium vegetables, especially onions, are good sources of flavonols (quercetin), previously known as 'Vitamin P' from one of the earliest studies [245]. Like hesperidin, quercetin also decreased permeability and fragility of capillary walls. However, there are limited evidence on the effects of isolated flavonols on the development of atherosclerosis [229]. Lignans exist in all vegetable subgroups, and common examples include lariciresinol, pinoresinol and secoisolariciresinol. The evidence for intake of lignans and its effects on improving CVD risk factors (BP, lipid profile and lipoproteins) in RCTs are lacking [246]. In addition, estimating lignan intake is also analytically challenging [247], which possibly led to inconclusive results on the association between lignans and CVD. Furthermore, rich sources of lignans consist of flaxseed and sesame, while other sources of vegetables contain significantly less lignan content [246].

Considering all the evidence given above, if beneficial effects of all (poly)phenols are responsible for lowered fatal CVD risk, then associations should also be seen for other FV subgroup intakes. However, no association was found between intakes of *Brassicaceae*, fruit vegetables, pod vegetables, stalk & root vegetables, or pomes and CVD risk in UKWCS,

despite high levels of consumption, in contrast to other studies [116, 117, 197, 217, 242]. Further investigations into other FV subgroups 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 (poly)phenols, 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 (poly)phenol. Additionally, variance in dietary assessment methods may also cause variation through different portion sizes or design of the FFQ itself. Moreover, some studies did not include vegetables from composite dishes [194, 197, 214, 218]. As the proportion of vegetables consumed within composite dishes are higher than fruits, failure of inclusion could lead to error in estimation of total vegetable intakes, and further possible errors in point estimates.

It is also important to note that other components in fruits, such as dietary fibre, nitrates, carotenoids and glucosinolates in *Brassicaceae* may also play a role in CVD prevention besides (poly)phenols. For example, one recent MA of cohort studies reported an inverse association between FV fibre and CHD risk, although numbers of included studies were low and heterogeneity between studies was high [221]. Fibre from FV 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 [248]. Observational studies have also suggested that carotenoids (single and total) are associated with a lower CHD risk [249]. 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 [226]. With regard to glucosinolates, high intakes within animals studies reported improvements in endothelial function [250], while an observational study reported a linear association between cruciferous vegetable intake and CVD mortality [251]. However, there is limited evidence for the effects of glucosinolates in human RCTs.

3.5.4 Strengths and limitations

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 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 [201, 252] and other studies [194, 197], possibly due to over-reporting on FFQ in general [253], as observed in other cohort studies employing this method of dietary assessment [199]. In addition, results are more difficult to generalise 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 (poly)phenol content has also increased [191, 192]. Whilst inverse associations between FV intake and the risk of CVD have been observed, interpretation of the extent of causality should be undertaken with caution since with any observational study, there is a 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 FV intake [201] and CVD risks [15] differ between sex, although we do not have reason to suppose that the mechanism of action of FV on CVD risk may differ by sex. Further intervention studies on subgroups of FV divided by (poly)phenol 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 (poly)phenol profiles on risk of CVD. The estimation of FV intake is also strengthened by the

inclusion of other fruit sources such as dried fruit, juices or processed fruits and composite vegetable dishes. 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 (poly)phenol composition, the impacts of food processing on (poly)phenols and metabolite composition in the body, ensuring that the fruit groupings applied here were sensible with regard to the variety of (poly)phenols in each fruit group.

3.6 Summary

In conclusion, greater consumption of total fruit, total vegetable, fresh fruit, fresh grapes were seen to be protectively associated with fatal CVD risk in the UKWCS. This finding is aligned with widely promoted guidelines promoting FV 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 FV type is important. Until further knowledge is obtained from intervention studies, consumption of a wide variety of different types of FV are recommended.

Chapter 4
Fruit intake and incidence of cardiovascular disease in the UK Women's Cohort Study

4.1 Abstract

In Chapter 3, it was concluded that high total fruit intake was negatively associated with risk of CVD mortality, however, there was no particular fruit type that was more important than others. The current chapter aims to improve the quality of outcome measure, by investigating the association between total fruit, fruit subgroup intake according to (poly)phenol content and CVD incidence in the UKWCS. Total fruit intake (g/day) derived from a 217-item food frequency questionnaire, was obtained from 26,794 women (aged 35 to 69 years) at baseline from 1995 to 1998. Fruit intakes were sub-categorised according to similarities in (poly)phenol profile from Phenol Explorer, including berries, citrus, drupes, pomes and tropical fruits. CVD incidence events were derived from data linkage to Hospital Episode Statistics (HES) and Myocardial Ischaemia National Audit Project (MINAP) databases. During a mean follow-up period of 16.4 years, 291 CVD incident events (152 CHD, 142 stroke) were observed. Survival analysis was conducted using participants free from history of CVD at baseline. Moderate consumption of total fruit (302 – 571 g/day), fresh fruit and juice (291 – 554 g/day) and orange juice (116 – 145 g/day) was associated with a lower risk total stroke incidence, however, not statistically significant for dose response. Increasing intake of berries by 80 g portions were protective against risk of chronic coronary events, especially within non-smoking and non-obese women, while greater intakes of citrus fruit was inversely associated with risk of total CVD in postmenopausal women. Overall, the findings of this study provide further evidence, in addition to those in Chapter 3 to suggest that the consumption of berries and citrus fruits should be promoted for cardiovascular health. It is also important to note that this particular study is constrained by the low number of incident cases, thus results should be interpreted cautiously.

4.2 Background

The association between total fruit intake and CVD mortality was investigated in Chapter 3, where higher total fruit intake, especially fresh fruit and grapes were found to be protective against risk of fatal CVD. Several studies on the association between fruit intake and fatal CVD [83, 215, 218, 233], fatal CHD [84, 86, 205, 210] and fatal stroke [85] are in agreement with the study findings. However, Chapter 3 only investigated mortality data, which meant that any non-fatal events were unknown and misclassified as non-cases. Re-investigating using incidence data could possibly improve the quality of analysis as non-cases and incident cases would be correctly classified. In addition, the current study also intends to subcategorise CHD and stroke further, thus investigating the relationship between fruit intake and the incidence of myocardial infarction (MI), acute coronary syndrome (ACS), chronic coronary events (CCE), haemorrhagic stroke (HS), ischaemic stroke (IS) and unclassified stroke (USt). As discussed in Chapter 3 Section 3.5.2, although CHD and stroke share some common aetiology, such as the process of atherosclerosis, distinct differences exist between these two conditions. Stroke manifests in the brain, while CHD occurs in the heart. In addition, 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 [3, 5]. For example, ischaemic stroke is mostly driven by atherosclerosis, while haemorrhagic stroke is the rupturing of blood vessels, causing bleeding into the brain (Chapter 1 Section 1.1.1). Therefore, further insights into the association between these separate conditions and total fruit, fruit subgroup intake could potentially help generate more, or reconfirm hypotheses with regard to the mechanism of (poly)phenols, should there be any significant associations.

Therefore, the aim of this chapter is to further explore the association between total fruit, fruit subgroup intake according to similarities in (poly)phenol profile [111] and risk of CVD incidence using data from the UKWCS.

4.3 Methods

4.3.1 Dietary exposure

Intakes of fresh fruits, dried fruits, pure fruit juices and processed fruits from the FFQ were combined to generate total fruit intake, as reported in Chapter 2, Section 2.6.1. Consumption was expressed as grams of fruit per day (g/day).

4.3.2 Incidence outcomes

Incidence data was available for participants who had provided information at baseline to allow tracing of their records through HES and MINAP. The types of CVD events explored include total CVD, total CHD and total stroke, as well as subcategories of CHD and stroke incidence. CHD incidence was divided into three broad categories: MI, ACS and CCE, while stroke was divided into HS (consisting of subarachnoid, intracerebral, intracranial haemorrhage), IS (consisting of cerebral infarction) and unclassified stroke (USt) (Table 4.1). Since access to the HES and MINAP was restricted due to ethical reasons, the linkage of the HES, MINAP and UKWCS was conducted by Dr. Diane Threapleton, who also ran the statistical analysis detailed in the following sections.

Table 4.1 The classification of coronary heart disease and stroke categories by ICD10 codes

		Incidence outcomes	Corresponding disease (ICD10 codes)
Total Cardiovascular Disease	Total Coronary Heart Disease	Myocardial infarction	Acute myocardial infarction (I21.0 – I21.4, I21.9) Subsequent myocardial infarction (I22.0 – I22.1, I22.8 – I22.9)
		Acute coronary syndrome	Unstable angina (I20.0) Acute myocardial infarction (I21.0 – I21.4, I21.9) Subsequent myocardial infarction (I22.0 – I22.1, I22.8 – I22.9) Other forms and unspecified acute ischaemic heart disease (I24.8 – I24.9)
		Chronic coronary events	Angina pectoris (I20.1, I20.8 – I20.9) Atherosclerotic heart disease (I25.0 – I25.1) Old myocardial infarction (I25.2) Aneurysm of heart (I25.3) Ischaemic cardiomyopathy (I25.5) Silent myocardial ischaemia (I25.6) Other forms and unspecified chronic ischaemic disease (I25.8 – I25.9)
		Others	Cardiac arrest (I46.0 – I46.1, I46.9) Re-entry ventricular arrhythmia (I47.0) Ventricular tachycardia (I47.2) Ventricular fibrillation and flutter (I49.0)
	Total stroke	Subarachnoid haemorrhage	Subarachnoid haemorrhage in various locations (I600-I609)
		Intracerebral haemorrhage	Intracerebral haemorrhage in various locations (I610 – I616, I618 – I619)
		Intracranial haemorrhage	Intracranial haemorrhage in various locations (I620 – I621, I629)
		Cerebral infarction	Cerebral infarction in various locations (I630 – I636, I638 – I639)
		Unclassified stroke	Unclassified stroke (I64X)

4.3.3 Statistical method and design

4.3.3.1 Outliers and exclusions

The procedure for omitting outliers and implementing exclusions is documented in Chapter 2, Section 2.5.1. Additional criteria were also implemented. In brief, participants who met the following criteria were excluded:

1. Non-English participants (n = 3872)
   - Northern Ireland and Scottish residents were not covered by HES
2. No, or incorrect NHS number provided at baseline FFQ, (n = 1013)
3. Requested drop out from participant (n = 1)

4. Extreme energy intakes (<500 kcal/day & >6000 kcal/day) (n = 488)
5. Previous self-reported heart attacks, angina, cancer, diabetes and stroke at baseline (n = 4,011).
6. Participants who died of CVD or any other disease within one year of baseline (n = 129)
7. Participants without survival outcomes (n = 5)
8. Extreme fruit intakes (n = 578)

There were 26,794 participants eligible for inclusion after the application of the exclusion criteria above.

4.3.3.2 Confounding

The current analysis was based on the DAG from Chapter 2, Section 2.5.1 to provide evidence for inclusion of potential confounders. These confounders were previously explored as a correlation matrix. Results showed that none of the potential confounders were correlated to each other, thus multicollinearity was unlikely. Univariate analysis was also conducted to explore the relationship between the variable of interest and outcome. The models used in these analyses were:

1. Age (years)
2. Age (years), BMI (kg/m^2), moderate physical activity (Yes/No), smoking status (smoker v.s. non-smoker), alcohol intake (ethanol g/day) and socio-economic status (professional/managerial, intermediate or routine/manual).
3. In addition to model 2, energy intake (kcal/day) (data not shown).

Intakes of total vegetable would be adjusted for when modelling the association between total fruit and CVD. When investigating subgroups of fruit, mutual adjustments would be made.

4.3.3.3 Descriptive statistics

Descriptive statistics were explored as part of the Chapter 2 Section 2.6.2 by dividing according total fruit quintiles before exclusions listed in Section 4.3.3.1. Baseline characteristics by fruit quintiles after exclusions and by disease status, into CHD, stroke and non-cases, were previously explored (Chapter 3). It should be noted that due to access restrictions to datasets, there were 19 (0.07%) additional participants within the dataset when exposure intakes were generated. However, as the figure is negligible in comparison to the total sample, reported intake values should still be sufficiently accurate.

4.3.3.4 Survival analysis

Survival analysis was conducted using the Cox proportional hazards models to calculate a HR and 95% CI [231]. Time of survival was determined by the date the questionnaire was received until death or censor date. The censor date applied to patients who had died of a different disease, or for surviving patients. The last censor date in the current analysis for surviving patients was at 3rd October 2012. The risk of CVD incidence 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, sensitivity analysis and effect modifications were also conducted in a similar manner to Chapter 3 Section 3.3.3.4, with the exception of not exploring parental history of CVD. A summary of exclusion criteria and analysis plan is provided in Figure 4.1.

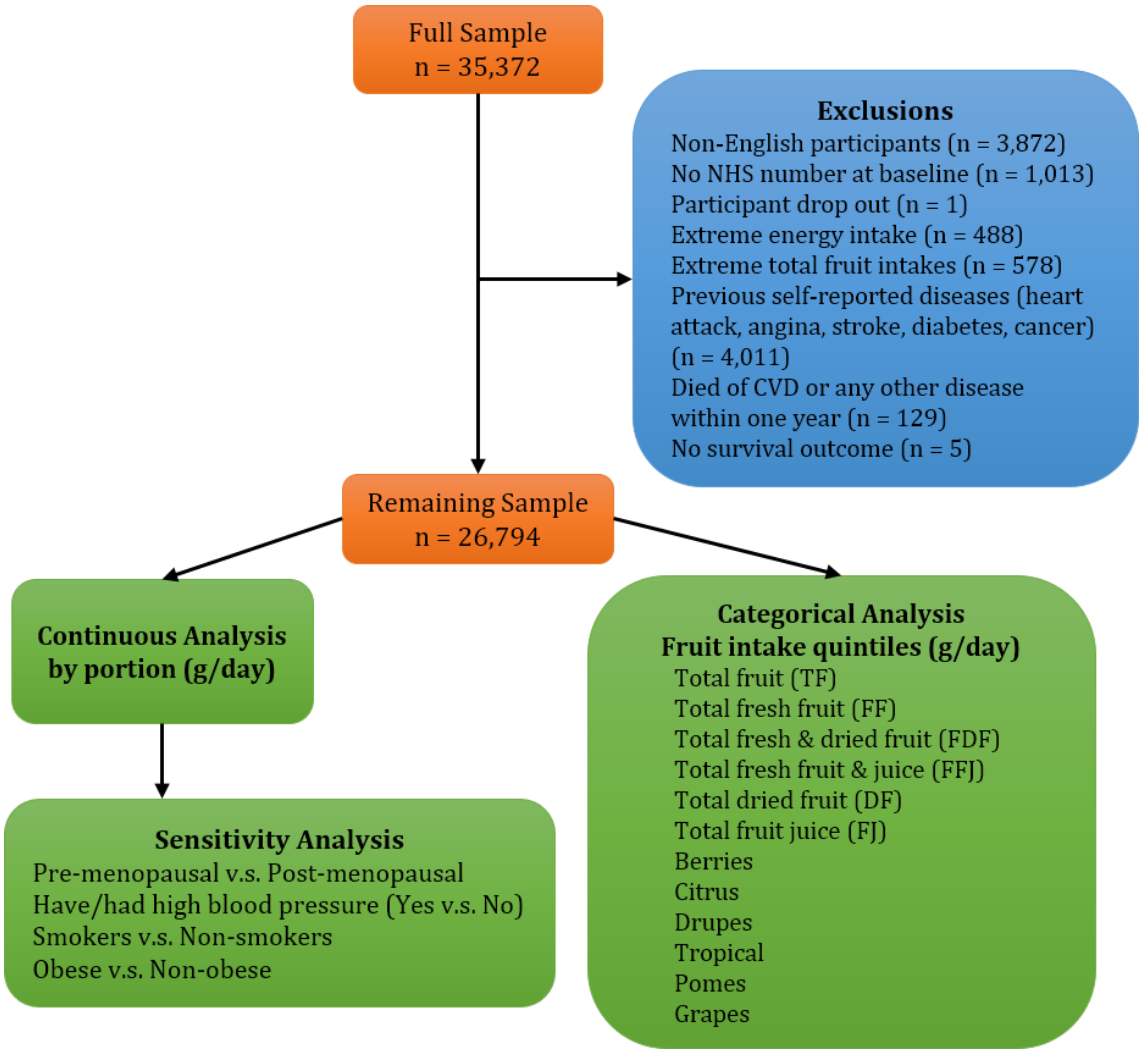


Figure 4.1 Summary flowchart of the current study exclusion criteria and analysis plan

4.3.3.5 Testing for statistical assumptions

Statistical assumptions were not tested in this chapter. However, because the statistical model applied here was highly similar to Chapter 3, in addition to the fulfilment of statistical assumptions proven in Chapter 3, statistical assumptions here were most likely fulfilled. Statistical significance was determined by 2-sided *p*-value of ≤0.05 for 95% CI. Stata version 12.0 [232] was used for all statistical analysis.

4.4 Results

4.4.1 Baseline characteristics

The baseline characteristics of participants were previously reported in Chapter 3 Section 3.4.1.

4.4.2 Survival Analysis

4.4.2.1 Full Cohort

After an average follow-up of 16.4. years, 291 CVD incidences were observed, where 152 were CHD related, and 142 were of stroke. In particular, there were 78 MI, 133 ACS and 193 CCS cases, and 58 HS, 63 IS and 48 USt cases. In summary, age-adjusted HR tended to be less than 1 in consumers versus non-consumers, with little evidence of dose response. Further adjustment for confounders attenuated relationships, and were all non-significant.

Table 4.4 provides the results for total CHD, total stroke and total CVD incidence. Previously significant associations found in Chapter 3 are mostly attenuated here, where the odd category of TF (302 – 571 g/day), FFJ (291 – 554 g/day) was associated with 42% to 56% lower total stroke incidence. Likewise, the second quintile of orange juice intake (116 – 145 g/day) was associated with 61% (95% CI 0.18 to 0.86) lower incidence of total CHD. In addition, incidence of total CVD was also 51% (95% CI 0.29 to 0.82) and 32% (95% CI 0.48 to 0.96) lower for second (~20 g/day) and fourth quintile (116 – 145 g/day) for the intake of orange juice. Interestingly, intake of pomes was associated with a higher risk of total CVD incidence (HR 1.10, 95% CI 1.00 to 1.20). By subtypes of CHD, every 80 g portion of berries was associated with 66% (95% CI 0.13 to 0.87) lower risk of CCE incidence (Table 4.2). This association was not found within Chapter 3 (as CHD mortality). Within subtypes of stroke, although moderate consumption of FDF (222 – 306 g/day) was significantly associated with a 60% (95% CI 0.17 to 0.94) lower risk of IS, and risk of USt incidence was 67% to 79% lower for participants consuming moderate amounts of TF (302 – 411 g/day)

and FFJ (291 – 554 g/day), results should be interpreted cautiously due to small case numbers (Table 4.3). This association was also not found within Chapter 3 (as stroke mortality) Moderate total citrus consumption was associated with a 71% to 72% (95% CI 0.08 to 1.00, 0.09 to 0.94 respectively) lower risk of USt. The intake of approximately 20 g of orange juice was also associated with 88% (95% CI 0.01 to 0.91) lower risk of HS, however, there was only one HS incidence case within that quantile. Every portion of pomes was also associated with 29% (95% CI 1.00 to 1.65) higher risk of USt.

Table 4.2 Total fruit, fruit subgroup intake and the risk of myocardial infarction, acute coronary syndrome and chronic coronary event incidence (expressed as HR and 95% CI)

	Intake (g/day)	Myocardial Infarction			Acute Coronary Syndrome			Chronic Coronary Event		
		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	13	1	1	15	1	1	25	1	1
Q2	200 – 302	14	0.67 (0.44, 1.01)	0.85 (0.39, 1.81)	25	0.70 (0.50, 0.97)	1.37 (0.72, 2.61)	32	0.68 (0.51, 0.90)	1.01 (0.60, 1.72)
Q3	302 – 411	19	0.84 (0.57, 1.23)	1.10 (0.54, 2.28)	33	0.86 (0.63, 1.17)	1.78 (0.96, 3.33)	52	0.93 (0.72, 1.20)	1.53 (0.94, 2.49)
Q4	411 – 571	18	0.59 (0.39, 0.90)	0.98 (0.46, 2.05)	28	0.62 (0.44, 0.86)	1.44 (0.76, 2.76)	42	0.77 (0.59, 1.00)	1.16 (0.69, 1.93)
Q5	571 – 3713	14	0.63 (0.42, 0.95)	0.81 (0.36, 1.84)	32	0.84 (0.62, 1.14)	1.85 (0.96, 3.57)	42	0.83 (0.64, 1.07)	1.21 (0.71, 2.06)
p trend			0.238	0.517		0.700	0.329		0.457	0.917
HR per 80 g/day		78	0.97 (0.94, 1.02)	0.97 (0.90, 1.05)	133	0.99 (0.96, 1.02)	1.03 (0.97, 1.08)	193	0.99 (0.97, 1.01)	1.00 (0.95, 1.04)
Fresh Fruit Intake										
Q1	0 – 133	14	1	1	17	1	1	22	1	1
Q2	133 – 210	12	0.97 (0.64, 1.46)	0.64 (0.29, 1.40)	21	0.99 (0.71, 1.36)	0.98 (0.51, 1.88)	36	0.76 (0.58, 1.00)	1.25 (0.73, 2.13)
Q3	210 – 292	21	0.84 (0.55, 1.28)	1.02 (0.51, 2.05)	37	0.81 (0.58, 1.14)	1.63 (0.90, 2.93)	48	0.86 (0.66, 1.12)	1.53 (0.91, 2.57)
Q4	292 – 418	17	0.88 (0.58, 1.33)	0.78 (0.37, 1.64)	28	0.93 (0.67, 1.28)	1.18 (0.63, 2.20)	44	0.83 (0.64, 1.08)	1.30 (0.76, 2.21)
Q5	418 – 3404	14	0.71 (0.46, 1.10)	0.67 (0.30, 1.52)	30	0.87 (0.63, 1.21)	1.39 (0.73, 2.64)	43	0.79 (0.61, 1.03)	1.31 (0.76, 2.29)
p trend			0.205	0.680		0.394	0.273		0.340	0.719
HR per 80 g/day		78	0.97 (0.92, 1.02)	0.98 (0.89, 1.08)	133	0.98 (0.95, 1.02)	1.03 (0.97, 1.10)	193	0.98 (0.95, 1.02)	1.01 (0.96, 1.07)
Fresh Fruit and Juice Intake										
Q1	0 – 190	14	1	1	17	1	1	23	1	1
Q2	190 – 291	13	0.60 (0.40, 0.91)	0.75 (0.35, 1.60)	24	0.65 (0.47, 0.90)	1.19 (0.64, 2.23)	34	0.74 (0.56, 0.99)	1.20 (0.71, 2.05)
Q3	291 – 397	20	0.79 (0.54, 1.15)	1.09 (0.54, 2.21)	33	0.85 (0.63, 1.16)	1.58 (0.87, 2.87)	50	1.01 (0.78, 1.31)	1.62 (0.98, 2.68)
Q4	397 – 554	17	0.59 (0.39, 0.88)	0.86 (0.41, 1.80)	27	0.59 (0.43, 0.82)	1.23 (0.65, 2.29)	47	0.83 (0.63, 1.08)	1.43 (0.85, 2.38)
Q5	554 – 3694	14	0.56 (0.37, 0.84)	0.78 (0.35, 1.75)	32	0.78 (0.58, 1.06)	1.68 (0.89, 3.15)	39	0.85 (0.65, 1.10)	1.26 (0.73, 2.19)
p trend			0.197	0.460		0.656	0.394		0.515	0.992
HR per 80 g/day		78	0.97 (0.93, 1.01)	0.97 (0.89, 1.05)	133	0.99 (0.96, 1.02)	1.02 (0.97, 1.08)	193	0.99 (0.97, 1.02)	1.00 (0.95, 1.05)
Fresh and Dried Fruit Intake										
Q1	0 – 142	13	1	1	17	1	1	24	1	1
Q2	142 – 222	12	0.88 (0.58, 1.34)	0.70 (0.31, 1.55)	20	0.88 (0.64, 1.22)	0.96 (0.50, 1.84)	34	0.72 (0.54, 0.94)	1.11 (0.65, 1.89)
Q3	222 – 306	23	0.86 (0.57, 1.31)	1.19 (0.59, 2.40)	38	0.77 (0.55, 1.07)	1.64 (0.91, 2.96)	48	0.83 (0.64, 1.08)	1.38 (0.83, 2.27)
Q4	306 – 437	17	0.84 (0.56, 1.27)	0.82 (0.38, 1.75)	31	0.89 (0.65, 1.22)	1.29 (0.69, 2.39)	44	0.80 (0.61, 1.03)	1.18 (0.70, 1.98)
Q5	437 – 3423	13	0.67 (0.43, 1.03)	0.65 (0.28, 1.51)	27	0.77 (0.55, 1.06)	1.21 (0.63, 2.34)	43	0.75 (0.57, 0.97)	1.18 (0.69, 2.03)
p trend			0.256	0.756		0.442	0.215		0.290	0.811
HR per 80 g/day		78	0.97 (0.92, 1.02)	0.98 (0.90, 1.08)	133	0.98 (0.95, 1.02)	1.04 (0.98, 1.10)	193	0.98 (0.95, 1.01)	1.01 (0.95, 1.06)

(Table 4.2 continued)

	Intake (g/day)	Myocardial Infarction			Acute Coronary Syndrome			Chronic Coronary Event		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Dried Fruit Intake										
Q1	0 – 1.2	11	1	1	20	1	1	33	1	1
Q2	1.3 – 2.8	11	0.99 (0.63, 1.57)	0.92 (0.40, 2.14)	16	0.90 (0.64, 1.28)	0.73 (0.38, 1.41)	32	0.91 (0.69, 1.20)	0.85 (0.52, 1.39)
Q3	2.8 – 5.1	18	1.16 (0.75, 1.80)	1.25 (0.59, 2.67)	32	1.08 (0.78, 1.49)	1.25 (0.71, 2.20)	36	1.02 (0.78, 1.33)	0.82 (0.51, 1.31)
Q4	5.1 – 12.5	21	1.11 (0.72, 1.71)	1.28 (0.61, 2.70)	32	0.97 (0.70, 1.35)	1.14 (0.64, 2.01)	47	1.02 (0.78, 1.33)	0.95 (0.60, 1.49)
Q5	12.5 – 469	17	1.08 (0.70, 1.64)	0.89 (0.41, 1.96)	33	0.92 (0.67, 1.28)	1.05 (0.59, 1.87)	45	0.83 (0.64, 1.09)	0.80 (0.50, 1.28)
p trend			0.362	0.389		0.552	0.117		0.198	0.283
HR per 25 g/day		78	1.05 (0.94, 1.17)	1.09 (0.90, 1.32)	133	1.03 (0.93, 1.13)	1.11 (0.97, 1.27)	193	0.93 (0.83, 1.04)	0.89 (0.72, 1.10)
Fruit Juice Intake										
Q1	0 – 10	21	1	1	34	1	1	45	1	1
Q2	13 – 30	16	1.01 (0.68, 1.49)	1.12 (0.58, 2.16)	25	1.08 (0.80, 1.47)	1.04 (0.62, 1.76)	34	0.83 (0.63, 1.08)	1.03 (0.66, 1.61)
Q3	41 – 116	13	0.73 (0.50, 1.08)	0.65 (0.33, 1.31)	22	0.76 (0.56, 1.03)	0.66 (0.38, 1.13)	45	0.81 (0.64, 1.03)	0.97 (0.64, 1.47)
Q4	119 – 148	14	0.76 (0.50, 1.16)	0.95 (0.48, 1.88)	23	0.79 (0.57, 1.10)	0.97 (0.57, 1.65)	34	0.77 (0.59, 1.01)	1.05 (0.67, 1.65)
Q5	155 – 1740	14	0.89 (0.61, 1.31)	0.87 (0.44, 1.74)	29	0.98 (0.73, 1.32)	1.09 (0.66, 1.81)	35	0.88 (0.69, 1.13)	0.92 (0.58, 1.44)
p trend			0.582	0.409		0.560	0.902		0.761	0.516
HR per 125 g/day		78	0.96 (0.83, 1.11)	0.89 (0.67, 1.18)	133	1.03 (0.93, 1.14)	0.99 (0.81, 1.20)	193	1.01 (0.93, 1.10)	0.95 (0.80, 1.12)
Total Citrus Intake										
Non-Consumers	0	2	1	1	4	1	1	12	1	1
Q1	1.8 – 22	22	1.18 (0.62, 2.25)	2.58 (0.60, 11.0)	36	1.01 (0.62, 1.64)	1.91 (0.68, 5.39)	37	0.78 (0.53, 1.14)	0.63 (0.33, 1.22)
Q2	23 – 60	12	1.00 (0.51, 1.95)	1.70 (0.38, 7.63)	21	0.93 (0.57, 1.54)	1.27 (0.43, 3.73)	32	0.68 (0.45, 1.00)	0.61 (0.31, 1.18)
Q3	64 – 102	15	0.87 (0.44, 1.70)	1.76 (0.40, 7.74)	23	0.73 (0.44, 1.21)	1.21 (0.42, 3.52)	35	0.72 (0.49, 1.07)	0.59 (0.31, 1.14)
Q4	112 – 182	16	0.87 (0.45, 1.68)	1.78 (0.41, 7.82)	29	0.76 (0.46, 1.25)	1.41 (0.49, 1.04)	54	0.70 (0.47, 1.02)	0.82 (0.43, 1.54)
Q5	190 – 1422	11	1.06 (0.54, 2.09)	1.82 (0.40, 8.33)	20	0.94 (0.57, 1.57)	1.38 (0.47, 4.09)	23	0.74 (0.50, 1.11)	0.49 (0.24, 1.00)
p trend			0.671	0.451		0.999	0.380		0.668	0.350
HR per 80g/day		78	0.98 (0.89, 1.08)	0.93 (0.76, 1.13)	133	1.00 (0.93, 1.08)	0.94 (0.81, 1.08)	193	0.99 (0.92, 1.05)	0.94 (0.84, 1.06)
Citrus Fruit Intake										
Non-Consumers	0	5	1	1	8	1	1	18	1	1
Q1	1.8 – 6.4	22	1.18 (0.69, 2.03)	1.29 (0.49, 3.43)	33	0.93 (0.63, 1.38)	1.13 (0.52, 2.46)	44	0.72 (0.53, 0.96)	0.65 (0.37, 1.13)
Q2	12.9	8	0.90 (0.49, 1.65)	0.89 (0.29, 2.74)	17	0.74 (0.47, 1.16)	1.07 (0.46, 2.49)	28	0.60 (0.43, 0.85)	0.74 (0.41, 1.35)
Q3	36.8	24	1.20 (0.69, 2.07)	1.70 (0.65, 4.50)	40	0.97 (0.65, 1.45)	1.62 (0.76, 3.48)	53	0.64 (0.47, 0.88)	0.90 (0.53, 1.55)
Q4	73.6	7	1.19 (0.64, 2.23)	1.28 (0.40, 4.08)	13	0.99 (0.62, 1.57)	1.32 (0.54, 3.22)	17	0.72 (0.50, 1.04)	0.71 (0.36, 1.39)
Q5	92 – 552	12	1.02 (0.58, 1.80)	0.95 (0.33, 2.77)	22	0.88 (0.58, 1.33)	0.97 (0.43, 2.22)	33	0.67 (0.48, 0.91)	0.62 (0.35, 1.12)
p trend			0.968	0.410		0.925	0.319		0.392	0.184
HR per 80 g/day		78	1.00 (0.82, 1.21)	0.84 (0.55, 1.27)	133	1.01 (0.87, 1.17)	0.86 (0.63, 1.16)	193	0.94 (0.83, 1.08)	0.84 (0.65, 1.09)

(Table 4.2 continued)

	Intake (g/day)	Myocardial Infarction			Acute Coronary Syndrome			Chronic Coronary Event		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Orange Juice Intake										
Non-Consumers	0	11	1	1	23	1	1	39	1	1
Q1	2.9 – 10.1	27	0.91 (0.61, 1.35)	1.20 (0.59, 2.44)	44	0.95 (0.70, 1.29)	0.89 (0.53, 1.48)	45	0.71 (0.55, 0.92)	0.52 (0.34, 0.80)
Q2	20.3	5	1.02 (0.62, 1.68)	0.71 (0.24, 2.07)	7	0.84 (0.56, 1.26)	0.42 (0.18, 0.99)	18	0.67 (0.48, 0.94)	0.60 (0.34, 1.05)
Q3	58	11	0.77 (0.47, 1.24)	0.94 (0.40, 2.19)	18	0.82 (0.57, 1.18)	0.69 (0.37, 1.28)	29	0.72 (0.54, 0.97)	0.62 (0.38, 1.01)
Q4	116 – 145	23	0.93 (0.62, 1.39)	1.19 (0.57, 2.46)	38	0.85 (0.62, 1.16)	0.87 (0.52, 1.47)	58	0.78 (0.61, 1.00)	0.75 (0.50, 1.13)
Q5	362 – 870	1	0.63 (0.25, 1.61)	0.49 (0.06, 3.80)	3	0.90 (0.48, 1.67)	0.62 (0.18, 2.07)	4	0.79 (0.48, 1.31)	0.44 (0.16, 1.24)
p trend			0.612	0.676		0.952	0.645		0.997	0.732
HR per 250 g/day		78	0.90 (0.61, 1.34)	0.86 (0.41, 1.77)	133	0.99 (0.74, 1.33)	0.88 (0.51, 1.51)	193	1.00 (0.78, 1.27)	0.93 (0.60, 1.43)
Total Berries Intake										
Q1	0 – 1.6	12	1	1	18	1	1	30	1	1
Q2	1.7 – 4.3	22	0.86 (0.59, 1.26)	1.33 (0.66, 2.69)	31	0.87 (0.64, 1.18)	1.24 (0.69, 2.22)	45	1.00 (0.77, 1.31)	1.06 (0.67, 1.69)
Q3	4.3 – 8.0	12	0.66 (0.42, 1.02)	0.91 (0.41, 2.04)	27	0.88 (0.63, 1.22)	1.35 (0.74, 2.46)	41	1.13 (0.86, 1.48)	1.20 (0.74, 1.93)
Q4	8.1 – 15.3	17	0.69 (0.46, 1.02)	0.91 (0.43, 1.92)	30	0.77 (0.56, 1.05)	1.06 (0.59, 1.93)	44	0.98 (0.75, 1.27)	0.90 (0.56, 1.45)
Q5	15.4 – 365	15	0.64 (0.43, 0.97)	0.85 (0.38, 1.89)	27	0.71 (0.51, 0.98)	0.97 (0.52, 1.82)	33	0.75 (0.56, 1.00)	0.65 (0.39, 1.10)
p trend			0.087	0.452		0.155	0.973		0.439	0.024
HR per 80 g/day		78	0.53 (0.25, 1.10)	0.64 (0.20, 2.06)	133	0.72 (0.46, 1.13)	0.99 (0.59, 1.66)	193	0.89 (0.66, 1.19)	0.33 (0.13, 0.87)
Total Pomes Intake										
Q1	0 – 19	19	1	1	25	1	1	38	1	1
Q2	24 – 55	11	0.81 (0.55, 1.20)	0.54 (0.25, 1.14)	22	0.88 (0.65, 1.19)	0.80 (0.45, 1.43)	30	0.86 (0.67, 1.11)	0.68 (0.42, 1.10)
Q3	62 – 102	20	0.84 (0.56, 1.25)	1.03 (0.54, 1.96)	31	0.82 (0.59, 1.12)	1.21 (0.70, 2.06)	40	0.85 (0.65, 1.10)	0.97 (0.62, 1.53)
Q4	108 – 133	10	0.72 (0.48, 1.10)	0.55 (0.25, 1.21)	20	0.70 (0.50, 0.98)	0.83 (0.45, 1.52)	35	0.75 (0.57, 0.99)	0.89 (0.55, 1.43)
Q5	139 – 1392	18	0.63 (0.42, 0.95)	0.85 (0.41, 1.73)	35	0.83 (0.61, 1.13)	1.23 (0.70, 2.16)	50	0.82 (0.63, 1.05)	1.06 (0.67, 1.69)
p trend			0.104	0.647		0.363	0.241		0.162	0.273
HR per 80 g/day		78	0.90 (0.80, 1.02)	1.04 (0.87, 1.26)	133	0.96 (0.88, 1.05)	1.08 (0.95, 1.23)	193	0.95 (0.88, 1.02)	1.06 (0.95, 1.19)
Total Tropical Intake										
Q1	0 – 18	17	1	1	24	1	1	33	1	1
Q2	18 – 45	20	0.84 (0.57, 1.23)	1.12 (0.59, 2.15)	32	0.91 (0.67, 1.24)	1.26 (0.74, 2.14)	40	0.99 (0.76, 1.29)	1.14 (0.71, 1.80)
Q3	45 – 76	17	0.72 (0.47, 1.10)	1.08 (0.55, 2.13)	30	0.99 (0.72, 1.36)	1.35 (0.79, 2.32)	38	1.12 (0.86, 1.47)	1.24 (0.78, 1.99)
Q4	76 – 107	13	0.73 (0.49, 1.09)	0.68 (0.33, 1.41)	25	0.87 (0.64, 1.19)	0.94 (0.53, 1.66)	35	0.87 (0.67, 1.14)	0.96 (0.59, 1.55)
Q5	107 – 1235	11	0.78 (0.52, 1.16)	0.64 (0.29, 1.43)	22	0.79 (0.67, 1.24)	0.88 (0.48, 1.61)	47	1.03 (0.79, 1.34)	1.44 (0.89, 2.32)
p trend			0.323	0.386		0.127	0.495		0.643	0.107
HR per 80 g/day		78	0.91 (0.77, 1.09)	0.86 (0.60, 1.22)	133	0.90 (0.78, 1.03)	0.92 (0.72, 1.17)	193	0.97 (0.88, 1.08)	1.16 (0.97, 1.38)

(Table 4.2 continued)

	Intake (g/day)	Myocardial Infarction			Acute Coronary Syndrome			Chronic Coronary Event		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Drupes Intake										
Q1	0 – 1.2	15	1	1	20	1	1	30	1	1
Q2	1.2 – 2.7	14	1.01 (0.68, 1.51)	0.94 (0.45, 1.96)	24	1.15 (0.83, 1.59)	1.17 (0.64, 2.12)	45	1.17 (0.90, 1.52)	1.40 (0.88, 2.22)
Q3	2.7 – 5.9	13	0.68 (0.44, 1.06)	0.84 (0.40, 1.79)	27	0.89 (0.64, 1.26)	1.23 (0.69, 2.22)	38	1.03 (0.79, 1.35)	1.07 (0.66, 1.74)
Q4	5.9 – 10.5	19	1.02 (0.68, 1.53)	1.28 (0.64, 2.60)	33	1.26 (0.92, 1.73)	1.55 (0.88, 2.75)	48	1.04 (0.80, 1.37)	1.35 (0.85, 2.16)
Q5	10.5 – 166	17	1.00 (0.67, 1.50)	1.33 (0.61, 2.91)	29	1.10 (0.79, 1.53)	1.42 (0.76, 2.66)	32	1.02 (0.78, 1.34)	0.85 (0.49, 1.46)
p trend			0.375	0.724		0.942	0.423		0.763	0.082
HR per 80g/day		78	0.56 (0.15, 2.02)	1.50 (0.15, 14.6)	133	0.97 (0.40, 2.31)	1.85 (0.41, 8.29)	193	0.89 (0.43, 1.86)	0.22 (0.04, 1.21)
Grapes Intake										
Q1	0 – 2	21	1	1	31	1	1	43	1	1
Q2	7	15	0.84 (0.57, 1.24)	0.65 (0.34, 1.28)	26	0.81 (0.60, 1.10)	0.73 (0.43, 1.24)	42	0.88 (0.69, 1.12)	0.83 (0.54, 1.27)
Q3	14	16	1.02 (0.68, 1.53)	1.09 (0.56, 2.11)	25	0.97 (0.71, 1.33)	1.05 (0.61, 1.79)	27	0.78 (0.60, 1.02)	0.76 (0.47, 1.24)
Q4	40	16	1.01 (0.68, 1.51)	0.96 (0.50, 1.88)	32	1.04 (0.77, 1.42)	1.22 (0.73, 2.02)	45	0.96 (0.75, 1.24)	1.20 (0.78, 1.84)
Q5	80 – 600	10	1.09 (0.71, 1.67)	0.91 (0.41, 2.02)	19	1.13 (0.81, 1.57)	1.10 (0.60, 2.00)	36	0.98 (0.74, 1.29)	1.54 (0.96, 2.46)
p trend			0.863	0.688		0.963	0.739		0.664	0.066
HR per 80g/day		78	0.98 (0.81, 1.20)	0.91 (0.58, 1.43)	133	1.00 (0.86, 1.16)	1.04 (0.81, 1.35)	193	1.03 (0.91, 1.15)	1.17 (0.99, 1.39)

[a] Cases 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

Table 4.3 Total fruit, fruit subgroup intake and the risk of haemorrhagic, ischaemic and unclassified stroke incidence (expressed as HR and 95% CI)

	Intake (g/day)	Haemorrhagic Stroke			Ischaemic Stroke			Unclassified Stroke		
		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	10	1	1	17	1	1	15	1	1
Q2	200 – 302	15	1.05 (0.62, 1.77)	1.35 (0.60, 3.03)	11	0.85 (0.56, 1.30)	0.48 (0.22, 1.03)	9	0.40 (0.23, 0.72)	0.52 (0.21, 1.26)
Q3	302 – 411	11	1.02 (0.60, 1.72)	0.97 (0.40, 2.34)	12	0.60 (0.38, 0.95)	0.50 (0.23, 1.07)	6	0.44 (0.25, 0.76)	0.29 (0.10, 0.82)
Q4	411 – 571	7	0.69 (0.39, 1.22)	0.61 (0.22, 1.66)	13	0.53 (0.33, 0.85)	0.51 (0.24, 1.09)	8	0.54 (0.33, 0.89)	0.33 (0.12, 0.88)
Q5	571 – 3713	10	0.72 (0.41, 1.26)	0.98 (0.38, 2.54)	13	0.53 (0.33, 0.84)	0.56 (0.25, 1.24)	10	0.41 (0.24, 0.70)	0.64 (0.25, 1.68)
p trend			0.126	0.710		0.037	0.667		0.252	0.923
HR per 80 g/day		53	0.96 (0.90, 1.01)	0.98 (0.89, 1.08)	66	0.95 (0.90, 1.00)	0.98 (0.90, 1.07)	48	0.95 (0.88, 1.03)	0.99 (0.82, 1.19)
Fresh Fruit Intake										
Q1	0 – 133	8	1	1	14	1	1	11	1	1
Q2	133 – 210	13	1.09 (0.63, 1.89)	1.46 (0.60, 3.56)	15	0.76 (0.50, 1.17)	0.78 (0.37, 1.63)	11	0.45 (0.26, 0.78)	0.63 (0.25, 1.57)
Q3	210 – 292	12	1.14 (0.66, 1.95)	1.30 (0.52, 3.27)	10	0.56 (0.35, 0.88)	0.45 (0.20, 1.04)	8	0.59 (0.35, 1.00)	0.52 (0.20, 1.35)
Q4	292 – 418	11	1.01 (0.58, 1.74)	1.18 (0.45, 3.10)	12	0.45 (0.28, 0.73)	0.52 (0.23, 1.17)	10	0.31 (0.17, 0.58)	0.46 (0.17, 1.24)
Q5	418 – 3404	9	0.64 (0.35, 1.17)	1.09 (0.39, 3.04)	15	0.51 (0.32, 0.80)	0.73 (0.33, 1.63)	8	0.54 (0.32, 0.90)	0.59 (0.21, 1.70)
p trend			0.202	0.641		0.028	0.728		0.484	0.923
HR per 80 g/day		53	0.95 (0.89, 1.02)	0.97 (0.86, 1.10)	66	0.93 (0.87, 0.99)	0.98 (0.88, 1.09)	48	0.96 (0.86, 1.07)	0.99 (0.77, 1.26)
Fresh Fruit and Juice Intake										
Q1	0 – 190	13	1	1	17	1	1	16	1	1
Q2	190 – 291	14	0.93 (0.56, 1.56)	0.96 (0.45, 2.07)	13	0.85 (0.56, 1.28)	0.59 (0.28, 1.22)	9	0.42 (0.24, 0.73)	0.51 (0.21, 1.20)
Q3	291 – 397	9	0.88 (0.52, 1.47)	0.60 (0.25, 1.43)	11	0.58 (0.36, 0.92)	0.47 (0.21, 1.02)	5	0.35 (0.20, 0.63)	0.21 (0.07, 0.67)
Q4	397 – 554	7	0.56 (0.32, 1.00)	0.45 (0.17, 1.18)	12	0.49 (0.30, 0.78)	0.47 (0.22, 1.02)	8	0.55 (0.34, 0.91)	0.30 (0.12, 0.79)
Q5	554 – 3694	10	0.65 (0.37, 1.12)	0.74 (0.30, 1.83)	13	0.52 (0.33, 0.83)	0.59 (0.27, 1.30)	10	0.39 (0.23, 0.68)	0.64 (0.25, 1.63)
p trend			0.132	0.664		0.041	0.723		0.288	0.966
HR per 80 g/day		53	0.96 (0.90, 1.01)	0.98 (0.88, 1.08)	66	0.95 (0.90, 1.00)	0.98 (0.90, 1.07)	48	0.95 (0.88, 1.04)	0.99 (0.82, 1.20)
Fresh and Dried Fruit Intake										
Q1	0 – 142	10	1	1	14	1	1	10	1	1
Q2	142 – 222	10	0.83 (0.48, 1.44)	0.92 (0.38, 2.23)	16	0.76 (0.50, 1.15)	0.83 (0.40, 1.72)	11	0.43 (0.25, 0.76)	0.76 (0.32, 1.84)
Q3	222 – 306	13	1.02 (0.61, 1.72)	1.10 (0.47, 2.58)	9	0.47 (0.29, 0.75)	0.40 (0.17, 0.94)	8	0.54 (0.32, 0.92)	0.51 (0.19, 1.35)
Q4	306 – 437	10	0.81 (0.47, 1.40)	0.85 (0.33, 2.13)	11	0.46 (0.29, 0.74)	0.47 (0.20, 1.07)	11	0.36 (0.20, 0.64)	0.59 (0.23, 1.53)
Q5	437 – 3423	10	0.61 (0.34, 1.10)	0.94 (0.36, 2.47)	16	0.49 (0.31, 0.77)	0.75 (0.34, 1.66)	8	0.51 (0.30, 0.86)	0.64 (0.22, 1.81)
p trend			0.190	0.697		0.024	0.661		0.427	0.874
HR per 80 g/day		53	0.95 (0.89, 1.02)	0.98 (0.87, 1.10)	66	0.93 (0.87, 0.99)	0.98 (0.88, 1.08)	48	0.96 (0.86, 1.06)	0.98 (0.77, 1.24)

(Table 4.3 continued)

	Intake (g/day)	Haemorrhagic Stroke			Ischaemic Stroke			Unclassified Stroke		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Dried Fruit Intake										
Q1	0 – 1.2	7	1	1	12	1	1	11	1	1
Q2	1.3 – 2.8	5	0.96 (0.53, 1.74)	0.69 (0.22, 2.19)	11	0.76 (0.47, 1.22)	0.81 (0.35, 1.83)	4	0.64 (0.36, 1.15)	0.34 (0.10, 1.13)
Q3	2.8 – 5.1	15	1.21 (0.70, 2.11)	1.92 (0.77, 4.74)	16	0.99 (0.64, 1.53)	0.98 (0.46, 2.08)	11	0.81 (0.47, 1.39)	0.83 (0.35, 1.97)
Q4	5.1 – 12.5	11	1.09 (0.62, 1.90)	1.33 (0.50, 3.49)	15	0.69 (0.43, 1.10)	0.79 (0.36, 1.72)	13	0.61 (0.35, 1.06)	0.82 (0.37, 1.80)
Q5	12.5 – 469	15	1.06 (0.61, 1.84)	1.73 (0.68, 4.41)	12	0.58 (0.36, 0.93)	0.54 (0.23, 1.23)	9	0.62 (0.36, 1.06)	0.52 (0.20, 1.35)
p trend			0.499	0.546		0.296	0.369		0.124	0.324
HR per 25 g/day		53	0.92 (0.74, 1.16)	1.08 (0.85, 1.37)	66	0.90 (0.74, 1.10)	0.84 (0.57, 1.23)	48	0.79 (0.58, 1.07)	0.77 (0.45, 1.30)
Fruit Juice Intake										
Q1	0 – 10	20	1	1	20	1	1	16	1	1
Q2	13 – 30	8	0.56 (0.32, 0.99)	0.57 (0.25, 1.29)	13	0.78 (0.49, 1.25)	1.01 (0.50, 2.04)	9	0.94 (0.55, 1.61)	1.13 (0.49, 2.63)
Q3	41 – 116	11	0.79 (0.50, 1.24)	0.57 (0.27, 1.20)	15	0.93 (0.63, 1.39)	0.86 (0.44, 1.70)	11	0.81 (0.50, 1.31)	0.77 (0.33, 1.81)
Q4	119 – 148	7	0.55 (0.31, 0.97)	0.55 (0.23, 1.32)	7	0.66 (0.41, 1.06)	0.52 (0.22, 1.23)	6	0.57 (0.32, 1.01)	0.63 (0.23, 1.69)
Q5	155 – 1740	7	0.56 (0.33,0.96)	0.47 (0.20, 1.14)	11	0.72 (0.46, 1.12)	0.77 (0.36, 1.64)	6	0.58 (0.33, 1.02)	0.61 (0.23, 1.66)
p trend			0.305	0.918		0.602	0.894		0.247	0.929
HR per 125 g/day		53	0.90 (0.73, 1.10)	0.98 (0.72, 1.34)	66	0.96 (0.81, 1.12)	0.98 (0.74, 1.30)	48	0.85 (0.65, 1.12)	1.02 (0.60, 1.74)
Total Citrus Intake										
Non-Consumers	0	2	1	1	5	1	1	6	1	1
Q1	1.8 – 22	15	1.38 (0.58, 3.27)	1.50 (0.34, 6.61)	15	0.67 (0.36, 1.23)	0.68 (0.24, 1.88)	11	0.50 (0.25, 1.00)	0.43 (0.15, 1.25)
Q2	23 – 60	8	0.97 (0.40, 2.40)	0.99 (0.21, 4.71)	11	0.85 (0.46, 1.57)	0.62 (0.21, 1.80)	6	0.35 (0.16, 0.76)	0.28 (0.08, 1.00)
Q3	64 – 102	14	1.15 (0.48, 2.78)	1.61 (0.36, 7.16)	14	0.60 (0.32, 1.12)	0.65 (0.23, 1.83)	12	0.63 (0.32, 1.23)	0.46 (0.15, 1.41)
Q4	112 – 182	6	0.68 (0.27, 1.70)	0.63 (0.12, 3.15)	14	0.60 (0.33, 1.12)	0.62 (0.22, 1.73)	8	0.52 (0.26, 1.01)	0.29 (0.09, 0.94)
Q5	190 – 1422	8	0.81 (0.32, 2.08)	1.42 (0.29, 6.83)	7	0.39 (0.19, 0.80)	0.46 (0.14, 1.49)	5	0.34 (0.15, 0.74)	0.36 (0.09, 1.41)
p trend			0.107	0.517		0.131	0.979		0.553	0.977
HR per 80g/day		53	0.88 (0.76, 1.03)	0.92 (0.72, 1.18)	66	0.91 (0.80, 1.03)	1.00 (0.82, 1.22)	48	0.95 (0.80, 1.13)	1.01 (0.63, 1.60)
Citrus Fruit Intake										
Non-Consumers	0	4	1	1	5	1	1	6	1	1
Q1	1.8 – 6.4	20	1.17 (0.62, 2.22)	1.41 (0.48, 4.16)	22	1.08 (0.63, 1.87)	1.31 (0.49, 3.49)	15	0.96 (0.50, 1.83)	0.80 (0.28, 2.27)
Q2	12.9	5	0.62 (0.29, 1.35)	0.67 (0.18, 2.50)	6	0.69 (0.36, 1.33)	0.67 (0.20, 2.21)	8	1.03 (0.51, 2.08)	0.93 (0.30, 2.90)
Q3	36.8	9	0.80 (0.41, 1.59)	0.81 (0.24, 2.64)	16	1.06 (0.61, 1.85)	1.18 (0.43, 3.25)	9	0.54 (0.26, 1.12)	0.51 (0.16, 1.64)
Q4	73.6	8	1.06 (0.50, 2.27)	1.92 (0.57, 6.52)	7	0.70 (0.34, 1.44)	1.30 (0.41, 4.15)	1	0.83 (0.36, 1.87)	0.23 (0.02, 2.11)
Q5	92 – 552	7	0.56 (0.26, 1.19)	0.80 (0.23, 2.83)	10	0.70 (0.38, 1.28)	0.80 (0.27, 2.38)	9	0.95 (0.49, 1.86)	0.65 (0.19, 2.27)
p trend			0.232	0.649		0.191	0.612		0.782	0.463
HR per 80 g/day		53	0.83 (0.61, 1.12)	0.89 (0.53, 1.48)	66	0.84 (0.66, 1.09)	0.89 (0.58, 1.38)	48	0.96 (0.71, 1.29)	0.75 (0.35, 1.62)

(Table 4.3 continued)

	Intake (g/day)	Haemorrhagic Stroke			Ischaemic Stroke			Unclassified Stroke		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Orange Juice Intake										
Non-Consumers	0	11	1	1	12	1	1	14	1	1
Q1	2.9 – 10.1	18	1.07 (0.63, 1.81)	0.75 (0.35, 1.59)	22	0.62 (0.41, 0.94)	0.91 (0.45, 1.86)	11	0.56 (0.34, 0.93)	0.48 (0.21, 1.11)
Q2	20.3	1	0.73 (0.35, 1.51)	0.12 (0.01, 0.91)	9	0.80 (0.48, 1.36)	1.29 (0.54, 3.11)	4	0.62 (0.31, 1.24)	0.48 (0.13, 1.77)
Q3	58	12	1.31 (0.74, 2.32)	0.97 (0.42, 2.23)	8	0.63 (0.39, 1.04)	0.68 (0.27, 1.67)	8	0.59 (0.32, 1.07)	0.63 (0.24, 1.69)
Q4	116 – 145	9	0.67 (0.38, 1.20)	0.46 (0.19, 1.14)	12	0.52 (0.34, 0.81)	0.59 (0.26, 1.32)	10	0.54 (0.33, 0.90)	0.48 (0.19, 1.19)
Q5	362 – 870	2	0.65 (0.19, 2.19)	0.91 (0.20, 4.17)	3	0.71 (0.30, 1.67)	1.57 (0.43, 5.65)	1	0.47 (0.14, 1.55)	0.72 (0.09, 5.63)
p trend			0.204	0.607		0.283	0.784		0.588	0.715
HR per 250 g/day		53	0.69 (0.38, 1.23)	0.79 (0.31, 1.96)	66	0.77 (0.48, 1.24)	1.10 (0.54, 2.26)	48	0.81 (0.38, 1.72)	1.30 (0.31, 5.37)
Total Berries Intake										
Q1	0 – 1.6	13	1	1	11	1	1	7	1	1
Q2	1.7 – 4.3	7	0.53 (0.30, 0.95)	0.43 (0.17, 1.09)	17	0.83 (0.54, 1.28)	1.12 (0.53, 2.41)	16	1.57 (0.91, 2.70)	2.68 (1.01, 7.06)
Q3	4.3 – 8.0	6	0.76 (0.44, 1.34)	0.51 (0.19, 1.36)	14	0.73 (0.45, 1.18)	1.20 (0.54, 2.67)	7	0.56 (0.27, 1.17)	1.46 (0.46, 4.59)
Q4	8.1 – 15.3	9	0.79 (0.47, 1.31)	0.59 (0.24, 1.41)	8	0.56 (0.35, 0.90)	0.48 (0.19, 1.20)	8	1.02 (0.57, 1.82)	1.03 (0.34, 3.11)
Q5	15.4 – 365	18	0.95 (0.57, 1.56)	1.43 (0.65, 3.14)	16	0.75 (0.49, 1.17)	1.05 (0.47, 2.36)	10	0.89 (0.49, 1.61)	1.60 (0.58, 4.41)
p trend			0.901	0.329		0.565	0.243		0.462	0.410
HR per 80 g/day		53	1.03 (0.63, 1.69)	1.34 (0.74, 2.41)	66	0.85 (0.49, 1.47)	0.36 (0.06, 2.00)	48	0.74 (0.34, 1.63)	0.53 (0.11, 2.42)
Total Pomes Intake										
Q1	0 – 19	13	1	1	15	1	1	14	1	1
Q2	24 – 55	14	0.78 (0.48, 1.27)	1.03 (0.48, 2.21)	16	1.00 (0.65, 1.53)	0.99 (0.49, 2.03)	8	0.59 (0.34, 1.02)	0.66 (0.27, 1.61)
Q3	62 – 102	9	0.68 (0.40, 1.15)	0.71 (0.30, 1.70)	12	0.69 (0.42, 1.12)	0.78 (0.36, 1.70)	5	0.55 (0.31, 0.97)	0.41 (0.14, 1.18)
Q4	108 – 133	7	0.42 (0.23, 0.78)	0.58 (0.23, 1.51)	6	0.77 (0.48, 1.24)	0.40 (0.15, 1.06)	11	0.72 (0.42, 1.23)	0.95 (0.43, 2.06)
Q5	139 – 1392	10	0.72 (0.44, 1.19)	0.72 (0.29, 1.80)	17	0.73 (0.46, 1.14)	1.04 (0.48, 2.24)	10	0.66 (0.39, 1.10)	0.73 (0.33, 1.63)
p trend			0.214	0.234		0.447	0.491		0.783	0.046
HR per 80 g/day		53	0.90 (0.77, 1.06)	0.83 (0.62, 1.12)	66	0.95 (0.84, 1.08)	1.07 (0.88, 1.30)	48	1.03 (0.85, 1.24)	1.29 (1.00, 1.65)
Total Tropical Intake										
Q1	0 – 18	14	1	1	13	1	1	15	1	1
Q2	18 – 45	5	0.82 (0.47, 1.44)	0.36 (0.13, 1.02)	18	0.81 (0.53, 1.22)	1.31 (0.64, 2.68)	11	0.82 (0.50, 1.35)	0.68 (0.31, 1.50)
Q3	45 – 76	8	0.77 (0.42, 1.40)	0.75 (0.31, 1.82)	10	0.59 (0.37, 0.96)	0.88 (0.38, 2.02)	8	0.63 (0.35, 1.13)	0.54 (0.22, 1.33)
Q4	76 – 107	15	1.19 (0.72, 1.97)	1.21 (0.57, 2.57)	13	0.70 (0.46, 1.07)	0.90 (0.41, 1.97)	9	0.53 (0.31, 0.92)	0.47 (0.19, 1.18)
Q5	107 – 1235	11	1.06 (0.63, 1.80)	1.18 (0.50, 2.82)	12	0.50 (0.31, 0.81)	1.03 (0.45, 2.39)	5	0.72 (0.42, 1.24)	0.47 (0.17, 1.28)
p trend			0.961	0.330		0.016	0.715		0.627	0.819
HR per 80 g/day		53	1.00 (0.82, 1.24)	1.20 (0.83, 1.72)	66	0.76 (0.6, 0.95)	0.93 (0.64, 1.35)	48	0.91 (0.64, 1.31)	0.90 (0.35, 2.27)

(Table 4.3 continued)

	Intake (g/day)	Haemorrhagic Stroke			Ischaemic Stroke			Unclassified Stroke		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Drupes Intake										
Q1	0 – 1.2	12	1	1	14	1	1	12	1	1
Q2	1.2 – 2.7	11	1.14 (0.69, 1.90)	0.93 (0.41, 2.11)	12	1.04 (0.68, 1.61)	0.86 (0.39, 1.86)	14	0.90 (0.54, 1.48)	1.27 (0.56, 2.86)
Q3	2.7 – 5.9	11	0.83 (0.48, 1.42)	0.94 (0.41, 2.18)	13	0.80 (0.51, 1.27)	0.89 (0.41, 1.91)	9	0.85 (0.51, 1.40)	0.81 (0.33, 2.01)
Q4	5.9 – 10.5	8	0.74 (0.42, 1.31)	0.71 (0.28, 1.79)	19	0.85 (0.54, 1.34)	1.39 (0.68, 2.87)	11	0.55 (0.31, 1.00)	1.02 (0.40, 2.59)
Q5	10.5 – 166	11	0.91 (0.53, 1.56)	1.16 (0.46, 2.93)	8	0.69 (0.43, 1.12)	0.63 (0.24, 1.64)	2	0.50 (0.27, 0.92)	0.28 (0.06, 1.38)
p trend			0.833	0.540		0.737	0.095		0.331	0.141
HR per 80g/day		53	0.85 (0.19, 3.77)	2.17 (0.18, 26.1)	66	0.80 (0.21, 3.01)	4.95 (0.76, 32.3)	48	0.24 (0.01, 4.19)	0.01 (0.00, 4.27)
Grapes Intake										
Q1	0 – 2	14	1	1	21	1	1	16	1	1
Q2	7	17	0.84 (0.53, 1.33)	1.08 (0.53, 2.20)	16	0.76 (0.52, 1.12)	0.72 (0.37, 1.38)	10	0.66 (0.40, 1.10)	0.67 (0.28, 1.59)
Q3	14	5	0.59 (0.34, 1.04)	0.47 (0.17, 1.32)	9	0.54 (0.34, 0.86)	0.62 (0.28, 1.36)	9	0.93 (0.56, 1.54)	1.11 (0.45, 2.70)
Q4	40	13	0.88 (0.54, 1.44)	1.20 (0.55, 2.60)	8	0.35 (0.20, 0.59)	0.49 (0.21, 1.12)	10	0.64 (0.37, 1.10)	0.90 (0.36, 2.25)
Q5	80 – 600	4	0.50 (0.25, 0.98)	0.60 (0.19, 1.92)	12	0.88 (0.57, 1.36)	1.10 (0.51, 2.33)	3	0.59 (0.31, 1.11)	0.52 (0.13, 2.08)
p trend			0.057	0.385		0.245	0.695		0.046	0.271
HR per 80g/day		53	0.62 (0.39, 1.01)	0.72 (0.34, 1.52)	66	0.84 (0.64, 1.12)	0.91 (0.56, 1.47)	48	0.64 (0.42, 0.99)	0.63 (0.27, 1.44)

[a] Cases 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

Table 4.4 Total fruit, fruit subgroup intake and the risk of total coronary heart disease, total stroke and total cardiovascular disease incidence (expressed as HR and 95% CI)

	Intake (g/day)	Total Coronary Heart Disease			Total Stroke			Total Cardiovascular Disease		
		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	21	1	1	32	1	1	52	1	1
Q2	200 – 302	27	0.61 (0.45, 0.83)	1.05 (0.59, 1.86)	28	0.81 (0.59, 1.10)	0.68 (0.41, 1.14)	55	0.70 (0.56, 0.87)	0.84 (0.57, 1.23)
Q3	302 – 411	37	0.74 (0.56, 0.99)	1.41 (0.82, 2.44)	24	0.73 (0.53, 1.00)	0.56 (0.33, 0.97)	61	0.74 (0.60, 0.91)	0.91 (0.62, 1.33)
Q4	411 – 571	34	0.60 (0.45, 0.80)	1.23 (0.70, 2.16)	26	0.66 (0.48, 0.91)	0.58 (0.34, 1.00)	58	0.62 (0.50, 0.77)	0.81 (0.55, 1.20)
Q5	571 – 3713	33	0.75 (0.57, 0.99)	1.32 (0.73, 2.38)	32	0.64 (0.47, 0.88)	0.81 (0.47, 1.38)	65	0.71 (0.58, 0.88)	1.03 (0.69, 1.53)
p trend			0.351	0.678		0.044	0.776		0.059	0.573
HR per 80 g/day		152	0.99 (0.96, 1.01)	1.01 (0.96, 1.06)	142	0.97 (0.94, 1.00)	1.01 (0.95, 1.06)	291	0.98 (0.96, 1.00)	1.01 (0.97, 1.05)
Fresh Fruit Intake										
Q1	0 – 133	21	1	1	26	1	1	46	1	1
Q2	133 – 210	25	0.81 (0.60, 1.09)	0.94 (0.52, 1.70)	33	0.80 (0.59, 1.09)	0.97 (0.58, 1.64)	57	0.80 (0.64, 0.99)	0.96 (0.65, 1.43)
Q3	210 – 292	42	0.72 (0.53, 0.97)	1.48 (0.87, 2.55)	23	0.74 (0.54, 1.01)	0.61 (0.34, 1.08)	64	0.72 (0.58, 0.90)	0.99 (0.67, 1.47)
Q4	292 – 418	31	0.79 (0.59, 1.06)	1.04 (0.59, 1.86)	29	0.62 (0.45, 0.85)	0.74 (0.42, 1.28)	60	0.71 (0.57, 0.88)	0.89 (0.70, 1.60)
Q5	418 – 3404	33	0.75 (0.56, 1.00)	1.22 (0.67, 2.20)	31	0.65 (0.47, 0.89)	0.89 (0.50, 1.58)	64	0.70 (0.57, 0.88)	1.06 (0.70, 1.60)
p trend			0.187	0.501		0.043	0.946		0.031	0.502
HR per 80 g/day		152	0.98 (0.94, 1.01)	1.02 (0.96, 1.09)	142	0.96 (0.92, 1.00)	1.00 (0.93, 1.07)	291	0.97 (0.94, 1.00)	1.01 (0.97, 1.06)
Fresh Fruit and Juice Intake										
Q1	0 – 190	23	1	1	36	1	1	58	1	1
Q2	190 – 291	26	0.58 (0.43, 0.78)	0.94 (0.54, 1.66)	28	0.78 (0.57, 1.05)	0.62 (0.38, 1.02)	54	0.67 (0.54, 0.83)	0.75 (0.52, 1.10)
Q3	291 – 397	37	0.75 (0.57, 0.99)	1.29 (0.76, 2.20)	21	0.64 (0.47, 0.88)	0.44 (0.25, 0.76)	57	0.70 (0.56, 0.86)	0.76 (0.52, 1.11)
Q4	397 – 554	33	0.57 (0.43, 0.77)	1.09 (0.63, 1.89)	25	0.60 (0.44, 0.83)	0.49 (0.29, 0.84)	57	0.59 (0.47, 0.73)	0.71 (0.49, 1.04)
Q5	554 – 3694	33	0.71 (0.53, 0.93)	1.24 (0.70, 2.20)	32	0.61 (0.44, 0.83)	0.73 (0.43, 1.24)	65	0.67 (0.54, 0.82)	0.94 (0.64, 1.39)
p trend			0.354	0.741		0.050	0.731		0.066	0.588
HR per 80 g/day		152	0.99 (0.96, 1.01)	1.01 (0.96, 1.06)	142	0.97 (0.94, 1.00)	1.01 (0.95, 1.07)	291	0.98 (0.96, 1.00)	1.01 (0.97, 1.05)
Fresh and Dried Fruit Intake										
Q1	0 – 142	21	1	1	26	1	1	46	1	1
Q2	142 – 222	24	0.74 (0.55, 0.99)	0.93 (0.51, 1.68)	32	0.74 (0.54, 1.01)	0.96 (0.57, 1.62)	55	0.73 (0.59, 0.90)	0.95 (0.64, 1.41)
Q3	222 – 306	41	0.67 (0.50, 0.90)	1.43 (0.83, 2.46)	23	0.66 (0.48, 0.91)	0.60 (0.34, 1.06)	63	0.66 (0.53, 0.82)	0.97 (0.65, 1.43)
Q4	306 – 437	36	0.78 (0.59, 1.03)	1.20 (0.68, 2.11)	28	0.60 (0.43, 0.82)	0.70 (0.40, 1.23)	64	0.70 (0.56, 0.86)	0.94 (0.63, 1.40)
Q5	437 – 3423	30	0.67 (0.50, 0.90)	1.08 (0.59, 1.98)	33	0.63 (0.46, 0.86)	0.93 (0.53, 1.64)	63	0.66 (0.53, 0.81)	1.02 (0.67, 1.54)
p trend			0.189	0.443		0.036	0.997		0.028	0.487
HR per 80 g/day		152	0.98 (0.94, 1.01)	1.02 (0.96, 1.09)	142	0.96 (0.92, 1.00)	1.00 (0.93, 1.07)	291	0.97 (0.94, 1.00)	1.02 (0.97, 1.06)

(Table 4.4 continued)

	Intake (g/day)	Total Coronary Heart Disease			Total Stroke			Total Cardiovascular Disease		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Dried Fruit Intake										
Q1	0 – 1.2	25	1	1	26	1	1	50	1	1
Q2	1.3 – 2.8	20	0.82 (0.60, 1.12)	0.73 (0.41, 1.33)	17	0.80 (0.57, 1.11)	0.58 (0.32, 1.08)	37	0.81 (0.64, 1.02)	0.67 (0.44, 1.03)
Q3	2.8 – 5.1	34	0.99 (0.74, 1.33)	1.06 (0.63, 1.79)	35	0.94 (0.68, 1.28)	1.03 (0.62, 1.72)	68	0.96 (0.77, 1.19)	1.05 (0.73, 1.52)
Q4	5.1 – 12.5	36	0.90 (0.67, 1.20)	1.02 (0.60, 1.71)	32	0.74 (0.53, 1.02)	0.83 (0.49, 1.40)	68	0.83 (0.67, 1.04)	0.93 (0.64, 1.36)
Q5	12.5 – 469	37	0.80 (0.60, 1.08)	0.93 (0.55, 1.58)	32	0.75 (0.55, 1.03)	0.72 (0.42, 1.23)	68	0.77 (0.62, 0.96)	0.82 (0.56, 1.20)
p trend			0.752	0.311		0.237	0.575		0.318	0.727
HR per 25 g/day		152	0.98 (0.89, 1.09)	1.08 (0.93, 1.24)	142	0.92 (0.81, 1.05)	0.94 (0.75, 1.17)	291	0.96 (0.88, 1.04)	1.02 (0.90, 1.16)
Fruit Juice Intake										
Q1	0 – 10	40	1	1	45	1	1	84	1	1
Q2	13 – 30	28	0.97 (0.73, 1.29)	1.00 (0.62, 1.63)	24	0.73 (0.53, 1.02)	0.81 (0.49, 1.33)	52	0.87 (0.70, 1.08)	0.91 (0.64, 1.29)
Q3	41 – 116	27	0.75 (0.57, 0.99)	0.69 (0.42, 1.13)	32	0.91 (0.69, 1.20)	0.79 (0.50, 1.25)	59	0.82 (0.68, 1.00)	0.74 (0.53, 1.04)
Q4	119 – 148	24	0.76 (0.56, 1.02)	0.86 (0.52, 1.44)	18	0.66 (0.48, 0.92)	0.60 (0.35, 1.05)	41	0.70 (0.56, 0.87)	0.72 (0.49, 1.04)
Q5	155 – 1740	33	0.92 (0.70, 1.21)	1.06 (0.66, 1.69)	23	0.68 (0.50, 0.93)	0.71 (0.42, 1.18)	55	0.81 (0.66, 1.00)	0.87 (0.61, 1.22)
p trend			0.717	0.636		0.513	0.550		0.892	0.973
HR per 125 g/day		152	1.02 (0.92, 1.12)	0.95 (0.79, 1.15)	142	0.96 (0.86, 1.08)	1.05 (0.88, 1.26)	291	0.99 (0.92, 1.07)	1.00 (0.87, 1.14)
Total Citrus Intake										
Non-Consumers	0	5	1	1	10	1	1	15	1	1
Q1	1.8 – 22	42	1.14 (0.73, 1.79)	1.79 (0.71, 4.55)	35	0.87 (0.56, 1.35)	0.77 (0.38, 1.57)	76	1.01 (0.73, 1.39)	1.10 (0.63, 1.92)
Q2	23 – 60	23	0.89 (0.56, 1.43)	1.14 (0.43, 3.01)	20	0.76 (0.48, 1.21)	0.54 (0.25, 1.17)	42	0.83 (0.60, 1.16)	0.72 (0.40, 1.30)
Q3	64 – 102	25	0.78 (0.49, 1.24)	1.07 (0.41, 2.81)	31	0.76 (0.48, 1.20)	0.72 (0.35, 1.47)	56	0.78 (0.56, 1.09)	0.83 (0.47, 1.46)
Q4	112 – 182	36	0.82 (0.52, 1.30)	1.43 (0.56, 3.66)	27	0.70 (0.45, 1.10)	0.58 (0.28, 1.22)	62	0.75 (0.54, 1.04)	0.85 (0.48, 1.50)
Q5	190 – 1422	21	0.94 (0.59, 1.51)	1.19 (0.44, 3.19)	19	0.55 (0.34, 0.91)	0.62 (0.28, 1.36)	40	0.76 (0.54, 1.07)	0.80 (0.44, 1.47)
p trend			0.587	0.261		0.156	0.982		0.217	0.422
HR per 80g/day		152	0.98 (0.91, 1.05)	0.92 (0.80, 1.06)	142	0.94 (0.87, 1.02)	1.00 (0.87, 1.15)	291	0.97 (0.92, 1.02)	0.96 (0.87, 1.06)
Citrus Fruit Intake										
Non-Consumers	0	9	1	1	12	1	1	21	1	1
Q1	1.8 – 6.4	41	0.92 (0.65, 1.31)	1.26 (0.61, 2.60)	47	1.14 (0.78, 1.68)	1.16 (0.61, 2.20)	87	1.04 (0.80, 1.35)	1.19 (0.73, 1.92)
Q2	12.9	19	0.71 (0.47, 1.06)	1.08 (0.48, 2.39)	19	0.82 (0.53, 1.27)	0.87 (0.42, 1.80)	38	0.78 (0.58, 1.06)	0.95 (0.56, 1.63)
Q3	36.8	43	0.81 (0.56, 1.16)	1.57 (0.76, 3.24)	28	0.93 (0.62, 1.39)	0.84 (0.42, 1.66)	69	0.89 (0.67, 1.16)	1.12 (0.69, 1.84)
Q4	73.6	16	0.87 (0.57, 1.33)	1.48 (0.65, 3.38)	12	0.82 (0.50, 1.34)	0.91 (0.40, 2.04)	28	0.86 (0.62, 1.19)	1.15 (0.65, 2.04)
Q5	92 – 552	24	0.78 (0.54, 1.13)	0.97 (0.44, 2.11)	24	0.80 (0.53, 1.21)	0.78 (0.39, 1.59)	48	0.82 (0.62, 1.09)	0.86 (0.51, 1.45)
p trend			0.429	0.232		0.085	0.236		0.111	0.091
HR per 80 g/day		152	0.94 (0.81, 1.09)	0.84 (0.63, 1.12)	142	0.86 (0.72, 1.02)	0.83 (0.61, 1.13)	291	0.91 (0.82, 1.02)	0.83 (0.67, 1.03)

(Table 4.4 continued)

	Intake (g/day)	Total Coronary Heart Disease			Total Stroke			Total Cardiovascular Disease		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Orange Juice Intake										
Non-Consumers	0	29	1	1	29	1	1	58	1	1
Q1	2.9 – 10.1	48	0.89 (0.67, 1.17)	0.77 (0.49, 1.23)	43	0.76 (0.57, 1.02)	0.73 (0.45, 1.17)	89	0.82 (0.67, 1.00)	0.73 (0.52, 1.02)
Q2	20.3	8	0.74 (0.51, 1.09)	0.39 (0.18, 0.86)	11	0.76 (0.51, 1.13)	0.60 (0.30, 1.21)	19	0.75 (0.57, 0.99)	0.49 (0.29, 0.82)
Q3	58	21	0.80 (0.58, 1.12)	0.65 (0.37, 1.14)	24	0.84 (0.60, 1.17)	0.82 (0.47, 1.41)	45	0.80 (0.63, 1.02)	0.72 (0.48, 1.07)
Q4	116 – 145	43	0.81 (0.61, 1.08)	0.79 (0.49, 1.28)	29	0.64 (0.47, 0.87)	0.58 (0.35, 0.98)	71	0.72 (0.58, 0.89)	0.68 (0.48, 0.96)
Q5	362 – 870	3	0.78 (0.44, 1.41)	0.49 (0.15, 1.64)	6	0.78 (0.43, 1.44)	1.21 (0.50, 2.95)	9	0.79 (0.52, 1.21)	0.82 (0.40, 1.66)
p trend			0.853	0.520		0.487	0.456		0.586	0.960
HR per 250 g/day		152	0.97 (0.74, 1.28)	0.84 (0.50, 1.41)	142	0.90 (0.66, 1.22)	1.19 (0.75, 1.90)	291	0.94 (0.77, 1.16)	1.01 (0.71, 1.43)
Total Berries Intake										
Q1	0 – 1.6	25	1	1	25	1	1	50	1	1
Q2	1.7 – 4.3	34	0.82 (0.62, 1.08)	0.98 (0.59, 1.65)	31	0.93 (0.68, 1.27)	0.92 (0.54, 1.57)	63	0.85 (0.69, 1.05)	0.93 (0.64, 1.34)
Q3	4.3 – 8.0	28	0.75 (0.55, 1.02)	1.02 (0.59, 1.75)	23	0.77 (0.54, 1.09)	0.89 (0.50, 1.58)	51	0.76 (0.60, 0.96)	0.95 (0.64, 1.41)
Q4	8.1 – 15.3	33	0.74 (0.56, 0.99)	0.85 (0.50, 1.44)	24	0.77 (0.56, 1.06)	0.66 (0.37, 1.17)	57	0.75 (0.60, 0.92)	0.75 (0.51, 1.10)
Q5	15.4 – 365	32	0.69 (0.51, 0.92)	0.85 (0.49, 1.47)	39	0.90 (0.66, 1.23)	1.18 (0.69, 2.01)	70	0.78 (0.63, 0.96)	0.98 (0.67, 1.44)
p trend			0.149	0.984		0.532	0.665		0.154	0.775
HR per 80 g/day		152	0.74 (0.50, 1.11)	1.00 (0.62, 1.63)	142	0.89 (0.63, 1.27)	0.87 (0.45, 1.65)	291	0.82 (0.63, 1.07)	0.94 (0.64, 1.40)
Total Pomes Intake										
Q1	0 – 19	28	1	1	32	1	1	59	1	1
Q2	24 – 55	26	0.88 (0.66, 1.16)	0.86 (0.50, 1.47)	32	0.89 (0.65, 1.20)	0.94 (0.57, 1.54)	57	0.89 (0.72, 1.09)	0.90 (0.62, 1.30)
Q3	62 – 102	36	0.81 (0.60, 1.09)	1.27 (0.76, 2.10)	22	0.73 (0.53, 1.02)	0.68 (0.39, 1.18)	57	0.77 (0.62, 0.96)	0.95 (0.65, 1.38)
Q4	108 – 133	24	0.72 (0.53, 0.98)	0.91 (0.52, 1.60)	22	0.72 (0.52, 1.00)	0.71 (0.40, 1.24)	46	0.73 (0.59, 0.92)	0.81 (0.55, 1.21)
Q5	139 – 1392	38	0.82 (0.62, 1.08)	1.23 (0.72, 2.10)	34	0.82 (0.61, 1.11)	0.99 (0.58, 1.68)	72	0.82 (0.67, 1.01)	1.12 (0.76, 1.63)
p trend			0.263	0.285		0.819	0.093		0.369	0.040
HR per 80 g/day		152	0.95 (0.88, 1.03)	1.07 (0.94, 1.21)	142	0.99 (0.91, 1.07)	1.11 (0.98, 1.26)	291	0.97 (0.92, 1.03)	1.10 (1.00, 1.20)
Total Tropical Intake										
Q1	0 – 18	30	1	1	32	1	1	59	1	1
Q2	18 – 45	37	0.91 (0.69, 1.21)	1.17 (0.72, 1.90)	28	0.86 (0.64, 1.17)	0.84 (0.50, 1.40)	65	0.92 (0.75, 1.13)	1.05 (0.74, 1.50)
Q3	45 – 76	31	0.87 (0.64, 1.17)	1.13 (0.68, 1.88)	21	0.71 (0.51, 0.99)	0.77 (0.44, 1.33)	52	0.82 (0.65, 1.03)	0.99 (0.68, 1.45)
Q4	76 – 107	29	0.81 (0.61, 1.08)	0.89 (0.53, 1.49)	33	0.84 (0.63, 1.14)	0.97 (0.59, 1.59)	62	0.84 (0.68, 1.03)	0.97 (0.67, 1.39)
Q5	107 – 1235	25	0.83 (0.62, 1.11)	0.83 (0.47, 1.45)	28	0.76 (0.56, 1.05)	1.02 (0.59, 1.75)	53	0.81 (0.66, 1.01)	0.96 (0.64, 1.42)
p trend			0.173	0.388		0.167	0.622		0.067	0.876
HR per 80 g/day		152	0.92 (0.81, 1.04)	0.90 (0.71, 1.14)	142	0.91 (0.79, 1.04)	1.06 (0.84, 1.34)	291	0.92 (0.84, 1.01)	0.99 (0.84, 1.16)

(Table 4.4 continued)

	Intake (g/day)	Total Coronary Heart Disease			Total Stroke			Total Cardiovascular Disease		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total Drupes Intake										
Q1	0 – 1.2	29	1	1	30	1	1	58	1	1
Q2	1.2 – 2.7	26	0.99 (0.74, 1.32)	0.88 (0.51, 1.49)	30	1.08 (0.80, 1.45)	0.99 (0.59, 1.64)	56	1.02 (0.83, 1.25)	0.95 (0.65, 1.37)
Q3	2.7 – 5.9	30	0.76 (0.56, 1.03)	0.95 (0.56, 1.59)	30	0.87 (0.64, 1.19)	0.93 (0.55, 1.55)	59	0.80 (0.65, 1.00)	0.93 (0.64, 1.35)
Q4	5.9 – 10.5	35	1.03 (0.77, 1.37)	1.14 (0.69, 1.90)	32	0.75 (0.54, 1.04)	1.03 (0.62, 1.73)	66	0.89 (0.72, 1.11)	1.08 (0.75, 1.56)
Q5	10.5 – 166	32	0.93 (0.69, 1.25)	1.10 (0.63, 1.92)	20	0.71 (0.51, 0.99)	0.67 (0.36, 1.25)	52	0.83 (0.67, 1.04)	0.88 (0.58, 1.34)
p trend			0.472	0.590		0.398	0.634		0.345	0.474
HR per 80g/day		152	0.73 (0.31, 1.72)	1.51 (0.34, 6.81)	142	0.66 (0.25, 1.72)	1.49 (0.29, 7.68)	291	0.73 (0.39, 1.39)	1.50 (0.49, 4.57)
Grapes Intake										
Q1	0 – 2	38	1	1	40	1	1	76	1	1
Q2	7	30	0.73 (0.55, 0.96)	0.69 (0.43, 1.12)	38	0.76 (0.58, 1.00)	0.86 (0.55, 1.35)	68	0.76 (0.62, 0.92)	0.80 (0.57, 1.11)
Q3	14	27	0.82 (0.62, 1.10)	0.94 (0.57, 1.55)	20	0.64 (0.47, 0.88)	0.68 (0.39, 1.17)	47	0.73 (0.59, 0.91)	0.83 (0.57, 1.19)
Q4	40	34	0.88 (0.66, 1.16)	1.07 (0.67, 1.72)	26	0.64 (0.46, 0.87)	0.80 (0.48, 1.33)	60	0.78 (0.63, 0.96)	0.96 (0.68, 1.35)
Q5	80 – 600	23	1.04 (0.77, 1.40)	1.12 (0.65, 1.94)	18	0.72 (0.52, 1.00)	0.82 (0.46, 1.47)	40	0.90 (0.72, 1.12)	0.96 (0.64, 1.43)
p trend			0.685	0.522		0.023	0.212		0.254	0.652
HR per 80g/day		152	1.03 (0.90, 1.17)	1.08 (0.86, 1.35)	142	0.77 (0.61, 0.96)	0.78 (0.52, 1.15)	291	0.93 (0.83, 1.05)	0.95 (0.77, 1.17)

[a] Cases 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

4.4.2.2 Sensitivity Analysis

4.4.2.2.1 Postmenopausal women

In a subpopulation of postmenopausal women (Table B.1), total CVD was 25% (95% CI 0.57 to 0.99) lower for every portion of citrus fruit. The adverse association previously found in the full cohort also remained significant here, where every 80 g of pomes was associated with a 24% (95% CI 1.09 to 1.40) higher risk of total stroke and a 16% (95% CI 1.05, 1.27) higher risk of total CVD.

4.4.2.2.2 Non-smokers

Every additional portion of berries was associated with 69% (95% CI 0.11 to 0.86) lower risk of CCE incidence in non-smoking women. The risk of total stroke and total CVD was higher by 15% (95% CI 1.02 to 1.30) and 11% (95% CI 1.01 to 1.21) respectively with every portion of pomes, similar to associations reported above (Table B.2).

4.4.2.2.3 Normotensive and hypertensive women

Within a subpopulation of hypertensive women (Table B.3), consumption of tropical fruit was not protective against CCE incidence, and risk was 39% (95% CI 1.04 to 1.87) higher with every portion consumed. Similarly, every portion of FDF was associated with 25% (95% CI 1.06 to 1.48) higher risk of total CVD. The intake of pomes was also associated with a higher risk of total stroke and total CVD by 21% (95% CI 1.04 to 1.42) and 15% (95% CI 1.00 to 1.31) respectively. Interestingly, no adverse association for the intake of pomes was reported within normotensive women (Table B.4), however, there was also no significant protective associations.

4.4.2.2.4 Non-obese

Similar to the subpopulation of non-smokers, within non-obese participants (Table B.5), every 80 g of berries was protectively associated with risk of CCE incidence, where risk was lower by 72% (95% CI 0.10 to 0.79). The adverse association between intake of pomes and total stroke, total CVD was also observed here. Risk of these outcomes were 14% (95% CI 1.00 to 1.30) and 12% (95% CI 1.02 to 1.23) higher respectively.

4.5 Discussion

4.5.1 Summary of results

The objective of this study was to investigate the association between different subgroups of fruit and the risk of CVD incidence. Incidence of total stroke was lower in participants who consumed moderate amounts of TF, FFJ and orange juice, however, due to the absence of a significant linear trend, the association for lower stroke risk and increasing TF, FFJ and orange juice could not be confirmed. In terms of fruit subgroups, the intake of total pomes was associated with a higher incidence of total CVD. However, increasing intake of berries by portions was protective against risk of CCE. No evidence of association was determined for intake of FF, total dried fruit, total fruit juice, citrus fruit, drupes, grapes and tropical fruit in the full cohort.

Within sensitivity analyses, consumption of pomes was associated with 11% to 16% increase in risk of total CVD within subpopulations of postmenopausal, non-smoking, hypertensive and non-obese women, but not within normotensive women. The intake of pomes was also associated with higher total stroke risk in non-smoking women. In addition, hypertensive women also had a higher risk of total CVD with increasing intakes of total dried fruit. However, the intake of citrus fruit was inversely associated with the risk of CVD within postmenopausal women, and consumption of berries lowered risk of CCE within non-obese and non-smoking women. However, the CI for some associations was particularly wide, in addition to the small number of cases, findings should be carefully interpreted.

4.5.2 General comparison to literature

As explained earlier in Section 4.2, several studies have found an inverse association between higher fruit intake and lower risk of CVD mortality. Within studies that include incidence as an outcome, results appear to be less agreeable with the former finding among other studies. Results from the current study for total CVD are in agreement with the Women's Health Study [196], where the risk of CVD incidence was not significantly lower with higher intakes of fruit by serving/day [HR 0.96 (95% CI 0.70 to 1.33)] in comparison to the lowest consumers. Similarly, higher fruit intake was also not associated with a lower risk of MI in the multivariate adjusted model in comparison to the lowest consumers [HR 0.66 (95% CI 0.36 to 1.22)]. With regard to CHD incidence, pooled results for Nurses' Health Study (NHS) and Health Professional's Follow-Up Study (HPFS), as well as the PRIME study report a significant association between higher fruit intake and lower risk of CHD [205,

210]. However, associations were inconclusive in recent studies conducted in Denmark and China [216, 237], in agreement with the current study findings. On the other hand, the Diet, Cancer and Health study reported a protective association between fruit intake and ischemic stroke [214], which was not detected in the current study. Contradictory results to the present findings were also reported in the MORGEN study, where white coloured FVs (55% consists of pomes) were associated with lower incidence of stroke [242]. A Japanese cohort also reported lower risk of ischemic stroke with higher consumption of citrus fruits [213].

As discussed in Chapter 3 Section 3.5.2, CHD and stroke were studied in combination because these conditions share some common aetiology. However, separate exploration is warranted due to the effects of different biological mechanisms and the involvement of different risk factors [3, 5]. In addition, the current study had further divided CHD as a collection of coronary diseases down to specific conditions such as MI, or acute and chronic events. Theoretically speaking, the inclusion of both CHD and stroke outcomes (and additionally by subcategories) within the current cohort would provide a broader overview in comparison to other studies, allowing the formation of more specific hypotheses surrounding the mechanisms of the CVD event if significant associations were detected. However, from the evidence given above, heterogeneity may exist due to inconsistent conclusions deriving from different studies (though no formal statistics test was conducted), and may be attributed to the variation in consumption pattern between countries [205, 210, 213, 242], characteristics of participants, or simply due to the limited number of cases within the current study which may result in false positives or null associations because of wide CIs.

4.5.3 Relevance with (poly)phenol mechanisms

As mentioned in Chapter 3 Section 3.5.3, there are multiple studies *in vitro* and *in vivo* that support the association between hesperidin from citrus fruits and risk of stroke. However, a significant dose response was not found in the current study when investigating the same relationship using incidence data. This could be due to residual confounding, as similar results were reported in Chapter 3 Section 3.5.3. A possible explanation relates to the definition of mortality and incidence, where the former is associated with likelihood of death from the disease, and the latter is associated with prevention of the disease occurrence. So far, evidence from observational studies points towards a lower risk of CVD mortality with greater fruit intake [83], indicating that derived benefits may help prevent death. It is also not certain if greater fruit intake improves survival against CVD events.

However, there are few observational studies which address if higher fruit and fruit subgroup intakes can prevent the manifestation of CVD, with the exception of the Jichi Medical School Cohort Study from Japan [213]. Thus more evidence from studies are required to ascertain if fruit and fruit subgroup intakes are associated with the prevention or survival odds of CVD.

Contrary to the adverse association found in this study between pomes and CVD risk, significant inverse associations had been reported between intakes of apples and pears and CVD risk in observational studies [117, 254]. However, there is limited evidence to support the beneficial effect of (poly)phenols from apples on markers of CVD and BP. Apple and apple juices were reported to improve lipid profiles in some intervention studies [236, 255, 256], but contrasting results were also reported elsewhere [257]. From the sensitivity analysis, women who were normotensive did not present with a higher risk of CVD with increasing intake of pomes, thus the adverse association could be due to effect modification of hypertension. An alternative explanation may be related to reverse causality, however, participants who died within a year were excluded to minimize this effect.

On the association between berries and risk of CCE, there were no associations reported in other cohort studies that are in agreement with the current findings. Surprisingly, a higher risk of stroke, especially cerebral infarction and subarachnoid haemorrhage with greater intakes of berries was observed in a Swedish cohort [197]. However, anthocyanins from berries have been associated with 'healthy' blood lipid profiles, [120] and are also anti-inflammatory [163]. A recent human study reported an improvement in plasma lipid profile, specifically lower levels of LDL-C, as well as improved platelet function after supplementation of 500 g of fresh strawberries for 30 days [258]. High levels of LDL and platelet activity are known to play a role in the development of CCE related mechanisms, such as atherosclerosis [259], thus a reduction could lower risk of CCE.

Within hypertensive individuals, increasing portions of dried fruits (25 g) were adversely associated with total CVD risk. Dried fruit here consist mostly of raisins, sultanas and currants, which are rich in dietary fibre, phytochemicals (such as quercetin, kaempferol, caftaric acid and coutaric acid) and potassium [260]. In contrast to evidence from literature, higher consumption of raisins are associated with lower BP and LDL-C [261]. Intake of raisins (160 g/day) over six weeks in a human intervention trial also lowered levels of cytokine and cellular adhesion molecules, which may potentially decelerate or prevent the development of atherosclerosis by reducing the adhesion of monocytes on the vascular endothelium, which in turn affects the production of foam cells [262]. Thus, the results

observed here could also be partly due to residual confounding, or effect modification of hypertension itself, as the intake of dried fruits within normotensive participants were not associated with risk of total CVD.

Possible explanations in relation to null associations have been previously elaborated in Chapter 3 Section 3.5.3. In summary, low case numbers, low intakes (in addition to the application of quintiles), and a low concentration of (poly)phenols *in vivo* could be the reason why no associations were observed. Other than (poly)phenols, possible mechanisms of other components within fruits such as dietary fibre and carotenoids are also reported in Chapter 3 Section 3.5.3, and may serve as an alternative explanation for associations observed, or act synergistically with (poly)phenols.

4.5.4 Strengths and limitations

The strengths and limitations documented in Chapter 3 Section 3.5.4 apply directly to the current analysis. In addition, the case numbers are relatively less in comparison to other studies, so results should be interpreted cautiously. However, the limitation relating to misclassifying non-fatal cases mentioned previously no longer apply due to the application of incidence data. The current analysis could also be subjected to a higher chance of type 1 error as 95% CI is reported instead of 99% CI.

4.6 Summary

To conclude, a greater consumption of berries was seen to be protectively associated with risk of CCE especially within non-obese, non-smoking women, and a higher intake of citrus fruit was beneficial in lowering total CVD within postmenopausal women. Further investigations from intervention studies or RCTs are recommended for the consumption of berries and citrus fruits to assess its relationship with CVD risk in the population. Overall, the findings of this study provided further evidence in addition to Chapter 3 to suggest that the consumption of berries and citrus fruits should be promoted for cardiovascular health.

Chapter 5
Coffee and tea intake and cardiovascular disease mortality in the UK Women's Cohort Study

5.1 Abstract

Coffee and tea are widely consumed beverages and known to exhibit various effects on health. Coffee has been reported to have significant adverse association with CVD risk, possibly due to ingestion of diterpenes. However, recent meta-analyses now suggest that the previously reported adverse association between coffee and CVD is no longer significant. Most observational studies found a significant inverse association between increased coffee intake and CVD risk. On the other hand, there is an increasing amount of evidence that higher black and green tea intake is associated with lower stroke risk. The aim of the study is to investigate whether there are adverse associations for coffee with CVD risk and an inverse association for tea with CVD risk in the UKWCS. Total coffee and tea intake (g/day) was derived from a 217-item FFQ, was obtained from 30,458 women (aged 35 to 69 years) at baseline from 1995–1998. Coffee and tea intakes were also further divided into regular coffee, decaffeinated coffee and black tea. Mortality events were derived from the NHS Central Register. During the mean follow-up period of 16.7 years, 296 fatal CVD deaths (143 coronary heart disease (CHD), 153 stroke) were observed. Survival analysis was conducted using participants free from history of CVD at baseline. There was no significant adverse association between coffee and CVD risk. There was also no significant inverse association between tea and CVD risk. These findings are partially supported by studies in the literature, but is contradictory with recent meta-analyses. Findings from the current study add to the evidence pool in literature, and further investigations are required by optimising methodology.

5.2 Background

Coffee and tea are the most commonly consumed non-alcoholic beverages in the world after water [263]. Coffee contains bioactive components such as caffeine (30 to 300 mg/cup depending on type of brew), chlorogenic acids and diterpenes (cafestol, kahweol)

[137], while bioactive components in tea are mostly caffeine, and flavanols, consisting of catechin, and its isomers and derivatives [264]. Diterpenes in unfiltered coffee are known to exhibit cholesterol-raising effects, potentially leading to an increased risk of cardiovascular disease (CVD) [265]. Caffeine also increases heart rate and BP which could affect the risk of CVD. However, it is recently reported that caffeine do not cause adverse effects when caffeine from coffee or tea is consumed *ad libitum* [138]. In addition, (poly)phenols in both beverages are suggested to counter negative aspects from diterpenes and caffeine [266], while association between long-term tea consumption and CVD risk is uncertain [141].

The current pool of evidence for the association between coffee consumption and CVD risk is inconsistent. Previous MAs suggested a higher risk of coronary heart disease (CHD) mortality with a higher intake of coffee [90, 91]. However, results from a recent meta-analyses contradict the former findings [92, 93]. The risk of stroke had been studied in some detail, but results are inconsistent. A weak to moderate protective association was observed for risk of stroke by coffee consumption in two MAs [267, 268]. However, the Nurses' Health Study did not find a significant association with higher coffee consumption and the risk of stroke. An inverse association was found for decaffeinated coffee and risk of stroke instead [269], suggesting that caffeine may be the culprit for the former null finding. On the other hand, evidence in the literature for tea intake and CVD risk was also inconsistent over the last decade. Despite multiple findings that act in either directions, a review of meta-analyses proposed that evidence for tea consumption (black and green) and stroke was the strongest out of all CVD outcomes [96]. A more recent MA also reported a lower cardiac death, CHD and stroke incidence with increasing tea intake [270].

As findings are inconclusive, and coffee and tea intakes were not studied in the current cohort, the aim of the current study was to explore the association between coffee, tea intake and risk of CVD mortality using data from the UKWCS.

5.3 Method

5.3.1 Dietary exposure

Total coffee intake was generated by combining regular coffee and decaffeinated coffee from the FFQ. Both types of coffee were studied as a single variable due to the minor differences in (poly)phenol profile (chlorogenic acids), however, the degree of roasting may affect the quantity of chlorogenic acids within different brews [271]. Caffeine was also

previously associated with increased CVD risk, especially BP, though evidence had been inconsistent [272]. Therefore, regular coffee was investigated separately from decaffeinated coffee. Likewise, black tea was investigated separately from herbal tea because its (poly)phenol profile is different. Herbal tea represents a general term for a collection of less commonly drunk tea in the UK. Depending on the variety of herbs used, each specific type of herbal tea would contain a different (poly)phenol profile, thus it would be difficult to investigate unless information on specific herbal tea intake was available. In addition, due to the wide variety of herbal tea, consumption levels for each particular tea might too small for analysis. Herbal tea was therefore not investigated as an individual variable. Consumption was expressed as g/day.

5.3.2 Mortality outcomes

Mortality outcomes for the current analysis are described in Chapter 3 Section 3.3.2.

5.3.3 Statistical method and design

5.3.3.1 Outliers and exclusions

The procedure for omitting outliers and implementing exclusions is documented in Chapter 2 Section 2.5. In brief, participants who met the following criteria were excluded:

1. No, or incorrect NHS number provided at baseline FFQ, (n = 695)
2. Extreme energy intakes (<500 kcal/day & >6000 kcal/day) (n = 86)
3. Extreme total coffee (> 2000 g/day, equivalent to 8 cups) or tea (> 3000 g/day, equivalent to 12 cups) intakes (n = 21 & 0 respectively)
4. Previous self-reported heart attacks, angina, cancer, diabetes and stroke at baseline (n = 4014).

In total, 4780 participants were excluded for the analysis of coffee, and 4778 participants were excluded for the analysis of tea.

5.3.3.2 Confounding

The current analysis is based on the DAG from Chapter 2 Section 2.5.2 to provide evidence for inclusion of potential confounders. These confounders are previously explored as a correlation matrix. Results show that none of the potential confounders are correlated to each other, thus multicollinearity is unlikely. Univariate analyses were also conducted to explore the relationship between the variable of interest and outcome. The models used in the current analyses are:

1. Age (years)

2. Age (years), BMI (kg/m^2), moderate physical activity (Yes/No), smoking status (smoker v.s. non-smoker), alcohol intake (ethanol g/day) and socio-economic status (professional/managerial, intermediate or routine/manual).
3. In addition to model 2, energy intake (kcal/day) (data not shown).

Models that investigated coffee would adjust for tea intake, and vice versa.

5.3.3.3 Descriptive statistics

Characteristics of participants prior to the application of exclusion criteria were explored as part of the Chapter 2 Section 2.6 (Table 2.8). Baseline characteristics by coffee or tea quintiles after the application of listed exclusions (Section 5.3.3.1) and by disease status, into CHD, stroke and non-cases, was explored and reported here.

5.3.3.4 Survival analysis

Survival analysis was conducted using the Cox proportional hazards models to calculate a HR and 95% CI (or 99% CI for sensitivity analysis) [231]. Details of the survival analysis parameters were reported in Chapter 3 Section 3.3.3.4. Linear trend was tested by calculating increments of coffee or tea intake according to a typical portion size of 250 g, which is representative of a typical cup or mug [176]. Sensitivity analysis and effect modifications were also conducted in a similar manner to Chapter 3 Section 3.3.3.4. A summary of exclusion criteria and analysis plan is provided in Figure 5.1 & Figure 5.2.

5.3.3.5 Testing for statistical assumptions

Statistical assumptions were tested according to procedure reported in Chapter 2 Section 2.4.2. Schoenfeld residuals and log-minus-lot plot for both total coffee and total tea fully-adjusted models suggested that statistical assumptions were fulfilled. Statistical significance was determined by 2-sided p-value of ≤0.05 for 95% CI, or ≤0.01 for 99% CI. Stata version 13.0 [273] was used for all statistical analysis.

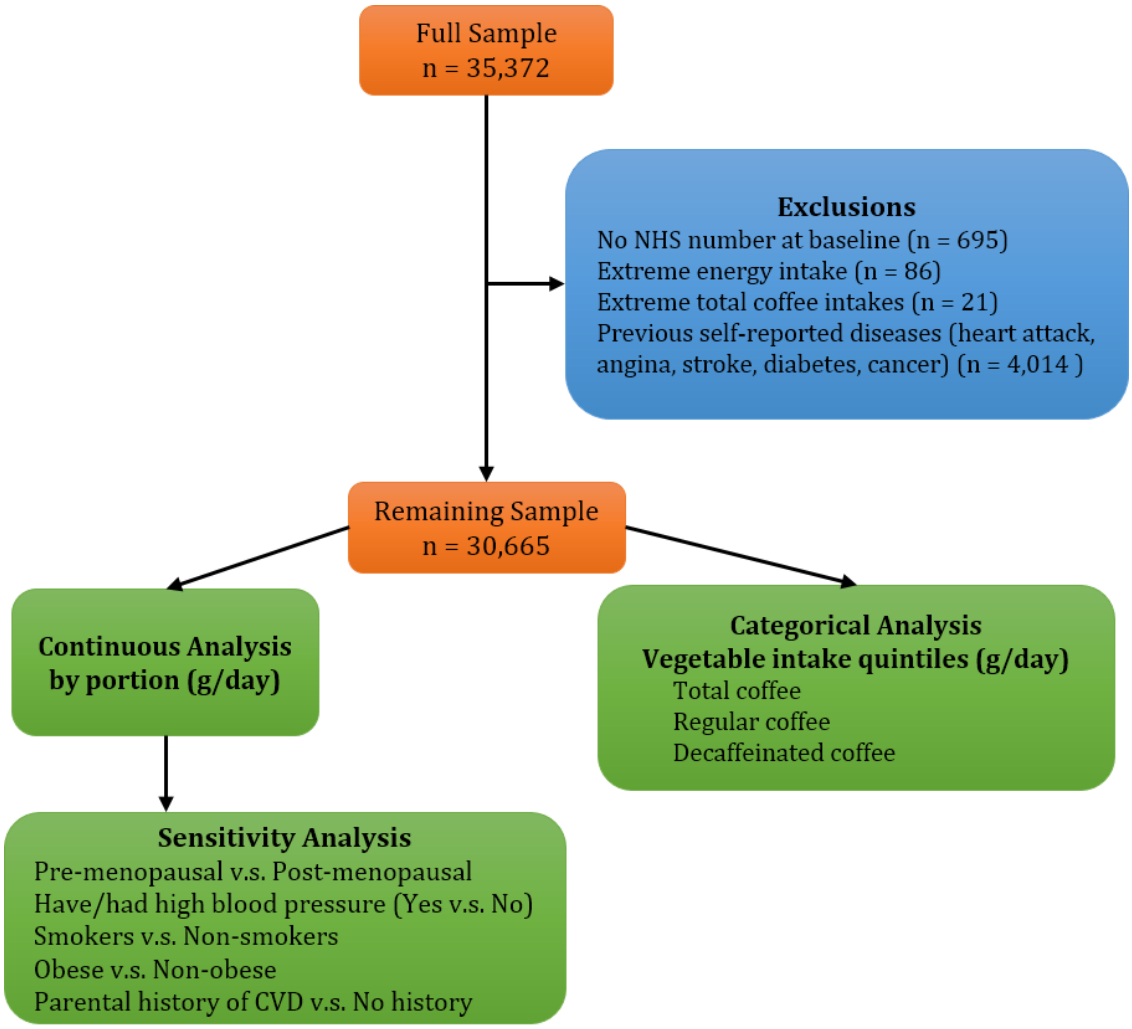


Figure 5.1 Summary flowchart of the current study exclusion criteria and analysis plan for coffee

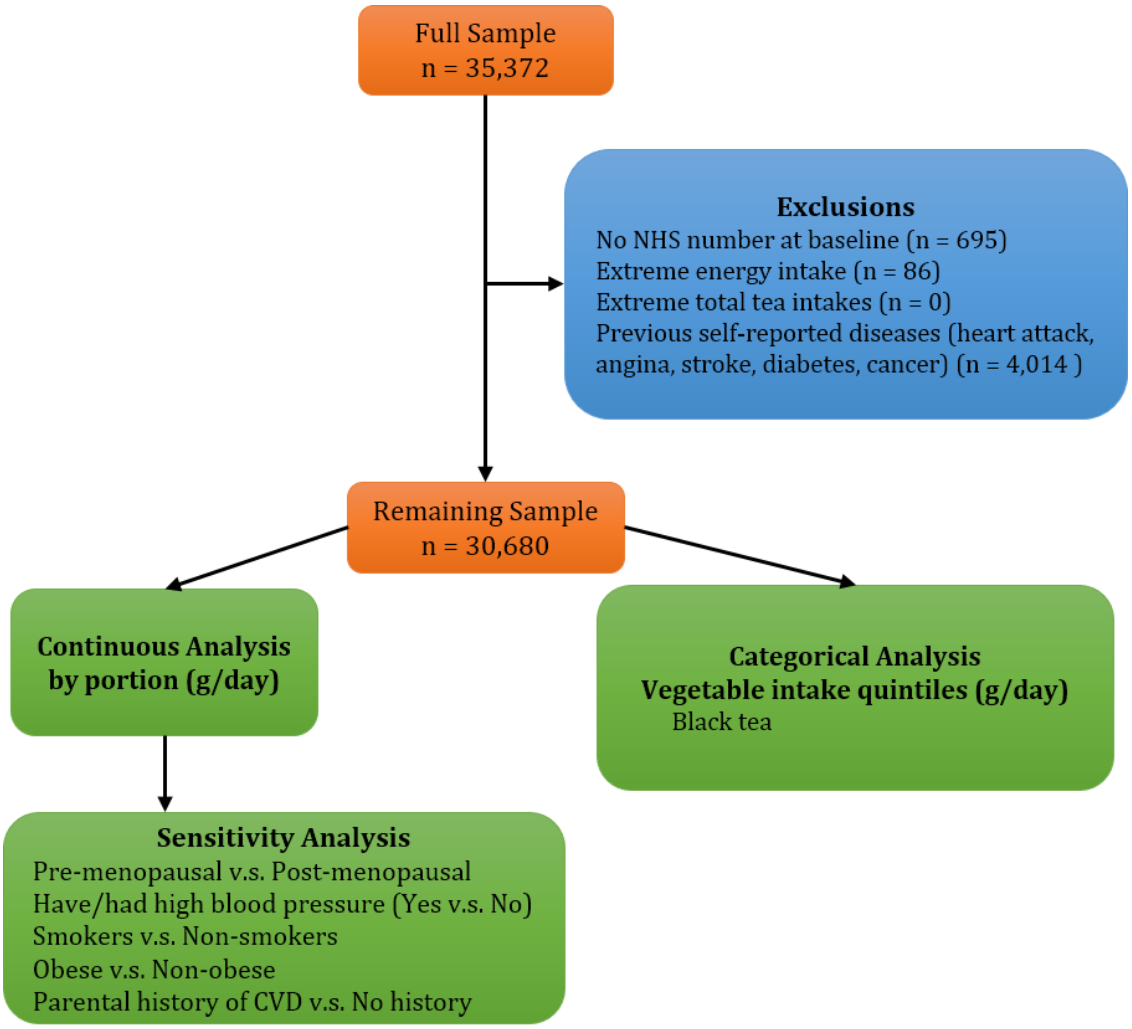


Figure 5.2 Summary flowchart of the current study exclusion criteria and analysis plan for tea

5.4 Results

5.4.1 Baseline characteristics

Baseline characteristics by case status are reported in Table 5.1 and Table 5.2. During the follow-up period from 1995 to 2013, there were 296 cases of CVD mortality (143 CHD cases, 153 stroke cases) in the coffee and tea analysis. The proportion of participants between cases and non-cases are similar in both analyses, and consistent with previous results investigating fruit intake and CVD mortality (Chapter 3). Fatal CVD cases tend to be older, with a higher BMI and larger waist circumference than non-cases. Fatal CVD cases also tend to be smokers and non-vegetarians, have lower physical activity levels, and are less likely to be supplement users. In general, fatal CVD cases tend to be from a lower socio-economic class. Non-cases have the highest proportion of participants in the

professional/managerial class, fatal CHD cases have the highest proportion within the intermediate class while fatal stroke cases have the highest proportion within the routine/manual class when compared across all three classes. Fatal CVD cases are also less likely to be married than non-cases and more likely to be well-educated. In addition, fatal CVD cases are twice as likely to report medical conditions compared to non-cases. FV intakes were lower in fatal CVD cases compared to non-cases. This is also reflected in portions of FV consumed. Coffee consumption was highest in fatal CHD cases, while non-cases consumed the most tea.

Baseline characteristics for participants by quintiles of coffee and tea intake are reported in Table 5.3 & Table 5.4. In general, participants who consume higher amounts of coffee tend to consume lower amounts of tea across the quintiles. This association is also observed vice versa. High coffee consumers are also more likely to be supplement users and consume more alcohol, with a slightly higher energy intake across the quintiles. However, participants who have higher intakes of tea are more likely to consume lower amounts of alcohol and have a higher energy intake across the quintiles. Trends across other variables in relation to tea or coffee are varied with no clear direction, though there are significant differences between quintiles. In addition, participants consume similar amounts of FVs regardless of the amount of coffee or tea intake.

Table 5.1 Baseline characteristics for CHD mortality, stroke mortality and non-fatal cases for the analysis of coffee consumption, expressed as mean and standard deviation for continuous variables, % and 95% CI for categorical variables

	CHD Mortality Cases	Stroke Mortality Cases	Non-cases
No. of cases (n)	143	153	30384
Age, years (SD)	63.4 (8.0)	64.0 (8.2)	51.5 (9.0)
BMI, kg/m^2 (SD)	25.7 (4.8)	24.4 (4.2)	24.3 (4.2)
Waist circumference, cm (SD)	77.0 (11.5)	75.6 (10.1)	73.1 (9.0)
Supplement users (%, 95% CI)	52.6 (44.6, 60.6)	52.9 (45.0, 60.8)	57.7 (57.1, 58.3)
Non-smokers (%, 95% CI)	81.7 (75.9, 87.5)	83.8 (78.4, 89.2)	89.5 (89.1, 89.8)
Moderately active/Active (%, 95% CI)	38.2 (30.4, 45.6)	39.0 (31.6, 46.3)	59.7 (59.1, 60.3)
Vegetarian/Vegan (%, 95% CI)	22.3 (16.0, 28.6)	19.5 (13.7, 25.3)	28.6 (28.1, 29.1)
Socio-economic status (%, 95% CI)			
Professional/Managerial	55.9 (48.2, 63.6)	57.4 (49.9, 64.9)	63.8 (63.2, 64.3)
Intermediate	36.6 (29.2, 44.0)	31.4 (24.4, 38.4)	27.2 (26.7, 27.7)
Routine and Manual	7.4 (3.4, 11.4)	11.2 (6.4, 15.9)	9.0 (8.7, 9.3)
Married/Living as married (%, 95% CI)	54.2 (46.6, 61.8)	54.5 (47.1, 61.9)	76.1 (75.6, 76.6)
Highest Educational Qualification (%, 95% CI)			
No Education	30.8 (23.2, 38.4)	36.0 (28.2, 43.8)	15.6 (15.2, 16.0)
O-Level	28.0 (20.6, 35.4)	20.4 (13.9, 26.9)	31.6 (31.0, 32.1)
A-Level	19.6 (13.1, 26.1)	23.1 (16.3, 29.9)	24.9 (24.4, 25.4)
Degree	21.7 (14.9, 28.5)	20.4 (13.9, 26.9)	27.9 (27.4, 28.4)
History of parental cancer/heart disease (%, 95% CI)	69.6 (62.6, 76.6)	62.8 (55.6, 70.0)	66.1 (65.6, 66.6)
Had/Have high blood pressure (%, 95% CI)	38.7 (31.1, 46.2)	36.9 (29.4, 44.4)	15.1 (14.7, 15.5)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	11.7 (6.5, 16.9)	13.8 (8.3, 19.3)	6.4 (6.1, 6.7)
Energy intake, kcal/day (SD)	2256 (723)	2245 (690)	2346 (709)
Alcohol intake, g/day (SD)	5.4 (8.8)	7.4 (9.6)	8.8 (10.5)
Total vegetables, g/day (SD)	296 (187)	276 (162)	315 (180)
Total fruits, g/day (SD)	372 (289)	379 (283)	411 (281)
Total coffee, g/day (SD)	366 (341)	330 (333)	381 (348)
Black tea, g/day (SD)	759 (510)	728 (526)	675 (509)
Portions of vegetables, no. of 80 g/day (SD)	4.8 (3.4)	4.4 (2.6)	5.2 (2.9)
Portions of fruit, no. of 80 g/day (SD)	4.6 (3.6)	4.7 (3.5)	5.2 (4.1)

Table 5.2 Baseline characteristics for CHD mortality, stroke mortality and non-fatal cases for the analysis of tea consumption, expressed as mean and standard deviation for continuous variables, % and 95% CI for categorical variables

	CHD Mortality Cases	Stroke Mortality Cases	Non-cases
No. of cases (n)	143	153	30384
Age, years (SD)	63.4 (8.0)	64.0 (8.2)	51.5 (9.0)
BMI, kg/m^2 (SD)	25.7 (4.8)	24.4 (4.2)	24.3 (4.2)
Waist circumference, cm (SD)	77.0 (11.5)	75.6 (10.1)	73.1 (9.0)
Supplement users (%, 95% CI)	52.6 (44.6, 60.6)	52.9 (45.0, 60.8)	57.7 (57.1, 58.3)
Non-smokers (%, 95% CI)	81.7 (75.9, 87.5)	83.8 (78.4, 89.2)	89.5 (89.1, 89.8)
Moderately active/Active (%, 95% CI)	38.2 (30.4, 46.0)	39.0 (31.6, 46.3)	59.7 (59.1, 60.3)
Vegetarian/Vegan (%, 95% CI)	22.3 (16.0, 28.6)	19.5 (13.7, 25.3)	28.6 (28.1, 29.1)
Socio-economic status (%, 95% CI)			
Professional/Managerial	55.9 (48.2, 63.6)	57.4 (49.9, 64.9)	63.8 (63.2, 64.3)
Intermediate	36.7 (29.2, 44.0)	31.4 (24.4, 38.4)	27.2 (26.7, 27.7)
Routine and Manual	7.4 (3.4, 11.4)	11.2 (6.4, 15.9)	9.0 (8.7, 9.3)
Married/Living as married (%, 95% CI)	54.2 (46.6, 61.8)	54.5 (47.1, 61.9)	76.1 (75.6, 76.6)
Highest Educational Qualification (%, 95% CI)			
No Education	30.8 (23.2, 38.4)	36.0 (28.2, 43.8)	15.6 (15.2, 16.0)
O-Level	28.0 (20.6, 35.4)	20.4 (13.9, 26.9)	31.6 (31.0, 32.1)
A-Level	19.6 (13.1, 26.1)	23.1 (16.3, 29.9)	24.9 (24.4, 25.4)
Degree	21.6 (14.9, 28.3)	20.4 (13.9, 26.9)	27.8 (27.3, 28.3)
History of parental cancer/heart disease (%, 95% CI)	69.6 (62.6, 76.6)	62.8 (55.6, 70.0)	66.1 (65.6, 66.6)
Had/Have high blood pressure (%, 95% CI)	38.7 (31.1, 46.2)	36.9 (29.4, 44.4)	15.1 (14.7, 15.5)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	11.7 (6.8, 16.9)	13.8 (8.3, 19.3)	6.4 (6.1, 6.7)
Energy intake, kcal/day (SD)	2256 (723)	2245 (690)	2345 (709)
Alcohol intake, g/day (SD)	5.4 (8.8)	7.4 (9.6)	8.8 (10.5)
Total vegetables, g/day (SD)	296 (187)	276 (162)	315 (180)
Total fruits, g/day (SD)	372 (289)	379 (283)	411 (281)
Total coffee, g/day (SD)	366 (341)	330 (333)	382 (351)
Black tea, g/day (SD)	759 (510)	730 (526)	675 (509)
Portions of vegetables, no. of 80 g/day (SD)	4.8 (3.4)	4.4 (2.6)	5.2 (2.9)
Portions of fruit, no. of 80 g/day (SD)	4.6 (3.6)	4.7 (3.5)	5.2 (4.1)

Table 5.3 Baseline characteristics of total coffee intake, expressed as mean and standard deviation for participants in the UKWCS including dietary habit, lifestyle habits, socio economic status and medical history

	Coffee consumption including decaffeinated coffee (g/day)				
	0 – 27	**30 – 190**	**194 – 475**	**479 – 665**	**855 – 1995**
General					
Participants (n)	7006	6324	7609	4097	5629
Age, years (SD)	50.6 (8.9)	52.7 (9.6)	52.6 (9.3)	51.3 (8.9)	50.7 (8.4)
BMI, kg/m^2 (SD)	24.1(4.3)	24.2 (4.1)	24.3 (4.0)	24.2 (4.0)	24.9 (4.7)
Waist circumference, cm (SD)	72.6 (9.1)	73.4 (9.0)	73.3 (9.0)	73.1 (8.4)	73.4 (9.2)
Dietary Intake					
Energy, kcal/day (SD)	2256 (697)	2349 (718)	2354 (687)	2427 (689)	2378 (748)
Alcohol, g/day (SD)	6.8 (9.7)	8.5 (10.6)	9.3 (10.4)	9.7 (9.7)	10.2 (11.5)
Total vegetables, g/day (SD)	321 (197)	313 (178)	312 (167)	313 (162)	313 (187)
Total fruit, g/day (SD)	413 (308)	409 (263)	413 (264)	415 (257)	403 (301)
Black tea, g/day (SD)	804 (560)	818 (484)	676 (454)	619 (440)	400 (465)
Portions of fruit, no. of 80 g/day (SD)	5.2 (4.3)	5.2 (4.0)	5.2 (3.9)	5.3 (4.0)	5.1 (4.4)
Portions of vegetables, no. of 80 g/day (SD)	5.3 (3.1)	5.2 (2.9)	5.2 (2.7)	5.2 (2.6)	5.1 (3.1)
Lifestyle Habits					
Supplement users (%, 95% CI)	61.4 (60.2, 62.6)	61.0 (59.7, 62.3)	56.2 (55.0, 57.4)	58.1 (56.5, 59.7)	51.3 (49.9, 52.7)
Non-smokers (%, 95% CI)	91.6 (90.9, 92.2)	90.2 (89.5, 90.9)	90.4 (89.7, 91.1)	91.5 (90.6, 92.3)	82.7 (81.7, 83.7)
Moderately Active/Active (%, 95% CI)	59.4 (58.2, 60.8)	58.7 (57.5, 59.9)	60.6 (59.5, 61.7)	62.5 (61.0, 64.0)	56.9 (55.6, 58.2)
Vegetarian/Vegan (%, 95% CI)	35.8 (34.7, 36.9)	28.5 (27.4, 29.6)	25.1 (24.1, 26.1)	25.9 (24.6, 27.2)	25.9 (24.8, 27.0)
Socio Economic Status					
High school education & above (%, 95% CI)	51.4 (50.2, 52.6)	50.4 (49.1, 51.7)	52.9 (51.7, 54.1)	59.0 (57.4, 60.6)	51.8 (50.4, 53.2)
Married/Living as Married (%, 95% CI)	74.1 (73.1, 75.1)	74.9 (73.8, 76.0)	77.6 (76.7, 78.5)	77.6 (76.3, 78.9)	75.7 (74.6, 76.8)
Professional & Managerial job holders (%, 95% CI)	63.2 (62.1, 64.3)	62.1 (60.9, 63.3)	62.3 (61.2, 63.4)	67.7 (66.3, 69.1)	65.2 (63.9, 66.4)
Medical History					
History of parental cancer/heart disease (%, 95% CI)	64.7 (63.6, 65.8)	66.7 (65.5, 67.9)	67.0 (65.9, 68.1)	65.5 (64.0, 67.0)	66.3 (65.0, 67.5)
Had/Have high blood pressure (%, 95% CI)	14.9 (14.0, 15.8)	16.5 (15.6, 17.4)	15.7 (14.9, 16.5)	15.7 (14.6, 16.8)	14.1 (13.2, 15.0)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	5.7 (5.1, 6.3)	7.0 (6.3, 7.6)	7.0 (6.4, 7.6)	6.4 (5.6, 7.2)	6.1 (5.5, 6.7)

Table 5.4 Baseline characteristics of black tea intake, expressed as mean and standard deviation for participants in the UKWCS including dietary habit, lifestyle habits, socio economic status and medical history

	Black tea consumption (g/day)			
	0 – 104	**208 – 650**	**1170**	**1560**
General				
Participants (n)	7104	13362	6888	3326
Age, years (SD)	50.5 (8.6)	52.0 (9.2)	52.1 (9.3)	51.8 (9.3)
BMI, kg/m^2 (SD)	24.5 (4.8)	24.2 (4.0)	24.3 (4.0)	24.5 (4.2)
Waist circumference, cm (SD)	73.0 (9.4)	73.1 (8.8)	73.3 (8.6)	73.6 (9.6)
Dietary Intake				
Energy, kcal/day (SD)	2214 (709)	2341 (688)	2420 (694)	2484 (777)
Alcohol, g/day (SD)	8.9 (11.4)	9.6 (10.5)	7.9 (9.3)	7.2 (10.4)
Total vegetables, g/day (SD)	321 (195)	313 (169)	313 (174)	311 (195)
Total fruit, g/day (SD)	422 (315)	415 (263)	403 (267)	387 (299)
Total coffee, g/day (SD)	528 (420)	397 (313)	279 (292)	221 (305)
Portions of fruit, no. of 80 g/day (SD)	5.3 (4.3)	5.3 (4.1)	5.2 (4.0)	5.0 (4.4)
Portions of vegetables, no. of 80 g/day (SD)	5.3 (3.1)	5.2 (2.8)	5.1 (2.8)	5.1 (3.2)
Lifestyle Habits				
Supplement users (%, 95% CI)	59.0 (57.8, 60.2)	57.0 (56.1, 57.9)	57.9 (56.6, 59.1)	57.2 (55.4, 58.9)
Non-smokers (%, 95% CI)	87.5 (86.7, 88.2)	90.6 (90.1, 91.1)	91.0 (90.3, 91.6)	85.3 (84.1, 86.5)
Moderately Active/Active (%, 95% CI)	60.0 (58.8, 61.2)	60.7 (59.9, 61.5)	58.5 (57.3, 59.7)	55.6 (53.9, 57.4)
Vegetarian/Vegan (%, 95% CI)	34.7 (33.6, 35.8)	26.3 (25.5, 27.0)	26.4 (25.4, 27.5)	28.5 (27.0, 30.1)
Socio Economic Status				
High school education & above (%, 95% CI)	54.7 (52.6, 56.9)	54.7 (53.2, 56.3)	46.2 (47.3, 51.6)	46.5 (43.6, 49.5)
Married/Living as Married (%, 95% CI)	71.8 (70.7, 72.8)	77.7 (77.0, 78.4)	77.4 (76.4, 78.4)	74.1 (72.5, 75.6)
Professional & Managerial job holders (%, 95% CI)	65.8 (64.7, 66.9)	64.2 (63.4, 65.1)	61.9 (60.7, 63.0)	61.0 (59.3, 62.6)
Medical History				
History of parental cancer/heart disease (%, 95% CI)	65.0 (63.8, 66.1)	66.0 (65.2, 66.8)	67.0 (65.9, 68.1)	66.9 (65.3, 68.5)
Had/Have high blood pressure (%, 95% CI)	14.3 (13.5, 15.1)	15.3 (14.6, 15.9)	16.5 (15.6, 17.4)	16.0 (14.7, 17.3)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	5.5 (4.9, 6.0)	6.8 (6.3, 7.2)	6.9 (6.3, 7.5)	6.7 (5.9, 7.7)

5.4.2 Survival Analysis

5.4.2.1 Full cohort

In the fully adjusted model (Table 5.5), HR and 95% CI for increasing quintiles of coffee and tea intake are presented with analysis of linear association addressing dose response. When coffee and tea were examined, there were no significant associations with CVD outcome in age-only or fully-adjusted models. There were also no significant associations between coffee, decaffeinated coffee and CVD outcomes in both models.

5.4.2.2 Sensitivity analysis

In the sensitivity analysis for coffee, tea and coffee subgroups (Table C.1), there were no significant associations with CVD outcome both the age-only or fully-adjusted models.

Table 5.5 Total coffee, tea intake and cardiovascular mortality risk (expressed as HR and 95% CI)

	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 Coffee										
Q1	0 – 27	25	1	1	36	1	1	58	1	1
Q2	30 – 190	45	1.40 (0.90, 2.16)	1.46 (0.89, 2.39)	43	1.00 (0.66, 1.50)	0.93 (0.59, 1.45)	85	1.17 (0.87, 1.58)	1.14 (0.82, 1.58)
Q3	194 – 475	32	0.78 (0.49, 1.26)	0.92 (0.54, 1.56)	39	0.77 (0.51, 1.18)	0.74 (0.47, 1.17)	71	0.78 (0.57, 1.07)	0.81 (0.57, 1.14)
Q4	479 – 665	14	0.74 (0.40, 1.36)	0.91 (0.47, 1.77)	16	0.69 (0.39, 1.20)	0.69 (0.38, 1.25)	28	0.71 (0.47, 1.07)	0.78 (0.50, 1.21)
Q5	855 – 1995	27	1.32 (0.81, 2.17)	1.35 (0.76, 2.40)	19	0.77 (0.46, 1.29)	0.67 (0.37, 1.19)	46	1.02 (0.71, 1.44)	0.94 (0.63, 1.41)
p trend			0.917	0.893		0.192	0.131		0.314	0.317
HR per 250 g/day			0.99 (0.88, 1.12)	1.01 (0.88, 1.15)		0.92 (0.82, 1.04)	0.90 (0.78, 1.03)		0.96 (0.88, 1.04)	0.95 (0.86, 1.05)
Coffee (no decaff)										
Q1	0	29	1	1	39	1	1	66	1	1
Q2	4 – 76	31	0.91 (0.57, 1.43)	1.08 (0.65, 1.79)	30	0.73 (0.47, 1.14)	0.76 (0.47, 1.23)	59	0.81 (0.59, 1.11)	0.90 (0.63, 1.27)
Q3	152 – 190	32	0.91 (0.58, 1.42)	1.06 (0.64, 1.76)	34	0.76 (0.50, 1.17)	0.78 (0.49, 1.25)	64	0.83 (0.61, 1.13)	0.90 (0.64, 1.26)
Q4	475	33	0.72 (0.46, 1.14)	0.88 (0.53, 1.45)	38	0.73 (0.48, 1.10)	0.71 (0.45, 1.12)	69	0.73 (0.54, 0.98)	0.78 (0.56, 1.09)
Q5	855 – 1140	18	1.05 (0.62, 1.79)	1.05 (0.57, 1.94)	12	0.63 (0.35, 1.13)	0.53 (0.27, 1.04)	30	0.82 (0.55, 1.21)	0.76 (0.49, 1.18)
p trend			0.695	0.698		0.213	0.116		0.244	0.160
HR per 250 g/day			0.97 (0.85, 1.11)	0.97 (0.84, 1.12)		0.92 (0.80, 1.05)	0.89 (0.76, 1.03)		0.94 (0.86, 1.04)	0.93 (0.84, 1.03)
Decaffeinated Coffee										
Q1	0	83	1	1	80	1	1	163	1	1
Q2	3.8 – 76	13	0.67 (0.38, 1.17)	0.76 (0.42, 1.36)	10	0.64 (0.36, 1.14)	0.99 (0.80, 1.22)	23	0.65 (0.44, 0.98)	0.68 (0.44, 1.05)
Q3	152 – 190	31	0.94 (0.65, 1.37)	0.94 (0.62, 1.42)	48	1.31 (0.94, 1.84)	1.18 (1.16, 1.21)	79	1.13 (0.88, 1.44)	1.21 (0.92, 1.59)
Q4	475	16	0.87 (0.52, 1.43)	0.91 (0.53, 1.55)	15	0.84 (0.50, 1.41)	0.99 (0.95, 1.03)	31	0.85 (0.60, 1.23)	0.91 (0.62, 1.34)
p trend	855 – 1140		0.678	0.442		0.791	0.143		0.921	0.626
HR per 250 g/day			1.04 (0.86, 1.25)	1.08 (0.89, 1.30)		0.97 (0.80, 1.18)	0.61 (0.32, 1.18)		1.01 (0.88, 1.15)	1.03 (0.90, 1.19)
Black Tea										
Q1	0 – 104	23	1	1	29	1	1	52	1	1
Q2	208 – 650	62	1.19 (0.77,1.88)	1.23 (0.75, 2.00)	60	0.82 (0.52, 1.29)	0.85 (0.54, 1.34)	122	0.90 (0.67, 1.21)	0.99 (0.71, 1.38)
Q3	1170	39	1.41 (0.87, 2.29)	1.41 (0.83, 2.42)	39	0.98 (0.60, 1.60)	1.04 (0.63, 1.72)	78	1.11 (0.81, 1.53)	1.16 (0.80, 1.66)
Q4	1560	15	1.52 (0.87, 2.67)	1.12 (0.57, 2.19)	21	1.13 (0.63, 2.01)	1.22 (0.68, 2.18)	36	1.19 (0.81, 1.73)	1.12 (0.72, 1.74)
p trend			0.175	0.626		0.476	0.314		0.225	0.412
HR per 250 g/day			1.05 (0.98, 1.14)	1.02 (0.94, 1.11)		1.03 (0.95, 1.12)	1.04 (0.96, 1.14)		1.03 (0.98, 1.09)	1.02 (0.96, 1.09)

[a] Cases apply to fully-adjusted models

[b] Adjusted for age, BMI, physical activity, smoking status, socio-economic status, alcohol intake and tea intake when investigating coffee, and vice versa.

5.5 Discussion

5.5.1 Summary of results

The objective of this study was to study the association between coffee, tea intake and risk of CVD. The present results indicate no association between coffee intake and the risk of CVD, and no association for higher tea intake and the risk of CVD. Although directions of associations for coffee tend to be inverse, point estimates and tests for linear association were not statistically significant. In contrast, risk estimates for tea tend to be positive, but also not statistically significant. When participants were stratified into subgroups, there were no significant associations between coffee, tea intake and CVD.

5.5.2 General comparison with literature

Findings for coffee intake here are in agreement with a few studies which investigated CVD mortality [274, 275], CHD and stroke mortality [276], and MI incidence [277] recently. No positive association with increasing coffee intake and the risk of CVD were reported in the studies above. Recent MAs report a significant non-linear inverse associations between CVD risk and higher coffee intake [93, 278]. Specifically, an 18% lower significant relative risk (RR) (95% CI 0.73 to 0.92) of CHD with moderate coffee consumption (1 to 3 cups in US, 3 to 4 cups in Europe) in women alone, or 13% lower RR (95% CI 0.80 to 0.96) of CHD in men and women followed-up for less than 10 years [92]. The direction of association is similar to the current study, which observed a 24% (95% CI 0.49 to 1.18) lower risk in CVD in women with the highest coffee consumption (855 to 1140 g/day, or 3.5 to 4.5 cups), but the association was not statistically significant. Other cohort studies also reported an inverse association between greater intake of coffee and fatal CHD or fatal stroke risk. The risk of fatal heart disease and stroke was 28% (95% CI 0.59 to 0.88) and 16% (95% CI 0.56 to 1.25) lower respectively in women who consumed six cups of coffee or more per day, compared to non-consumers. This association is also observed in men at the same coffee consumption levels [279]. However, a Japanese cohort only reported a significant negative association in women for higher intake of coffee and CVD, especially CHD, but not in men [280]. Women from the Nurses' Health Study also had a lower risk of stroke with increasing coffee intake. In summary, though studies conducted recently do not suggest an adverse association with higher coffee intake and CVD risk in general, results are still inconsistent.

With regard to tea intake and CVD risk, the evidence had been reviewed extensively. An earlier MA on tea and CVD risk suggested a borderline statistically significant lower incidence of MI by 11% (95% CI 0.79 to 1.01) with three cups of tea [281]. However, the

authors stated that heterogeneity was very high amongst studies for reliable conclusions to be drawn. Heterogeneity resulted from several factors. Firstly, publication bias for studies reporting an inverse association between greater tea intake and lower CVD risk. Secondly, the direction of association for UK and Australia were also positive for CHD and stroke respectively with greater tea intake, in contrast to a negative association reported in continental Europe. Thirdly, all but one Japanese study were ambiguous when assessing tea intake. Details to variety of tea (green, black or others), and preparation methods were unavailable in dietary assessments. As (poly)phenol profile and levels vary according to these factors, failure to account for the type of tea and brewing methods may contribute to large error estimates when attributing the mechanisms to (poly)phenols [281].

Within the latest SR and MA of prospective cohort studies, higher tea intake was associated with a lower cardiac death, CHD incidence and stroke mortality, specifically, a lower risk of cerebral infarction [270]. In addition, dose response meta-analysis reported a significantly reduced risk in cardiac death, CHD and stroke incidence, specifically cerebral infarction and intracerebral haemorrhage, but not stroke mortality with increments of three cups of tea. Sensitivity analyses revealed attenuated associations with risk of CHD, unless participants were European, or consumed black tea. Associations for all sensitivity analyses in Zhang *et. al* [270] by sex, country and type of tea were also attenuated for stroke mortality, in agreement with findings here. In another recent review of five MAs, a lower risk of stroke (mortality and incidence) was associated with greater tea (black and green), or greater flavonoid consumption in general [96]. These results are in contrast to Zhang *et. al* [270]. However, evidence of bias were found or not addressed in flavonoid meta-analyses. Case control studies were also included in three out of five these meta-analyses, which have a higher likelihood of recall and selection bias, and reverse causality. Thus in comparison to Zhang *et. al* [270], the quality of evidence presented here is relatively inferior and less reliable [96].

No association for tea consumption and CHD [282] or vascular death [275] was also reported in other studies, but a significant linear association between high consumption of tea and lower CHD risk was reported in the Dutch EPIC-NL cohort [276]. Interestingly, studies conducted within the UK, including the UKWCS all report a positive association with increasing black tea intake, although risk estimates tend to be attenuated adjusting for confounders [283, 284]. In summary, results in literature generally report an inverse association with higher tea consumption, with a minority number of studies reporting null significance.

5.5.3 Relevance with (poly)phenol mechanisms

Coffee intake was associated with an increase in CVD risk. MAs in the past have reported a positive association between CVD risk and high coffee consumption [90, 91]. Inconsistent conclusions from recent studies in contrast to these MAs could be due to various reasons. The three major components within coffee are caffeine, chlorogenic acids and diterpenes. Previous studies have revealed high levels of diterpenes (6 to 12 mg/cup) in boiled coffee prior to the popularization of instant or filtered coffee (0.6 mg/cup) [266]. This may have contributed to the positive association, due to cholesterol raising effects of diterpenes [265, 285], by decreasing bile acid formation and regulation of cholesterol biosynthesis [286]. Adverse effects of caffeine on cardiovascular factors were also previously suggested, however, further investigation revealed no adverse association with high caffeine intake in observational studies and RCTs [138]. The proposed protective component suggested to be chlorogenic acids, reported to improve endothelial and vascular function, producing an anti-hypertensive effect by mechanisms such as reducing free radical production, scavenging free radicals and stimulating NO production [148]. A SR and MA of RCTs on the supplementation effect of chlorogenic acids also reported a significant reduction in BP following an increase in the consumption of chlorogenic acids [152]. However, heterogeneity for methodology and study designs are high. In summary, the current study acknowledges the proposed evidence in literature on caffeine, and investigated caffeinated and decaffeinated coffee separately. However, no significant associations were detected. Levels of consumption were likely too low and varied to produce a reliable risk estimate.

On the other hand, the results of the investigation between tea consumption and risk of CVD were also inconsistent prior to recent findings. Green tea is more popularly consumed in Asian countries, where significant findings were previously reported [141]. Zhang *et. al* [270] also observed statistically significant findings in Asian populations with greater tea consumption and a lower risk of cardiac death. Caffeine levels in tea is approximately half of reported levels in coffee [287], and is unlikely to cause any adverse association for the reasons stated above. Tea flavonoids such as catechins (green tea) and theaflavins (black tea) inhibited the development of atherosclerotic lesions in animal models by lowering aortic cholesterol and triglyceride content [288] and improved endothelial function by improving NO-dependent vasodilation in animals and humans [141]. However, no significant association between higher tea intake and lower CVD mortality was found in the current study, despite the evidence from literature.

Inconsistent methodology between studies might have led to inconsistent results, in this case, non-significant associations. The UKWCS used FFQs to collect dietary data, as it is a better representation of yearlong dietary habits. However, information on brewing methods, composition or variety of coffee beans were ambiguous, for example, instant and ground coffee were combined as a single variable. These factors could affect the levels of diterpenes, caffeine and chlorogenic acids [266]. Likewise, multiple factors could also affect the levels of catechins and theaflavins within tea, such as variety, growth conditions, processing and brewing methods [289]. Cup sizes also varied across studies. Associations with CVD risk are then harder to detect if the quality of data on coffee, tea and its components are not precise enough. This is a limitation the current study also faced. In addition, heterogeneity could also exist by geographical location, as suggested by the positive associations found in UK cohorts [283, 284], including the current study, and may suggest differences in habit of tea preparation and consumption between UK and continental Europe.

The likelihood of detecting an association also increases if disease outcomes were more specific. The current study is limited to mortality, however, there were enough cases to investigate CHD and stroke separately, as the aetiology of those two diseases are different [3, 5]. CVD, CHD and stroke incidence was not studied here, thus it was not possible to suggest if higher tea consumption prevent stroke events in comparison to preventing death from stroke. For example, within Zhang *et. al* [270] all point estimates were attenuated for stroke mortality sensitivity analyses, but not for stroke incidence in men, Asian populations and for green tea. Thus future studies examining both mortality and incidence are preferred to investigate if differences exist.

Heavy consumption of coffee was associated with 'unhealthy' lifestyle factors, such as cigarette smoking, and was previously suggested as a reason why coffee drinkers appeared to have a higher risk of MI [91, 290]. However, the current study did adjust for smoking in acknowledgement to this and stratified the analysis by smoking status (non-smokers), with no significant associations found. It was also suggested that studies are more likely to report a significant positive association if follow-up time is shorter, as effects of coffee tend to be acute rather than chronic on CHD [291]. In addition, although social class was adjusted for using SES, there could be residual confounding SES could not account for, which may be why no protective associations were detected.

5.5.4 Strength and limitations

In addition to the discussion above, strengths for this study have been previously elaborated in Chapter 3, in relation to the 'health-conscious' study design and wide diversity of dietary intakes and patterns. However, the following limitations should be considered. Limitations in relation to considering only mortality data, few case numbers, incomplete follow-up, missing information on some covariates, as well as collection of dietary data at only one time point were also elaborated in the Chapter 3. More specific dietary intakes relating to coffee and tea components or disease outcomes, such as risk factors are recommended to improve the analysis.

5.6 Summary

In conclusion, the study did not find an association with coffee consumption and fatal CVD risk, nor a significant association with consumption of tea with fatal CVD in the UKWCS. Findings for coffee, although not significant are in agreement with literature, but findings for tea contrast with other non-UK studies. Further optimisation of methodology is required before conclusions can be drawn.

Chapter 6
Fruit, vegetable intake and the incidence of self-reported blood pressure in the UK Women's Cohort Study

6.1 Abstract

High blood pressure (HBP) is currently the leading risk factor for global disease burden. High FV intake is associated with a lower risk of hypertension in intervention and observational studies, however, FV types have been less frequently explored. This study aimed to explore the association between FV and respective subgroups and self-reported HBP in the UKWCS within a sub-cohort with follow-up. Total FV intake (g/day) derived from a 217-item FFQ, was obtained from 9,402 women (aged 35 to 69 years) at baseline from 1995 to 1998. FV intakes were sub-categorised according to similarities in (poly)phenol profile from Phenol Explorer, including berries, citrus, drupes, pomes, tropical fruits, *Allium* species, *Brassicaceae* species, fruit vegetables, pod vegetables and stalk & root vegetables. Incidence of self-reported HBP was reported through the phase 2 questionnaire. After a follow-up period of approximately five years, 716 incident self-reported HBP cases were observed. Logistic regression was conducted using participants free from history of CVD at baseline. Total FV intake, and especially total vegetable intake was associated with lower odds of self-reported HBP, with a 2% (95% CI 0.95 to 1.00) and 5% (95% CI 0.90 to 0.99) reduction in odds for each 80 g/day portion consumed respectively. With regard to subgroups, the intake of pomes and fruit vegetables significantly reduced odds of self-reported HBP by 11% (99% CI 0.80 to 0.99) and 18% (99% CI 0.67 to 1.00) respectively with each additional portion. In conclusion, the findings from this study provide strong evidence that total FV intake, especially vegetables are protective against odds of self-reported HBP. In particular, higher intakes of pomes and fruit vegetables may be particularly beneficial in terms of lowering odds of self-reported HBP, offering potential as a primary prevention to lower CVD.

6.2 Background

High blood pressure (HBP), previously defined in Chapter 1 Section 1.1.1.5.1, is the leading risk factor for global disease burden [292]. It is also a major risk factor for CVD, prevalent in 31% men and 26% women in the UK [293]. Diet is one of the modifiable factors known to play a prominent role in the development of HBP [294]. Increased FV intake have been reported to decrease BP in hypertensive and normotensive individuals [80]. Observational studies investigating FV intake and BP are also consistent with findings from the former study [295-300]. However, limited evidence exists for specific fruit or vegetable subgroups [301]. On the other hand, higher potassium [302] and lower sodium [303] consumption were also recommended to lower BP. Beneficial effects for potassium supplements had been previously reported in a MA of RCTs, causing an average reduction of -3.1 mmHg and -2.0 mmHg in systolic (SBP) and diastolic blood pressure (DBP) [302]. However, a recent RCT failed to replicate BP lowering effects of increased potassium intake from the diet and supplementation [304]. Furthermore, the Dietary Approaches to Stop Hypertension (DASH) trial [80] caused a greater reduction in SBP and DBP by -3.5 mmHg and -2.1 mmHg within normotensive subjects compared to a MA of RCTs investigating potassium [302]. Thus the BP lowering effect may not be fully accounted for by high potassium content, and warrants further investigation using whole foods instead of single nutrients.

As emphasized in previous chapters, FVs contain various nutrients and (poly)phenols, which are known to exhibit favourable effects on hypertension. Specifically, the incidence of hypertension was 8% lower in relation to higher habitual anthocyanin intake, predominantly from strawberries and blueberries [305]. Intervention studies on hesperidin, the main bioavailable flavonoid in citrus fruit, also reported favourable effects on HBP [126, 150, 151]. However, there are few studies to support the effect of other FV subgroups on incidence of HBP. In addition, very few studies have also examined incident HBP and the relationship between fruit or vegetable subgroups.

The aim of the current study was to explore the association between total FV intake and subgroups of FV intake according to similarities in (poly)phenol profile with reference to Phenol Explorer [111] and incidence of self-reported HBP within the UK Women's Cohort Study.

6.3 Methods

6.3.1 Dietary exposure

As described in Chapter 2 Section 2.6.1, total FV intakes were generated by combining multiple variables from the FFQ which recorded intakes of fresh fruits, dried fruits, pure fruit juices and processed fruits for fruits, and intakes of fresh vegetables and vegetables from composite dishes for vegetables.

6.3.2 Incidence outcomes

Data on self-reported HBP were available for participants who had answered the question 'Have your doctor ever told you that you have, or have had, any of the following conditions?' at baseline and at the follow-up phase 2 questionnaire (64% of participants provided this). The definition of BP statuses are reported in Table 6.1.

Table 6.1 Matrix to define BP status for participants with follow-up

	Response at baseline	
Response at phase 2	Yes	No
Yes	Prevalent	Incidence
No	Recovered	Non-cases

6.3.3 Statistical method and design

6.3.3.1 Outliers and exclusions

The procedure for omitting outliers and implementing exclusions is documented in Chapter 2 Section 2.5. In brief, participants who met the following criteria were excluded:

1. No, or incorrect NHS number provided at baseline FFQ, (n = 695)
2. Extreme energy intakes (<500 kcal/day & >6000 kcal/day) (n = 86)
3. Previous self-reported heart attacks, angina, cancer, diabetes and stroke at baseline (n = 4,014).
4. Outliers/Missing data for BMI (n = 1361)
5. Outliers for alcohol intake (n = 9)
6. No self-reported HBP data in Phase 2 (n = 22646)
7. Prevalent cases (n = 1663)
8. Recovered cases (n = 399)
9. Extreme total fruit intake (n = 284)
10. Extreme total vegetable intake (n = 59)

There were 9,402 participants eligible for inclusion after the application of the exclusion criteria above.

6.3.3.2 Confounding

The current analysis is based on the DAG from Chapter 2, Section 2.5.1 which was used to guide the selection of potential confounders. These confounders were previously explored as a correlation matrix (see Chapter 2). The results show that none of the potential confounders are correlated with each other, thus multicollinearity is unlikely. Univariate analyses were also conducted to explore the relationship between the variable of interest and outcome. The models used in the current analyses are:

1. Age (years, categorical)
2. Age (years, categorical), BMI (kg/m^2), moderate physical activity (Yes/No), smoking status (smoker v.s. non-smoker), alcohol intake (alcohol g/day), socio-economic status (professional/managerial, intermediate or routine/manual), family history of HBP (Yes/No), self-reported history of hypercholesterolaemia (Yes/No) (data not shown)
3. Model 2 and in addition, energy intake (kcal/day)

Total vegetable intake was adjusted for when modelling the association between total fruit and self-reported HBP. When investigating subgroups of fruits, mutual adjustments were also made. Salt and sodium intake was not adjusted for, as likelihood ratio tests suggest no significant difference between inclusion and exclusion of these variables in the model.

6.3.3.3 Descriptive statistics

Descriptive statistics were explored as part of the Chapter 2, Section 2.6.2 . These baseline characteristics were explored by dividing participants into total FV quintiles before exclusions listed in Section 6.3.3.1. Baseline characteristics by FV quintiles after exclusions and by disease status, into incident cases, recovered cases, prevalent cases and non-cases, were also explored and reported here.

6.3.3.4 Logistic Regression

Logistic regression was conducted to calculate odds ratios (OR) and 95% or 99% CI of self-reported HBP incidence [182]. A binary variable was created to categorise participants as having developed HBP (coded as 1) or not (coded as 0). The odds of self-reported HBP were determined by comparing each intake group with the reference group

which included the lowest consumers, (or non-consumers). Increments of fruit intake according to typical portion size (80g, or 125 g for fruit juice, 250 g for orange juice) [176] were also regressed to assess if there was a linear association with odds of self-reported HBP.

Effect modification was explored by stratification of subgroups of participants selected *a priori*. Variables investigated included BMI (obese v. non-obese), smoking (smoking v. non-smoking), menopausal status (pre-menopausal v. post-menopausal) and parental history of CVD. However, due to inadequate cases of self-reported HBP (<50), these analyses were ultimately restricted to not include smokers. A summary of exclusion criteria and analysis plan is provided in Figure 6.1.

6.3.3.5 Testing for statistical assumptions

Statistical assumptions were tested according to procedure reported in Chapter 2, Section 2.4.2.2. Goodness of fit was assessed by Hosmer-Lemeshow test where predicted risks were compared to observed risks. An insignificant chi-squared *p-value* suggested that there is no evidence the model is ill-fitted.

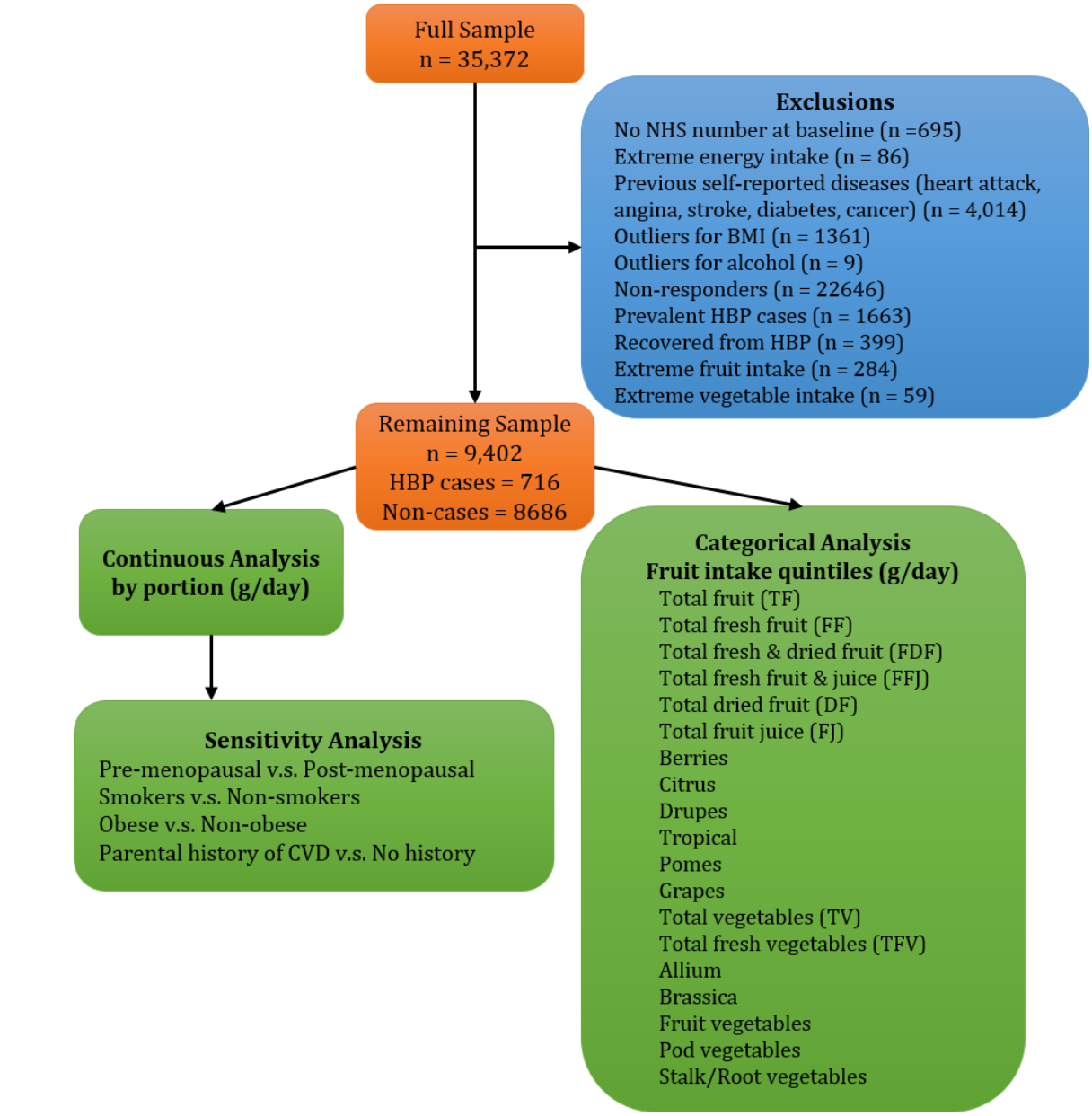


Figure 6.1 Summary flowchart for the current study exclusion criteria and analysis plan

6.4 Results

6.4.1 Baseline characteristics

After exclusion criteria were applied, 9,402 eligible participants were left for inclusion in the analysis. The baseline characteristics of participants by case status, are reported in Table 6.2. Non-cases and recovered cases tended to be younger than incident and prevalent cases, with a lower BMI and smaller waist circumference. However, non-cases had the highest energy and total vegetable intake, while prevalent cases consumed the most fruits. Prevalent cases were least likely to be vegetarian/vegans, moderately active, and most likely to be smokers. Incident cases were most likely to consume supplements out of the four groups. Non-cases contained the highest proportion of participants with a professional/managerial job, and smallest proportion of intermediate and routine/manual job holders, while incident cases had the highest proportion of the latter profession. Interestingly, incident cases consisted of the highest proportion of degree holders, while recovered cases consist of the least. Across all self-reported medical conditions and history, non-cases had the lowest proportion of participants with history of parental cancer or heart disease, family history of HBP and self-reported high cholesterol, while prevalent cases had the highest proportion of participants with the listed medical conditions and history.

When participants were divided according to FV intakes (Table 6.3), those who consumed more FVs tended to be older, with a lower BMI and smaller waist circumference. Participants who consumed more FVs tended to have a higher energy intake and lower alcohol intake. They were also more likely to be vegetarians/vegans, non-smokers, supplement users and moderately active. In addition, higher FV consumers also tended to be educated and hold a professional or managerial job. Despite the lower proportion of participants with family history of HBP, higher FV consumers were more likely to report a history of parental cancer or heart disease, as well as self-reported high cholesterol.

Table 6.2 Baseline characteristics of participant by self-reported HBP incidence, prevalence, recovered and non-cases.

	Incident cases	Non-cases	Prevalent cases	Recovered cases
No. of cases (n)	716	8686	1270	340
Age[a] , years (SD)	54.9 (8.4)	50.6 (8.6)	57.0 (8.8)	50.3 (8.1)
BMI, kg/m^2 (SD)	25.3 (4.3)	23.6 (3.6)	25.9 (4.7)	25.3 (5.5)
Waist circumference, cm (SD)	75.6 (9.9)	72.3 (8.2)	77.1 (9.9)	74.3 (9.4)
Energy intake, kcal/day (SD)	2318 (716)	2776 (671)	2302 (682)	2321 (719)
Alcohol intake, g/day (SD)	8.8 (10.7)	8.8 (9.9)	7.9 (10.0)	8.6 (9.7)
Total fruits and vegetables, g/day (SD)	721 (345)	733 (342)	731 (343)	732 (315)
Total vegetables, g/day (SD)	314 (168)	323 (165)	313 (161)	321 (161)
Total fruits & Juice, g/day (SD)	407 (245)	410 (243)	418 (244)	411 (222)
Portions of vegetables, no./day	5.2 (2.7)	5.4 (2.7)	5.2 (2.7)	5.3 (2.7)
Portions of fruits, no./day	5.3 (3.9)	5.3 (3.8)	5.4 (3.7)	5.3 (3.5)
Vegetarian/Vegan status (%, 95% CI)	24.2 (21.2, 27.4)	35.0 (34.0, 36.0)	23.9 (21.7, 26.4)	32.6 (27.9, 37.8)
Non-smokers (%, 95% CI)	92.6 (90.4, 94.3)	91.1 (90.4, 91.6)	93.3 (91.9, 94.6)	93.2 (90.0, 95.5)
Supplement users (%, 95% CI)	60.4 (56.6, 64.0)	60.1 (59.0, 61.2)	58.9 (56.0, 61.7)	58.6 (53.1, 63.9)
Moderately Active/Active (%, 95% CI)	56.8 (53.1, 60.5)	64.3 (63.3, 65.3)	56.3 (53.5, 59.0)	64.1 (58.8, 69.1)
Socio-economic status (%, 95% CI)				
Professional/Managerial (%, 95% CI)	63.7 (60.1, 67.2)	68.0 (67.0, 68.9)	60.7 (58.0, 63.4)	63.7 (58.4, 68.7)
Intermediate	26.3 (23.2, 29.7)	25.0 (24.1, 25.9)	30.6 (28.1, 33.2)	28.6 (24.0, 33.7)
Routine and manual	9.9 (7.9, 12.3)	7.0 (6.5, 7.6)	8.7 (7.2, 10.4)	7.7 (5.3, 11.0)
Highest Educational Qualification (%, 95% CI)				
No Education	11.0 (10.3, 11.7)	17.7 (14.9, 20.8)	9.8 (7.0, 13.6)	19.8 (17.6, 22.2)
O-Level	30.1 (29.1, 31.1)	29.8 (26.4, 33.4)	32.0 (27.1, 37.3)	28.6 (26.0, 31.3)
A-Level	25.7 (24.7, 26.6)	26.7 (23.5, 30.3)	28.9 (24.2, 34.1)	28.8 (26.2, 31.5)
Degree	33.2 (32.2, 34.2)	25.8 (22.6, 29.3)	29.2 (24.5, 34.4)	22.8 (20.4, 25.3)
History of parental cancer/heart disease (%, 95% CI)	69.5 (66.0, 72.8)	65.5 (64.5, 66.5)	75.7 (73.2, 78.0)	68.1 (63.0, 72.9)
Family history of high blood pressure (%, 95% CI)	45.6 (42.0, 49.3)	32.8 (31.8, 33.8)	50.9 (48.2, 53.7)	43.8 (38.6, 49.1)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	7.4 (5.7, 9.6)	4.3 (3.8, 4.7)	20.4 (18.1, 22.9)	9.1 (6.3, 12.8)

Table 6.3 Baseline characteristics of participants by total FV intakes expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables after the application of exclusion criteria

	Total fruit and vegetable consumption (g/day)				
	10 - 451	**451 - 604**	**604 - 759**	**759 - 974**	**974 - 2704**
General					
Participants (n)	1878	1886	1894	1870	1874
Age, years (SD)	49.8 (8.4)	50.9 (8.7)	51.1 (8.8)	51.4 (8.7)	51.7 (8.7)
BMI, kg/m^2 (SD)	24.0 (3.8)	23.7 (3.7)	23.8 (3.8)	23.5 (3.4)	23.5 (3.9)
Waist circumference, cm (SD)	72.8 (9.0)	73.1 (8.3)	72.3 (8.2)	72.5 (8.0)	72.2 (8.5)
Dietary Intake					
Energy, kcal/day (SD)	1895 (553)	2120 (560)	2237 (606)	2435 (636)	2712 (709)
Alcohol, g/day (SD)	9.0 (11.5)	9.1 (9.8)	9.2 (9.9)	8.6 (9.2)	8.1 (9.3)
Total fruit & juice, g/day (SD)	165 (76)	281 (79)	369 (93)	485 (118)	752 (245)
Total vegetable , g/day (SD)	172 (65)	248 (76)	308 (93)	373 (114)	511 (199)
Portions of fruit, no./day (SD)	2.1 (1.2)	3.7 (1.6)	4.8 (1.8)	6.2 (2.3)	9.8 (5.0)
Portions of vegetables , no./day (SD)	2.8 (1.2)	4.1 (1.3)	5.1 (1.6)	6.2 (1.9)	8.4 (3.2)
Lifestyle Habits					
Vegetarian/Vegan Status (%, 95% CI)	24.5 (22.6, 26.5)	28.8 (26.8, 30.9)	34.9 (32.8, 37.1)	36.9 (34.8, 39.2)	45.9 (43.6, 48.1)
Non-smokers (%, 95% CI)	85.3 (83.7, 86.9)	91.0 (89.7, 92.2)	92.6 (91.3, 93.7)	93.4 (92.2, 94.5)	93.5 (92.3, 94.6)
Use of supplements (%, 95% CI)	53.1 (50.8, 55.5)	56.0 (53.7, 58.4)	59.8 (57.5, 62.1)	63.8 (61.5, 66.1)	68.0 (65.7, 70.2)
Moderately Active/Active(%, 95% CI)	52.9 (50.6, 55.1)	60.6 (58.3, 62.8)	64.3 (62.1, 66.4)	68.4 (66.3, 70.5)	72.6 (70.5, 74.6)
Socio Economic Status					
High school education & above(%, 95% CI)	51.1 (47.1, 55.2)	59.3 (55.1, 63.6)	60.7 (56.5, 65.0)	60.0 (55.9, 64.4)	61.0 (56.7, 65.4)
Professional & Managerial job holders (%, 95% CI)	63.2 (61.0 65.4)	66.5 (64.3, 68.6)	67.0 (64.8, 69.1)	70.0 (67.9, 72.1)	71.6 (69.5, 73.6)
Medical History					
History of parental cancer/heart disease (%, 95% CI)	63.5 (61.3, 65.6)	65.1 (62.9, 67.2)	65.9 (63.7, 68.0)	66.5 (64.3, 68.6)	68.0 (65.9, 70.1)
Family history of high blood pressure (%, 95% CI)	67.1 (64.9, 69.2)	65.4 (63.2, 67.5)	67.7 (65.6, 69.8)	66.5 (64.3, 68.6)	64.3 (62.1, 66.5)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	3.8 (3.0, 4.7)	4.1 (3.3, 5.1)	4.3 (3.4, 5.3)	5.1 (4.2, 6.2)	5.3 (4.3, 6.4)

6.4.2 Logistic Regression

6.4.2.1 Full cohort

The odds of HBP and 95% or 99% CI are presented by increasing quantiles of FV intakes, as well as by portion to address linear association (Table 6.4). The odds of HBP incidence were 25% (95% CI 0.57 to 0.99) lower among participants who consumed >12 portions of FV per day. With every additional 80 g portion, odds of HBP incidence decreased by 2% (95% CI 0.95 to 1.00). Participants who consumed >5.5 portions of fresh and dried fruit per day had a 25% (95% CI 0.57 to 0.99) lower odds of HBP incidence compared with lowest consumers. However, there is no significant linear association by portion was observed. Point estimates also did not appear to be linear. There were no other significant associations between total fruit intake and odds of HBP. With regard to fruit subgroups, participants who consumed >2 portions of pomes had a 42% (99% CI 0.40 to 0.86) lower odds of HBP compared to lowest consumers. This association was also significant for every additional portion of pomes consumed, where odds of HBP was 11% (99% CI 0.80 to 0.99) lower. The remaining subgroups of fruit were not associated with change in odds of HBP.

When total vegetable intake was examined, there was an inverse association for the odds of HBP with higher intakes of total vegetables. Odds of HBP was a third lower (0.66, 95% CI 0.50 to 0.87) among participants who consumed >5.5 portions of vegetables compared to the lowest consumers. For every additional portion consumed, odds of HBP was 5% lower (95% CI 0.90 to 0.99). A similar association was also reported for the intake of fruit vegetables, where odds of HBP was 38% (99% CI 0.43 to 0.91) lower in the highest consuming quantile compared to the lowest. Every 80 g portion of fruit vegetable was also significantly associated with 18% (99% CI 0.67 to 1.00) lower odds of HBP. No other significant associations were detected for other vegetable subgroups and odds of HBP.

Table 6.4 Total fruit, total vegetable, FV subgroup intake and odds of self-reported HBP incidence

	Intake (g/day)	Odds of high blood pressure (95% or 99%* CI)		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total fruit & vegetable				
Q1	10 – 451	150	1	1
Q2	451 – 604	136	0.84 (0.66, 1.07)	0.81 (0.63, 1.04)
Q3	604 – 759	137	0.84 (0.66, 1.07)	0.81 (0.63, 1.05)
Q4	759 – 974	124	0.75 (0.59, 0.96)	0.73 (0.56, 0.95)
Q5	974 – 2704	137	0.83 (0.66, 1.06)	0.75 (0.57, 0.99)
p trend			0.093	0.028
OR per 80 g/day			0.98 (0.97, 1.00)	0.98 (0.95, 1.00)
Total fruit				
Q1	0 – 216	145	1	1
Q2	216 – 316	146	0.94 (0.74, 1.19)	0.95 (0.74, 1.22)
Q3	316 – 419	125	0.77 (0.61, 0.99)	0.83 (0.64, 1.08)
Q4	419 – 573	128	0.78 (0.61, 0.99)	0.82 (0.62, 1.06)
Q5	574 – 1494	140	0.86 (0.68, 1.09)	0.93 (0.71, 1.23)
p trend			0.231	0.620
OR per 80 g/day			0.98 (0.96, 1.01)	0.99 (0.96, 1.02)
Fresh fruit				
Q1	0 – 145	153	1	1
Q2	145 – 221	129	0.80 (0.63, 1.01)	0.78 (0.60, 1.00)
Q3	222 – 302	154	0.92 (0.73, 1.15)	0.90 (0.70, 1.16)
Q4	302 – 420	118	0.64 (0.50, 0.82)	0.69 (0.53, 0.90)
Q5	421 – 1477	130	0.73 (0.57, 0.93)	0.76 (0.57, 1.00)
p trend			0.070	0.405
OR per 80 g/day			0.97 (0.94, 1.00)	0.98 (0.95, 1.02)
Fresh fruit & juice				
Q1	0 – 206	144	1	1
Q2	206 – 303	146	0.95 (0.75, 1.21)	0.98 (0.76, 1.25)
Q3	303 – 405	124	0.79 (0.62, 1.01)	0.84 (0.65, 1.10)
Q4	405 – 557	132	0.81 (0.64, 1.03)	0.86 (0.66, 1.11)
Q5	557 – 1488	138	0.87 (0.68, 1.10)	0.94 (0.71, 1.24)
p trend			0.245	0.614
OR per 80 g/day			0.98 (0.96, 1.01)	0.99 (0.96, 1.02)
Fresh & dried fruit				
Q1	0 – 154	157	1	1
Q2	154 – 234	124	0.73 (0.58, 0.94)	0.72 (0.56, 0.93)
Q3	234 – 317	151	0.86 (0.69, 1.09)	0.85 (0.66, 1.09)
Q4	317 – 440	119	0.62 (0.49, 0.80)	0.68 (0.52, 0.89)
Q5	440 – 1480	133	0.73 (0.57, 0.93)	0.75 (0.57, 0.99)
p trend			0.066	0.414
OR per 80 g/day			0.97 (0.94, 1.00)	0.98 (0.95, 1.02)
Dried fruit*				
Q1	0 – 1.5	138	1	1
Q2	1.5 – 2.8	129	0.92 (0.66, 1.27)	0.91 (0.65, 1.27)
Q3	3 – 6	133	0.85 (0.62, 1.18)	0.88 (0.62, 1.23)
Q4	6 – 14	148	0.93 (0.68, 1.28)	1.03 (0.73, 1.44)
Q5	14 – 436	136	0.86 (0.62, 1.18)	0.96 (0.68, 1.37)
p trend			0.788	0.571
OR per 25 g/day			0.98 (0.86, 1.13)	1.03 (0.89, 1.19)
Fruit juice*				
Q1	0 – 10	149	1	1
Q2	13 – 41	145	0.97 (0.71, 1.33)	0.97 (0.70, 1.34)
Q3	58 – 116	158	1.19 (0.88, 1.61)	1.15 (0.84, 1.59)
Q4	119 – 148	104	1.04 (0.74, 1.45)	1.00 (0.70, 1.43)
Q5	155 – 1015	128	0.98 (0.71, 1.35)	0.97 (0.69, 1.36)
p trend			0.493	0.723
OR per 125 g/day			1.03 (0.92, 1.15)	1.02 (0.90, 1.14)
Total citrus*				
Non-Consumers	0	23	1	1
Q1	2 – 22	139	0.99 (0.56, 1.77)	0.90 (0.48, 1.68)
Q2	23 – 60	116	0.86 (0.48, 1.54)	0.81 (0.43, 1.53)
Q3	64 – 102	144	0.98 (0.55, 1.74)	0.98 (0.53, 1.84)
Q4	112 – 182	169	1.04 (0.59, 1.84)	0.99 (0.53, 1.85)
Q5	190 – 962	93	0.91 (0.50, 1.66)	0.94 (0.49, 1.80)
p trend			0.743	0.351
OR per 80g/day			1.01 (0.93, 1.09)	1.03 (0.95, 1.12)

(Table 6.4 continued)

	Intake (g/day)	Odds of high blood pressure (95% or 99%* CI)		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]
Citrus fruit*				
Non-Consumers	0	44	1	1
Q1	2 – 6	208	1.03 (0.67, 1.59)	1.02 (0.65, 1.62)
Q2	13	102	0.92 (0.57, 1.47)	0.93 (0.57, 1.54)
Q3	37	145	0.86 (0.55, 1.34)	0.87 (0.54, 1.40)
Q4	74	61	0.84 (0.50, 1.41)	0.95 (0.55, 1.65)
Q5	92 – 552	124	0.89 (0.56, 1.40)	1.01 (0.62, 1.66)
p trend			0.979	0.137
OR per 80 g/day			1.00 (0.85, 1.17)	1.10 (0.93, 1.31)
Orange juice*				
Non-Consumers	0	91	1	1
Q1	3 – 10	181	0.77 (0.55, 1.08)	0.75 (0.52, 1.07)
Q2	20	81	0.86 (0.55, 1.30)	0.91 (0.60, 1.40)
Q3	58	136	1.04 (0.72, 1.49)	1.00 (0.68, 1.47)
Q4	116 – 145	175	0.86 (0.61, 1.21)	0.84 (0.59, 1.21)
Q5	362 – 870	20	0.83 (0.43, 1.59)	0.80 (0.40, 1.58)
p trend			0.678	0.783
OR per 250 g/day			1.05 (0.78, 1.41)	1.03 (0.75 ,1.41)
Total berries*				
Q1	0 – 2	140	1	1
Q2	2 – 4	133	1.04 (0.75, 1.44)	1.04 (0.75, 1.46)
Q3	4 – 8	128	0.92 (0.67, 1.28)	0.92 (0.65, 1.29)
Q4	8 – 16	141	1.00 (0.73, 1.37)	1.01 (0.72, 1.41)
Q5	16 – 365	142	0.93 (0.68, 1.28)	0.98 (0.69, 1.40)
p trend			0.447	0.355
OR per 80 g/day			0.90 (0.64, 1.28)	0.87 (0.59, 1.28)
Total grapes*				
Q1	0 – 2	144	1	1
Q2	7	176	0.94 (0.70, 1.26)	0.94 (0.69, 1.28)
Q3	14	134	1.00 (0.73, 1.37)	1.00 (0.72, 1.40)
Q4	40	145	1.09 (0.80, 1.48)	1.12 (0.80, 1.55)
Q5	80 – 600	85	1.04 (0.72, 1.50)	1.20 (0.80, 1.78)
p trend			0.248	0.082
OR per 80 g/day			1.07 (0.91, 1.26)	1.12 (0.95, 1.32)
Total pomes*				
Q1	0 – 24	166	1	1
Q2	24 – 55	127	0.68 (0.50, 0.93)	0.70 (0.50, 0.96)
Q3	62 – 102	146	0.85 (0.63, 1.15)	0.90 (0.65, 1.24)
Q4	108 – 140	152	0.76 (0.57, 1.03)	0.81 (0.59, 1.12)
Q5	162 – 1044	93	0.56 (0.40, 0.79)	0.58 (0.40, 0.86)
p trend			0.001	0.007
OR per 80 g/day			0.88 (0.80, 0.97)	0.89 (0.80, 0.99)
Total drupes*				
Q1	0 – 1	140	1	1
Q2	1 – 3	152	1.04 (0.76, 1.43)	1.05 (0.76, 1.46)
Q3	3 – 7	140	0.99 (0.72, 1.36)	1.02 (0.73, 1.43)
Q4	7 – 11	123	0.91 (0.66, 1.26)	0.90 (0.63, 1.28)
Q5	11 – 115	129	0.88 (0.64, 1.22)	0.96 (0.65, 1.40)
p trend			0.481	0.988
OR per 80 g/day			0.78 (0.31, 1.93)	1.00 (0.35, 2.85)
Total tropical*				
Q1	0 – 18	141	1	1
Q2	18 – 45	161	1.05 (0.77, 1.43)	1.05 (0.76, 1.44)
Q3	45 – 80	116	0.78 (0.56, 1.09)	0.77 (0.54, 1.09)
Q4	80 – 107	119	0.82 (0.59, 1.14)	0.80 (0.57, 1.14)
Q5	108 – 666	147	0.95 (0.70, 1.30)	1.05 (0.74, 1.49)
p trend			0.821	0.635
OR per 80 g/day			0.99 (0.86, 1.13)	1.03 (0.88, 1.20)

(Table 6.4 continued)

	Intake (g/day)	Odds of high blood pressure (95% or 99%* CI)		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total vegetable				
Q1	0.4 – 188	163	1	1
Q2	188 – 257	140	0.81 (0.64, 1.03)	0.77 (0.60, 0.98)
Q3	257 – 332	129	0.73 (0.58, 0.93)	0.70 (0.55, 0.91)
Q4	332 – 436	123	0.71 (0.56, 0.90)	0.64 (0.49, 0.83)
Q5	436 – 1460	129	0.77 (0.60, 0.97)	0.66 (0.50, 0.87)
p trend			0.084	0.018
OR per 80 g/day			0.97 (0.93, 1.00)	0.95 (0.90, 0.99)
Fresh vegetable*				
Q1	0.4 – 159	147	1	1
Q2	160 – 218	140	0.90 (0.66, 1.24)	0.89 (0.64, 1.23)
Q3	218 – 284	129	0.79 (0.57, 1.09)	0.77 (0.55, 1.08)
Q4	284 – 373	142	0.90 (0.66, 1.23)	0.86 (0.61, 1.21)
Q5	373 – 1416	126	0.79 (0.58, 1.09)	0.72 (0.50, 1.05)
p trend			0.138	0.072
OR per 80 g/day			0.97 (0.91, 1.02)	0.95 (0.89, 1.02)
Allium*				
Q1	0 – 3	179	1	1
Q2	3 – 6	139	0.82 (0.61, 1.11)	0.88 (0.64, 1.20)
Q3	6 – 11	123	0.72 (0.52, 0.98)	0.78 (0.56, 1.09)
Q4	11 – 13	109	0.75 (0.55, 1.03)	0.78 (0.55, 1.11)
Q5	13 – 82	134	0.81 (0.60, 1.09)	0.92 (0.64, 1.32)
p trend			0.453	0.760
OR per 80 g/day			0.83 (0.43, 1.59)	1.10 (0.50, 2.41)
Brassicaceae*				
Q1	0 – 34	142	1	1
Q2	34 – 55	127	0.86 (0.62, 1.20)	0.82 (0.59, 1.15)
Q3	55 – 80	138	0.92 (0.67, 1.26)	0.89 (0.64, 1.24)
Q4	81 – 125	142	0.91 (0.66, 1.26)	0.90 (0.64, 1.27)
Q5	125 – 774	135	0.85 (0.62, 1.17)	0.78 (0.54, 1.13)
p trend			0.540	0.540
OR per 80 g/day			0.97 (0.85, 1.10)	0.96 (0.83, 1.12)
Fruit vegetable*				
Q1	0 – 37	171	1	1
Q2	37 – 55	146	0.85 (0.63, 1.15)	0.82 (0.60, 1.13)
Q3	55 – 82	137	0.84(0.62 ,1.14)	0.78 (0.56, 1.07)
Q4	82 – 110	117	0.66 (0.48, 0.91)	0.63 (0.45, 0.89)
Q5	110 – 645	113	0.66 (0.48, 0.91)	0.62 (0.43, 0.91)
p trend			0.003	0.010
OR per 80 g/day			0.83 (0.70, 0.97)	0.82 (0.67, 1.00)
Pod vegetable*				
Q1	0 – 12	140	1	1
Q2	12 – 21	147	1.17 (0.85, 1.59)	1.10 (0.79, 1.52)
Q3	21 – 37	114	1.07 (0.77, 1.50)	1.08 (0.76, 1.53)
Q4	37 – 47	139	1.07 (0.78, 1.47)	1.11 (0.79, 1.55)
Q5	50 – 375	144	1.21 (0.88, 1.65)	1.26 (0.88, 1.79)
p trend			0.224	0.111
OR per 80 g/day			1.16 (0.85, 1.58)	1.26 (0.87, 1.84)
Stalk & root vegetable*				
Q1	0 – 17	150	1	1
Q2	17 – 30	139	0.88 (0.64, 1.20)	0.88 (0.63, 1.22)
Q3	30 – 42	121	0.79 (0.57, 1.09)	0.78 (0.56, 1.11)
Q4	42 – 63	131	0.80 (0.59, 1.11)	0.83 (0.59, 1.18)
Q5	63 – 404	143	0.87 (0.64, 1.19)	0.98 (0.67, 1.44)
p trend			0.226	0.938
OR per 80 g/day			0.88 (0.68, 1.15)	0.99 (0.71, 1.37)

[a] Cases apply to fully-adjusted models

[b] Adjusted for age (categorical), BMI, physical activity, energy intake, smoking status, socio-economic status, alcohol intake, family history of HBP, self-reported history of hypercholesterolaemia, mutual adjustment for total fruit or total vegetable intake and mutual adjustments for fruits/vegetables that are not in the exposure category

6.4.2.2 Sensitivity analysis

6.4.2.2.1 Obese v.s. Non-obese

Within women in both subpopulations, there were no significant associations between total FV, total fruit and total vegetable intakes and odds of HBP (Table D.1). Within obese women, every 80 g portion of grapes was adversely associated with 75% (99% CI 1.03 to 2.99) higher odds of HBP. This association was not detected within non-obese, women, instead, every 80 g portion of fruit vegetables was inversely associated with 19% (99% CI 0.65 to 1.00) lower odds of HBP. The intake of pomes was also significantly associated with 10% lower odds of HBP when the model was age-adjusted, however, the association disappeared when the model was fully-adjusted. No significant associations were detected for FV subgroups.

6.4.2.2.2 Menopausal status

There were no significant associations between FV intake and odds of HBP when analyses were restricted to postmenopausal women (Table D.2). The odds of HBP were lower for every additional portion of pomes by 17% (99% CI 0.70 to 0.99) and by 28% (99% CI 0.54 to 0.96) for every portion of fruit vegetables when the model was age-adjusted. No significant associations were found for premenopausal women when models were fully-adjusted.

6.4.2.2.3 Parental history of CVD

No significant associations were detected for FV intake and odds of HBP within women who had parental history of CVD (Table D.3). The odds of HBP were 4% (99% CI 0.92 to 1.00) lower for every additional portion of total FV intake for participants without parental history of CVD. The odds of HBP were also lower for every additional portion of pomes by 16% (99% CI 0.73 to 0.97) and by 24% (99% CI 0.60 to 0.95) for every portion of fruit vegetables when the model was age-adjusted in participants without parental history of CVD. However, these associations were no longer significant when the model was fully-adjusted.

6.4.2.2.4 Non-smokers

The odds of HBP was 3% (99% CI 0.95 to 1.00) lower for every portion of total FV within non-smokers (Table D.4). In addition, intake of pomes and fruit vegetables was associated with 11% (99% CI 0.79 to 0.99) and 19% (99% CI 0.66 to 0.99) lower odds of

HBP respectively within non-smokers for every additional portion. There were no other associations detected for subgroups of fruit or vegetables.

6.5 Discussion

6.5.1 Summary of results

The objective of this study was to investigate the association between different subgroups of FV and the incidence of self-reported HBP. Findings from the current study observed a lower odds of self-reported HBP with higher intake of total FVs, as well as total vegetables. In terms of FV subgroups, greater intake of total pomes and fruit vegetables were associated with a lower odds of self-reported HBP. No evidence of association was determined for the remaining fruit or vegetable subgroups in the full cohort.

With regard to subgroup analyses, significant associations reported above were restricted to non-smokers, and partially restricted to non-obese women and those with no parental history of CVD. Consumption of grapes were also associated with nearly two-fold increase in odds of self-reported HBP. However, there were few cases and CIs were particularly wide, thus this finding needs to be further verified and carefully interpreted.

6.5.2 General comparison with literature

In general, findings here support results from previous observational studies investigating the association between total FV intake and HBP from different countries [298, 300], despite methodological differences with regard to the outcome. The latter studies utilised standard procedure involving a mercury sphygmomanometer to attain measured BP in mmHg, while the current study relied on self-reported general practitioner's diagnosis. There are certain methodological limitations with regard to the reliability of self-reported data, and is a potential limitation in this study. With regard to the exposure, an improvement was made in the current study where total FVs included food items which were part of a composite dish, which may or may not be the case in other cohorts.

The results reported above are supported by findings from the DASH trial [80]. In addition, other studies also investigated dietary patterns rather than subgroups of FVs, where the results are also supportive for the current findings [306, 307]. Furthermore, dietary patterns, greater FV intake and lower sodium consumption has the strongest evidence for association with lower BP [294]. Findings from dietary patterns are also easily applied to public health recommendations specific to the habitual diet of the particular country. However, the concept of a dietary pattern may introduce challenges when trying

to investigate the actual properties within the fruit or vegetable which may be associated with lower BP.

When examining FV intakes separately, findings tend to vary across cohorts. Two studies are in agreement with the current findings [295, 296], however, some studies also report lower BP incidence or risk of HBP with higher intake of fruits [295, 297, 299, 301], which was not found in the current study, despite the reported high intakes of total fruit in general. Kim et al. reported higher BP in association with higher consumption of Kimchi and salty vegetables native to Korea [300]. While these types of vegetables are not commonly consumed in UK, the finding prompts further investigation into differences between raw and cooked/processed vegetables, in particular, the addition of salt. In terms of FV subgroups, results from the Nurses' Health Study are supportive of the findings on the intake of pomes and fruit vegetables in the current study, specifically, a higher intake of apples and aubergines were associated with lower BP [295]. However, favourable associations between lower BP and greater intake of oranges and grapes were also found in the Nurses' Health Study, but not here.

6.5.3 Relevance with (poly)phenol mechanisms

In previous intervention studies which examined nutrients in FVs, such as potassium supplementation [224, 302], there was inconsistent evidence for effects of potassium on HBP for normotensive populations, while evidence suggests that lowering sodium intakes [116, 224, 308] are beneficial towards lowering BP. There are also other nutrients in FVs which have significant association with CVD risk including fibre [221, 248], glucosinolates [251] and "antioxidants" such as carotenoids [249] and (poly)phenols, which may also exhibit certain effects on HBP, either independent of or synergistically with potassium and sodium. As explained in Chapter 3, Section 3.5.3, pomes are rich in flavanols, especially catechin and proanthocyanidins [309, 310]. Significant associations were also found between intakes of apples and pears and CVD risk in observational studies [117, 254]. However, there is limited evidence to support the beneficial effect of (poly)phenols from apples on markers of CVD and BP. Apple and apple juices were reported to improve lipid profiles in some intervention studies [236, 255, 256], but contrasting results using freeze dried apples were also reported elsewhere [257]. Non-significance in the latter study could be due to a relatively smaller dose of apple, and differences in processing effects (freeze drying). Interestingly, despite evidence from RCTs to support the association between citrus fruits (or hesperidin) and effects on BP [150, 151], a significant association was not observed in the current study. Further inspection into intakes of berries, drupes and

tropical fruit also revealed relatively low intakes, which may somewhat explain the lack of association.

On the other hand, fruit vegetables mainly consist of tomatoes and peppers. Tomatoes are rich in quercetin, lignans and caffeic acid, while peppers (red, yellow and green) are also rich in quercetin, as well as lignans and luteolin. It was previously elaborated that quercetin exhibited the ability to decrease permeability and fragility of capillary walls, which were symptoms that manifests in hypertension [245]. Limited evidence from a human clinical trial show promise of an anti-hypertensive effect for a high dose of quercetin within stage 1 hypertensive patients, however, this effect was not observed in pre-hypertensive patients. In addition, the administered quercetin dosage was also much greater than the amount a normal diet could provide [311]. Evidence on the effects of isolated flavonols on the development of atherosclerosis are also limited [229].

The current study observed a null association between the *Allium* subgroup and incidence of self-reported BP, possibly because the subgroup does not contain onions, one of the richest sources of quercetin. Thus, supposing that the association is due to high intakes of quercetin within tomatoes and peppers, the concentration of quercetin overall may not be high enough *in vivo* within the *Allium* subgroup to have any mechanistic effects, which resulted in the lack of association. The intake of lignans, potential effects on improving CVD risk factors in RCTs [246], and the limitations of the current methodology surrounding literature [247] have been reviewed in Chapter 3. Despite its availability in all the remaining vegetable subgroups (*Brassicaceae*, pod and stalk & root vegetables), concentrations of lignans are relatively low, thus in isolation, none of these vegetable types provided sufficient amounts of the most potent types of (poly)phenols, resulting in non-significant associations.

6.5.4 Strengths and limitations

The following limitations should be considered when interpreting the results of the current study. Limitations in relation to usage of the FFQ, missing information on some covariates, collection of dietary data at only one time point, variation in availability of foods from different time periods were elaborated in the Chapter 3. Furthermore, application of the study findings is also restricted to women only.

Strengths for this study have been previously elaborated in Chapter 3, in relation to advantageous usage of Phenol Explorer, the larger sample size compared to other studies, the design of the 'health-conscious' cohort and a wide diversity in dietary intakes and patterns. This is also the first study which extensively investigated the effects of subgroups

of FVs according to (poly)phenol profiles on incidence of self-reported HBP. The estimation of total FV intake is also strengthened by the inclusion of other fruit sources such as dried fruit, juices or processed fruits, and vegetables from composite dishes.

6.6 Summary

In conclusion, a greater consumption of total FV intake, especially total vegetables, fruit vegetables, and pomes were associated with lower odds of self-reported HBP in the UKWCS. This finding is aligned with Chapter 3 and Chapter 4, as well as current literature promoting high FV dietary patterns, and guidelines promoting FVs consumption for health. Further investigations are recommended using measured BP instead of self-reported data (which will be explored in Chapter 10), and interventions are recommended for the consumption of pome fruits and fruit vegetables to assess its relationship with HBP development.

Chapter 7
Coffee, tea intake and incidence of self-reported blood pressure in the UK Women's Cohort Study

7.1 Abstract

Chapter 6 explored the association between FV intake, and the odds of self-reported HBP. This study aimed to explore the association between coffee, coffee subgroups and tea and self-reported HBP in the UKWCS. Total coffee and tea intake (g/day) derived from a 217-item food frequency questionnaire, was obtained from 9,467 women (aged 35 to 69 years) at baseline from 1995 to 1998. Coffee intakes were also further explored by type into regular coffee and decaffeinated coffee. Incidence of self-reported HBP was derived through the phase 2 follow up questionnaire. After a follow-up period of approximately five years, 721 incident self-reported HBP cases were observed. Logistic regression was conducted using participants free from history of CVD at baseline. Total coffee and total tea intake were not found to be associated with odds of self-reported HBP. In conclusion, the lack of association with coffee is aligned with evidence current literature, but results for the null association between black tea intake and HBP were not. Until further methodological improvements are made in future cohort or RCTs, the association between coffee, tea and HBP remains controversial.

7.2 Background

The association between coffee, tea intake and CVD mortality was explored previously (Chapter 5) due to inconsistent evidence in literature. The findings reveal no associations between either beverage type and CVD mortality risk in the UKWCS. As explained earlier (Chapter 5) with regard to the limitations of mortality rates, this chapter intends to reinvestigate by improving specificity of the outcome. CVD was introduced in Chapter 1 as a collection of diseases, its development influenced by multiple biological, environmental and behavioural risk factors. The present chapter will place emphasis on HBP, as it is the leading risk factor for global disease burden [292] and currently prevalent in 31% men and 26% women in the United Kingdom (UK) [293]. By improving the

specificity of the outcome relative to CVD mortality, this chapter will explore and generate hypotheses based on mechanisms of (poly)phenols on BP.

Chapter 5 Section 5.2 introduced coffee and tea as the most commonly consumed non-alcoholic beverages in the world after water [263]. These beverages contain various bioactive components, such as caffeine in both coffee and tea, chlorogenic acids and diterpenes in coffee [137], catechins and derivatives in tea [264]. These bioactive components may impact or act on CVD risk factors. Previous research suggested that diterpenes in unfiltered coffee raised serum cholesterol [265]. Caffeine is known to exhibit an acute pressor effect up to three hours after administration as demonstrated in RCTs. This effect is known to vary by hypertensive status, mental or physical stress, by age, and especially in habitual consumers, where heavy coffee drinkers are more likely to build a tolerance to the acute pressor effect [312, 313]. Recent evidence from a SR and MAs did not suggest an adverse association between BP and habitual coffee consumption within hypertensive [314] and normotensive individuals [315]. More importantly, a scientific opinion based on SRs and MAs concluded no adverse effects when caffeine from coffee or tea is consumed *ad libitum* [138]. In addition, (poly)phenols in both beverages are suggested to counter negative aspects from diterpenes and caffeine [266]. Chlorogenic acids (from various sources, including coffee) were found to significantly reduce both SBP and DBP within a SR and MA of RCTs, but the majority of the trials were conducted in Japan [152]. A SR and MA of catechins from green tea and BP also reached a similar conclusion, however, heterogeneity was high in the analysis of DBP [153]. Findings from prospective cohort studies are also inconclusive, most likely due to methodological variances, such as ambiguous assessment of coffee and tea intakes. A U-shaped association for incident hypertension was observed across coffee intakes ranging from none to >5 cups/day [316], while a SR and MA analysing a highly similar set of cohort studies in comparison to the former study showed no association between coffee and HBP incidence [315].

As earlier research findings are inconclusive, the aim of the current study was to explore the association between coffee, tea intake and the risk of self-reported HBP incidence using data from the UKWCS.

7.3 Methods

7.3.1 Dietary exposure

Total coffee and black tea intakes were generated by combining multiple variables from the FFQ which recorded intakes of regular coffee and decaffeinated coffee documented in Chapter 2, Section 2.6.1. There were no missing data for coffee or tea intakes. Consumption was expressed as grams of coffee or tea intake per day (g/day).

7.3.2 Incidence outcomes

Incidence outcome for the current analysis is equivalent to the outcome reported in Chapter 6, Section 6.3.2.

7.3.3 Statistical method and design

7.3.3.1 Outliers and exclusions

The procedure for omitting outliers and implementing exclusions is documented in Chapter 2, Section 2.5.1. In brief, participants who met the following criteria were excluded:

1. No, or incorrect NHS number provided at baseline FFQ, (n = 695)
2. Extreme energy intakes (<500 kcal/day & >6000 kcal/day) (n = 86)
3. Previous self-reported heart attacks, angina, cancer, diabetes and stroke at baseline (n = 4,014).
4. Outliers/Missing data for BMI (n = 1361)
5. Outliers for alcohol intake (n = 9)
6. No self-reported HBP data in Phase 2 (n = 22646)
7. Prevalent cases (n = 1663)
8. Recovered cases (n = 399)
9. Extreme coffee intake (n = 21)

There were 9,467 participants eligible for inclusion after the application of the exclusion criteria above.

7.3.3.2 Confounding

The current analysis is based on the DAG from Chapter 2, Section 2.5.1 to provide evidence for inclusion of potential confounders. These confounders were previously explored as a correlation matrix. Results showed that none of the potential confounders were correlated to each other, thus multicollinearity is unlikely. Univariate analysis was also

conducted to explore the relationship between the variable of interest and outcome. The models used in these analyses are:

1. Age (years, categorical)
2. Age (years, categorical), BMI (kg/m^2), moderate physical activity (Yes/No), smoking status (smoker v.s. non-smoker), alcohol intake (alcohol g/day), socio-economic status (professional/managerial, intermediate or routine/manual), family history of HBP (Yes/No), self-reported history of hypercholesterolaemia (Yes/No) (data not shown)
3. Model 2 and in addition, energy intake (kcal/day)

Tea intake was adjusted for when modelling the association between total coffee and self-reported HBP, and *vice versa*. Salt and sodium intake was not adjusted for, as likelihood ratio tests suggest no significant difference between inclusion and exclusion of these variables in the model.

7.3.3.3 Descriptive statistics

Descriptive statistics were explored as part of the Chapter 2, Section 2.6.2. These baseline characteristics were explored by dividing according total coffee and tea quantiles before exclusions listed in Section 7.3.3.2. Baseline characteristics by coffee and tea quantiles after exclusions, as well as by disease status, into incident cases, recovered cases, prevalent cases and non-cases, was also explored and reported in the current chapter.

7.3.3.4 Logistic Regression

Logistic regression was conducted in a similar manner documented in Chapter 6, Section 6.3.3.4. OR was reported with 95% or 99% CI of self-reported HBP incidence [182]. The odds of self-reported HBP was determined by comparing each intake group with the reference group which included the lowest consumers, (or non-consumers). Increments of coffee or tea intake according to typical portion size (250 g) [176] were also regressed to assess if there is a linear association with odds of self-reported HBP.

Stratification for types of coffee consumed was also assessed, where participants were divided into those who only consumed regular coffee and those who only consumed decaffeinated coffee. Effect modification was explored by stratification of subgroups of participants selected *a priori*. Variables investigated included BMI (obese v. non-obese), smoking (smoking v. non-smoking), menopausal status (pre-menopausal v. post-menopausal) and parental history of CVD. However, these analyses were ultimately

restricted to not include smokers due to low case numbers. A summary of exclusion criteria and analysis plan is provided in Figure 7.1.

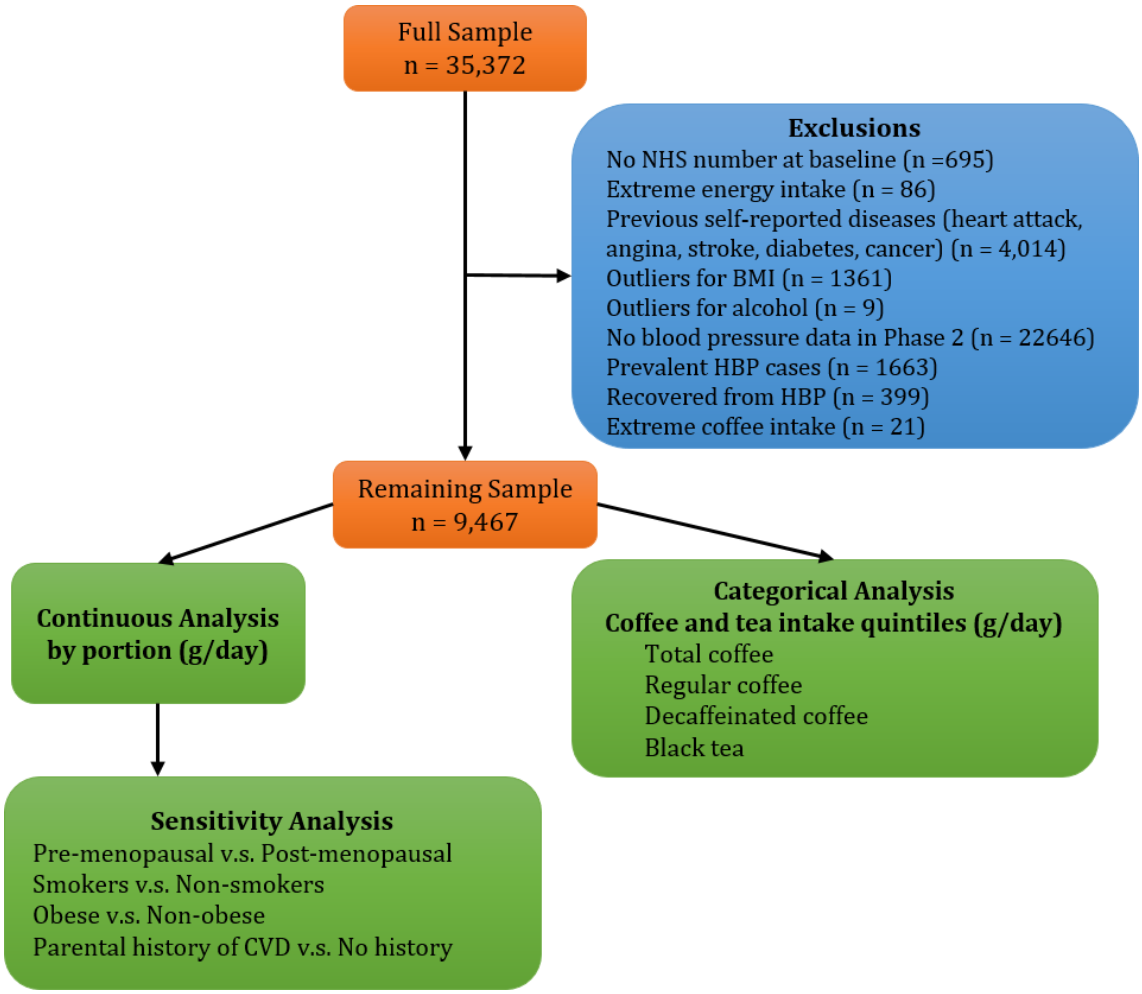


Figure 7.1 Summary flowchart of the current study exclusion criteria and analysis plan

7.3.3.5 Testing for statistical assumptions

Statistical assumptions were tested according to procedure reported in Chapter 2, Section 2.4.2.2. Goodness of fit was assessed by Hosmer-Lemeshow test where predicted risks were compared to observed risks. An insignificant chi-squared *p-value* suggested that there is no evidence the model is ill-fitted.

7.4 Results

7.4.1 Baseline characteristics

A total of 9,467 eligible participants were included within the analysis after the application of exclusions. The baseline characteristics of participants by case status, were presented in Table 7.1. In general, recovered and non-cases were younger, and more likely to possess traits which were 'health-conscious', while incident and prevalent cases shared similar tendencies. Specifically, recovered and non-cases were younger in comparison to incident and prevalent cases, whereas prevalent cases tended to be the oldest on average. Non-cases tended to have the lowest BMI and waist circumference compared to other subpopulations. Non-cases were also more likely to have a lower energy intake, while incident cases had the highest energy intake. In terms of dietary preferences, salt and sodium intakes were highest within recovered cases, in contrast to non-cases with the lowest intakes. Prevalent cases were more likely to consume the least amount of alcohol, total vegetables, and coffee. While recovered cases tended to consume the least amount of fruits, they were more likely to consume the most tea. With regard to lifestyle habits, prevalent cases had the lowest proportion of vegetarians, but the highest proportion of non-smokers. Incident cases were more likely to be supplement users. Prevalent cases were least likely to be moderately active participants, *vice versa* for non-cases. When participants were divided according to SES status, non-cases had the highest proportion of participants holding a professional/managerial job, and the lowest proportion of participants holding intermediate, routine and manual jobs when compared across the subgroups. Prevalent cases had the highest proportion of participants with no education, while non-cases had the highest proportion of participants who were degree holders. With regard to medical history, non-cases were less likely to have a history of parental cancer/heart disease, family history of HBP and high cholesterol, while prevalent cases had a greater tendency of reporting medical histories mentioned above .

When participants were divided according to intakes of total coffee (Table 7.2), participants who consumed the least coffee tended to be the youngest, with the lowest BMI and smallest waist circumference, as well as lowest energy, total salt, sodium and alcohol intakes. This is consistent with the previous chapter (Chapter 6). Participants who consumed the least coffee tended to consume highest amount of FVs overall. The proportion of vegetarians were also highest among participants who consumed least amount of coffee. Percentages from Table 7.2 show no apparent trend for non-smokers, but highest coffee consumers had the lowest proportion of non-smokers compared to other quintiles, as well

as the lowest proportion of supplement users and moderately active participants. In terms of SES, participants from the fourth coffee quintile had the highest proportion of participants with high school education and above as well as professional & managerial jobs. There were no apparent trends for the history of parental cancer/heart disease and family history of HBP. Interestingly, lowest and highest coffee consumers have the smallest proportion of participants with high cholesterol, while the third quintile consuming between one to two cups of coffee had the highest proportion.

Participants were also divided according to black tea consumption quartiles (Table 7.3), and the patterns observed here are similar in comparison to above. Participants who consume less black tea were more likely to be younger, with a lower BMI, smaller waist circumference and lower energy, total salt and sodium intake. The lowest black tea consumers were also more likely to consume the greatest amount of FVs, as well as coffee. In terms of lifestyle habits, the proportion of vegetarians/vegans and supplement users decreased significantly across the quartiles. The proportion of non-smokers tend to be higher across the quartiles, but was lowest in the highest quartile. The proportion of participants who were moderately active was the lowest among consumers who consumed highest intake of tea. Low black tea consumers tended to have a higher proportion of participants who were well educated, with professional & managerial jobs compared to high black tea consumers. In terms of medical history, low black tea consumers had a smaller proportion of participants with a history of parental cancer/heart disease, family history of HBP and high cholesterol.

Table 7.1 Baseline characteristics of participant by self-reported HBP incidence, prevalence, recovered and non-cases

	Incident cases	Non-cases	Prevalent cases	Recovered cases
No. of cases (n)	721	8746	1276	341
Age, years (SD)	54.9 (8.4)	50.6 (8.6)	57.0 (8.8)	50.3 (8.1)
BMI, kg/m^2 (SD)	25.3 (4.3)	23.6 (3.6)	26.0 (4.7)	25.3 (5.5)
Waist circumference, cm (SD)	75.6 (9.9)	72.3 (8.2)	77.1 (9.9)	74.3 (9.4)
Energy intake, kcal/day (SD)	2332 (738)	2284 (681)	2308 (686)	2329 (736)
Alcohol intake, g/day (SD)	8.8 (10.7)	8.8 (9.9)	7.9 (10.0)	8.6 (9.7)
Sodium intake, g/day (SD)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	3.2 (1.1)
Total salt intake, g/day (SD)	7.9 (2.6)	7.8 (2.6)	8.0 (2.6)	8.1 (2.8)
Total fruits and vegetables, g/day (SD)	736 (390)	746 (377)	742 (371)	737 (326)
Total vegetables, g/day (SD)	320 (190)	326 (173)	314 (162)	321 (160)
Total fruits & juice, g/day (SD)	416 (267)	420 (273)	427 (278)	416 (238)
Portions of vegetables, no./day (SD)	5.3 (3.0)	5.4 (2.9)	5.2 (2.7)	5.3 (2.7)
Portions of fruits, no./day (SD)	5.4 (4.1)	5.5 (4.2)	5.5 (3.9)	5.3 (3.6)
Total coffee, g/day (SD)	398 (336)	383 (348)	372 (335)	399 (331)
Total tea, g/day (SD)	671 (506)	667 (509)	706 (508)	713 (508)
Vegetarian/Vegan Status (%, 95% CI)	24.5 (21.5, 27.8)	35.2 (34.2, 36.2)	24.0 (21.7, 26.4)	32.5 (27.8, 37.7)
Non-smokers (%, 95% CI)	92.6 (90.5, 94.3)	91.1 (90.5, 91.7)	93.3 (91.8, 94.5)	93.2 (90.0, 95.5)
Supplement users (%, 95% CI)	60.5 (56.7, 64.2)	60.1 (59.0, 61.2)	58.9 (56.1, 61.7)	58.7 (53.3, 64.0)
Moderately Active/Active (%, 95% CI)	56.7 (53.0, 60.3)	64.5 (63.5, 65.5)	56.2 (53.4, 58.9)	64.0 (58.6, 68.9)
Socio-economic status (%, 95% CI)				
Professional/Managerial	63.7 (60.1, 67.2)	68.0 (67.0, 69.0)	60.7 (57.9, 63.4)	63.5 (58.3, 68.5)
Intermediate	26.3 (23.2, 29.7)	25.0 (24.1, 58.9)	30.7 (28.2, 33.3)	28.8 (24.2, 33.9)
Routine and manual	10.0 (8.0, 12.4)	7.0 (6.5, 7.6)	8.6 (7.2, 10.3)	7.6 (5.2, 11.0)
Highest educational qualification (%, 95% CI)				
No Education	17.9 (15.1, 21.0)	10.9 (10.3, 11.6)	19.9 (17.7, 22.3)	9.8 (7.0, 13.6)
O-Level	29.8 (26.4, 33.4)	30.0 (29.1, 31.1)	28.5 (26.0, 31.2)	32.0 (27.1, 37.3)
A-Level	26.6 (23.3, 30.1)	25.7 (24.7, 26.6)	28.7 (26.2, 31.4)	28.9 (24.2, 34.1)
Degree	25.8 (22.6, 29.3)	33.3 (2102, 34.3)	22.8 (20.5, 25.4)	29.2 (24.5, 34.4)
History of parental cancer/heart disease (%, 95% CI)	69.5 (66.0, 72.7)	65.4 (64.3, 66.3)	75.7 (73.2, 77.9)	68.2 (63.1, 73.0)
Family history of high blood pressure (%, 95% CI)	45.6 (42.0, 49.3)	32.7 (31.7, 33.7)	51.0 (48.3, 53.8)	43.7 (38.5, 49.0)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	7.5 (5.8, 9.7)	4.2 (3.8, 4.7)	20.5 (18.2, 23.0)	9.1 (6.3, 12.8)

Table 7.2 Baseline characteristics of participants by total coffee intakes, expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables after the application of exclusion criteria

	Total coffee consumption (including decaffeinated coffee) (g/day)				
	0 – 27	**30 – 190**	**194 – 475**	**479 – 665**	**855 – 1995**
General					
Participants (n)	2129	1886	2344	1371	1737
Age, years (SD)	49.8 (8.4)	52.2 (9.1)	51.8 (8.8)	50.8 (8.7)	50.2 (8.0)
BMI, kg/m^2 (SD)	23.4 (3.9)	23.6 (3.6)	23.8 (3.6)	23.7 (3.5)	24.2 (3.8)
Waist circumference, cm (SD)	71.8 (8.2)	72.7 (8.5)	72.7 (8.5)	72.7 (8.0)	72.9 (8.8)
Dietary Intake					
Energy, kcal/day (SD)	2209 (668)	2298 (686)	2296 (665)	2363 (697)	2304 (714)
Alcohol, g/day (SD)	6.8 (9.3)	8.4 (9.8)	9.3 (10.0)	9.3 (9.1)	10.4 (11.0)
Sodium , g/day (SD)	3.0 (1.0)	3.1 (1.0)	3.1 (1.0)	3.2 (1.0)	3.1 (1.1)
Total salt , g/day (SD)	7.6 (2.6)	7.9 (2.6)	7.9 (2.5)	8.1 (2.5)	8.0 (2.7)
Total fruit & vegetables, g/day (SD)	762 (420)	747 (365)	739 (350)	748 (356)	729 (393)
Total fruit & juice, g/day (SD)	422 (297)	422 (258)	419 (257)	427 (260)	408 (283)
Total vegetable, g/day (SD)	339 (189)	325 (172)	320 (158)	321 (164)	320 (187)
Black tea, g/day (SD)	779 (560)	813 (490)	683 (458)	610 (439)	392 (461)
Portions of fruit, no./day (SD)	5.6 (4.6)	5.4 (3.9)	5.5 (4.0)	5.6 (4.2)	5.3 (4.4)
Portions of vegetables, no./day (SD)	5.6 (3.1)	5.4 (2.9)	5.3 (2.6)	5.3 (2.6)	5.3 (3.1)
Lifestyle Habits					
Vegetarian/Vegan Status (%, 95% CI)	43.4 (41.3, 45.6)	36.0 (33.9, 38.2)	29.8 (28.0, 31.7)	30.4 (28.0, 32.9)	30.8 (28.7, 33.1)
Non-smokers (%, 95% CI)	93.2 (92.1, 94.2)	92.0 (90.7, 93.1)	91.8 (90.6, 92.8)	93.4 (92.0, 94.6)	85.3 (83.5, 86.8)
Use of supplements (%, 95% CI)	65.4 (63.3, 67.5)	63.4 (61.1, 65.7)	57.9 (55.8, 59.9)	60.3 (57.5, 62.9)	53.3 (50.9, 55.7)
Moderately active/Active (%, 95% CI)	65.6 (63.5, 67.6)	62.6 (60.3, 64.7)	65.3 (63.3, 67.2)	67.2 (64.6, 69.7)	58.7 (56.4, 61.0)
Socio Economic Status					
High school education & above (%, 95% CI)	57.8 (54.0, 61.9)	56.1 (52.0, 60.4)	59.3 (55.6, 63.2)	61.0 (56.1, 66.1)	58.6 (54.4, 63.2)
Professional & Managerial job holders (%, 95% CI)	67.1 (65.0, 69.1)	67.1 (65.0, 69.2)	66.4 (64.4, 68.2)	70.1 (67.6, 72.5)	68.7 (66.5, 70.9)
Medical History					
History of parental cancer/heart disease (%, 95% CI)	64.5 (62.4, 66.5)	66.4 (64.2, 68.5)	66.7 (64.8, 68.6)	64.0 (61.5, 66.5)	66.2 (64.0, 68.4)
Family history of high blood pressure (%, 95% CI)	34.7 (32.7, 36.8)	31.8 (29.7, 33.9)	33.4 (31.5, 35.3)	35.4 (32.9, 38.0)	33.6 (31.4, 35.9)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	3.4 (2.7, 4.3)	4.8 (3.9, 5.9)	6.1 (5.2, 7.1)	4.1 (3.1, 5.3)	3.6 (2.8, 4.6)

Table 7.3 Baseline characteristics of participants by total tea intakes, expressed as mean and standard deviation for continuous variables, percentage and 95% CI for categorical variables after the application of exclusion criteria

	Total black tea consumption (g/day)			
	0 – 36	**104 – 650**	**1170**	**1560**
General				
Participants (n)	1952	4410	2121	984
Age, years (SD)	50.3 (8.5)	51.1 (8.7)	51.3 (8.8)	50.9 (8.8)
BMI, kg/m^2 (SD)	23.8 (4.0)	23.6 (3.6)	23.7 (3.5)	24.2 (4.1)
Waist circumference, cm (SD)	72.4 (8.9)	72.3 (8.2)	72.6 (8.0)	73.9 (9.1)
Dietary Intake				
Energy, kcal/day (SD)	2155 (688)	2282 (670)	2362 (670)	2419 (734)
Alcohol, g/day (SD)	8.2 (10.7)	9.6 (10.0)	8.2 (9.0)	7.6 (10.0)
Sodium , g/day (SD)	2.9 (1.0)	3.1 (1.0)	3.2 (1.0)	3.4 (1.1)
Total salt , g/day (SD)	7.3 (2.6)	7.8 (2.5)	8.2 (2.5)	8.6 (2.9)
Total fruit & vegetables, g/day (SD)	774 (425)	746 (360)	733 (365)	712 (383)
Total fruit & juice, g/day (SD)	441 (310)	424 (261)	407 (258)	385 (267)
Total vegetable, g/day (SD)	333 (188)	321 (167)	326 (173)	327 (184)
Total coffee, g/day (SD)	529 (419)	408 (317)	273 (289)	229 (298)
Portions of fruit, no./day (SD)	5.6 (4.5)	5.5 (4.1)	5.4 (4.1)	5.1 (4.2)
Portions of vegetables, no./day (SD)	5.6 (3.2)	5.3 (2.7)	5.4 (2.8)	5.4 (3.0)
Lifestyle Habits				
Vegetarian/Vegan Status (%, 95% CI)	41.5 (39.3, 43.7)	32.1 (30.7, 33.5)	32.6 (30.7, 34.6)	34.3 (31.4, 37.4)
Non-smokers (%, 95% CI)	90.2 (88.8, 91.4)	91.6 (90.8, 92.4)	92.2 (91.0, 93.3)	89.0 (86.9, 90.8)
Use of supplements (%, 95% CI)	63.1 (60.9, 65.3)	59.3 (57.8, 60.8)	59.7 (57.5, 61.8)	59.0 (55.7, 62.1)
Moderately active/Active (%, 95% CI)	63.5 (61.4, 65.7)	65.2 (63.8, 66.6)	62.5 (60.4, 64.6)	61.7 (58.7, 64.7)
Socio Economic Status				
High school education & above (%, 95% CI)	59.5 (55.4, 63.8)	60.7 (58.0, 62.6)	55.6 (51.8, 59.7)	52.4 (46.8, 58.3)
Professional & Managerial job holders (%, 95% CI)	68.8 (66.6, 70.8)	68.4 (67.0, 69.7)	65.8 (63.8, 67.8)	66.1 (63.1, 69.0)
Medical History				
History of parental cancer/heart disease (%, 95% CI)	66.5 (64.3, 68.5)	64.5 (63.1, 65.9)	66.8 (64.7, 68.8)	66.7 (63.7, 69.6)
Family history of high blood pressure (%, 95% CI)	33.0 (31.0, 35.2)	33.6 (32.2, 35.0)	34.2 (32.2, 36.3)	34.3 (31.4, 37.4)
Had/Have high cholesterol/hyperlipidaemia (%, 95% CI)	3.9 (3.2, 4.9)	4.6 (4.0, 5.3)	4.5 (3.7, 5.5)	5.0 (3.8, 6.5)

7.4.2 Logistic Regression

7.4.2.1 Full cohort

The table below presents the odds of self-reported HBP for total coffee and tea by quintiles of intake (Table 7.4). There were no significant associations found for total coffee, regular coffee, decaffeinated coffee and black tea with the odds of self-reported HBP in both the age-adjusted model and the fully-adjusted model.

Table 7.4 Total black tea, coffee and coffee subgroup intake and odds of self-reported HBP incidence

	Intake (g/day)	Odds of high blood pressure (95% CI)		
		Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total coffee				
Q1	0 – 27	131	1	1
Q2	30 – 190	145	1.13 (0.89, 1.44)	1.14 (0.88, 1.46)
Q3	194 – 475	183	1.15 (0.91, 1.44)	1.11 (0.87, 1.41)
Q4	479 – 665	103	1.15 (0.88, 1.50)	1.10 (0.84, 1.46)
Q5	855 – 1995	127	1.17 (0.92, 1.51)	1.03 (0.79, 1.35)
p trend			0.287	0.797
OR per 250 g/day			1.03 (0.97, 1.09)	0.99 (0.93, 1.05)
Regular coffee				
Q1	0	128	1	1
Q2	4 – 76	149	1.03 (0.81, 1.31)	1.04 (0.81, 1.34)
Q3	152 – 190	126	1.06 (0.82, 1.36)	1.08 (0.83, 1.41)
Q4	475	201	1.19 (0.95, 1.49)	1.14 (0.90, 1.45)
Q5	855 – 1140	85	1.01 (0.77, 1.34)	0.89 (0.66, 1.19)
p trend			0.555	0.568
OR per 250 g/day			1.02 (0.96, 1.08)	0.98 (0.92, 1.05)
Decaffeinated coffee				
Q1	0	342	1	1
Q2	4	102	1.04 (0.83, 1.31)	1.04 (0.82, 1.31)
Q3	13 – 190	150	0.93 (0.77, 1.14)	0.96 (0.78, 1.17)
Q4	475 – 1140	95	1.12 (0.88, 1.41)	1.08 (0.85, 1.38)
p trend			0.386	0.669
OR per 250 g/day			1.04 (0.95, 1.14)	1.02 (0.93, 1.12)
Black tea				
Q1	0 – 36	131	1	1
Q2	104 – 650	331	1.06 (0.86, 1.30)	1.07 (0.86, 1.33)
Q3	1170	151	0.99 (0.78, 1.25)	0.97 (0.75, 1.25)
Q4	1560	76	1.07 (0.80, 1.43)	1.02 (0.74, 1.39)
p trend			0.951	0.761
OR per 250 g/day			1.00 (0.96, 1.04)	0.99 (0.95, 1.03)

[a] Cases apply to fully-adjusted models
[b] Adjusted for age (categorical), BMI, energy intake, physical activity, smoking status, socio-economic status, alcohol intake, family history of HBP, self-reported history of hypercholesterolaemia, mutual adjustment for total coffee or black tea intake

7.4.2.2 Sensitivity Analysis

Results from the sensitivity analyses suggest that the odds of self-reported HBP were lower in regular coffee drinkers for the fully-adjusted model, however, not statistically significant. There were also no other significant associations found within obese, non-obese, non-smoking, postmenopausal, premenopausal subpopulations with and without parental history of CVD (Table E.1).

7.5 Discussion

7.5.1 Summary of results

The objective of this study was to explore the association between coffee, tea intake and the risk of self-reported incident HBP. Results show no association for higher coffee or tea intake and the risk of self-reported incident HBP in UKWCS. The direction of associations for total coffee tend to be inverse, but point estimates and tests for linear association were not significant. When participants were stratified into subgroups, associations between coffee, tea intake and incident outcomes were also not significant.

7.5.2 General comparison to literature

Findings from the current study are aligned with the recent MAs which reported no association between coffee consumption and the risk of incident hypertension when comparing between the highest and lowest consumers [315, 316]. Slightly elevated risk was reported for the risk of self-reported HBP within light to moderate consumers (1 to 3 cups/day) [316]. Furthermore, SR and MA of ten recent RCTs also show no association between coffee intake and BP [315], thus more evidence is required for further investigation before conclusions can be drawn. With regard to the findings for black tea intake, it was not possible to make a direct comparison with other studies as there was a lack of studies which investigated black tea consumption and hypertension incidence. However, there is evidence from two SRs and MAs of RCTs to suggest a small but significant BP lowering effect with regular consumption of black tea [154, 317]. However, some RCTs had a relatively small sample size, and there was some evidence of heterogeneity for DBP results within Liu *et. al* [317], thus results should be interpreted carefully.

Overall, there are some methodological concerns which exist in previous studies that could have led to inconsistent results. Firstly, coffee and tea consist of multiple components, of which may exert effects on BP. The concentrations of these compounds within are largely varied due to multiple factors, such as variety of beans, processing methods, such as roasting and brewing for coffee [266, 318, 319] and fermenting processes for tea [289, 320]. Variance in portion sizes and food composition databases used in different cohorts could also add to the observed heterogeneity. As the current study used a FFQ to estimate intake of coffee and tea, this would be a potential limitation the study faced. However, the FFQ, in comparison to single food diary records or 24-hour recalls, is a better measure of habitual diet, and more appropriate to survey large populations. Secondly, RCTs have demonstrated an acute pressor effect caused by ingestion of caffeine up to three hours. This effect is known

to vary in previous trials by hypertensive status, mental or physical stress, by age, and especially habitual consumers, where heavy coffee drinkers are more likely to build a tolerance to the acute pressor effect [312, 313]. This may cause additional variation within RCTs or cohort studies, leading to errors in measured BP. Thus in response, the current study attempted to explore associations by habitual consumption of regular and decaffeinated coffee, as well as by menopausal status (related to age), however, no associations were found. Within studies that investigate incident hypertension, despite the specificity in comparison to e.g. CVD mortality or incidence, the quality of outcome may also impact on the risk estimates. Self-reported HBP reported through a medical practitioner, is considered to be an inferior option in comparison to measured BP, although instances of 'white coat hypertension' may be prevalent. Furthermore, genetic factors such as CYP1A2 genotype, which influences caffeine intake and metabolism, may also modify the association between coffee consumption and BP [321]. As the cohort did not have data on this particular genotype, further sensitivity analysis could not be conducted. However, the study adjusted and conducted sensitivity analysis for smoking status, which is thought to induce CYP1A2 activity [322], and its effects on non-smokers and smokers may vary [323].

7.5.3 Relevance with (poly)phenols

Other than caffeine, chlorogenic acids also exist abundantly within coffee, where habitual drinkers may consume up to 2 g/day, exceeding the amount consumed from FVs in total [266]. High intakes of chlorogenic acids have been reported to lower SBP and DBP significantly by -4.31 mmHg (95% CI 5.60 to -3.01 mmHg) and -3.68 mmHg (95% CI -3.91 to -3.45 mmHg) respectively within a SR and MA of RCTs [152]. There is a number of mechanisms linking chlorogenic acids and its metabolites to a BP lowering effect. One third of the chlorogenic acids are absorbed in the small intestine, the remaining two thirds are intensively metabolised in the colon by microflora, where its metabolites are reabsorbed back into the bloodstream [148]. NO is a vasodilator [324] and regulates the arterial wall tone. One of the suggested mechanisms include increasing NO bioavailability in aortic rings which were pre-contracted using phenylephrine (vasoconstrictor), which enhances endothelial-dependent vasodilation, a function directly related to BP. This effect is seen especially when ferulic acid was administered *in vitro* and *in vivo*. Urinary NO metabolites also increased when chlorogenic acids were consumed *in vivo*, indicating higher levels of NO bioavailability [148]. Other mechanisms include reduced radical production, as well as scavenging free radicals directly [148, 325]. Alternatively, chlorogenic acid metabolites may

also inhibit platelet activity, exerting anti-thrombotic effects, preventing formation of blood clots which may lead to the onset of CVD, such as MI [266].

On the other hand, various amounts of flavanols, such as catechin, epicatechin, epigallocatechin and epigallocatechin gallate are found in green tea [141]. These compounds may polymerise after fermentation to form theaflavins and thearubigins, which is abundant in black tea [320]. Flavanols exhibit similar functions to chlorogenic acids by improving endothelial function, demonstrated by significant improvements of flow-mediated dilation in trials, as well as enhancing NO status [141]. Despite the evidence reported above from RCTs, limitations in methodology within cohort studies might introduce errors when calculating risk estimates. As emphasized throughout the thesis, UKWCS was designed to be a 'health-conscious' cohort to accommodate wide diversity of dietary intakes. In comparison to the general population, these women might be more likely to have a higher physical activity level, smoke less, more likely to be vegetarian etc.. Under these circumstances, perhaps this could be why no additional benefit from higher coffee or tea consumption could be detected, but it is more likely due to the broad exposure and outcome measures.

7.5.4 Strengths and limitations

The following limitations should be considered when interpreting the results of the current study. As reviewed previously, limitations surrounding missing information on some model covariates, the usage of the FFQ and methodological limitations of observational studies were elaborated in the previous chapters (Chapter 3 and Chapter 6). Furthermore, application of the study findings is also restricted to women only.

This analysis also has certain strengths mentioned in previous chapters, attributed to the advantageous usage of Phenol Explorer, the larger sample size compared to other studies, the design of the 'health-conscious' cohort and a wide diversity in dietary intakes and patterns. These factors help to facilitate the elucidation of associations between chronic disease and dietary intake.

7.6 Summary

In conclusion, coffee and tea intakes were not associated with odds of self-reported HBP in the UKWCS. Findings for coffee were consistent with results from Chapter 5 and current literature, but results for the association between black tea intake and HBP were not. The chapter raised some methodological concerns which may have led to the current conclusion, despite using the best available data and methods for this cohort. Overall, improvements with methodology in the future is required before further investigations are conducted in both prospective cohorts and RCTs.

Chapter 8
Fruit, coffee and tea intake in the UK Women's Cohort Study: Impact of dietary assessment methods

8.1 Abstract

The relationship between various (poly)phenol-rich dietary sources and CVD outcomes were investigated in previous chapters. However, there were no significant associations between some fruit subgroups, vegetables, coffee and tea and CVD outcomes. The current chapter attempts to investigate whether FFQ derived food groups are comparable with intakes derived using an alternative method of dietary assessment to form an opinion about the robustness of the four-day weighted food diaries as the reference method. Individual fruit intake from the FFQ was combined and analysed as total fruit intake, and sub-categorised into berries, citrus, drupes, pomes and tropical fruit intake (same as previous chapters). Coffee and tea intakes were also derived in a similar manner from the FFQ. Individual food items recorded in the food diaries were combined to form the same subgroups as a comparison to the FFQ. Statistical analyses used to assess relative validity included correlations, cross-tabulation and the Kappa statistic.

Results from the study show a good correlation for coffee and tea intakes using different methods, but only a slight to fair correlation for fruit subgroup intakes. Using the Kappa's statistic, there is also a slight to fair agreement across the fruit, where drupes had the lowest extent of agreement. Drupes were also the most grossly misclassified group compared to other dietary variables. The agreement for coffee and tea subgroups were both good, and tea had the highest extent of agreement. In the interpretation of these findings, an important limitation should be noted, where the administration of the FFQ and the food diary is five years apart. Thus the low extent of agreement between certain fruit subgroups could be due to dietary changes overtime instead. In conclusion, despite the limitations of the study design and findings here, the inclusion of this chapter provided a deeper understanding to the design of the FFQ and the food diary, which may be useful for further discussion and evaluation within this thesis.

8.2 Background

The FFQ is the most widely used dietary assessment method for use within large prospective cohorts, and are often tailored to be food or nutrient specific [326]. Reviewing the relative validity of FFQs is important as low validity may affect the outcome of the diet-disease relationship. In analyses such as logistic regression and survival analyses, the exposure of interest is often expressed in categories. Thus, the ability to rank participants correctly according to groups of intake is important, as misclassification may affect the risk estimate of the disease outcome [185]. However, there are advantages to using the FFQ to study diet-disease relationship. It is inexpensive, quick to administer, and easy to process after initial setup of database. The FFQ can also take into account mid- to long-term dietary habits spanning from weeks to a year, depending on the time frame of measurement in the study. The food diary is also capable of capturing dietary data over long periods of time if multiple diaries were completed over time at different time points. However, the application of this assessment is usually restricted to a limited number of days for practical purposes, due to the time required to process the collected data. Dietary assessment methods are vulnerable to some unavoidable errors. The FFQ relies on memory, question interpretation by participants and it is also dependent on a pre-defined food list [185]. On the other hand, the food diary is capable of recording diet in an open-ended manner with no restrictions to food lists or portion sizes. If completed prospectively, it is also less likely to be susceptible to memory errors. As the two methods are largely different in terms of possible errors, the food diary is recommended to be appropriate as a reference to study the relative validity of the FFQ [185, 253]. Furthermore, the relative validity of food groups such as fruit, coffee and tea had not been studied in this cohort. Therefore, the aim of this study is to evaluate the ability of the FFQ to rank individuals correctly into consumption groups. Findings from this chapter would help explain if associations (or the lack of) may be explained by the ability to quantify or rank women using the FFQ. Objectives of this chapter are as follows:

- Compare measured intakes (g/day) of fruit, fruit subgroup, coffee and tea between food diaries and baseline FFQ to examine the relative validity of baseline FFQ.
- To assess whether the baseline FFQ is capable of allocating women into similar categories as the food diaries based on total fruit, fruit subgroup, coffee and tea intake from both methods, thus addressing the extent of agreement between the two methods.

- To identify the percentage of women who were misclassified into extreme total fruit, fruit subgroup, coffee and tea intake categories.

8.3 Method

8.3.1 Study population

Four-day weighed food diaries were collected between 1999 and 2002. These were mailed to all women who had previously consented for re-contact and with no notification of death. There were 12,453 women who responded, and 2136 completed food diaries that were fully coded at the time of analysis. Women who had missing baseline FFQ data were excluded (n = 15). A single participant who reported consuming >8000 g/day of total fresh fruit intake in the baseline FFQ was also excluded, because she was considered to be an extreme outlier. Therefore, the final sub-population for comparison of baseline FFQ with food diary consisted of 2120 women.

8.3.2 Dietary data

Dietary data for the current analysis was obtained from the baseline FFQ and four-day weighed food diaries, previously introduced in Chapter 2 Section 2.2.2.2.

8.3.2.1 Food frequency questionnaire

Development and application of the baseline FFQ was previously explained in Chapter 2 Section 2.2.2.1. Details for the creation of total fruit, fruit subgroup variables can be found in Chapter 2 Section 2.6.1, where the only exception is the inclusion of grapes in the berry subgroup. Coffee and tea variables used in this chapter were the same as reported variables in Chapter 5 Section 5.3.1.

8.3.2.2 Four-day weighed food diary

Four-day weighed food diaries were coded directly using McCance & Widdowson's *The Composition of Foods* (5th Edition) [168], through 'DANTE' (Chapter 2 Section 2.2.2.2). The food items were combined using a similar method according to the FFQ. In the example of generating 'pomes', food codes which consist of single ingredients, such as 'apples' or 'pears' were grouped as a category. Categories form include total fresh fruit, which consist of berries (including grapes), total citrus (including fresh orange juice), drupes, pomes and tropical fruit, total coffee, and black tea. These categories were applied through 'DANTE' to food diary intakes where mean intake in g/day for each category was then generated for

each individual, depending on how many days were completed for the food diary. These intakes were subsequently compared with the mean intakes derived from the FFQ.

Table 8.1 shows the total number of food codes from *McCance & Widdowson's The Composition of Foods* (5th Edition) that were used for each investigated food variable from the FFQ and food diaries. There is a significantly less amount of items that were used in the FFQ compared to the food diaries, especially for coffee. Basic nutrient intakes were also generated for comparison with the FFQ.

Table 8.1 Total number of food codes within each investigated dietary variable from the food diary and baseline FFQ (% of food codes in FFQ over total number of food codes used in food diary)

Dietary Variable	Total no. of food codes	
	Food Diary	Baseline FFQ
Total fresh fruit	153	53 (35%)
Berries	43	14 (32%)
Citrus	23	9(39%)
Drupes	26	12 (46%)
Pomes	41	10 (24%)
Tropical fruit	20	8 (40%)
Coffee	15	1 (6%)
Black tea	6	1 (16%)

8.3.3 Statistical analysis

Baseline characteristics of women who completed the FFQ and food diaries were explored and tabulated. Normality of relevant variables were evaluated using histograms and descriptive statistics. If the data is normal, paired t-tests were conducted to assess significantly difference between mean intakes of fruit, coffee and tea intakes for FFQ and food diaries. If the dietary variables were not normally distributed, the non-parametric equivalent, Wilcoxon signed-rank test was used instead.

The correlation coefficient was calculated for fruit, coffee and tea intakes to assess the relationship between the two dietary assessment methods. The Pearson correlation was applied to normally distributed variables, while variables that are not normally distributed used Spearman's rank correlation. However, correlation only examines the degree of association instead of agreement between the two methods. It also ignores any systematic bias that maybe present [327]. The recommended approach would be the application of the Bland-Altman plot [328]. The Bland-Altman plot is a graphical approach to visualise the extent of agreement between two methods, by plotting the mean of the two measures, against the difference between the two measurements. Mean difference between the two measurements would be the estimated bias, and the 95% limits of agreement would be equivalent to the mean difference ±1.96 SD. Assumptions for the 95% limits of agreement

were also checked by plotting a histogram for the mean difference to assess whether they approximately follow a normal distribution. If the measurements are not normal, a log transformation was applied and the 95% limits of agreement were interpreted as ratios after back transformation (antilog) [329]. However, as the data was still not suitable for analysis after log transformation, this method was ultimately not applied.

The remaining alternative was to assess the extent of agreement objectively between the two dietary assessments, and evaluate the ability for both methods to rank women into the same category. Thus, the Kappa statistic (K) was applied [330]. This approach is based on the difference between the expected agreement by chance and actual agreement that is present. Firstly, women from the FFQ and food diaries were classified into approximately equal intake quintiles. The first quintile contained women with the lowest dietary intake, while the fifth quintile consisted of women with the highest intake. Cross tabulation and percentages were then derived for women classified into the same, adjacent or extreme quintile. However, due to the narrow range of intakes derived from some dietary variables (e.g. drupes), or the artificial linearity from converting frequency to g/day (e.g. black tea), some categories were unable to be forced into five approximately equal quintiles. Therefore, dietary intakes were also divided into quartiles and tertiles. The weighted Kappa (K_w) was also calculated to minimize misclassification, as it assigns weight to adjacent categories. Thus, if a participant was placed in the lowest intake quintile on the food diary, but third quintile in the FFQ, it would be credited as partial agreement [331].

The interpretation of Kappa statistics is shown in Table 8.2, where 0 is equivalent to no agreement, and 1 is perfect agreement. For the purpose of application, this meant that when K = 0, the two methods are entirely different in measurement, and when K = 1, the measurements between the methods are exactly the same. In other words, the Kappa statistic reports whether women who are categorised into the highest intake quintile in the FFQ, are also categorised into the highest intake quintile in the food diary, reflecting the ability of FFQ to rank participants correctly into consumption groups.

Table 8.2 Interpretation of Kappa statistics [330]

Kappa Statistic	Strength of Agreement
<0.00	Poor
0.00 – 0.20	Slight
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Substantial
0.81 – 1.00	Almost Perfect

8.4 Results

8.4.1 Baseline characteristics

The baseline characteristics of women with fully coded food diaries, were explored alongside the UKWCS cohort. Women with fully coded food diaries tend to be older, and were more likely to be moderately active, vegetarians/vegans, were non-smokers and supplement users. Women with fully coded food diaries were also more likely to be from a professional/managerial class, and a degree holder. Nutrient intakes do not differ greatly between women with fully coded diaries and the full cohort. This showed that the sub-population of women who completed food diaries were generally a good representative of the full cohort (Table 8.3).

Table 8.3 Baseline characteristics of women who completed the baseline FFQ and fully coded food diaries

	Participants with completed food diary	Full Cohort
Participants (n)	2136	35372
Age, years (SD)	54.5 (9.3)	52.3 (9.3)
BMI, kg/m^2 (SD)	24.2 (4.0)	24.5 (4.4)
Supplement users (%, 95% CI)	61.4 (59.2, 63.5)	57.8 (57.3, 58.3)
Non-smokers (%, 95% CI)	91.3 (90.1, 92.4)	89.2 (88.9, 89.5)
Moderately active (%, 95% CI)	60.3 (58.2, 62.4)	58.3 (57.8, 58.9)
Vegetarians/Vegans (%, 95% CI)	30.0 (28.4, 32.3)	27.7 (27.2, 28.1)
Socio-Economic Status (%, 95% CI)		
Professional/Managerial	65.1 (63.0, 67.1)	63.2 (62.7, 63.7)
Intermediate	27.0 (25.2, 29.0)	27.5 (27.0, 28.0)
Routine and manual	7.9 (6.8, 9.1)	9.3 (9.0, 9.6)
Degree holder (%, 95% CI)	26.5 (24.7, 28.4)	24.9 (24.4, 25.3)
Energy, kcal/day (SD)	2292 (828)	2291 (797)
Carbohydrate, % of total energy (SD)	54.8 (6.4)	54.7 (6.5)
Total fat, % of total energy (SD)	33.1 (6.0)	33.1 (5.9)
Protein, % of total energy (SD)	15.8 (2.7)	15.9 (2.8)
Total sugar, g/day (SD)	150 (63)	150 (65)
Fibre, g/day (SD)	26.3 (11.7)	25.6 (11.0)
Alcohol, g/day (SD)	8.0 (9.7)	8.7 (10.3)

However, the baseline FFQ reported a significantly higher energy and nutrient intake (except for alcohol, percentage of energy from fat and protein) compared to the food diary. The baseline FFQ also significantly over-reported on all fruit groups, coffee and tea intakes except drupes (Table 8.4). SDs for consumption of fruit groups, coffee and black tea in the FFQ were generally wider than the reported values for food diaries, indicating there was a greater variation of consumption when dietary intakes were reported through the baseline FFQ, with the exception of drupe consumption. When percentage distributions of fruit

groups were compared, there was a relatively small difference between the two assessment methods. The baseline FFQ reported a lower percentage distribution of drupe intake (3% in baseline FFQ, 10% in food diary), and a slightly higher percentage distribution of berries (12% berries in baseline FFQ, 9% in food diary) when compared to the food diary. In both assessments, citrus (33% in baseline FFQ, 31% in food diary) and pomes (32% in baseline FFQ, 26% in food diary) were the most frequently consumed fruit type, followed by tropical fruits (26% for both assessment methods).

Table 8.4 Differences between nutrient and dietary intakes of fruit, coffee and black tea variables derived using the FFQ and food diaries, by paired t-test† or Wilcoxon signed-rank test‡ (n = 2120)

Dietary Variables	FFQ	Food Diary	Difference
Energy†, kcal/day (SD)	2292 (828)	1813 (424)	479*
Carbohydrate†, % of total energy (SD)	54.8 (6.4)	50.9 (8.0)	3.9*
Total fat†, % of total energy (SD)	33.1 (6.0)	33.1 (6.9)	0
Protein†, % of total energy (SD)	15.8 (2.7)	15.9 (3.6)	-0.1
Total sugar†, g/day (SD)	150 (63)	108 (39)	42*
Fibre†, g/day (SD)	26.3 (11.7)	17.4 (6.4)	8.9*
Alcohol‡, g/day (SD)	8.1 (9.7)	9.0 (12.0)	-0.9
Total fresh fruit‡, g/day (SD)	318 (275)	201 (147)	117*
Berries‡, g/day (SD)	41 (62)	23 (40)	18*
Citrus‡, g/day (SD)	104 (108)	79 (95)	25*
Drupes‡, g/day (SD)	7 (10)	23 (50)	-16
Pomes‡, g/day (SD)	107 (107)	62 (73)	45*
Tropical‡, g/day (SD)	74 (90)	53 (53)	21*
Coffee‡, g/day (SD)	391 (352)	342 (347)	49*
Black tea‡, g/day (SD)	664 (514)	514 (453)	150*

**p-value* <0.001

Correlations for all dietary intake categories were calculated using Spearman correlations, as the distributions for dietary intakes were not normal (Table 8.5). Intakes of coffee and black tea were the most strongly correlated between the two dietary assessment methods, while intake of drupes was weakly correlated, consistent with findings for the previous section. All the correlations were also statistically significant.

Table 8.5 Correlations between the mean intake of total fresh fruit, fruit subgroup, coffee and black tea from the FFQ and food diary

	Correlation	*p-value*
Total Fruit	0.41 (0.38, 0.45)	*<0.001*
Citrus	0.41 (0.38, 0.45)	
Berries	0.22 (0.18, 0.26)	
Drupes	0.15 (0.10, 0.19)	
Pomes	0.43 (0.39, 0.46)	
Tropical	0.43 (0.39, 0.46)	
Coffee	0.66 (0.63, 0.68)	
Black tea	0.72 (0.70, 0.74)	

8.4.2 Degree of agreement between the FFQ and food diaries

Bland-Altman plot measures the mean difference between two dietary assessment methods as consumption increases and is the preferred method to assess extent of agreement between two measures. As most of the data was not normally distributed, the Bland-Altman plot was not a suitable method to assess agreement.

The Kappa statistic was used instead to assess the extent of agreement categorically. The degree of agreement for un-weighted Kappa between quintiles of dietary intake ranged from slight to fair, where intake of drupes had the lowest agreement (K = 0.050). As the number of quantiles decreased, the Kappa statistic for all dietary variables naturally increased [179]. However, the weighted Kappa statistics were less affected by the number of categories, and reports slight agreement was observed for total fresh fruit, citrus, berries and drupes, fair agreement for pomes and tropical fruits, and a moderate agreement for coffee and black tea consumption.

Table 8.6 Degree of agreement between the mean intake of total fresh fruit, fruit subgroup, coffee and black tea from the FFQ and food diary

	Five Quantiles		Four Quantiles		Three Quantiles	
	Kappa	Weighted Kappa	Kappa	Weighted Kappa	Kappa	Weighted Kappa
Total Fruit	0.132	0.272	0.175	0.281	0.217	0.288
Citrus	0.140	0.283	0.189	0.305	0.222	0.289
Berries	0.070	0.148	0.097	0.155	0.128	0.159
Drupes	0.050	0.093	0.053	0.091	0.068	0.090
Pomes	0.167	0.306	0.198	0.310	0.218	0.291
Tropical	0.159	0.304	0.198	0.306	0.239	0.308
Coffee	0.295	0.482	0.374	0.514	0.373	0.469
Black tea	0.319	0.484	0.354	0.491	0.476	0.566

The FFQ was also assessed for the ability to rank women into appropriate dietary intake groups, using food diary groups as the reference. This was assessed using quintiles initially, followed by quartiles and tertiles. Table 8.7 reports the percentage of agreement for each dietary variable divided by quintiles between the FFQ and food diary. Within dietary intakes that were successfully divided into quintiles, majority of participants with extreme consumption levels were classified within the same quintile, ranging from 6.1% to 13.1%. Gross misclassification occurred from 0.5% to 2.5%. Proportion of women who were grossly misclassified are higher within intakes of berries, drupes and tea, of the unequal number of quantiles.

In summary, there were 0.6 to 15.2% of women who were grossly misclassified in general, that is when women who were classified in the lowest intake group within the baseline FFQ was classified in the highest intake group according to food diary, or *vice versa* (Table 8.8). Intake of berries and drupes had the largest proportion of women who were grossly misclassified (10% and 15.2% respectively) compared to other dietary variables, while coffee and tea had the least proportion women who were grossly misclassified (1.2% and 0.6% respectively). With regard to the consumption of citrus, pomes and tropical fruit, these categories had 4.2%, 3.9% and 3.4% of women who were grossly misclassified respectively. The proportion of grossly misclassified women were also considered to be low when investigating total fruit intake, at 2.7%.

Majority of the women were classified within one adjacent quintile, except for coffee and black tea intake, where a larger proportion of the women (43.6% and 45.8% respectively) were correctly classified compared to fruit subgroups (Table 8.8). The distribution of intakes of some dietary variables meant it was not possible to equally divide into quintiles, e.g. berries, drupes and black tea consumption, as the reported consumption values were not linear. Further analyses were therefore conducted in quartiles and tertiles (Table 8.9, Table 8.10, Table 8.11, Table 8.12).

Table 8.7 Percentage of participants in total fresh fruit, citrus fruit, berries, pomes, drupes, tropical fruit, coffee and tea quintiles by FFQ and food diary consumption quintiles

				Baseline FFQ			
	Total fresh fruit	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	178 (8.4%)	103 (4.9%)	66 (3.1%)	45 (2.1%)	36 (1.7%)	428
	2th	114 (5.4%)	95 (4.5%)	81 (3.8%)	72 (3.4%)	58 (2.7%)	420
	3rd	70 (3.3%)	96 (4.5%)	101 (4.8%)	87 (4.1%)	71 (3.3%)	425
	4th	41 (1.9%)	83 (3.9%)	93 (4.4%)	111 (5.2%)	97 (4.6%)	425
	Highest intake	21 (1.0%)	47 (2.2%)	83 (3.9%)	109 (5.1%)	162 (7.6%)	422
	Total	424	424	424	424	424	2120
				Baseline FFQ			
	Total citrus fruit	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	286 (13.5%)	148 (7.0%)	121 (5.7%)	104 (4.9%)	54 (2.5%)	713
	2th	40 (1.9%)	34 (1.6%)	30 (1.4%)	24 (1.1%)	10 (0.5%)	138
	3rd	84 (4.0%)	102 (4.8%)	85 (4.0%)	113 (5.3%)	43 (2.0%)	427
	4th	41 (1.9%)	83 (3.9%)	77 (3.6%)	135 (6.4%)	82 (3.9%)	418
	Highest intake	36 (1.7%)	40 (1.9%)	66 (3.1%)	152 (7.2%)	130 (6.1%)	424
	Total	487	407	379	528	319	2120
				Baseline FFQ			
	Berries	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	278 (13.2%)	241 (11.4%)	221 (10.5%)	182 (8.6%)	149 (7.1%)	1071
	2th	-	-	-	-	-	-
	3rd	32 (1.5 %)	41 (1.9%)	49 (2.3%)	56 (2.7%)	43 (2.0%)	221
	4th	64 (3.0%)	71 (3.4%)	82 (3.9%)	84 (4.0%)	94 (4.5%)	395
	Highest intake	62 (2.9%)	55 (2.6%)	73 (3.5%)	94 (4.5%)	135 (6.4%)	419
	Total	436	408	425	416	421	2106
				Baseline FFQ			
	Pomes	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	278 (13.1%)	128 (6.0%)	109 (5.1%)	67 (3.2%)	53 (2.5%)	635
	2th	47 (2.2%)	62 (2.9%)	54 (2.5%)	37 (1.7%)	28 (1.3%)	228
	3rd	72 (3.4%)	84 (4.0%)	96 (4.5%)	98 (4.6%)	60 (2.8%)	410
	4th	47 (2.2%)	61 (2.9%)	105 (5.0%)	113 (5.3%)	97 (4.6%)	423
	Highest intake	29 (1.4%)	47 (2.2%)	79 (3.7%)	103 (4.9%)	166 (7.8%)	424
	Total	473	382	443	418	404	2120
				Baseline FFQ			
	Drupes	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	361 (17.3%)	299 (14.3%)	252 (12.0%)	261 (12.5%)	274 (13.1%)	1447
	2th	-	-	-	-	-	-
	3rd	-	-	-	-	-	-
	4th	35 (1.7%)	50 (2.4%)	57 (2.7%)	50 (2.4%)	39 (1.9%)	231
	Highest intake	44 (2.1%)	71 (3.4%)	88 (4.2%)	106 (5.1%)	105 (5.0%)	414
	Total	440	420	397	417	418	2092
				Baseline FFQ			
	Tropical	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	231 (10.9%)	131 (6.2%)	80 (3.8%)	56 (2.6%)	45 (2.1%)	543
	2th	73 (3.4%)	65 (3.1%)	86 (4.1%)	40 (1.9%)	43 (2.0%)	307
	3rd	58 (2.7%)	103 (4.9%)	120 (5.7%)	82 (3.9%)	66 (3.1%)	429
	4th	55 (2.6%)	60 (2.8%)	95 (4.5%)	115 (5.4%)	92 (4.3%)	417
	Highest intake	28 (1.3%)	45 (2.1%)	64 (3.0%)	122 (5.8%)	165 (7.8%)	424
	Total	445	404	445	415	411	2120
				Baseline FFQ			
	Coffee	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	270 (12.7%)	83 (3.9%)	47 (2.2%)	13 (0.6%)	11 (0.5%)	424
	2th	110 (5.2%)	158 (7.5%)	95 (4.5%)	45 (2.1%)	26 (1.2%)	434
	3rd	39 (1.8%)	115 (5.4%)	155 (7.3%)	65 (3.1%)	40 (1.9%)	414
	4th	31 (1.5%)	54 (2.5%)	158 (7.5%)	89 (4.2%)	93 (4.4%)	425
	Highest intake	14 (0.7%)	22 (1.0%)	77 (3.6%)	58 (2.7%)	252 (11.9%)	423
	Total	464	432	532	270	422	2120
				Baseline FFQ			
	Black tea	Lowest intake	2th	3rd	4th	Highest intake	Total
Food diary	Lowest intake	345 (16.3%)	64 (3.0%)	-	17 (0.8%)	6 (0.3%)	432
	2th	71 (3.3%)	299 (14.1%)	-	35 (1.7%)	11 (0.5%)	416
	3rd	21 (1.0%)	306 (14.4%)	-	82 (3.9%)	18 (0.8%)	427
	4th	9 (0.4%)	212 (10.0%)	-	167 (7.9%)	43 (2.0%)	431
	Highest intake	7 (0.3%)	93 (4.4%)	-	161 (7.6%)	153 (7.2%)	414
	Total	453	974	-	462	231	2120

Table 8.8 Cumulative percentage of total fresh fruit, fruit subgroup, coffee and black tea derived from the baseline FFQ and food diary

Extent of Agreement (%)	Total Fruits	Berries	Citrus	Drupes	Pomes	Tropical	Coffee	Black tea
Exact	30.5	25.9	31.6	24.7	33.7	32.8	43.6	45.8
Within 1 adjacent quantile	36.8	28.9	35.1	23.9	33.8	37.0	36.7	34.3
Within 2 adjacent quantile	21.0	20.9	19.9	18.6	19.7	17.4	14.2	13.5
Within 3 adjacent quantile	9.0	14.2	9.2	17.5	8.9	9.4	4.3	6.1
Grossly misclassified	2.7	10.0	4.2	15.2	3.9	3.4	1.2	0.6

When variables were divided into quartiles and cross tabulated, the extent of agreement improved. Women were mostly classified in the exact quartile, except for total fruit intake (Table 8.9). However, the percentage of grossly misclassified participants had also increased, ranging between 1.3 to 18.8%. This pattern naturally reoccurred when dietary variables were divided into tertiles, and almost half of all women were classified in the exact tertile. Therefore, as the number of quantiles decreased, women were more likely to be classified in the exact quantile.

Table 8.9 Percentage of participants in total fresh fruit, citrus fruit, berries, pomes, drupes, tropical fruit, coffee and tea quintiles by FFQ and food diary consumption quartiles

		Baseline FFQ				
	Total fresh fruit	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	257 (12.1%)	126 (5.9%)	82 (3.9%)	72 (3.4%)	537
	2th	149 (7.0%)	154 (7.3%)	125 (5.9%)	95 (4.5%)	523
	3rd	79 (3.7%)	144 (6.8%)	171 (8.1%)	136 (6.4%)	530
	Highest intake	45 (2.1%)	106 (5.0%)	152 (7.2%)	227 (10.7%)	530
	Total	530	530	530	530	2120
		Baseline FFQ				
	Total citrus fruit	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	329 (15.5%)	167 (7.9%)	127 (6.0%)	90 (4.2%)	713
	2th	105 (5.0%)	106 (5.0%)	89 (4.2%)	48 (2.3%)	348
	3rd	86 (4.1%)	147 (6.9%)	169 (8.0%)	130 (6.1%)	532
	Highest intake	49 (2.3%)	79 (3.7%)	167 (7.9%)	232 (10.9%)	527
	Total	569	499	552	500	2120
		Baseline FFQ				
	Berries	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	340 (16.1%)	288 (13.7%)	247 (11.7%)	196 (9.3%)	1071
	2th	-	-	-	-	-
	3rd	99 (4.7%)	129 (6.1%)	149 (7.1%)	133 (6.3%)	510
	Highest intake	95 (4.5%)	102 (4.8%)	133 (6.3%)	195 (9.3%)	525
	Total	534	519	529	524	2106
		Baseline FFQ				
	Pomes	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	318 (15.0%)	163 (7.7%)	84 (4.0%)	70 (3.3%)	635
	2th	111 (5.2%)	133 (6.3%)	116 (5.5%)	66 (3.1%)	426
	3rd	87 (4.1%)	138 (6.5%)	178 (8.4%)	129 (6.1%)	532
	Highest intake	57 (2.7%)	96 (4.5%)	156 (7.4%)	218 (10.3%)	527
	Total	573	530	534	483	2120
		Baseline FFQ				
	Drupes	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	429 (20.5%)	352 (16.8%)	341 (16.3%)	325 (15.5%)	1447
	2th	-	-	-	-	-
	3rd	30 (1.4%)	41 (2.0%)	39 (1.9%)	30 (1.4%)	140
	Highest intake	68 (3.3%)	126 (6.0%)	175 (8.4%)	136 (6.5%)	505
	Total	527	519	555	491	2092
		Baseline FFQ				
	Tropical	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	262 (12.4%)	143 (6.7%)	80 (3.8%)	58 (2.7%)	543
	2th	126 (5.9%)	181 (8.5%)	123 (5.8%)	87 (4.1%)	517
	3rd	89 (4.2%)	126 (5.9%)	170 (8.0%)	148 (7.0%)	533
	Highest intake	53 (2.5%)	87 (4.1%)	155 (7.3%)	232 (10.9%)	527
	Total	530	537	528	525	2120
		Baseline FFQ				
	Coffee	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	367 (17.3%)	105 (5.0%)	48 (2.3%)	23 (1.1%)	543
	2th	125 (5.9%)	218 (10.3%)	119 (5.6%)	56 (2.6%)	518
	3rd	59 (2.8%)	137 (6.5%)	220 (10.4%)	113 (5.3%)	529
	Highest intake	24 (1.1%)	44 (2.1%)	142 (6.7%)	320 (15.1%)	530
	Total	575	504	529	512	2120
		Baseline FFQ				
	Black tea	Lowest intake	2th	3rd	Highest intake	Total
Food diary	Lowest intake	416 (19.6%)	84 (4.0%)	23 (1.1%)	9 (0.4%)	532
	2th	101 (4.8%)	363 (17.1%)	68 (3.2%)	15 (0.7%)	547
	3rd	27 (1.3%)	285 (13.4%)	154 (7.3%)	45 (2.1%)	511
	Highest intake	18 (0.8%)	133 (6.3%)	217 (10.2%)	162 (7.6%)	530
	Total	562	865	462	231	2120

Table 8.10 Cumulative percentage of total fresh fruit, fruit subgroup, coffee and black tea derived from the baseline FFQ and food diary

Extent of Agreement (%)	Total Fruits	Berries	Citrus	Drupes	Pomes	Tropical	Coffee	Black tea
Exact	38.2	32.5	39.4	28.9	40.0	39.9	53.1	51.7
Within 1 adjacent quantile	39.2	32.4	38.0	28.6	38.3	38.7	35.0	37.7
Within 2 adjacent quantile	17.1	21.3	16.0	23.8	15.7	16.2	9.8	9.3
Grossly misclassified	5.5	13.8	6.6	18.8	6.0	5.2	2.2	1.3

Table 8.11 Percentage of participants in total fresh fruit, citrus fruit, berries, pomes, drupes, tropical fruit, coffee and tea quintiles by FFQ and food diary consumption tertiles

		Baseline FFQ			
	Total fresh fruit	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	383 (18.1%)	189 (8.9%)	136 (6.4%)	708
	2th	224 (10.6%)	272 (12.8%)	211 (10.0%)	707
	Highest intake	100 (4.7%)	246 (11.6%)	359 (16.9%)	705
	Total	707	707	706	2120
		Baseline FFQ			
	Total citrus fruit	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	395 (18.6%)	194 (9.2%)	124 (5.8%)	713
	2th	248 (11.7%)	281 (13.3%)	203 (9.6%)	732
	Highest intake	114 (5.4%)	216 (10.2%)	345 (16.3%)	675
	Total	757	691	672	2120
		Baseline FFQ			
	Berries	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	441 (20.9%)	354 (16.8%)	276 (13.1%)	1071
	2th	88 (4.2%)	135 (6.4%)	118 (5.6%)	341
	Highest intake	176 (8.4%)	211 (10.0%)	307 (14.6%)	694
	Total	705	700	701	2106
		Baseline FFQ			
	Pomes	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	390 (18.4%)	212 (10.0%)	111 (5.2%)	713
	2th	225 (10.6%)	290 (13.7%)	222 (10.5%)	737
	Highest intake	107 (5.0%)	227 (10.7%)	336 (15.8%)	670
	Total	722	729	669	2120
		Baseline FFQ			
	Drupes	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	551 (26.3%)	442 (21.1%)	454 (21.7%)	1447
	2th	-	-	-	-
	Highest intake	149 (7.1%)	254 (12.1%)	242 (11.6%)	645
	Total	700	696	696	2092
		Baseline FFQ			
	Tropical	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	390 (18.4%)	205 (9.7%)	115 (5.4%)	710
	2th	212 (10.0%)	279 (13.2%)	215 (10.1%)	706
	Highest intake	117 (5.5%)	211 (10.0%)	376 (17.7%)	704
	Total	719	695	706	2120
		Baseline FFQ			
	Coffee	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	547 (25.8%)	102 (4.8%)	63 (3.0%)	712
	2th	266 (12.5%)	247 (11.7%)	189 (8.9%)	702
	Highest intake	83 (3.9%)	183 (8.6%)	440 (20.8%)	706
	Total	896	532	692	2120
		Baseline FFQ			
	Black tea	Lowest intake	2th	Highest intake	Total
Food diary	Lowest intake	560 (26.4%)	110 (5.2%)	42 (2.0%)	712
	2th	157 (7.4%)	362 (17.1%)	193 (9.1%)	712
	Highest intake	40 (1.9%)	198 (9.3%)	458 (21.6%)	696
	Total	757	670	693	2120

Table 8.12 Cumulative percentage of total fresh fruit, fruit subgroup, coffee and black tea derived from the baseline FFQ and food diary

Extent of Agreement (%)	Total Fruits	Berries	Citrus	Drupes	Pomes	Tropical	Coffee	Black tea
Exact	47.8	41.9	48.2	37.9	47.9	49.3	58.2	65.1
Within 1 adjacent quantile	41.0	36.6	40.6	33.3	41.8	39.8	34.9	31.0
Grossly misclassified	11.1	21.5	11.2	28.8	10.3	10.9	6.9	3.9

8.5 Discussion

8.5.1 Summary of results

The aim of the study was to evaluate the ability of the baseline FFQ to rank individuals correctly into consumption groups, by application of the Kappa statistic and cross-tabulation. Descriptive statistics suggested that the subpopulation of women with fully coded food diary was a good representative of the full cohort. In general, most mean intakes of fruit, coffee and tea were significantly higher in the baseline FFQ compared to food diary. Based on the results of the weighted Kappa, the extent of agreement between both dietary methods ranged from slight to fair for intakes of fruit and fruit subgroups, while there was a moderate agreement for the intakes of coffee and tea. When quintiles of dietary intakes were cross-tabulated, 0.6 to 15.2% of women were grossly misclassified in general. However, both assessments were able to classify 80% of women at least within one adjacent coffee and tea quantile, while 48.6% to 69.8% of women were classified in within at least one adjacent quintile for the intakes of fruit and fruit subgroups.

8.5.2 General comparison of dietary intakes between the FFQ and food diaries

Characteristics of nutrient and dietary intakes indicated that there might be some form of estimation bias, either over-estimation within the baseline FFQ or under-estimation within the food diary. A study is also in agreement with the findings of the current study [332]. There are two factors which may influence estimates of reported intake. It was previously suggested that the increased number of food items may be associated with higher total intake [195]. The median frequency of fruits consumed per week (8.4, 15.0, 15.4) appeared to increase with the number of fruit variables in the questionnaire respectively (6, 14, 15), but there were also contradictory findings from another study [332]. The Oxford FFQ which listed 11 fruit variables had a lower intake (219 g/day) compared to the Cambridge FFQ which lists 9 fruit variables (231 g/day). Portions sizes could also affect the translation to amounts within FFQ-derived items. In the current study, the intake of drupes in the baseline FFQ was much lower than the reported food diary intake

as a smaller portion size was applied when compared to other types of fruit (data not shown). This led to a discrepancy between FFQ and food diaries for the intake of drupes. In spite of this, the FFQ tend to consistently report higher absolute intakes overall compared to food diary intakes in the current study, which may be due to the presence of an underlying, and possibly unavoidable systematic bias. However, if both methods are able to rank the majority of women within one adjacent or in the exact quantile, it demonstrates that the FFQ is able to rank women correctly according to their dietary intake quantiles relative to the food diary.

In addition, the FFQ is structured in a different format from the food diary. FFQ food variables often contain one or more food code (e.g. apples, stewed apples, cooked apples classed as 'apples'), and may also include additional FFQ food variables that asks for the frequency of consumption for composite or homemade dishes (e.g. apple pie, apple crumble). Participants would potentially over report or double report their intakes [326]. However, it may be more likely that there is a tendency to report more socially acceptable foods (fruits), especially in a health-conscious cohort [333].

Application of the FFQ is usually the preferred approach when studying the relationship between diet and disease in large prospective cohorts [164]. In general, FFQs are quick, cheap and easy to process when compared to administering food diaries, which can be more time-consuming and difficult to process. The FFQ also have the advantage of recording long-term habitual diet in addition to the advantages above, and take seasonal variability into account. Food diaries on the other hand, are more suitable for recording high quality 'snapshots' of dietary data, which may or may not reflect usual habitual diet, depending on the length of the record (e.g. three, four, seven or two week food diary). Since all dietary assessments have their own limitations, the method of dietary assessment needs to be tailored for the appropriate research question.

8.5.3 Correlation and extent of agreement between the FFQ and food diaries

In terms of correlations, results showed that the correlation between FFQ and food diaries varied, ranging from 0.15 to 0.72, where coffee and tea (0.66 and 0.72 respectively) have a higher correlation between the two methods than fruit and fruit subgroup intakes (0.15 to 0.43). Coffee and tea are often consumed in standard portion sizes. As habitual consumption of coffee and tea are usually consistent, it is less likely to under- or over-report intakes. It is also less likely for participants to misreport intakes of coffee and tea due to social acceptability. In terms of total fruit and fruit subgroups, berries (0.22) and drupes

(0.15) were poorly correlated between the baseline FFQ and food diaries. Similar results were reported in Andersen *et. al* [334], where the correlation for 'other fruits and berries' (excluding apples, pears and citrus fruits) between 14-day weighted food record and a short FFQ was also 0.22 within Norwegian men. However, the correlation for 'apples, pears' (0.58) and 'citrus fruits' (0.45) were higher than the current study. The higher correlation co-efficient may be attributed to the shorter time period (1.5 – 2 months) between the administration of two dietary assessments, compared to approximately five years for the current study. Berries and drupes may also be less frequently consumed, in addition to seasonality and the food diaries' inability to capture long-term habitual diet, intakes of these fruits may not reflect usual intake depending on the time the diet was captured.

Validation studies on FFQ and food diaries in the literature generally report reasonable correlations between the two dietary assessments for macronutrient and micronutrient intakes [172, 335-337]. However, when dietary variables are classed into food groups, some studies report that the FFQ performs less well for FV intakes [335, 338]. There is also variation in the methodology between studies. Some included multiple 24-hour recalls [339], or single 24-hour recalls and other types of FFQ as the method of comparison [332]. 24-hour recalls may potentially share the same sources of error, relating to memory and the perception of portion sizes. It is also more representative to record data over a longer period of time, as single 24-hour recalls only provide a snapshot of dietary habits on a particular day. Food diaries are generally less susceptible to memory or portion size errors, as they are recorded by meals on the same day [185], although it is recognised that food diaries are filled in at the end of the day, rather than prospectively. An alternative method to validate intakes of FVs from the FFQ include the analysis of biomarkers, such as flavonoids and carotenoids from urine [340] or plasma [341]. In the study by Brantsæter *et. al* [340], flavonoids (phloretin, hesperidin and kaempferol were shown to correlate strongly with total fruits, citrus fruits/juice and tea intake respectively, and thus are interpreted as suitable biomarkers for validation. Similarly, β-cryptoxanthin, α-carotene and lycopene were strong predictors for intake of fruits, 'carrots and vegetables' and tomatoes respectively [341]. There are obvious advantages to using biomarkers as a form of validation for dietary assessments, due to the differences in sources of possible errors. Assessment of biomarkers are not hindered by recall or memory error, and may not necessarily rely on the integrity of the food composition database as a FFQ or food diary would rely on. However, it can be susceptible to biological or technical errors, as well as inter-individual variation. It is important to note that biomarkers can also be potentially affected by other factors such as metabolism and rate of utilisation within the body. Pollard

et. al [342] had previously investigated the validity of plasma-based biomarkers in a sub-sample of women from UKWCS, and found no association between plasma biomarkers and FV intakes. While certain biomarkers can be good indicators of specific nutrient intake from food in general, physiological processes can also influence levels of biomarkers within the body, thus it is not recommended to act as a proxy measure of any specific nutrient or food intake [342]. However, it is a good alternative in terms of methodology for relative validity studies.

In terms of the extent of agreement between the FFQ and food diary, the extent of exact agreement between the two dietary assessment methods when dietary variables were divided into quintiles was slight to fair (K_w = 0.093 to 0.484), and was similar whether it was divided into quartiles (K_w = 0.091 to 0.514) or tertiles (K_w = 0.090 to 0.566). The percentage of exact agreement in fruit and fruit subgroup variables was between 24.7% to 33.7%, while for coffee and tea, it was between 43.6% to 45.8%. Only 0.6% to 1.2% of participants were grossly misclassified for tea and coffee respectively. 2.7% to 15.2% of participants were grossly misclassified for total fruit and fruit subgroup intakes. Decreasing the number of quantiles naturally increased extent of agreement as well as misclassification. Wong *et. al* [338] supports the current study findings for total fruit intake, where 10% of New Zealand adolescent participants between 14 to 18 years were grossly misclassified, which was similar to 11.1% in the current study. Bonifacj *et. al* [335] reported 11% grossly misclassified participants for citrus fruits in quartiles, which is higher than the current study (6.6%) in a French Mediterranean region. Additional direct comparisons with other studies are difficult as there are few studies that validated fruit subgroup intakes in the way undertaken by the current study. In particular, there is also a gap of approximately five years between the administration of the baseline FFQ and food diary in the current study. Diet changes are highly likely to have occurred between this time period. Therefore, results here should be interpreted cautiously, as the low extent of agreement could be due to dietary changes over time instead. Despite the FFQ showing reasonable ability to broadly classify women correctly into exact quantiles, misclassification is high for fruit subgroups such as berries and drupes, thus the risk estimates produced are less likely to be relatively valid when studying the relationship between these fruit groups and disease outcome.

8.6 Summary

The current study reviewed the strengths and weaknesses of the FFQ and food diary, and provided a deeper understanding to the design of both dietary assessment methods. Results from the current study indicated a fair extent of agreement for FFQ-derived intakes of consumption of total fruit, citrus, pomes, tropical fruits, coffee and tea, but not for berries and drupe consumption in the FFQ when compared to the food diaries. However, results from cross-tabulation suggest that the FFQ is broadly able to classify women in correct quantiles of intake However, an important limitation should be noted, where the administration of the FFQ and food diary is five years apart. Thus the low extent of agreement between certain fruit subgroups could be due to dietary changes overtime instead. Nonetheless, as no dietary assessment measures diet without error, it is important to consider the possible measurement errors in the FFQ, which may have led to some of the null association findings in the previous chapters addressing the relationship between FV, coffee and tea intake and CVD related outcomes. In conclusion, findings here are useful for further discussion and evaluation within the scope of this thesis, bearing in the mind the limitation of the study design. In terms of future work, investigating more specific disease outcomes (such as BP) using food diary data instead of the FFQ would be recommended.

Chapter 9
(Poly)phenols in processed fruit beverages in UK: Evaluation of its importance in dietary collection methods

9.1 Abstract

This chapter reports the total (poly)phenol content in selected fruit beverages, including juices, fruit drinks and concentrates, for where existing information on (poly)phenol content was lacking or inadequate. The Folin-Ciocalteu assay was applied as a screening test to include or eliminate samples for quantification of specific major (poly)phenols by HPLC. Fruit smoothies and cranberry juice had the highest total phenolic content (TPC) in comparison to mixed fruit juices and fruit concentrates. Blackcurrant concentrates were analysed further to quantify major anthocyanins, where reported values were similar to other studies [343, 344]. In conclusion, both methods were suitable to generate TPC and quantify (poly)phenols efficiently. Findings also supported analyses conducted in previous chapters to include fruit juices and smoothies as part of 'total fruit intake'. In addition, limitations with estimation errors should be considered in dietary assessments and food databases when generating total (poly)phenol intakes. The chapter also highlights the importance of analysing processed foods to update (poly)phenol databases to estimate (poly)phenol intake more accurately in the future.

9.2 Background

Fruits in general are known to be a good source of (poly)phenols. In previous chapters, fruit subgroups such as berries and citrus were reported to lower risk of CVD in the UKWCS (Chapter 3 and Chapter 4), and hypotheses based on (poly)phenol mechanisms were generated to explain the observations. Dietary assessments for the UKWCS and NDNS RP were conducted nearly two decades apart. Between this period, fruit based processed products, such as fruit beverages, became more commonly consumed. Little is known about the (poly)phenol content of these beverages, and few studies have investigated them [192, 345, 346]. There was also little or no relevant data on these foods in the (poly)phenol database, Phenol Explorer [111]. Before (poly)phenol intakes could be estimated in these

populations to explore the hypotheses, limitations in the (poly)phenol database should be addressed.

The Folin-Ciocalteu assay is one of the most commonly used methods to estimate total phenolic content (TPC), and is based on an oxidation/reduction reaction [347]. Singleton *et. al* [348] developed this from the Folin-Dennis reagent. The assay is based on the reduction of tungstates and molybdates in an alkaline condition to form a blue coloured compound, which can be measured using a spectrophotometer. In the context of this chapter, this assay functions as a screening test to eliminate samples with low TPC. Further analysis using HPLC was applied to allow quantification of (poly)phenols for food samples which have a high TPC content, ensuring that the compounds quantified would most likely to play a role *in vivo*.

The aim of the study was to determine the TPC of selected fruit beverages, quantify major (poly)phenols in fruit samples with a high TPC. Firstly, to provide novel data which could potentially be included in (poly)phenol databases. Secondly, to address the significance of fruit based beverages if (poly)phenol intakes were to be estimated in the general population or cohort.

9.3 Materials and methods

9.3.1 Materials

9.3.1.1 Reagents and standards

Folin-Ciocalteu reagent, sodium carbonate, caffeic acid, catechin, gallic acid, glucose, sucrose, fructose, and formic acid (HPLC grade) were purchased from Sigma Aldrich (Dorset, UK). Methanol, ethanol and acetonitrile was obtained from Fisher Scientific (Loughborough, UK). Cyanidin-3-*O*-rutinoside (CY3RUT), delphinidin-3-*O*-rutinoside (DP3RUT), myricetin-3-*O*-rhamnoside (also known as myricitrin) (MY3RNS) nicotinic acid and ascorbic acid were provided by Extrasynthese (Genay, France). A Millipore Milli-Q water purifying system (Millipore, Hertfordshire, UK) was used to provide deionised and ultrapure water (≥ 18.2 MΩ cm at 25 °C) for all assays, reagent preparation and HPLC analyses.

9.3.1.2 Samples

All beverages analysed in this study were purchased in local supermarkets based in Leeds, UK, between November 2011 and March 2012. Orange concentrates were acquired

from Sainsbury's and Waitrose outlets, Leeds, UK. Pineapple juices, Oceanspray cranberry juices, Britvic J2O juices, Sun Exotic Tropical fruit juice were purchased from Morrisons, Leeds, UK. Ribena concentrate and squashes, Robinsons fruit concentrate and Innocent fruit smoothies were purchased from ASDA, Leeds, UK. The Co-operative cranberry, blackberry and raspberry smoothie was acquired from the Leeds University Union convenience store. Other supermarket branded juices, concentrates or squashes were purchased in their respective supermarket outlets, such as ASDA, Sainsbury's, Morrison's, Marks & Spencer and Tesco, Leeds, UK. Samples were opened, aliquoted (2 mL) and stored at -20°C on the day of purchase. Analyses were carried out within one month of storage.

9.3.2 Methods

The following section determines the approach to conduct the Folin-Ciocalteu assay. The analysis performed in this chapter was done in collaboration with Dr. Hanis Matsura Yahya, who published part of the results in her thesis, Chapter 3 [349].

9.3.2.1 Standard & reagent preparation for Folin-Ciocalteu assay

Samples mentioned in the previous section were extracted and diluted differently according to the type of food matrix, resulting in various centrifugation and homogenisation times (Table 9.1) for Folin-Ciocalteu assay. A standard curve for gallic acid at 0, 25, 50, 75, 100, 125, 150, 175 and 200 µg/mL was prepared for each Folin-Ciocalteu assay using a 1 mg/mL stock solution. Folin-Ciocalteu reagent (1:10, v/v) was also freshly prepared for each experiment as it degraded under the light. 1M sodium carbonate and 80% methanol was stored at ambient temperatures for a period of no longer than six months.

9.3.2.2 Folin-Ciocalteu assay

For analysis, 5 mL of diluted Folin-Ciocalteu reagent (1:10, v/v) was added to 1 mL of diluted sample (Table 9.1), followed by the addition of 4 mL of 1M sodium carbonate within 3 – 8 min. The mixtures were vortexed for 5 sec between the additions of each solution. The mixtures were then incubated in a water bath at 26°C for 2 hours in Grant GLS Aqua 12 Plus water bath (26 °C) (Grant Instruments, Cambridgeshire, UK). Absorbance was measured in Cecil Aquarius CE 7200 Double Beam Spectrophotometer (Cecil Instruments Ltd, Cambridgeshire, UK) at 765 nm, using 2.5 mL plastic disposable cuvettes (Fisher Scientific, Loughborough, UK), and distilled water as the blank reference sample. TPC were expressed in the units of gallic acid equivalents (GAE) per serving size after substituting absorbance values into the gallic acid standard curve ($R^2 < 0.995$), where the standard curve for gallic acid was also produced according to the steps above. The majority of samples were tested

in double duplicate format: 1) Duplicate extractions and 2) duplicates for each extraction, equating to four replicates per sample, unless stated otherwise. This method of replication allows the identification of errors within single extraction and between multiple extractions. For samples which did not undergo the double duplicate format, a triplicate format was applied.

Table 9.1 Detailed extraction methods for different categories of fresh and commercial samples from supermarkets (Leeds, UK).

Sample Category	Extraction Method
Fruit Juice Concentrate or Juice ***without*** bits	1:1 dilution with 80% methanol, followed by vortex for at least 30 sec. Left in room temperature to extract for a few minutes before further dilution if required, usually 1:10.
Fruit Juice ***with*** bits	Requires 1:2 dilution with 80% methanol, followed by vortex for at least 30 sec. The mixture is then centrifuged at 3000 g, 4˚C for 15 min in Eppendorf 5810R centrifuge for larger volumes (>2 mL) (Eppendorf UK Limited, Stevenage, UK) or IEC MicroCL 17 centrifuge for smaller volumes (< 2 mL) (Thermo Electron Corporation, Massachusetts, US). The supernatant is extracted and stored separately. This process is repeated for another two times to ensure maximum extraction from the solids. The supernatants are combined together for centrifugation at 3000 g, 4˚C for 5 min.
Thick Fruit Juices & Fruit Smoothies	The food sample is homogenised in POLYTRON™ PT 1600E Benchtop Homogenizer (Kinematica, Schweiz, Switzerland) for 1 min 30 sec to 2 min. The remainder of the procedure is same as 'fruit juice with bits'.

9.3.2.3 Validation of the Folin-Ciocalteu assay

Two trials were conducted to validate the standards and interferences within the Folin-Ciocalteu assay. Gallic acid as the reference for the current analysis was compared with caffeic acid, catechin (of which both were commonly used as standards in other studies), CY3RUT and DP3RUT which are major anthocyanins in blackcurrant concentrates. The Folin-Ciocalteu assay is also known to be subject to chemical interference by other compounds [350], including glucose, sucrose, fructose, ascorbic acid and sodium metabisulphite which are common in fruit beverages. Standard curves were calculated to see how much interference these compounds could cause. Both trials followed the standard procedure for extraction in Table 9.1 where applicable, and the preparation of a standard curve and Folin-Ciocalteu assay was described in Section 9.3.2.1, with the exception of increasing the concentration range for including fructose, ascorbic acid and sodium metabisulphite up to 300 µg/mL, and up to 450 µg/mL for glucose and sucrose.

Correction of ascorbic acid interference was conducted by modifying the Folin-Ciocalteu assay according to Perla *et. al* [351]. Sodium carbonate was replaced with an equal amount of distilled water in the assay to identify any reducing interference in the samples.

In addition, a trial was established by conducting the Folin-Ciocalteu assay described in Section 9.3.2.2 on two pineapple juice samples (Morrison's and Tropicana Pineapple Juice). The results from this trial were compared to values from the Phenol Explorer [111].

A spiking trial was also conducted to determine whether changes in absorbance originate from either the sample, ascorbic acid or standard, using Tesco's Blackcurrant High Juice 50% concentrate (BHJ) as an example. The sample was spiked with a) 200 µg/mL of gallic acid, and b) 200 µg/mL of ascorbic acid separately and compared with the absorbance of the original sample, 200 µg/mL of gallic acid and 200 µg/mL of ascorbic acid (Table 9.2). Both the Folin-Ciocalteu assay (Section 9.3.2.2), and the correction assay [351] conducted for this trial in duplicate. Standard curves for gallic acid and ascorbic acid were also prepared according to Section 9.3.2.1.

Table 9.2 The format of the spiking trial

Folin-Ciocalteu assay	Ascorbic acid correction assay [351]
BHJ	BHJ
Gallic acid (GA) (200 µg/mL)	GA (200 µg/mL)
Ascorbic acid (AA) (200 µg/mL)	AA (200 µg/mL)
BHJ + GA (200 µg/mL)[a]	BHJ + GA (200 µg/mL)[a]
BHJ + AA (200 µg/mL)[b]	BHJ + AA (200 µg/mL)[b]

[a]72 µL of undiluted BHJ, 160 µL of gallic acid stock solution at 1 mg/mL and 1368 µL of 80% methanol
[b]72 µL of undiluted BHJ, 160 µL of ascorbic acid stock solution at 1 mg/mL and 1368 µL of 80% methanol

9.3.2.4 High performance liquid chromatography analysis

Blackcurrant concentrate samples that yielded GAE >100 mg/serving size of 250 mL were selected for HPLC analysis. Samples that yielded a lower GAE were not analysed as 1) the amount detected within the sample might be insignificant or 2) HPLC is not sensitive enough to detect compounds in minute amounts.

Standard curves for CY3RUT and DP3RUT were prepared using 50% ethanol (v/v) for concentrations 10, 50, 100, 200, 250, 300, 350, 400 µM, in triplicates. These standards were chosen as they are known to be present in juices after processing, and are major anthocyanins present within blackcurrants [352, 353]. Standard curves were prepared in a darkened fume cupboard, as anthocyanins are sensitive to light [121], and analysed in triplicate. MY3RNS was chosen as the internal standard, due to the similarity in chemical structure with CY3RUT and DP3RUT. Its retention time was also similar to both standards. A standard curve for MY3RNS was also made according to the description above, and added to CY3RUT and DP3RUT standards in amber vials (to prevent degradation by light), with a proportion of 30 µl to 20 µl for standard to internal standard respectively, at the same concentration for each standard.

Extraction methods for samples used were similar to those described for the Folin-Ciocalteu assay (Table 9.1), with some minor changes. In brief, a 1:10 dilution was made with the sample using 80% methanol (HPLC grade) in a 10 mL volumetric flask, followed by vortexing for at least 30 seconds. The sample was then left at room temperature to extract for a few minutes. This was followed by filtration through a 0.2 µM PTFE filter into a 2 mL eppendorf tube, discarding the first few drops. 30 µl was then pipetted into an amber vial (to prevent degradation by light), followed by the addition of 20 µl of 50 µM MY3RNS to check for consistency of retention time. Samples were prepared and analysed in triplicate.

High performance liquid chromatography (HPLC) for quantification of major anthocyanins was performed on an Agilent 1200 SL system (Agilent technologies, Dorset, UK) fitted with a degasser, column oven (30 °C), binary pump, auto-sampler (4 °C) and a diode array detector measuring at 350 nm (MY3RNS) and 520 nm (CY3RUT and DP3RUT). The stationary phase used for the current analysis was a Zorbax Eclipse XDB-C18 Rapid Resolution HT column, at 4.6 x 50 mm, 1.8 µM particle size (Agilent technologies, Dorset, UK). The mobile phase consist of 0.5% formic acid in deionised water as solvent A, 0.5% formic acid in acetonitrile as solvent B. Solvents were sonicated for at least 30 minutes to remove air prior to analysis. The flow rate was 0.5 mL/min. The gradient was as follows for solvent B: at 0 – 5 min, 5%; 5 – 20 min, 10 – 40%; 20 – 25 min, 40 – 90%; 25 – 29 min, 90%; 29 – 30 min, back to 5%; 30 – 33 min, 5%.

The same HPLC system was used to quantify ascorbic acid levels within blackcurrant concentrates, using nicotinic acid as the internal standard. Samples were prepared as above, but spiked with nicotinic acid instead of MY3RNS as the internal standard. Standard curves for ascorbic acid and nicotinic acid were prepared using 50% ethanol for concentrations 10, 50, 100, 200, 250, 300, 350, 500, 750, 1000 µM, in triplicates. These compounds were measured at 260 nm and 245 nm respectively. The stationary phase used for the current analysis was a Waters µBondapak C-18 column, at 3.9 x 300 mm (Waters, UK). The mobile phase consisted of 0.2% formic acid in deionised water as solvent A, 0.2% formic acid in acetonitrile as solvent B. The flow rate was 1 mL/min. The gradient was as follows for solvent B: at 0 – 6 min, 5 – 95%; 6 – 12 min, 95%; 12 – 18 min, 95% – 5%; 18 – 24 min, 5%; 24 – 44 min, 5%.

9.3.2.5 Statistical analyses

The Shapiro-Wilk's test was applied to assess normality of data distribution as a pre-requisite for the one-way analysis of variance (ANOVA) to determine whether TPC in samples is statistically different. For normally distributed data, one-way ANOVA

determined if differences overall are statistically significant. This was followed by a Bonferroni post-hoc test to report statistical difference by *p-value* between each sample. For data which are not normally distributed, the non-parametric Kruskal-Wallis one-way ANOVA was applied to report if samples overall are statistically different. Statistical significance was determined by 2-sided p-value of ≤0.05 for GAE in mg/serving size before correction for ascorbic acid content. Stata version 13.0 was used for all statistical analysis [273].

9.4 Results and Discussion

9.4.1 Validation of the Folin-Ciocalteu assay

The parameters for the Folin-Ciocalteu assay was validated in the current study because research studies in literature had varied parameters, such as 1) Duration of incubation; 2) Temperature of incubation; 3) Timing of acid and alkaline solution; 4) Proportion of acid and alkaline solution, 5) Type of standard to use and 6) Interferences.

As the potential intention was to obtain data in a suitable form for Phenol Explorer, it was important that the method used was as similar as possible to the references within the database. Data from US [354] and UK [355] added by researchers from Phenol Explorer referenced the original method of Singleton *et. al* [348]. In addition, in the early trials of the assay, leaving the samples at room temperature, such as in a Chinese study Xu *et. al* [129] and the PREDIMED trial [356], resulted in a polynomial standard curve, when it was supposed to be linear, due to the fluctuating temperature in the laboratory. Thus, a water bath at 26°C was implemented into the method.

In the original paper by Singleton *et. al* [348], it was suggested that temperature could be increased in proportion to decrease incubation time, if samples were left on the bench at a low room temperature. In addition, some references from Phenol Explorer did use a higher temperature at 40°C [357-359], but the amount of sodium carbonate had to be altered, otherwise there would be possibilities of colour fading [348]. This phenomenon was also reported in another study [359]. To ensure the stability and repeatability of the assay, 26°C was used to reflect a stable room temperature.

The proportion and timing of adding Folin-Ciocalteu reagent (acidic solution) and sodium carbonate (alkaline solution) also affected the repeatability of the assay. Trials showed that if the timing for addition of acid was not followed strictly, erratic results would be obtained. For this reason, the original parameters from Singleton *et. al* [348] were used in this study.

9.4.1.1 Comparison of different standards

Figure 9.1 illustrates the standard curves for gallic acid, caffeic acid, catechin, CY3RUT and DP3RUT. Gallic acid was the standard used in the current study, where the range of concentration and absorbance was the highest in comparison to all other compounds. Caffeic acid had a lower sensitivity, thus was not advantageous over gallic acid. The curve for catechin was comparable to gallic acid, but the compound was more expensive, and sensitive towards light [360], and thus may be less reproducible if a standard curve was required to be made for every experiment. However, caffeic acid [127] and catechin [146, 356] were used within other studies. CY3RUT and DP3RUT were also similar to gallic acid, however, these compounds were very expensive and light sensitive. After consideration of these factors, and bearing in mind practices reported in Phenol Explorer, gallic acid was selected as the best choice of standard. In addition, standardising the procedure would allow better comparisons with other sources from Phenol Explorer.

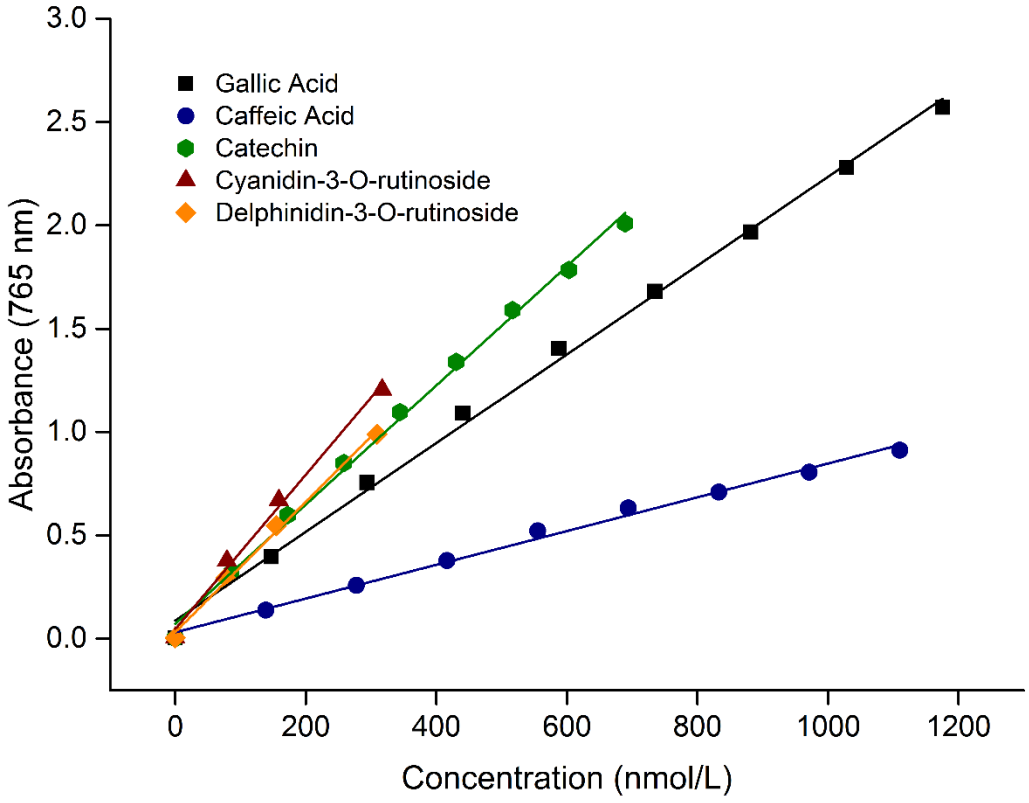


Figure 9.1 Standard curves for gallic acid, caffeic acid, catechin, cyanidin-3-O-rutinoside and delphinidin-3-O-rutinoside using the Folin-Ciocalteu assay expressed as absorbance measured at 765 nm.

9.4.1.2 Influence of interferences

Sodium metabisulphite, fructose, glucose and sucrose, commonly found in fruit based beverages, were investigated for their interference in the Folin-Ciocalteu assay (Figure 9.2). From the figure below, it was possible to conclude that none of these compounds had a significant effect on the assay, as they did not react across the concentration range, based on negligible absorbance. Therefore, no corrections were made for the presence of these compounds.

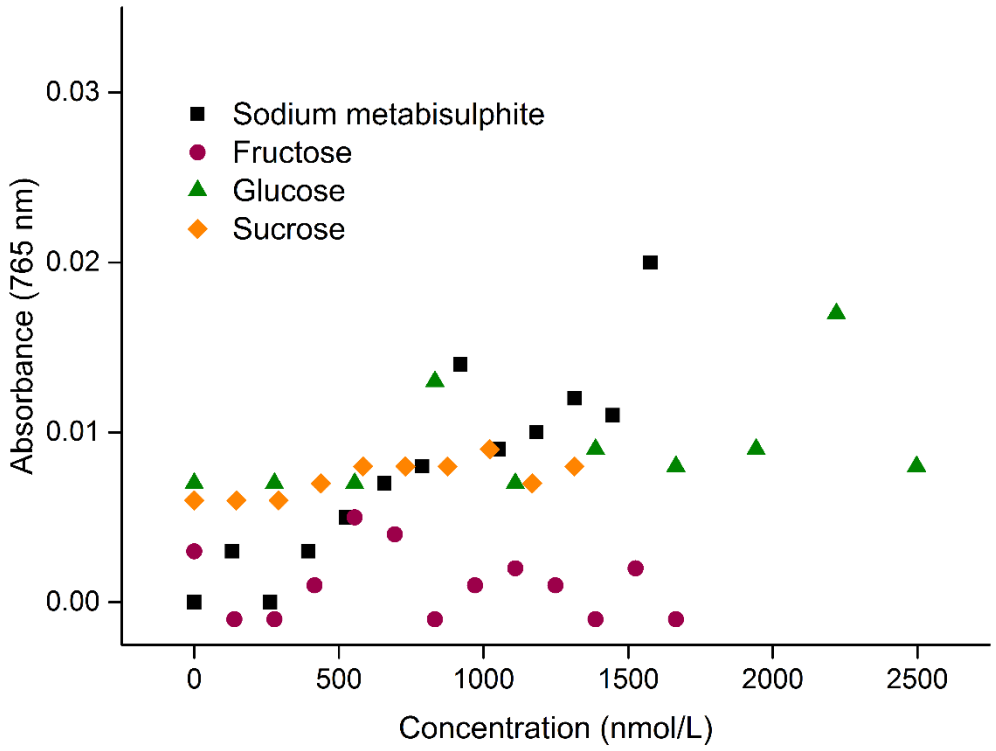


Figure 9.2 Response of various concentrations of sodium metabisulphite, fructose, glucose and sucrose using Folin-Ciocalteu assay expressed as absorbance measured at 765 nm.

9.4.1.3 Preliminary trial using pineapple juice

Two brands of pineapple juice were tested and compared with Phenol Explorer to assess the validity of the assay (Table 9.3). In comparison to Phenol Explorer, the TPC of Tropicana Pineapple Juice was higher than the results from Phenol Explorer. In comparison to other studies, the TPC of pineapple juice was 40 mg/100 g [146]; 48 mg/100 g [361] and 94 mg/ 100g [358]; where the highest value of 174 mg/100 g is from a study conducted in US by Wu *et. al* [362]. A study from UK by Mullen *et. al* [346] conducted the Folin-Ciocalteu assay on a commercial product, Tesco Pure Pineapple juice, where the GAE is 2 mmol/L, equivalent to 34 mg/ 100 mL, similar to the results obtained. Differences observed between

studies could be due to various factors, such as the variety of pineapples used, recipe and processing differences. Variation in parameters of the Folin-Ciocalteu assay within different studies could also affect the estimation of TPC. Nevertheless, Morrison's Pineapple Juice had a similar TPC in comparison to the Phenol Explorer, confirming the validity of the assay.

Table 9.3 Total phenolic content of pineapple juices from Phenol Explorer and the current study measured by the Folin-Ciocalteu assay expressed as mean (standard deviation)

	Phenol Explorer	Tropicana Pineapple Juice (n=3)	Morrison's Pineapple Juice (n = 3)
Total phenolic content (GAE mg/100 mL)	35.8	68.8 (2.1)	39.9 (1.8)

9.4.1.4 Spiking trial

Results of the spiking trial are presented in Table 9.4. TPC of gallic acid and ascorbic acid is 70.2 µg/mL and 125.7 µg/mL respectively according to the Folin-Ciocalteu assay, and 22.2 µg/mL and 50.8 µg/mL according to the correction assay. When assays were conducted on samples containing either gallic acid or ascorbic acid, and blackcurrant concentrate in combination, measured TPC was 190.6 µg/mL and 240.5 µg/mL respectively for Folin-Ciocalteu assay and 45.6 µg/mL and 71.5 µg/mL respectively for the correction assay. These results were similar in comparison to results in the right column in Table 9.4, derived by adding TPC of each component tested separately. Deviance from measured TPC was between 7.2 to 15.2% for the Folin-Ciocalteu assay, and 11.1 to 30.1% for the correction assay. This trial therefore confirmed that the increased TPC did come from the addition of a known concentration of gallic acid or ascorbic acid.

Table 9.4 Total phenolic content of a blackcurrant concentrate (BHJ), gallic acid, ascorbic acid, and spiked BHJ samples with gallic acid and ascorbic acid measured using the Folin-Ciocalteu assay, expressed as mean and standard deviation

Folin-Ciocalteu assay Samples	**Total phenolic content (µg/mL) (n = 2)**	**Total phenolic content after addition/subtraction of standards (µg/mL) (n = 2)**
Tesco's Blackcurrant High Juice 50% (BHJ)[a]	135.3 (2.9)	[d-b]BHJ without GA: 120.4 (-11.2%) [e-c]BHJ without AA: 114.8 (-15.2%)
Gallic acid (GA) (200 µg/mL)[b]	70.2 (0.2)	
Ascorbic acid (AA) (200 µg/mL)[c]	125.7 (6.7)	
BHJ + GA (200 µg/mL)[d]	190.6 (1.3)	[a+b]BHJ with GA: 205.5 (+7.2%)
BHJ + AA (200 µg/mL)[e]	240.5 (18.4)	[a+c]BHJ with AA: (+7.8%)
Ascorbic acid correction assay Samples	**Total phenolic content (µg/mL) (n = 2)**	**Total phenolic content after addition/subtraction of standards (µg/mL) (n = 2)**
BHJ[f]	29.6 (0.4)	[i-g]BHJ without GA: 23.4 (-20.9%) [j-h]BHJ without AA: 20.7 (-30.1%)
GA (200 µg/mL)[g]	22.2 (1.0)	
AA (200 µg/mL)[h]	50.8 (1.6)	
BHJ + GA (200 µg/mL)[i]	45.6 (0.4)	[f+g]BHJ with GA: 51.8 (+12.0%)
BHJ + AA (200 µg/mL)[j]	71.5 (0.6)	[f+h]BHJ with AA: 80.4 (+11.1%)

9.4.2 Total phenolic content in fruit based beverages

9.4.2.1 Fruit juices and smoothies

TPC of five cranberry juices are reported in Figure 9.3, where TPC overall was statistically different, determined by one-way ANOVA. Juices containing additives such as sweeteners, or named 'juice drink', had a significantly lower TPC in contrast to cranberry 'juices'. Oceanspray Cranberry Classic Light with Sweetener had the lowest TPC at 115.8 ± 20.3 GAE mg/serving size, while a serving of Oceanspray 100% Juice Cranberry Blend (OJCB) provided 271.3 ± 13.7 GAE mg of phenolic content. As compared to Phenol Explorer, OJCB had the closest value to the citied reference of cranberry fruit (data for juice was unavailable) with a TPC of 337 – 360 mg/serving [363]. However, OJCB consist of a blend of cranberries and grapes, and which the latter is known to contribute to high phenolic content, consisting mainly of anthocyanins. In comparison to the literature outside Phenol Explorer, the results obtained were similar for the same commercial product, Oceanspray Cranberry Classic (OCC) (230 mg/serving size), at a TPC of 195 mg/serving size from a different study [346], once again suggesting that the method used in the current study is valid.

Figure 9.4 provides the TPC of various mixed fruit juices. Results here were incomparable to other studies, due to differences in methods and samples. The range of measured TPC was very wide, ranging from ASDA's Apple & Blackberry Juice Drink with 59.4 ± 1.8 GAE mg/serving size to Tropicana Pomegranate, Grape and Apple juice containing 224.5 ± 3.0 GAE mg/serving size. The Kruskal-Wallis ANOVA determined that the TPC here was significantly different overall (*p-value <0.001*). Judging by the name of the product, 'juice drinks' tended to have a lower TPC in comparison to 'juices'. Among the five samples with the highest TPC, fruits included were citrus fruits, cranberry, pomegranate, grape, apple, peach, mango and papaya within the beverages. According to Phenol Explorer, these fruits all yield a high TPC value in Folin-Ciocalteu assay [146, 361-364]. However, some of these fruits also contained a high amount of ascorbic acid, which could cause an overestimation of TPC. As for mixed fruit juices with lower TPC, several reasons were proposed: 1) The fresh fruit juices could be diluted with water, with flavourings and sugar added instead; 2) The juices were sieved, hence the (poly)phenols that remained in the bits could have been removed; or 3) Other sources of interference were present in large amounts within the juices. This figure illustrates that the term 'mixed fruit juices' was very broad in terms of estimating TPC.

The TPC for fruit smoothies are reported in Figure 9.5. Fruit smoothies had a higher overall TPC than cranberry and mixed fruit juices, which ranged from 145.4 ± 1.9 to 247.2 ± 19.2 GAE mg/250 mL. The Kruskal-Wallis ANOVA also determined that the overall TPC content here are statistically different (*p-value = 0.006*). From the names of the smoothies, those containing berries were more likely to have a higher TPC, as agreed in a study analysing from German smoothies [365]. Smoothies which only consist of fruits such as mango, orange and pineapple also had the lowest TPC in that particular study, similar to the findings here. The TPC of German commercial smoothies ranged from 127.5 to 532.5 GAE mg/250 g [365]. The study suggested that fruit smoothies with high TPC contained fruit purees, in comparison to fruit smoothies without fruit purees, indicating differences in ingredient composition and processing could affect the outcome of TPC greatly. Varying processing effects and duration of storage could have also caused the differences in TPC [366]. Fruit smoothies in this study were frozen at -20°C instead of storage at 4°C, it is unclear if different storage temperatures may impact on the stability of (poly)phenols. In comparison to mixed fruit juices, the significance in the removal of pulp and bits was observed here. According to the label on the beverage, smoothies were not diluted and do not contain additives, which meant that it is possible that the higher the percentage of real fruit or fruit juices could be associated with a higher TPC. The same observation was also reported in Müller *et. al* [365].

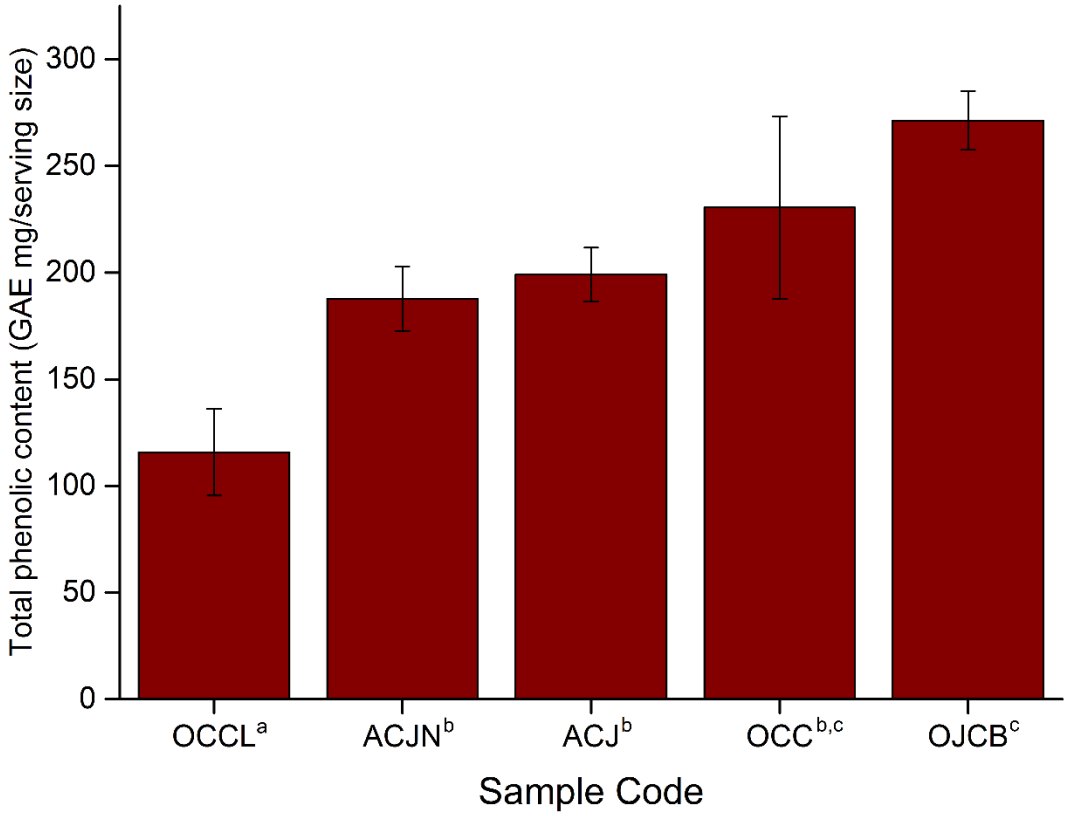


Figure 9.3 Total phenolic content in gallic acid equivalents for cranberry juices measured by the Folin-Ciocalteu assay, expressed as mean and standard deviation (replicates = 3). Samples that share a different alphabet expressed as significantly different using one-way ANOVA and Bonferroni post-hoc test (*p<0.05*).

Serving size: 250 mL; Full sample name in the order of presentation: **OCCL** (Oceanspray Cranberry Classic Light with Sweetener), **ACJN** (ASDA's Cranberry Juice Drink with No Added Sugar), **ACJ** (ASDA's Cranberry Juice Drink), **OCC** (Oceanspray Cranberry Classic), **OJCB** (Oceanspray 100% Juice Cranberry Blend)

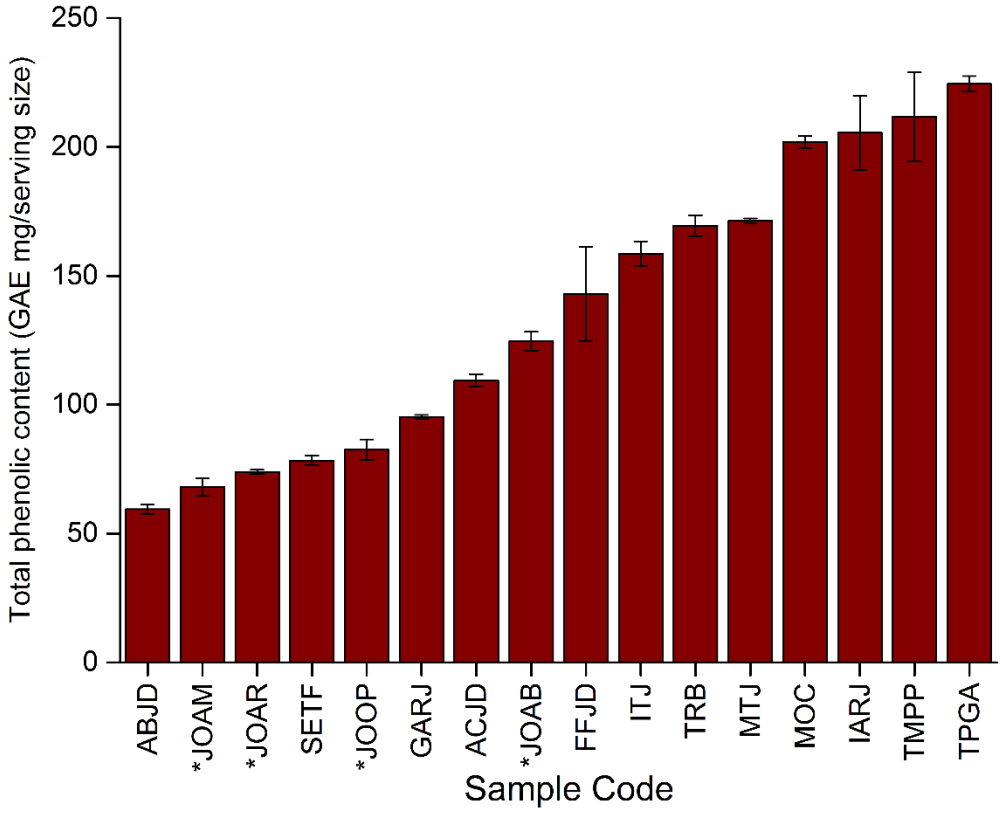


Figure 9.4 Total phenolic content in gallic acid equivalents for mixed fruit juices measured by the Folin-Ciocalteu assay, expressed as mean and standard deviation (replicates = 3, *replicates = 4)

Serving size: 250 mL; Full sample name: **ABJD** (ASDA's Apple & Blackberry Juice Drink), **JOAM** (J2O Apple and Mango), **JOAR** (J2O Apple and Raspberry), **SETF** (Sun Exotic Tropical Fruit), **JOOP** (J2O Orange and Passionfruit), **GARJ** (ASDA's Grape, Apple & Raspberry Juice Drink), **ACJD** (ASDA's Citrus Juice Drink), **JOAB** (J2O Apple and Blackberry), **FFJD** (ASDA's Forest Fruits Juice Drink), **ITJ** (Innocent Tropical Juice), **TRB** (Tropicana Ruby Breakfast), **MTJ** (Morrison's Tropical Juice), **MOC** (Morrison's Orange and Cranberry), **IARJ** (Innocent Apple & Raspberry Juice), **TMPP** (Tropicana Mango, Peach and Papaya), **TPGA** (Tropicana Pomegranate, Grape and Apple)

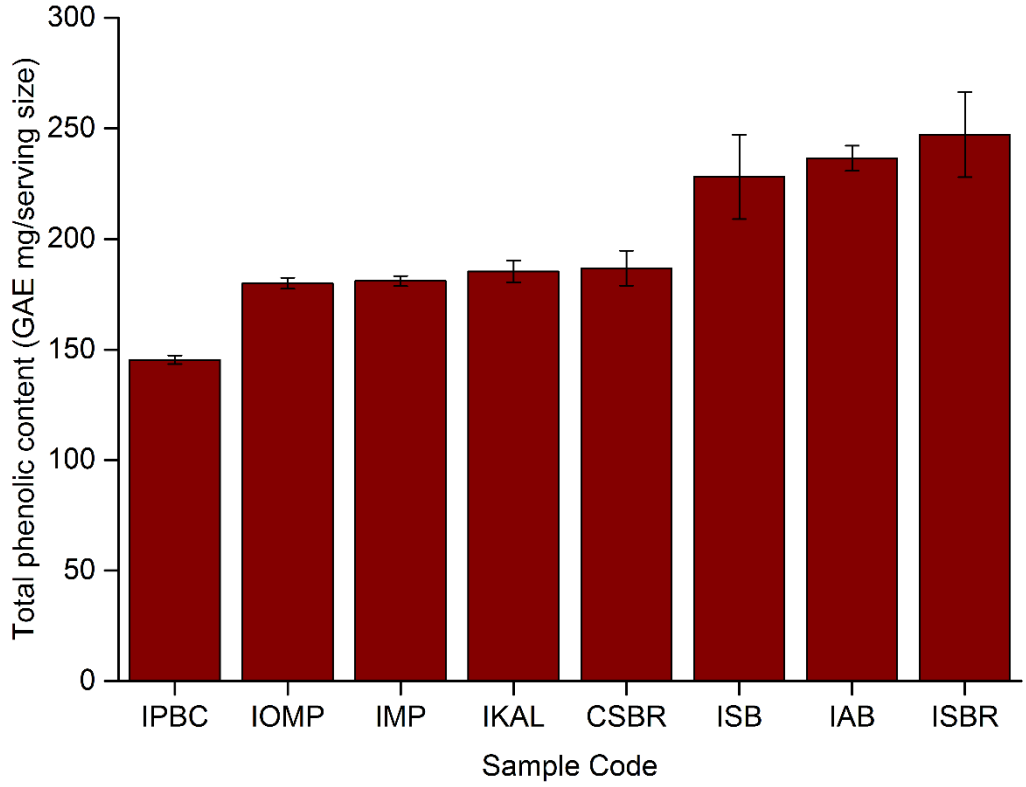


Figure 9.5 Total phenolic content in gallic acid equivalents for fruit smoothies measured by the Folin-Ciocalteu assay, expressed as mean and standard deviation (replicates = 3)

Serving size: 250 mL; Full sample name: **IPBC** (Innocent Pineapple, Banana and Coconut), **IOMP** (Innocent for Kids: Orange, Mangoes and Pineapple), **IMP** (Innocent Mango and Passionfruit), **IKAL** (Innocent Kiwi, Apples and Limes), **CSBR** (Co-operative Cranberry, Blackberry and Raspberry), **ISB** (Innocent Strawberries and Bananas), **IAB** (Innocent for Kids: Apples and Blackcurrants), **ISBR** (Innocent for Kids: Strawberries, Blackberries and Raspberries)

9.4.2.2 Concentrates

The Folin-Ciocalteu assay results for five different orange concentrates, both with and without ascorbic acid correction are presented in Figure 9.6. In general, the content of TPC were statistically different, determined by the Kruskal-Wallis ANOVA (*p-value <0.001*). The concentrates with the term 'high juice' tended to have a higher phenolic content compared to 'squash'. Sainsbury's Basics Double Strength Orange Squash had the lowest phenolic content (7.9 ± 0.1 GAE mg/serving size), while Waitrose High Juice Orange Squash had the highest phenolic content (82.2 ± 1.4 GAE mg/serving size). In terms of estimated ascorbic acid content, this seemed to increase with increasing TPC (Figure 9.6).

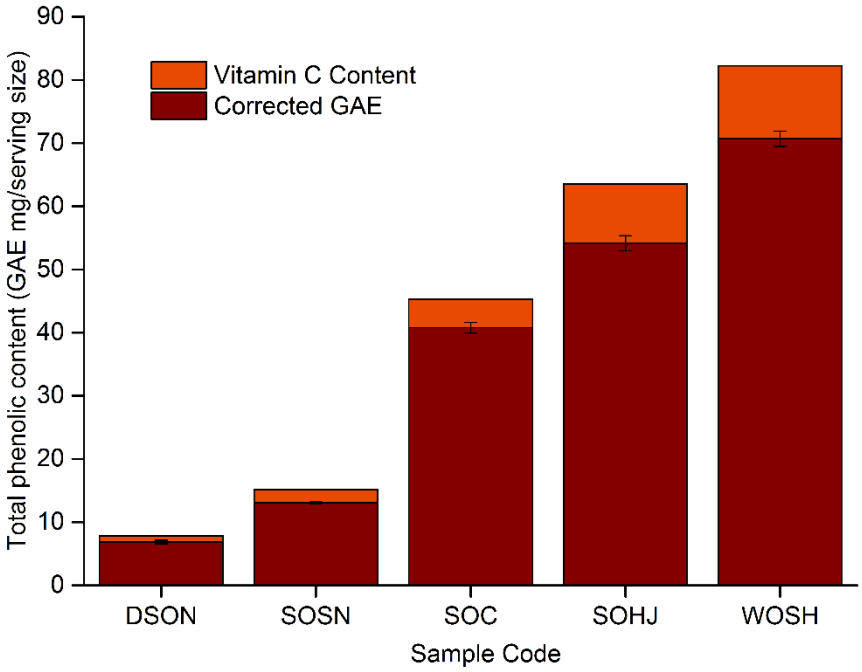


Figure 9.6 Total phenolic content in gallic acid equivalents and estimated vitamin C content for orange concentrates measured by the Folin-Ciocalteu assay, expressed as mean and standard deviation (replicates = 4)

Serving size: 250 mL after dilution; Full sample name: **DSON** (Sainsbury's Basics Double Strength Orange Squash), **SOSN** (Orange Squash by Sainsbury's), **SOC** (Orange Cordial by Sainsbury's), **SOHJ** (High Juice Orange by Sainsbury's), **WOSH** (Waitrose High Juice Orange Squash)

With regard to blackcurrant concentrates within 30 different types tested, a large variation of phenolic content was observed (Figure 9.7), ranging from 0 to 135.9 ± 8.7 GAE mg/serving size, with a mean of 43.2 ± 3.0 GAE mg/serving size after correcting for ascorbic acid content. The Kruskal-Wallis ANOVA also confirmed that TPC here are statistically different in general (*p-value <0.001*). With the exception of two blackcurrant concentrates with the lowest phenolic content, the estimated ascorbic acid levels generally follow a similar pattern described above. Samples which consisted of both 'apple and blackcurrant' or 'double strength' were more likely to have a lower phenolic content, compared to blackcurrant only concentrates, as well as 'cordials' or 'high juice'. The figure illustrates clearly the wide extent of variation in phenolic content within a specific type of product.

There have not been many reported analyses of fruit juice concentrates, but there were a few studies that the results may be compared with. A Spanish study by Bermúdez-Soto *et. al* [352] used the same reference method for Folin-Ciocalteu assay and reported the TPC of blackcurrant concentrate to be 117 mg/serving size. This is similar to the TPC of commercial blackcurrant concentrates on the high end of the graph, such as High Juice Blackcurrant by Sainsbury's (SBHJ). Other samples had extremely low GAE, which might be

due to processing effects, such as the extent of dilution and proportion of blackcurrant fruit. Even so, the concentrates contained considerably less TPC when compared to the data on Phenol Explorer on fresh blackcurrant fruits, where the average was 821 mg/ 100g [354, 357, 367]. The difference in phenolic content was reasonable as they were mostly anthocyanins, which were likely to degrade up to >90% during processing that involving exposure to heat, pH change and light [368]. However, a study also suggested that there were no significant losses of anthocyanins in commercial processing [345]. Enzyme treatments were also suggested to increase phenolic content within blackcurrant juice to 650 – 665 mg/ 100 mL GAE [369].

Overall by sample groups, fruit juices and smoothies had a higher TPC in comparison to made-up concentrates. (Table 9.5). Of the juice based drinks, mixed fruit juices had the lowest TPC, followed by fruit smoothies and cranberry juice, while blackcurrant concentrates had a slightly higher TPC than orange concentrates. In conclusion for this section, the Folin-Ciocalteu assay was able to effectively act as a screening assay to differentiate fruit beverages according to TPC. Parameters in the Folin-Ciocalteu assay here had also been tested, thus it would also be possible to apply this method directly to future studies. In addition, the correction for ascorbic acid was also important as it was demonstrated to interfere with the assay.

Alternative methods are also available to measure antioxidant activity [347], but these methods were not adopted here because the study was only interested in separating 'low' TPC and 'high' TPC samples. Antioxidant activity is not one of the possible mechanisms of (poly)phenols *in vivo*, where these compounds also exhibit various other effects. Therefore, application of other antioxidant assays suggested in Prior *et. al* [347] is not reflective of the mechanistic effects occurring *in vivo*, and does not account for bioavailability.

Table 9.5 Total phenolic measured by Folin-Ciocalteu assay by sample group, expressed as mg/serving size (250 mL) without ascorbic acid correction

Sample group	**Total phenolic content**, (GAE mg/serving size) (mean ± SD)	**Total phenolic content**, (GAE mg/serving size) (min – max)	**Kruskal-Wallis one-way ANOVA,** *(p-value)*
Cranberry juice	200.9 ± 20.9	116 – 271	
Mixed fruit juice	136.1 ± 5.2	59.4 – 212	
Fruit smoothies	198.8 ± 8.0	145 – 247	<0.001
Orange concentrates	42.8 ± 0.8	8 – 63	
Blackcurrant concentrates	54.4 ±2.9	5 – 153	

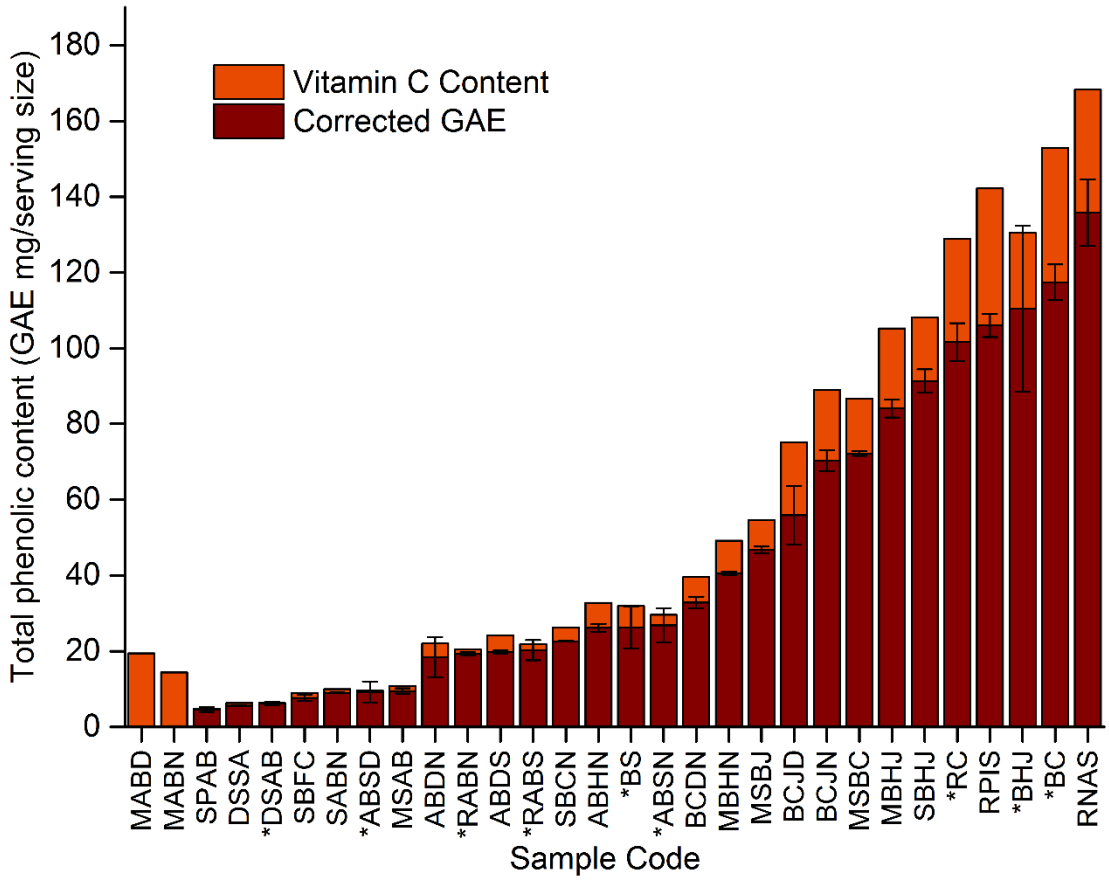


Figure 9.7 Total phenolic content in gallic acid equivalents and estimated vitamin C content for blackcurrant concentrates measured by the Folin-Ciocalteu assay, expressed as mean and standard deviation (replicates = 4, *replicates = 3)

Serving size: 250 mL after dilution; Full sample name: **MABD** (Morrisons Double Strength Apple & Blackcurrant Squash No Added Sugar), **MABN** (Morrisons Apple & Blackcurrant Squash No Added Sugar), **SPAB** (ASDA Smart Price Apple & Blackcurrant Double Strength Squash No Added Sugar), **DSSA** (Sainsbury's Basics Double Strength Apple and Blackcurrant Squash), **DSAB** (Tesco's Value Double Strength Apple and Blackcurrant Squash No Added Sugar), **SBFC** (Schweppes Blackcurrant Flavour Cordial), **SABN** (Apple and Blackcurrant Squash by Sainsbury's), **ABSD** (Tesco's Apple and Blackcurrant Squash Double Strength), **MSAB** (Simply M&S Apple & Blackcurrant Squash No Added Sugar), **ABDN** (ASDA Apple & Blackcurrant Double Strength Squash No Added Sugar), **RABN** (Robinson's Apple and Blackcurrant No Added Sugar), **ABDS** (ASDA Apple & Blackcurrant Double Strength Squash), **RABS** (Robinson's Apple and Blackcurrant), **SBCN** (Blackcurrant Squash by Sainsbury's), **ABHN** (ASDA 50% Fruit High Juice Apple & Blackcurrant No Added Sugar), **BS** (Tesco's Blackcurrant Squash Double Strength), **ABSN** (Tesco's Apple and Blackcurrant Squash Double Strength No Added Sugar), **BCDN** (ASDA Blackcurrant Double Strength Squash No Added Sugar), **MBHN** (Marks & Spencer Blackcurrant High Juice No Added Sugar), **MSBJ** (Marks & Spencer Blackcurrant High Juice), **BCJD** (ASDA Blackcurrant Juice Drink), **BCJN** (ASDA Blackcurrant Juice Drink No Added Sugar), **MSBC** (Marks & Spencer British Blackcurrant Cordial), **MBHJ** (Morrisons Blackcurrant High Juice 45% Fruit Juice), **SBHJ** (High Juice Blackcurrant by Sainsbury's), **RC** (Ribena Concentrate), **RPIS** (Ribena Plus Immunity Support), **BHJ** (Tesco's Blackcurrant High Juice 50%), **BC** (Tesco's Blackcurrant Cordial (25% Fruit Juice)), **RNAS** (Ribena No Added Sugar)

9.4.3 Quantification of major anthocyanins in blackcurrant concentrates using HPLC

9.4.3.1 Method development

Prior to HPLC analysis, the method had to be validated. Compounds in blackcurrant juice, which were mostly anthocyanins, could not be separated using the original parameters (Figure 9.8). In addition, the chemical structures of CY3RUT and DP3RUT were very similar, which made separation even more difficult (Chapter 1 Section 1.2.3.1.1). The initial solvents used contained 0.1% of formic acid, equivalent to pH 2.9. Anthocyanins are largely affected by pH, capable of existing in different chemical forms under different pH conditions [121, 370]. The most stable form is at pH 1, where the red flavylium cation is dominant, contributing to produce red and purple colour within the food matrix. As the pH increases, the predominant form of anthocyanin changes. At pH 2 – 4, the blue quinoidal species dominates, and at pH 5 – 6 the colourless carbinol pseudo-base dominates. At pH 7 and above, the anthocyanin will degrade. If the acidity of the solvent is increased, separation might improve as there would be more of the red flavylium cation, improving sensitivity of the anthocyanin detected. Therefore, the concentration of formic acid was increased to lower the pH to 2, which should allow better separation of peaks for CY3RUT and DP3RUT (Figure 9.9).

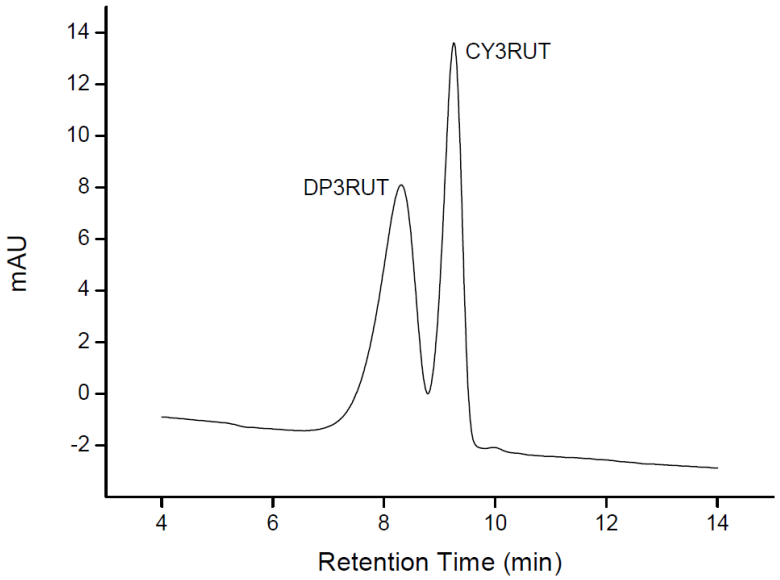


Figure 9.8 A section of the chromatogram of compounds delphinidin-3-O-rutinoside and cyanidin-3-O-rutinoside using 0.1% formic acid solvents (both A and B).

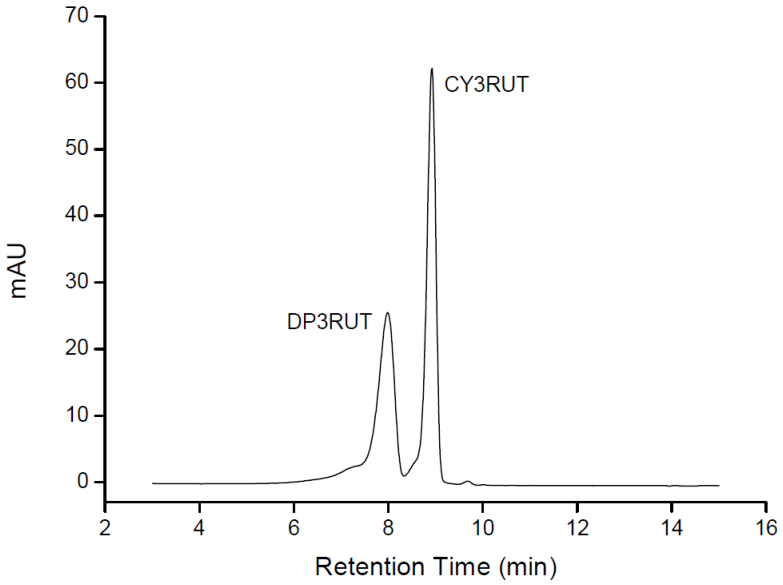


Figure 9.9 A section of the chromatogram of compounds delphinidin-3-O-rutinoside and cyanidin-3-O-rutinoside using 0.5% formic acid solvents (both A and B).

9.4.3.2 Standard curves and chromatograms

Levels of CY3RUT, DP3RUT and ascorbic acid in blackcurrant concentrates with over 100 GAE mg/serving size measured from the Folin-Ciocalteu assay were further quantified using HPLC.

Figure 9.10 and Figure 9.11 report the typical standard curve for the three compounds of interest, as well as for the internal standard nicotinic acid.

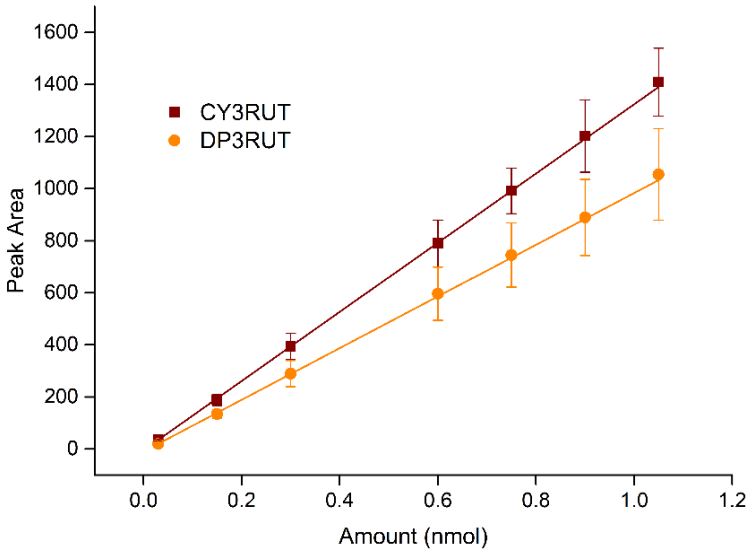


Figure 9.10 Standard curves for cyanidin-3-*O*-rutinoside and delphinidin-3-*O*-rutinoside quantified by HPLC, expressed in mean and standard deviation in nmol (replicates = 3)

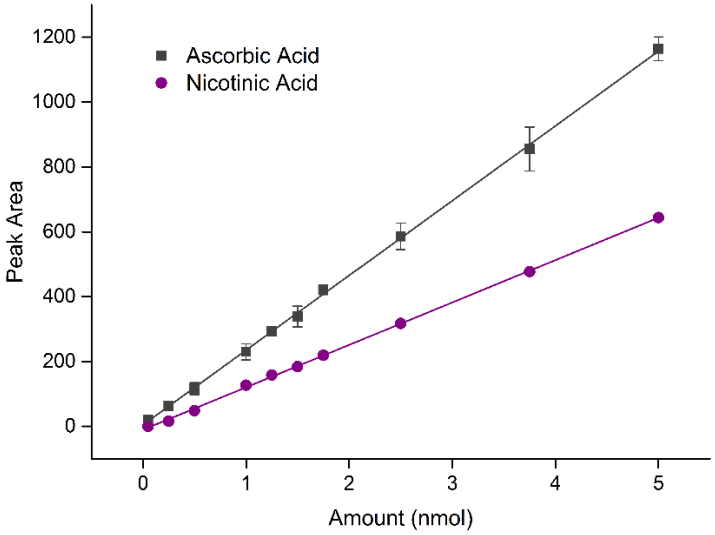


Figure 9.11 Standard curves for ascorbic acid and nicotinic acid quantified by HPLC, expressed in mean and standard deviation in nmol (replicates = 3)

9.4.3.3 Content of ascorbic acid and anthocyanins in blackcurrant concentrates

Figure 9.12 illustrates the typical chromatograms obtained from HPLC analysis for a blackcurrant concentrate, while Figure 9.13 provides an overview of CY3RUT and DP3RUT content within the beverages. The proportion of CY3RUT to DP3RUT was consistent throughout all samples and compared to Phenol Explorer. The range of total anthocyanins was between 4.5 to 35.3 mg/50 mL of undiluted concentrate, while the average amount was 12.6 mg/50 mL. Ribena Plus Immunity Support had the lowest levels of total anthocyanins within 50 mL of undiluted concentrate (4.51 mg/50 mL), while Marks & Spencer British Blackcurrant Cordial had the highest total anthocyanin content (35.3 mg/50 mL). The latter cordial was able to provide major anthocyanins equivalent 6 to 8 g of blackcurrants (≈15% of reported values in Phenol Explorer).

In terms of specific anthocyanins, the levels of CY3RUT and DP3RUT within blackcurrant concentrates ranged between 1.5 to 10.5 mg/50 mL and 3.0 to 11.6 mg/50 mL of undiluted concentrate, and the mean was 3.9 ± 2.6 mg/50 mL and 8.6 ± 6.1 mg/50 mL respectively. The Kruskal-Wallis ANOVA determined statistically different levels of CY3RUT and DP3RUT between these samples overall (*p-value <0.001*). In comparison to other studies, the findings from this experiment were similar to a study on European fruit juices by Mattila *et. al* [343], where the range reported was 4.3 – 58 mg/250 mL on a ready-to-drink basis (directly comparable to 50 mL of undiluted concentrate). UK commercial

blackcurrant concentrates tested within that study had an average anthocyanin content of 7.5 mg/250 mL on a ready-to-drink basis. The authors were also able to identify delphinidin-3-O-glucoside and cyanidin-3-O-glucoside as a different method to the current study was used. In a Spanish study by Bermúdez-Soto *et. al* [352], the reported values for total phenolics in HPLC and Folin-Ciocalteu assay were extremely high, as compared to the results from this study. Total phenolics detected by HPLC were 1480 mg/100 mL and for Folin-Ciocalteu were 2340 mg/100 mL, which was ten times greater than the amount detected here. However, the amount of total anthocyanins (7.8 mg/100 mL) was lower than all the samples in this study. Total anthocyanin content for RC, BHJ and BC were also similar to the results from Hollands *et. al* [344] (UK), which ranged from 4.1 to 32.2 mg/50 mL of undiluted blackcurrant squashes and cordials. However, the current method was unable to detect other anthocyanins in comparison to Hollands *et. al* [344]. To conclude, total anthocyanin levels quantified from the current analysis are similar to other studies, with the exception of Bermúdez-Soto *et. al* [352].

When findings from the current study were compared to HPLC analysis of fresh blackcurrant in Phenol Explorer, the average amount of CY3RUT is 80.4 mg/50 g, which was about ten times greater than blackcurrant concentrates. This was also consistent for DP3RUT [354, 371]. From the evaluation above, it is possible to conclude that processing fresh blackcurrants into cordials, squash and concentrates reduces the amount of anthocyanins greatly. This is reasonable as anthocyanins are known to be unstable at higher temperatures [121, 372], through hydrolysis of sugars attached. The aglycones generated would also breakdown further as they are also unstable [372]. The yield of anthocyanins in blackcurrant juice could be increased by using pectinolytic enzymatic treatments, [369, 373].

Quantified anthocyanin levels here were also significantly less than estimates using the Folin-Ciocalteu assay (though no statistical tests were conducted). This was expected as Folin-Ciocalteu assay was likely to be interfered by components such as ascorbic acid, thus it was also quantified in the next section.

Data produced from HPLC provided a better estimation on the amount of anthocyanins are consumed via blackcurrant concentrate drinks. From the findings of this study, it was possible to conclude that blackcurrant concentrates are unlikely to contribute greatly to total (poly)phenol intakes, unless it was consumed in high quantities.

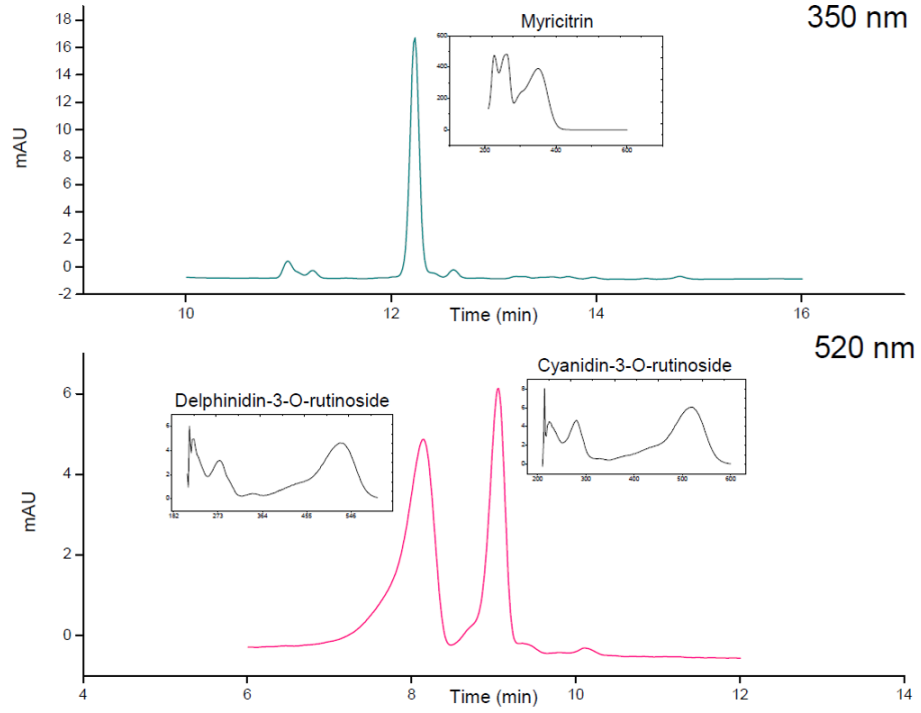


Figure 9.12 Example HPLC chromatograms of myricitrin, delphinidin-3-*O*-rutinoside and cyanidin-3-*O*-rutinoside, and their respective UV absorption spectras from Ribena No Added Sugar sample

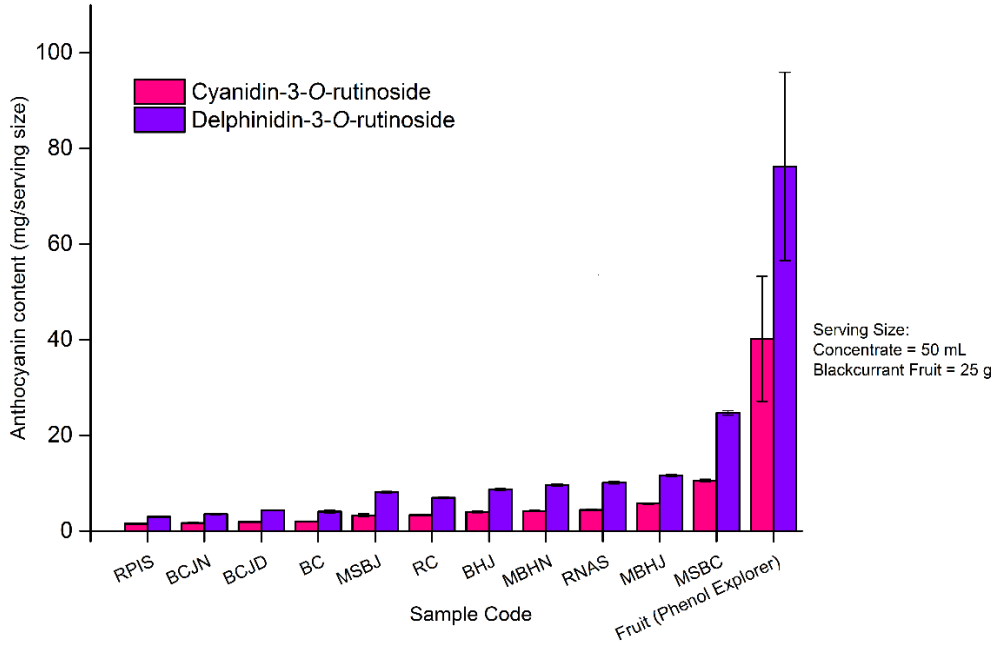


Figure 9.13 Amount of cyanidin-3-*O*-rutinoside and delphinidin-3-*O*-rutinoside quantified using HPLC in blackcurrant concentrates in comparison to blackcurrant fruit from Phenol Explorer, expressed as mean and standard deviation (replicates = 9)

Full sample name: **RPIS** (Ribena Plus Immunity Support), **BCJN** (ASDA Blackcurrant Juice Drink No Added Sugar), **BCJD** (ASDA Blackcurrant Juice Drink), **BC** (Tesco's Blackcurrant Cordial (25% Fruit Juice), **MSBJ** (Marks & Spencer Blackcurrant High Juice), **RC** (Ribena Concentrate), **BHJ** (Tesco's Blackcurrant High Juice 50%), **MBHN** (Marks & Spencer Blackcurrant High Juice No Added Sugar), **RNAS** (Ribena No Added Sugar), **MBHJ** (Morrisons Blackcurrant High Juice 45% Fruit Juice), **MSBC** (Marks & Spencer British Blackcurrant Cordial)

In terms of ascorbic acid content, a typical chromatogram is presented in Figure 9.14, while Figure 9.16 shows the levels of ascorbic acid content within blackcurrant concentrates by serving size. The beverages provided between 11 to 144 mg/50 mL of ascorbic acid in an undiluted form, where the average level is 76.9 ± 48.3 mg/50 mL, adequate to achieve the reference nutrient intake for both male and females (40 mg/day) [374]. The Kruskal-Wallis ANOVA also confirmed that ascorbic acid content in blackcurrant concentrates are statistically different from each other (*p-value <0.001*).

When ascorbic acid content was plotted against levels of anthocyanin within blackcurrant concentrates (Figure 9.15), graphically, no distinct patterns observed were observed. Moreover, the correlation between the two was -0.40, suggesting that there was only a weak negative correlation between ascorbic acid and anthocyanin content.

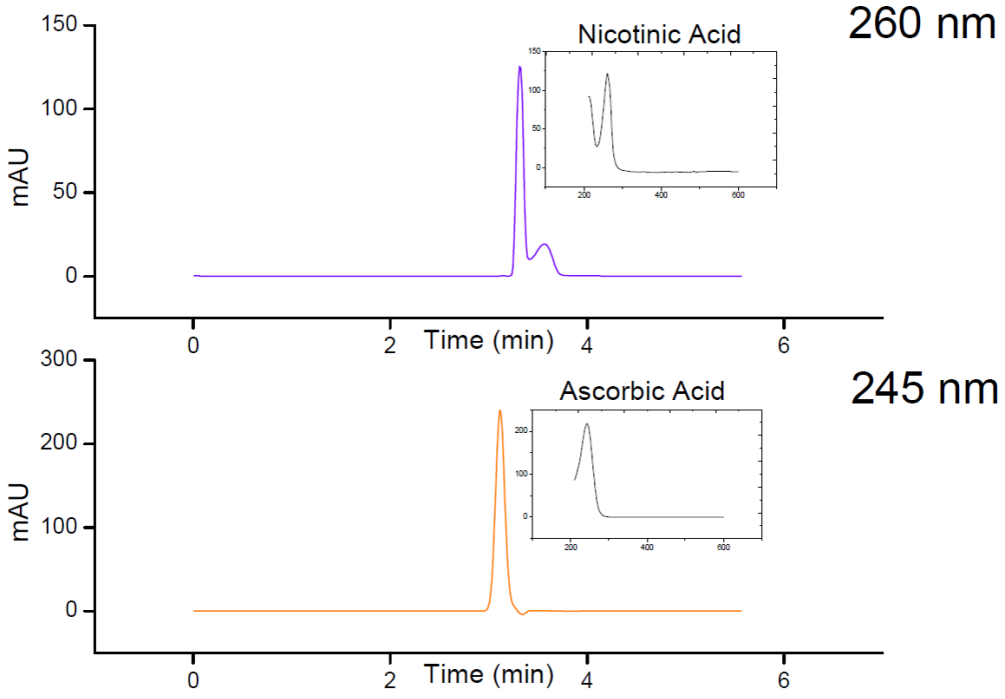


Figure 9.14 Example HPLC chromatograms of ascorbic acid and nicotinic acid, and their respective UV absorption spectras from Ribena No Added Sugar sample

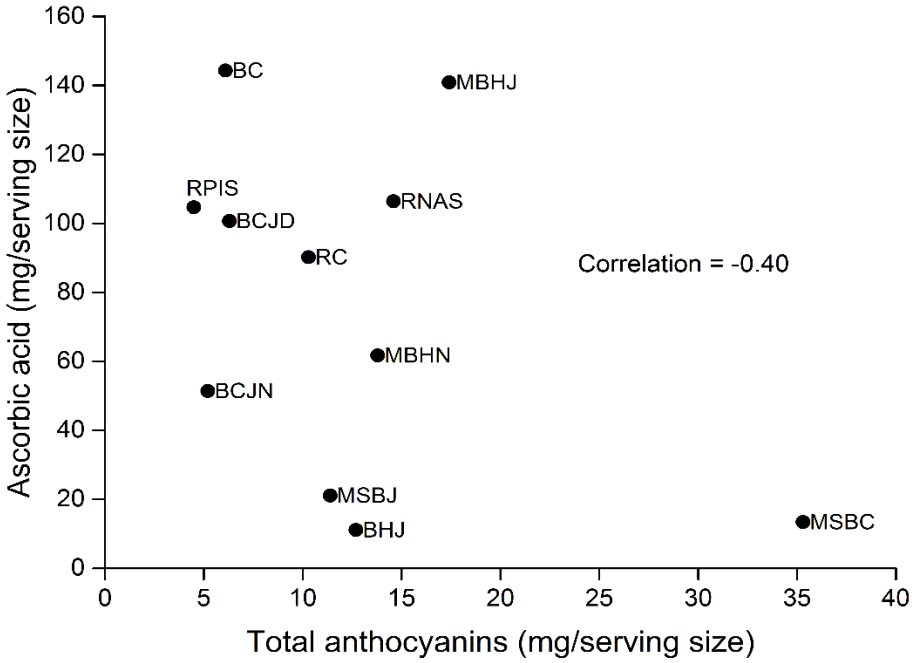


Figure 9.15 Scatter graph showing the association and correlation between ascorbic acid and total anthocyanin content quantified by HPLC in blackcurrant concentrates

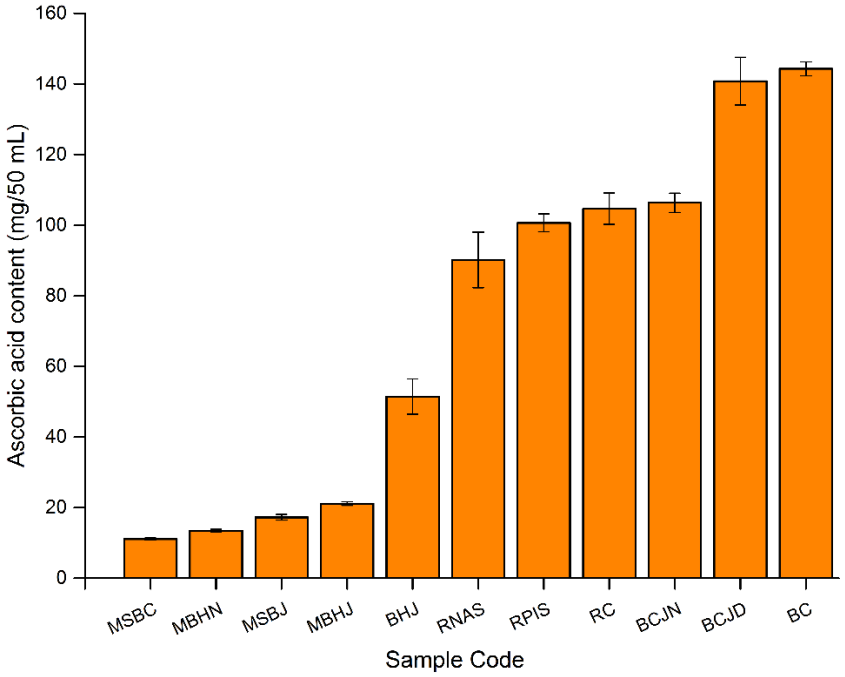


Figure 9.16 Amount of ascorbic acid quantified using HPLC in blackcurrant concentrates, expressed as mean and standard deviation (replicates = 9)

Full sample name: **MSBC** (Marks & Spencer British Blackcurrant Cordial), **MBHN** (Marks & Spencer Blackcurrant High Juice No Added Sugar), **MSBJ** (Marks & Spencer Blackcurrant High Juice), **MBHJ** (Morrisons Blackcurrant High Juice 45% Fruit Juice), **BHJ** (Tesco's Blackcurrant High Juice 50%), **RNAS** (Ribena No Added Sugar), **RPIS** (Ribena Plus Immunity Support), **RC** (Ribena Concentrate), **BCJN** (ASDA Blackcurrant Juice Drink No Added Sugar), **BCJD** (ASDA Blackcurrant Juice Drink), **BC** (Tesco's Blackcurrant Cordial (25% Fruit Juice))

The HPLC method applied here is a suitable method to quantify major (poly)phenols within fruit beverages, as exhibited above. Minor components were not quantified because the HPLC method was not sensitive enough. It was also unlikely for these components to have concentration high enough *in vivo* to exhibit mechanistic effects after considering the variation in bioavailability as well. Alternative methods such as mass spectrometry could quantify minor components to complete the (poly)phenol profile of blackcurrant concentrates.

9.4.4 Importance in the assessment of total dietary (poly)phenol intakes

The data obtained in this study revealed the importance of including pure fruit juices and smoothies when collecting dietary data, whether to estimate total fruit intake, or to estimate TPC and specific (poly)phenol intake. This implication was based on the higher TPC in fruit smoothies and some fruit juices in comparison to concentrates. Assuming that the percentage of real fruit would be higher in smoothies than concentrates, it would contribute more to (poly)phenol intakes. In addition for the same reason mentioned above, concentrates, juice with or without bits and fruit smoothies should not be included in the same category in dietary assessment methods where possible, to avoid or minimise estimation error.

This estimation error could result from a number of factors. Firstly, the variation in TPC observed within blackcurrant concentrates revealed a limitation in taking an average value to represent a particular food item within dietary assessments. This could be due to processing effects, which had been elaborated above, or because of the natural variation in (poly)phenol content that exists within cultivars of the same fruit, and their growing conditions. In relation to FFQs, variables from the FFQ usually represent multiple food items categorised together. For example, if fruit based beverages were all grouped under 'fruit juice', the limitation mentioned in the previous paragraph would apply. Similarly, grouping all citrus related food items under 'citrus' fruit could also result in the same problem, if the intention of the study was to estimate dietary (poly)phenol intake. A food diary could possibly minimise this type of error by asking for further details on fruit beverages drunk by matching items to the exact, or closest items on the food database. However, both the FFQ and food diary are reliant on food databases to translate food items into nutrient, mineral and phytochemical intakes. Food databases usually store average values of food items, instead of having an entry for each item. Thus, this is a limitation which should be recognised when estimating TPC or (poly)phenol intakes. To overcome this limitation, food

analyses on items which are not in (poly)phenol databases (USDA, Phenol Explorer) should be conducted to fill in gaps, in order to estimate TPC and specific (poly)phenol intake more accurately.

In reflection to the analysis completed in previous chapters using the UKWCS (Chapter 3, Chapter 4 and Chapter 6), the results from this study support the methodology where fruit juices were included as part of the estimated total fruit intake. The current results also support the methodology adapted in Chapter 10, however, due to the low variation in consumption, smoothies and fruit juices were categorised together. If (poly)phenol intakes were to be estimated in the future, it would be ideal if the two categories were investigated separately.

9.5 Summary

In conclusion, fruit smoothies and cranberry juice have the highest TPC, and would most likely make a potential contribution to the estimation of total (poly)phenol intakes, but further analyses using HPLC would be required for verification. CY3RUT and DP3RUT in blackcurrant concentrates were successfully quantified. A substantial consumption of blackcurrant concentrates containing high amounts of anthocyanins would also contribute to anthocyanin intake in general populations. Results from this chapter also supported methodology adopted in previous chapters (Chapter 3, Chapter 4, Chapter 6 and Chapter 10).

Chapter 10
Fruit, vegetable intake and blood pressure measurements within adults in the National Diet and Nutrition Survey Rolling Programme (2008 – 2012)

10.1 Abstract

Chapter 6 explored the association between FV intake, and the odds of self-reported HBP. This study aimed to explore the association between total FV, and fruit, vegetable subgroups and measured BP in the NDNS RP 2008 to 2012. Total FV intake (g/day) derived from a four-day food diary, was obtained from 1,002 participants (aged 19 to 91 years) from 2008 to 2012 who were not on BP lowering medication. FV intakes were also further grouped by (poly)phenol profile into berries, citrus, drupes, pomes and tropical fruit, and *Allium*, *Brassicaceae*, fruit vegetables, pod vegetables and stalk/root vegetables. BP (mmHg) was measured during a nurse visit. Participants were also divided into hypertensive and normotensive categories. Multivariate regression and logistic regression were conducted respectively for measured BP and hypertensive status. Higher intakes of total FV was associated with lower odds of BP. Greater consumption of total fruit intake was negatively associated with lower BP, and this persisted in subgroups of non-obese, elderly and male subpopulations. Moderate intake of pomes was also associated with lower SBP in general, and with lower DBP in the elderly population. Total vegetable and vegetable subgroups were not associated with lower BP. This finding is aligned with Chapter 6 investigating UKWCS and current literature promoting high FV intakes. Further interventions are recommended for consumption of pome fruits to assess its relationship with BP lowering effects in the normotensive population as a form of preventing HBP development.

10.2 Background

The relationship between FV intake was explored in the UKWCS previously in Chapter 6. A greater intake of total FVs, especially vegetables, pomes and fruit vegetables was associated with a lower odds of self-reported HBP. Chapter 8 assessed the relative validity of the FFQ against the food diary, and discussed the strengths and limitations of both dietary assessments. In comparison to the FFQ, despite only taking a snapshot of diet

which may or may not be reflective of habitual intake, food diaries are less likely to overestimate intakes, and capture higher quality dietary data. FV intakes in the UKWCS were also collected two decades ago, and were possibly not reflective of current diets, due to the increased availability and variation of foods overtime. In addition, self-reported HBP could likely to be subject to misreporting since many individuals would be unaware they have HBP. On the basis of the same literature discussed in Chapter 6, the current chapter aims to overcome previous limitations, and improve the quality of exposure and outcome. Measured BP (mmHg) using the National Diet and Nutrition Survey Rolling Programme (NDNS RP) 2008 – 2012, and its association with total FV intake and subgroups of FV intake according to similarities in (poly)phenol profile with reference to Phenol Explorer [111] will be explored here.

10.3 Method

10.3.1 Dietary exposure

The generation of total FV intakes, fruit subgroup and vegetable subgroup intakes was documented in Chapter 2, Section 2.7.1. There were no missing data for both intakes. Consumption was expressed as grams of fruit or vegetable intake per day (g/day).

10.3.2 Measurement outcome

BP measurement was available for participants who gave consent to nurse visits. The procedures have been described in Chapter 2 Section 2.3.3.3. An average of three valid systolic and diastolic measurements for each eligible participant was calculated in millimetres of mercury (mmHg). Participants were also divided into non-hypertensive and hypertensive categories. Hypertension is defined by a SBP of 140 mmHg and above, and/or DBP of 90 mmHg and above.

10.3.3 Statistical method and design

10.3.3.1 Outliers and exclusions

The procedure for omitting outliers and implementing exclusions is documented in Chapter 2, Section 2.5.1. In brief, participants who met the following criteria were excluded:

1. Participants younger than 19 years (n = 2073)
2. Participants with no valid BP readings (n = 866)
3. Participants who consume BP related medication (n = 211).

- ❖ The current study intended to study a healthy population. Participants who consume BP related medication may have their condition controlled, thus potentially misclassifying them as non-hypertensive. These participants may also have changed their diet due to their BP related condition, so their dietary intake may have been different before they knew they were hypertensive.

4. Participant who consumed more than 300 g alcohol on average per day (n = 1) and participants who had less than 500 kcal/day energy intake (n = 3).

10.3.3.2 Confounding

The concept of confounding was explained in Chapter 2, and the current analysis is based on the DAG from Chapter 2, Section 2.5.1 to provide evidence for inclusion of potential confounders. These confounders were previously explored as a correlation matrix. Results showed that none of the potential confounders were correlated to each other, thus multicollinearity is unlikely (Table 10.1). Univariate analysis was also conducted prior to the DAG to explore the relationship between the variable of interest and outcome. These univariate analyses support findings of the literature that hypertension is related to increasing age, smoking status, obesity, SES and alcohol drinking, and helped to guide model development (Table 10.2).

Table 10.1 Correlation between variables included in the model

Correlation	Age	BMI	Energy	Physical activity	Smoking	SES	Alcohol
Age	1.00						
BMI	0.15	1.00					
Energy	-0.06	-0.07	1.00				
Physical activity	-0.06	-0.09	0.12	1.00			
Smoking	0.05	-0.01	0.09	-0.01	1.00		
SES	-0.03	0.05	-0.02	0.01	-0.15	1.00	
Alcohol	<-0.01	0.04	0.13	0.09	-0.11	-0.09	1.00

Table 10.2 Univariate analyses of potential confounders and BP (mmHg) and odds ratio of hypertension per unit increment for continuous variables or by category for categorical variables

Variable of Interest	Systolic BP (mmHg)	Diastolic BP (mmHg)	Hypertension (Odds ratio)
Age (years)	0.37 (0.31, 0.43)	0.09 (0.05, 0.13)	1.04 (1.03, 1.06)
BMI (kg/m²)			
Underweight	0	0	1
Normal	4.08 (-1.46, 12.8)	5.78 (-0.02, 11.6)	1.38 (0.17, 11.0)
Overweight	11.0 (2.28, 19.7)	10.4 (4.64, 16.2)	2.76 (0.35, 21.7)
Obese	14.0 (5.3, 22.8)	14.8 (8.9, 20.6)	4.19 (0.53, 33.0)
Missing	12.4 (2.59, 22.2)	11.9 (5.3, 18.4)	3.93 (0.45, 34.4)
Energy (kcal/day)	0.003 (0.001, 0.005)	0.00 (-0.00, 0.00)	1.00 (1.00, 1.00)
Physical Activity (hr/day)			
0 to 0.4 hours	0	0	1
0.4 to 1.3 hours	-2.11 (-4.94, 0.72)	-0.26 (-2.19, 1.67)	0.59 (0.36, 0.95)
>1.3 hours	1.36 (-1.47, 4.19)	0.48 (-1.46, 2.41)	1.06 (0.68, 1.64)
Missing	1.09 (-1.58, 3.76)	0.58 (-1.24, 2.41)	0.89 (0.58, 1.36)
Smoking Status			
Current smoker	0	0	1
Ex-regular smoker	2.12 (-1.02, 5.27)	0.85 (-1.29, 3.00)	1.51 (0.92, 2.48)
Never regular smoker	-0.38 (-3.12, 2.35)	0.76 (-1.11, 2.62)	0.92 (0.58, 1.45)
Socioeconomic Status (SES)			
Professional/Managerial	0	0	1
Intermediate	0.89 (-1.70, 3.48)	-1.16 (-2.93, 0.61)	1.00 (0.64, 1.55)
Routine/Manual	1.46 (-0.78, 3.71)	-0.07 (-1.60, 1.46)	1.48 (1.04, 2.12)
Alcohol (g/day)	0.12 (0.07, 0.17)	0.09 (0.06, 0.13)	1.01 (1.00, 1.02)

The models used in these analysis are:

1. Age (years)
2. Age (years), BMI (underweight, normal, overweight, obese and missing), physical activity(categorical), smoking status (current smoker v.s. ex-smoker v.s. never-smoker), alcohol intake (g/day) and socio-economic status (professional/managerial, intermediate or routine/manual).
3. In addition to model 2, energy intake (kcal/day) was also included.

Models that investigated FV subgroups by (poly)phenol profile were further adjusted for total vegetable and total fruit intakes respectively. The non-exposure group was also adjusted for in addition to the appropriate total fruit or vegetable intakes. This is because of possible confounding [plausible biological mechanisms of (poly)phenols] for the association between the investigated exposure and outcome. In particular, it is important to note that participants with missing information in BMI (n = 38) and physical activity (n = 299) were allocated in a 'missing' category to retain maximum number of people within the analysis.

10.3.3.3 Descriptive statistics

Characteristics of participants such as anthropometric measures, dietary habits and lifestyle habits were explored by dividing into tertiles or non-consumers and consumers. Total FVs, total fruit, total vegetables, fruit subgroups and vegetable subgroups were

divided into low, medium and high categories, with the exception of berries, drupes, dried fruit, *Brassicaceae* (and other leaves), and pod vegetables, which were divided into non-consumers and consumers. Total fruit juice was categorised into non-consumers, low and high consumers. The characteristics were explored by dividing participants into being hypertensive by 140/90 mmHg and normotensive after exclusion to observe if significant differences exist between those groups.

10.3.3.4 Multiple linear regression

Multiple regression was conducted to calculate change in SBP and DBP (mmHg) (individually) and 95% CI (or 99% CI for secondary and sensitivity analysis). For each dietary exposure variable, participants were divided into appropriate groups as mentioned in the previous section. Difference in BP was determined by comparing each intake group with the reference group, which included either the lowest consumers, or non-consumers. Linear association was also tested by calculating increments of fruit or vegetable intake by 80 g portions. Sensitivity analysis was performed by including adjustment for energy intake (kcal/day) in the models stated above, as well as exploring subgroups of variables for sex (male v.s. female), age groups (19 – 64 years v.s. 65+ years), BMI (obese v. non-obese), non-smokers, participants with no long-standing CVD related illness and participants not using statins.

10.3.3.5 Logistic regression

Logistic regression was conducted to calculate the odds ratios (OR) of hypertension and 95% CI (or 99% CI for secondary and sensitivity analysis). The method of analysis including the division of participants into intake groups, linear association and sensitivity analysis is the same as Section 10.3.3.4. However, instead of determining change in BP in mmHg, logistic regression generates an odds ratio to determine the increased odds of being hypertensive (%).

10.3.3.6 Testing for statistical assumptions

Some assumptions had to be fulfilled to validate correct application of the models, described in Chapter 2 Section 2.4.2. The linear regression requires normality to be assessed as shown in Figure 10.2, while Figure 10.3 shows an example of a Q-Q plot, which is reasonably close to normality except for the extreme right. Figure 10.4 also depicts a typical scatter graph with a cloud-like distribution, which fulfils the model assumptions.

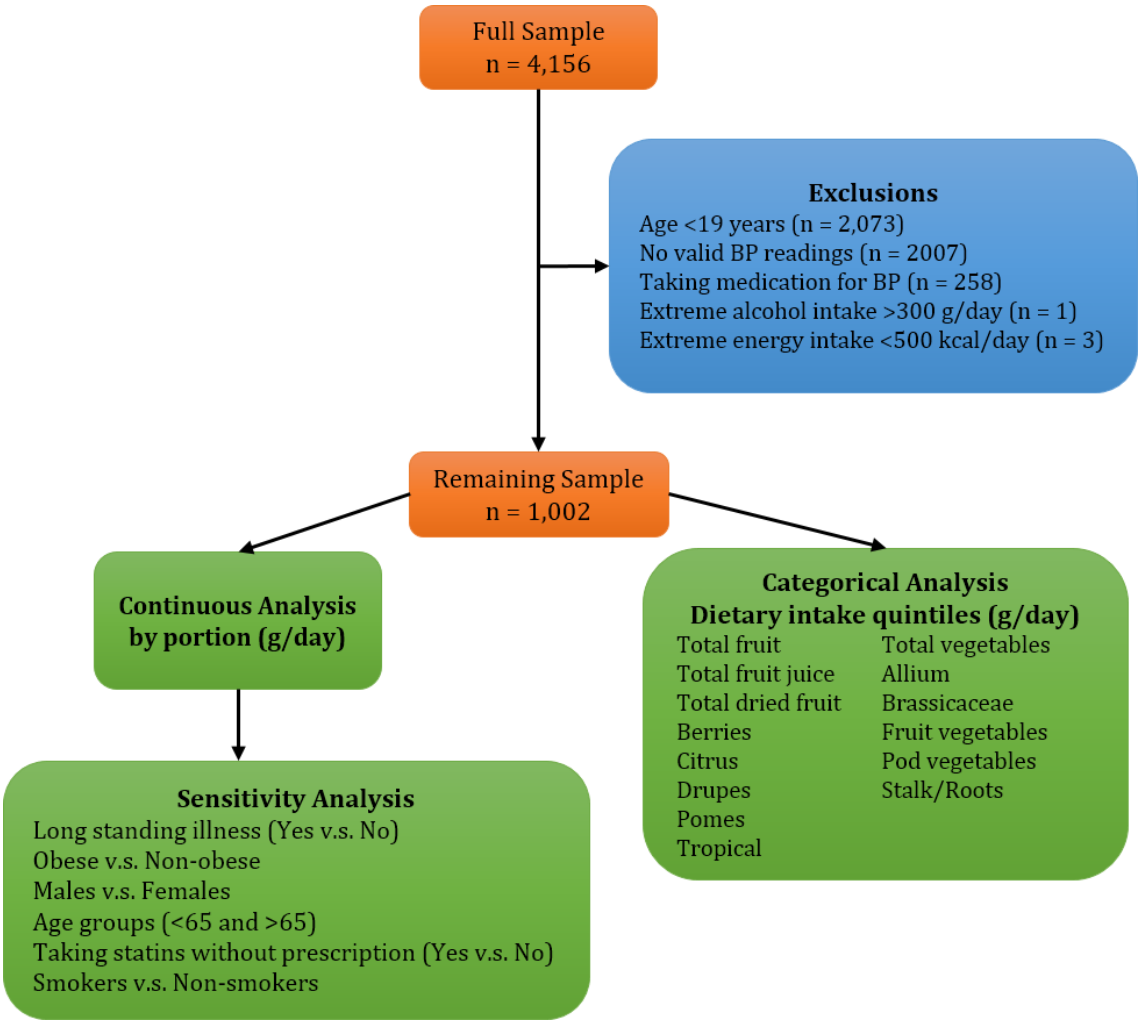


Figure 10.1 Summary flowchart of the current study exclusion criteria and analysis plan

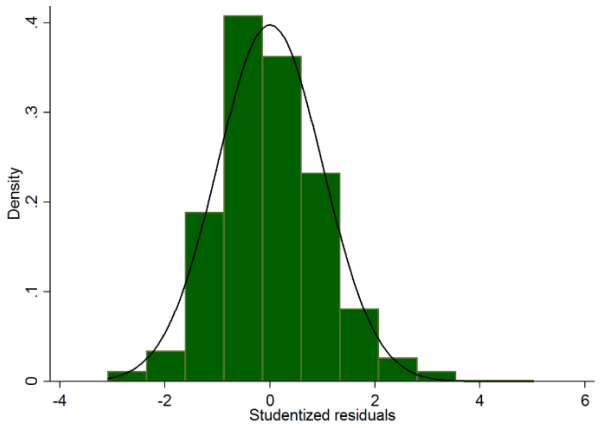


Figure 10.2 Histogram of studentised residuals for a fully-adjusted multiple linear regression model investigating fruit intake and BP (mmHg)

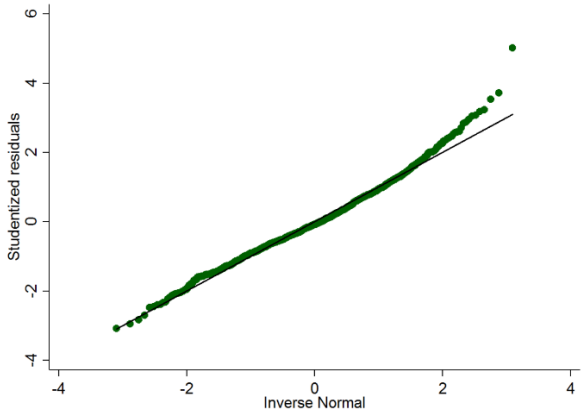


Figure 10.3 An inverse normal plot (Q-Q plot) for a fully-adjusted multiple linear regression model investigating fruit intake and BP (mmHg)

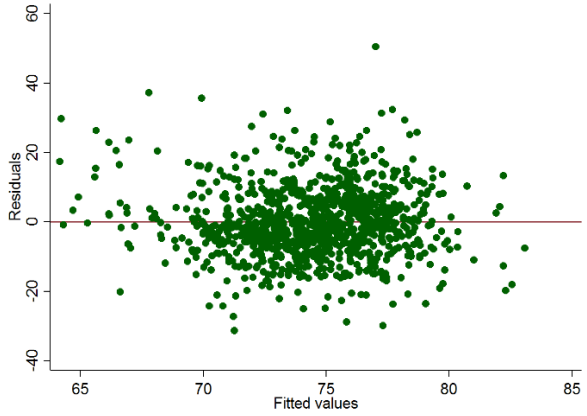


Figure 10.4 Scatter plot of residuals versus fitted values for a fully-adjusted multiple linear regression model investigating fruit intake and BP (mmHg)

10.4 Results

10.4.1 Participant characteristics

Total FV intakes in NDNS RP prior to the application of exclusion criteria were described in Chapter 2 Section 2.7.1. After exclusions were applied (Table 10.3), mean age increased with greater total FVs consumption. The likelihood to hold a professional and managerial job, be a vegetarian, non-smoker, and to consume supplements was also higher with increasing intake of total FVs. In terms of dietary intake, energy intake tended to be higher with higher intake of total FVs. A similar pattern was also observed for other nutrient intakes. However, the percentage of energy from carbohydrates was not different across the tertiles, while a downward trend was observed for the percentage of energy from total fat and saturated fat, despite an increase in energy intake across the tertiles.

Participant characteristics were also explored by dividing into hypertensive and normotensive categories, defined by a BP of 140/90 mmHg (Table 10.4). Mean age was higher for hypertensive individuals, compared to normotensive. The former participants were also more likely to be obese and have a larger waist circumference. They were also more likely to be smokers, consume statins and come from routine/manual SES. Hypertensive participants were also less likely to consume supplements, have a higher energy and alcohol intake.

Table 10.3 Participant characteristics by total FV intake in the NDNS RP adult population

	Total fruit and vegetable intake (g/day)		
	0 - 211	**211 - 358**	**358 - 1554**
General			
Participants (n)	334	334	334
Age (years) (SD)	42.7 (15.9)	48.2 (14.8)	50.0 (14.9)
19 – 64 years (%, 95% CI)	89.5 (85.7, 92.4)	83.8 (79.5, 87.4)	81.1 (76.6, 85.0)
65 + years (%, 95% CI)	10.5 (7.6, 14.2)	16.2 (12.6, 20.5)	18.9 (15.0, 23.4)
BMI (kg/m^2) (%, 95% CI)			
Underweight (<18.5 kg/m^2)	1.8 (0.8, 3.9)	1.5 (0.6, 3.5)	0.3 (0.0, 2.1)
Normal (18.5 to 24.9 kg/m^2)	28.1 (23.6, 33.2)	29.9 (25.2, 35.1)	41.3 (36.1, 46.7)
Overweight (25.0 to 29.9 kg/m^2)	38.0 (32.9, 43.4)	37.4 (32.4, 42.7)	32.0 (27.2, 37.2)
Obese (>30.0 kg/m^2)	28.1 (23.6, 33.2)	27.8 (23.3, 32.9)	22.1 (18.0, 26.9)
Missing	3.9 (2.3, 6.6)	3.3 (1.8, 5.8)	4.2 (2.5, 7.0)
Non-obese (<29.9 kg/m^2)	70.7 (65.5, 75.4)	71.2 (66.0, 75.9)	76.9 (71.9, 81.2)
Obese (>30.0 kg/m^2)	29.3 (24.5, 34.5)	28.8 (24.1, 34.0)	23.1 (18.8, 28.1)
Waist circumference (cm) (SD)	93.4 (14.1)	92.8 (13.6)	90.8 (13.3)
Systolic blood pressure (mmHg) (SD)	125 (15)	126 (15)	125 (16)
Diastolic blood pressure (mmHg) (SD)	75 (11)	75 (11)	74 (10)
Hypertensive (140/90 mmHg) (%, 95% CI)	20.3 (16.4, 25.0)	18.9 (15.0, 23.4)	18.3 (14.5, 22.8)
Dietary intake			
Total energy (kcal/d) (SD)	1722 (585)	1869 (552)	1970 (535)
Total energy –no alcohol (kcal/d) (SD)	1621 (533)	1777 (529)	1873 (503)
Alcohol (g/d) (SD)	14.5 (21.9)	13.3 (18.4)	13.9 (18.7)
Carbohydrates (g/d) (SD)	204 (73)	224 (72)	239 (69)
% Energy from carbohydrates (%) (SD)	47.2 (6.6)	47.4 (6.1)	48.0 (6.5)
Protein (g/d) (SD)	66.7 (32.6)	75.4 (20.6)	82.8 (25.2)
% Energy from protein (%) (SD)	16.7 (4.3)	17.4 (3.8)	18.0 (4.0)
Total fat (g/d) (SD)	65.6 (25.0)	70.4 (26.9)	71.7 (25.4)
% Energy from Total fat (%) (SD)	36.1 (5.8)	35.1 (5.8)	34.0 (6.3)
Saturated fat (g/d) (SD)	24.3 (10.0)	26.6 (11.9)	25.9 (10.9)
% Energy from Saturated fat (%) (SD)	13.4 (3.2)	13.1 (3.1)	12.2 (3.3)
Sodium (mg/d) (SD)	2127 (797)	2291 (826)	2363 (863)
Portions of fruits & vegetables (no./d) (SD)	2.1 (0.8)	4.1 (0.8)	7.0 (2.0)
Lifestyle habits			
Vegetarian/Vegan status (%, 95% CI)	1.5 (0.6, 3.5)	3.0 (1.6, 5.5)	3.3 (1.8, 5.8)
Non-smokers (%, 95% CI)	49.7 (44.3, 55.1)	61.4 (56.0, 66.4)	70.0 (64.9, 74.7)
Ex-regular smoker (%, 95% CI)	19.8 (15.8, 24.4)	28.7 (24.1, 33.8)	22.7 (18.6, 27.6)
Current smokers (%, 95% CI)	30.5 (25.8, 35.7)	9.9 (7.1, 13.6)	7.2 (4.8, 10.5)
Cigarettes smoked (no./d) (SD)	3.7 (6.9)	0.9 (3.3)	0.7 (3.5)
Supplement users (%, 95% CI)	27.5 (23.0, 32.6)	37.7 (32.7, 43.1)	45.8 (40.5, 51.2)
Statin users (%, 95% CI)	3.6 (2.0, 6.2)	6.3 (4.1, 9.5)	5.7 (3.6, 8.7)
Moderately/Vigorously active (%, 95% CI)			
0 to 0.4 hours	30.2 (25.5, 35.3)	24.2 (20.0, 29.1)	15.9 (12.3, 20.2)
0.4 to 1.3 hours	21.2 (17.2, 26.0)	24.2 (19.9, 29.1)	24.5 (20.2, 29.5)
>1.3 hours	21.2 (17.2, 26.0)	21.8 (17.7, 26.6)	26.9 (22.4, 32.0)
Missing	27.2 (22.7, 32.3)	29.6 (25.0, 34.8)	32.6 (27.8, 37.9)
Socio-economic status			
Professional & managerial (%, 95% CI)	39.4 (34.2, 44.8)	50.0 (44.3, 55.1)	53.0 (47.6, 58.3)
Intermediate (%, 95% CI)	17.6 (13.8, 22.1)	21.2 (17.1, 26.0)	20.8 (16.7, 25.5)
Routine & manual (%, 95% CI)	40.9 (35.7, 46.3)	27.6 (23.0, 32.7)	23.8 (19.5, 28.7)
Unemployed (%, 95% CI)	2.1 (1.0, 4.4)	1.5 (0.6, 3.6)	2.4 (1.2, 4.7)

Table 10.4 Characteristics by HBP status in the NDNS RP adult population

	High Blood Pressure >140/90	
	No	Yes
General		
Participants (n)	810	192
Age (years) (SD)	44.9 (14.9)	55.6 (15.3)
19 – 64 years (%, 95% CI)	88.6 (86.2, 90.6)	68.7 (86.3, 90.6)
65 + years (%, 95% CI)	11.3 (9.3, 13.7)	31.2 (25.1, 38.2)
BMI (kg/m^2) (%, 95% CI)		
Underweight (<18.5 kg/m^2)	1.3 (0.7, 2.4)	0.5 (0.1, 3.6)
Normal (18.5 to 24.9 kg/m^2)	36.4 (33.2, 39.8)	19.3 (14.3, 25.5)
Overweight (25.0 to 29.9 kg/m^2)	35.4 (32.2, 38.8)	37.5 (30.9, 44.6)
Obese (>30.0 kg/m^2)	23.3 (20.5, 26.4)	37.5 (30.9, 44.6)
Missing	3.4 (2.4, 5.0)	5.2 (2.8, 9.4)
Non-obese (<29.9 kg/m^2)	75.8 (72.7, 78.7)	60.4 (53.1, 67.3)
Obese (>30.0 kg/m^2)	24.2 (21.3, 27.3)	39.6 (32.7, 46.9)
Waist circumference (cm) (SD)	91.0 (13.4)	98.2 (13.2)
Systolic blood pressure (mmHg) (SD)	120 (10)	148 (11)
Diastolic blood pressure (mmHg) (SD)	71.5 (8.5)	86.2 (10.7)
Dietary intake		
Total energy (kcal/d) (SD)	1843 (557)	1902 (602)
Total energy –no alcohol (kcal/d) (SD)	1753 (526)	1772 (555)
Alcohol (g/d) (SD)	12.8 (18.5)	18.5 (23.8)
Carbohydrates (g/d) (SD)	222 (72)	222 (75)
% Energy from carbohydrates (%) (SD)	47.6 (6.4)	47.1 (6.5)
Protein (g/d) (SD)	74.5 (23.8)	77.1 (39.0)
% Energy from protein (%) (SD)	17.3 (4.0)	17.5 (4.2)
Total fat (g/d) (SD)	69.1 (26.0)	70.0 (25.2)
% Energy from Total fat (%) (SD)	35.0 (6.1)	35.4 (5.6)
Saturated fat (g/d) (SD)	25.5 (11.1)	26.2 (10.2)
% Energy from Saturated fat (%) (SD)	12.9 (3.3)	13.2 (2.9)
Sodium (mg/d) (SD)	2257 (828)	2273 (861)
Portions of fruits & vegetables (no./d) (SD)	4.5 (2.4)	4.2 (2.3)
Total fruit (g/d) (SD)	115 (109)	107 (106)
Total vegetables (g/d) (SD)	193 (111)	187 (107)
Lifestyle habits		
Vegetarian/Vegan status (%, 95% CI)	2.6 (1.7, 3.9)	2.6 (1.1, 6.1)
Non-smokers (%, 95% CI)		
Ex-regular smoker (%, 95% CI)	62.0 (58.6, 65.3)	53.6 (58.6, 65.3)
Current smokers (%, 95% CI)	22.0 (19.2, 25.0)	31.2 (25.1, 38.2)
Cigarettes smoked (no./d) (SD)	16.0 (13.7, 18.7)	15.1 (10.7, 20.9)
Supplement users (%, 95% CI)	37.3 (34.0, 40.7)	35.9 (29.4, 43.0)
Statin users (%, 95% CI)	4.4 (3.2, 6.1)	8.3 (9.4, 9.7)
Moderately/Vigorously active (%, 95% CI)		
0 to 0.4 hours	22.8 (20.1, 25.9)	26.0 (20.3, 32.7)
0.4 to 1.3 hours	24.9 (22.1, 28.0)	16.7 (12.0, 22.6)
>1.3 hours	22.5 (19.7, 25.5)	27.1 (21.2, 33.8)
Missing	29.7 (26.7, 33.0)	30.2 (24.1, 37.0)
Socio-economic status		
Socio economic status (%, 95% CI)		
Professional & managerial	48.6 (45.1, 52.0)	42.4 (35.6, 49.5)
Intermediate	20.3 (17.7, 23.3)	17.8 (13.0, 23.9)
Routine & manual	29.1 (26.0, 32.3)	37.7 (31.1, 44.8)
Unemployed	2.0 (1.2, 3.2)	2.1 (0.8, 5.5)

10.4.2 Multivariate Regression

10.4.2.1 Full Cohort

In the full energy adjusted model (Table 10.5), SBP and DBP was not associated with the consumption of total FVs by quantiles of intake. However, there was a significant linear association, where every portion (80 g) of fruit or vegetable was associated with lower SBP by -0.47 mmHg (95% CI -0.90 to -0.05). Every portion of fruit or vegetable was also associated with lower DBP by -0.35 mmHg (95% CI -0.65 to -0.05). When investigating FV intakes separately, total vegetable, total fruit juice and dried fruits were not associated with SBP or DBP (Table 10.6). There was a significant dose response of -0.65 mmHg DBP (95% CI -1.16 to -0.13) for every additional portion of fruit intake, but this relationship was not observed in a stepwise increase of fruit consumption by quantiles (Table 10.5).

When FV subgroups by (poly)phenol profile were examined, a moderate intake of pomes was associated with a lower DBP by -3.24 mmHg (99% CI -6.23 to -0.26) (Table 10.5). However, no significant linear association was detected compared with non-consumers. A low consumption of root vegetables was associated with a lower SBP by -2.91 mmHg (99% CI -5.72 to -0.10), but the strength of association was attenuated with higher intakes of root vegetables (Table 10.6).

Table 10.5 Total FV, total fruit and fruit subgroup intakes and change in SBP and DBP (mmHg) within adults in the NDNS cohort

Dietary Exposure *(n = 1002)*	Intake (g/day)	**SYSTOLIC BP** β-coefficient (95% or 99%* CI)			**DIASTOLIC BP** β-coefficient (95% or 99%* CI)		
		Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total Fruits & Vegetables							
Low	0 – 211	0	0	0	0	0	0
Medium	212 – 358	-1.11 (-3.34, 1.13)	-0.21 (-2.43, 2.00)	-0.73 (-2.95, 1.48)	-0.24 (-1.86, 1.38)	0.03 (-1.53, 1.60)	-0.04 (-1.62, 1.53)
High	358 – 1554	-2.32 (-4.58, -0.07)	-0.94 (-3.24, 1.35)	-1.76 (-4.08, 0.55)	-1.62 (-3.25, 0.01)	-0.96 (-2.58, 0.66)	-1.08 (-2.73, 0.56)
p trend	80	-0.57 (-0.98, -0.15)	-0.28 (-0.70, 0.13)	-0.47 (-0.90, -0.05)	-0.45 (-0.75, -0.15)	-0.31 (-0.61, -0.02)	-0.35 (-0.65, -0.05)
Total Fruits							
Low	0 – 48	0	0	0	0	0	0
Medium	48 – 134	-1.60 (-3.21, 0.01)	-1.19 (-3.41, 1.04)	-1.31 (-3.51, 0.90)	-1.60 (-3.21, 0.01)	-0.77 (-2.34, 0.80)	-0.79 (-2.36, 0.78)
High	134 – 749	-2.44 (-4.09, -0.80)	-0.83 (-3.22, 1.55)	-1.19 (-3.56, 1.18)	-2.44 (-4.09, -0.80)	-1.34 (-3.02, 0.35)	-1.39 (-3.08, 0.29)
p trend	80	-0.91 (-1.60, -0.22)	-0.28 (-1.00, 0.44)	-0.46 (-1.18, 0.26)	-0.95 (-1.44, -0.45)	-0.62 (-1.13, -0.10)	-0.65 (-1.16, -0.13)
Berries*							
Non-consumers	0	0	0	0	0	0	0
Consumers	2 – 308	-3.35 (-5.89, -0.80)	-2.06 (-4.63, 0.51)	-2.01 (-4.56, 0.53)	-1.54 (-3.40, 0.31)	-0.68 (-2.49, 1.14)	-0.67 (-2.48, 1.15)
p trend	80	-1.49 (-4.32, 1.34)	-0.93 (-3.74, 1.87)	-0.94 (-3.73, 1.84)	-1.17 (-3.23, 0.88)	-0.81 (-2.79, 1.17)	-0.81 (-2.79, 1.17)
Citrus*							
Low	0	0	0	0	0	0	0
Medium	0 – 40	-3.15 (-6.39, 0.08)	-2.28 (-5.44, 0.88)	-2.35 (-5.49, 0.78)	-1.81 (-4.16, 0.54)	-1.17 (-3.40, 1.06)	-1.19 (-3.42, 1.05)
High	41 – 1344	-0.09 (-2.77, 2.60)	1.09 (-1.62, 3.79)	0.80 (-1.89, 3.49)	-1.03 (-2.98, 0.92)	-0.10 (-2.01, 1.81)	-0.16 (-2.08, 1.76)
p trend	80	0.10 (-0.81, 1.02)	0.38 (-0.53, 1.30)	0.18 (-0.74, 1.10)	-0.30 (-0.97, 0.36)	-0.13 (-0.77, 0.52)	-0.17 (-0.83, 0.48)
Drupes*							
Non-consumers	0	0	0	0	0	0	0
Consumers	1 – 288	-1.09 (-4.27, 2.09)	0.47 (-2.71, 3.64)	0.61 (-2.54, 3.76)	-1.88 (-4.18, 0.42)	-0.34 (-2.58, 1.90)	-0.30 (-2.54, 1.94)
p trend	80	2.64 (-1.09, 6.38)	4.27 (0.62, 7.91)	4.17 (0.55, 7.79)	-0.75 (-3.46, 1.96)	0.74 (-1.84, 3.32)	0.71 (-1.87, 3.30)
Pomes*							
Low	0	0	0	0	0	0	0
Medium	0.6 – 48.7	-4.17 (-7.20, -1.14)	-3.41(-6.41, -0.40)	-3.24 (-6.23, -0.26)	-1.51 (-3.72, 0.69)	-1.02 (-3.15, 1.11)	-0.98 (-3.11, 1.14)
High	49.2 – 425	-2.65 (-5.38, 0.07)	-1.21 (-4.00, 1.57)	-1.39 (-4.16, 1.38)	-1.80 (-3.79, 0.19)	-0.66 (-2.64, 1.31)	-0.70 (-2.68, 1.27)
p trend	80	-1.18 (-2.75, 0.38)	-0.39 (-1.94, 1.17)	-0.64 (-2.20, 0.91)	-1.29 (-2.43, -0.16)	-0.62 (-1.72, 0.47)	-0.68 (-1.79, 0.42)
Tropical fruits*							
Low	0	0	0	0	0	0	0
Medium	3.2 – 37.5	-2.47 (-5.56, 0.62)	-1.88 (-4.89, 1.12)	-1.77 (-4.76, 1.21)	-2.19 (-4.43, 0.05)	-1.82 (-3.94, 0.30)	-1.80 (-3.92, 0.32)
High	40 – 225	-1.26 (-4.02, 1.49)	-0.17 (-2.90, 2.57)	-0.19 (-2.91, 2.52)	-1.48 (-3.48, 0.51)	-0.74 (-2.67, 1.19)	-0.75(-2.67, 1.18)
p trend	80	-0.62 (-2.93, 1.69)	0.27 (-2.05, 2.60)	0.19 (-2.11, 2.50)	-0.93 (-2.60, 0.75)	-0.18 (-1.82, 1.46)	-0.20 (-1.84, 1.44)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

Table 10.6 Total vegetable, vegetable subgroup, total fruit juice, and dried fruit intakes and change in SBP and DBP (mmHg) within adults in the NDNS cohort

Dietary Exposure *(n = 1002)*	Intake (g/day)	**SYSTOLIC BP** β-coefficient (95% or 99%* CI), *p-value*			**DIASTOLIC BP** β-coefficient (95% or 99%* CI), *p-value*		
		Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total vegetables							
Low	0 – 134	0	0	0	0	0	0
Medium	134 – 217	-0.18 (-2.40, 2.04)	-0.26 (-2.42, 1.91)	0.53 (-2.69, 1.63)	0.50 (-1.12, 2.11)	0.32 (-1.21, 1.85)	0.25 (-1.28, 1.79)
High	217 – 1168	-1.04 (-3.27, 1.19)	-0.50 (-2.75, 1.75)	-1.02 (-3.28, 1.23)	-0.55 (-2.16, 1.07)	-0.13 (-1.72, 1.46)	-0.25 (-1.85, 1.35)
p trend	80	-0.60 (-1.26, 0.05)	-0.42 (-1.10, 0.25)	-0.58 (-1.26, 0.09)	-0.28 (-0.76, 0.19)	-0.09 (-0.56, 0.38)	-0.12 (-0.60, 0.35)
Allium*							
Low	0 – 2.5	0	0	0	0	0	0
Medium	2.6 – 18.7	-1.60 (-4.51, 1.32)	-1.33 (-4.16, 1.50)	-1.15 (-3.96, 1.66)	-0.79 (-2.90, 1.33)	-0.75 (-2.75, 1.24)	-0.71 (-2.71, 1.29)
High	18.8 – 176	-1.47 (-4.37, 1.42)	-0.52 (-3.47, 2.43)	-0.60 (-3.53, 2.33)	-0.25 (-2.35, 1.85)	-0.03 (-2.12, 2.05)	-0.05 (-2.14, 2.03)
p trend	80	-0.92 (-5.21, 3.36)	0.74 (-3.70, 5.19)	0.43 (-3.99, 4.85)	0.31 (-2.80, 3.42)	1.01 (-2.12, 4.15)	0.94 (-2.19, 4.08)
Brassicaceae*							
Non-consumers	0	0	0	0	0	0	0
Consumers	0.4 – 201	-1.71 (-4.52, 1.09)	-1.40 (-4.15, 1.36)	-1.14 (-3.88, 1.60)	-0.53 (-2.57, 1.50)	-0.48 (-2.42, 1.46)	-0.42 (-2.37, 1.52)
p trend	80	-1.89 (-5.39, 1.62)	-1.18 (-4.70, 2.33)	-1.09 (-4.58, 2.40)	-1.35 (-3.90, 1.19)	-0.70 (-3.18, 1.78)	-0.68 (-3.16, 1.80)
Fruit vegetables*							
Low	0 – 16.4	0	0	0	0	0	0
Medium	16.6 – 60.0	-3.44 (-6.34, -0.54)	-2.63 (-5.51, 0.25)	-2.55 (-5.41, 0.31)	-1.36 (-3.47, 0.75)	-0.76 (-2.80, 1.27)	-0.74 (-2.77, 1.29)
High	60.0 – 684	-2.55 (-5.46, 0.37)	-1.02 (-4.08, 2.05)	-0.68 (-3.73, 2.37)	-0.67 (-2.79, 1.45)	0.62 (-1.54, 2.78)	0.71 (-1.46, 2.88)
p trend	80	-1.18 (-2.82, 0.47)	-0.39 (-2.12, 1.34)	-0.29 (-2.01, 1.43)	-0.41 (-1.61, 0.79)	0.37 (-0.85, 1.59)	0.39 (-0.83, 1.62)
Pod vegetables*							
Non-consumers	0	0	0	0	0	0	0
Consumers	0.1 – 150	-1.57 (-4.00, 0.85)	-1.54 (-3.89, 0.80)	-1.60 (-3.93, 0.73)	-0.56 (-2.32, 1.19)	-0.53 (-2.19, 1.13)	-0.54 (-2.20, 1.11)
p trend	80	-0.68 (-5.85, 4.48)	-0.79 (-5.79, 4.20)	-1.36 (-6.33, 3.61)	0.28 (-3.47, 4.02)	0.30 (-3.22, 3.83)	0.18 (-3.36, 3.71)
Stalk & root vegetables*							
Low	0	0	0	0	0	0	0
Medium	0.2 – 25	-3.89 (-6.80, -0.99)	-3.15 (-5.97, -0.32)	-2.91 (-5.72, -0.10)	-0.98 (-3.09, 1.14)	-0.55 (-2.55, 1.46)	-0.49 (-2.50, 1.51)
High	25 – 190	-1.35 (-4.28, 1.59)	0.12 (-2.82, 3.07)	0.20 (-2.72, 3.12)	-1.16 (-3.30, 0.98)	-0.21(-2.30, 1.88)	-0.19 (-2.28, 1.90)
p trend	80	-0.99 (-4.49, 2.52)	0.55 (-2.98, 4.09)	0.52 (-2.99, 4.03)	-1.47 (-4.01, 1.07)	-0.35 (-2.85, 2.14)	-0.36 (-2.86, 2.13)
Total fruit juice							
Non-consumers	0	0	0	0	0	0	0
Low	0 – 37.5	-2.84 (-6.10, 0.42)	-2.04 (-5.20, 1.13)	-2.21 (-5.35, 0.93)	-1.23 (-3.60, 1.14)	-0.63 (-2.86, 1.61)	-0.66 (-2.90, 1.58)
High	38.2 – 1385	-0.93 (-4.19, 2.34)	0.53 (-2.72, 3.79)	-0.05 (-3.31, 3.20)	-1.08 (-3.45, 1.29)	-0.11 (-2.41, 2.19)	-0.22 (-2.54, 2.10)
p trend	125	0.31 (-1.19, 1.82)	1.00 (-0.49, 2.49)	0.52 (-1.00, 2.03)	-0.53 (-1.63, 0.56)	-0.12 (-1.17, 0.93)	-0.22 (-1.30, 0.85)
Dried fruits							
Non-consumers	0	0	0	0	0	0	0
Consumers	0 – 130	-1.47 (-3.88, 0.94)	-0.15 (-2.57, 2.27)	-0.56 (-2.97, 1.86)	-0.83 (-2.58, 0.92)	0.08 (-1.63, 1.79)	-0.01 (-1.73, 1.71)
p trend	25	-0.14 (-2.95, 2.66)	1.44 (-1.34, 4.23)	0.86 (-1.93, 3.65)	-0.85 (-2.88, 1.19)	0.54 (-1.42, 2.51)	0.42 (-1.57, 2.40)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

10.4.2.2 Sensitivity Analysis

10.4.2.2.1 No longstanding illness

No associations were found for adults with no longstanding CVD illness between SBP or DBP and all dietary intakes. (Table F.1).

10.4.2.2.2 Obese v.s. non-obese

Within non-obese participants, the association between total fruit and DBP persisted, lowering DBP by -0.81 mmHg (99% CI -1.59 to -0.03) for every portion of fruit consumed (Table F.1). Unexpectedly, obese participants had a higher SBP (3.14 mmHg, 99% CI 0.21 to 6.06) with increasing citrus portions (Table F.1).

10.4.2.2.3 Sex

Participants who were male (Table F.1) had a lower DBP by -1.30 mmHg (99% CI -2.34 to -0.34) for total fruit intake. However, female participants had a higher SBP by 5.34 mmHg (99% CI 0.77 to 9.90) with increasing citrus intake (Table F.1).

10.4.2.2.4 Age groups

There were no significant associations between total FV intake and SBP or DBP within participants aged 19-64 years (Table F.1). With regard to participants aged 65 years and above, associations were observed between intake of total fruit and pomes and lower DBP by -1.93 mmHg (99% CI -3.27 to -0.59) and -3.29 mmHg (99% CI -5.56 to -1.03) respectively (Table F.1).

10.4.2.2.5 Statins

Interestingly, SBP was found to be adversely associated with every portion of drupes by 5.05 mmHg (99% CI 1.27 to 8.82) (Table F.1) in the subpopulation who do not consume statins. The subpopulation of participants who consume statins were too small to be studied.

10.4.2.2.6 Smoking

Likewise, the population of smokers were not large enough to be analysed as CIs would be too wide. No associations were found for non-smoking adults between all dietary intakes and SBP or DBP (Table F.1).

10.4.3 Logistic Regression

10.4.3.1 Full Cohort

In the full energy adjusted model (Table 10.7), there were no significant associations between the odds of HBP and total FV consumption, although generally odds of hypertension were lower with increasing intakes. However, there was a borderline significant linear trend, where every 80 g portion of fruit or vegetable was associated with 8% lower odds of HBP (95% CI 0.83 to 1.00). No significant associations were found for total fruit and total vegetable intake when explored separately. When FV subgroups by (poly)phenol profile were examined, there were also no significant associations found for odds of HBP and all fruit, vegetable subgroups.

10.4.3.2 Sensitivity Analysis

In general, no associations were observed between odds of HBP and participants who were in sub-populations without longstanding CVD illness (Table F.2), were obese (Table F.4), female (Table F.6), by age group (Table F.7 & Table F.8), who did not consume statins (Table F.9) and non-smokers (Table F.10). However, every 80 g portion of total fruit was associated with 28% lower odds of HBP within non-obese participants (Table F.3). Interestingly, the odds of HBP was nearly halved with every 125 g of total fruit juice within male adults (Table F.5).

Table 10.7 Odds of HBP and FV intakes and fruit, vegetable subgroup intakes within adults in the NDNS RP cohort

n = 1002	Intake (g/day)	Odds of high blood pressure			
		Cases [a]	Age Adjusted	Fully-Adjusted [b]	Fully-Adjusted w/Energy [c]
Total fruits & vegetables[1]					
Low	0 – 211	68	1	1	1
Medium	212 – 358	63	0.71 (0.47, 1.06)	0.80 (0.52, 1.23)	0.78 (0.51, 1.20)
High	358 – 1554	61	0.62 (0.41, 0.93)	0.72 (0.46, 1.12)	0.69 (0.44, 1.09)
p trend	80	192	0.90 (0.83, 0.97)	0.93 (0.85, 1.01)	0.92 (0.84, 1.00)
Total fruits[1]					
Low	0 – 48	70	1	1	1
Medium	48 – 134	61	0.70 (0.47, 1.05)	0.80 (0.52, 1.23)	0.79 (0.51, 1.22)
High	134 – 749	61	0.55 (0.36, 0.83)	0.70 (0.44, 1.10)	0.69 (0.43, 1.09)
p trend	80	192	0.82 (0.72, 0.94)	0.88 (0.76, 1.02)	0.88 (0.76, 1.02)
Total fruit juice[2]					
Non-consumers	0	50	1	1	1
Low	0 – 37.5	76	0.72 (0.41, 1.26)	0.86 (0.47, 1.55)	0.85 (0.47, 1.54)
High	38.2 – 1385	66	0.63 (0.36, 1.12)	0.82 (0.44, 1.53)	0.80 (0.43, 1.49)
p trend	80	192	0.75 (0.52, 1.06)	0.84 (0.59, 1.21)	0.82 (0.57, 1.18)
Dried fruits[2]					
Non-consumers	0	93	1	1	1
Consumers	0 – 130	99	0.68 (0.44, 1.05)	0.83 (0.52, 1.33)	0.80 (0.50, 1.29)
p trend	80	192	0.71 (0.41, 1.23)	0.97 (0.56, 1.69)	0.93 (0.53, 1.63)
Berries[2]					
Non-consumers	0	127	1	1	1
Consumers	2 – 308	65	0.80 (0.50, 1.27)	1.00 (0.61, 1.66)	1.00 (0.60, 1.66)
p trend	80	192	0.78 (0.44, 1.37)	0.87 (0.50, 1.50)	0.87 (0.50, 1.51)
Citrus[2]					
Low	0	103	1	1	1
Medium	0 – 40	28	0.57 (0.30, 1.06)	0.64 (0.34, 1.23)	0.65 (0.34, 1.24)
High	41 – 1344	61	0.78 (0.48, 1.26)	0.93 (0.55, 1.57)	0.92 (0.55, 1.56)
p trend	80	192	0.87 (0.70, 1.08)	0.92 (0.74, 1.15)	0.91 (0.73, 1.14)
Drupes[2]					
Non-consumers	0	155	1	1	1
Consumers	1 – 288	37	0.75 (0.42, 1.31)	0.98 (0.53, 1.81)	0.99 (0.54, 1.82)
p trend	80	192	0.89 (0.48, 1.64)	1.17 (0.62, 2.23)	1.17 (0.62, 2.21)
Pomes[2]					
Low	0	101	1	1	1
Medium	1.1 – 48.7	34	0.55 (0.31, 0.98)	0.66 (0.35, 1.22)	0.66 (0.35, 1.22)
High	49.2 – 425	57	0.61 (0.37, 1.00)	0.80 (0.47, 1.39)	0.80 (0.46, 1.37)
p trend	80	192	0.72 (0.52, 1.00)	0.84 (0.60, 1.18)	0.83 (0.59, 1.17)
Tropical fruits[2]					
Low	0	94	1	1	1
Medium	3.2 – 37.5	33	0.63 (0.35, 1.13)	0.65 (0.35, 1.22)	0.65 (0.35, 1.22)
High	40 – 225	65	0.75 (0.46, 1.23)	0.91 (0.54, 1.53)	0.90 (0.53, 1.53)
p trend	80	192	0.78 (0.52, 1.19)	0.92 (0.59, 1.46)	0.92 (0.58, 1.45)
Total vegetables[1]					
Low	0 – 134	67	1	1	1
Medium	134 – 217	61	0.79 (0.52, 1.18)	0.81 (0.53, 1.23)	0.79 (0.51, 1.20)
High	217 – 1168	64	0.80 (0.53, 1.19)	0.93 (0.60, 1.44)	0.90 (0.58, 1.40)
p trend	80	192	0.92 (0.81, 1.04)	0.97 (0.84, 1.11)	0.96 (0.83, 1.10)
Allium[2]					
Low	0 – 2.5	70	1	1	1
Medium	2.6 – 18.7	65	0.92 (0.55, 1.55)	0.96 (0.56, 1.65)	0.97 (0.56, 1.66)
High	18.8 – 176	57	0.80 (0.47, 1.35)	0.89 (0.50, 1.59)	0.90 (0.50, 1.61)
p trend	80	192	1.01 (0.46, 2.21)	1.33 (0.55, 3.18)	1.33 (0.55, 3.17)
Brassicaceae[2]					
Non-consumers	0	43	1	1	1
Consumers	0.4 – 201	149	0.93 (0.56, 1.57)	1.02 (0.59, 1.77)	1.04 (0.60, 1.79)
p trend	80	192	0.75 (0.40, 1.42)	0.91 (0.46, 1.81)	0.91 (0.45, 1.81)
Fruit vegetables[2]					
Low	0 – 16.4	68	1	1	1
Medium	16.6 – 60.0	55	0.73 (0.42, 1.25)	0.89 (0.50, 1.57)	0.88 (0.50, 1.56)
High	60.0 – 684	69	0.89 (0.53, 1.49)	1.31 (0.72, 2.36)	1.32 (0.73, 2.39)
p trend	80	192	0.95 (0.69, 1.29)	1.15 (0.81, 1.62)	1.15 (0.82, 1.62)
Pod vegetables [2]					
Non-consumers	0	99	1	1	1
Consumers	0.1 – 150	93	0.74 (0.48, 1.14)	0.75 (0.47, 1.18)	0.75 (0.47, 1.18)
p trend	80	192	0.71 (0.27, 1.82)	0.75 (0.28, 2.00)	0.72 (0.27, 1.94)
Stalk & root vegetables [2]					
Low	0	67	1	1	1
Medium	0.2 – 25	50	0.61 (0.35, 1.07)	0.67 (0.38, 1.19)	0.68 (0.38, 1.21)
High	25 – 190	75	0.88 (0.52, 1.47)	1.11 (0.63, 1.95)	1.12 (0.63, 1.96)
p trend	80	192	0.90 (0.49, 1.66)	1.19 (0.61, 2.35)	1.19 (0.60, 2.33)

[a] Cases apply to fully-adjusted models

[b] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[c] Adjusted for all the above and energy intake

10.5 Discussion

10.5.1 Summary of results

The objective of the study was to investigate the association between total FV intake and BP in healthy adults. A lower odds of HBP with higher total FV intake was observed, and higher intake of total FVs was associated with lower SBP and DBP. Specifically, greater fruit intake, especially a moderate intake of pomes was associated with lower SBP. However, no evidence of association was determined for berries, drupes, tropical fruit, total vegetable and vegetable subgroups.

10.5.2 General comparison to literature

In general, findings from the current study are in line with the results from Chapter 6, and also support previous observational studies investigating the association between total FV intake and HBP from different countries [296-298, 300]. Also mentioned in Chapter 6, results are consistent with the findings from RCTs investigating dietary patterns rich in FVs [80, 306, 307]. The strengths and limitations for investigating FV rich dietary patterns and the association with BP have been discussed in detail within Chapter 6. Briefly, evidence for the relationship with greater potassium intakes is fairly consistent with the exception of a recent RCT [224, 302], while the association between sodium intakes and BP have been established [116, 224, 308]. Participants in the current study reported a higher sodium intake when FV intake was higher, however, the two might not necessarily be correlated (correlation co-efficient = 0.10) or causally linked, but might reflect greater energy intakes reported by highest FV consumers, or the presence of more under-reporting generally in the lowest FV consumers. There are other nutrients in FV which have a significant association with CVD risk including fibre [248] and “antioxidants” known as (poly)phenols, which may also generate certain effects on BP. Thus, like the previous chapters, separate examination of FVs is warranted.

When investigating FVs separately, findings tended to vary across studies. Higher fruit intake was associated with lower DBP in men and higher SBP in women in a Korean cohort [300], compared to the association found only for lower DBP with greater fruit intake (as well as in men, but not women) in the current study. A significant association between higher vegetable intake and lower odds of HBP was also previously reported, contrasting with the current study [296, 297]. This could be due to the variation in consumption patterns between countries and dietary assessments between cohorts [296, 297, 300]. Studies which utilised FFQ were also more likely to report higher mean FV intakes than the

current study (305 g/day) [296, 300], possibly due to over-reporting on the FFQ [253]. In addition, total fruits and total vegetables in the current study contain food items which have been cooked or processed in some way, which might not be the case in other cohorts. Kim et al. reported higher BP in association with higher consumption of Kimchi and salty vegetables native to Korea [300]. While these types of vegetables are not commonly consumed in UK, the finding warrants further investigation into differences between raw and cooked/process vegetables, or with the addition of salt, and may also explain the null association in the current study.

Interestingly, total fruit juice was associated with a lower odds of HBP in male, but not female adults, however, fruit juice was inconsistently associated with lower SBP or DBP in the current study. Previous MA on RCTs investigating effects of fruit juice and BP reported a borderline significant effect on DBP (-2.07 mmHg, 95% CI -3.75 to -0.39) was observed [375]. Other studies have also report null association between fruit juice and BP in Western countries from the INTERMAP study [376]. The null association could be due to the wide range of fruits incorporated into the fruit juice category, leading to a varied (poly)phenol profile. However, it is more likely that the diversity of fruit juice consumption is relatively narrow within this population.

10.5.3 Relevance to (poly)phenol mechanisms

With regard to subgroup analyses, moderate consumption of pomes was associated with lower SBP, consistent with findings from an observational study [301] and Chapter 6, most likely because pomes are the most commonly consumed fruit in the UK (Chapter 2). As elaborated before, pomes are rich in flavanols, especially catechin and proanthocyanidins [309, 310]. Significant associations were reported between intakes of apples and pears and CVD risk in observational studies [117, 254]. However, there is limited evidence to support the beneficial effect of (poly)phenols from apples on markers of CVD and BP. Apple and apple juices were reported to improve lipid profiles in some intervention studies [236, 255, 256], but contrasting results using freeze dried apples were also reported elsewhere [257]. Non-significance in the latter study could be because of a relatively smaller dose of apple, and differences in processing effects (freeze drying).

Null associations for other FV subgroups, as well as for investigation by hypertensive status could be explained by low intake levels, limited variations in consumption, errors in estimation or under-reporting, low power or residual confounding. Furthermore, variables here contain raw and cooked variations in each FV subgroup, therefore it is probable that processing effects may have altered the (poly)phenol content

within and its bioavailability in the human body [112]. However, the separation of raw and cooked variations of each FV is not warranted due to low intakes.

10.5.4 Strengths and limitations

There are a few other limitations to the current study. The current sample size of the study is small, particularly for exploration of FV subgroups, or within restricted subpopulations. In contrast to the UKWCS, there is less variation in dietary habits. Cross-sectional studies only contain dietary intakes from one time point, thus only reflective for the particular time period the analysis was conducted. The NDNS RP was never intended to represent habitual diets of each individual, but to provide a snapshot of intakes representative of the UK population. The design of the study also does not allow diet to be monitored over time, and would require further investigation by follow-up or intervention to provide further supportive evidence for the findings drawn. In addition, the study is limited by missing data within model variables such as physical activity. Although the proportion of missing data is subsequently allocated into a separate category, it may introduce residual confounding. Caution should also be exercised when interpreting causality in cross-sectional studies, as there could be potential biases acting in either direction from incomplete adjustment for confounding, measurement error in the exposure estimate, and other unknown biases in participant selection or data collection. The direction of causality is also unknown in cross-sectional studies.

However, the current study has several strengths. The NDNS RP utilizes four-day food diaries, which capture dietary intakes in detail compared to FFQs used in other studies and previous chapters investigating UKWCS. Furthermore, to our knowledge, this is the first study that has extensively investigated the effects of subgroups of FVs by (poly)phenol profiles on BP. The inclusion of fresh and cooked food items also improves estimation of dietary intake to a certain extent, reflecting actual consumption behaviour. In addition, using Phenol Explorer as a reference database for sub-dividing fruit intake has certain advantages. This is because extensive methods were implemented to collect high-quality literature articles on (poly)phenol composition, the impact of food processing on (poly)phenols and metabolite composition in the body, which ensured that the subgroups applied here were sensible with regard to the variety of (poly)phenols in each fruit or vegetable subgroup [112].

10.6 Summary

A higher intake of total FV was associated with lower odds of BP. Greater consumption of total fruit intake was negatively associated with lower BP, and this association persisted in subgroups of non-obese, elderly and male subpopulations. Moderate intake of pomes was also associated with lower SBP in general, and with a lower DBP in the elderly population. Total vegetable and selected vegetable subgroups were not associated with lower BP within adults in the NDNS RP, although in general, the direction of point estimates indicated inverse associations, whilst not formally achieving statistical significance. This finding is aligned with current literature promoting high FV dietary patterns, as well as widely promoted guidelines promoting FVs consumption for health. Further interventions are recommended for the consumption of pome fruits to assess its relationship with BP lowering effects in the normotensive population as a form of preventing HBP development.

Chapter 11
Final Discussion

11.1 State of the art

Diet is one of the key modifiable factors that affect CVD risk, and high quantities of FVs have been observed to lower CVD risk in observational studies [83]. However, it is unknown if a specific fruit or vegetable, or FV subgroup, is potentially more important than others. A small number of studies have investigated berries, citrus, green leafy, cruciferous and *Allium* vegetables [197, 205], whereas evidence for the remaining FV subgroups is limited. The evidence for total vegetable intake and CVD risk is also somewhat inconsistent across observational studies. The DASH trial [80] was reported to lower BP substantially in hypertensive and normotensive participants, but the specific effects of particular FVs were also unknown. In addition, the relationship between coffee, tea and CVD risk is also inconsistent within observational studies studying CVD risk and BP (as reported in Chapter 5 and Chapter 7). FVs, coffee and tea are rich sources of various (poly)phenols. Chapter 1 summarised beneficial effects of (poly)phenols on CVD risk factors within human studies, such as improved endothelial function and improved blood lipid profiles. Cell and animal studies also demonstrated the effect of (poly)phenols on biological mechanisms relating to BP, lipid profile, diabetes, obesity and inflammation. On the other hand, there is also missing information on many commonly consumed foods within the (poly)phenol database, Phenol Explorer, where the (poly)phenol content of processed foods is largely unquantified.

11.2 Novel findings from this thesis

- The first study to examine the relationship between FV and respective subgroup intakes by (poly)phenol profiles and the risk of CVD (Chapter 3 and Chapter 4), as well as the incidence of self-reported BP in the UK (Chapter 6).
- Provided novel and missing information by investigating previously unexplored fruit subgroups, such as drupes and tropical fruit.
- Provided additional evidence for the association between coffee, tea and CVD mortality (Chapter 5) and self-reported BP (Chapter 7) to the current inconsistent evidence pool.

- Chapter 9 provided TPC of 64 fruit concentrates and juices, and quantified major anthocyanins in blackcurrant concentrates, which is additional data for potential inclusion in the Phenol Explorer.
- Although the association between FV intake and BP have previously been studied [296-298, 300], Chapter 10 presented results on the association of FVs and subgroup intakes by (poly)phenol profiles and measured BP using the latest NDNS RP dataset, and is one of the first studies to do so.

11.3 Summary of thesis findings

For the first time in both the UKWCS cohort and the NDNS RP population, the association between dietary sources of (poly)phenols by FVs and respective subgroups, as well as coffee and tea intake have been extensively investigated.

Chapter 2 presented the statistical methodology and models based on the literature review on CVD pathophysiology, CVD risk factors, (poly)phenols overview, absorption, bioavailability and biological activities of (poly)phenols, as well as mechanisms of (poly)phenols on CVD risk factors conducted in Chapter 1. The study design of the UKWCS and the NDNS RP population, CVD dietary recommendations requirements were also reported in Chapter 2, along with participant characteristics and the intakes of dietary sources of (poly)phenols. Differences in the intake of (poly)phenol-rich foods, study design and methodology between the UKWCS and the NDNS RP were briefly compared here. Key findings from this thesis, ranked by the strength of evidence are summarised in Table 11.1.

Table 11.1 Summary of key findings from this thesis

	Exposure	Outcome
Convincing	↑Total fruit, ↑fresh fruit	↓Fatal CVD
Probable	↑Citrus, ↑grapes ↑Citrus, ↑total vegetable ↑Total FV, ↑total vegetable, ↑pomes, ↑fruit vegetables	↓Fatal CVD ↓Fatal stroke ↓ Self-reported HBP
Limited - Suggestive	↑Berries ↑Citrus fruit ↑Orange juice ↑Total FV, ↑total fruit	↓Chronic coronary events ↓CVD incidence ↓Stroke incidence ↓Measured BP
Inconclusive	Coffee, tea	Fatal CVD, self-reported HBP

Convincing: Significant association with higher intakes, significant linear association
Probable: Only one of the above; self-reported HBP
Limited – Suggestive: Low case numbers; Cross-sectional design
Inconclusive: Null association; inconsistent/inconclusive evidence in literature

In addition, Chapter 8 investigated the relative validity of the FFQ and food diary in the UKWCS, recognising the strengths and weaknesses of the FFQ and food diary. Chapter 9 reported the analysis of processed fruit based beverages to assess the levels of

(poly)phenols for updating the (poly)phenol database, Phenol Explorer. This chapter also evaluated the importance of including these beverages to estimate (poly)phenol intake. A large variability in the TPC and major anthocyanins were reported in blackcurrant concentrates, suggesting the presence of bias and error if estimating (poly)phenol intakes at an individual level.

11.4 Summary discussion

Summarising evidence from the thesis, the strength of evidence for higher fruit intake and lower CVD risk is stronger in comparison to vegetables. In particular, it is likely that a greater consumption of citrus fruits and grapes are associated with a lower risk of CVD. However, the strength of evidence for the fruit subgroups and CVD incidence is weak, due to low case numbers and a low diversity of fruit subgroup intakes in Chapter 4. Evidence from this chapter is therefore only suggestive and carries little weight. Fruit intake in general appeared to be more associated with CHD outcomes (with the exception of citrus and its relationship with stroke), while vegetables was strictly associated with stroke in this thesis, though the association with CVD incidence was not investigated as part of this thesis. It is unknown if further investigations between vegetables and CVD incidence would allow associations to emerge. Nevertheless, findings support the idea that the aetiology of CHD and stroke are different (as discussed in Chapter 3), thus CVD risk is possibly lowered by different (poly)phenol mechanisms elaborated in Chapter 1. Further evidence to support this includes the association between citrus and stroke, but not with CHD. This is further complimented by other cohort findings [213] and human studies which report a lower BP with the consumption of orange juice [150, 151].

When examining BP as the outcome, the overall strength of evidence indicate that a greater intake of total FVs is likely to be associated with a lower incidence of self-reported HBP, while the strength of evidence for lower measured BP is limited. Total vegetable intake, fruit vegetables and pomes are also likely to be associated with lower incidence of self-reported HBP in the UKWCS, while limited evidence suggest that total fruit was associated with a lower DBP in the NDNS RP. Fundamentally, these are two different representations of UK populations at different time points. By design, findings from the UKWCS carry more weight in comparison to the NDNS RP as it is a prospective cohort with a larger sample size, therefore evidence generated are ranked as probable. The NDNS RP has a smaller sample, but is more representative of the general population. Both studies adapted different dietary assessments where the UKWCS FFQ is more representative of

habitual intake, in comparison to a food diary which offers high quality snapshots (Chapter 8). However, HBP was self-reported in the UKWCS, which was prone to different errors compared to a better alternative of measured BP by the nurse in the NDNS RP. Despite the limitations by design as a cross-sectional study, the analysis conducted using the NDNS RP are generally in agreement with UKWCS, thus offering limited or suggestive evidence to back up the findings from the UKWCS.

As elaborated in Chapter 1, Chapter 3, Chapter 4, Chapter 5, Chapter 6 and Chapter 7, there is a large substantial body of evidence to support the beneficial effects of various (poly)phenols on CVD risk factors. (Poly)phenols may directly act on biological mechanisms associated with the development of atherosclerosis, such as blood lipid levels, endothelial function and inflammation [3], or through other diseases such as diabetes and obesity, where the manifestation of latter risk factors could further increase CVD risk. As previously stated, (poly)phenols are also not the only compounds present within FVs, coffee and tea. Perhaps associations observed could be the result of other nutrients or phytochemicals, such as dietary fibre, carotenoids, vitamin C and potassium [377]. However, evidence from RCTs have not been supportive of single nutrient supplementation [70]. Alternatively, associations detected could also be a synergistic interaction between multiple nutrients and (poly)phenols, but results here are unable to provide any causal evidence. Thus, further investigation is required from intervention studies and RCTs to confirm the mechanistic role of FVs.

Null associations were reported between coffee, tea and CVD mortality and BP, despite both being rich in (poly)phenols. The lack of association could be due to limitations within dietary assessments to accurately capture and reflect levels of (poly)phenols consumed (discussed in Chapter 5). This is supported by Chapter 8, where coffee and tea intakes were strongly correlated between the FFQ and food diary. The extent of agreement was also better than the FVs. Coffee and tea (poly)phenols could also have acted through a different biological pathway instead of BP related biological factors. For example, a systematic review reported that coffee consumption is associated with a lower risk of type 2 diabetes [378], and supporting evidence for the mechanisms of (poly)phenols on diabetes is listed in Chapter 1. In addition, Chapter 1 also reported the effects of catechins on the mechanisms of diabetes and obesity.

Sensitivity analyses in both populations show attenuated associations in subpopulations of obese, hypertensive or smoking participants, which suggests that a high consumption of FVs in the presence of these CVD risk factors is could be less mechanistically

effective, although this could only be confirmed in an RCT among at risk populations. Alternatively, participants could also be consuming less FVs, or the variation in consumption within these at risk populations may be relatively smaller, thus leading to an attenuated association. In addition, sensitivity analyses reported a 99% CI to reduce type I error (false positive), thus associations which could have been borderline significant became attenuated, although the direction of risk estimates tend to be inverse. Occasionally, consumption of specific fruits were also significantly and adversely associated with CVD risk. However, it is well-known from multiple observational studies and trials that fruits are beneficial against CVD risk instead of exhibiting harmful effects. Thus, the observation is most likely due to reverse causality, in other words, participants in NDNS RP who were female or obese with a higher SBP tend to consume more citrus fruits, leading to the presumed adverse association observed.

The relative validity study conducted in Chapter 8 provides some support for the methodology applied in the analysis of the UKWCS when dividing participants into quantiles of fruit, fruit subgroup, coffee and tea intake. This chapter concluded that the UKWCS FFQ was able to capture and categorise women broadly into low, medium and high intakes relative to the food diary (with the exception of drupes intake) with minimal gross misclassification. However, it is important to note the time difference (five years) between the completion of the FFQ and food diary as a limitation. As diet is likely to have changed throughout this period, a higher percentage of gross misclassification is more likely to be observed. The relative validity of vegetable intake was not assessed as analyses of vegetable intake and CVD outcomes were conducted after this relative validity study. However, based on the results above, observed vegetable intakes and derived CIs for the analyses, the relative validity for vegetables using FFQs are most likely similar to or slightly weaker in comparison to fruit intake, which could be the cause of null association findings in contrast to other studies on vegetable intake and CVD risk [205, 208, 212].

The presence of null associations could also be explained from the results provided in Chapter 9. The variance in the levels of (poly)phenols within fruit juices and concentrates introduced additional errors, seen in the example of the blackcurrant concentrate. As discussed before, the amount of (poly)phenols in coffee and tea were also subjected to variation by multiple processing and brewing factors. Furthermore, different cultivars of the same fruit or vegetable also contains varying amounts of (poly)phenols. Thus, when a mean value is generated within a food or (poly)phenol database to represent the particular food type, it is likely to introduce measurement variance and errors. In addition to the current gap of knowledge within (poly)phenol databases, estimated intakes could be

inaccurate and subjected to huge variations if estimating (poly)phenol intakes at an individual level.

11.5 Strengths and limitations

One of the key strengths of this thesis is the multidisciplinary approach to incorporate subclasses of (poly)phenols into classifications of FVs to study its association with CVD using epidemiological methods. Previous studies have either studied this association through intakes of total FVs [83], or (poly)phenols by subclass [118]. As emphasised in Chapter 1, (poly)phenols are not consumed by class. Although conclusions from studies conducted by Knekt *et. al* [116] and Mink *et. al* [117] could offer insight to specific classes of (poly)phenol which exhibit beneficial effects, they do not reflect how the food containing (poly)phenols were consumed and in what quantities. Thus, the work completed in this thesis offer a practical approach to determine which FVs, consumed in feasible quantities, are particularly important in the diet and may be investigated further in RCTs [379]. Emphasis should be placed on fruits such as berries, citrus and pomes, and vegetables such as fruit vegetables.

The inclusion of cooked or processed FVs in the definition of 'total fruit' and 'total vegetable' also provide a relatively more comprehensive and complete estimate over studies which did not. This is especially important when the evidence from Chapter 9 revealed the possibility of high TPC and high levels of quantifiable (poly)phenol compounds within some smoothies and fruit juices. When these products are consumed in moderate or high amounts, they may contribute significantly to total (poly)phenol intake.

Since CVD aetiology may differ, this thesis examined the association between FVs, coffee and tea CVD outcomes by CHD and stroke separately, as well as by subtypes of CHD and stroke in Chapter 4. The work completed in this thesis also extends towards the understanding of the association between FVs, coffee and tea intake and BP (self-reported and measured), a major risk factor of CVD. This lends support to human studies already undertaken, as well as aid in the hypothesis generation for further intervention studies.

Additionally, analyses were conducted in two UK populations. Although diet was only captured once at baseline in UKWCS, and once in the NDNS RP, comparison of the two populations can provide a bigger picture of the association between FV intake and CVD risk or its risk factors. The frequency of FVs consumption were also shown to remain relatively similar, although women in the UKWCS seem to consume more by intake. Strengths of the

UKWCS which have been discussed in previous chapters, include a long follow-up period and a wide diversity of intakes.

One of the limitations relates to the applicability of the results described here towards other populations, due to the higher proportion of vegetarians, higher level of 'health-consciousness' and all-women population in the UKWCS. However, results from the UKWCS and the NDNS RP appear to be generally similar, and perhaps even complementary. Although there is no hypothesis to suggest if there would be any mechanistic differences between men and women in the way they respond to FVs, differences detected within sensitivity analyses conducted in the NDNS RP population may warrant further research.

Limitations in epidemiological methods should be noted here, in relation to the interpretation of the extent of causality. There is also 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. In particular, models applied here do not adjust for environmental factors such as the location of habitation and deprivation scores, or additionally for other dietary components associated with CVD, such as red meat intake, which may contribute to residual confounding. Instances of multiple testing are also present due to the extensive amount of analyses. However, this is a necessary approach if associations between FV subgroups and types of CVD are to be elucidated. Therefore, where appropriate, wider CIs were adapted in multiple chapters to reduce false positives, especially in secondary and sensitivity analyses. Additionally, the general application of dividing intakes of exposures into five categories (quintiles) despite the narrow range of intakes (e.g. *Allium*, berries, drupes, tropical fruits etc.) adds to the limitation of the thesis, and could also be a cause of null associations. Different approaches of categorisation (tertiles, consumers v.s. non-consumers) could have been adapted as a better fit for FV intakes with narrow ranges, such as in Chapter 10, as a more robust statistical approach. Lastly, alternative categorisation methods for FV subgroups, such as principle component analysis or cluster analyses could have been adapted as a more objective approach. However, findings from this approach may lead to an alternative research direction.

11.6 Recommendations for future work

11.6.1 For UKWCS

The association between vegetable, vegetable subgroup intake and CVD incidence could be investigated, as the increased specificity of disease outcome could reveal associations that were attenuated when analysing data as total CVD mortality. In addition, the relative validity between the FFQ and food diary for vegetable intakes within the UKWCS could also be studied to cast light on potential exposure misclassification.

Other sources of (poly)phenols such as dark chocolate (cocoa), wine and beer are also warranted for study. In this cohort, complementary to the (poly)phenol rich foods groups analysed here, dietary patterns previously derived using cluster analysis [165] from the UKWCS could be examined for its relationship with chronic diseases. A dietary pattern associated with a lower risk of chronic disease based on UK diet could be recommended, and more easily implemented towards public health.

Investigations into other CVD risk factors such as diabetes and obesity are also warranted. Obesity is a major CVD risk factor, and beneficial associations observed in non-obese populations between (poly)phenol-rich foods and CVD risk tend to be attenuated in both the UKWCS and the NDNS RP populations. Bertoia *et. al* [380] recently reported weight change over four years associated with a higher consumption of fruits and non-starchy vegetables, specifically berries (-0.5 kg), pomes (-0.5 kg) and cauliflower (-0.6 kg). Evidence for berry (poly)phenols on mechanisms of obesity supports this finding, and warrants further research within the cohort.

11.6.2 For NDNS RP

The NDNS RP database grows yearly with the addition of a thousand people per year, and the power to detect associations will increase over time. Investigations into other CVD risk factors and predictors, such as obesity or weight gain, diabetes and measured blood lipid profiles (total cholesterol, HDL-C, LDL-C etc.) in association with (poly)phenol-rich foods could be investigated. Other dietary sources of (poly)phenols, such as coffee, tea, dark chocolate, wine and beer could also be studied to understand if any specific source of (poly)phenols is particularly important, and worthy of further investigation by interventions or RCTs.

With regard to the improvements in methodology here, methods to disaggregate food diary variables with two or more inseparable fruit or vegetable intakes could be developed

to allow improved accuracy when estimating specific fruit or vegetable intakes, as these foods were excluded in the current analysis. The impact of excluding this data is unknown. Despite null associations detected in coffee, tea intakes and CVD risk within the UKWCS, other studies [96] support the association between coffee, tea intake and BP, and could be investigated in the NDNS RP. In addition, linkage with the MINAP, HES or by following-up using other case ascertainment methods could allow survival analyses to be conducted between diet and chronic disease.

11.6.3 For other future studies

Improvements in reducing measurement error in epidemiological studies is crucial in order to better estimate the risk of chronic diseases and its association with diet. Results from Chapter 9 revealed the limitation of taking an average value to represent multiple variations of the same product of the same name, for example, blackcurrant concentrate or cranberry juice. The extent that this type of error influences nutrient estimates in various foods is unknown, but it is an important limitation that should be recognised if (poly)phenol consumption in individuals are to be estimated. The application of food diaries can overcome this error by asking participants to provide information, such as the brand name, or product name of food, as well as the nutrition back-of-pack label or ingredients list. However, unless information on cultivars from fresh FVs are both available in the Phenol Explorer and in retail stores, this limitation will remain. In addition, if food databases do not contain the relevant nutritional information for the particular food, an alternative food most similar based on nutrient levels would be coded as substitute. This would reduce precision and accuracy of dietary estimates. Moreover, the availability of processed foods such as microwavable, pre-packaged foods is increasing. Recipes within these foods are also subject to change depending on public health policies [381]. Therefore, the first recommendation is to provide up-to-date and precise nutritional composition data to improve dietary intake estimates. Secondly, future research should also focus on quantifying (poly)phenols within processed foods which includes plant-based foods, as omission could possibly introduce under-reported (poly)phenol intakes. Until (poly)phenols are quantified in these foods, it is unknown to what extent the error in estimating (poly)phenol intakes are. Most importantly, the adaptation of mixed methods is highly recommended if individual (poly)phenol intakes are to be estimated. Dietary intakes should be collected through FFQs and/or questionnaires, and food diaries and/or (multiple) 24-hour recalls. The application of multiple dietary assessment methods would capture habitual and high quality dietary intakes, and counter limitations arising from each assessment method. Validation studies

can then be conducted to provide correction factors for under- or over-reporting. The collection of tissue samples such as urine and plasma allow (poly)phenols of interest to be identified simply for compliance, or as an objective measure against reported intakes from dietary assessments for validation or correction of intakes.

11.6.4 For future intervention studies and clinical trials

Evidence surrounding the beneficial association between FVs and CVD comes largely from observational studies, and there is a lack of interventions or clinical trials which directly assess the mechanistic effects of FVs on CVD risk factors or markers [379]. Such studies are expensive, time consuming, in addition, requires vigorous adherence to protocol from the participants. To effectively assess whether an increased FV consumption could possibly decrease CVD risk, interventions and RCTs in the UK should focus on providing a control diet (typical of general UK diet in terms of nutrient composition) and FV-rich diet [or (poly)phenol rich diet] which is strictly prepared, controlled and consumed on site, in a specific population (at risk or healthy only), similar to the DASH trial [80]. Endpoints such as BP, endothelial function, measured blood lipid profile, serum glucose levels (risk factor for type 2 diabetes), inflammatory markers could be measured depending on the study's interest. Although such a design may not be reflective of diet consumed *ad libitum* in the general population, and the duration of the study would most likely be short- to medium-term, such a design is best able to generate efficacy, since dietary parameters are tightly controlled. In combination with questionnaires to assess lifestyle factors such as physical activity, smoking habits, and environmental conditions, confounding could also be potentially adjusted for.

Dietary biomarkers are commonly measured in blood and urine (to a lesser extent), and range from a high specificity for a particular food (nutritional biomarkers), to being broadly specific for food groups. However, global assays (such as the Folin-Ciocalteu assay) applied to quantify, for example TPC, is subjected to interference, while levels of vitamin C could be influenced by multiple factors [382]. A novel alternative such as food metabolomics, allow the identification of existing and novel biomarkers which could be associated with particular foods and dietary patterns. These could then be correlated or associated with disease outcome, thereby providing causal evidence between foods and disease risk [382]. An example of a study applying this method is the INTERMAP study, which identified different metabolite compositions in Western and Asian populations from 24-hour urine samples using proton nuclear magnetic resonance. The study also identified a significant adverse association between alanine and BP, and a significant inverse

association between hippurate and BP [383]. Such an approach could be implemented in future trials to aid the confirmation of associations detected in observational studies, such as those observed in this thesis.

11.6.5 For public health implementation

In response to the dietary guidelines for the prevention of CVD stated in Chapter 1, the findings from this thesis supports the 'five-a-day' FV health message as stated. Current guidelines promoted in the National Health Service [384] include:

- FVs, including those cooked as composite dishes, frozen, tinned, dried (no more than 30 g recommended) and in ready meals
- Beans and pulses (only count as one portion despite amount consumed)
- Unsweetened, 100% pure fruit juice (a glass, 125 g, only count as one portion despite amount consumed)
- Fruit smoothies (one or more portion per day, depending on recipe and serving size)
- Excluding starchy vegetables, such as potatoes

Firstly, the ultimate goal is to generate enough evidence from RCTs to prioritise certain FVs, including findings here in relation to berries, citrus, pomes and fruit vegetables as part of the 'five-a-day' health message in precedence over other subgroups. Evidence from prospective cohorts alone, such as the UKWCS, is unable to make an impact on policy, due to a lack of causal evidence. Based on the findings from Chapter 9, to maximise (poly)phenol delivery, fruits are recommended to be consumed raw, and not in the form of a juice, juice drink or concentrate. From a (poly)phenol perspective, this challenges the current guidelines where a glass of fruit juice is acknowledged as part of the 'five-a-day'. However, from a public health perspective, for part of the population which do not consume any FVs, a glass of fruit juice does more benefit than none at all. Further investigation is needed to determine effects of processing on vegetables. Recommendations as to whether 'five-a-day' should include a specific number of fruits or vegetables is not possible, until evidence from RCTs are available.

In addition, because consumers might lack knowledge about [385], or have varying perceptions on portion sizes [386], public health recommendations should also focus on educating consumers about the importance of increasing the frequency of FV consumption, understanding and perceiving portion sizes of specific FVs. Ashfield-Watt and colleagues reported average serving sizes of fruits consumed from 31 to 168 g/day, and for vegetables

from 26 to 147 g/day within the EPIC-Norfolk cohort [386]. Variation in portion sizes consumed is also large within single fruits such as strawberries (60 to 150 g), or vegetables, such as carrots (39 to 72 g). While the authors conclude that frequency is a relatively more important contributor, helping consumers to understand the '80 g' portion size, and increasing FVs commonly consumed as smaller portions (such as blackcurrant, kiwi, lettuce, pepper and cucumber) is equally important to help boost overall intakes. Increasing availability of FVs in retail, and in turn informing or educating the UK population about greater consumption of a variety of FVs, and is also recommended to help reach the 'five-a-day' target. This could be achieved in the form of an intervention or cooking classes to promote recipes which incorporate less commonly consumed FVs.

11.7 Summary of conclusions

- Fruit and vegetables are recommended as a prevention to lower CVD risk, and are inversely associated within multiple observational studies globally.
- Fruits, vegetables, as well as coffee and tea are (poly)phenol-rich foods. Cell culture, animal and human studies support the mechanistic effects of (poly)phenols on CVD risk factors.
- In a health-conscious cohort of UK women (UKWCS), total fruit and vegetables, especially total fruit, berries, citrus and grapes consumption is associated with a lower risk of CVD risk, while a greater intake of total vegetables, pomes and fruit vegetables are associated with a lower incidence of self-reported HBP.
- Findings from the NDNS RP reveal a lower SBP with increasing total fruit and vegetables and total fruit intake, while pomes intake was associated with a lower DBP.
- Attenuated associations in subpopulations with CVD risk factors suggest that protective effects are more apparent in healthy subpopulations, and further research is warranted in populations with a high risk of CVD.
- Coffee and tea are not significantly associated with a lower risk of CVD or BP as a key risk factor in both UK populations, although they are (poly)phenol-rich. Potential mechanisms for (poly)phenols from coffee and tea may possibly act through other biological pathways rather than through BP.

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Table A.1 Total fruit, fruit subgroup intake and cardiovascular mortality risk within non-smoking, non-obese, normotensive, hypertensive women, women with and without parental history and postmenopausal women in UKWCS (expressed as HR and 99% CI)

Non-smokers	**CHD**			**Stroke**			**CVD**		
Intake (80 g/day)	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Non-smokers									
Total fruit	117	0.93 (0.85, 1.00)	0.94 (0.86, 1.03)	128	0.93 (0.86, 1.01)	0.95 (0.87, 1.04)	245	0.93 (0.88, 0.98)	0.95 (0.89, 1.01)
Fresh fruit	117	0.91 (0.82, 1.01)	0.91 (0.80, 1.03)	128	0.92 (0.83, 1.02)	0.94 (0.84, 1.05)	245	0.91 (0.85, 0.98)	0.93 (0.85, 1.01)
Fresh fruit and juice	117	0.93 (0.85, 1.01)	0.94 (0.86, 1.04)	128	0.93 (0.86, 1.01)	0.95 (0.87, 1.04)	245	0.93 (0.88, 0.98)	0.95 (0.89, 1.01)
Fresh and dried fruit	117	0.91 (0.82, 1.00)	0.91 (0.80, 1.02)	128	0.92 (0.84, 1.01)	0.94 (0.84, 1.05)	245	0.91 (0.85, 0.98)	0.92 (0.85, 1.00)
Total dried fruit *(25 g/day)*	117	0.78 (0.54, 1.12)	0.83 (0.57, 1.22)	128	0.85 (0.62, 1.17)	0.95 (0.70, 1.28)	245	0.82 (0.64, 1.04)	0.89 (0.70, 1.14)
Fruit juice *(125 g/day)*	117	0.92 (0.71, 1.20)	1.01 (0.76, 1.32)	128	0.89 (0.69, 1.16)	0.94 (0.71, 1.24)	245	0.91 (0.75, 1.10)	0.97 (0.80, 1.18)
Total citrus	117	0.85 (0.69, 1.04)	0.89 (0.72, 1.11)	128	0.90 (0.75, 1.08)	0.93 (0.77, 1.14)	245	0.87 (0.76, 1.00)	0.91 (0.79, 1.06)
Citrus fruit	117	0.74 (0.48, 1.13)	0.80 (0.50, 1.27)	128	0.84 (0.58, 1.22)	0.90 (0.60, 1.35)	245	0.79 (0.60, 1.05)	0.85 (0.63, 1.16)
Orange Juice *(250 g/day)*	117	0.65 (0.30, 1.40)	0.76 (0.33, 1.72)	128	0.73 (0.36, 1.49)	0.82 (0.39, 1.75)	245	0.69 (0.41, 1.16)	0.79 (0.45, 1.38)
Berries	117	1.14 (0.59, 2.18)	1.49 (0.87, 2.55)	128	0.46 (0.12, 1.68)	0.75 (0.23, 2.46)	245	0.84 (0.44, 1.59)	1.19 (0.71, 2.00)
Pomes	117	0.88 (0.71, 1.09)	0.95 (0.75, 1.21)	128	1.00 (0.83, 1.19)	1.12 (0.92, 1.36)	245	0.94 (0.82, 1.08)	1.04 (0.90, 1.21)
Tropical fruit	117	0.84 (0.61, 1.17)	0.84 (0.57, 1.23)	128	0.86 (0.63, 1.17)	0.88 (0.61, 1.27)	245	0.85 (0.68, 1.07)	0.86 (0.66, 1.12)
Drupes	117	0.10 (0.00, 2.00)	0.37 (0.01, 10.0)	128	0.24 (0.02, 3.25)	0.31 (0.01, 7.82)	245	0.16 (0.02, 1.15)	0.33 (0.03, 3.40)
Grapes	117	0.77 (0.47, 1.26)	0.70 (0.37, 1.31)	128	0.51 (0.27, 0.98)	0.63 (0.33, 1.21)	245	0.64 (0.43, 0.96)	0.66 (0.42, 1.04)
Non-obese									
Total fruit	119	0.92 (0.85, 1.01)	0.94 (0.86, 1.03)	136	0.90 (0.83, 0.97)	0.95 (0.87, 1.04)	255	0.91 (0.86, 0.97)	0.94 (0.88, 1.01)
Fresh fruit	119	0.90 (0.80, 1.00)	0.91 (0.80, 1.03)	136	0.89 (0.80, 0.98)	0.94 (0.84, 1.06)	255	0.89 (0.83, 0.96)	0.93 (0.85, 1.01)
Fresh fruit and juice	119	0.93 (0.85, 1.01)	0.94 (0.86, 1.04)	136	0.90 (0.83, 0.98)	0.95 (0.87, 1.04)	255	0.91 (0.86, 0.97)	0.95 (0.89, 1.01)
Fresh and dried fruit	119	0.90 (0.81, 1.00)	0.90 (0.80, 1.02)	136	0.88 (0.80, 0.98)	0.94 (0.84, 1.05)	255	0.89 (0.83, 0.96)	0.92 (0.85, 1.00)
Total dried fruit *(25 g/day)*	119	0.80 (0.56, 1.14)	0.81 (0.56, 1.18)	136	0.72 (0.49, 1.04)	0.86 (0.61, 1.22)	255	0.76 (0.58, 0.98)	0.84 (0.65, 1.08)
Fruit juice *(125 g/day)*	119	0.96 (0.74, 1.24)	1.02 (0.78, 1.32)	136	0.83 (0.63, 1.10)	0.93 (0.71, 1.22)	255	0.89 (0.74, 1.08)	0.97 (0.80, 1.17)
Total citrus	119	0.84 (0.68, 1.03)	0.90 (0.73, 1.11)	136	0.86 (0.71, 1.04)	0.94 (0.77, 1.14)	255	0.85 (0.74, 0.98)	0.92 (0.80, 1.06)
Citrus fruit	119	0.63 (0.39, 1.02)	0.73 (0.45, 1.19)	136	0.82 (0.57, 1.20)	0.97 (0.66, 1.43)	255	0.74 (0.55, 0.99)	0.86 (0.63, 1.16)
Orange Juice *(250 g/day)*	119	0.71 (0.33, 1.54)	0.85 (0.39, 1.83)	136	0.62 (0.29, 1.31)	0.78 (0.37, 1.65)	255	0.66 (0.39, 1.14)	0.81 (0.47, 1.38)
Berries	119	1.16 (0.60, 2.25)	1.42 (0.80, 2.50)	136	0.40 (0.10, 1.57)	0.77 (0.24, 2.52)	255	0.81 (0.41, 1.60)	1.16 (0.68, 1.98)
Pomes	119	0.90 (0.72, 1.12)	0.99 (0.78, 1.25)	136	0.93 (0.76, 1.13)	1.08 (0.88, 1.34)	255	0.91 (0.79, 1.06)	1.04 (0.89, 1.21)
Tropical fruit	119	0.78 (0.54, 1.10)	0.84 (0.58, 1.24)	136	0.85 (0.63, 1.16)	0.97 (0.68, 1.37)	255	0.82 (0.65, 1.03)	0.91 (0.70, 1.17)
Drupes	119	0.12 (0.01, 2.47)	0.29 (0.01, 7.80)	136	0.05 (0.00, 1.09)	0.09 (0.01, 3.48)	255	0.08 (0.01, 0.67)	0.17 (0.01, 1.96)
Grapes	119	0.67 (0.37, 1.20)	0.68 (0.36, 1.31)	136	0.42 (0.21, 0.85)	0.58 (0.29, 1.16)	255	0.54 (0.34, 0.85)	0.63 (0.39, 1.02)

(Table A.1 continued)

Intake (80 g/day)	CHD			Stroke			CVD		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Normotensive									
Total fruit	88	0.91 (0.82, 1.01)	0.91 (0.81, 1.02)	86	0.87 (0.79, 0.97)	0.92 (0.81, 1.03)	174	0.89 (0.83, 0.96)	0.91 (0.84, 0.99)
Fresh fruit	88	0.87 (0.76, 0.99)	0.84 (0.72, 0.99)	86	0.84 (0.74, 0.97)	0.89 (0.76, 1.04)	174	0.86 (0.78, 0.94)	0.86 (0.77, 0.98)
Fresh fruit and juice	88	0.91 (0.82, 1.01)	0.91 (0.81, 1.03)	86	0.87 (0.78, 0.97)	0.92 (0.81, 1.03)	174	0.89 (0.83, 0.96)	0.92 (0.84, 1.00)
Fresh and dried fruit	88	0.87 (0.76, 0.99)	0.84 (0.72, 0.98)	86	0.84 (0.74, 0.96)	0.89 (0.76, 1.04)	174	0.86 (0.78, 0.94)	0.86 (0.77, 0.96)
Total dried fruit *(25 g/day)*	88	0.73 (0.46, 1.18)	0.75 (0.45, 1.25)	86	0.73 (0.46, 1.16)	0.87 (0.55, 1.36)	174	0.73 (0.53, 1.02)	0.81 (0.58, 1.14)
Fruit juice *(125 g/day)*	88	0.97 (0.71, 1.31)	1.07 (0.79, 1.43)	86	0.83 (0.59, 1.17)	0.92 (0.64, 1.30)	174	0.90 (0.72, 1.13)	1.00 (0.79, 1.25)
Total citrus	88	0.80 (0.62, 1.03)	0.87 (0.67, 1.14)	86	0.82 (0.64, 1.05)	0.91 (0.70, 1.18)	174	0.81 (0.68, 0.97)	0.89 (0.74, 1.07)
Citrus fruit	88	0.53 (0.29, 0.98)	0.57 (0.29, 1.12)	86	0.64 (0.37, 1.10)	0.73 (0.40, 1.33)	174	0.59 (0.39, 0.88)	0.65 (0.41, 1.02)
Orange Juice *(250 g/day)*	88	0.67 (0.26, 1.70)	0.90 (0.36, 2.21)	86	0.65 (0.26, 1.64)	0.87 (0.35, 2.19)	174	0.66 (0.34, 1.27)	0.88 (0.46, 1.69)
Berries	88	0.47 (0.09, 2.32)	0.85 (0.22, 3.23)	86	0.43 (0.08, 2.19)	0.88 (0.24, 3.25)	174	0.45 (0.14, 1.41)	0.86 (0.34, 2.21)
Pomes	88	0.92 (0.71, 1.18)	1.05 (0.80, 1.36)	86	0.89 (0.69, 1.14)	1.08 (0.83, 1.41)	174	0.90 (0.75, 108)	1.06 (0.88, 1.28)
Tropical fruit	88	0.71 (0.46, 1.09)	0.70 (0.42, 1.17)	86	0.76 (0.51, 1.14)	0.88 (0.55, 1.41)	174	0.74 (0.55, 0.99)	0.79 (0.56, 1.12)
Drupes	88	0.04 (0.00, 2.16)	0.15 (0.00, 14.2)	86	0.06 (0.00, 2.40)	0.25 (0.00, 20.2)	174	0.05 (0.00, 0.75)	0.19 (0.01, 4.54)
Grapes	88	0.85 (0.50, 1.45)	0.81 (0.41, 1.60)	86	0.27 (0.10, 0.75)	0.39 (0.14, 1.12)	174	0.57 (0.33, 0.98)	0.61 (0.33, 1.12)
Hypertensive									
Total fruit	51	0.96 (0.85, 1.07)	0.96 (0.84, 1.10)	55	1.00 (0.90, 1.12)	1.03 (0.91, 1.16)	106	0.98 (0.91, 1.06)	0.99 (0.91, 1.09)
Fresh fruit	51	0.94 (0.82, 1.09)	0.96 (0.81, 1.14)	55	1.01 (0.88, 1.16)	1.03 (0.89, 1.20)	106	0.98 (0.88, 1.08)	1.00 (0.89, 1.12)
Fresh fruit and juice	51	0.96 (0.85, 1.08)	0.96 (0.84, 1.10)	55	1.00 (0.90, 1.12)	1.02 (0.90, 1.16)	106	0.98 (0.90, 1.06)	0.99 (0.90, 1.09)
Fresh and dried fruit	51	0.94 (0.82, 1.09)	0.96 (0.82, 1.13)	55	1.01 (0.89, 1.15)	1.04 (0.90, 1.20)	106	0.98 (0.89, 1.08)	1.00 (0.90, 1.11)
Total dried fruit *(25 g/day)*	51	0.96 (0.66, 1.38)	0.98 (0.69, 1.39)	55	1.03 (0.77, 1.37)	1.07 (0.81, 1.41)	106	1.00 (0.79, 1.25)	1.03 (0.83, 1.28)
Fruit juice *(125 g/day)*	51	0.96 (0.65, 1.42)	0.92 (0.59, 1.43)	55	0.98 (0.66, 1.45)	1.00 (0.67, 1.49)	106	0.97 (0.74, 1.28)	0.96 (0.71, 1.29)
Total citrus	51	0.95 (0.73, 1.23)	0.95 (0.70, 1.28)	55	0.97 (0.74, 1.26)	0.96 (0.72, 1.28)	106	0.96 (0.79, 1.15)	0.95 (0.77, 1.17)
Citrus fruit	51	0.86 (0.49, 1.53)	0.93 (0.50, 1.73)	55	1.19 (0.80, 1.79)	1.23 (0.76, 2.01)	106	1.04 (0.74, 1.46)	1.09 (0.74, 1.60)
Orange Juice *(250 g/day)*	51	0.91 (0.33, 2.49)	0.83 (0.26, 2.70)	55	0.61 (0.18, 2.02)	0.59 (0.17, 2.11)	106	0.76 (0.35, 1.65)	0.70 (0.30, 1.66)
Berries	51	1.58 (0.85, 2.94)	2.07 (1.10, 3.91)	55	0.75 (0.15, 3.76)	0.90 (0.19, 4.32)	106	1.29 (0.70, 2.38)	1.59 (0.88, 2.87)
Pomes	51	0.81 (0.57, 1.15)	0.84 (0.57, 1.23)	55	1.08 (0.83, 1.40)	1.12 (0.85, 1.48)	106	0.95 (0.77, 1.18)	0.99 (0.79, 1.24)
Tropical fruit	51	0.97 (0.62, 1.52)	0.99 (0.61, 1.63)	55	1.01 (0.65, 1.58)	1.09 (0.66, 1.79)	106	0.99 (0.72, 1.36)	1.04 (0.73, 1.48)
Drupes	51	0.37 (0.01, 15.3)	0.78 (0.01, 46.7)	55	1.26 (0.05, 29.1)	0.82 (0.02, 37.6)	106	0.71 (0.06, 8.00)	0.77 (0.05, 12.7)
Grapes	51	0.79 (0.39, 1.62)	0.68 (0.25, 1.84)	55	0.74 (0.33, 1.65)	0.80 (0.33, 1.78)	106	0.77 (0.45, 1.31)	0.73 (0.38, 1.39)

(Table A.1 continued)

	CHD			Stroke			CVD		
Intake (80 g/day)	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
WITH Parental History of CVD									
Total fruit	63	0.94 (0.84, 1.04)	0.94 (0.83, 1.07)	60	0.94 (0.84, 1.05)	0.97 (0.86, 1.10)	123	0.94 (0.87, 1.01)	0.96 (0.88, 1.05)
Fresh fruit	63	0.93 (0.81, 1.06)	0.93 (0.79, 1.09)	60	0.91 (0.79, 1.06)	0.95 (0.80, 1.12)	123	0.92 (0.84, 1.02)	0.94 (0.84, 1.05)
Fresh fruit and juice	63	0.94 (0.85, 1.05)	0.95 (0.83, 1.08)	60	0.94 (0.84, 1.05)	0.97 (0.86, 1.11)	123	0.94 (0.87, 1.02)	0.96 (0.88, 1.05)
Fresh and dried fruit	63	0.92 (0.81, 1.05)	0.92 (0.78, 1.08)	60	0.91 (0.79, 1.05)	0.95 (0.81, 1.11)	123	0.92 (0.84, 1.01)	0.94 (0.84, 1.05)
Total dried fruit *(25 g/day)*	63	0.68 (0.39, 1.18)	0.72 (0.39, 1.33)	60	0.88 (0.57, 1.36)	0.94 (0.62, 1.43)	123	0.78 (0.55, 1.11)	0.85 (0.59, 1.22)
Fruit juice *(125 g/day)*	63	0.93 (0.65, 1.32)	0.99 (0.68, 1.42)	60	0.97 (0.67, 1.39)	1.04 (0.73, 1.49)	123	0.95 (0.73, 1.22)	1.01 (0.78, 1.31)
Total citrus	63	0.84 (0.64, 1.11)	0.89 (0.66, 1.19)	60	0.89 (0.68, 1.17)	0.97 (0.73, 1.27)	123	0.87 (0.71, 1.05)	0.92 (0.75, 1.13)
Citrus fruit	63	0.75 (0.43, 1.32)	0.83 (0.44, 1.55)	60	0.67 (0.35, 1.27)	0.77 (0.40, 1.50)	123	0.71 (0.47, 1.09)	0.80 (0.51, 1.26)
Orange Juice *(250 g/day)*	63	0.61 (0.21, 1.77)	0.70 (0.23, 2.16)	60	0.87 (0.32, 2.33)	1.08 (0.42, 2.77)	123	0.73 (0.35, 1.51)	0.88 (0.42, 1.83)
Berries	63	1.28 (0.61, 2.69)	1.52 (0.79, 2.95)	60	0.87 (0.24, 3.14)	1.20 (0.41, 3.52)	123	1.12 (0.58, 2.16)	1.39 (0.79, 2.46)
Pomes	63	0.81 (0.60, 1.10)	0.85 (0.60, 1.21)	60	0.91 (0.68, 1.21)	0.99 (0.72, 1.37)	123	0.86 (0.70, 1.06)	0.92 (0.73, 1.17)
Tropical fruit	63	0.95 (0.64, 1.43)	0.93 (0.57, 1.52)	60	0.77 (0.47, 1.26)	0.80 (0.46, 1.39)	123	0.87 (0.64, 1.19)	0.86 (0.60, 1.25)
Drupes	63	0.13 (0.00, 6.14)	0.25 (0.00, 23.7)	60	0.63 (0.02, 17.6)	2.91 (0.09, 88.8)	123	0.30 (0.02, 3.77)	0.94 (0.06, 15.5)
Grapes	63	0.87 (0.47, 1.64)	0.78 (0.34, 1.78)	60	0.73 (0.32, 1.62)	0.85 (0.39, 1.85)	123	0.81 (0.49, 1.33)	0.83 (0.47, 1.46)
NO Parental History of CVD									
Total fruit	79	0.89 (0.80, 0.99)	0.91 (0.80, 1.03)	92	0.90 (0.81, 0.99)	0.94 (0.84, 1.05)	171	0.89 (0.83, 0.96)	0.93 (0.85, 1.01)
Fresh fruit	79	0.84 (0.73, 0.97)	0.85 (0.71, 1.00)	92	0.89 (0.79, 1.01)	0.96 (0.83, 1.10)	171	0.87 (0.79, 0.95)	0.91 (0.81, 1.01)
Fresh fruit and juice	79	0.89 (0.80, 0.99)	0.91 (0.80, 1.03)	92	0.90 (0.81, 0.99)	0.94 (0.84, 1.06)	171	0.89 (0.83, 0.96)	0.93 (0.85, 1.01)
Fresh and dried fruit	79	0.85 (0.74, 0.97)	0.85 (0.72, 1.00)	92	0.89 (0.79, 1.00)	0.95 (0.83, 1.09)	171	0.87 (0.79, 0.95)	0.91 (0.82, 1.01)
Total dried fruit *(25 g/day)*	79	0.86 (0.58, 1.29)	0.94 (0.65, 1.34)	92	0.73 (0.46, 1.14)	0.92 (0.61, 1.38)	171	0.79 (0.58, 1.07)	0.93 (0.70, 1.23)
Fruit juice *(125 g/day)*	79	0.93 (0.67, 1.29)	1.02 (0.73, 1.41)	92	0.79 (0.56, 1.11)	0.84 (0.58, 1.21)	171	0.86 (0.68, 1.09)	0.92 (0.72, 1.18)
Total citrus	79	0.83 (0.65, 1.07)	0.90 (0.69, 1.18)	92	0.87 (0.70, 1.09)	0.90 (0.70, 1.15)	171	0.85 (0.72, 1.01)	0.90 (0.75, 1.08)
Citrus fruit	79	0.57 (0.31, 1.04)	0.64 (0.32, 1.26)	92	0.93 (0.62, 1.39)	1.05 (0.68, 1.64)	171	0.77 (0.55, 1.09)	0.87 (0.60, 1.27)
Orange Juice *(250 g/day)*	79	0.75 (0.30, 1.86)	0.93 (0.37, 2.33)	92	0.55 (0.22, 1.37)	0.55 (0.20, 1.55)	171	0.64 (0.33, 1.22)	0.72 (0.36, 1.44)
Berries	79	0.58 (0.13, 2.60)	1.14 (0.41, 3.16)	92	0.25 (0.04, 1.57)	0.62 (0.11, 3.40)	171	0.39 (0.12, 1.30)	0.91 (0.36, 2.29)
Pomes	79	0.91 (0.69, 1.18)	1.07 (0.80, 1.41)	92	0.95 (0.75, 1.20)	1.17 (0.92, 1.50)	171	0.93 (0.78, 1.11)	1.13 (0.94, 1.36)
Tropical fruit	79	0.65 (0.41, 1.03)	0.75 (0.44, 1.27)	92	0.88 (0.62, 1.26)	1.03 (0.68, 1.56)	171	0.78 (0.58, 1.04)	0.90 (0.64, 1.25)
Drupes	79	0.03 (0.00, 2.06)	0.25 (0.00, 20.5)	92	0.06 (0.00, 2.14)	0.05 (0.00, 5.36)	171	0.05 (0.00, 0.70)	0.11 (0.00, 2.85)
Grapes	79	0.69 (0.35, 1.34)	0.62 (0.26, 1.50)	92	0.30 (0.12, 0.77)	0.45 (0.18, 1.15)	171	0.48 (0.27, 0.85)	0.53 (0.28, 1.01)

(Table A.1 continued)

Postmenopausal	**CHD**			**Stroke**			**CVD**		
Intake (80 g/day)	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Total fruit	131	0.91 (0.84, 0.98)	0.93 (0.85, 1.02)	138	0.93 (0.86, 1.00)	0.97 (0.90, 1.06)	269	0.92 (0.87, 0.97)	0.95 (0.90, 1.02)
Fresh fruit	131	0.88 (0.80, 0.98)	0.90 (0.80, 1.02)	138	0.92 (0.83, 1.01)	0.97 (0.87, 1.08)	269	0.90 (0.84, 0.97)	0.94 (0.86, 1.01)
Fresh fruit and juice	131	0.91 (0.84, 0.98)	0.93 (0.85, 1.02)	138	0.93 (0.87, 1.01)	0.98 (0.90, 1.06)	269	0.92 (0.87, 0.97)	0.96 (0.90, 1.02)
Fresh and dried fruit	131	0.88 (0.80, 0.97)	0.90 (0.80, 1.01)	138	0.92 (0.83, 1.00)	0.97 (0.87, 1.07)	269	0.90 (0.84, 0.96)	0.93 (0.86, 1.01)
Total dried fruit *(25 g/day)*	131	0.78 (0.55, 1.10)	0.85 (0.60, 1.21)	138	0.80 (0.58, 1.10)	0.93 (0.69, 1.25)	269	0.79 (0.62, 1.00)	0.89 (0.71, 1.12)
Fruit juice *(125 g/day)*	131	0.90 (0.69, 1.16)	0.98 (0.76, 1.27)	138	0.92 (0.72, 1.18)	0.98 (0.76, 1.27)	269	0.91 (0.76, 1.08)	0.98 (0.82, 1.18)
Total citrus	131	0.83 (0.68, 1.00)	0.89 (0.72, 1.10)	138	0.91 (0.77, 1.08)	0.95 (0.79, 1.15)	269	0.87 (0.76, 0.99)	0.92 (0.80, 1.06)
Citrus fruit	131	0.63 (0.40, 0.97)	0.74 (0.46, 1.19)	138	0.86 (0.61, 1.22)	0.95 (0.65, 1.39)	269	0.75 (0.57, 0.99)	0.85 (0.63, 1.14)
Orange Juice *(250 g/day)*	131	0.67 (0.32, 1.37)	0.80 (0.38, 1.70)	138	0.77 (0.39, 1.52)	0.86 (0.43, 1.75)	269	0.72 (0.44, 1.18)	0.83 (0.50, 1.39)
Berries	131	1.02 (0.50, 2.07)	1.44 (0.83, 2.49)	138	0.54 (0.17, 1.72)	0.93 (0.6, 2.40)	269	0.80 (0.42, 1.51)	1.22 (0.75, 1.98)
Pomes	131	0.87 (0.70, 1.07)	0.99 (0.80, 1.24)	138	0.98 (0.82, 1.17)	1.15 (0.95, 1.39)	269	0.93 (0.81, 1.06)	1.08 (0.93, 1.24)
Tropical fruit	131	0.79 (0.57, 1.09)	0.82 (0.57, 1.20)	138	0.88 (0.65, 1.18)	0.94 (0.66, 1.32)	269	0.83 (0.67, 1.04)	0.88 (0.68, 1.13)
Drupes	131	0.07 (0.00, 1.28)	0.32 (0.01, 8.07)	138	0.23 (0.02, 2.86)	0.38 (0.02, 8.43)	269	0.13 (0.02, 0.89)	0.35 (0.04, 3.27)
Grapes	131	0.69 (0.41, 1.17)	0.69 (0.37, 1.28)	138	0.43 (0.22, 0.84)	0.56 (0.29, 1.11)	269	0.56 (0.37, 0.86)	0.62 (0.39, 0.99)

[a] Cases 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

Table A.2 Sensitivity analysis of total vegetable and vegetable subgroups and cardiovascular mortality risk by non-obese, non-smokers and self-reported HBP

	CHD			Stroke			CVD		
Intake (80 g/day)	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Non-obese									
Total vegetables	120	0.97 (0.87, 1.09)	1.04 (0.93, 1.17)	137	0.86 (0.77, 0.97)	0.89 (0.78, 1.02)	257	0.92 (0.85, 0.99)	0.97 (0.89, 1.06)
Fresh vegetables	120	0.99 (0.87, 1.11)	1.08 (0.95, 1.23)	137	0.84 (0.74, 0.97)	0.90 (0.78, 1.05)	257	0.91 (0.83, 1.00)	0.99 (0.90, 1.10)
Allium	120	0.44 (0.09, 2.12)	0.50 (0.09, 2.85)	137	0.31 (0.07, 1.44)	0.62 (0.10, 3.70)	257	0.37 (0.12, 1.10)	0.55 (0.16, 1.92)
Brassicaceae	120	1.01 (0.78, 1.30)	1.07 (0.80, 1.42)	137	0.75 (0.56, 1.01)	0.87 (0.62, 1.22)	257	0.87 (0.72, 1.06)	0.97 (0.78, 1.21)
Fruit vegetables	120	0.89 (0.62, 1.26)	1.03 (0.70, 1.50)	137	0.76 (0.53, 1.08)	0.99 (0.67, 1.48)	257	0.82 (0.63, 1.05)	1.01 (0.76, 1.33)
Pod vegetables	120	1.48 (0.82, 2.65)	1.80 (1.02, 3.20)	137	0.65 (0.32, 1.32)	1.10 (0.49, 2.50)	257	1.00 (0.62, 1.60)	1.48 (0.89, 2.45)
Stalk & root vegetables	120	0.85 (0.49, 1.50)	0.92 (0.46, 1.85)	137	0.61 (0.34, 1.09)	0.97 (0.48, 1.92)	257	0.72 (0.48, 1.08)	0.94 (0.58, 1.54)
Non-smokers									
Total vegetables	117	0.96 (0.86, 1.07)	1.01 (0.89, 1.15)	129	0.93 (0.83, 1.04)	0.92 (0.81, 1.05)	246	0.94 (0.87, 1.02)	0.96 (0.88, 1.06)
Fresh vegetables	117	0.96 (0.85, 1.09)	1.03 (0.89, 1.19)	129	0.91 (0.81, 1.03)	0.92 (0.79, 1.07)	246	0.94 (0.86, 1.02)	0.97 (0.87, 1.08)
Allium	117	0.25 (0.05, 1.34)	0.41 (0.06, 2.62)	129	0.76 (0.20, 2.86)	0.87 (0.16, 4.75)	246	0.47 (0.17, 1.34)	0.60 (0.17, 2.12)
Brassicaceae	117	1.00 (0.78, 1.29)	1.09 (0.81, 1.47)	129	0.89 (0.68, 1.15)	0.88 (0.63, 1.22)	246	0.94 (0.79, 1.13)	0.98 (0.79, 1.23)
Fruit vegetables	117	0.85 (0.59, 1.21)	0.91 (0.59, 1.41)	129	0.82 (0.58, 1.16)	1.03 (0.70, 1.53)	246	0.83 (0.65, 1.07)	0.97 (0.73, 1.30)
Pod vegetables	117	1.21 (0.65, 2.28)	1.67 (0.82, 3.38)	129	0.73 (0.36, 1.45)	0.97 (0.42, 2.26)	246	0.94 (0.59, 1.51)	1.30 (0.74, 2.26)
Stalk & root vegetables	117	0.79 (0.45, 1.40)	0.91 (0.43, 1.89)	129	0.76 (0.44, 1.32)	0.90 (0.44, 1.84)	246	0.78 (0.52, 1.15)	0.90 (0.54, 1.51)
Self-reported HBP									
Total vegetables	51	0.99 (0.84, 1.17)	1.07 (0.89, 1.27)	55	0.93 (0.78, 1.11)	0.91 (0.74, 1.12)	106	0.96 (0.85, 1.09)	0.99 (0.87, 1.14)
Fresh vegetables	51	1.01 (0.85, 1.20)	1.11 (0.92, 1.33)	55	0.92 (0.75, 1.12)	0.90 (0.71, 1.13)	106	0.97 (0.85, 1.10)	1.01 (0.87, 1.17)
Allium	51	1.32 (0.19, 9.01)	1.81 (0.18, 17.7)	55	0.95 (0.11, 8.03)	1.73 (0.14, 21.2)	106	1.13 (0.27, 4.73)	1.76 (0.32, 9.57)
Brassicaceae	51	1.14 (0.82, 1.57)	1.32 (0.96, 1.83)	55	0.85 (0.55, 1.33)	0.86 (0.51, 1.46)	106	1.01 (0.77, 1.32)	1.12 (0.84, 1.51)
Fruit vegetables	51	0.67 (0.36, 1.23)	0.51 (0.23, 1.13)	55	0.90 (0.53, 1.52)	0.94 (0.51, 1.74)	106	0.78 (0.52, 1.17)	0.71 (0.43, 1.17)
Pod vegetables	51	1.89 (1.04, 3.44)	2.37 (1.31, 4.29)	55	0.78 (0.26, 2.33)	1.20 (0.36, 3.93)	106	1.40 (0.79, 2.49)	1.89 (1.09, 3.30)
Stalk & root vegetables	51	0.94 (0.42, 2.12)	1.19 (0.43, 3.25)	55	0.78 (0.32, 1.91)	0.94 (0.31, 2.89)	106	0.86 (0.47, 1.57)	1.06 (0.50, 2.24)
NO Self-reported HBP									
Total vegetables	89	0.93 (0.81, 1.07)	0.99 (0.86, 1.16)	87	0.88 (0.76, 1.01)	0.90 (0.76, 1.07)	176	0.90 (0.82, 1.00)	0.95 (0.85, 1.06)
Fresh vegetables	89	0.93 (0.80, 1.09)	1.02 (0.86, 1.21)	87	0.89 (0.76, 1.04)	0.94 (0.78, 1.14)	176	0.91 (0.82, 1.01)	0.98 (0.87, 1.11)
Allium	89	0.13 (0.01, 1.16)	0.17 (0.01, 1.85)	87	0.40 (0.07, 2.41)	0.66 (0.07, 5.99)	176	0.24 (0.06, 0.98)	0.33 (0.06, 1.70)
Brassicaceae	89	0.92 (0.67, 1.27)	0.98 (0.67, 1.41)	87	0.86 (0.62, 1.19)	0.88 (0.58, 1.33)	176	0.89 (0.70, 1.12)	0.93 (0.70, 1.23)
Fruit vegetables	89	0.90 (0.60, 1.36)	1.19 (0.79 ,1.80)	87	0.79 (0.51, 1.21)	1.12 (0.70, 1.78)	176	0.85 (0.63, 1.14)	1.16 (0.85, 1.58)
Pod vegetables	89	0.73 (0.30, 1.74)	0.94 (0.34, 2.56)	87	0.78 (0.34, 1.80)	1.38 (0.52, 3.65)	176	0.76 (0.41, 1.38)	1.13 (0.56, 2.29)
Stalk & root vegetables	89	0.64 (0.31, 1.33)	0.69 (0.28, 1.74)	87	0.57 (0.28, 1.18)	0.71 (0.27, 1.84)	176	0.61 (0.36, 1.01)	0.70 (0.36 ,1.36)

(Table A.2 continued)

	CHD			Stroke			CVD		
Intake (80 g/day)	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Postmenopausal									
Total vegetables	132	0.93 (0.84, 1.04)	1.00 (0.88, 1.13)	139	0.91 (0.81, 1.01)	0.91 (0.80, 1.03)	171	0.92 (0.85, 0.99)	0.95 (0.87, 1.04)
Fresh vegetables	132	0.94 (0.83, 1.06)	1.03 (0.90, 1.18)	139	0.90 (0.80, 1.01)	0.93 (0.80, 1.07)	171	0.92 (0.84, 1.00)	0.98 (0.89, 1.08)
Allium	132	0.29 (0.06, 1.35)	0.56 (0.10, 3.11)	139	0.67 (0.19, 2.43)	0.93 (0.18, 4.78)	171	0.46 (0.17, 1.24)	0.71 (0.22, 2.34)
Brassicaceae	132	0.96 (0.75, 1.22)	1.07 (0.80, 1.42)	139	0.86 (0.66, 1.11)	0.90 (0.66, 1.24)	171	0.91 (0.76, 1.08)	0.99 (0.80, 1.22)
Fruit vegetables	132	0.80 (0.57, 1.14)	0.95 (0.64, 1.42)	139	0.81 (0.58, 1.13)	1.03 (0.71, 1.51)	171	0.81 (0.63, 1.03)	0.99 (0.75, 1.30)
Pod vegetables	132	1.16 (0.64, 2.12)	1.77 (0.91, 3.44)	139	0.72 (0.37, 1.41)	1.06 (0.47, 2.36)	171	0.92 (0.59, 1.45)	1.39 (0.82, 2.36)
Stalk & root vegetables	132	0.72 (0.41, 1.24)	0.89 (0.44, 1.79)	139	0.71 (0.42, 1.22)	0.97 (0.49, 1.90)	171	0.71 (0.49, 1.05)	0.93 (0.57, 1.51)
Parental history of CVD									
Total vegetables	63	0.98 (0.85, 1.13)	1.05 (0.89, 1.24)	60	0.95 (0.81, 1.11)	0.94 (0.78, 1.13)	123	0.97 (0.87, 1.07)	1.00 (0.88, 1.13)
Fresh vegetables	63	1.01 (0.86, 1.18)	1.12 (0.94, 1.34)	60	0.93 (0.78, 1.12)	0.99 (0.80, 1.22)	123	0.97 (0.87, 1.10)	1.06 (0.92, 1.21)
Allium	63	0.44 (0.06, 3.49)	0.56 (0.05, 5.81)	60	0.72 (0.10, 5.39)	0.55 (0.40, 7.67)	123	0.56 (0.13, 2.38)	0.57 (0.10, 3.25)
Brassicaceae	63	1.07 (0.78, 1.48)	1.23 (0.84, 1.80)	60	0.95 (0.66, 1.38)	1.01 (0.65, 1.57)	123	1.02 (0.80, 1.30)	1.12 (0.84, 1.50)
Fruit vegetables	63	0.92 (0.59, 1.44)	0.95 (0.53, 1.70)	60	0.82 (0.49, 1.37)	1.05 (0.60, 1.84)	123	0.88 (0.62, 1.23)	1.00 (0.67, 1.49)
Pod vegetables	63	1.37 (0.61, 3.08)	1.68 (0.74, 3.83)	60	0.89 (0.33, 2.39)	1.01 (0.29, 3.55)	123	1.14 (0.60, 2.15)	1.38 (0.64, 2.97)
Stalk & root vegetables	63	0.99 (0.49, 2.01)	1.23 (0.50, 3.07)	60	0.79 (0.36, 1.77)	1.13 (0.44, 2.92)	123	0.90 (0.53, 1.53)	1.19 (0.62, 2.31)
NO **Parental history of CVD**									
Total vegetables	80	0.93 (0.81, 1.07)	1.01 (0.86, 1.18)	93	0.85 (0.74, 0.98)	0.88 (0.75, 1.04)	173	0.89 (0.80, 0.98)	0.94 (0.84, 1.06)
Fresh vegetables	80	0.94 (0.80, 1.09)	1.03 (0.87, 1.23)	93	0.84 (0.72, 0.99)	0.86 (0.71, 1.05)	173	0.89 (0.79, 0.99)	0.95 (0.83, 1.08)
Allium	80	0.19 (0.02, 1.65)	0.28 (0.02, 3.15)	93	0.47 (0.09, 2.50)	1.08 (0.14, 8.41)	173	0.32 (0.09, 1.22)	0.57 (0.12, 2.74)
Brassicaceae	80	0.96 (0.70, 1.32)	1.01 (0.69, 1.47)	93	0.76 (0.54, 1.08)	0.80 (0.52, 1.24)	173	0.85 (0.68, 1.08)	0.90 (0.68, 1.21)
Fruit vegetables	80	0.80 (0.51, 1.26)	1.07 (0.67, 1.71)	93	0.72 (0.47, 1.12)	0.98 (0.59, 1.60)	173	0.76 (0.55, 1.04)	1.02 (0.73, 1.44)
Pod vegetables	80	1.16 (0.53, 2.53)	1.63 (0.69, 3.86)	93	0.60 (0.26, 1.41)	1.16 (0.44, 3.06)	173	0.84 (0.47, 1.50)	1.38 (0.72, 2.65)
Stalk & root vegetables	80	0.60 (0.28, 1.29)	0.64 (0.24, 1.73)	93	0.55 (0.27, 1.12)	0.70 (0.27, 1.83)	173	0.57 (0.34, 0.96)	0.67 (0.33, 1.33)

[a] Cases apply to fully-adjusted models

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

Table B.1 Total fruit intake, fruit subgroup intake and risk of myocardial infarction, acute coronary syndrome, chronic coronary event, total coronary heart disease, total stroke and total cardiovascular disease incidence in postmenopausal women (expressed as HR and 95% CI)

Postmenopausal Women	**Myocardial Infarction**, n = 52		**Acute Coronary Syndrome**, n = 82		**Chronic Coronary Event**, n = 113	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.97 (0.92, 1.02)	0.99 (0.90, 1.09)	1.00 (0.96, 1.03)	1.04 (0.98, 1.11)	0.97 (0.94, 1.01)	0.99 (0.93, 1.05)
Fresh fruit	0.95 (0.89, 1.02)	0.99 (0.88, 1.11)	0.99 (0.94, 1.04)	1.06 (0.98, 1.14)	0.98 (0.94, 1.02)	1.00 (0.93, 1.07)
Fresh fruit and juice	0.97 (0.92, 1.02)	0.99 (0.90, 1.09)	0.99 (0.96, 1.03)	1.04 (0.97, 1.11)	0.97 (0.94, 1.01)	0.99 (0.93, 1.06)
Fresh and dried fruit	0.95 (0.90, 1.02)	0.99 (0.89, 1.11)	0.99 (0.95, 1.04)	1.06 (0.99, 1.14)	0.98 (0.94, 1.02)	0.99 (0.92, 1.06)
Total dried fruit *(25 g/day)*	1.03 (0.89, 1.18)	1.05 (0.83, 1.33)	1.03 (0.93, 1.15)	1.09 (0.93, 1.28)	0.94 (0.82, 1.07)	0.75 (0.55, 1.03)
Fruit juice *(125 g/day)*	1.00 (0.84, 1.18)	0.96 (0.70, 1.33)	1.02 (0.90, 1.17)	0.96 (0.75, 1.24)	0.90 (0.79, 1.03)	0.96 (0.78, 1.18)
Total citrus	0.96 (0.85, 1.09)	0.97 (0.77, 1.22)	0.98 (0.89, 1.08)	0.92 (0.77, 1.11)	0.92 (0.84, 1.01)	0.94 (0.81, 1.10)
Citrus fruit	0.89 (0.68, 1.16)	0.86 (0.51, 1.43)	0.95 (0.78, 1.16)	0.83 (0.57, 1.23)	0.90 (0.75, 1.08)	0.89 (0.65, 1.23)
Orange Juice *(250 g/day)*	0.94 (0.58, 1.52)	1.00 (0.43, 2.32)	0.97 (0.66, 1.42)	0.84 (0.42, 1.69)	0.76 (0.53, 1.10)	0.86 (0.48, 1.54)
Berries	0.32 (0.11, 0.95)	0.76 (0.22, 2.64)	0.75 (0.44, 1.28)	1.14 (0.67, 1.94)	0.83 (0.55, 1.25)	0.32 (0.09, 1.07)
Pomes	0.91 (0.78, 1.05)	1.01 (0.80, 1.26)	0.98 (0.88, 1.08)	1.07 (0.91, 1.25)	0.96 (0.88, 1.05)	1.07 (0.93, 1.23)
Tropical fruit	0.87 (0.69, 1.09)	0.74 (0.47, 1.17)	0.89 (0.74, 1.06)	0.82 (0.59, 1.13)	0.91 (0.78, 1.06)	1.02 (0.79, 1.32)
Drupes	0.26 (0.04, 1.70)	1.66 (0.11, 25.6)	1.11 (0.37, 3.35)	2.74 (0.45, 16.4)	0.84 (0.30, 2.33)	0.31 (0.03, 2.99)
Grapes	1.01 (0.81, 1.26)	0.99 (0.63, 1.55)	1.04 (0.89, 1.23)	1.10 (0.84, 1.43)	1.07 (0.93, 1.22)	1.15 (0.92, 1.42)

(Table B.1 continued)

Postmenopausal Women	**Total Coronary Heart Disease**, n = 98		**Total Stroke**, n = 89		**Total Cardiovascular Disease**, n = 185	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.98 (0.95, 1.02)	1.02 (0.96, 1.08)	0.98 (0.94, 1.02)	1.02 (0.95, 1.09)	0.98 (0.96, 1.01)	1.02 (0.97, 1.07)
Fresh fruit	0.97 (0.93, 1.02)	1.04 (0.96, 1.12)	0.97 (0.93, 1.02)	1.03 (0.95, 1.11)	0.98 (0.94, 1.01)	1.03 (0.98, 1.09)
Fresh fruit and juice	0.98 (0.95, 1.02)	1.02 (0.95, 1.08)	0.98 (0.94, 1.02)	1.02 (0.95, 1.09)	0.98 (0.96, 1.01)	1.02 (0.97, 1.07)
Fresh and dried fruit	0.97 (0.93, 1.02)	1.04 (0.96, 1.11)	0.97 (0.93, 1.02)	1.02 (0.94, 1.11)	0.98 (0.94, 1.01)	1.03 (0.98, 1.09)
Total dried fruit *(25 g/day)*	0.99 (0.88, 1.11)	1.05 (0.88, 1.25)	0.94 (0.81, 1.09)	0.93 (0.71, 1.21)	0.97 (0.88, 1.06)	1.00 (0.86, 1.17)
Fruit juice *(125 g/day)*	1.02 (0.91, 1.15)	0.94 (0.74, 1.19)	1.00 (0.87, 1.14)	1.02 (0.81, 1.28)	1.01 (0.92, 1.10)	0.96 (0.81, 1.14)
Total citrus	0.97 (0.88, 1.06)	0.91 (0.76, 1.08)	0.96 (0.87, 1.06)	0.98 (0.82, 1.16)	0.97 (0.90, 1.04)	0.94 (0.83, 1.06)
Citrus fruit	0.87 (0.72, 1.06)	0.78 (0.54, 1.13)	0.88 (0.72, 1.09)	0.73 (0.49, 1.09)	0.89 (0.77, 1.02)	0.75 (0.57, 0.99)
Orange Juice *(250 g/day)*	1.00 (0.71, 1.41)	0.84 (0.44, 1.59)	0.97 (0.66, 1.41)	1.19 (0.67, 2.14)	0.98 (0.76, 1.27)	1.00 (0.65, 1.55)
Berries	0.77 (0.48, 1.24)	1.10 (0.65, 1.88)	0.99 (0.68, 1.46)	0.67 (0.26, 1.72)	0.89 (0.66, 1.20)	0.92 (0.57, 1.49)
Pomes	0.96 (0.87, 1.06)	1.06 (0.92, 1.23)	1.05 (0.96, 1.15)	1.24 (1.09, 1.40)	1.01 (0.94, 1.08)	1.16 (1.05, 1.27)
Tropical fruit	0.89 (0.75, 1.04)	0.80 (0.59, 1.09)	0.92 (0.78, 1.09)	1.01 (0.75, 1.36)	0.91 (0.80, 1.02)	0.91 (0.74, 1.13)
Drupes	0.78 (0.26, 2.37)	1.85 (0.29, 11.8)	0.51 (0.14, 1.89)	0.07 (0.00, 1.43)	0.69 (0.30, 1.61)	0.54 (0.10,, 2.89)
Grapes	1.02 (0.88, 1.20)	1.14 (0.91, 1.44)	0.77 (0.59, 1.01)	0.79 (0.49, 1.25)	0.94 (0.82, 1.07)	1.00 (0.81, 1.25)

[a] 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

Table B.2 Total fruit, fruit subgroup intake and risk of myocardial infarction, acute coronary syndrome, chronic coronary event, ischaemic stroke, total coronary heart disease, total stroke, total cardiovascular disease incidence in non-smoking women (expressed as HR and 95% CI)

Non-Smokers	**Myocardial Infarction**, n = 68		**Acute Coronary Syndrome**, n = 117		**Chronic Coronary Event**, n = 173	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.98 (0.94, 1.03), 0.435	0.98 (0.90, 1.06), 0.572	0.99 (0.96, 1.03), 0.802	1.02 (0.96, 1.08), 0.571	1.00 (0.97, 1.02), 0.847	1.00 (0.95, 1.05), 0.938
Fresh fruit	0.98 (0.92, 1.04), 0.469	0.98 (0.88, 1.08), 0.668	0.99 (0.95, 1.03), 0.574	1.02 (0.95, 1.09), 0.608	0.99 (0.96, 1.03), 0.665	1.01 (0.95, 1.07), 0.823
Fresh fruit and juice	0.98 (0.93, 1.02), 0.356	0.97 (0.89, 1.06), 0.490	0.99 (0.96, 1.03), 0.740	1.01 (0.95, 1.07), 0.689	1.00 (0.97, 1.02), 0.912	1.00 (0.95, 1.05), 0.991
Fresh and dried fruit	0.98 (0.93, 1.04), 0.578	0.98 (0.89, 1.09), 0.776	0.99 (0.95, 1.03), 0.646	1.02 (0.96, 1.09), 0.479	0.99 (0.96, 1.02), 0.601	1.00 (0.95, 1.06), 0.911
Total dried fruit *(25 g/day)*	1.09 (0.97, 1.22), 0.143	1.11 (0.94, 1.33), 0.223	1.05 (0.94, 1.16), 0.372	1.13 (1.00, 1.28), 0.055	0.94 (0.94, 1.06), 0.306	0.90 (0.73, 1.11), 0.320
Fruit juice *(125 g/day)*	0.94 (0.79, 1.11), 0.462	0.90 (0.67, 1.21), 0.487	1.02 (0.91, 1.14), 0.759	0.99 (0.81, 1.21), 0.954	1.03 (0.94, 1.12), 0.574	0.97 (0.82, 1.15), 0.714
Total citrus	0.98 (0.87, 1.09), 0.695	0.96 (0.79, 1.18), 0.717	1.00 (0.92, 1.08), 0.938	0.95 (0.82, 1.11), 0.513	0.99 (0.93, 1.06), 0.863	0.95 (0.83, 1.07), 0.391
Citrus fruit	1.03 (0.84, 1.27), 0.766	0.93 (0.61, 1.40), 0.717	1.03 (0.88, 1.20), 0.723	0.90 (0.66, 1.23), 0.500	0.95 (0.82, 1.09), 0.457	0.82 (0.62, 1.08), 0.153
Orange Juice *(250 g/day)*	0.85 (0.54, 1.35), 0.497	0.92 (0.43, 1.94), 0.825	0.95 (0.68, 1.32), 0.748	0.89 (0.50, 1.58), 0.699	1.03 (0.80, 1.33), 0.803	0.96 (0.61, 1.50), 0.852
Berries	0.56 (0.25, 1.23), 0.147	0.30 (0.05, 1.69), 0.173	0.54 (0.29, 0.99), 0.048	0.40 (0.13, 1.28), 0.125	0.94 (0.70, 1.26), 0.682	0.31 (0.11, 0.86), 0.025
Pomes	0.96 (0.84, 1.08), 0.498	1.05 (0.87, 1.27), 0.613	0.99 (0.90, 1.08), 0.776	1.05 (0.91, 1.21), 0.469	0.98 (0.91, 1.05), 0.547	1.09 (0.98, 1.22), 0.120
Tropical fruit	0.96 (0.79, 1.16), 0.673	0.86 (0.60, 1.25), 0.434	0.92 (0.80, 1.07), 0.287	0.94 (0.73, 1.21), 0.628	0.99 (0.89, 1.11), 0.931	1.16 (0.97, 1.40), 0.106
Drupes	0.70 (0.17, 2.79), 0.609	1.21 (0.10, 14.5), 0.883	0.98 (0.38, 2.52), 0.960	1.15 (0.20, 6.70), 0.877	1.02 (0.47, 2.18), 0.964	0.24 (0.04, 1.48), 0.125
Grapes	0.97 (0.78, 1.21), 0.807	0.84 (0.50, 1.41), 0.503	1.00 (0.85, 1.18), 0.984	1.04 (0.79, 1.37), 0.778	1.02 (0.90, 1.16), 0.711	1.09 (0.89, 1.34), 0.410

(Table B.2 continued)

Non-Smokers	**Ischaemic Stroke**, n = 61	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.95 (0.90, 1.00), 0.061	0.98 (0.90, 1.08), 0.749
Fresh fruit	0.93 (0.87, 1.00), 0.041	0.98 (0.88, 1.09), 0.747
Fresh fruit and juice	0.95 (0.90, 1.00). 0.064	0.99 (0.90, 1.08). 0.797
Fresh and dried fruit	0.93 (0.87, 1.00), 0.039	0.98 (0.88, 1.09), 0.693
Total dried fruit *(25 g/day)*	0.93 (0.76, 1.13), 0.458	0.87 (0.60, 1.26), 0.466
Fruit juice *(125 g/day)*	0.97 (0.81, 1.15), 0.703	1.00 (0.75, 1.33), 0.978
Total citrus	0.92 (0.80, 1.04), 0.190	0.98 (0.80, 1.21), 0.889
Citrus fruit	0.84 (0.64, 1.10), 0.203	0.81 (0.51, 1.30), 0.392
Orange Juice *(250 g/day)*	0.80 (0.49, 1.33), 0.399	1.14 (0.55, 2.37), 0.723
Berries	0.88 (0.50, 1.54), 0.647	0.40 (0.07, 2.16), 0.290
Pomes	0.98 (0.86, 1.11), 0.760	1.10 (0.90, 1.33), 0.345
Tropical fruit	0.70 (0.54, 0.90), 0.005	0.95 (0.65, 1.39), 0.807
Drupes	0.69 (0.15, 3.07), 0.627	5.78 (0.93, 35.9), 0.060
Grapes	0.83 (0.61, 1.13), 0.240	0.87 (0.52, 1.47), 0.614

(Table B.2 continued)

Non-Smokers	**Total Coronary Heart Disease**, n = 132		**Total Stroke**, n = 126		**Total Cardiovascular Disease**, n = 256	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.99 (0.96, 1.02), 0.564	1.01 (0.95, 1.06), 0.831	0.98 (0.94, 1.01), 0.174	1.01 (0.96, 1.07), 0.604	0.98 (0.96, 1.01), 0.217	1.01 (0.97, 1.05), 0.592
Fresh fruit	0.98 (0.95, 1.02), 0.437	1.01 (0.94, 1.08), 0.785	0.97 (0.93, 1.01), 0.134	1.01 (0.94, 1.08), 0.825	0.98 (0.95, 1.01), 0.142	1.01 (0.96, 1.06), 0.659
Fresh fruit and juice	0.99 (0.96, 1.02), 0.562	1.00 (0.95, 1.06), 0.923	0.98 (0.94, 1.01), 0.181	1.02 (0.96, 1.08), 0.563	0.98 (0.96, 1.01), 0.223	1.01 (0.97, 1.05), 0.624
Fresh and dried fruit	0.98 (0.95,, 1.02), 0.443	1.01 (0.95, 1.08), 0.683	0.97 (0.93, 1.01), 0.129	1.00 (0.94, 1.08), 0.874	0.98 (0.95, 1.01), 0.139	1.01 (0.96, 1.06), 0.619
Total dried fruit *(25 g/day)*	0.99 (0.89, 1.11), 0.918	1.10 (0.95, 1.26), 0.189	0.96 (0.85, 1.09), 0.557	0.94 (0.75, 1.18), 0.609	0.98 (0.90, 1.06), 0.621	1.04 (0.92, 1.17), 0.555
Fruit juice *(125 g/day)*	1.01 (0.91, 1.12), 0.883	0.97 (0.80, 1.18), 0.785	0.99 (0.88, 1.11), 0.825	1.08 (0.90, 1.29), 0.409	1.00 (0.92, 1.08), 0.996	1.02 (0.89, 1.16), 0.801
Total citrus	0.98 (0.91, 1.06), 0.647	0.95 (0.82, 1.09), 0.466	0.96 (0.88, 1.04), 0.344	1.01 (0.88, 1.16), 0.908	0.97 (0.92, 1.03), 0.402	0.98 (0.88, 1.08), 0.654
Citrus fruit	0.97 (0.83, 1.14), 0.729	0.88 (0.65, 1.18), 0.396	0.88 (0.73, 1.05), 0.162	0.81 (0.59, 1.11), 0.197	0.93 (0.83, 1.05), 0.266	0.84 (0.68, 1.05), 0.131
Orange Juice *(250 g/day)*	0.95 (0.70, 1.28), 0.722	0.90 (0.53, 1.54), 0.710	0.95 (0.69, 1.31), 0.763	1.26 (0.78, 2.03), 0.347	0.96 (0.77, 1.20), 0.731	1.07 (0.75, 1.54), 0.703
Berries	0.62 (0.37, 1.04), 0.069	0.48 (0.17, 1.34), 0.163	0.88 (0.60, 1.30), 0.531	0.73 (0.33, 1.62), 0.435	0.76 (0.55, 1.04), 0.083	0.59 (0.31, 1.14), 0.116
Pomes	0.99 (0.91, 1.07). 0.757	1.06 (0.93, 1.21). 0.391	1.02 (0.94, 1.11), 0.635	1.15 (1.02, 1.30), 0.027	1.00 (0.95, 1.06), 0.877	1.11 (1.01, 1.21), 0.024
Tropical fruit	0.95 (0.83, 1.08), 0.442	0.91 (0.71, 1.17), 0.462	0.91 (0.78, 1.05), 0.185	1.07 (0.85, 1.37), 0.550	0.93 (0.85, 1.03), 0.178	1.00 (0.84, 1.19), 1.000
Drupes	0.73 (0.28, 1.89). 0.522	1.03 (0.18, 5.80). 0.977	0.56 (0.19, 1.63), 0.287	0.87 (0.13, 5.82), 0.890	0.67 (0.33, 1.37), 0.275	0.93 (0.26, 3.37), 0.913
Grapes	1.03 (0.90, 1.18), 0.652	1.07 (0.83, 1.37), 0.593	0.77 (0.61, 0.98), 0.033	0.75 (0.49, 1.14), 0.175	0.93 (0.83, 1.05), 0.275	0.93 (0.74, 1.16), 0.518

[a] 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

Table B.3 Total fruit, fruit subgroup intake and risk of chronic coronary events, total stroke and total cardiovascular disease in hypertensive women (expressed as HR and 95% CI)

Hypertensives	**Chronic Coronary Event**, n = 54		**Total Stroke**, n = 51		**Total Cardiovascular Disease**, n = 91	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	1.01 (0.97, 1.06), 0.491	1.00 (0.91, 1.09), 0.970	0.99 (0.94, 1.05), 0.879	1.05 (0.98, 1.13), 0.144	1.00 (0.96, 1.03), 0.915	1.04 (0.98, 1.11). 0.142
Fresh fruit	1.01 (0.96, 1.07), 0.602	1.01 (0.91, 1.12), 0.838	0.99 (0.92, 1.06), 0.756	1.04 (0.95, 1.14), 0.363	0.99 (0.95, 1.04), 0.743	1.04 (0.97, 1.11), 0.250
Fresh fruit and juice	1.02 (0.98, 1.06), 0.407	1.01 (0.92, 1.10), 0.849	1.00 (0.94, 1.05), 0.923	1.05 (0.98, 1.14), 0.148	1.00 (0.96, 1.03), 0.852	1.04 (0.98, 1.10), 0.206
Fresh and dried fruit	1.01 (0.96, 1.06), 0.718	1.00 (0.90, 1.11), 0.976	0.99 (0.92, 1.05), 0.710	1.04 (0.95, 1.15), 0.350	0.99 (0.95, 1.04), 0.818	1.05 (0.98, 1.12), 0.167
Total dried fruit *(25 g/day)*	0.83 (0.65, 1.06), 0.135	0.57 (0.31, 1.03), 0.063	0.93 (0.73, 1.17), 0.528	1.05 (0.79, 1.39), 0.735	1.05 (0.94, 1.17), 0.387	1.25 (1.06, 1.48), 0.008
Fruit juice *(125 g/day)*	1.07 (0.92, 1.23), 0.371	1.00 (0.74, 1.36), 0.979	1.04 (0.86, 1.25), 0.702	1.17 (0.94, 1.45), 0.152	1.01 (0.89, 1.16), 0.838	1.06 (0.86, 1.31), 0.576
Total citrus	0.98 (0.87, 1.10), 0.746	0.93 (0.74, 1.15), 0.501	1.00 (0.88, 1.15), 0.938	1.07 (0.89, 1.29), 0.461	0.99 (0.90, 1.09), 0.901	0.98 (0.83, 1.15), 0.771
Citrus fruit	0.99 (0.79, 1.24), 0.921	0.79 (0.48, 1.29), 0.349	0.95 (0.72, 1.26), 0.746	0.84 (0.52, 1.34), 0.460	0.98 (0.81, 1.18), 0.848	0.81 (0.56, 1.16), 0.248
Orange Juice *(250 g/day)*	0.92 (0.59, 1.45), 0.732	0.90 (0.40, 1.99), 0.791	1.09 (0.64, 1.84), 0.753	1.49 (0.83, 2.68), 0.176	0.99 (0.68, 1.44), 0.974	1.10 (0.63, 1.92), 0.725
Berries	1.04 (0.67, 1.61), 0.859	0.30 (0.04, 1.97), 0.208	0.82 (0.40, 1.69), 0.594	0.87 (0.22, 3.41), 0.838	0.88 (0.56, 1.39), 0.587	1.27 (0.58, 2.79), 0.547
Pomes	0.98 (0.87, 1.11), 0.787	1.08 (0.88, 1.33), 0.445	1.07 (0.94, 1.21), 0.295	1.21 (1.04, 1.42), 0.014	1.00 (0.91, 1.11), 0.957	1.15 (1.00, 1.31), 0.047
Tropical fruit	1.09 (0.92, 1.28), 0.323	1.39 (1.04, 1.87), 0.027	1.04 (0.84, 1.29), 0.721	1.13 (0.82, 1.56), 0.451	1.03 (0.89, 1.20), 0.675	1.07 (0.84, 1.38), 0.573
Drupes	0.98 (0.25, 3.82), 0.981	0.35 (0.02, 7.32), 0.501	0.26 (0.03, 2.14), 0.209	0.17 (0.00, 5.97), 0.333	0.63 (0.18, 2.18), 0.470	1.32 (0.19, 9.15), 0.779
Grapes	1.10 (0.92, 1.30), 0.294	0.96 (0.56, 1.63), 0.874	0.82 (0.57, 1.19), 0.302	0.82 (0.45, 1.49), 0.523	0.97 (0.80, 1.16), 0.740	0.80 (0.51, 1.26), 0.343

Table B.4 Total fruit, fruit subgroup and risk of myocardial infarction, acute coronary syndrome, chronic coronary event, total coronary heart disease, total stroke and total cardiovascular disease in normotensive women (expressed as HR and 95% CI)

Non-Hypertensives	**Myocardial Infarction**, n = 57		**Acute Coronary Syndrome**, n = 101		**Chronic Coronary Event**, n = 139	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.97 (0.93, 1.02), 0.306	0.94 (0.85, 1.04), 0.258	0.99 (0.96, 1.03), 0.720	1.02 (0.96, 1.08), 0.571	0.98 (0.95,, 1.01), 0.207	1.00 (0.94, 1.05), 0.903
Fresh fruit	0.95 (0.89, 1.02), 0.162	0.91 (0.80, 1.04), 0.186	0.98 (0.94, 1.03), 0.474	1.02 (0.94, 1.10), 0.593	0.97 (0.93, 1.01), 0.159	1.01 (0.94, 1.08), 0.769
Fresh fruit and juice	0.97 (0.93, 1.02), 0.312	0.95 (0.86, 1.05), 0.306	0.99 (0.96, 1.03), 0.754	1.02 (0.96, 1.08), 0.554	0.98 (0.95, 1.01), 0.209	1.00 (0.94, 1.05), 0.916
Fresh and dried fruit	0.96 (0.90, 1.02), 0.160	0.91 (0.80, 1.03), 0.148	0.98 (0.94, 1.03), 0.448	1.02 (0.95, 1.10), 0.613	0.97 (0.93, 1.01), 0.158	1.01 (0.95, 1.07), 0.791
Total dried fruit *(25 g/day)*	0.96 (0.79, 1.16), 0.661	0.68 (0.41, 1.13), 0.134	0.95 (0.82, 1.11), 0.535	0.98 (0.78, 1.24), 0.891	0.97 (0.87, 1.10), 0.673	0.98 (0.80, 1.20), 0.843
Fruit juice *(125 g/day)*	1.02 (0.88, 1.19), 0.762	1.02 (0.76, 1.36), 0.892	1.04 (0.92, 1.17), 0.538	1.03 (0.84, 1.27), 0.753	0.99 (0.89, 1.10), 0.821	0.93 (0.76, 1.13), 0.466
Total citrus	1.00 (0.89, 1.12), 0.969	1.00 (0.80, 1.25), 0.986	1.00 (0.92, 1.09), 0.971	0.98 (0.84, 1.15), 0.832	0.99 (0.91, 1.06), 0.753	0.95 (0.83, 1.10), 0.507
Citrus fruit	0.99 (0.78, 1.25), 0.910	0.81 (0.47, 1.37), 0.428	0.98 (0.82, 1.18), 0.875	0.89 (0.63, 1.26), 0.520	0.93 (0.79, 1.09), 0.379	0.87 (0.64, 1.17), 0.363
Orange Juice *(250 g/day)*	1.03 (0.66, 1.59), 0.905	1.20 (0.56, 2.56), 0.632	1.02 (0.73, 1.44), 0.887	1.04 (0.58, 1.87), 0.897	1.02 (0.77, 1.36), 0.882	0.93 (0.56, 1.56), 0.794
Berries	0.40 (0.15, 1.09), 0.073	0.38 (0.06, 2.52), 0.316	0.72 (0.43, 1.23), 0.232	0.97 (0.53, 1.76), 0.914	0.82 (0.56, 1.21), 0.328	0.35 (0.11, 1.05), 0.061
Pomes	0.89 (0.77, 1.03), 0.115	1.03 (0.82, 1.29), 0.791	0.96 (0.87, 1.07), 0.498	1.08 (0.92, 1.26), 0.333	0.94 (0.86, 1.02), 0.156	1.06 (0.92, 1.21), 0.415
Tropical fruit	0.88 (0.71, 1.09), 0.258	0.69 (0.43, 1.11), 0.124	0.89 (0.76, 1.05), 0.189	0.85 (0.63, 1.15), 0.298	0.92 (0.80, 1.05), 0.230	1.05 (0.83, 1.31), 0.686
Drupes	0.33 (0.06, 1.80), 0.200	0.28 (0.01, 10.7), 0.494	0.90 (0.32, 2.54), 0.838	1.01 (0.14, 7.34), 0.993	0.89 (0.37, 2.14), 0.795	0.19 (0.02, 1.54), 0.121
Grapes	0.98 (0.77, 1.25), 0.862	1.04 (0.69, 1.56), 0.844	1.03 (0.87, 1.22), 0.693	1.10 (0.86, 1.41), 0.450	0.98 (0.84, 1.15), 0.859	1.22 (1.02, 1.46), 0.028

(Table B.4 continued)

Non-Hypertensives	**Total Coronary Heart Disease**, n = 112		**Total Stroke**, n = 91		**Total Cardiovascular Disease**, n = 200	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.98 (0.95, 1.01), 0.284	1.01 (0.95, 1.07), 0.827	0.95 (0.92, 0.99), 0.025	0.97 (0.90, 1.04), 0.410	0.97 (0.95, 1.00), 0.036	0.99 (0.94, 1.04), 0.736
Fresh fruit	0.97 (0.93, 1.01), 0.150	1.01 (0.94, 1.09), 0.686	0.94 (0.90, 0.99), 0.029	0.96 (0.87, 1.06), 0.443	0.96 (0.93, 0.99), 0.021	1.00 (0.94, 1.06), 0.941
Fresh fruit and juice	0.98 (0.95, 1.02), 0.333	1.01 (0.95, 1.07), 0.777	0.95 (0.92, 0.99), 0.026	0.97 (0.90, 1.05), 0.455	0.97 (0.95, 1.00), 0.044	0.99 (0.95, 1.04), 0.811
Fresh and dried fruit	0.97 (0.92, 1.01), 0.121	1.01 (0.94, 1.09), 0.746	0.95 (0.90, 0.99), 0.027	0.96 (0.87, 1.05), 0.390	0.96 (0.93, 0.99), 0.016	0.99 (0.94, 1.05), 0.844
Total dried fruit *(25 g/day)*	0.88 (0.75, 1.04), 0.135	0.92 (0.71, 1.19), 0.529	0.93 (0.80, 1.09), 0.372	0.85 (0.61, 1.17), 0.314	0.91 (0.82, 1.02), 0.110	0.89 (0.72, 1.09), 0.263
Fruit juice *(125 g/day)*	1.03 (0.91, 1.15), 0.632	0.99 (0.80, 1.22), 0.918	0.93 (0.81, 1.07), 0.328	0.97 (0.76, 1.23), 0.812	0.99 (0.90, 1.08), 0.787	0.97 (0.82, 1.14), 0.711
Total citrus	0.98 (0.90, 1.07), 0.650	0.96 (0.82, 1.12), 0.628	0.91 (0.83, 1.01), 0.084	0.94 (0.79, 1.13), 0.540	0.95 (0.89, 1.02), 0.162	0.95 (0.84, 1.07), 0.438
Citrus fruit	0.92 (0.77, 1.10), 0.366	0.88 (0.63, 1.23), 0.458	0.82 (0.66, 1.02), 0.071	0.84 (0.56, 1.24), 0.383	0.89 (0.77, 1.02), 0.087	0.86 (0.67, 1.11), 0.259
Orange Juice *(250 g/day)*	1.00 (0.72, 1.37), 0.994	0.96 (0.54, 1.71), 0.887	0.82 (0.56, 1.19). 0.298	0.93 (0.48, 1.80), 0.825	0.92 (0.71, 1.17). 0.496	0.94 (0.61, 1.47), 0.794
Berries	0.67 (0.40, 1.13), 0.137	0.92 (0.49, 1.71), 0.783	0.93 (0.62, 1.39), 0.722	0.96 (0.48, 1.94), 0.917	0.81 (0.59, 1.12), 0.201	0.93 (0.58, 1.50), 0.777
Pomes	0.96 (0.87, 1.06), 0.408	1.09 (0.94, 1.26), 0.239	0.95 (0.86, 1.05), 0.353	0.99 (0.82, 1.20), 0.915	0.96 (0.90, 1.03), 0.295	1.06 (0.94, 1.19), 0.358
Tropical fruit	0.87 (0.74, 1.01), 0.077	0.82 (0.61, 1.10), 0.190	0.85 (0.71, 1.00), 0.058	0.94 (0.68, 1.30), 0.715	0.86 (0.77, 0.97), 0.013	0.89 (0.71, 1.10), 0.284
Drupes	0.62 (0.22, 1.80), 0.382	0.97 (0.14, 6.78), 0.973	0.90 (0.31, 2.58), 0.843	5.09 (0.89, 29.2), 0.068	0.79 (0.38, 1.66), 0.537	2.11 (0.56, 7.92), 0.267
Grapes	1.02 (0.87, 1.19), 0.835	1.12 (0.89, 1.41), 0.347	0.75 (0.57, 0.99), 0.045	0.75 (0.44, 1.27), 0.278	0.92 (0.80, 1.06), 0.268	1.00 (0.79, 1.25), 0.978

[a] 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

Table B.5 Total fruit, fruit subgroup and risk myocardial infarction, acute coronary syndrome, chronic coronary event, ischaemic stroke, total coronary heart disease, total stroke and total cardiovascular disease in non-obese women (expressed as HR and 95% CI)

Non-Obese	**Myocardial Infarction**, n = 70		**Acute Coronary Syndrome**, n = 119		**Chronic Coronary Event**, n = 174	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.97 (0.93, 1.02), 0.219	0.95 (0.87, 1.04), 0.318	0.99 (0.96, 1.03), 0.724	1.02 (0.97, 1.08), 0.427	0.99 (0.96, 1.02), 0.527	0.99 (0.95, 1.04), 0.842
Fresh fruit	0.96 (0.90, 1.02), 0.170	0.96 (0.86, 1.07), 0.436	0.98 (0.94, 1.02), 0.403	1.04 (0.97, 1.11), 0.273	0.99 (0.95, 1.02), 0.453	1.01 (0.95, 1.07), 0.692
Fresh fruit and juice	0.97 (0.92, 1.02), 0.206	0.96 (0.87, 1.05), 0.347	0.99 (0.96, 1.03), 0.724	1.02 (0.97, 1.08), 0.428	0.99 (0.96, 1.02), 0.564	1.00 (0.95, 1.05), 0.905
Fresh and dried fruit	0.96 (0.91, 1.02), 0.185	0.95 (0.86, 1.06), 0.394	0.98 (0.94, 1.02), 0.411	1.04 (0.97, 1.11), 0.276	0.99 (0.95, 1.02), 0.417	1.01 (0.95, 1.07), 0.773
Total dried fruit *(25 g/day)*	1.01 (0.87, 1.16), 0.933	0.86 (0.60, 1.23), 0.407	0.99 (0.88, 1.12), 0.925	1.02 (0.83, 1.24), 0.864	0.96 (0.86, 1.07), 0.431	0.90 (0.73, 1.12), 0.356
Fruit juice *(125 g/day)*	0.98 (0.84, 1.14), 0.765	0.91 (0.68, 1.22), 0.541	1.04 (0.94, 1.16), 0.444	0.97 (0.79, 1.20), 0.810	1.00 (0.91, 1.10), 0.926	0.92 (0.77, 1.10), 0.343
Total citrus	0.99 (0.89, 1.10), 0.910	0.96 (0.78, 1.17), 0.679	1.00 (0.92, 1.08), 0.994	0.92 (0.79, 1.08), 0.301	0.99 (0.92, 1.06), 0.703	0.92 (0.81, 1.05), 0.214
Citrus fruit	1.02 (0.83, 1.25), 0.878	0.87 (0.57, 1.35), 0.545	0.99 (0.84, 1.17), 0.918	0.87 (0.64, 1.18), 0.373	0.96 (0.83, 1.10), 0.555	0.84 (0.64, 1.09), 0.186
Orange Juice *(250 g/day)*	0.95 (0.62, 1.45), 0.812	0.95 (0.45, 2.00), 0.892	1.01 (0.73, 1.39), 0.956	0.81 (0.45, 1.46), 0.482	0.98 (0.75, 1.29), 0.914	0.84 (0.52, 1.36), 0.486
Berries	0.48 (0.21, 1.12), 0.091	0.33 (0.06, 1.84), 0.207	0.74 (0.45, 1.19), 0.213	0.92 (0.51, 1.68), 0.797	0.82 (0.57, 1.18), 0.284	0.28 (0.10, 0.79), 0.017
Pomes	0.88 (0.77, 1.01), 0.066	1.02 (0.82, 1.26), 0.851	0.96 (0.87, 1.05), 0.367	1.09 (0.94, 1.25), 0.242	0.96 (0.88, 1.04), 0.293	1.08 (0.96, 1.22), 0.181
Tropical fruit	0.88 (0.72, 1.07), 0.201	0.87 (0.60, 1.27), 0.470	0.90 (0.78, 1.05), 0.185	0.94 (0.73, 1.22), 0.651	0.98 (0.87, 1.10), 0.770	1.15 (0.96, 1.39), 0.129
Drupes	0.64 (0.16, 2.52), 0.524	1.44 (0.12, 16.6), 0.771	1.01 (0.40, 2.57), 0.983	1.91 (0.40, 8.97), 0.414	1.03 (0.47, 2.25), 0.940	0.17 (0.03, 1.07), 0.060
Grapes	0.99 (0.80, 1.22), 0.918	0.99 (0.64, 1.52), 0.958	1.02 (0.87, 1.19), 0.821	1.10 (0.85, 1.41), 0.466	1.03 (0.90, 1.17), 0.677	1.17 (0.97, 1.41), 0.098

(Table B.5 continued)

Non-Obese	**Ischaemic Stroke**, n = 63	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.94 (0.89, 0.99), 0.024	0.98 (0.89, 1.07), 0.670
Fresh fruit	0.91 (0.85, 0.98), 0.012	0.97 (0.87, 1.09), 0.670
Fresh fruit and juice	0.94 (0.89, 0.99), 0.025	0.98 (0.89, 1.08), 0.709
Fresh and dried fruit	0.91 (0.85, 0.98), 0.012	0.97 (0.87, 1.09), 0.625
Total dried fruit *(25 g/day)*	0.94 (0.77, 1.13), 0.494	0.88 (0.61, 1.28), 0.515
Fruit juice *(125 g/day)*	0.96 (0.81, 1.15), 0.693	0.99 (0.74, 1.33), 0.970
Total citrus	0.90 (0.78, 1.03), 0.120	1.02 (0.84, 1.25), 0.808
Citrus fruit	0.81 (0.61, 1.08), 0.148	0.91 (0.58, 1.41), 0.666
Orange Juice *(250 g/day)*	0.76 (0.45, 1.27), 0.297	1.22 (0.60, 2.49), 0.575
Berries	0.78 (0.40, 1.49), 0.452	0.28 (0.04, 1.87), 0.188
Pomes	0.91 (0.79, 1.05), 0.211	1.09 (0.88, 1.34), 0.429
Tropical fruit	0.73 (0.56, 0.93), 0.013	0.89 (0.60, 1.33), 0.578
Drupes	0.70 (0.16, 3.15), 0.644	4.70 (0.74, 29.8), 0.101
Grapes	0.83 (0.61, 1.13), 0.246	0.91 (0.55, 1.51), 0.718

(Table B.5 continued)

Non-Obese	**Total Coronary Heart Disease**, n = 136		**Total Stroke**, n = 132		**Total Cardiovascular Disease**, n = 265	
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]	Age Adjusted	Fully-Adjusted [a]
Total fruit	0.98 (0.95, 1.01), 0.276	1.01 (0.95, 1.06), 0.802	0.96 (0.83, 1.00), 0.033	1.01 (0.95, 1.07), 0.800	0.97 (0.95, 1.00). 0.041	1.01 (0.97, 1.05), 0.677
Fresh fruit	0.97 (0.93, 1.01), 0.161	1.02 (0.96, 1.09), 0.500	0.95 (0.91, 0.99), 0.031	1.01 (0.94, 1.08), 0.835	0.96 (0.94, 0.99), 0.023	1.02 (0.97, 1.07), 0.440
Fresh fruit and juice	0.98 (0.95, 1.01), 0.296	1.01 (0.95, 1.07), 0.775	0.96 (0.93, 1.00), 0.037	1.01 (0.95, 1.07), 0.759	0.97 (0.95, 1.00), 0.048	1.01 (0.97, 1.05), 0.631
Fresh and dried fruit	0.97 (0.93, 1.01), 0.149	1.02 (0.96, 1.09), 0.533	0.95 (0.91, 0.99), 0.027	1.00 (0.94, 1.08), 0.882	0.96 (0.94, 0.99), 0.019	1.02 (0.97, 1.07), 0.491
Total dried fruit *(25 g/day)*	0.95 (0.84, 1.08), 0.441	0.96 (0.78, 1.19), 0.749	0.93 (0.81, 1.06), 0.295	0.94 (0.75, 1.18), 0.621	0.94 (0.86, 1.03), 0.226	0.95 (0.82, 1.11), 0.562
Fruit juice *(125 g/day)*	1.01 (0.91, 1.13), 0.798	0.94 (0.77, 1.15), 0.571	0.96 (0.85, 1.08), 0.492	1.03 (0.85, 1.24), 0.782	0.99 (0.91, 1.07), 0.828	0.98 (0.85, 1.12), 0.738
Total citrus	0.97 (0.90, 1.05), 0.486	0.92 (0.79, 1.06), 0.245	0.94 (0.86, 1.03), 0.206	1.00 (0.87, 1.15), 0.999	0.96 (0.91, 1.02), 0.206	0.96 (0.86, 1.06), 0.402
Citrus fruit	0.94 (0.80, 1.10), 0.432	0.85 (0.63, 1.15), 0.297	0.86 (0.71, 1.03), 0.112	0.85 (0.62, 1.16), 0.300	0.91 (0.80, 1.02), 0.121	0.85 (0.68, 1.05), 0.142
Orange Juice *(250 g/day)*	0.94 (0.69, 1.28), 0.705	0.80 (0.46, 1.40), 0.443	0.90 (0.65, 1.26), 0.560	1.18 (0.72, 1.93), 0.519	0.93 (0.74, 1.17), 0.546	0.98 (0.67, 1.42), 0.917
Berries	0.78 (0.51, 1.19), 0.244	0.93 (0.53, 1.64), 0.806	0.87 (0.58, 1.29), 0.489	0.86 (0.44, 1.69), 0.661	0.82 (0.62, 1.10), 0.198	0.89 (0.58, 1.39), 0.621
Pomes	0.96 (0.88, 1.04), 0.341	1.08 (0.95, 1.24), 0.237	0.98 (0.90, 1.08), 0.730	1.14 (1.00, 1.30), 0.050	0.98 (0.92, 1.04), 0.465	1.12 (1.02, 1.23), 0.019
Tropical fruit	0.89 (0.77, 1.02), 0.096	0.91 (0.71, 1.16), 0.448	0.90 (0.77, 1.04), 0.158	1.05 (0.83, 1.34), 0.668	0.90 (0.81, 1.00), 0.044	0.99 (0.83, 1.18), 0.910
Drupes	0.80 (0.31, 2.02), 0.633	1.65 (0.35, 7.69), 0.523	0.55 (0.18, 1.65), 0.289	1.40 (0.25, 7.66), 0.700	0.71 (0.35, 1.45), 0.352	1.53 (0.49, 4.83), 0.465
Grapes	0.99 (0.85, 1.16), 0.945	1.11 (0.88, 1.40), 0.372	0.71 (0.54, 0.93), 0.012	0.75 (0.49, 1.14), 0.181	0.89 (0.78, 1.02), 0.093	0.96 (0.77, 1.19), 0.723

[a] 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

Table C.1 Sensitivity analysis of total vegetable, coffee, tea intake and cardiovascular mortality risk by menopausal status, non-smokers, normotensive and non-obese participants (expressed as HR and 99% CI)

Intake (250 g/day)	CHD			Stroke			CVD		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Postmenopausal women									
Total coffee	132	0.97 (0.82, 1.14)	0.99 (0.82, 1.19)	139	0.93 (0.78, 1.10)	0.91 (0.75, 1.10)	271	0.95 (0.84, 1.07)	0.95 (0.83, 1.08)
Coffee (without decaff)	132	0.95 (0.79, 1.14)	0.95 (0.78, 1.17)	139	0.92 (0.77, 1.11)	0.89 (0.72, 1.10)	271	0.93 (0.82, 1.06)	0.92 (0.80, 1.07)
Decaffeinated coffee	132	1.03 (0.80, 1.33)	1.07 (0.82, 1.40)	139	0.99 (0.76, 1.28)	1.00 (0.75, 1.34)	271	1.01 (0.84, 1.21)	1.04 (0.85, 1.27)
Black tea	132	1.07 (0.99, 1.16)	1.04 (0.96, 1.14)	139	1.01 (0.93, 1.09)	1.04 (0.95, 1.13)	271	1.04 (0.98, 1.10)	1.04 (0.98, 1.11)
Non-smokers									
Total coffee	117	0.88 (0.73, 1.06)	0.90 (0.73, 1.11)	129	0.91 (0.77, 1.09)	0.89 (0.73, 1.09)	246	0.90 (0.79, 1.02)	0.89 (0.77, 1.03)
Coffee (without decaff)	117	0.86 (0.70, 1.06)	0.87 (0.69, 1.10)	129	0.88 (0.72, 1.08)	0.86 (0.68, 1.08)	246	0.87 (0.75, 1.01)	0.86 (0.73, 1.02)
Decaffeinated coffee	117	0.98 (0.73, 1.30)	1.01 (0.75, 1.37)	129	1.03 (0.79, 1.34)	1.03 (0.77, 1.37)	246	1.01 (0.83, 1.22)	1.02 (0.83, 1.26)
Black tea	117	1.06 (0.98, 1.15)	1.01 (0.92, 1.11)	129	1.01 (0.93, 1.09)	1.03 (0.94, 1.12)	246	1.03 (0.97, 1.10)	1.02 (0.96, 1.09)
No high blood pressure									
Total coffee	89	1.06 (0.87, 1.29)	1.06 (0.85, 1.30)	87	0.99 (0.81, 1.20)	0.97 (0.77, 1.21)	176	1.02 (0.89, 1.18)	1.01 (0.87, 1.18)
Coffee (without decaff)	89	1.04 (0.84, 1.29)	1.03 (0.82, 1.29)	87	1.01 (0.82, 1.26)	1.00 (0.79, 1.27)	176	1.03 (0.88, 1.20)	1.01 (0.86, 1.20)
Decaffeinated coffee	89	1.07 (0.79, 1.46)	1.07 (0.78, 1.48)	87	0.93 (0.65, 1.32)	0.92 (0.62, 1.35)	176	1.00 (0.79, 1.26)	1.00 (0.78, 1.28)
Black tea	89	0.99 (0.90, 1.10)	0.99 (0.88, 1.10)	87	1.01 (0.91, 1.11)	1.04 (0.94, 1.17)	176	1.00 (0.93, 1.07)	1.01 (0.94, 1.10)
Non-obese									
Total coffee	71	1.05 (0.84, 1.32)	1.08 (0.85, 1.38)	94	1.01 (0.82, 1.23)	1.01 (0.81, 1.26)	165	1.03 (0.88, 1.19)	1.04 (0.88, 1.22)
Coffee (without decaff)	71	0.98 (0.75, 1.27)	1.00 (0.75, 1.31)	94	1.03 (0.83, 1.28)	1.00 (0.79, 1.27)	165	1.01 (0.86, 1.19)	1.00 (0.83, 1.19)
Decaffeinated coffee	71	1.16 (0.84, 1.61)	1.20 (0.85, 1.70)	94	0.94 (0.66, 1.34)	1.02 (0.71, 1.45)	165	1.04 (0.82, 1.32)	1.10 (0.86, 1.41)
Black tea	71	1.04 (0.92, 1.16)	1.05 (0.93, 1.18)	94	0.98 (0.89, 1.08)	1.02 (0.92, 1.14)	165	1.00 (0.93, 1.08)	1.03 (0.95, 1.12)
WITH parental history of CVD									
Total coffee	63	0.99 (0.79, 1.25)	1.00 (0.77, 1.30)	60	0.89 (0.69, 1.16)	0.91 (0.68, 1.23)	123	0.95 (0.80, 1.13)	0.96 (0.79, 1.17)
Coffee (without decaff)	63	0.92 (0.71, 1.21)	0.91 (0.68, 1.23)	60	0.88 (0.65, 1.18)	0.84 (0.59, 1.18)	123	0.90 (0.74, 1.10)	0.88 (0.70, 1.10)
Decaffeinated coffee	63	1.12 (0.82, 1.54)	1.16 (0.83, 1.63)	60	0.98 (0.66, 1.45)	1.11 (0.75, 1.66)	123	1.06 (0.82, 1.36)	1.14 (0.88, 1.48)
Black tea	63	1.07 (0.92, 1.24)	1.01 (0.85, 1.19)	60	1.13 (0.97, 1.33)	1.15 (0.96, 1.37)	123	1.10 (0.98, 1.22)	1.07 (0.95, 1.21)
NO parental history of CVD									
Total coffee	80	0.99 (0.80, 1.23)	1.01 (0.80, 1.28)	93	0.94 (0.77, 1.15)	0.89 (0.70, 1.12)	173	0.96 (0.83, 1.11)	0.94 (0.80, 1.11)
Coffee (without decaff)	80	1.02 (0.81, 1.27)	1.02 (0.79, 1.30)	93	0.94 (0.76, 1.17)	0.91 (0.71, 1.16)	173	0.97 (0.83, 1.14)	0.96 (0.80, 1.14)
Decaffeinated coffee	80	0.94 (0.65, 1.37)	1.00 (0.68, 1.46)	93	0.97 (0.70, 1.35)	0.91 (0.62, 1.34)	173	0.96 (0.75, 1.23)	0.95 (0.73, 1.25)
Black tea	80	1.04 (0.91, 1.19)	1.04 (0.89, 1.20)	93	0.95 (0.84, 1.07)	0.96 (0.83, 1.10)	173	0.99 (0.90, 1.08)	0.99 (0.90, 1.10)

[a] Cases apply to fully-adjusted models

[b] Adjusted for age, BMI, physical activity, smoking status, socio-economic status, alcohol intake and tea intake when investigating coffee, and vice versa.

Appendix D Chapter 6 sensitivity analyses

Table D.1 Total fruit, total vegetable, fruit and vegetable subgroup intake and the odds of self-reported HBP incidence within obese and non-obese subpopulations

Intake (80 g/day)	Odds of high blood pressure (99% CI)		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Obese			
Total fruit & vegetable intake	81	1.00 (0.93, 1.07)	0.96 (0.88, 1.04)
Total fruit intake	81	1.00 (0.91, 1.11)	0.97 (0.86, 1.10)
Fresh fruit intake	81	1.00 (0.89, 1.12)	0.97 (0.84, 1.11)
Fresh fruit and juice intake	81	1.00 (0.91, 1.10)	0.97 (0.86, 1.09)
Fresh and dried fruit intake	81	1.00 (0.90, 1.13)	0.97 (0.85, 1.12)
Total dried fruit intake *(25 g/day)*	81	1.33 (0.83, 2.15)	1.21 (0.72, 2.03)
Fruit juice intake *(125 g/day)*	81	1.02 (0.71, 1.46)	0.95 (0.64, 1.41)
Total citrus intake	81	0.91 (0.70, 1.19)	0.92 (0.70, 1.22)
Citrus fruit intake	81	0.83 (0.45, 1.52)	0.89 (0.46, 1.72)
Orange Juice Intake *(250 g/day)*	81	0.77 (0.29, 2.09)	0.78 (0.28, 2.16)
Total berries intake	81	1.33 (0.61, 2.93)	0.75 (0.15, 3.68)
Total grapes intake	81	1.57 (1.04, 2.38)	1.75 (1.03, 2.99)
Total pomes intake	81	0.77 (0.56, 1.05)	0.73 (0.52, 1.03)
Total drupes intake	81	1.81 (0.12, 27.9)	1.85 (0.08, 41.7)
Total tropical intake	81	1.07 (0.74, 1.55)	1.06 (0.68, 1.66)
Total vegetable intake	81	0.97 (0.84, 1.13)	0.93 (0.77, 1.11)
Fresh vegetable intake	81	1.01 (0.85, 1.20)	1.01 (0.81, 1.25)
Allium intake	81	1.05 (0.16, 6.95)	1.43 (0.14, 14.9)
Brassicaceae intake	81	1.09 (0.75, 1.57)	1.16 (0.74, 1.82)
Fruit vegetable intake	81	0.93 (0.57, 1.49)	0.97 (0.57, 1.69)
Pod vegetable intake	81	1.18 (0.45, 3.04)	1.05 (0.32, 3.41)
Stalk/root vegetable intake	81	1.02 (0.45, 2.31)	0.93 (0.29, 2.97)
Non-obese			
Total fruit & vegetable intake	603	0.98 (0.96, 1.01)	0.98 (0.95, 1.01)
Total fruit intake	603	0.98 (0.95, 1.02)	1.00 (0.95, 1.04)
Fresh fruit intake	603	0.97 (0.92, 1.01)	0.99 (0.94, 1.04)
Fresh fruit and juice intake	603	0.98 (0.95, 1.02)	1.00 (0.95, 1.04)
Fresh and dried fruit intake	603	0.97 (0.92, 1.01)	0.99 (0.94, 1.04)
Total dried fruit intake *(25 g/day)*	603	0.98 (0.84, 1.14)	1.03 (0.88, 1.20)
Fruit juice intake *(125 g/day)*	603	1.03 (0.92, 1.16)	1.02 (0.90, 1.16)
Total citrus intake	603	1.03 (0.94, 1.11)	1.04 (0.96, 1.14)
Citrus fruit intake	603	1.03 (0.87, 1.22)	1.13 (0.94, 1.35)
Orange Juice Intake *(250 g/day)*	603	1.09 (0.80, 1.50)	1.07 (0.77, 1.49)
Total berries intake	603	0.85 (0.58, 1.26)	0.88 (0.59, 1.32)
Total grapes intake	603	0.99 (0.81, 1.20)	1.05 (0.86, 1.28)
Total pomes intake	603	0.90 (0.81, 1.00)	0.93 (0.83, 1.04)
Total drupes intake	603	0.75 (0.28, 1.96)	0.91 (0.30, 2.76)
Total tropical intake	603	0.97 (0.84, 1.13)	1.02 (0.86, 1.20)
Total vegetable intake	603	0.97 (0.92, 1.02)	0.95 (0.89, 1.01)
Fresh vegetable intake	603	0.96 (0.90, 1.02)	0.95 (0.88, 1.02)
Allium intake	603	0.81 (0.40, 1.63)	1.08 (0.47, 2.51)
Brassicaceae intake	603	0.95 (0.83, 1.09)	0.94 (0.80, 1.11)
Fruit vegetable intake	603	0.82 (0.69, 0.98)	0.81 (0.65, 1.00)
Pod vegetable intake	603	1.15 (0.83, 1.60)	1.29 (0.87, 1.93)
Stalk/root vegetable intake	603	0.88 (0.67, 1.16)	1.00 (0.71, 1.41)

[a] Cases apply to fully adjusted model only

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

Table D.2 Total fruit, total vegetable, fruit and vegetable subgroup intake and the odds of self-reported HBP incidence within pre-menopausal and post-menopausal subpopulations

Intake (80 g/day)	Odds of high blood pressure (99% CI)		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Postmenopausal			
Total fruit & vegetable intake	440	0.99 (0.96, 1.02)	0.98 (0.94, 1.01)
Total fruit intake	440	0.98 (0.94, 1.03)	0.99 (0.94, 1.04)
Fresh fruit intake	440	0.99 (0.93, 1.04)	1.00 (0.94, 1.06)
Fresh fruit and juice intake	440	0.98 (0.94, 1.03)	0.98 (0.94, 1.04)
Fresh and dried fruit intake	440	0.99 (0.94, 1.04)	1.00 (0.94, 1.06)
Total dried fruit intake *(25 g/day)*	440	1.02 (0.87, 1.19)	1.05 (0.89, 1.24)
Fruit juice intake *(125 g/day)*	440	0.95 (0.83, 1.10)	0.92 (0.79, 1.08)
Total citrus intake	440	0.98 (0.89, 1.08)	0.99 (0.89, 1.10)
Citrus fruit intake	440	1.03 (0.85, 1.26)	1.10 (0.89, 1.36)
Orange Juice Intake *(250 g/day)*	440	0.88 (0.59, 1.31)	0.84 (0.56, 1.28)
Total berries intake	440	0.84 (0.55, 1.29)	0.81 (0.51, 1.29)
Total grapes intake	440	1.08 (0.90, 1.29)	1.10 (0.91, 1.33)
Total pomes intake	440	0.91 (0.81, 1.02)	0.91 (0.79, 1.04)
Total drupes intake	440	1.19 (0.39, 3.64)	1.33 (0.36, 4.87)
Total tropical intake	440	1.05 (0.89, 1.24)	1.08 (0.89, 1.30)
Total vegetable intake	440	0.98 (0.92, 1.04)	0.96 (0.89, 1.03)
Fresh vegetable intake	440	0.98 (0.92, 1.05)	0.97 (0.89, 1.05)
Allium intake	440	1.09 (0.51, 2.36)	1.34(0.53, 3.40)
Brassicaceae intake	440	0.96 (0.83, 1.12)	0.93 (0.78, 1.12)
Fruit vegetable intake	440	0.89 (0.73, 1.09)	0.86 (0.67, 1.10)
Pod vegetable intake	440	1.32 (0.90, 1.93)	1.44 (0.90, 2.30)
Stalk/root vegetable intake	440	0.88 (0.64, 1.21)	0.94 (0.63, 1.41)
Premenopausal			
Total fruit & vegetable intake	244	0.97 (0.93, 1.02)	0.97 (0.92, 1.02)
Total fruit intake	244	0.98 (0.92, 1.04)	1.00 (0.93, 1.07)
Fresh fruit intake	244	0.94 (0.87, 1.01)	0.95 (0.88, 1.04)
Fresh fruit and juice intake	244	0.98 (0.93, 1.04)	1.00 (0.93, 1.07)
Fresh and dried fruit intake	244	0.94 (0.87, 1.01)	0.95 (0.88, 1.04)
Total dried fruit intake *(25 g/day)*	244	0.88 (0.66, 1.19)	0.95 (0.70, 1.29)
Fruit juice intake *(125 g/day)*	244	1.15 (0.98, 1.36)	1.16 (0.97, 1.30)
Total citrus intake	244	1.06 (0.93, 1.20)	1.11 (0.97, 1.26)
Citrus fruit intake	244	0.93 (0.70, 1.25)	1.11 (0.82, 1.51)
Orange Juice Intake *(250 g/day)*	244	1.36 (0.87, 2.14)	1.39 (0.87, 2.21)
Total berries intake	244	1.07 (0.58, 1.95)	1.05 (0.50, 2.21)
Total grapes intake	244	1.06 (0.74, 1.50)	1.20 (0.83, 1.73)
Total pomes intake	244	0.83 (0.70, 0.99)	0.86 (0.71, 1.04)
Total drupes intake	244	0.38 (0.07, 1.89)	0.73 (0.12, 4.42)
Total tropical intake	244	0.88 (0.69, 1.12)	0.95 (0.73, 1.24)
Total vegetable intake	244	0.94 (0.86, 1.02)	0.93 (0.83, 1.02)
Fresh vegetable intake	244	0.93 (0.84, 1.03)	0.93 (0.82, 1.05)
Allium intake	244	0.42 (0.12, 1.49)	0.71 (0.16, 3.10)
Brassicaceae intake	244	0.98 (0.78, 1.24)	1.03 (0.78, 1.35)
Fruit vegetable intake	244	0.72 (0.54, 0.96)	0.76 (0.54, 1.06)
Pod vegetable intake	244	0.90 (0.52, 1.57)	1.03 (0.53, 1.98)
Stalk/root vegetable intake	244	0.88 (0.55, 1.41)	1.10 (0.62, 1.93)

[a] Cases apply to fully adjusted model only

[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

Table D.3 Total fruit, total vegetable, fruit and vegetable subgroup intake and the odds of self-reported HBP incidence within subpopulations with and without parental history of CVD

Intake (80 g/day)	Odds of high blood pressure (99% CI)		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Parental history of CVD			
Total fruit & vegetable intake	383	1.00 (0.97, 1.04)	0.99 (0.95, 1.03)
Total fruit intake	383	1.01 (0.96, 1.06)	1.01 (0.96, 1.07)
Fresh fruit intake	383	0.99 (0.93, 1.05)	1.00 (0.93, 1.07)
Fresh fruit and juice intake	383	1.01 (0.96, 1.06)	1.01 (0.95, 1.07)
Fresh and dried fruit intake	383	0.99 (0.93, 1.05)	1.00 (0.93, 1.07)
Total dried fruit intake *(25 g/day)*	383	1.06 (0.89, 1.25)	1.09 (0.91, 1.30)
Fruit juice intake *(125 g/day)*	383	1.11 (0.95, 1.29)	1.08 (0.91, 1.27)
Total citrus intake	383	1.07 (0.96, 1.19)	1.09 (0.97, 1.21)
Citrus fruit intake	383	1.05 (0.84, 1.32)	1.15 (0.90, 1.46)
Orange Juice Intake *(250 g/day)*	383	1.29 (0.87, 1.92)	1.26 (0.84, 1.90)
Total berries intake	383	1.03 (0.66, 1.61)	0.92 (0.54, 1.58)
Total grapes intake	383	0.96 (0.70, 1.30)	0.94 (0.68, 1.30)
Total pomes intake	383	0.92 (0.80, 1.05)	0.92 (0.79, 1.08)
Total drupes intake	383	0.60 (0.15, 2.44)	0.52 (0.10, 2.80)
Total tropical intake	383	1.05 (0.87, 1.28)	1.08 (0.87, 1.35)
Total vegetable intake	383	1.00 (0.93, 1.07)	0.95 (0.87, 1.04)
Fresh vegetable intake	383	1.00 (0.92, 1.08)	0.94 (0.84, 1.04)
Allium intake	383	1.22 (0.47, 3.17)	1.45 (0.45, 4.67)
Brassicaceae intake	383	0.99 (0.82, 1.19)	0.91 (0.72, 1.14)
Fruit vegetable intake	383	0.91 (0.72, 1.15)	0.88 (0.66, 1.17)
Pod vegetable intake	383	1.30 (0.82, 2.07)	1.24 (0.69, 2.22)
Stalk/root vegetable intake	383	0.91 (0.62, 1.33)	0.80 (0.48, 1.33)
No parental history of CVD			
Total fruit & vegetable intake	300	0.97 (0.93, 1.00)	0.96 (0.92, 1.00)
Total fruit intake	300	0.96 (0.92, 1.01)	0.97 (0.92, 1.03)
Fresh fruit intake	300	0.95 (0.89, 1.01)	0.97 (0.91, 1.04)
Fresh fruit and juice intake	300	0.96 (0.92, 1.01)	0.97 (0.92, 1.03)
Fresh and dried fruit intake	300	0.95 (0.89, 1.01)	0.97 (0.91, 1.04)
Total dried fruit intake *(25 g/day)*	300	0.89 (0.71, 1.11)	0.94 (0.74, 1.20)
Fruit juice intake *(125 g/day)*	300	0.96 (0.82, 1.12)	0.96 (0.81, 1.14)
Total citrus intake	300	0.95 (0.85, 1.06)	0.97 (0.86, 1.10)
Citrus fruit intake	300	0.94 (0.74, 1.19)	1.05 (0.82, 1.35)
Orange Juice Intake *(250 g/day)*	300	0.84 (0.54, 1.31)	0.82 (0.51, 1.32)
Total berries intake	300	0.77 (0.44, 1.34)	0.82 (0.47, 1.45)
Total grapes intake	300	1.14 (0.95, 1.38)	1.23 (1.02, 1.49)
Total pomes intake	300	0.84 (0.73, 0.97)	0.87 (0.74, 1.01)
Total drupes intake	300	0.91 (0.28, 3.00)	1.57 (0.42, 5.89)
Total tropical intake	300	0.93 (0.77, 1.12)	0.98 (0.79, 1.21)
Total vegetable intake	300	0.94 (0.87, 1.01)	0.94 (0.86, 1.02)
Fresh vegetable intake	300	0.94 (0.87, 1.02)	0.96 (0.88, 1.06)
Allium intake	300	0.60 (0.24, 1.50)	0.87 (0.30, 2.53)
Brassicaceae intake	300	0.95 (0.80, 1.13)	1.02 (0.83, 1.25)
Fruit vegetable intake	300	0.76 (0.60, 0.95)	0.78 (0.59, 1.03)
Pod vegetable intake	300	1.04 (0.68, 1.58)	1.28 (0.77, 2.11)
Stalk/root vegetable intake	300	0.86 (0.60, 1.24)	1.18 (0.76, 1.82)

[a] Cases apply to fully adjusted model only

[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

Table D.4 Total fruit, total vegetable, fruit and vegetable subgroup intake and the odds of self-reported HBP incidence within non-smoking women

Intake (80 g/day)	Odds of high blood pressure (99% CI)		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Non-smokers			
Total fruit & vegetable intake	632	0.99 (0.96, 1.01)	0.97 (0.95, 1.00)
Total fruit intake	632	0.99 (0.95, 1.02)	0.99 (0.95, 1.03)
Fresh fruit intake	632	0.97 (0.93, 1.01)	0.98 (0.93, 1.03)
Fresh fruit and juice intake	632	0.99 (0.95, 1.02)	0.99 (0.95, 1.03)
Fresh and dried fruit intake	632	0.97 (0.93, 1.01)	0.98 (0.93, 1.03)
Total dried fruit intake *(25 g/day)*	632	0.99 (0.86, 1.14)	1.03 (0.89, 1.19)
Fruit juice intake *(125 g/day)*	632	1.05 (0.93, 1.17)	1.02 (0.90, 1.15)
Total citrus intake	632	1.02 (0.94, 1.11)	1.04 (0.95, 1.13)
Citrus fruit intake	632	0.99 (0.84, 1.18)	1.10 (0.92, 1.31)
Orange Juice Intake *(250 g/day)*	632	1.11 (0.82, 1.51)	1.07 (0.78, 1.48)
Total berries intake	632	0.93 (0.66, 1.31)	0.88 (0.60, 1.31)
Total grapes intake	632	1.08 (0.92, 1.28)	1.13 (0.95, 1.35)
Total pomes intake	632	0.88 (0.79, 0.97)	0.89 (0.79, 0.99)
Total drupes intake	632	0.82 (0.32, 2.07)	1.01 (0.35, 2.95)
Total tropical intake	632	1.00 (0.87, 1.15)	1.04 (0.89, 1.21)
Total vegetable intake	632	0.97 (0.92, 1.02)	0.95 (0.89, 1.01)
Fresh vegetable intake	632	0.97 (0.92, 1.03)	0.96 (0.89, 1.03)
Allium intake	632	0.91 (0.47, 1.78)	1.20 (0.54, 2.69)
Brassicaceae intake	632	0.98 (0.86, 1.11)	0.97 (0.83, 1.13)
Fruit vegetable intake	632	0.83 (0.70, 0.98)	0.81 (0.66, 0.99)
Pod vegetable intake	632	1.20 (0.88, 1.65)	1.32 (0.89, 1.94)
Stalk/root vegetable intake	632	0.90 (0.69, 1.19)	1.00 (0.71, 1.41)

[a] Cases apply to fully adjusted model only

[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

Appendix E Chapter 7 sensitivity analyses

Table E.1 Total black tea, coffee and coffee subgroup intake and the odds of self-reported HBP incidence stratified by coffee preference, obese/non-obese, smoking, menopausal status and parental history of CVD

Intake (250 g/day)	Odds of high blood pressure (95% or 99%* CI)		
	Cases [a]	Age Adjusted	Fully-Adjusted [b]
Coffee preference			
Regular coffee drinkers	277	0.98 (0.88, 1.08)	0.91 (0.81, 1.02)
Decaffeinated coffee drinkers	63	1.07 (0.86, 1.33)	1.03 (0.81, 1.31)
Obese*			
Total coffee	82	1.08 (0.88, 1.33)	0.99 (0.79, 1.25)
Regular coffee	82	1.10 (0.89, 1.38)	1.04 (0.82, 1.33)
Decaffeinated coffee	82	0.99 (0.71, 1.36)	0.90 (0.63, 1.29)
Black tea	82	0.98 (0.85, 1.12)	0.95 (0.81, 1.12)
Regular coffee drinkers	40	0.95 (0.67, 1.33)	0.87 (0.58, 1.30)
Non-obese*			
Total coffee	607	1.02 (0.94, 1.10)	0.98 (0.90, 1.07)
Regular coffee	607	1.00 (0.92, 1.09)	0.96 (0.87, 1.05)
Decaffeinated coffee	607	1.04 (0.92, 1.18)	1.03 (0.91, 1.18)
Black tea	607	1.00 (0.95, 1.06)	1.00 (0.94, 1.06)
Regular coffee drinkers	237	0.97 (0.85, 1.12)	0.90 (0.77, 1.06)
Non-smokers*			
Total coffee	637	1.05 (0.97, 1.13)	1.01 (0.93, 1.10)
Regular coffee	637	1.05 (0.96, 1.14)	1.01 (0.92, 1.10)
Decaffeinated coffee	637	1.03 (0.91, 1.16)	1.01 (0.89, 1.15)
Black tea	637	0.99 (0.94, 1.04)	0.99 (0.94, 1.05)
Regular coffee drinkers	255	1.00 (0.87, 1.15)	0.92 (0.79, 1.08)
Postmenopausal*			
Total coffee	442	1.01 (0.92, 1.11)	1.00 (0.90, 1.10)
Regular coffee	442	1.02 (0.92, 1.13)	1.00 (0.89, 1.12)
Decaffeinated coffee	442	1.00 (0.85, 1.17)	0.99 (0.84, 1.17)
Black tea	442	1.02 (0.96, 1.09)	1.02 (0.95, 1.09)
Regular coffee drinkers	194	1.01 (0.86, 1.18)	0.99 (0.82, 1.19)
Premenopausal*			
Total coffee	247	1.05 (0.94, 1.18)	0.98 (0.86, 1.11)
Regular coffee	247	1.02 (0.90, 1.16)	0.95 (0.83, 1.09)
Decaffeinated coffee	247	1.10 (0.92, 1.31)	1.05 (0.87, 1.26)
Black tea	247	0.96 (0.89, 1.04)	0.96 (0.88, 1.05)
Regular coffee drinkers	83	0.92 (0.74, 1.15)	0.79 (0.61, 1.02)
NO parental history of CVD*			
Total coffee	387	1.03 (0.94, 1.14)	0.99 (0.89, 1.10)
Regular coffee	387	1.00 (0.90, 1.12)	0.96 (0.85, 1.07)
Decaffeinated coffee	387	1.08 (0.93, 1.26)	1.07 (0.91, 1.25)
Black tea	387	1.00 (0.94, 1.07)	0.99 (0.92, 1.07)
Regular coffee drinkers	157	0.98 (0.83, 1.17)	0.90 (0.75, 1.10)
WITH parental history of CVD*			
Total coffee	301	1.02 (0.92, 1.14)	0.99 (0.88, 1.12)
Regular coffee	301	1.03 (0.92, 1.16)	1.01 (0.89, 1.15)
Decaffeinated coffee	301	0.99 (0.82, 1.19)	0.97 (0.80, 1.17)
Black tea	301	0.99 (0.92, 1.07)	0.99 (0.91, 1.08)
Regular coffee drinkers	120	0.97 (0.80, 1.18)	0.93 (0.74, 1.17)

[a] Cases apply to fully-adjusted models

[b] Adjusted for age (categorical), BMI, energy intake, physical activity, smoking status, socio-economic status, alcohol intake, family history of HBP, self-reported history of hypercholesterolaemia, mutual adjustment for total coffee or black tea intake

Table F.1 FV intakes and fruit, vegetable subgroup intakes and change in SBP (mmHg) within adults with no self-reported longstanding CVD, by obesity status, sex, age group, and among non-statin users, and non-smokers in the NDNS cohort

	SYSTOLIC BP β-coefficient (99% CI), p-value			**DIASTOLIC BP** β-coefficient (99% CI), p-value		
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
No longstanding CVD						
Total fruit & vegetables	-0.59 (-1.15, -0.02)	-0.30 (-0.87, 0.27)	-0.50 (-1.08, 0.08)	-0.44 (-0.85, -0.02)	-0.27 (-0.68, 0.13)	-0.31 (-0.72 ,0.10)
Total fruit	-0.93 (-1.88, 0.01)	-0.32 (-1.31, 0.67)	-0.51 (-1.50, 0.47)	-0.90 (-1.58, -0.21)	-0.56 (-1.26, 0.14)	-0.60 (-1.30, 0.10)
Total fruit juice	0.31 (-1.19, 1.82)	1.09 (-0.43, 2.62)	0.59 (-0.95, 2.14)	-0.60 (-1.72, 0.52)	-0.16 (-1.24, 0.92)	-0.27 (-1.37, 0.83)
Dried fruits	0.57 (-2.33, 3.47)	2.18 (-0.68, 5.03)	1.51 (-1.35, 4.37)	-0.52 (-2.62, 1.58)	0.90 (-1.12, 2.91)	0.76 (-1.28, 2.79)
Berries	-1.44 (-4.34, 1.45)	-0.85 (-3.71, 2.01)	-0.86 (-3.69, 1.98)	-1.08 (-3.18, 1.02)	-0.64 (-2.66, 1.38)	-0.64 (-2.66, 1.38)
Citrus	0.09 (-0.85, 1.03)	0.39 (-0.54, 1.33)	0.20 (-0.73, 1.14)	-0.31 (-0.99, 0.37)	-0.14 (-0.80, 0.52)	-0.18 (-0.84, 0.49)
Drupes	2.74 (-1.15, 6.64)	4.31 (0.53, 8.08)	4.23 (0.49, 7.97)	-0.54 (-3.38, 2.29)	0.94 (-1.73, 3.61)	0.92 (-1.75, 3.59)
Pomes	-1.29 (-2.88, 0.30)	-0.58 (-2.16, 0.99)	-0.90 (-2.47, 0.67)	-1.27 (-2.42, -0.12)	-0.64 (-1.75, 0.47)	-0.71 (-1.83, 0.41)
Tropical fruits	-0.70 (-3.12, 1.72)	-0.02 (-2.43, 2.39)	-0.13 (-2.52, 2.26)	-1.00 (-2.76, 0.75)	-0.39 (-2.09, 1.31)	-0.41 (-2.11, 1.28)
Total vegetables	-0.62 (-1.51, 0.27)	-0.28 (-1.20, 0.63)	-0.49 (-1.40, 0.42)	-0.28 (-0.93, 0.37)	-0.02 (-0.66, 0.62)	-0.06 (-0.71, 0.59)
Allium	-0.60 (-5.07, 3.86)	1.06 (-3.52, 5.64)	0.75 (-3.78, 5.28)	0.64 (-2.60, 3.88)	1.48 (-1.74, 4.71)	1.42 (-1.80, 4.65)
Brassicaceae	-1.85 (-5.45, 1.75)	-0.76 (-4.38, 2.87)	-0.67 (-4.26, 2.92)	-1.70 (-4.31, 0.91)	-0.84 (-3.40, 1.71)	-0.83 (-3.38, 1.72)
Fruit vegetables	-1.34 (-3.05, 0.37)	-0.31 (-2.11, 1.48)	-0.26 (-2.04, 1.52)	-0.39 (-1.63, 0.86)	0.54 (-0.72, 1.81)	0.56 (-0.71, 1.82)
Pod vegetables	-0.48 (-5.81, 4.84)	-0.39 (-5.52, 4.73)	-0.98 (-6.06, 4.10)	0.57 (-3.30, 4.43)	0.58 (-3.02, 4.19)	0.47 (-3.14, 4.09)
Root vegetables	-1.14 (-4.75, 2.46)	0.47 (-3.16, 4.11)	0.51 (-3.09, 4.11)	-1.46 (-4.07, 1.15)	-0.27 (-2.84, 2.29)	-0.27 (-2.83, 2.29)
Non-obese						
Total fruit & vegetables	-0.74 (-1.33, -0.15)	-0.47 (-1.08, 0.15)	-0.69 (-1.31, -0.06)	-0.41 (-0.84, 0.01)	-0.32 (-0.76, 0.12)	-0.35 (-0.81, 0.10)
Total fruit	-1.25 (-2.24, -0.26)	-0.68 (-1.76, 0.40)	-0.91 (-1.99, 0.17)	-0.93 (-1.64, -0.21)	-0.78 (-1.55, -0.01)	-0.81 (-1.59, -0.03)
Total fruit juice	0.31 (-1.19, 1.82)	0.64 (-0.90, 2.17)	0.11 (-1.45, 1.68)	-0.34 (-1.45, 0.76)	-0.41 (-1.51, 0.69)	-0.52 (-1.65, 0.61)
Dried fruits	-0.75 (-3.60, 2.11)	0.44 (-2.42, 3.29)	-0.26 (-3.13, 2.60)	-0.94 (-3.00, 1.20)	-0.22 (-2.27, 1.82)	-0.38 (-2.45, 1.69)
Berries	-1.76 (-5.09, 1.58)	-0.80 (-4.16, 2.56)	-0.89 (-4.22, 2.44)	-1.00 (-3.41, 1.41)	-0.56 (-2.96, 1.85)	-0.58 (-2.98, 1.83)
Citrus	-0.05 (-0.97, 0.87)	0.08 (-0.86, 1.03)	-0.18 (-1.14, 0.77)	-0.29 (-0.95, 0.37)	-0.37 (-1.05, 0.30)	-0.43 (-1.12, 0.26)
Drupes	2.17 (-1.74, 6.08)	3.60 (-0.27, 7.46)	3.55 (-0.27, 7.38)	0.26 (-2.57, 3.09)	1.24 (-1.53, 4.01)	1.23 (-1.54, 4.00)
Pomes	-1.25 (-2.90, 0.39)	-0.57 (-2.23, 1.09)	-0.81 (-2.46, 0.84)	-1.01 (-2.20, 0.18)	-0.56 (-1.75, 0.63)	-0.61 (-1.80, 0.58)
Tropical fruits	-1.10 (-3.65, 1.44)	0.13 (-2.46, 2.73)	0.06 (-2.50, 2.64)	-1.44 (-3.28, 0.39)	-0.70 (-2.56, 1.15)	-0.72 (-2.58, 1.14)
Total vegetables	-0.75 (-1.69, 0.19)	-0.28 (-1.28, 0.71)	-0.49 (-1.49, 0.50)	-0.22 (-0.90, 0.46)	0.08 (-0.63, 0.79)	0.05 (-0.67, 0.77)
Allium	-1.75 (-6.33, 2.83)	-0.04 (-4.82, 4.73)	-0.27 (-5.00, 4.45)	0.37 (-2.95, 3.68)	1.00 (-2.42, 4.43)	0.97 (-2.45, 4.39)
Brassicaceae	-2.77 (-6.68, 1.14)	-1.47 (-5.47, 2.54)	-1.63 (-5.60, 2.33)	-0.83 (-3.66, 2.01)	0.11 (-2.76, 2.98)	0.08 (-2.79, 2.96)
Fruit vegetables	-1.36 (-3.17, 0.45)	-0.25 (-2.21, 1.71)	-0.19 (-2.13, 1.75)	-0.52 (-1.83, 0.79)	0.11 (-1.29, 1.52)	0.12 (-1.28, 1.53)
Pod vegetables	-1.22 (-7.18, 4.73)	-1.13 (-6.95, 4.68)	-2.00 (-7.79, 3.78)	-0.23 (-4.54, 4.07)	-0.15 (-4.32, 4.02)	-0.29 (-4.47, 3.90)
Root vegetables	-1.88 (-5.72, 1.95)	-0.26 (-4.20, 3.67)	-0.43 (-4.32, 3.47)	-1.78 (-4.55, 0.98)	-1.01 (-3.83, 1.81)	-1.03 (-3.85, 1.79)

(Table F.1 continued)

	SYSTOLIC BP β-coefficient (99% CI), p-value			**DIASTOLIC BP** β-coefficient (99% CI), p-value		
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Obese						
Total fruit & vegetables	0.05 (-1.22, 1.33)	0.01 (-1.28, 1.31)	-0.17 (-1.48, 1.14)	-0.17 (-1.04, 0.69)	-0.29 (-1.17, 0.58)	-0.33 (-1.23, 0.56)
Total fruit	0.22 (-1.80, 2.26)	0.42 (-1.70, 2.53)	0.29 (-1.82, 2.39)	-0.25 (-1.63, 1.12)	-0.21 (-1.64, 1.23)	-0.23 (-1.67, 1.21)
Total fruit juice	0.31 (-1.19, 1.82)	3.83 (-0.84, 8.50)	3.33 (-1.37, 8.03)	1.41 (-1.71, 4.54)	1.94 (-1.247, 5.12)	1.86 (-1.36, 5.08)
Dried fruits	8.47 (-0.02, 17.0)	6.74 (-2.27, 15.7)	6.38 (-2.59, 15.3)	4.52 (-1.26, 10.3)	3.71 (-2.44, 9.87)	3.65 (-2.52, 9.83)
Berries	-1.96 (-7.13, 3.21)	-2.40 (-7.69, 2.89)	-2.38 (-7.65, 2.88)	-1.94 (-5.43, 1.56)	-2.10 (-5.71, 1.51)	-2.09 (-5.71, 1.52)
Citrus	2.53 (-0.37, 5.43)	3.12 (0.17, 6.07)	3.14 (0.21, 6.06)	1.66 (-0.31, 3.63)	1.94 (-0.06, 3.94)	1.94 (-0.06, 3.95)
Drupes	8.41 (-1.81, 18.6)	7.38 (-2.90, 17.7)	6.78 (-3.49, 17.0)	1.19 (-5.79, 8.18)	0.62 (-6.42, 7.67)	0.51 (-6.57, 7.59)
Pomes	0.04 (-3.84, 3.91)	0.08 (-4.01, 4.18)	-0.41 (-4.53, 3.71)	-0.94 (-3.56, 1.68)	-0.95 (-3.74, 1.83)	-1.07 (-3.89, 1.76)
Tropical fruits	1.50 (-3.56, 6.56)	0.75 (-4.50, 5.99)	0.58 (-4.64, 5.81)	1.17 (-2.25, 4.60)	0.99 (-2.58, 4.57)	0.96 (-2.62, 4.54)
Total vegetables	-0.08 (-2.04, 1.88)	-0.37 (-2.42, 1.68)	-0.61 (-2.67, 1.45)	-0.17 (-1.49, 1.16)	-0.38 (-1.77, 1.01)	-0.43 (-1.84, 0.98)
Allium	-0.06 (-10.7, 10.6)	-2.62 (-14.1, 8.89)	-3.09 (-14.5, 8.36)	-0.09 (-7.32, 7.13)	-1.99 (-9.80, 5.82)	-2.09 (-9.92, 5.74)
Brassicaceae	-0.64 (-7.86, 6.58)	-0.85 (-8.61, 6.90)	-0.32 (-8.05, 7.41)	-2.63 (-7.50, 2.24)	-2.90 (-8.15, 2.34)	-2.81 (-8.09, 2.46)
Fruit vegetables	0.18 (-3.57, 3.94)	0.34 (-3.60, 4.27)	0.47 (-3.44, 4.38)	0.57 (-1.97, 3.11)	0.84 (-1.82, 3.50)	0.88 (-1.79, 3.54)
Pod vegetables	-0.41 (-10.8, 9.99)	-0.05 (-10.6, 10.5)	-0.58 (-11.1, 9.92)	0.50 (-6.54, 7.55)	0.99 (-6.17, 8.15)	0.88 (-6.30, 8.06)
Root vegetables	-0.09 (-8.51, 8.33)	-0.92 (-9.65, 7.81)	-0.51 (-9.19, 8.18)	1.45 (-4.25, 7.15)	1.56 (-4.35, 7.48)	1.66 (-4.27, 7.59)
Male	-0.46 (-1.21, 0.28)	-0.31 (-1.07, 0.45)	-0.37 (-1.16, 0.42)	-0.58 (-1.21, 0.05)	-0.53 (-1.15, 0.09)	-0.57 (-1.21, 0.07)
Total fruit & vegetables	-0.82 (-2.02, 0.38)	-0.52 (-1.79, 0.76)	-0.57 (-1.86, 0.72)	-1.36 (-2.37, -0.36)	-1.25 (-2.29, -0.22)	-1.30 (-2.34, -0.25)
Total fruit	0.31 (-1.19, 1.82)	-0.43 (-2.19, 1.34)	-0.54 (-2.33, 1.26)	-1.08 (-2.55, 0.39)	-0.76 (-2.19, 0.67)	-0.85 (-2.30, 0.60)
Total fruit juice	-0.13 (-3.47, 3.20)	1.13 (-2.25, 4.50)	0.96 (-2.46, 4.38)	-1.25 (-4.07, 1.57)	0.05 (-2.69, 2.79)	-0.11 (-2.89, 2.66)
Dried fruits	-0.22 (-4.00, 3.56)	0.15 (-3.67, 3.98)	0.07 (-3.77, 3.91)	-1.69 (-4.88, 1.49)	-1.70 (-4.81, 1.40)	-1.78 (-4.89, 1.33)
Berries	-0.66 (-1.72, 0.38)	-0.44 (-1.51, 0.62)	-0.49 (-1.57, 0.58)	-0.78 (-1.67, 0.10)	-0.61 (-1.48, 0.25)	-0.66 (-1.54, 0.21)
Citrus	2.04 (-3.65, 7.74)	4.15 (-1.59, 9.90)	3.99 (-1.78, 9.76)	-1.62 (-6.44, 3.20)	1.16 (-3.51, 5.84)	1.01 (-3.69, 5.71)
Drupes	-0.70 (-2.61, 1.22)	-0.11 (-2.08, 1.85)	-0.14 (-2.11, 1.82)	-1.33 (-2.95, 2.81)	-0.83 (-2.42, 0.77)	-0.85 (-2.45, 0.74)
Pomes	-0.57 (-3.58, 2.43)	0.99 (-2.11, 4.10)	0.99 (-2.12, 4.10)	-1.78 (-4.31, 0.75)	-0.35 (-2.88, 2.17)	-0.35 (-2.88, 2.17)
Tropical fruits	-0.35 (-1.51, 0.80)	-0.12 (-1.30, 1.05)	-0.19 (-1.38, 1.01)	-0.12 (-1.10, 0.85)	0.11 (-0.84, 1.06)	0.06 (-0.90, 1.03)
Total vegetables	-1.38 (-6.66, 3.91)	-0.70 (-6.36, 4.96)	-0.78 (-6.45, 4.89)	0.54 (-3.93, 5.01)	0.61 (-3.97, 5.20)	0.55 (-4.04, 5.15)
Allium	-2.28 (-6.85, 2.28)	-1.25 (-5.96, 3.45)	-1.29 (-6.00, 3.42)	-1.35 (-5.22, 2.51)	0.23 (-3.59, 4.05)	0.20 (-3.62, 4.02)
Brassicaceae	0.13 (-2.15, 2.40)	1.08 (-1.31, 3.48)	1.09 (-1.31, 3.49)	-0.47 (-2.39, 1.46)	0.21 (-1.74, 2.16)	0.21 (-1.74, 2.16)
Fruit vegetables	-1.44 (-8.34, 5.45)	-1.64 (-8.39, 5.11)	-1.90 (-8.70, 4.90)	-1.48 (-7.31, 4.36)	-1.22 (-6.69, 4.25)	-1.42 (-6.93, 4.09)
Pod vegetables	0.45 (-4.24, 5.15)	2.17 (-2.65, 7.00)	2.07 (-2.77, 6.91)	0.59 (-3.38, 4.56)	2.04 (-1.86, 5.95)	1.96 (-1.96, 5.89)
Root vegetables						

(Table F.1 continued)

	SYSTOLIC BP β-coefficient (99% CI), p-value			**DIASTOLIC BP** β-coefficient (99% CI), p-value		
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Female						
Total fruit & vegetables	-0.57 (-1.28, 0.15)	-0.11 (-0.85, 0.63)	-0.12 (-0.89, 0.64)	-0.37 (-0.87, 0.13)	-0.14 (-0.64, 0.36)	-0.13 (-0.65, 0.39)
Total fruit	-0.72 (-1.94, 0.50)	0.19 (-1.13, 1.52)	0.18 (-1.17, 1.52)	-0.56 (-1.41, 0.29)	-0.06 (-0.95, 0.84)	-0.05 (-0.96, 0.86)
Total fruit juice	0.31 (-1.19, 1.82)	2.08 (-0.32, 4.47)	2.15 (-0.31, 4.62)	-0.00 (-1.64, 1.64)	0.62 (-1.01, 2.25)	0.69 (-0.98, 2.36)
Dried fruits	-0.34 (-4.55, 3.88)	1.29 (-2.95, 5.53)	1.36 (-2.92, 5.64)	-0.48 (-3.42, 2.46)	0.89 (-1.98, 3.76)	0.97 (-1.93, 3.87)
Berries	-1.67 (-5.50, 2.14)	-0.91 (-4.72, 2.90)	-0.90 (-4.71, 2.91)	-0.47 (-3.13, 2.20)	0.04 (-2.54, 2.62)	0.05 (-2.54, 2.63)
Citrus	0.50 (-0.94, 1.94)	1.06 (-0.43, 2.56)	1.07 (-0.43, 2.58)	0.22 (-0.79, 1.22)	0.55 (-0.46, 1.56)	0.56 (-0.46, 1.58)
Drupes	3.74 (-0.91, 8.39)	5.33 (-0.77, 9.89)	5.34 (0.77, 9.90)	0.15 (-3.10, 3.40)	1.23 (-1.87, 4.34)	1.25 (-1.86, 4.35)
Pomes	-1.90 (-4.18, 0.37)	-1.03 (-3.32, 1.25)	-1.01 (-3.32, 1.30)	-1.41 (-2.99, 0.17)	-0.62 (-2.17, 0.92)	-0.59 (-2.16, 0.97)
Tropical fruits	-0.13 (-3.31, 3.05)	0.48 (-2.77, 3.74)	0.51 (-2.75, 3.78)	-0.15 (-2.36, 2.07)	0.06 (-2.15, 2.26)	0.08 (-2.13, 2.30)
Total vegetables	-0.83 (-2.00, 0.33)	-0.39 (-1.64, 0.86)	-0.40 (-1.66, 0.86)	-0.47 (-1.28, 0.34)	-0.21 (-1.06, 0.63)	-0.21 (-1.06, 0.65)
Allium	-1.19 (-7.39, 5.01)	1.37 (-5.05, 7.78)	1.37 (-5.05, 7.80)	-0.40 (-4.72, 3.93)	1.30 (-3.03, 5.64)	1.30 (-3.04, 5.64)
Brassicaceae	-0.15 (-4.99, 4.70)	0.66 (-4.30, 5.61)	0.66 (-4.30, 5.62)	-1.34 (-4.71, 2.03)	-1.23 (-4.57, 2.12)	-1.23 (-4.58, 2.12)
Fruit vegetables	-1.48 (-3.66, 0.69)	-0.54 (-2.91, 1.83)	-0.54 (-2.91, 1.83)	-0.30 (-1.82, 1.22)	0.70 (-0.89, 2.30)	0.70 (-0.89, 2.30)
Pod vegetables	0.34 (-6.61, 7.30)	0.71 (-6.19, 7.62)	0.68 (-6.25, 7.61)	1.46 (-3.38, 6.31)	1.13 (-3.53, 5.80)	1.17 (-3.51, 5.85)
Root vegetables	-0.97 (-5.68, 3.75)	0.70 (-4.14, 5.54)	0.70 (-4.14, 5.55)	-2.77 (-6.05, 0.50)	-2.13 (-5.40, 1.13)	-2.13 (-5.40, 1.13)
19 to 64 years						
Total fruit & vegetables	-0.68 (-1.27, -0.09)	-0.29 (-0.88, 0.31)	-0.48 (-1.08, 0.12)	-0.58 (-1.01, -0.15)	-0.34 (-0.77, 0.09)	-0.38 (-0.82, 0.06)
Total fruit	-0.96 (-1.99, 0.06)	0.00 (-1.07, 1.07)	-0.21 (-1.27, 0.86)	-1.00 (-1.75, -0.25)	-0.39 (-1.17, 0.39)	-0.44 (-1.22, 0.34)
Total fruit juice	0.31 (-1.19, 1.82)	0.92 (-0.59, 2.44)	0.44 (-1.10, 1.98)	-0.55 (-1.70, 0.58)	-0.08 (-1.19, 1.02)	-0.21 (-1.33, 0.92)
Dried fruits	0.28 (-2.92, 3.47)	1.90 (-1.19, 4.99)	1.24 (-1.85, 4.33)	-1.20 (-3.55, 1.14)	0.11 (-2.14, 2.35)	-0.06 (-2.33, 2.20)
Berries	-1.37 (-4.44, 1.70)	-0.28 (-3.27, 2.71)	-0.22 (-3.19, 2.74)	-1.74 (-4.00, 0.51)	-0.94 (-3.11, 1.24)	-0.92 (-3.10, 1.25)
Citrus	0.14 (-0.80, 1.08)	0.48 (-0.45, 1.41)	0.29 (-0.63, 1.22)	-0.29 (-0.98, 0.40)	-0.01 (-0.69, 0.67)	-0.06 (-0.74, 0.62)
Drupes	1.77 (-2.98, 6.53)	3.76 (-0.83, 8.34)	3.57 (-0.97, 8.12)	-1.21 (-4.69, 2.28)	0.74 (-2.60, 4.09)	0.70 (-2.64, 4.04)
Pomes	-0.73 (-2.47, 1.02)	0.25 (-1.45, 1.95)	-0.08 (-1.78, 1.62)	-0.80 (-2.08, 0.48)	-0.01 (-1.25, 1.22)	-0.10 (-1.34, 1.15)
Tropical fruits	-0.80 (-3.34, 1.74)	0.56 (-1.96, 3.09)	0.49 (-2.01, 3.00)	-1.10 (-2.96, 0.76)	-0.03 (-1.87, 1.81)	-0.05 (-1.88, 1.79)
Total vegetables	-0.87 (-1.78, 0.04)	-0.52 (-1.46, 0.42)	-0.70 (-1.64, 0.23)	-0.59 (-1.26, 0.08)	-0.29 (-0.97, 0.38)	-0.34 (-1.02, 0.35)
Allium	-1.67 (-6.20, 2.87)	0.21 (-4.43, 4.85)	-0.09 (-4.69, 4.50)	-0.76 (-4.09, 2.57)	0.42 (-2.94, 3.79)	0.36 (-3.01, 3.73)
Brassicaceae	-3.04 (-6.82, 0.74)	-1.70 (-5.47, 2.07)	-1.51 (-5.25, 2.22)	-2.73 (-5.50, 0.04)	-1.71 (-4.44, 1.03)	-1.67 (-4.41, 1.07)
Fruit vegetables	-1.83 (-3.57, -0.08)	-0.78 (-2.62, 1.07)	-0.71 (-2.54, 1.12)	-1.15 (-2.43, 0.13)	-0.25 (-1.59, 1.09)	-0.23 (-1.58, 1.11)
Pod vegetables	1.02 (-4.60, 6.65)	1.19 (-4.18, 6.56)	0.55 (-4.77, 5.88)	0.04 (-4.08, 4.17)	-0.02 (-3.92, 3.88)	-0.16 (-4.07, 3.75)
Root vegetables	-2.57 (-6.49, 1.35)	-0.04 (-3.98, 3.89)	0.02 (-3.87, 3.92)	-1.77 (-4.64, 1.11)	0.31 (-2.54, 3.17)	0.33 (-2.53, 3.19)

(Table F.1 continued)

	SYSTOLIC BP β-coefficient (99% CI), p-value			**DIASTOLIC BP** β-coefficient (99% CI), p-value		
Intake (80 g/day)	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
65+ years						
Total fruit & vegetables	-0.24 (-1.73, 1.25)	0.13 (-1.53, 1.80)	0.03 (-1.70, 1.75)	-0.59 (-1.48, 0.29)	-0.79 (-1.76, 0.17)	-0.81 (-1.82, 0.19)
Total fruit	-1.02 (-3.10, 1.06)	-0.77 (-3.12, 1.57)	-0.81 (-3.18, 1.55)	-1.55 (-2.76, -0.34)	-1.94 (-3.27, -0.62)	-1.93 (-3.27, -0.59)
Total fruit juice	0.31 (-1.19, 1.82)	1.45 (-4.43, 7.34)	1.27 (-4.90, 7.44)	-0.73 (-4.09, 2.63)	-0.28 (-3.61, 3.04)	-0.21 (-3.70, 3.28)
Dried fruits	-1.56 (-7.76, 4.63)	-2.16 (-9.40, 5.08)	-2.28 (-9.58, 5.01)	-0.19 (-3.91, 3.53)	0.63 (-3.51, 4.77)	0.61 (-3.57, 4.79)
Berries	-2.94 (-10.6, 4.74)	-1.61 (-10.0, 6.77)	-1.75 (-10.2, 6.69)	-0.88 (-5.50, 3.73)	-0.51 (-5.30, 4.29)	-0.54 (-5.37, 4.30)
Citrus	-0.53 (-4.07, 3.00)	-0.25 (-4.02, 3.53)	-0.46 (-4.45, 3.52)	-1.52 (-3.62, 0.58)	-1.29 (-3.45, 0.87)	-1.34 (-3.62, 0.94)
Drupes	3.93 (-2.62, 10.5)	4.61 (-2.30, 11.5)	4.68 (-2.24, 11.6)	0.26 (-3.69, 4.22)	0.73 (-3.24, 4.70)	0.75 (-3.23, 4.74)
Pomes	-2.85 (-6.52, 0.81)	-3.55 (-7.49, 0.40)	-3.54 (-7.50, 0.41)	-2.97 (-5.11, -0.84)	-3.29 (-5.55, -1.04)	-3.29 (-5.56, -1.03)
Tropical fruits	-0.24 (-6.04, 5.56)	1.18 (-5.22, 7.59)	1.12 (-5.32, 7.56)	-1.70 (-5.16 ,1.76)	-1.05 (-4.72, 2.62)	-1.06 (-4.75, 2.63)
Total vegetables	0.88 (-1.77, 3.53)	1.39 (-1.45, 4.23)	1.26 (-1.68, 4.21)	0.62 (-0.96, 2.21)	-0.80 (-0.80, 2.40)	0.84 (-0.82, 2.51)
Allium	3.34 (-9.95, 16.6)	1.36 (-13.3, 16.1)	1.31 (-13.4, 16.1)	2.54 (-5.42, 10.5)	0.95 (-7.36, 9.25)	0.96 (-7.37, 9.30)
Brassicaceae	3.09 (-6.54, 12.7)	4.02 (-6.45, 14.5)	3.79 (-6.85, 14.4)	2.60 (-3.17, 8.36)	3.51 (-2.39, 9.40)	3.63 (-2.35, 9.62)
Fruit vegetables	2.63 (-2.37, 7.62)	3.00 (-2.52, 8.53)	3.03 (-2.50, 8.57)	2.65 (-0.31, 5.61)	2.68 (-0.40, 5.77)	2.69 (-0.41, 5.79)
Pod vegetables	-8.81 (-22.2, 4.55)	-8.74 (-22.7, 5.27)	-.945 (-23.7, 4.83)	-1.35 (-9.43, 6.73)	-1.28 (-9.29, 6.72)	-1.19 (-9.37, 6.99)
Root vegetables	4.25 (-3.86, 12.4)	6.32 (-2.38, 15.0)	6.17 (-2.62, 14.9)	-0.65 (-5.55, 4.24)	-0.32 (-5.28, 4.63)	-0.27 (-5.28, 4.73)
No statins						
Total fruit & vegetables	-0.60 (-1.16 ,-0.04)	-0.29 (-0.86, 0.28)	-0.46 (-1.04, 0.11)	-0.48 (-0.89, -0.08)	-0.32 (-0.73 ,0.08)	-0.36 (-0.77, 0.05)
Total fruit	-0.90 (-1.82, 0.02)	-0.22 (-1.19, 0.75)	-0.40 (-1.37, 0.57)	-0.98 (-1.65 ,-0.31)	-0.62 (-1.31, 0.07)	-0.66 (-1.35, 0.03)
Total fruit juice	0.31 (-1.19, 1.82)	1.09 (-0.43, 2.61)	0.61 (-0.94, 2.16)	-0.56 (-1.69, 0.56)	-0.11 (-1.19, 0.97)	-0.22 (-1.33, 0.88)
Dried fruits	-0.03 (-2.84, 2.79)	1.43 (-1.37, 4.23)	0.88 (1.93, 3.69)	-0.72 (-2.78, 1.34)	0.62 (-1.37, 2.61)	0.49 (-1.51, 2.50)
Berries	-1.37 (-4.24, 1.51)	-0.71 (-3.57, 2.14)	-0.73 (-3.57, 2.10)	-1.20 (-3.30, 0.89)	-0.75 (-2.77, 1.27)	-0.75 (-2.78, 1.27)
Citrus	0.17 (-0.76, 1.11)	0.49 (-0.45, 1.43)	0.28 (-0.66, 1.23)	-0.30 (-0.99, 0.38)	-0.10 (-0.77, 0.56)	-0.15 (-0.83, 0.52)
Drupes	3.48 (-0.41, 7.37)	5.15 (1.35, 8.95)	5.05 (1.27, 8.82)	-0.48 (-3.34, 2.37)	1.17 (-1.54, 3.88)	1.15 (-1.56, 3.86)
Pomes	-1.20 (-2.80, 0.40)	-0.39(-1.99, 1.20)	-0.67 (-2.26, 0.92)	-1.40 (-2.56, -0.23)	-0.70 (1.83, 0.43)	-0.77 (-1.91, 0.36)
Tropical fruits	-0.82 (-3.22, 1.59)	0.16 (-2.26, 2.59)	0.10 (-2.30, 2.52)	-1.06 (-2.81, 0.70)	-0.24 (-1.97, 1.48)	-0.26 (-1.98, 1.46)
Total vegetables	-0.68 (-1.57, 0.20)	-0.35 (-1.27, 0.56)	-0.52 (-1.43, 0.39)	-0.31 (-0.96, 0.34)	-0.05 (-0.70, 0.59)	-0.09 (-0.74, 0.56)
Allium	-0.64 (-5.03, 3.75)	1.01 (-3.52, 5.54)	0.88 (-3.62 ,-5.38)	0.56 (-2.65, 3.77)	1.34 (-1.87, 4.54)	1.31 (-1.90 ,4.52)
Brassicaceae	-2.04 (-5.64, 1.56)	-0.86 (-4.50, 2.78)	-0.81 (-4.42, 2.79)	-1.47 (-4.10, 1.16)	-0.55 (-3.13, 2.03)	-0.54 (-3.12, 2.04)
Fruit vegetables	-1.38 (-3.05, 0.30)	-0.39 (-2.16, 1.37)	-0.30 (-2.05, 1.45)	-0.42 (-1.65, 0.80)	0.47 (-0.78, 1.72)	0.49 (-0.76, 1.74)
Pod vegetables	-1.22 (-6.48, 4.04)	-1.30 (-6.38, 3.78)	-1.86 (-6.91, 3.19)	0.10 (-3.74, 3.95)	-0.00 (-3.60, 3.60)	-0.11 (-3.72, 3.50)
Root vegetables	-0.81 (-4.39, 2.77)	1.04 (-2.58, 4.66)	0.96 (-2.63, 4.55)	-1.56 (-4.18, 1.05)	-0.41 (-2.97, 2.15)	-0.43 (-2.99, 2.14)

(Table F.1 continued)

Intake (80 g/day)	**SYSTOLIC BP** β-coefficient (99% CI), p-value			**DIASTOLIC BP** β-coefficient (99% CI), p-value		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Non-smokers						
Total fruit & vegetables	-0.63 (-1.32, 0.06)	-0.32 (-1.01, 0.36)	-0.51 (-1.20, 0.18)	-0.53 (-1.05, -0.01)	-0.24 (-0.74, 0.25)	-0.28 (-0.78, 0.23)
Total fruit	-0.76 (-1.87, 0.35)	-0.11 (-1.25, 1.03)	-0.35 (-1.49, 0.79)	-0.99 (-1.82, -0.17)	-0.52 (-1.35, 0.31)	-0.56 (-1.40, 0.27)
Total fruit juice	0.31 (-1.19, 1.82)	0.84 (-0.89, 2.56)	0.34 (-1.41, 2.10)	-0.75 (-2.07, 0.57)	-0.48 (-1.73, 0.78)	-0.60 (-1.89, 0.69)
Dried fruits	0.71 (-2.72, 4.14)	1.91 (-1.47, 5.29)	1.27 (-2.13, 4.66)	-0.67 (-3.23, 1.90)	0.65 (-1.80, 3.11)	0.50 (-1.99, 2.98)
Berries	-0.86 (-4.09, 2.36)	-0.33 (-3.48, 2.83)	-0.64 (-3.77, 2.50)	-1.42 (-3.83, 1.00)	-0.83 (-3.12, 1.46)	-0.91 (-3.20, 1.39)
Citrus	0.23 (-0.81, 1.28)	0.42 (-0.62, 1.45)	0.22 (-0.82, 1.26)	-0.30 (-1.08, 0.48)	-0.17 (-0.92, 0.58)	-0.22 (-0.98, 0.54)
Drupes	1.08 (-3.60, 5.76)	2.39 (-2.19, 6.98)	2.19 (-2.36, 6.74)	-0.81 (-4.32, 2.69)	0.76 (-2.58, 4.09)	0.71 (-2.63, 4.04)
Pomes	-1.31 (-3.26, 0.64)	-0.31 (-2.25, 1.61)	-0.49 (-2.41, 1.43)	-1.80 (-3.25, -0.35)	-0.76 (-2.16, 0.64)	-0.80 (-2.21, 0.60)
Tropical fruits	0.04 (-2.81, 2.88)	0.57 (-2.24, 3.38)	0.52 (-2.26, 3.31)	-0.74 (-2.87, 1.39)	-0.02 (-2.06, 2.02)	-0.03 (-2.07, 2.01)
Total vegetables	-0.84 (-1.95, 0.26)	-0.53 (-1.65, 0.58)	-0.66 (-1.77, 0.45)	-0.37 (-1.20, 0.46)	0.02 (-0.79, 0.83)	-0.00 (-0.82, 0.81)
Allium	-2.00 (-6.94, 2.93)	-1.04 (-6.14, 4.06)	-1.60 (-6.66, 3.47)	-0.43 (-4.14, 3.27)	0.21 (-3.49, 3.92)	0.11 (-3.61, 3.83)
Brassicaceae	-1.91 (-6.34, 2.53)	-1.21 (-5.59, 3.17)	-1.09 (-5.43, 3.25)	-1.43 (-4.75, 1.89)	-0.64 (-3.82, 2.54)	-0.62 (-3.80, 2.56)
Fruit vegetables	-1.78 (-3.93, 0.35)	-1.11 (-3.33, 1.11)	-0.95 (-3.15, 1.25)	-0.72 (-2.33, 0.88)	0.03 (-1.58, 1.64)	0.06 (-1.55, 1.67)
Pod vegetables	0.24 (-5.81, 6.29)	0.62 (-5.21, 6.46)	0.24 (-5.54, 6.02)	0.56 (-3.97, 5.09)	0.71 (-3.53, 4.94)	0.64 (-3.60, 4.88)
Root vegetables	-1.08 (-5.59, 3.43)	0.44 (-4.04, 4.92)	0.34 (-4.09, 4.78)	-1.78 (-5.15, 1.59)	-0.92 (-4.17, 2.34)	-0.93 (-4.19, 2.32)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

Table F.2 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within adults with no longstanding CVD illness in the NDNS RP cohort

Intake (80 g/day) n = 175	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.90 (0.80, 1.00)	0.92 (0.82, 1.04)	0.91 (0.81, 1.03)
Total fruits	0.83 (0.69, 0.99)	0.88 (0.72, 1.07)	0.87 (0.71, 1.06)
Total fruit juice *(125 g/day)*	0.75 (0.52, 1.09)	0.87 (0.60, 1.26)	0.84 (0.58, 1.23)
Dried fruits *(25 g/day)*	0.79 (0.46, 1.35)	1.06 (0.61, 1.84)	1.00 (0.56, 1.76)
Berries	0.76 (0.42, 1.38)	0.85 (0.48, 1.51)	0.85 (0.48, 1.51)
Citrus	0.88 (0.70, 1.10)	0.94 (0.75, 1.18)	0.93 (0.75, 1.17)
Drupes	0.94 (0.50, 1.77)	1.22 (0.63, 2.36)	1.21 (0.63, 2.33)
Pomes	0.71 (0.50, 1.00)	0.81 (0.57, 1.17)	0.80 (0.56, 1.14)
Tropical fruits	0.77 (0.49, 1.20)	0.85 (0.53, 1.38)	0.84 (0.52, 1.37)
Total vegetables	0.92 (0.77, 1.09)	0.97 (0.80, 1.17)	0.95 (0.79, 1.16)
Allium	1.14 (0.50, 2.57)	1.53 (0.62, 3.80)	1.53 (0.62, 3.77)
Brassicaceae	0.77 (0.40, 1.49)	0.93 (0.45, 1.91)	0.93 (0.45, 1.91)
Fruit vegetables	0.92 (0.65, 1.29)	1.11 (0.77, 1.60)	1.11 (0.77, 1.60)
Pod vegetables	0.73 (0.27, 1.96)	0.78 (0.28, 2.15)	0.74 (0.27, 2.07)
Root vegetables	0.91 (0.48, 1.72)	1.19 (0.58, 2.41)	1.19 (0.58, 2.42)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

Table F.3 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within non-obese adults in the NDNS RP cohort

Intake (80 g/day) n =110	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.85 (0.74, 0.98)	0.87 (0.75, 1.02)	0.87 (0.74, 1.01)
Total fruits	0.70 (0.54, 0.91)	0.73 (0.54, 0.97)	0.72 (0.54, 0.97)
Total fruit juice *(125 g/day)*	0.75 (0.49, 1.15)	0.76 (0.49, 1.20)	0.75 (0.48, 1.18)
Dried fruits *(25 g/day)*	0.64 (0.32, 1.27)	0.83 (0.43, 1.63)	0.80 (0.40, 1.60)
Berries	0.82 (0.37, 1.80)	1.02 (0.47, 2.21)	1.02 (0.47, 2.20)
Citrus	0.80 (0.60, 1.08)	0.82 (0.60, 1.11)	0.81 (0.59, 1.10)
Drupes	0.77 (0.36, 1.66)	0.96 (0.44, 2.12)	0.96 (0.44, 2.12)
Pomes	0.64 (0.41, 0.99)	0.73 (0.46, 1.15)	0.73 (0.46, 1.15)
Tropical fruits	0.69 (0.40, 1.19)	0.84 (0.46, 1.54)	0.84 (0.46, 1.54)
Total vegetables	0.91 (0.73, 1.13)	1.01 (0.80, 1.29)	1.01 (0.79, 1.28)
Allium	1.08 (0.41, 2.84)	1.43 (0.48, 4.25)	1.43 (0.48, 4.24)
Brassicaceae	0.67 (0.29, 1.53)	0.89 (0.36, 2.24)	0.88 (0.35, 2.22)
Fruit vegetables	0.87 (0.57, 1.33)	1.08 (0.67, 1.75)	1.08 (0.67, 1.75)
Pod vegetables	0.60 (0.17, 2.14)	0.63 (0.17, 2.35)	0.61 (0.16, 2.32)
Root vegetables	0.80 (0.36, 1.79)	1.04 (0.42, 2.57)	1.04 (0.42, 2.56)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

Table F.4 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within obese adults in the NDNS RP cohort

Intake (80 g/day) n = 72	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.98 (0.81, 1.18)	0.98 (0.81, 1.19)	0.96 (0.79, 1.18)
Total fruits	1.04 (0.78, 1.38)	1.10 (0.81, 1.51)	1.09 (0.79, 1.49)
Total fruit juice *(125 g/day)*	0.87 (0.42, 1.80)	1.06 (0.49, 2.28)	1.00 (0.46, 2.17)
Dried fruits *(25 g/day)*	1.31 (0.41, 4.15)	1.38 (0.38, 5.08)	1.34 (0.36, 4.89)
Berries	0.60 (0.23, 1.58)	0.59 (0.21, 1.62)	0.58 (0.21, 1.60)
Citrus	1.11 (0.73, 1.67)	1.22 (0.79, 1.89)	1.23 (0.80, 1.90)
Drupes	1.74 (0.44, 6.90)	1.75 (0.40, 7.65)	1.61 (0.37, 7.03)
Pomes	1.00 (0.57, 1.73)	1.12 (0.60, 2.09)	1.07 (0.57, 2.00)
Tropical fruits	1.12 (0.54, 2.29)	1.19 (0.54, 2.62)	1.17 (0.53, 2.58)
Total vegetables	0.92 (0.68, 1.24)	0.87 (0.62, 1.21)	0.84 (0.60, 1.18)
Allium	0.53 (0.09, 2.95)	0.46 (0.07, 3.16)	0.44 (0.06, 3.07)
Brassicaceae	0.73 (0.25, 2.17)	0.68 (0.21, 2.25)	0.70 (0.21, 2.35)
Fruit vegetables	1.17 (0.69, 1.99)	1.31 (0.74, 2.33)	1.34 (0.76, 2.38)
Pod vegetables	0.75 (0.15, 3.78)	0.70 (0.12, 4.06)	0.63 (0.10, 3.77)
Root vegetables	0.98 (0.29, 3.30)	1.13 (0.30, 4.23)	1.17 (0.31, 4.40)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category
[b] Adjusted for all the above and energy intake

Table F.5 Total FV, fruit and vegetable subgroups intakes and odds of HBP within male adults in the NDNS RP cohort

Intake (80 g/day) n = 102	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.93 (0.81, 1.08)	0.94 (0.81, 1.10)	0.95 (0.81, 1.11)
Total fruits	0.89 (0.71, 1.13)	0.92 (0.71, 1.20)	0.92 (0.71, 1.21)
Total fruit juice *(125 g/day)*	0.49 (0.27, 0.88)	0.53 (0.28, 0.98)	0.53 (0.28, 0.98)
Dried fruits *(25 g/day)*	0.84 (0.44, 1.62)	1.18 (0.60, 2.32)	1.18 (0.60, 2.34)
Berries	0.89 (0.43, 1.87)	0.94 (0.43, 2.03)	0.94 (0.43, 2.02)
Citrus	0.68 (0.47, 0.98)	0.71 (0.48, 1.04)	0.71 (0.48, 1.04)
Drupes	1.23 (0.46, 3.24)	2.39 (0.82, 6.98)	2.42 (0.82, 7.17)
Pomes	0.85 (0.58, 1.25)	0.96 (0.62, 1.48)	0.96 (0.62, 1.48)
Tropical fruits	0.76 (0.43, 1.36)	0.90 (0.47, 1.71)	0.90 (0.47, 1.71)
Total vegetables	0.94 (0.75, 1.17)	0.96 (0.75, 1.23)	0.97 (0.75, 1.24)
Allium	0.87 (0.31, 2.44)	0.99 (0.30, 3.28)	0.98 (0.29, 3.28)
Brassicaceae	0.70 (0.29, 1.69)	0.84 (0.32, 2.20)	0.84 (0.32, 2.21)
Fruit vegetables	1.13 (0.75, 1.70)	1.39 (0.87, 2.20)	1.39 (0.87, 2.21)
Pod vegetables	0.43 (0.10, 1.81)	0.39 (0.09, 1.76)	0.39 (0.09, 1.80)
Root vegetables	1.05 (0.45, 2.48)	1.45 (0.54, 3.88)	1.46 (0.54, 3.94)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category
[b] Adjusted for all the above and energy intake

Table F.6 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within female adults in the NDNS RP cohort

Intake (80 g/day) n = 90	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.86 (0.74, 1.01)	0.91 (0.77, 1.08)	0.91 (0.76, 1.08)
Total fruits	0.77 (0.59, 1.00)	0.84 (0.62, 1.12)	0.83 (0.61, 1.11)
Total fruit juice *(125 g/day)*	1.04 (0.67, 1.60)	1.33 (0.83, 2.12)	1.31 (0.81, 2.11)
Dried fruits *(25 g/day)*	0.55 (0.22, 1.39)	0.70 (0.26, 1.88)	0.68 (0.25, 1.85)
Berries	0.74 (0.32, 1.69)	0.84 (0.38, 1.90)	0.84 (0.37, 1.89)
Citrus	1.03 (0.80, 1.34)	1.16 (0.88, 1.53)	1.15 (0.87, 1.52)
Drupes	0.79 (0.35, 1.77)	0.95 (0.40, 2.28)	0.95 (0.39, 2.27)
Pomes	0.50 (0.26, 0.94)	0.57 (0.29, 1.15)	0.57 (0.28, 1.14)
Tropical fruits	0.84 (0.45, 1.54)	1.01 (0.52, 1.94)	1.00 (0.52, 1.93)
Total vegetables	0.87 (0.67, 1.13)	1.00 (0.75, 1.34)	1.00 (0.74, 1.34)
Allium	1.16 (0.35, 3.86)	2.02 (0.52, 7.84)	2.05 (0.52, 8.02)
Brassicaceae	0.87 (0.34, 2.21)	1.19 (0.43, 3.30)	1.19 (0.43, 3.30)
Fruit vegetables	0.79 (0.47, 1.32)	0.97 (0.56, 1.68)	0.98 (0.57, 1.68)
Pod vegetables	1.11 (0.31, 3.99)	1.51 (0.39, 5.76)	1.46 (0.38, 5.64)
Root vegetables	0.82 (0.34, 1.99)	0.12 (0.42, 3.00)	1.12 (0.42, 3.01)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

Table F.7 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within adults 19-64 years in the NDNS RP cohort

Intake (80 g/day) n = 132	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.86 (0.75, 0.98)	0.90 (0.78, 1.03)	0.89 (0.77, 1.03)
Total fruits	0.78 (0.63, 0.98)	0.89 (0.70, 1.14)	0.89 (0.69, 1.13)
Total fruit juice *(125 g/day)*	0.70 (0.46, 1.07)	0.81 (0.53, 1.25)	0.79 (0.52, 1.22)
Dried fruits *(25 g/day)*	0.66 (0.31, 1.40)	0.96 (0.46, 2.02)	0.92 (0.43, 1.95)
Berries	0.79 (0.41, 1.53)	0.94 (0.50, 1.77)	0.94 (0.50, 1.78)
Citrus	0.84 (0.65, 1.09)	0.92 (0.72, 1.19)	0.92 (0.72, 1.18)
Drupes	0.90 (0.38, 2.16)	1.44 (0.56, 3.69)	1.40 (0.55, 3.57)
Pomes	0.72 (0.48, 1.09)	0.89 (0.58, 1.37)	0.88 (0.58, 1.34)
Tropical fruits	0.73 (0.44, 1.22)	0.96 (0.55, 1.68)	0.95 (0.54, 1.67)
Total vegetables	0.85 (0.69, 1.04)	0.90 (0.72, 1.13)	0.89 (0.71, 1.12)
Allium	0.88 (0.35, 2.19)	1.28 (0.45, 3.68)	1.28 (0.45, 3.67)
Brassicaceae	0.51 (0.23, 1.15)	0.62 (0.25, 1.50)	0.62 (0.26, 1.51)
Fruit vegetables	0.82 (0.56, 1.21)	1.08 (0.71, 1.66)	1.09 (0.71, 1.66)
Pod vegetables	0.85 (0.29, 2.54)	0.95 (0.30, 2.97)	0.92 (0.29, 2.89)
Root vegetables	0.74 (0.34, 1.63)	1.31 (0.54, 3.17)	1.31 (0.54, 3.18)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake

Table F.8 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within adults 65+ years in the NDNS RP cohort

Intake (80 g/day)	Odds of high blood pressure (99% CI)		
n = 60	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.98 (0.81, 1.18)	1.02 (0.82, 1.27)	1.02 (0.81, 1.28)
Total fruits	0.87 (0.65, 1.16)	0.88 (0.63, 1.23)	0.88 (0.62, 1.23)
Total fruit juice *(125 g/day)*	0.90 (0.43, 1.85)	0.96 (0.44, 2.08)	0.95 (0.42, 2.14)
Dried fruits *(25 g/day)*	0.78 (0.34, 1.79)	0.66 (0.24, 1.84)	0.66 (0.23, 1.84)
Berries	0.70 (0.23, 2.14)	0.89 (0.26, 3.02)	0.88 (0.26, 3.00)
Citrus	0.95 (0.60, 1.50)	0.98 (0.60, 1.61)	0.98 (0.58, 1.65)
Drupes	0.86 (0.36, 2.06)	0.93 (0.35, 2.45)	0.93 (0.35, 2.46)
Pomes	0.71 (0.41, 1.24)	0.64 (0.35, 1.19)	0.64 (0.35, 1.19)
Tropical fruits	0.90 (0.42, 1.89)	1.08 (0.45, 2.54)	1.07 (0.45, 2.54)
Total vegetables	1.14 (0.81, 1.59)	1.25 (0.86, 1.83)	1.25 (0.84, 1.86)
Allium	1.64 (0.31, 8.68)	1.56 (0.23, 10.8)	1.56 (0.23, 10.8)
Brassicaceae	1.91 (0.56, 6.50)	2.73 (0.66, 11.2)	2.75 (0.66, 11.5)
Fruit vegetables	1.41 (0.74, 2.68)	1.51 (0.72, 3.16)	1.51 (0.72, 3.18)
Pod vegetables	0.43 (0.07, 2.78)	0.42 (0.06, 3.19)	0.40 (0.05, 3.22)
Root vegetables	1.25 (0.45, 3.51)	1.65 (0.51, 5.30)	1.65 (0.51, 5.33)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category
[b] Adjusted for all the above and energy intake

Table F.9 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within adults not consuming statins in the NDNS RP cohort

Intake (80 g/day)	Odds of high blood pressure (99% CI)		
n = 176	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.89 (0.80, 1.00)	0.92 (0.82, 1.04)	0.91 (0.81, 1.03)
Total fruits	0.81 (0.68, 0.98)	0.88 (0.72, 1.07)	0.87 (0.71, 1.06)
Total fruit juice *(125 g/day)*	0.77 (0.53, 1.11)	0.87 (0.60, 1.26)	0.85 (0.58, 1.23)
Dried fruits *(25 g/day)*	0.72 (0.42, 1.26)	0.97 (0.56, 1.70)	0.93 (0.53, 1.65)
Berries	0.80 (0.45, 1.43)	0.90 (0.51, 1.58)	0.90 (0.51, 1.58)
Citrus	0.89 (0.71, 1.11)	0.95 (0.76, 1.18)	0.94 (0.75, 1.17)
Drupes	0.98 (0.52, 1.85)	1.32 (0.68, 2.57)	1.31 (0.68, 2.53)
Pomes	0.72 (0.51, 1.02)	0.86 (0.60, 1.22)	0.85 (0.60, 1.21)
Tropical fruits	0.72 (0.46, 1.14)	0.85 (0.52, 1.39)	0.85 (0.52, 1.39)
Total vegetables	0.91 (0.76, 1.09)	0.97 (0.80, 1.17)	0.96 (0.79, 1.16)
Allium	1.13 (0.51, 2.53)	1.49 (0.61, 3.65)	1.50 (0.61, 3.67)
Brassicaceae	0.73 (0.38, 1.43)	0.91 (0.44, 1.86)	0.90 (0.44, 1.85)
Fruit vegetables	0.93 (0.67, 1.29)	1.13 (0.79, 1.61)	1.14 (0.80, 1.62)
Pod vegetables	0.64 (0.24, 1.74)	0.66 (0.23, 1.86)	0.63 (0.22, 1.80)
Root vegetables	0.97 (0.51, 1.81)	1.28 (0.64, 2.58)	1.28 (0.64, 2.56)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category
[b] Adjusted for all the above and energy intake

Table F.10 Total FV, fruit and vegetable subgroups intakes and the odds of HBP within non-smoking adults in the NDNS RP cohort

Intake (80 g/day) n = 103	Odds of high blood pressure (99% CI)		
	Age Adjusted	Fully-Adjusted [a]	Full Energy Adjusted [b]
Total fruits & vegetables	0.86 (0.75, 1.00)	0.89 (0.77, 1.04)	0.88 (0.75, 1.02)
Total fruits	0.82 (0.65, 1.03)	0.89 (0.69, 1.13)	0.87 (0.67, 1.11)
Total fruit juice *(125 g/day)*	0.71 (0.45, 1.13)	0.80 (0.51, 1.27)	0.77 (0.48, 1.22)
Dried fruits *(25 g/day)*	0.79 (0.39, 1.59)	1.04 (0.50, 2.15)	0.94 (0.44, 2.01)
Berries	0.88 (0.47, 1.66)	0.99 (0.52, 1.86)	0.95 (0.50, 1.81)
Citrus	0.88 (0.68, 1.14)	0.95 (0.73, 1.22)	0.93 (0.73, 1.20)
Drupes	0.88 (0.38, 2.04)	1.18 (0.49, 2.86)	1.13 (0.47, 2.71)
Pomes	0.65 (0.41, 1.05)	0.81 (0.50, 1.31)	0.79 (0.49, 1.28)
Tropical fruits	0.71 (0.41, 1.24)	0.79 (0.44, 1.43)	0.78 (0.43, 1.41)
Total vegetables	0.84 (0.66, 1.07)	0.90 (0.70, 1.15)	0.89 (0.69, 1.14)
Allium	0.99 (0.38, 2.57)	1.36 (0.45, 4.05)	1.33 (0.45, 3.96)
Brassicaceae	0.70 (0.29, 1.65)	0.81 (0.33, 2.03)	0.81 (0.32, 2.04)
Fruit vegetables	0.87 (0.56, 1.36)	1.08 (0.68, 1.71)	1.08 (0.68, 1.71)
Pod vegetables	0.92 (0.30, 2.84)	1.08 (0.34, 3.43)	1.05 (0.33, 3.32)
Root vegetables	0.65 (0.27, 1.58)	0.84 (0.32, 2.19)	0.85 (0.32, 2.21)

[a] Adjusted for age, BMI (categorical), physical activity (categorical), smoking status, socio-economic status, alcohol intake, mutual adjustment for total fruit or total vegetable intake, and mutual adjustment for fruit or vegetable not in the exposure category

[b] Adjusted for all the above and energy intake