THE RELATIONSHIP AMONGST DIETARY PATTERNS AND CARDIOVASCULAR RISK FACTORS IN CHINESE ADULTS

by

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ABSTRACT

China is facing epidemic of cardiovascular disease propelled by obesity, hypertension, dyslipidaemia, and hyperglycaemia. Epidemiological studies are continuing to show an increase in the prevalence of the aforementioned cardiovascular disease risk factors in the Chinese and studies are yet to shown signs of abating. Diet is able to affect the cardiovascular function by influencing the risk factors but very little is known about the diets of the Chinese. This thesis identified three dietary patterns (Non-nut and Non-cruciferous Vegetable, High Protein-High Fat, Omnivorous) using principal component factor analysis and examined the cross-sectional relationships with hyperglycaemia, hypertension, and metabolic syndrome in 20,146 middle-aged and older Chinese adults. The Non-nut and Non-cruciferous Vegetable diet was adversely associated with hyperglycaemia and the metabolic syndrome but showed no association with hypertension. The High Protein-High Fat diet was associated with reduced risk of hyperglycaemia and hypertension but exhibited no relationship with the metabolic syndrome. The Omnivorous diet was inversely associated with hyperglycaemia and the metabolic syndrome but demonstrated an adverse association with hypertension. In addition, the thesis developed a conceptual model and highlighted the putative mechanisms mediating the relationships between the High Protein-High Fat diet and cardiovascular disease risk factors using the structural equation model.

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LIST OF PUBLICATIONS

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ABBREVIATIONS

ABCA1	ATP-binding cassette transporter A1
ADA	American Dietetic Association
AMPK	AMP-activated protein kinase
ANOVA	Analysis of variance
Apo A1	Apolipoprotein A1
ATP III	Adult Treatment Panel III
BMI	Body mass index
CA	Cluster analysis
CFA	Confirmatory factor analysis
CF	Citrus fruit
CFI	Comparative fit index
CHD	Coronary heart disease
CI	Confidence interval
CV	Cruciferous vegetable
CVD	Cardiovascular disease
DASH	Dietary Approach to Stop Hypertension
EGIR	European Group for the Study of Insulin Resistance
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food frequency questionnaire
GBCS	Guangzhou Biobank Cohort Study
GHHARE	Guangzhou Health and Happiness Association for Respectable Elders
GLP-1	Glucagon-like peptide 1
HDL	High density lipoprotein
HR/OR	Hazard ratio/odds ratio
IDF	International Diabetes Federation
IL-1	Interleukin-1β
IL-6	Interleukin-6

InterAsia	International Collaborative Study of Cardiovascular Disease in Asia
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile range
KMO	Kaiser-Meyer-Olkin
LDL	Low density lipoprotein
MET	Metabolic equivalent
NCEP	National Cholesterol Education Program
NHS	Nurse's Health Study
OGTT	Oral glucose tolerance test
PCA	Principal component analysis
PCFA	Principal component factor analysis
PPAR	Peroxisome proliferator-activated receptor
PREDIMED	Prevrncion con Dieta Mediterranea
RAS	Renin-angiotensin system
RBP4	Retinol binding protein 4
RCT	Randomised controlled trial
RMSEA	Root mean square of approximation
RR	Relative risk
RRR	Reduced rank regression
SD	Standard deviation
SFFQ	Semi-quantitative food frequency questionnaire
SMHS	Shanghai Men's Health Study
SWHS	Shanghai Women's Health Study
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-α
TLI	Tucker-Lewis index
WHO	World Health Organisation
WHS	Women's Health Study

CHAPTER ONE

1.0

INTRODUCTION

Non-communicable conditions such as obesity, hypertension, dyslipidaemia, hyperglycaemia and diabetes mellitus, and cardiovascular disease (CVD) are complex, serious, and life threatening chronic conditions that have become a substantial burden in both the developed and developing nations [1-5]. The prevalence of these chronic conditions is reaching unprecedented levels [6, 7]. The World Health Organization (WHO) has projected that these chronic conditions will account for three-quarters of deaths by 2020 [7]. The basis for this projection is that in 2001, roughly 60% of 57 million reported deaths were due to chronic illnesses [8]. In 2012, 56 million deaths worldwide were reported and 68% of these were due to chronic diseases [9]. Over half of the deaths were attributable to CVD and over 40% of the deaths were in the elderly [9, 10]. There are now more individuals with these non-communicable diseases in China than in other economically developed nations grouped together [7].

China has undergone major industrialisation and economic development in the last 30 years, which has had a massive impact on the diet and lifestyle of the Chinese population [11]. Urbanisation and increasing use of technology has led to decreased physical activity. Increased deposable wealth has led to a considerable increase in consumption of calorie dense, refined foods, and a shift from plant to meat-based diets [12, 13]. The International Collaborative Study of Cardiovascular Disease in Asia (InterAsia) reported that 78.2% of the Chinese population are inactive [14]. The combination of these changes promotes obesity, high blood pressure, abnormal lipids, and high fasting plasma glucose, which significant determinants of CVD and subsequent mortality.

Diet is considered a major modifiable determinant of chronic disease [7]. Nutritional epidemiology focuses interest in the concept that several aspects of the diet or alterations in the diet have an effect on chronic diseases, both positively and negatively [7]. This notion is supported by epidemiological and randomised controlled trials (RCTs). Nutrition research has evolved over the last 125 years through an expanding knowledge base documenting how dietary nutrients and other bioactive compounds impact on health indices, and the associated mechanisms underlying disease [15-20]. The current knowledge regarding the relationship between diet and key chronic conditions relevant to the work in this thesis is discussed below.

1.1 Obesity

Obesity is an increase in adipose tissue to the extent that it impairs health [2, 21-23] and occurs when there is positive energy balance for a prolonged period. In clinical and epidemiological studies, proxy for overweight for height is estimated using weight and height measurements, which are used to calculate the body mass index (BMI) [24]. By dividing the body weight in kilograms by height in metres squared the BMI in kg/m^2 is calculated [24]. The WHO has defined obesity as a BMI $\geq 30 kg/m^2$ [21]. A limitation of BMI is that it does not take body fat distribution into consideration and is unable to differentiate between muscle and fat mass [25, 26]. Therefore, there has been a focus towards the use of waist circumference as a measure of metabolically active visceral fat [26, 27]. Waist circumference is positively correlated with visceral fat [23, 28, 29] and has been proposed as a more reliable measure of central obesity [26].

Despite the widespread use of waist circumference, no standardised protocol of waist circumference measurement has been established, which has resulted in use of variety of assessment techniques [30]. Four waist circumference measurements protocols are commonly used in research [26]. The first is measurement below the lowest ribs [31], the second is measurement at the narrowest waist [32], the third is measurement at the midpoint between the lowest rib and iliac crest [21, 33], and the fourth measurement is above the iliac crest [34]. Differences in the anatomical location of measurement and the choice of measurement site has been argued to influence the reliability of waist circumference measurements. Few studies have addressed this by comparing all four waist circumference protocols and the reliability coefficient of waist circumference measurements was high across all four anatomical sites (r = >0.98), which indicates a high degree of reproducibility [30, 35]. These studies have also highlighted that waist circumference is a highly reproducible measure of obesity, irrespective of the measurement site used. At present, studies are yet to demonstrate an advantage of one measurement site over the others.

There is no one universal waist circumference cut-point for different genders and ethnicities. For example, The ATP III has defined central obesity as having a waist circumference of ≥88 cm in females and ≥102cm in males for American adults whereas a cut-point of ≥80cm in females and ≥94cm in males has been proposed for European adults, and a cut-point of ≥80 cm in females and ≥90 cm in males has been proposed for Asian adults [36]. The waist circumference is a strong independent risk factor of hypertension, abnormal lipid levels, and hyperglycaemia [22, 27, 37, 38]. This relationship is independent of BMI [39].

By 2001, approximately 126 million middle-aged and older adults in China were classified as obese based on waist circumference cut-off points recommended for the Asian population [40]. A series of epidemiological studies have been carried out to estimate obesity prevalence in the Chinese. A cross-sectional study randomly selected 15,540 adults aged 35-74 years from Southern and Northern China and estimated obesity prevalence using the Asian specific waist circumference cut-off points [41]. The age standardised obesity prevalence was 13.9% (95% Confidence Interval 12.9-14.9) in females and 1.7% (95%CI 1.3-2.1) in males. The study also showed obesity rates were higher in urban areas compared to rural counterparts (27.3% vs. 13.4% in males and 43.8 vs. 36.6% in females).

The prevalence of obesity has increased progressively in China in the last two decades. A series of analyses conducted by the China Health and Nutrition Survey from 1991-2000 and 1991-2013 found that, over a 20-year period, obesity prevalence increased from 2.9% to 11.9% among females (age-standardised annual change in odds ratio (OR) 1.05, 95%CI 1.05-1.06) and from 4.6% to 11% among males (OR 1.08, 95%CI 1.07-1.09) [42]. The obesity prevalence figures of Chinese are lower compared to the estimates published by the UK and the US. The Health Survey for England recently reported the obesity prevalence to be 27% [43]. Using up-to-date information, the US National Health and Nutrition Survey [44] conducted in 2010 found obesity prevalence to be 35.7% (95%CI 33.8-37.7). Although the obesity prevalence in China appears not to be outstanding compared to the UK and US, China has the highest net population with obesity in the world [45]. If obesity prevalence in China stabilises, as in the U.S then obesity will continue to increase over the next few

years. Without effective interventions, China will follow the US footsteps into an obesity epidemic [42].

It is difficult to have a reliable estimate of the prevalence of obesity in China for several reasons. Firstly, there are apparently regional differences with higher prevalence of obesity in northern China compared to the south [40]. Secondly, studies have used different criteria for estimating obesity. Some studies have estimated the prevalence using the WHO's BMI cut-points, which are not applicable to Asians, being derived from predominantly Caucasian populations [46]. Some have suggested that Chinese experience obesity complications at a lower BMI and have recommended a lower BMI of $\geq 28.0 kg/m^2$ [47]. This recommendation has been reported to overestimate obesity prevalence in China, taking it to over quarter of a billion [46, 48]. Finally, studies of obesity prevalence in China demonstrate significant variation in study design and sampling.

1.2 Hypertension

Hypertension (high blood pressure) occurs when there is excess pressure in the arterial vessels as the blood circulates resulting in atherosclerosis and cardiovascular disease. Hypertension is an independent risk factor of coronary heart disease (CHD) and stroke [49]. However, the risk factors of hypertension are multifactorial and include both genetic and environmental factors [50, 51]. The British Hypertension Society [52] has defined hypertension as having a systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90mmHg (≥140/90mmHg) or receiving pharmacological treatment for hypertension. Having a systolic blood pressure ≥130 to <140mmHg and diastolic blood pressure ≥85 to <90mmHg is defined as pre-

hypertension.

The China Health and Nutrition Survey has evaluated the trends in hypertension prevalence through a series of surveys conducted in nine provinces. The study reported that in 1991, the estimated prevalence of hypertension was 14.5% and by 2009 it had reached 21.4% [53]. In 2005, hypertension was responsible for over 2 million premature deaths in adults aged greater than 40 years in China [54]. A national survey conducted between 2009 and 2010, in which, 50,171 participants were randomly selected from thirteen provinces from north and south China found age-standardised hypertension prevalence to be 29.6% (95%CI 28.9-30.4) [55]. More importantly, hypertension prevalence in the aforementioned Chinese study was comparable to the prevalence observed in the US National Health and Nutrition Examination Survey and Health Survey for England, which are 29% and 30%, respectively [56].

Dietary salt is a key contributor in the development of hypertension. Salt intake is very high in China and 80% of it comes from home cooking [57]. An up-to-date report has highlighted that 60% of Chinese with high blood pressure are salt sensitive [58], which is how blood pressure responds to dietary salt [59]. A family feeding intervention study carried out in north China also found higher level of salt sensitivity among the participants [60]. The study recruited 1,906 participants without chronic disease and current use of medication and discovered that not only did a high salt intervention followed for 7 days increased both systolic and diastolic blood pressure in females (6.4 mmHg, 95%CI 6.9-6.8 and 3.1 mmHg, 95%CI 2.7-3.5) and males by (5.2 mmHg, 95%CI 4.8-5.7 and 1.7 mmHg, 95%CI 1.4-2.1) but roughly 40% of the

participants were salt sensitive. Salt sensitivity has been argued to be associated with an increased risk of CVD mortality in both normotensive and hypertensive with higher mortality rates having been observed for salt sensitive individuals [61].

An RCT conducted in 412 hypertensive individuals demonstrated that salt sensitivity can be modulated by restricting salt intake and improving diet quality [62]. The study found that when salt intake was switched from high to low (sodium reduced by 100mmol per day) while maintaining normal eating habits for thirty days resulted in mean reduction in systolic and diastolic blood pressure by 6.7 mmHg and 3.5 mmHg, respectively. In comparison, participants who restricted their sodium intake by 100 mmol per day while consuming a vegetable and fruit based diet experienced a greater reduction in blood pressure (mean systolic 7.2 mmHg; mean diastolic 3.5 mmHg). This emphasises the significance of diet quality as a modulator of salt sensitivity of blood pressure.

1.3 Dyslipidaemia

Low high-density lipoprotein cholesterol (HDL-cholesterol) levels, high triglyceride levels, high total cholesterol, and higher low-density lipoprotein cholesterol (LDL-cholesterol) are key factors for cardiovascular risk [63]. High triglyceride and low HDL-cholesterol levels are independent risk factors for CVD [64]. High triglyceride levels are defined as ≥1.7mmol/L and the threshold for low HDL-cholesterol is ≤1.03mmol/L in men and ≤1.29mmol/L in women [63, 65]. Lipid abnormalities tend to cluster with obesity and hyperglycaemia (pre-diabetes and diabetes mellitus). They are key factors in the metabolic syndrome (see below) comprising of enlarged waist circumference, hyperglycaemia, and hypertension.

The prevalence of dyslipidaemia has been increasing in China for the past ten years. In 2005, dyslipidaemia prevalence among adults was found to be 22% [66]. A cross-sectional study recently estimated the in Chongqing, Southwest China [67]. The study randomly selected 5,375 residents and defined dyslipidaemia according to the National Cholesterol Education Program (NCEP) ATP-III criteria. Age-standardised prevalence of dyslipidaemia was estimated at 35.5% (95%CI 34.8-36.1). In another up-to-date analysis involving 387,825 Chinese adults, dyslipidaemia prevalence was 41.9% (95%CI 37.7-46.2) [68]. These figures are nearly twice as high as those observed in 2005. The Fourth Chinese National Nutrition and Health Survey [69], the InterAsia [70], and the Sino-MONICA [71] have all highlighted that China has a lower dyslipidaemia prevalence compared to the West. However, dyslipidaemia prevalence among the Chinese is reaching closer to a prevalence of 53%, which was detected among adults in the US National Health and Nutrition Examination Survey in 2012 [72].

1.4 Hyperglycaemia

Hyperglycaemia is a major risk factor for cardiovascular mortality, increasing its risk 4-fold [73, 74]. It is defined as having a fasting plasma glucose ≥5.6mmol/L or with a glucose tolerance test (OGTT), with glucose levels 2 hours after having an oral dose of ≥7.8mmol/L [75, 76]. Having a fasting plasma glucose ≥7.0mmol/L or 2h post-OGTT glucose ≥11.1mmol/L is defined as type 2 diabetes mellitus (T2DM). Pre-diabetes hyperglycaemia has been defined as having a fasting plasma glucose ≥5.6 to <7.0mmol/L [75]. The cut-points of fasting plasma glucose have been based on the threshold for the risk of development of micro-vascular complications [77]. In the last decade, the American Diabetes Association (ADA) and the WHO have revised their

diagnostic criteria. Studies conducted in the ethnic minorities have identified that fasting plasma glucose between 5.5mmol/L and 7.0mmol/L is associated with an increased risk of CVD whereas the threshold of 7.0mmol/L is more of an arbitrary figure [78].

The main risk factors of hyperglycaemia include non-modifiable factors such as family history and age [79], and modifiable factors such as obesity (particularly central obesity) [80, 81], diet [82, 83], low physical activity [84], and smoking [85].

Since the 1980s the prevalence of hyperglycaemia has dramatically increased in China from 1% in the 1980s to nearly 10% by 2010. The increased prevalence has been reported to affect affluent areas the most, unlike in western countries where diabetes is more prevalent in socially deprived areas and in poorer immigrant populations [86]. A cross-sectional study randomly selected 5,628 adults between age 20 and 94 years and used the ADA diagnostic criteria to estimate the prevalence of hyperglycaemia in Shanghai, China [87]. The age-standardised prevalence of hyperglycaemia was 6.9%. Another study conducted in Qingdao, China randomly selected 12,436 adults age 20 to 74 years and applied the WHO 1999 criteria to estimate hyperglycaemia prevalence [88]. The age-standardised prevalence of hyperglycaemia was 2.7% (95%CI 2.2-3.2) but the study also detected a higher prevalence of undiagnosed hyperglycaemia (4.2%, 95%CI 3.6-4.8).

The majority of epidemiological studies assessing hyperglycaemia prevalence in China are limited to specific regions and age groups; therefore, there are concerns about underestimation and overestimation of the prevalence. The prevalence of

hyperglycaemia also varies in different socioeconomic conditions. The criteria used to diagnose hyperglycaemia can also introduce limitations. For instance, the ADA does not recommend the use of OGTT in the diagnosis of hyperglycaemia, which is the gold standard for diagnosis according to the WHO [86]. It has been shown that neglecting the OGTT can result in underreporting and undiagnosed hyperglycaemia [89]. The variations in the study design and sampling between the studies also makes it relatively difficult to compare hyperglycaemia prevalence.

1.5 Metabolic syndrome

The metabolic syndrome is a cluster of three or more of the following; enlarged waist circumference, hypertension, high triglycerides, low HDL-cholesterol, and hyperglycaemia [90, 91]. Individuals who have the metabolic syndrome are at five-fold increased risk of developing T2DM and at three times greater risk of developing atherosclerosis [90]. At present, there is no universally accepted definition of the metabolic syndrome but different criteria have been proposed because of differences in opinions regarding its pathophysiology (Table 1.1).

The WHO set the first criterion in 1998, which stipulated that insulin resistance and micro albuminuria are the obligatory components [92]. In 1999, the European Group for the Study of Insulin Resistance (EGIR) introduced a new term "Insulin Resistance Syndrome," which excluded individuals with T2DM [93]. EGIR proposed this term due to co-occurrence of additional cardio-metabolic risk factors with insulin resistance [93]. Two years later, the NCEP identified a new and easy to use criteria for practical reasons [94]. Their criteria diagnosed individuals with metabolic syndrome if they had three or more of the risk factors mentioned above. In 2005, the

NCEP and the ADA updated the definition again [95]. The very same year, the International Diabetes Federation (IDF) considered waist circumference as an important risk factor in the pathophysiology of metabolic syndrome and introduced a new criteria which made waist circumference a core feature of it [4]. It has been argued that the waist circumference cut-points recommended for Caucasians are not representative for other ethnicities. Asians, for example have a higher body fat for a given BMI [96]. The diagnostic criterion was then refined to encompass ethnic differences in waist circumference. The Joint Interim Societies later suggested that no obligatory component is required and having minimum three of five components would qualify for the diagnosis of metabolic syndrome [90].

Several studies have estimated the prevalence of the metabolic syndrome. Past studies have used the NCEP ATP III criteria to estimate the prevalence, but limitations of using these criteria are the cut-points used for defining central obesity and hyperglycaemia, which are higher than recommended Asian thresholds. This results in the underestimation of the prevalence [97]. Some studies have addressed this by incorporating Asian specific waist circumference cut-points and a lower fasting glucose threshold [97-101].

The China Health and Nutrition Survey included 7,488 adults from nine provinces. By using the modified ATP-III criteria that incorporated a lower fasting glucose threshold and the Asian cut-point for obesity, the survey found that the age-adjusted prevalence of the metabolic syndrome was 21.3% (95%CI 20.4-22.2) [101]. An investigation into the Jiangsu area of China, where 3,914 participants were evaluated, found that the age-adjusted prevalence was 39.8% (95%CI 36.3-43.2) [102]. A survey

conducted in Beijing, China used the Joint Interim criteria among 2,334 older adults aged ≥60-years and found that the age-adjusted prevalence rate of metabolic syndrome was 58% (95%CI 56.0-60.2) [103]. Similar trends have been observed in surrounding areas such as Hong Kong. Thomas and colleagues [100] also applied the modified obesity and glucose cut-points to the ATP III criteria and found that the age-adjusted prevalence of the metabolic syndrome to be 21.9% (95%CI 20.4-23.4).

Table 1.1 Recommended criteria for the diagnosis of the metabolic syndrome.

World Health Organisation (1999)	EGIR (1999)	NCEP ATP III (2001)	International Diabetes Federation (2005)	Modified NCEP ATP III (2005)	Joint Interim Statement (2009)
Diabetes or insulin resistance or impaired glucose tolerance and two of the components below:	Insulin resistance and two of the components below:	Any of the three or more of the components below:	Ethnic specific waist cut-off and any two of the components below:	Any of the three or more of the components below:	Any of the three or more of the components below:
- Hypertension ≥140/90mmHg*	Fasting insulin in the first 25th percentile and hyperglycaemia ≥6.1mmol/L	- Hyperglycaemia ≥6.1mmol/L*	- Hyperglycaemia ≥5.6mmol/L	- Hyperglycaemia ≥5.6mmol/L*	- Hyperglycaemia ≥5.6mmol/L or diagnosed Type 2 diabetes mellitus*
- Triglycerides ≥1.7mmol/L	- Hypertension ≥130/85 mmHg*	- Hypertension ≥130/85 mmHg*	- Hypertension ≥130/85mmHg*	- Hypertension ≥130/85 mmHg*	- Hypertension ≥130/85 mmHg*
- HDL-cholesterol <0.9mmol/L in males and <1.0mmol/L in females	-Triglycerides ≥2.00mmol/L	- Triglycerides ≥1.69mmol/L*	- Triglycerides ≥1.69mmol/L*	- Triglycerides ≥1.7mmol/L*	- Triglycerides ≥1.7mmol/L*
- Body mass index >30 kg/m^2 or	- HDL-cholesterol <1.00mmol/L*	- HDL-cholesterol <1.04mmol/L in males and <1.30mmol/L in females*	HDL-cholesterol <1.04mmol/L in males and <1.30mmol/L in females*	- HDL-cholesterol <1.03mmol/L in males and <1.30mmol/L in females*	- HDL-cholesterol <1.04mmol/L in males and <1.30mmol/L in females*
- Waist-hip-ratio >0.90 in males and >0.85 in females	- Waist circumference >94 cm in males and >80 cm in females	- Waist circumference >102 cm in males and >88 cm in females	- Waist circumference** >94 cm in males and >80 cm in females	- Waist circumference 94 to 101 cm in Caucasian males and 80-87 cm in Caucasian females. >90 cm for Asian American males and >80 cm for Asian American females	- Waist circumference** >102 cm in males and >88 cm in females
Micro-albuminuria: urinary albumin excretion ≥20 µg/min or albumin: creatinine ≥30 mg/g					

* or taking medication

** population and country specific cut-off points apply.

Reproduced based on idea of Huang [104]

1.6 Introduction to nutrition and nutrition research

A food is a substance that is consumed by a living organism (animal, plant, human) for development, growth, repair, and fuel [105]. A diet is the sum of the foods eaten by a living organism [106, 107].

1.6.1 The reductionism paradigm

The diet that people eat can determine their health [7]. The goal of preventive nutrition is to identify optimal diets that provide individuals with the means to live healthily and longer [15, 108]. To achieve this, extensive research has been conducted, but the researchers have restricted themselves to the "reductionist" approach in the past and this practice continues to be dominant [15, 108]. The reductionist paradigm studies the diet by its individual parts [108, 109], such that it only focuses on the relationship between a single food compound (a group, an item, a nutrient) and chronic disease (figure 1.1 illustrates this by showing double straight line blue arrows) [15, 107, 108, 110].

The relationships that have been widely studied to date are dietary fibre and CHD [111], fruit and vegetable intake and CHD [112], dairy intake and CVD [113], and meat intake and CVD and hyperglycaemia [114], to name a few examples. Furthermore, by deconstructing foods into nutrients, the physiological impact they have on animals and humans have been studied using RCTs. This has led to an understanding of the mechanistic effect of the nutrient [15, 109].

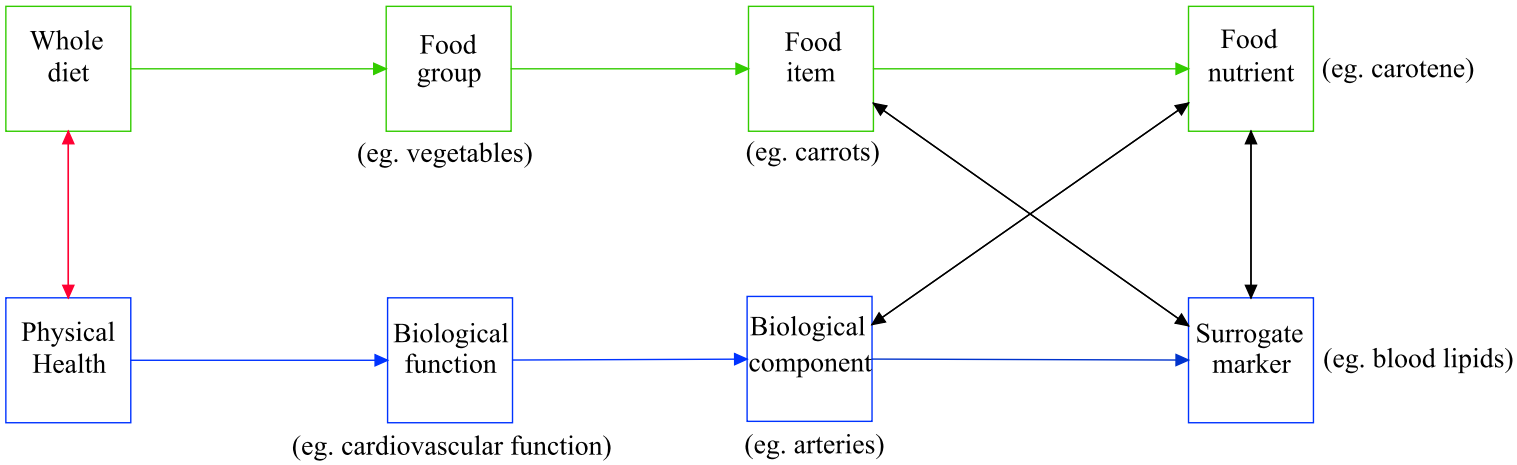


Figure 1.1 Visual presentation of analytical approaches employed in nutrition research. Blue arrows represent associations that are and have been commonly studied (impact of an individual food item or nutrient on a cardiovascular risk factor). Red arrows represent associations nutrition research has started to employ (assess the impact of whole diet on cardiovascular risk factor).

Diagram reproduced based on the idea of Hoffman [108]

1.6.2 Limitations of the reductionism approach

Despite the heavy use of individual food component analysis in the past, it has been recognised that the reductionist approach has key limitations [115].

1.6.2.1 Concept and design limitations

Foods contain a mixture of nutrients and individual food analyses are unable to assess the synergistic or antagonistic effects of nutrients contained in the foods [107, 110, 116, 117], or delineate the effects of nutrients that correlate [107, 110, 116]. For example, dietary fibre, phytochemicals, resistant starch, vitamins, minerals, and phenolic acids are constituents of whole-grain [118, 119]. The prospective analyses of the Nurse's Health Study (NHS; USA), including 75,521 participants aged 30-55 years, assessed the relationship between whole-grain intake and CHD [120]. A greater whole-grain intake was found to reduce the risk of CHD by 25% (Relative Risk 0.75, 95%CI 0.59-0.95) in the multivariable model. Although the study found an inverse relationship, it was unable to determine which nutrients in whole-grain was offering cardiovascular benefits. It was uncertain whether the beneficial effect was because of dietary fibre, vitamins, minerals, starch, or a synergistic effect due to the constituents. It was also difficult for the study to ascertain whether the reduced risk was related to differences in vegetable and/or fruit intake. For instance, it has been shown that a higher whole-grain intake is positively associated with a higher intake of fruits and vegetables which both contain similar nutrients to whole-grain [121, 122]. This suggests that the nutrients in the foods are related to each other [107, 110, 117]. Certain patterns are also strongly associated. For example, people who eat whole-grain also tend to consume more fruit and vegetables.

Another limitation of individual food analyses is that a food may produce favourable effect on one outcome and may affect another outcome differently [115]. An example is the impact of cruciferous vegetables on hyperglycaemia and hypertension. A analyses of the Shanghai Women's Health Study (SWHS; China) consisting of 64,191 females aged 40 to 70 years assessed the relationship between cruciferous vegetables and risk of hyperglycaemia [123]. After controlling for potential confounders the SWHS found that a greater intake of cruciferous vegetables was inversely associated with risk of hyperglycaemia (RR 0.70, 95%CI 0.56-0.86). In contrast, analysis of the Women's Health Study (WHS; USA) consisting of 28,082 females aged 39 to 89 years found a higher cruciferous vegetable intake to increase the risk of hypertension by 14% (Hazard Ratio 1.14, 95%CI 1.06-1.23) in the fully adjusted model [124]. This suggests that individual food analyses make it difficult to predict the effects a food will have on overall health.

1.6.2.2 Methodological challenges

Individual food analyses pose some methodological challenges. One is collinearity. For example, health conscious individuals have a higher intake of vegetable in their diet, which is positively associated with a higher fruit intake [125]. Since these foods are consumed together they have a high correlation coefficient value, which could result in collinearity [126, 127]. In regression models, collinearity can cause large standard errors that increase the uncertainty of the results. The regression analyses incorporating inter-correlated predicting factors may give invalid results about the influence they have on the disease [126].

When studying several foods, a potential pitfall is multiple comparison testing. Analyses of single food items increase the need of multiple comparison testing. This refers to where the relationship between the individual foods and the disease is assessed one at a time. This process may show a significant association by chance, especially false-positives [126, 128]. False-positives may also occur if a disease acts as a surrogate of the food item. An example is cheese and CVD mortality. Cheese has been shown to have no association with CVD mortality in prospective studies [129], but a positive relationship exists partly due to the fact that cheese is a marker of a "Western" or an unhealthy eating program for which, an adverse association with CVD mortality has been observed [130].

Considering the above mentioned arguments and deeper insight into nutrition and advances in methodology, nutrition researchers have looked beyond the reductionist paradigm and have focused on the holistic paradigm where a "whole diet" is and its impact on health considered [108].

1.6.3 Dietary assessment methods

Several methods have been developed to assess food intake of people and new methods are continuously being developed for this purpose. The widely-used methods are food frequency questionnaires (FFQ), 24-hour recalls, food and weighted food records, and diet histories [107, 131, 132]. In large epidemiological studies, the FFQ is frequently used tool [133]. The strengths and limitations are given after a brief description of these methods (Table 1.2).

1.6.3.1 Food frequency questionnaires

A FFQ captures the habitual diet of a respondent by asking the frequency of consumption during a reference period (daily, weekly, monthly, or yearly) [107, 134]. FFQs are based on either a short list of food items or an extensive list of items [135]. The lists are produced on the basis of main sources of food groups that are of interest or include items that explain the variability in food intake between people in the population, or foods commonly consumed by the study group [135]. FFQs can include food items ranging from 20 to 300. FFQs can be interview administered either by telephone or face-to-face or alternatively can self-administered using web-based or paper formats [132, 134].

The frequency of food consumption is assessed through a multiple response grid. The respondents are asked to specify how often a particular food or beverage is consumed with categories ranging from 'never' to '6+ per day' per day [134]. FFQs were developed to provide descriptive information about dietary consumption patterns. FFQs were then re-designed and ascribed portion sizes that provide nutrient information. Some FFQs such as the semi-quantitative also include portion size estimates where the respondents are asked to specify the frequency of portions of food items on a specific measure (e.g. 50 gram, 150 ml, ½ a cup, ¾ cup etc.) [134]. Some FFQs are also designed to include supplementary information on food preparation/cooking methods by specific types nutrient (e.g. sodium, fat etc.) whereas in others have open-ended sections, in which, respondents can specify items that are not specified in the list [135]. This can help determine the total diet of the respondent and may help identify individuals who have unusual eating habits.

FFQs are used in observational studies that examine association between diet and chronic diseases. To accomplish this the intake of individuals is ranked into low, medium, high or into tertiles, quartiles, and quintiles. The respondents can also be ranked broadly into specific food component categories. FFQs can also be used to identify dietary patterns using statistical approaches [136, 137]. FFQs are usually standardised therefore data entry and analyses is straight forward and can be performed in short time period. FFQs are also inexpensive and allow information on a large number of individuals to be obtained easily [134, 135].

The quality of data obtained from FFQs depends on its design. The FFQ is not very useful if it is poorly designed and does not contain a comprehensive food list that may represent dietary habits of the study group. An issue that is common in FFQ is the underestimation of unhealthy foods and overestimation of healthy foods. There is also evidence to suggest that overestimation increases with the length of the food list. It has also been shown that the likelihood of measurement error with FFQ is higher compared to other methods [134, 135]. There is also evidence that this can led to false negatives when assessing diet-disease relationship [138, 139].

1.6.3.2 24-hour recall

A 24-hour recall assesses an individuals food consumption in the preceding 24 hours [134]. This method has been used in several US national surveys because of its ability to obtained detailed information and due to a high response rate. The information is captured either via the internet, face-to-face interviews, and/or by the telephone [135]. In epidemiological studies, repeat or multiple 24-hour recalls are frequently used to adequately assess an individuals habitual diet because a single 24-hour recall has been

found to not be representative of such at an individual level and to catch variations in dietary intake [140].

The 24-hour recall assesses the order of food intake in a chronological order of consumption. Recalls use staged approaches to capture the dietary intake. The first stage includes and a list of foods and beverages where the respondent report everything he/she had to consumed in the previous day. The second stage includes collection of detailed information in which the respondent provides additional detail about the items in the list (e.g. meal time, full description of the food or drink including brand name where applicable, foods consumed in combination such as tea with sugar, recipes and preparation methods, food quantity, number of portions and portion sizes). The final stage involves an overview where the interviewer foods and beverages are reviewed in a chronological order. The interviewer also prompts for any information on eating occasions. In this step, any ambiguity regarding portion sizes, the type of food and beverage consumption is clarified [134, 135]. The 24-hour recall method has been shown to be particularly challenging for the elderly and for the children because of the involvement of various cognitive processes needed to recall the food items [141].

1.6.3.3 Weighted food records or diaries

Weighed food records is a detailed dietary assessment method that have commonly been used in surveys conducted in the UK [142]. Participants undertaking a weighed food record are provided weighing scales along with instructions and record sheets on how to record their food intake. Food portions on the plate are weighed and accurately described in ample detail on the record sheet. This allows for greater precision and

accuracy compared to regular food records. The composition of the dish, food preparation method, brand names, and supplementation are also recorded. For meals eaten out or at restaurants the descriptions of the amounts consumed is provided [134, 135].

Weighted records are usually kept for 3-7 days. The advantage of 7-day record is that dietary assessment in not biased towards certain days of the week, which is critical for foods consumed infrequently [135]. The method is believed to be most precise among dietary assessment methods but respondents may either subconsciously or consciously alter their dietary habits which affects its accuracy and reliability [143].

1.6.3.4 Diet histories

Diet history is a retrospective method used frequently in clinical practice [135]. Diet histories are used to obtain long term (e.g. 6 to 12 months) dietary intake of an individual [134]. It is also the method of choice of cohort studies of older adults [144-146]. It has been suggested that this method is suitable when detailed information about food intake at a specific life stage is needed at an individual level. The caveat is that respondent is willing to give an accurate account of past food intake [135].

Diet histories are structured interviews about habitual intake of food groups consumed in the past seven days followed by a cross check to clarify information about usual food intake in the past 6 to 12 months. Diet history consist of frequency of food consumption and 24-hour recalls [134, 135]. Portion sizes are estimated using photo models and household measures or alternatively checked by weighing [134, 135, 144].

Table 1.2 Strength and limitations of dietary assessment methods

Dietary assessment method	Strengths	Limitations
Food frequency questionnaire	- Have a low respondent burden - Assesses habitual food and beverage intake over an extended time period - Inexpensive and low cost compared to other assessment methods - Can be self administered through mail - Interview administered FFQ's allows more data collection and eliminate respondent literacy and numeracy skills - Open sections permits the respondent to specify foods not in the list - Can be modified to focus on specific food groups (e.g. dairy, fruits) or specific nutrients - Nutrient intake can be obtained with portion size estimates - Analyses of FFQ is quick if respondents' responses are standardised - Information on cooking/preparation procedures, condiment use, and seasonal items can be included - Data entry error is minimised with computer readable FFQs	- Reported intake can be limited because a comprehensive list of all foods and beverages cannot be included - Relies on respondent memory for accuracy - Underestimation (less reporting to unhealthy foods) and overestimation (over-reporting of healthy foods) can introduce bias - Requires literacy and numeracy skills for self-administered FFQ - Portion sizes can be difficult to estimate and sizes described as small, medium, large are not likely to have a commonly accepted meaning - Respondents may fulfill questionnaire for foods they are familiar with and not complete - Self-administered version may lead to misinterpretation of some questions - FFQs for a specific study group is unlikely to be appropriate for another unless eating habits are very similar - The food list in the FFQ may not reflect usual dietary patterns of the study group population - Basic food category FFQ can make take-away foods difficult for the respondents to classify

Table 1.2 Strength and limitations of dietary assessment methods cont.

Dietary assessment method	Strengths	Limitations
Food frequency questionnaire		- Validity can vary widely between foods and nutrients from the same FFQ - Grouping the foods into individual items can make some questions difficult to answer
24-hour recalls	- Low respondent burden - Does not alter the respondents dietary intake pattern - Does not require literacy - Quick to complete - Telephone 24-hour recalls are less expensive than 24-hour recall interviews - Web based procedures can reduce admin cost	- Single 24-hour recall does not represent the habitual food intake - Relies on memory to accurately recall diet intake - Potential of recall bias - Interview burden can be high and result in high cost - Repeat 24-hour recalls are required to represent habitual food intake but increases time and cost of analysis
Weighted food records	- Considered the gold standard in dietary assessment - Does not rely on respondents' individual memory and recall as the food/drink are recorded at the point of consumption - Portion sizes are not relied upon estimation - Capture items consumed on a regular basis	- Costly, labour intensive, and time consuming for respondent and researcher - Extracting nutrient data from the dietary data is difficult - High burden on the respondent, which can affect compliance - Requires literacy and numeric skills

Table 1.2 Strength and limitations of dietary assessment methods cont.

Dietary assessment method	Strengths	Limitations
Weighted food records	- Detailed descriptions of the foods consumed and all eating occasions are provided - Excellent estimates can be obtained for food items/groups, nutrients, and energy	- Respondents can modify their diet to make the recording process easier - Food eaten out can be difficult to weigh - Minimum 3 days are required because of daily variations in the diet. - More than 3 days of recording can result in less accuracy at the ends due to study fatigue - The respondents' intake recorded may not represent their typical diet - Foods consumed less than twice per week may not be captured
Diet records	- Requires literacy and numeracy skills - Captures the respondents diet in detail and one interview is necessary for a particular time period - Details of individual foods items and groups is captured - A detailed information about food eaten less frequently is obtained - Nutrient and energy estimates are reasonably accurate	- Interviewer needs to be knowledgeable about local foods - Dietary information is dependent upon the interviewers skill - Sessions lasts 60-90 min and can be burdensome for older individuals resulting in fatigue and not being able to complete the interview - High possibility of recall bias because the respondents may not remember everything they eat - Capturing erratic eating habits (e.g. shift workers) is a challenge

Table 1.2 Strength and limitations of dietary assessment methods cont.

Dietary assessment method	Strengths	Limitations
Diet records		- Underestimation (less reporting to unhealthy foods) and overestimation (over-reporting of healthy foods) can introduce bias - Portion sizes of past meals can be difficult to estimate and requires food models and photographs to aid in the estimation of portion sizes - Telephone interviews are difficult to conduct and may necessitate home visits for completion of records - A costly procedure because it requires food coding and highly trained staff

Adapted from Medical Research Council [135]

1.6.4 Dietary patterns

Dietary patterns are defined as the variety, quantity, and frequency of consumption of foods and beverages [106]. The rationale for examining dietary patterns is simple. It accounts for the cumulative effects of a range of individual foods [116, 117]. Dietary pattern methods were developed on the basis of two principles. The first is that compared to individual foods, a whole diet pattern can describe more variation in how and what people really eat. The second is that a composite of many different foods could provide a better understanding of the overall role of diet [105, 107, 110, 115-117, 128].

In observational epidemiology, diets cannot be measured directly and therefore depend on statistical extrapolation methods [116, 117, 147]. There are two approaches of examining dietary patterns and these are through a priori and a posteriori methods [110, 116, 117, 147]. A priori, also called beforehand, is hypothesis oriented, whereas a posteriori is empirically derived, and thus not pre-defined [116, 147, 148]. Both approaches are described below.

1.6.5 Hypotheses oriented – a priori methods

1.6.5.1 Dietary scores and indices

Hypothesis-oriented dietary patterns have several categories [149]. These are food-based diet scores [149, 150], diet index scores [149, 151], diet diversity score [149, 152], and nutrient adequacy scores [149]. All scores or indices are based on prior or current nutritional knowledge hence the term a priori [117, 153]. Hypothesis-oriented scores are constructed by combining foods items, food groups, nutrients, or a combination of all three [154].

Diet scores contain a number of dietary factors, for which an individual is allocated a point for intake above a certain cut-point and then an overall score is calculated that aims to rank individuals to determine how close their eating habits are to the pre-specified dietary recommendations/guidelines [155-157]. For example, a diet score uses food items that are believed to be beneficial or harmful for health. Higher points are given for a greater intake of the foods that are deemed beneficial. Few or no points are given for foods that are considered harmful [155, 158, 159]. An overall summary score is then generated by combining the scores already given to the foods [155-159]. The summary scores are either used as a continuous score or used as categorical variables (dichotomised or percentiles) in statistical analyses, and the relationship between the final score and the chronic disease is then assessed [126].

The attractive feature of hypothesis-oriented diet scores is that it allows the researcher to assess if his/her study sample meets the diet recommendations. These are based on current knowledge and are only as good as the evidence and recommendations they are based on [148, 149]. They rely on the information at hand but are subject to many arbitrary decisions that are needed to develop a score [148, 160]. These include dietary factors to be included, how to quantify their intake, selection of cut-points to be used, and how to score them [117, 160]. The characteristics of diet scores are shown in Table 1.3.

1.6.5.2 Pre-existing hypothesis-oriented dietary patterns

Several diet scores have been developed in the last twenty years [154, 160]. Most diet scores have been modifications of diet plans such as the Mediterranean Diet and Dietary Approach to Stop Hypertension (DASH). Others are modification of indices

which are based on national guidelines for a healthy diet. A breakdown of these are provided in Appendix 1.

Table 1.3 Characteristics of diet score and indices methods.

Rationale	Characteristics	Arbitrary Considerations	Strengths	Limitations
- To assess if study participants meet the guidelines of the diet	- Determines the diet quality of individuals by ranking them from low to high	- Decide which items to include (food groups, or individual foods, or nutrients)	- Aims to characterise the total diet	- Indices that allocate points to component consider intake variability but not the amount
- To assess the frequency of consumption of healthy and unhealthy foods	- Those with a medium score are susceptible to mixture of various exposures	- Selection of number of items to include in the development of the score/index	- Intuitively appealing	- Relies on the dietary guideline it's based on and are not disease specific
	- Counts the number of items that are frequently eaten together	- Whether or not to adjust for energy	- Analytically simple	- Relies on arbitrary decisions
	- Forms a gradient	- Decide how to scale and score the diet, and how to select a cut-off criterion	- Reproducible and comparable	- Quality of the food pattern and the results are dependent on the quality of the information the method is using
		- Whether or not an item should carry more weight in the score or not	- Outcomes are easily interpretable and may show to be meaningful	

Adapted from Slattery [128]; Moeller et al. [149]; Wirfalt et al. [161]

1.6.6 Hypothesis oriented dietary patterns and cardiovascular risk factors

Many investigations, especially clinical, have been conducted to determine which diets are efficient in modifying surrogate markers of CVD hence lowering the risk of CVD. The dietary patterns that have been most extensively studied are the Mediterranean [162-167], the DASH [62, 168-170], the High Protein-High Fat [165, 171, 172], low-fat, low-saturated fat [167, 173], and low-glycaemic index diets. The Mediterranean [162-166], the DASH [62, 168-170], and the High Protein-High Fat diets [165, 171, 172] are well studied because RCTs have shown that these can reduce weight and improve a range of cardiovascular risk factors, which are clinically related to a lower risk of occurrences of adverse outcomes. RCTs also suggest that in comparison, the low-fat, low-saturated fat, and low-glycaemic index diets produce less cardiovascular benefits [167, 173]. The High Protein-High Fat diet is described in detail in subsequent chapters therefore this section will focus on the association between the Mediterranean and the DASH diets and surrogated markers.

1.6.7 The Mediterranean diet

The Mediterranean diet was described in the 1960s and the adherence to this diet was argued to reduce risk of CVD and increased longevity in individuals living in the Mediterranean region [174]. There are many variations of the Mediterranean diet in the literature, but the definition of it is consistent amongst studies because all emphasise increased consumption of similar foods [175, 176]. These include a higher intake of fruits, vegetables, grains preferably whole-grain, nuts/legumes/pulses, olive oil with a moderate intake of meats/fish, red wine, dairy, and a lower intake of confectionary [177]. Some Mediterranean diets give an overview of the frequency and

the amounts of the foods that should be consumed. For instance, the frequency of intake includes daily, weekly, biweekly, and monthly. The amount, however, is given in subjective terms that include high, low, moderate etc. [175]. The number of serving of foods is absent in most studies. Furthermore, most have also failed to specify the amount consumed of tea/coffee, condiments, sauces, and spreads [175].

1.6.7.1 The Mediterranean diet and waist circumference

A meta-analysis of 5 RCTs (n = 2,522 participants) with 2 year follow-up was carried out to assess the effects of the Mediterranean diet on waist circumference [178]. Roughly, 1,581 subjects were randomised to the Mediterranean and 941 to the low-fat diet. After 2 years the weighed mean difference in waist circumference between the Mediterranean and the low-fat diet was -0.89 cm (95%CI -1.96 to 0.18). Significant heterogeneity was observed amongst studies. Most did not perform an intention-to-treat analysis and several RCTs gave greater support to the Mediterranean diet group. Generalisability to other populations is difficult because over half of the studies were performed in the Mediterranean region where lifestyle and eating habits are different than of those in other western and Asian countries [119].

1.6.7.2 The Mediterranean diet and blood pressure

The effects of the Mediterranean diet on blood pressure were reported in the secondary analysis of the Prevención con Dieta Mediterránea or the "PREDIMED" study (Spain) [179]. Briefly, the PREDIMED randomised 7,447 participants at risk of CVD to: Mediterranean diet with nuts "MD+nuts" (n = 2,454); Mediterranean diet with virgin olive oil "MD+EVOO" (n = 2,441); the low-fat diet (n = 2,350). The Mediterranean groups were given dietary guidelines at baseline and quarterly

thereafter. The low-fat diet group received usual care and verbal encouragement to help maintain the diet. The intervention was stopped after a median 4.8 years due to early benefits of the diets on the cardiovascular function. Results according to intention-to-treat analysis showed that after 4 years, compared to the low fat diet, the MD+nuts and the MD+EVOO diets reduced diastolic blood pressure by -0.65mmHg (95%CI -1.15 to -0.15) and -1.53mmHg (95%CI -2.01 to -1.04), but the effect was not deemed to be clinically important. The relationship with systolic blood pressure was non-significant.

1.6.7.3 The Mediterranean diet and dyslipidaemia

A systematic review and meta-analysis of 29 RCTs (n = 4,105) determined the effects of the Mediterranean on dyslipidaemia [180]. The review found that 2,202 participants were randomised to the Mediterranean diet and 1,903 to the control diets. The results showed that a closer adherence to the Mediterranean diet was associated with no significant increase in HDL-cholesterol (0.03mmol/L, 95%CI 0.01-0.05) and reduction in triglycerides (-0.06mmol/L, 95%CI -0.12 to -0.02) compared to the control diets. The results of this review are unreliable because of serious heterogeneity between the RCTs and pooling of results from non-congruent studies.

1.6.7.4 The Mediterranean diet and hyperglycaemia

The effects of the Mediterranean diet on hyperglycaemia were studied by an RCT [181]. It recruited 215 participants and randomised them to the Mediterranean diet restricted in carbohydrates (n = 108) or the low-fat diet (n = 107). The Mediterranean diet consumed 50% energy from complex carbohydrates and replaced red meats with poultry and fish. Energy intake was similar in both groups (1,800 kilocalories per day

for males; 1,500 kilocalories per day for females). The groups received dietary advice monthly for one year and then bimonthly thereafter. Twenty participants were lost to follow-up and the results were performed using intention-to-treat analysis. The Mediterranean diet lowered hyperglycaemia by -0.9mmol/L (95%CI -1.6 to -0.2) compared to the low-fat diet. Although the Mediterranean diet appeared to improve glycaemia beyond that of the control diet, more studies are needed to verify this.

1.6.7.5 The Mediterranean diet and metabolic syndrome

The PREDIMED study also assessed the effect of the Mediterranean diet on the metabolic syndrome in high-risk participants. A unique feature of this study was that it was able to assess the one year effect of the dietary interventions on metabolic syndrome status [164], which was defined according to the ATP III criteria [182]. The study randomised 1,224 participants to the MD+nuts (n = 419), MD+EVOO (n = 423), and control (n = 404) diets. Of the 1,224 participants, 61% had the metabolic syndrome. After one year the OR of reversion of metabolic syndrome was 1.7 (95%CI 1.1-2.7) and 1.4 (95%CI 0.8-2.1) for the MD+nuts and MD+EVOO diets compared to the control diet. This relationship was independent of prognostic factors, which suggests that the diet may reduce the risk of metabolic syndrome [164]. The intervention studied participants at higher risk of CVD, it shows the benefits of the diet in this population, but the results cannot be extrapolated to other populations.

1.6.8 Dietary Approaches to Stop Hypertension

The DASH diet was developed by the National Heart, Blood and Lung Institute in 1997 as a non-pharmacological intervention to lower blood pressure in individuals with hypertension who are at risk of developing CVD [183]. The DASH diet trial

(USA) was designed with the aim that one food is unlikely to produce blood pressure lowering effect as well as a combination diet with variety of foods [184]. The DASH diet emphasises a higher intake of fruit, vegetables, whole-grains, nuts/seeds/legumes, low-fat dairy, and lower consumption of lean meats, sweetened beverages [62, 168]. This combination ensures that the diet has sufficient nutrients like protein, fibre, potassium, magnesium, and calcium [183], all that have been shown to lower blood pressure [168, 169]. The combination of these foods also ensured that the diet met nutrient requirements recommended by the US Institute of Medicine [183].

1.6.8.1 Dietary Approaches to Stop Hypertension and waist circumference

An RCT compared the effects of the DASH diet to a weight reducing and a control diet to determine the effects on waist circumference [169]. The study randomised 116 participants with the metabolic syndrome to either: a 500 calorie deficit DASH diet (n = 38); a 500 calorie deficit weight reducing diet (n = 38); or the control diet (n = 40). Nutritionists working on the study delivered the intervention and met with the DASH diet group monthly for counselling, whereas the weight reducing and the control groups received no support. The results were analysed using intention-to-treat method and stratified by gender. The DASH diet was found to be more effective in reducing waist circumference in males (-9.0cm, 95%CI -12.0 to -6.0) and females (-4.0cm, 95%CI -6.0 to -2.0) compared to the weight reducing and control diets. The DASH group receiving greater support could have biased the results towards the benefit in the DASH group. The DASH diet may be effective in reducing waist circumference in high-risk individuals, but more RCTs are needed to substantiate this.

1.6.8.2 Dietary Approaches to Stop Hypertension and blood pressure

The most impressive benefits of the DASH diet are related to blood pressure, its primary aim. The DASH trial was an short-term adequately designed study, which randomised 459 hypertensive participants to DASH diet (*n* = 151); control diet, which was typical American diet (*n* = 154); and fruit and vegetables diet (*n* = 154) [184]. For 8 weeks, all participants in the DASH and fruit and vegetable were provided with foods including prepared meals to consume. The control group maintained their usual eating habits. The drop out rate was not substantial and the results were analysed according intention-to-treat. The DASH diet reduced systolic and diastolic blood pressure by -5.5mmHg (95%CI -7.4 to -3.7) and -3.0mmHg (95%CI -4.3 to -1.6) compared to the control diet. The fruit and vegetable diet also led to reduction in systolic blood pressure by -2.8mmHg (95%CI -4.7 to -0.9) compared to the control diet. The two-fold reduction in blood pressure detected with the DASH diet suggests that other components of the DASH diet besides fruits and vegetables offer benefit beyond that of fruit and vegetable alone on blood pressure. The effects were more pronounced in those with hypertension at baseline. These results were subsequently confirmed in the DASH-sodium trial [62] and in the PREMIER study [185].

1.6.8.3 Dietary Approaches to Stop Hypertension and dyslipidaemia

A handful of RCTs have tested the relationship between the DASH diet and lipids in secondary analyses, but the results across studies are inconsistent with the majority reporting no relationship. A systematic review was performed to clarify this [186]. The review included 12 RCTs (*n* = 1,263) with study duration from 2 weeks to 6 months. Six hundred and thirty-three participants were randomised to the DASH diet and 633 to the control diets (typical, low-fat, healthy, DASH combined with exercise,

weight loss diet). The authors found no association between the DASH diet and HDL-cholesterol (0.003mmol/L, 95%CI -0.05 to 0.05) and triglycerides (-0.005mmol/L, 95%CI -0.06 to 0.05). There was significant heterogeneity between studies. Most studies performed no intention-to-treat analysis, the diet was not homogeneously prescribed across studies, and there was pooling of incongruent studies.

1.6.8.4 Dietary Approaches to Stop Hypertension and hyperglycaemia

RCTs have assessed the relationship between the DASH diet and hyperglycaemia, but the results across studies are contradictory. RCTs were either too short in duration or had a very small sample size to detect an effect. A systematic review and meta-analysis of 9 RCTs with follow-up from 13 weeks to 16 months evaluated the impact on glycaemia [187]. The review included information from 974 participants in which 485 participants were randomised to the DASH diet and 489 assigned to the control diet. The review found no significant effect of the DASH diet on hyperglycaemia (-0.26mmol/L, 95%CI -0.56 to 0.05). Significant heterogeneity between studies was detected. Most studies were not blinded and the diet was not homogeneously prescribed across studies which suggests inappropriate pooling of studies. Robust intervention studies that address the effects of the DASH diet on glycaemia are still needed.

1.6.8.5 Dietary Approaches to Stop Hypertension and metabolic syndrome

No RCTs to date have assessed the relationship between the DASH diet and the metabolic syndrome in adults. A cross-sectional study assessed if adherence to guidelines closer to the DASH diet was associated with a lower risk of developing metabolic syndrome in 420 randomly selected healthy Iranian nurses [188]. The

participants' diet was assessed using a validated 106-item semi-quantitative food frequency questionnaire (SFFQ), in which the participants described how frequently they consumed the foods during the day. Food items were arbitrarily categorised into eight DASH diet components. The study used an internally validated scoring approach ranking the participants' food intake according to quintiles [189]. For fruits, vegetables, whole-grain, legumes/nuts, and low-fat dairy, the participants received a score from 1 to 5. The scoring was reversed for red and processed meat, sweetened beverages, and sodium assigning higher points for a lower intake and lower points for a higher intake. The sum of all eight components resulted in the total DASH-style diet score. The metabolic syndrome was defined using the Joint Interim Statement [90]. In the multivariable model the DASH-style diet was inversely associated with the metabolic syndrome (OR 0.22, 95%CI 0.09-0.74) [188]. This approach is unable to adequately reflect a participant's adherence to the diet recommendation. The quintile ranking assumes that participants, who otherwise may not consume the diet, are within the 25th percentile of the guidelines potentially resulting in biased estimates. This study also had a relatively small sample size and a wider confidence interval, raising the uncertainty of the findings. Due to cross-sectional design, the study was unable to infer causality and establish temporality.

1.6.9 Lack of weight loss adjustment in randomised controlled trials

Improvements in the surrogated markers in RCTs have been frequently observed with intervention diets comparison to control diets [171]. It is yet to be clarified which diets are most optimal for reducing the risk of CVD. Most diets in RCTs have resulted in weight loss, which is a major determinant for improvements in the surrogated markers [190]. In studies where weight loss between treatment groups was not

significant, a correlation between weight loss and cardiovascular risk factors has been detected indicating the importance of weight loss. Trials have frequently failed to adjust for the effects of weight loss between treatment groups making it difficult to determine whether it is the diet or weight loss that is responsible for the improvements. Future trials are encouraged to re-evaluate their study design to address this. Trials should adjust for weight loss in the analysis and ensure that treatment arms are iso-energetic, which balances the energy expenditure of participants [191]. If these factors are not accounted for then the results of the RCTs are likely to be speculative.

1.6.10 Empirical – a posteriori methods

Empirically derived dietary patterns are identified using multivariate analysis techniques such as principal component factor analysis (PCFA) or principal component analysis (PCA) [122, 192], cluster analysis (CA) [193, 194], and reduced rank regression (RRR) [195, 196]. Epidemiologists use these techniques when they have dietary information at hand, but do not wish to infer what the diets of their study group are, hence preferring data-driven approaches.

1.6.10.1 Principal component factor analysis

PCFA is a variance reduction statistical analysis technique that combines food items based on how strongly they correlate with each other [116, 147-149]. PCFA is a algebraic method that reduces the number of highly correlated food items into a smaller number of components or factors [126]. Each component has a specific combination of foods that are either positively or negatively correlated with the

component. These components are the underlying dietary patterns or eigenvectors [116, 197].

The dietary patterns identified by the PCFA corresponds with the number of food items that are entered into PCFA, the reason being that PCFA uses all nutritional information for extraction without loss of information [126]. However, retaining all patterns is difficult, therefore studies select fewer dietary patterns that explain most of the information [126]. Dietary patterns are usually retained if they have an eigenvalue above 1 and scree plot test [137, 198-200]. An eigenvalue is a unit of amount of variation explained by a dietary pattern [201]. It explains how important a dietary pattern is in distinguishing the nutritional information it is using and allows the researcher to determine if the dietary pattern explains enough variability so that it is of importance [128]. Some studies, however, have arbitrarily set higher eigenvalues to reduce the number of dietary patterns especially when a large number of dietary patterns in the study have an eigenvalue above 1 and its difficult to keep them all due to the interpretation issue [202-207].

The dietary patterns identified by PCFA are not always interpretable after extraction. If the initially extracted dietary patterns are not interpretable then rotation is usually performed on the patterns to simplify their structure, which geometrically transforms the dietary pattern structure and aligns a small group of food items with a specific dietary pattern [126, 128, 208]. Rotation does not affect the relationship between the food items and the dietary patterns. The commonly used rotation methods are orthogonal (varimax) and oblique (promax) [208]. In dietary pattern analysis the orthogonal method is preferable because orthogonal rotation ensures that the dietary

patterns are independent of each other. All independent dietary patterns can be included in the regression model as collinearity is no longer an issue [153]. A summary score is then calculated for each individual for each dietary pattern, which represents an individual's concordance to a particular dietary pattern [161, 192]. The scores are subsequently used in regression or correlation analyses to assess the relationship with chronic disease [116, 121, 122, 137, 192, 205].

PCFA is helpful in exploring what lies beneath the nutritional information when no specific hypotheses have been formulated [149, 161]. However, PCFA involves a great deal of subjectivity on the researcher's part [128, 147, 149, 161]. The terminology of PCFA is described in Table 1.4 and Table 1.5 provides an overview of the characteristics, strengths, and limitations of PCFA.

Table 1.4 Terminology of principal component factor analysis method.

Principal Component Factor Analysis	Eigenvector	Eigenvalue	Scree Plot	Orthogonal Rotation	Factor Loading
- Is a multivariate statistical analyses technique	- An eigenvector is a vector that represent the "characteristic" of a "matrix," in which, a set of numbers are arranged into fixed number of column and rows	- It's a specific value that represent the characteristic of the overall matrix of the eigenvector	- A visual graph that plots the number of factors and their corresponding eigenvalue in order of extraction or in a descending order	- A geometric spinning process that maintains the axes of the factors at 90 degrees.	- Is a correlation coefficient between the variable and the factor, which aims to help understand the degree of strength of the relationship between the two
	- A dietary pattern is an eigenvector	- It explains the amount of variance that a factor has	- It also shows the shape of the curve to assist in evaluating the cut-off point	- Orthogonal rotation keeps a factor independent of or to all orthogonally rotated factors	

Adapted from Hair et al. [209]; Kline [210]

Table 1.5 Characteristics of principal component factor analysis method.

Rationale	Characteristics	Arbitrary Considerations	Strengths	Limitations
- To reflect dietary habits	- Identifies composites of diets based on how well food items correlate with each other	- Whether or not to reduce the numbers of variables	- Information may be used to generate hypothesis and theory	- Data is limited on validity and reproducibility
	- Subjects are allocated a low, medium, and high diet score on each pattern, which conforms their adherence	- Whether or not to adjust for energy	- Able to characterise the total diet	- Relies on arbitrary decisions by the researcher
	- Forms a gradient	- Numbers of factors to retain	- Good statistical power	- Rigorous tests to assess validity is performed by few
		- Choice of eigenvalue and rotation	- Help describe eating behaviours	- Interpretation may be difficult
		- Selection of scoring coefficients cut-off criteria	- Can help determine if pattern analysis provide more information than individual foods	- Quality of the food pattern and the results are dependent on the quality of the information the method is using
		- How to label the dietary pattern		

Adapted from Slattery [128]; Michels and Schulze [147]; Moeller et al. [149]; Wirfalt et al. [161]; Newby et al. [211]

1.6.10.2 Cluster analysis

CA is a multivariate analyses technique that takes a different approach to PCFA. CA generates clusters of people who share similar eating habits [149, 212, 213]. CA uses geometry or a geometric measure of dissimilarity known as the Euclidean distance to accomplish this. The Euclidean distance is defined as measure of a distance between two people or two objects [209, 214]. The similarity between people is determined according to this distance. For a number of food items inputted into CA, the people are placed according to their scores on them. People who are closer to each other on the scores are considered similar [214].

Once the similarity between people is captured, an algorithm is used for dietary pattern recognition. CA uses the Ward's (the hierarchical) and the K-Means (non-hierarchical) algorithms [211] but the latter (K-Means) is preferred [161, 194]. There is a fundamental difference between the two methods. The Ward's method generates dietary patterns and continues to do so until the clustering procedure is complete. Upon completion the dietary patterns are selected by examining a dendrogram [214]. If employing the K-means method, it is a pre-requisite to identify the numbers of dietary patterns to be extracted in advance [149, 161]. After extracting the dietary patterns they are examined to see if the patterns are interpretable. CA places the participants to one cluster only. The dietary patterns themselves are then used as an independent factor in correlation or regression analysis [193].

One limitation is that it involves a great deal of subjectivity. Table 1.6 lists the characteristics, strengths, and limitations of CA. The interpretation of CA-derived dietary patterns can sometimes be more difficult than that of PCFA [194]. The reason

Table 1.6 Characteristics of the cluster analysis method.

Rationale	Characteristics	Arbitrary Considerations	Strengths	Limitations
- To reflect dietary habits	- Identifies categories of clusters but does not consider individuals variation in the diet	- Selection between standardisation and energy adjustment of food items for initial analysis	- Information may be used to generate hypothesis and theory	- Does not form a gradient
	- Large clusters indicate diets consumed by many and small clusters indicate diets consumed by a few	- How many clusters to identify	- Able to characterise the total diet	- Limited statistical power - Data is limited on validity and reproducibility
	- Small clusters are driven be outliers	- Which cluster to report	- Help describe eating behaviours	- Relies on arbitrary decisions
	- Foods that are consumed by many are less helpful in defining the clusters	- Which clusters to include in subsequent analysis		- Rigorous tests to assess validity is performed by few
		- How to interpret and label the clusters		- Interpretation may be difficult
				- Quality of the food patterns and the results are dependent on the quality of the information the method is using

Adapted from Slattery [128]; Michels and Schulze [147]; Moeller et al. [149]; Wirfalt et al. [161]; Newby et al. [211]

for this is that CA can produce patterns that are relatively similar as shown in the dietary pattern study conducted in Chinese [193].

1.6.10.3 Reduced rank regression

RRR is a recently developed technique that has been used by a few investigators [195]. RRR bears similarities to PCFA but is dependent on two sets of factors, the predictors and the responses [147, 149, 161, 215]. The rationale behind RRR is to combine a prior knowledge with an a posteriori analytical method, which some believe makes RRR a hybrid of a priori and a posteriori methods [195].

In RRR, the predictors are the foods and the responses are the risk factors of a disease [196, 216]. The responses are selected a priori based on the evidence that they are intermediates on the causal pathway between the foods and the disease [216]. By using this information RRR identifies a dietary pattern that is the predictor of a disease [216, 217]. Simply, RRR is a PCFA performed on predictors with a subsequent linear regression performed on PCFA of responses [147, 161]. The RRR extracted dietary patterns are also retained on the basis of their eigenvalues [217]. Studies usually keep one dietary pattern because it explains the most information. A summary score is then calculated for each individual and for the dietary pattern, which are used in correlation and regression analyses [217].

Table 1.7 gives an overview of the characteristics, strengths, and limitations of RRR. It also relies on several arbitrary decisions [147, 149, 161]. RRR can provide information that can be used to generate a hypothesis [149, 161].

Table 1.7 Characteristics of reduced rank regression method.

Rationale	Characteristics	Arbitrary Considerations	Strengths	Limitations
- Identify dietary patterns that are predictors of outcome of interest	- Patterns include information on biological pathways - Forms a gradient	- Selection of response variable need careful thought - Whether or not to reduce the numbers of food items for analysis - Whether or not to adjust for energy - Selection of factor loading cut-off criteria - How to label the factor	- Information may be used to generate hypothesis and theory	- Response variables are necessary for the analyses - Numbers of factors need to be in accordance with numbers of response - Data is limited on validity and reproducibility - Relies on arbitrary decisions - Patterns identified do not represent people's diet habits - The association between RRR patterns and disease has not been well investigated - Diets may potentially serve as proxy for risk factors but the use beyond hypothesis generation that links food intake to disease is unclear

Adapted from Moeller et al. [149]; Michels and Schulze [147]; Wirfalt et al. [161]

1.6.10.4 An overview of comparison of principal component factor analysis and cluster analysis methods on identification of dietary patterns and their relationship with cardiovascular risk factors

Some researchers have compared PCFA and CA methods to ascertain how the diets may vary with different methodologies in the same study sample. Those that have accomplished this have found close similarities between dietary patterns derived from PCFA and CA [212, 218-221].

The Avon Longitudinal Study of Parents and Children (UK) study [221] assessed the participants' diets using a 94 item FFQ. The study categorised 94 items into 57 groups and used them in CA and PCFA. Dietary clusters were compared with PCFA patterns. CA identified three diets, "Processed," "Plant-based," and "Traditional." Dietary clusters were similar to the three dietary patterns extracted with PCFA and each principal component score was higher on average in the corresponding cluster. The Baltimore Longitudinal Study of Aging Study (USA) [219] also supported similarities between diets using both methods in theirs. The study extracted two patterns of middle-aged and older adults with each method. Dietary clusters identified with CA were "Healthy" and "Alcohol." Patterns extracted with PCFA were "Reduced Fat Dairy, Fruit and Fibre" and "Protein and Alcohol." CA scores were calculated and computed across the PCFA scores. Participants in the "Healthy" cluster had the highest mean factor score for "Reduced Fat Dairy, Fruit, and Fiber" diet and participants in the "Alcohol" cluster had the highest mean factor score for "Protein and alcohol" diet.

Surprisingly, no study has compared PCFA and CA diets in relation to enlarged waist circumference, hyperglycaemia, hypertension, or metabolic syndrome in the same

study sample except for the analyses performed by the Baltimore Longitudinal Study of Aging [219], in which, association with plasma lipids was examined. The relationship between the diets and plasma lipids showed that the CA's "Healthy" diet was inversely associated with triacylglycerols (-0.18mmol/L, 95%CI -0.33 to -0.03) whereas the "Alcohol" diet was adversely associated with total cholesterol (0.33mmol/L, 95%CI 0.07 to 0.59). Similar results were found for PCFA's diet. The "Reduced Fat Dairy, Fruit, and Fibre" diet was inversely associated with triacylglycerols (-0.08mmol/L, 95%CI -0.15 to -0.01) but the "Protein and Alcohol" diets was adversely associated with total cholesterol (0.04mmol/L, 95%CI 0.01 to 0.07).

In the literature, the prudent/healthy and Western/unhealthy diets have frequently been identified by PCFA and CA. In individual PCFA and CA studies, the evidence of adverse association between the Western/unhealthy diet and hyperglycaemia [206, 222-226], hypertension [204, 222, 227], and the metabolic syndrome [203, 204, 222] is consistent. The association between prudent/healthy diets and the aforementioned risk factors are mixed with either method in the literature where some studies [206, 228-230] have reported an inverse association and others [137, 203, 204, 227, 231, 232] have observed no association.

Dietary patterns are inherently complex and it is difficult or impossible to tease out the reason for discrepancy in the results. In ethnic minorities who have different dietary habits, a comparative evaluation of diets extracted from these methods and an investigation into the relationship with cardiovascular health has not been performed.

1.6.10.5 An overview of comparison of principal component factor analysis and reduced rank regression methods on identification of dietary patterns

There is also evidence of comparison between PCFA and RRR methods in the literature. Studies have found comparable dietary patterns using both methods but the primary focus has been on cardiovascular endpoints [233]. The European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study recently used the two methodologies and extracted three comparable patterns (Prudent, Western, and Traditional) in the analysis involving 34,644 participants. The study found that the association for endpoints such as coronary artery disease and stroke was stronger with the RRR diets than with the PCFA diets. This observation is consistent with the results of the Nutrition, Environment, and Cardiovascular Health Survey [218] where both methods were recently compared to determine the effects of the diets on cardiovascular risk. Both method identified two very similar patterns and were labeled “Prudent” and “Animal Protein and Alcohol.” The correlation between both patterns were high (Prudent $r = 0.61$ and Animal Protein and Alcohol $r = 0.57$). The results showed that Prudent diets extracted from both methods were associated with a lower cardiovascular risk whereas the Animal Protein and Alcohol patterns from both methodologies were associated with a higher cardiovascular risk.

1.6.10.6 The role of adding principal component factor analysis and reduced rank regression together in dietary pattern research

Studies that have used both methodologies have done with the aim to determine which results in stronger association with clinical endpoint. Although the underlying assumptions of PCFA and RRR methods are similar, the fundamental difference between the two is the element of a-priori knowledge when using RRR. RRR diets are identified from disease specific response variables, which can help with the

confirmation or rejection of a hypothesis. Such patterns usually are behaviorally irrelevant [234, 235]. On the other hand, PCFA identifies patterns that have public health relevance because they reflect how the participants could be eating [234, 235]. Studies that have used both methods have mostly been conducted in Caucasian [235-238]. To date, only one study has been conducted in the Chinese [234]. Currently, there is no consensus as to which of the two methods is more accurate. The reason being that the aims of both methods are distinct in their approaches and are designed to answer different questions.

1.6.10.7 A comparison of dietary patterns extracted by principal component factor analysis and hypothesis oriented methods

Despite ample research in a-priori and a-posteriori dietary patterns, an under-researched area in nutritional epidemiology is comparison of both approaches in the same study sample. Very few studies have managed to explore this [239, 240].

The EPIC Study [240] used the dietary information of 28,034 participants in their Greek branch to assess how diets extracted from the PCFA compare with a-priori Mediterranean diet. The study extracted four diets with PCFA and found the first diet to closely resemble their a-priori Mediterranean diet. Both patterns incorporated fruit, vegetables, legumes, fish, and olive oil. A strong positive correlation (r = 0.50) between the two was also observed. The ATTICA Study [239] arrived at similar conclusion.

The ATTICA Study [239] used the dietary data of 3,402 adults living in the Mediterranean region and performed their analysis in a stepwise manner. Firstly, they constructed an a-priori Mediterranean diet score on characteristics of the

Mediterranean diet, which has been the primary focus of the PREDIMED trial [179]. Secondly, they extracted a diet using PCFA and compared it to the Mediterranean diet. Thirdly, since the EPIC-Study had not examined the relationship with chronic disease, the team assessed the association with incidence of CVD. PCFA identified a "Plant-based Healthy" diet which closely resembled their a-priori Mediterranean diet. In the multivariable model, both diets were associated with a 6% (OR 0.94, 95%CI 0.90 to 0.97) lower risk of developing CVD [239]. These studies show that a-priori diets can be predicted by the PCFA methodology.

1.6.10.8 Empirically-derived dietary patterns

Empirical methods have been used extensively in epidemiology over the past decade. It has been shown that dietary patterns differ in composition and are associated with different surrogated markers (Appendix 2).

1.7 Summary

Studies in the past used to select a food group and/or nutrient and assessed how it related to chronic disease. As the field of nutrition started evolving it became apparent that single food group and nutrient analyses have several design and concept limitations. This shifted the focus towards dietary pattern analyses, which are relatively new approaches in nutritional epidemiology. Two approaches are used to summarize the dietary practices of a group under investigation. One is through development of diet scores and indices, which are constructed on established dietary guidelines. The other is through the use of statistical methods such as PCFA, RRR, and CA, which use mathematics and geometry to identify what people's dietary patterns could be like. Several dietary patterns have been developed and examined

over the years, among which, the Mediterranean diet and the DASH diet have been frequently studied. These diets recommended a higher intake of healthy foods that incorporate a mixture of whole-grains, fruits, vegetables, and nuts. RCTs have usually focused on surrogate markers but the results across studies for the Mediterranean and the DASH diets are inconsistent. The majority of evidence pertaining to the Mediterranean diet is limited to studies conducted in the Mediterranean regions, which limits their generalisability, therefore, more studies exploring how the diet influences cardiovascular risk factors across the world is still needed. The DASH diet was specifically designed for lowering blood pressure in individuals with high blood pressure or at risk of developing hypertension. At present there is clear evidence that the DASH diet is beneficial for blood pressure, but there is limited and no clear evidence that the diet is beneficial for reducing waist circumference, dyslipidaemia, and hyperglycaemia.

1.8 Aims of the thesis

The aim of this thesis is to assess how dietary patterns are associated with cardiovascular risk factors in middle-aged and older adults using data from the Guangzhou Biobank Cohort Study (GBCS). The objectives are to:

1) Extract dietary patterns using PCFA and use multivariable regression analyses to study the relationship with major cardiovascular risk factors such as hyperglycaemia, hypertension, and the metabolic syndrome.

2) Tease out and explore the complex pathways of dietary patterns and cardiovascular risk factors in a conceptual framework using structural equation modelling to address

the following:

a) The known relationship between waist circumference, systolic blood pressure, HDL-cholesterol, triglycerides, fasting plasma glucose;

b) Which cardiovascular risk factors are causally associated and which are non-causally associated with each other;

c) Identify the effects of diet on the aforementioned risk factors and highlight the underlying mechanisms of these effects.

CHAPTER TWO

2.0

METHODOLOGY

2.1 Introduction

This chapter aims to describe the study design of the GBCS and its study population and data collection methods. The chapter also describes the statistical analyses used to answer the research questions within this thesis.

2.1.1 Overview of the Guangzhou Biobank Cohort Study

The GBCS was established in 2003 and it is a collaboration between the Guangzhou Number 12 People's Hospital, and the Universities of Hong Kong and Birmingham. The GBCS recruited middle-aged and older adults aged 50-93 years from Guangzhou in Guangdong Province in Southern China, with the aim to assess the health and well being of Chinese as a result of modernisation and globalisation in China in the past 20 years. The cohort study collected detailed information pertaining to chronic diseases throughout the life course, which included medical history, genetics, lifestyle, environmental factors, occupational status, physical activity, and dietary habits [241]. Following the initial assessment between 2003 and 2006, the participants have been periodically followed-up and re-examined. The study is continuing to follow-up participants with an outcome and/or disease of interest and cause-specific mortality [241].

2.1.1.1 Study area

Located in Southern China, Guangzhou is the third largest city in China. With the population of approximately 10 million, Guangzhou is the provincial capital of Guangdong Province covering an area of 7,434.4 km^2 (Figure 2.1).

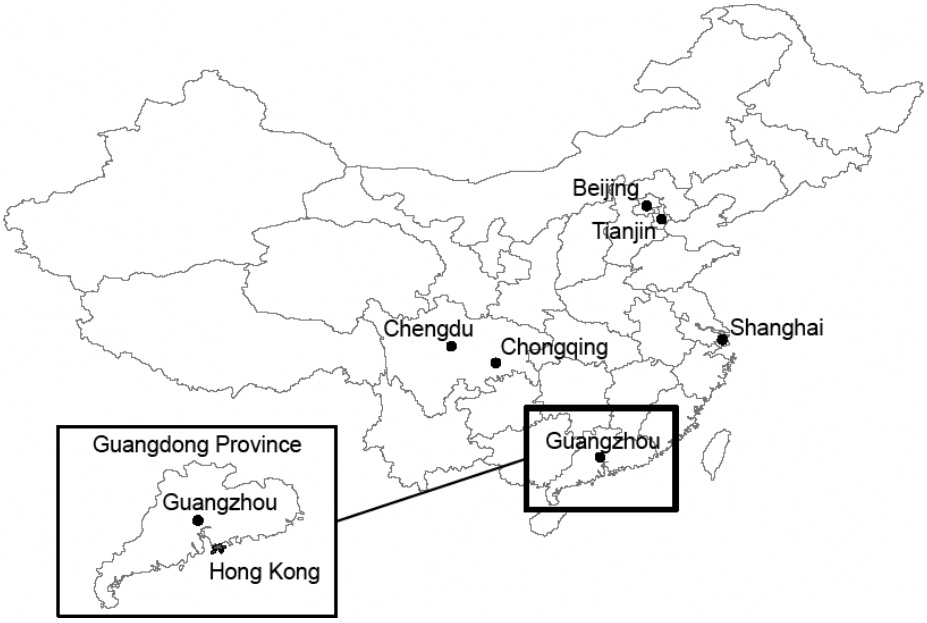


Figure 2.1 Figure illustrating Guangzhou, the capital of Guangdong Province located in Southern China.

Source; Jiang et al. 2006 [241]

2.1.1.2 Study design

The GBCS is an on-going prospective cohort study in China that began in 2003. This thesis used cross-sectional data from the GBCS.

2.1.1.3 Study facilitation

Primary care does not exist in China, therefore the Guangzhou Health and Happiness Association for the Respectable Elders "(GHHARE)," or "Guangzhou Zunlao Kangle Xiehui," which is a large unofficial organisation aligned with municipal government, was selected to facilitate this study. With branches located throughout the 10 districts of Guangzhou, the GHHARE welcomes members aged ≥50 years for a nominal monthly fee of 4 Yuan (US$1 = 8 Yuan) [241].

2.1.1.4 Recruitment phases

Participants were recruited into the study in three phases. Phase I – between September 2003 and November 2004, recruited 10,413 participants. Phase II – between April 2005 and May 2006, recruited 10,017 participants and phase III recruited 10,088 participants between September 2007 and February 2008. Altogether, 30,519 participants were recruited by 2008. Participants who were residents of Guangzhou, able to give informed consent, were ambulatory, and not being treated for life-threatening diseases were included. The study received ethical approval from the Medical Ethics Committee of the Guangzhou Medical Association. All subjects provided written informed consent before participation [241].

2.1.1.5 Initial assessment

Participants attended the Guangzhou Number 12 People's Hospital after an overnight fast. Fasting blood samples and urine specimens were collected upon arrival and the participants were provided free breakfast. Afterwards, the participants circulated through a series of stations for additional clinical measurements and interviews. Trained nurses conducted face-to-face interviews and collected information on the demographics, personal history, family history, disease history, cognition, socio-economic status, smoking history, physical activity, alcohol intake, and dietary habits. Data was entered into a computerised questionnaire system for analysis. Two hundred participants from phase I were re-interviewed after 1 month to assess the reliability of the questionnaire responses. Interclass correlation coefficient for continuous variables and kappa values for categorical variables showed the data to be reproducible [241].

2.2 Demographics and socioeconomic status assessment

The participants self-reported their age, educational level (primary or below/ secondary/ tertiary or above), occupation (manual/ non-manual/ other), household income (don't know/ <5000 RMB/ 5000 RMB/ 10,000 RMB/ 20,000 RMB/ 30,000 RMB/ ≥ 50,000 RMB). This information was used as proxy for socioeconomic status.

2.3 Health-related behaviour assessment

Physical activity during the previous 7 days was measured using the International Physical Activity Questionnaire (IPAQ) short-form. The participants were asked to report the frequency and duration of walking, all moderate, vigorous activities lasting at least 10 min, and time spent in sedentary activity (lying awake and sitting). The IPAQ information was converted to metabolic equivalent scores (MET•min•week^{-1}) for each type of activity. The MET score weighted each type of activity by its energy expenditure, using 1 MET for sitting, 3.3 METs for walking, 4 METs for moderate activity, and 8 METs for vigorous activity. Very active was defined as having vigorous activity at least 3 days a week, achieving at least 1500 metabolic equivalent (MET) minutes per week or activity on 7 days of the week achieving at least 3000 MET minutes per week. Minimally active was defined as having vigorous activity at least 3 days a week, achieving 480 METs, or at least 5 days of any combination of walking, moderate or vigorous activities achieving at least 600 METs. Participants who did not meet the criteria for very active or minimally active were considered inactive. Self-reported physical activity was validated using pedometer-measured steps method in a random sample of 224 participants [242]. Self-reported information on smoking status (never/ex-smokers/current) was also collected.

2.4 Anthropometric measurements

All anthropometric measurements were performed using a standardised protocol with participants wearing light indoor clothing and no shoes. Participant weight was measured using the mechanical scale (RGZ-120-RT, Wuxi Weighing Apparatus Factory, Wuxi, China). Participant height was measured in a standing position to the nearest 0.1cm. Participant BMI was calculated by dividing the weight (kg) by height (m) squared [weight (kg)/height $(m)^2$]. Participant waist circumference was measured at the smallest circumference between rib cage and iliac crest, or alternatively at the navel if not at natural waistline, using a standard tape measure in centimetres (cm) [241]. This measurement protocol was selected because it has previously been used in the China National Diabetes and Metabolic Disorders Study [33].

2.5 Biochemical assessment

2.5.1 Blood samples

Blood samples were collected using appropriate vacutainer tubes. Fasting plasma glucose and lipids such as total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol were analysed by using clinical chemistry analyser (Shimadzu CL-8000, Kyoto, Japan). All analyses were performed using standardised procedures at the Guangzhou Number 12 People's Hospital laboratory [241].

2.5.2 Blood pressure

Systolic blood pressure and diastolic blood pressure was measured in a seated position following 3-minutes' rest. Three measurements were recorded at 1-minute intervals using a digital sphygmomanometer (Omron 705CP; Tokyo, Japan). An

average of the last two measures were used to derive the mean systolic and diastolic blood pressure values.

2.6 Dietary assessment

2.6.1 The 266-item semi quantitative food frequency questionnaire

A 266-item SFFQ (Appendix 3) was used to capture the dietary habits of middle-aged and older adults in phases I and II. The 266-item SFFQ was designed and developed as part of a cardiovascular risk factor study to assess dietary habits of middle-aged and older adults in Hong Kong [243]. The questionnaire represented the most frequently consumed foods in Hong Kong.

The validity of the SFFQ was assessed by comparing the questionnaire results with approximates of energy, sodium, and potassium [243]. Energy intake was compared with estimates of energy expenditure values obtained by basal metabolic rate using a predictive equation developed for the Chinese [244]. Good correlation between energy intake and energy expenditure was detected. This finding was consistent with the results published by a previous study conducted in the Chinese [245]. The validation study collected a random spot urine specimen to estimate sodium and potassium intake. Single specimen underestimated the values for both nutrients by quarter to a third and 24-hour urine samples which estimate potassium and sodium levels more precisely were not collected due to lack of resources hence no conclusion regarding the FFQs accuracy in the quantification of these nutrients was made. The lack of availability of 24-hour urine samples also limited comparison between protein intake and urinary nitrogen. Furthermore, the SFFQ list included more foods than those available in the English food databases and Australian Chinese community upon

which the SFFQ was based [245]. This limited the quantification of soluble fibre and only allowed quantification of crude fibre. The associations of dietary cholesterol with plasma lipid was also assessed for validation purposes. The study detected a negative association between dietary cholesterol and HDL-cholesterol and a positive association with triglycerides and plasma cholesterol/HDL-cholesterol ratio. The study was unable to draw firm conclusions on the validity because the relationship between dietary cholesterol and plasma lipids is conflicting in the epidemiological literature and there is no strong evidence that plasma lipids are substantially affected by diet [243].

2.6.2 The 266-item list

The food items were split into seven categories comprising of (i) grains; (ii) vegetables; (iii) fruits; (iv) eggs/meats/fish/fowl; (v) drinks/beverages; (vi) dim sum/snacks; (vi) soups, (vii) fats and oil intake. Fifteen items were included in the cereals and grains (rice, noodles, breads) category; sixty items assessed vegetables (including soy and lentils); twenty-six items assessed fruits; twenty-nine items assessed meats; thirty-two items assessed fish; seven items assessed eggs; twenty-five items assessed beverages; forty-seven items assessed dim sum and snacks; six items assessed soups; and nine items assessed fats and oils. Information on ten food groups were missing in the dietary data as these were omitted in the collection in different study phases. Therefore, information on 256-items was used. The SFFQ assessed the frequency of consumption of these foods and beverages over a week.

2.7 Research questions

Research question 1: What are the underlying dietary patterns of participants enrolled in the GBCS?

Research question 2: What are the associations between the dietary patterns and major cardiovascular risk factors such as hyperglycaemia, hypertension, and the metabolic syndrome?

2.8 Statistical methods

2.8.1 Data cleaning and preparation

A file containing the participants' demographics, anthropometric measures, biochemical data, and dietary information was prepared in STATA 13.1. These were checked for data entry error, missing values, outliers, and normality. This was done by performing tabulations and examining the distributions of the variables using histograms and boxplots.

In the demographics, some of the participants' ages were missing in the dataset but participant's date of birth was available. Their age was calculated from when born until the day they were enrolled in the study. In the biochemical data, the participants' fasting plasma glucose and triglycerides were found to be positively skewed. Upon inspection, it was determined that this was not due to data entry error. Log transformation was used to normalise these variables.

The next step involved examining and cleaning the dietary data. The distribution of

foods was examined. The majority of the participants had not indicated consumption of particular food items in the SFFQ. It was decided on the assumption that the participants did not eat these foods, consumption was coded as zero. Upon further inspection, seven implausible values were identified. Six food items had one outlier and one item had two outliers on the frequency of consumption. These outliers were removed. Four food items (salad dressing, butter, margarine, and soft margarine) were removed because the participants reported not eating them. All food items were positively skewed and several transformations were tested to normalise them but no transformation method was able to achieve this.

2.9 Statistical analysis

2.9.1 Sample description

This part involved the description of participants' characteristics and the study variables. Population characteristics such age, BMI, waist circumference, fasting plasma glucose, blood pressure, total cholesterol, HDL-cholesterol, and LDL-cholesterol were examined using mean and standard deviation (SD) or median and interquartile range (IQR). Binary and ordinal categorical measures such as gender, education, smoking and physical activity were described using percentages and frequencies. Comparison for baseline characteristics was estimated using the chi square test for categorical variables and analysis of variance for continuous variables.

2.9.2 Identifying dietary pattern

To answer research question 1, the dietary information from phases I and II was used. In phase III, the study used a 66-item SFFQ to capture the dietary habits of participants. Dietary information from phase III could not be incorporated nor used

because the dietary information was incomparable to phases I and II. Therefore, dietary information from phase III was excluded. The 252 food items were combined into groups [211]. Two senior clinical dietitians were consulted for their expertise in forming the food groups and fifty-three food groups were formed [122, 246] (Appendix 4). Where possible, separate groups were created for low-fat (low-fat dishes), high-fat (fatty meats, fatty poultry), preserved etc. The frequency of consumption was summed across the food items for each food group. For example, eel, Japanese eel, mackerel, sardines, dace, and salmon were combined to form the "fatty fish" group, and a person reporting eating eel two times per week and salmon one time per week was classified as eating fatty fish three times per week.

PCFA was used to identify dietary patterns. PCFA was selected for several reasons. Firstly, this approach is the most frequently used method in dietary pattern studies and has been previously validated [121]. Secondly, it produces more interpretable dietary patterns compared to other approaches such as CA [194]. Finally, it is robust to non-normal data, as was the case in the dataset for this study [247].

2.9.2.1 Principal component factor analysis

PCFA is a variance reduction method that combines food groups that are highly correlated into a smaller number of components [126, 147]. The aim of PCFA is to identify linear composites of food groups that explain most variation in the diet. The linear components encompass a combination of food groups that are either negatively or positively correlated with the component [116, 147, 197]. The components are kept on the basis of their eigenvalue [137, 198-200], which explains how well the component is able to distinguish the nutritional information it is using. This allows the

researcher to determine whether the component explains enough variability so that it is of importance [128].

Table 2.1 gives an overview of the steps taken to identify dietary patterns. The steps are further described in detail below.

2.9.2.1.1 Barlett's test of sphericity and the Kaiser-Meyer-Olkin test

Barlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) test were performed before performing PCFA to assess sampling adequacy [199]. Large KMO values (max value 1) suggest that the PCFA is appropriate for the dataset and will produce reliable factors because an underlying relationship exists between the food items [248]. The KMO = 0.73 was detected indicating the data are appropriate for PCFA.

2.9.2.1.2 Factor identification

Fifty-three food groups were inputted into PCFA to determine the underlying structure of the diet information at hand and to derive the dietary patterns [249]. PCFA identified that the first factors had the highest eigenvalue (see Figure 2.2 for a graphical representation), which is defined as how much variance within the data a factor explains [250]. Multiple criteria were used to identify the numbers of factors or patterns to retain [251-253]. First, was the Kasier criteriton of an eigenvalue >1 [253, 254]. Second was the examination of the scree plot to identify breaks in the elbow or inflection point [253, 255, 256]. The third criterion included the interpretability of the factors [257]. The eigenvalue >1 criterion identified eighteen factors, making it difficult to retain that many for analysis. The examination of the scree plot, however, showed two inflection points. The first inflection point at factor (eigenvalue 1.65)

Table 2.1 Steps taken to derive and identify dietary patterns of middle-aged and older Chinese adults in the Guangzhou Biobank Cohort Study.

Step 1 Barlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) test	-	Barlett's test of sphericity was performed prior to PCFA to determine if the correlation matrix the PCFA will use could be translated into identity matrix.
	-	KMO test was used to determine whether PCFA was appropriate for the dataset and if it will produce reliable patterns. The KMO has a maximum value of 1 and the value of 0.73 was detected indicating the data are appropriate for PCFA.
Step 2 Factor or pattern identification	-	After inputting 53 food groups into PCFA, a scree plot was produced that showed the number of factors and their corresponding eigenvalue.
	-	Multiple criteria were used to help identify the numbers of factors to keep (eigenvalue >1, scree plot identifying inflection point, factor interpretability).
	-	The eigenvalue >1 criterion identified 18 factors, making it difficult to retain that many for analysis. Scree plot showed two inflection points, one at factor 4 and the second at factor 6 suggesting to retain either 3 or 5 factors.
	-	An examination of the factors showed that they had no simple structure, were not interpretable. Therefore orthogonal rotation was performed.
Step 3 Factor rotation (orthogonal)	-	Orthogonal rotation (varimax method) simplified the factor structure by loading a group of food items that had a higher value on to a single factor or as few factors as possible. Each food item were shown to belong to one or few factors.
	-	The rotation allowed the factors to be uncorrelated and be independent of each other.
Step 4 Factor structure	-	Rotation was applied to five factors but only the first 4 factors were interpretable whereas the fifth factor yielded no clear structure.
	-	Rotation was then applied to 4 factors and the structure of the 3 first factors were identical to the 3 first factors seen with 4 factor rotation. The structure of the 4th factor changed considerably and was not identical to the 4th factor seen with 5 factor rotation.
	-	Rotation was subsequently applied to 3 factors, which showed factors identical to the 3 factors seen with 4 and 5 factor rotation, hence 3 factors were retained.
Step 5 Factor loading cut-point criteria	-	A factor loading of >0.30 (which are interpreted as correlation coefficient) was used to identify foods contributing to the factors.
	-	The >0.30 cut-point was compared with the >0.15 and >0.20 cut-point criteria to detect differences in the diet structure.
	-	Factors were more interpretable with the >0.30 point hence this criterion was selected.
Step 6 Sensitivity analysis of factors	-	Patterns were stratified by gender to determine whether the diets differed in males and females.
	-	The results were similar and the data of males and females were then combined.
Step 7 Generating factor scores	-	Factor scores were generated for each of the 3 factors and for all participants.
	-	Factor scores were generated by summing up food item weightings by orthogonally transformed factor loadings.
	-	A higher score represented more frequent adherence to the diet and a lower score represented less frequent adherence.
	-	No cut-points are established for dietary pattern scores and the scores were divided into tertiles to be used in regression analysis.
Step 8 Labelling of factors	-	The factors were labelled qualitatively based on the interpretation of the factors.

suggesting two or three factors to retain and the second inflection point at factor six suggesting four or five factor to keep [256]. Factors are columns which are associated with rows that correspond with variables that are loaded across the factors [209]. An examination of the factors showed that the first five factors had no simple structure and were not interpretable.

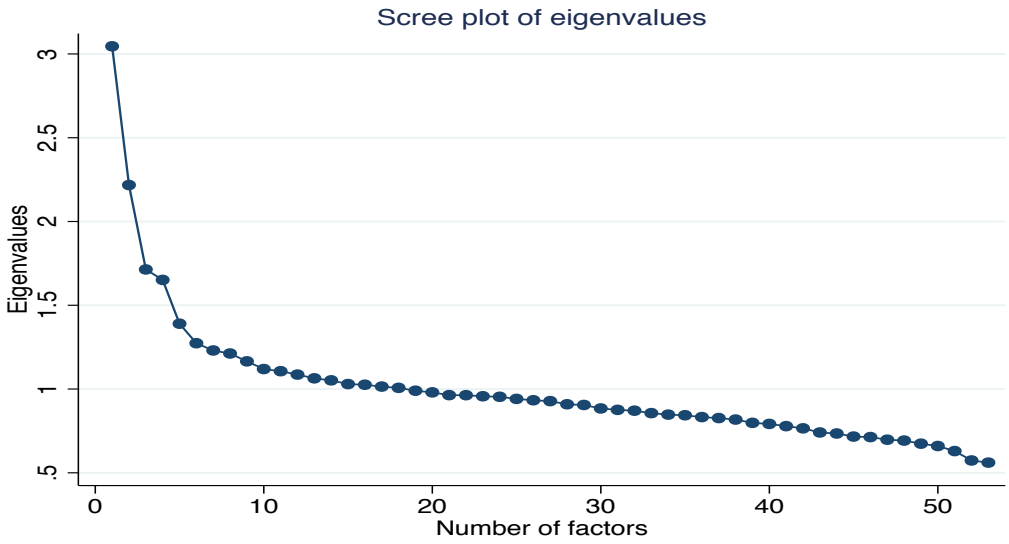


Figure 2.2 Scree plot demonstrating the number of patterns identified by the PCFA and their corresponding eigenvalue (which represent the amount of variation within the data a pattern is explaining). The scree plot show inflection point at pattern four (corresponding eigenvalue 1.65) suggesting that three patterns explain most of the variation in the dietary data.

2.9.2.1.3 Factor rotation

Rotation was applied on the factors to make the factor structure and their interpretation easier by loading variables that have a higher value on to single or as few factors as possible. Simplification of the column entail that the factor will have fewer variables that have a higher value [209]. Factors were orthogonally rotated using the varimax method [192, 206, 258]. Orthogonal rotation allowed the factors to be uncorrelated and independent of each other [259]. The varimax and promax

rotation methods are commonly applied in dietary patterns [130]. These rotations methods are preferable because they easily produce interpretable results [208]. The new set of factor results obtained from varimax rotation was compared with results of the un-rotated factors. After rotation a set of variables contributed heavily on one factor and less to the other factor, as such each food item belonged to one or few factors [192, 208]. To assess the robustness of the identified factors, varimax rotated results were cross-examined with promax rotation to observe differences in factors. Promax rotation yielded similar factor results to the varimax approach.

2.9.2.1.4 Factor structure

Rotation applied to the first five factors showed the first four to be interpretable but the fifth factor yielded no clear structure and was not interpretable. When rotation was subsequently applied to those four factors, the three first factors were identical to the three first factors seen with five factor rotation. The structure of the fourth factor, however, changed considerably and was not identical to the fourth factor seen with five factor rotation. Rotation was further applied to three factors, which showed factors identical to the three factors seen with four and five factor rotation, hence three factors were retained.

2.9.2.1.5 Factor loading cut-point criteria

A factor loading of >0.30 was used to identify foods contributing to the factors [122]. In PCFA, factor loadings are interpreted as correlation coefficients [259, 260]. Factor loadings range from -1 to +1 where the negative factor loadings are negatively associated and positive factor loadings are positively associated with the factor [260]. The >0.30 cut-point was compared with the >0.15 and >0.20 cut-point criteria to

detect differences in the diet structure. Factors were more interpretable with the >0.30 point hence this criterion was selected [122].

2.9.2.1.6 Sensitivity analysis of factors

In sensitivity analyses, PCFA was stratified by gender because dietary patterns have been shown to differ by gender in some studies [211, 261, 262], but not all [256, 263, 264]. The results were similar according to gender and the data of males and females were therefore combined. This is in agreement with previous studies [265].

2.9.2.1.7 Factor scores

Factor scores were generated for each of the three factors and for all participants [251, 259]. Factor scores were obtained by summing up food item weightings by orthogonally transformed factor loadings [257, 260]. The factor scores of varimax rotated factors were subsequently used in regression analysis because the results obtained from orthogonal rotation are less prone to collinearity [253, 257]. No cut-points have been established for dietary pattern scores, therefore the scores were divided into tertiles [266].

2.9.2.1.8 Labelling of factors

After examining the factors, the factors were labelled qualitatively based on the interpretation of the factors [253, 267].

2.9.3 Examining the association between dietary pattern scores and hyperglycaemia, hypertension, and the metabolic syndrome

To answer research question 2, cardiovascular risk factors were categorised into binary outcomes for hyperglycaemia, hypertension, and the metabolic syndrome.

Hyperglycaemia was defined according to the ADA diagnostic criteria [75] as having fasting plasma glucose ≥5.6mmol/L, physician-diagnosis of, or receiving treatment for T2DM. T2DM was defined as a fasting plasma glucose ≥7.0mmol/L or having a physician-diagnosis of, or receiving treatment for T2DM.

Hypertension was defined according to the British Hypertension Society [52] as having as a systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg (≥140/90mmHg), having physician-diagnosis of, or receiving treatment for hypertension. Pre-hypertension was defined as a systolic blood pressure ≥130 to <140mmHg and/or diastolic blood pressure ≥85 to <90mmHg without diagnosis of hypertension.

The metabolic syndrome was defined in accordance with the Joint Interim Statement [90], which require three or more of the following risk factors: (i) hyperglycaemia as having fasting plasma glucose ≥5.6mmol/L, physician-diagnosis of, or receiving treatment for T2DM; (ii) hypertension as having a systolic blood pressure ≥130mmHg and/or diastolic blood pressure ≥85mmHg (≥130/85mmHg), physician-diagnosis of, or receiving treatment for hypertension; (iii) low HDL-cholesterol levels as <1.29mmol/L in females and <1.03mmol/L in males, having physician-diagnosis of, or receiving treatment for low HDL-cholesterol; (iv) high triglycerides was defined as having triglycerides ≥1.7mmol/L, physician-diagnosis of, or receiving treatment for high triglycerides; (v) enlarged waist circumference as ≥90cm for Asian males and ≥80cm for Asian females. This criterion was used for a few reasons. Firstly, the Joint Interim Statement definition identified more participants with the metabolic syndrome

in this study who were at a higher risk of CVD compared to other definitions, an observation in agreement with past investigation conducted in South East Asians [268]. Secondly, the Joint Interim Statement definition has also shown to diagnose >99% of individuals who were diagnosed with other definition such as the IDF [268]. Thirdly, this definition has previously been used to diagnose participants with the metabolic syndrome in China National Nutrition and Health Survey, which is the largest nationally representative diet study conducted in China [269].

The relationships between dietary pattern scores and these risk factors were assessed using multivariable generalised linear Poisson regression with robust standard errors. Poisson regression with robust standard errors was used because it allows estimation of the risk [270]. In multivariable regression analysis, a number of potential confounders were added in a stepwise manner. The first multivariable model was crude. Non-modifiable factors such as age and gender were first added to the regression model. Then, contextual and behavioural risk factors such as education, occupation, physical activity, and smoking were added in the regression model. Finally, mediating variables, such as BMI, were added into the model. The confounders were selected a priori from the published literature.

2.9.3.1 Sensitivity analysis

Sensitivity analyses were performed to test the robustness of the results. These were performed to address the issue of potential reverse causation resulting from health problems or disease states leading to changes in the diet and thus obscuring potential true associations. The analyses included a) comparing non-diseased participants with participants at risk of developing the disease after excluding participants with the

disease, both newly and previously diagnosed; b) comparing non-diseased participants with participants at risk of developing the disease excluding participants with the disease, both newly and previously diagnosed but in the subgroup of participants who perceived themselves as having good self-rated health.

2.9.4 Data analysis software

The analyses were performed in statistical package STATA version 13.1.

CHAPTER THREE

3.0

ASSOCIATIONS BETWEEN DIETARY PATTERNS AND HYPERGLYCAEMIA – THE GUANGZHOU BIOBANK COHORT STUDY

3.1 Abstract

Objective: Diet is strongly related to the development of T2DM. However, few studies have explored the relationship between T2DM and dietary patterns in Chinese populations or addressed the mediating effect of BMI and waist circumference, which we investigated in this large community-based study. **Research design and methods:** Diet was assessed using a semi-quantitative food frequency questionnaire using data from 20,146 participants of the GBCS. T2DM was diagnosed based on a previous physician diagnosis or a fasting plasma glucose ≥7.0mmol/L; hyperglycaemia, fasting plasma glucose ≥5.6mmol/L or a previous diagnosis of T2DM; pre-diabetic hyperglycaemia, fasting plasma glucose ≥5.6-<7.0mmol/L with no previous diagnosis of T2DM. Dietary patterns were extracted using PCFA. **Results:** PCFA identified three dietary patterns: "Non-nut and Non-cruciferous Vegetable", "High Protein-High Fat", and "Omnivorous" diets. In the fully adjusted model, the Non-nut and Non-cruciferous Vegetable diet was associated with an increased risk of hyperglycaemia (RR 1.36, 95%CI 1.31-1.43). A lower risk was observed with the High Protein-High Fat (RR 0.88, 95%CI 0.85-0.92), and Omnivorous diets (RR 0.95, 95%CI 0.91-0.99). In sensitivity analyses, after excluding pre-diabetic hyperglycaemic subjects, results were similar (Non-nut and Non-cruciferous Vegetable diet, RR 1.42, 95%CI 1.31-1.54; High Protein-High Fat, RR 0.79, 95%CI 0.73-0.86), but was no longer significant for the Omnivorous diet. **Conclusion:** The Non-nut and Non-cruciferous Vegetable diet was associated with greater risk of hyperglycaemia and T2DM, while the High Protein-High Fat diet was associated with a lower risk. These associations, if confirmed to be causal, can inform public health approaches for tackling the emerging problem of diabetes in China.

3.2 Introduction

China has undergone major urbanisation and westernisation over the past 30 years, which has had a profound effect on Chinese lifestyles and behaviour [11]. This has led to adverse changes in dietary habits and physical inactivity, which have escalated the risk of T2DM [11, 12]. A recent report highlighted that the prevalence of T2DM has surpassed 10% in urban areas [11, 12].

Several prospective cohort studies investigating the contribution of diet on T2DM have been conducted predominantly in Caucasian populations [205, 229, 271]. Two cohort studies from the United States and Australia both identified two main dietary patterns: a "western" or "unhealthy" pattern characterised by a higher intake of fatty foods, desserts, sweets, refined grains, and alcohol; and a "prudent" or "healthy" dietary pattern, characterised by high intake of whole-grains, poultry, fruits and nuts [205, 271]. Both studies showed an increased incidence of T2DM with the western diet. However, less is known about the dietary practices in non-western cultures and emerging economies, particularly China.

In China, few dietary pattern studies have examined the association with T2DM and related disorders [193, 272, 273]. Chinese dietary patterns differ from those of Caucasian populations, as do food preparation methods and cooking styles, which may modify the relationship between dietary patterns and diseases including T2DM [274]. Furthermore, rapid socioeconomic changes may also modify the impact of the diet on T2DM risk. Therefore, using cross-sectional data from a large study of middle-aged and older participants living in urban Guangzhou, China [241], this study aimed to identify and characterise the dietary patterns of middle-aged and older

Chinese, and examine their association with hyperglycaemia and T2DM and whether these associations could be mediated through obesity.

3.3 Research design and methods

The GBCS, as previously described in more detail [241], is a collaboration among Guangzhou Number 12 People's Hospital, China, and the Universities of Hong Kong, China and Birmingham, UK. Thirty thousand five hundred and eighteen participants aged 50-93 years were enrolled in three phases, during 2003-2004 for phase 1 and 2005-2006 for phase 2. Phases 1 and 2 recruited 20,430 participants. Phase 3 was carried out during 2006-2007, which enrolled 10,088 participants. The present analyses used data from phases 1 and 2. Phase 3 data were not included because of lack of comparable dietary data due to shortening of the questionnaire. Participants who were capable of giving informed consent, were ambulatory and not being treated for life-threatening conditions were eligible for inclusion. Via face-to-face interview, participants completed a detailed computer-based questionnaire on demographic characteristics, physical activity level, smoking status and other lifestyle factors and exposures, and a detailed medical history. The participants provided written informed consent before data collection. Ethical approval was received from the Guangzhou Medical Ethics Committee of the Chinese Medical Association.

3.3.1 Assessment of glycaemia

Following an overnight fast, participants attended the examination centre and blood samples were collected before interviewing. T2DM was defined as a fasting plasma glucose ≥7.0mmol/L or having a physician-diagnosis of, or receiving treatment for, T2DM. Hyperglycaemia was classified according to the ADA diagnostic criteria [1].

Hyperglycaemia was defined as a fasting plasma glucose ≥5.6mmol/L or having T2DM as described above. A fasting plasma glucose ≥5.6-<7.0mmol/L without a previous diagnosis of T2DM was used to define pre-diabetic hyperglycaemia. These are standard cut-points that have been used for the Chinese population [275].

3.3.2 Dietary assessment

Dietary data were collected through a 266-item validated SFFQ for all participants recruited in phases 1 and 2 [243]. In the SFFQ, the participants were asked how frequently they consumed foods and beverages over a week. Information on ten food groups were missing in the dietary data as these were omitted in the collection in different study phases. Therefore, information on 256-items was used. The data were then checked for outliers and eight implausible values were identified. Six items had one outlier and one item had two outliers on the frequency of consumption. These outliers were removed. To extract the dietary patterns, 252 food items were categorised into 53 food groups based on similarity [121, 205, 271]. Four items (salad dressing, butter, margarine, and soft margarine) were excluded from the analyses because 99.9% participants reported not eating them. The food groups were measured in frequency per week [192].

3.3.3 Statistical analysis

Dietary patterns were extracted using PCFA on the 53 food groups. Factors were selected on the basis of eigenvalues of above 1.0 and the scree plot test. Twenty-three factors with an eigenvalue above 1.0 were identified. However, the scree plot showed an inflection point after the third factor, hence the first to third factors were retained [257]. Orthogonal (varimax) rotation was performed on the three factors to simplify

the factor structure and their interpretation. Dietary patterns were interpreted and labelled based on the ±0.30 factor loading cut-off point because food items above this cut-point were strongly correlated with the factor [122]. Summing up the food item weightings by the factor loadings of orthogonal transformed factors created a score for each pattern and each participant. This score determined how closely a participant followed each particular pattern [192]. All participants were then divided into tertiles based on each dietary pattern score. The population characteristics were summarised, stratified by tertiles of dietary patterns, using mean and SD or median and IQR for continuous variables and as percentages for categorical variables. Comparison for baseline characteristics across tertiles of dietary patterns was estimated using chi square test for categorical variables and analysis of variance (ANOVA) for continuous variables.

The association between hyperglycaemia (including T2DM) and each dietary pattern was assessed using multivariable generalised linear Poisson regression model with robust standard errors [270]. RR and 95%CIs were estimated for each tertile, with the first tertile as the reference group. A hierarchical approach was taken with the first model being univariate; the second adjusting for age (years) and gender; and the third model additionally adjusting for education (primary or below/secondary/tertiary), occupation (non-manual/manual/other), smoking (never/ex-smoker/current), and physical activity (IPAQ; inactive/minimally active/active). The fourth model additionally adjusted for potential mediating variables: BMI (kg/m^2), waist circumference (cm), systolic blood pressure (mmHg), and total cholesterol (mmol/L), and LDL-cholesterol (mmol/L). Alcohol was not adjusted for in the model because it

was incorporated in the dietary patterns. P for trend was estimated using generalised Poisson regression across tertiles of dietary patterns.

A series of sensitivity analyses were performed to test the robustness of the observations. We firstly evaluated the associations between the dietary patterns and T2DM after the exclusion of those with pre-diabetic hyperglycaemia. We then used two approaches to address the issue of potential reverse causation resulting from health problems or disease states leading to changes in the diet and thus obscuring potential true associations. These analyses involved: a) comparing normoglycaemic participants with those with hyperglycaemia after excluding those with T2DM (both newly and previously diagnosed); b) comparing the normoglycaemic with pre-diabetic hyperglycaemic, excluding those with newly and previously diagnosed T2DM, after restricting the sample to participants who perceived themselves as having good self-rated health. All the models for sensitivity analyses were fully adjusted.

Of the 20,430 participants, 284 had missing data on potential confounders; therefore the final analysis was restricted to 20,146 participants with complete data. All statistical analyses were performed using STATA (version 13.1, Stata Corp, College Station, Texas).

3.4 Results

Three dietary patterns were identified by PCFA. Of the 53 food groups, 25 contributed to the three patterns (Appendix 5). The first pattern was labelled as the "Non-nut and Non-cruciferous Vegetable" diet because it represented frequent intake

of a variety of vegetables, tomatoes, and mushrooms and fungi, eggs, fruits, and soy products. The second pattern was labelled "High Protein-High Fat" diet because of frequent intake of generally high protein foods like seafood, poultry, offal, beans and legumes, red meat, high protein-high fat dishes, yellow-orange fruit, and beverages. The third pattern was labelled the "Omnivorous" diet because of frequent intake of citrus fruits, cruciferous vegetables, preserved meats, other meats, and nuts. The three patterns explained 11.3% of the total variance of which the Non-nut and Non-cruciferous Vegetable diet accounted for most dietary variation. Means and SD of frequency intake of the food items were also summarised for each pattern (Appendix 6).

Of the 20,146 participants, 7,865 (39%) participants were hyperglycaemic, of whom 2,791 (14%) had T2DM. The characteristics of 20,146 participants stratified by dietary patterns are summarised in Table 3.1. The third tertile of Non-nut and Non-cruciferous Vegetable diet was associated with larger waist circumference, higher fasting plasma glucose, lower total- and LDL-cholesterol, less smoking, and greater physical activity. The third tertile of the High Protein-High Fat diet was associated with larger waist circumference, lower systolic blood pressure, and lower fasting plasma glucose. The pattern with physical activity was unclear. The third tertile of the Omnivorous diet was associated with lower waist circumference, higher blood pressure, higher cholesterol levels, and manual job.

The Non-nut and Non-cruciferous Vegetable diet was associated with an increased risk of hyperglycaemia in the third relative to the first tertile (RR 1.36, 95%CI 1.31-1.43) of the fully adjusted model (Table 3.2). In contrast, the High Protein-High Fat

diet was associated with a lower risk of hyperglycaemia in the second tertile (RR 0.94, 95%CI 0.91-0.98) and third tertile (RR 0.88, 95%CI 0.85-0.92) compared to the first tertile. An inverse relationship was also observed with the Omnivorous diet when comparing the third with the first tertile (RR 0.95, 95%CI 0.91-0.99).

In sensitivity analyses after excluding those with non-diabetic hyperglycaemia, after adjusting for all potential confounders, the third tertile of the Non-nut and Non-cruciferous Vegetable diet still showed an increased risk for T2DM (RR 1.42, 95%CI 1.31-1.54) relative to the first tertile (Table 3.2). Likewise, the third tertile of the High Protein-High Fat diet still showed a significant reduced risk (RR 0.79, 95%CI 0.73-0.86). An association was no longer observed for the Omnivorous diet (RR 0.97, 95%CI 0.89-1.05).

To address potential reverse causality, the relationship with hyperglycaemia was assessed after excluding participants with newly and previously diagnosed T2DM. The results were similar to those from the main analyses. The third tertile of the Non-nut and Non-cruciferous Vegetable diet showed an increased risk relative to the first in the fully adjusted model (RR 1.50, 95%CI 1.41-1.59), whereas a lower risk was observed for the third tertile of the High Protein-High Fat (RR 0.90, 95%CI 0.84-0.95), and Omnivorous diets (RR 0.92, 95%CI 0.87-0.97). Potential reverse causation was further assessed by restricting the sample to those with good self-rated health within the pre-diabetic hyperglycaemic group. Good self-rated health was reported by 16,704 participants, of whom 10,340 (62%) were normoglycaemic and 6,364 (38%) were hyperglycaemic. Of 6,364 hyperglycaemic participants with good self-rated health, 2,061 (12%) with newly and previously diagnosed T2DM were excluded. In

the fully adjusted model, a higher risk was seen in the third tertile of the Non-nut and Non-cruciferous Vegetable diet (RR 1.52, 95%CI 1.42-1.62). A lower risk was seen in the third tertile of the High Protein-High Fat (RR 0.89, 95%CI 0.84-0.95) and Omnivorous diets (RR 0.92, 95%CI 0.87-0.98).

3.5 Discussion

This study identified three dietary patterns in middle-aged and older Chinese adults. A frequent intake of the Non-nut and Non-cruciferous Vegetable diet, which accounted for most variation in the diet, was associated with an increased risk of hyperglycaemia. This association was independent of socioeconomic status, obesity, and other biological risk factors. The High Protein-High Fat diet was associated with a lower risk of hyperglycaemia. The Omnivorous diet showed an association with hyperglycaemia but not with T2DM alone. The associations after adjustments for obesity highlighted that the effects of the diets were, at least, independent of obesity.

3.5.1 The Non-nut and Non-Cruciferous Vegetable Diet

The deleterious effects on glycaemia associated with this dietary pattern could be due to a high glycaemic load. This diet was associated with starchy vegetables such as potatoes, sweet potatoes, sweet corn, which have been shown to have a high glycaemic load [276]. A recent systematic review and meta-analysis of 17 prospective studies with median follow-up from 4 to 14 years involving over 679,667 participants showed a high glycaemic load increased the risk of T2DM by 12% [277].

A potential physiological mechanism has been proposed that may explain the relationship between high glycaemic load and hyperglycaemia. Prolonged high

glycaemic load intake increases postprandial glucose and insulin requirements, which over time could lead to pancreatic beta-cell exhaustion and diabetes in susceptible individuals [119, 278]. A key mechanism may be through glucotoxicity [278].

3.5.2 The High Protein-High Fat Diet

The inverse association between the High Protein-High Fat diet and hyperglycaemia is in agreement with results of a systematic review of 14 RCTs, which evaluated the effects of High Protein-High Fat diet on glycaemia in 849 participants [279]. The review found that the diet lowered glucose by -0.57mmol/L.

Several mechanisms may explain the observed inverse association. One protective mechanism could be reduced insulin demand from a reduced carbohydrate intake, which is argued to lower the risk of hyperglycaemia by reducing pancreatic beta-cell overload [280]. Some amino acids in protein foods such as arginine and leucine could also be relevant for glucose homeostasis. Both have been suggested to improve beta-cell insulin release [281, 282]. Leucine has been shown to regulate ATP-sensitive K^+ activity and secrete insulin by triggering cytosolic calcium [282]. Arginine has been shown to stimulate incretin glucagon-like-peptide (GLP-1) production. In physiological studies, elevated GLP-1 levels have increased insulin secretion from pancreatic beta-cells [283].

The majority of RCTs evaluating the effects of high protein and high fat diet on glucose are short-term. Very few trials have been able to assess the long-term effects of the diet longer than one year [279]. The criticism of high protein and high fat diets is that they allow ad libitum intake of saturated fat at the expense of carbohydrates

[117]. There is some evidence that an increase in saturated fat intake is positively associated with hyperlipidaemia and obesity [284], as also seen in the current study. Prolonged intake may exacerbate obesity and offset beneficial effects on glucose, although in this population that would have only occurred after 1960s when the local economy rapidly developed.

3.5.3 The Omnivorous Diet

The Omnivorous diet, which is a unique observation in this study, was inversely associated with hyperglycaemia but was not associated with T2DM. This might be due to relatively small number of participants with T2DM in those with this diet. This diet is associated with what are generally believed to be healthy foods such as cruciferous vegetables, nuts, and citrus fruits [119]. A recent meta-analysis of 3 prospective studies found cruciferous vegetables to be associated with an 18% lower risk of T2DM [285]. In a systematic review of 10 short-term intervention studies involving 413 participants, nuts were shown to reduce fasting plasma glucose by -0.15mmol/L [286]. The evidence of an association with citrus fruit has not been adequately assessed. Intervention studies assessing effects of citrus fruit on glycaemia are scarce and prospective studies have shown no association with T2DM [287]. Citrus fruits, however, have been documented to be associated with a lower the risk of cardiovascular disease [119].

Mechanistically, cruciferous vegetables contain antioxidant compounds, including sulforaphane, which is hypothesised to lower glucose by reducing oxidative stress [288] and downstream beta-cell impairment [289]. Improvements in glycaemia with frequent nut intake may be via multiple potential mechanisms. Nuts are low in

carbohydrates and likely to contribute less to post-prandial glycaemia [290, 291]. They are also high in protein, amino acid arginine, and contain sizable essential fatty acids. These collectively have been reported to be beneficial for glucose homeostasis [292]. Essential fatty acids may improve insulin sensitivity and lower glucose through peroxisome proliferator-activated receptor (PPAR) mechanism by activating isoform $PPAR_y$ [293].

3.5.4 Strength and limitations

The main limitation of the study is its cross-sectional design limiting the inference of causality, and thus requires confirmation in prospective analyses. Despite addressing the major potential confounders, there is still the potential of residual confounding. There are also inherent limitations of assessing diet using methods such as the FFQ. Another limitation is the reliance of a single snapshot of the participants' dietary intake. A further limitation of a posteriori dietary pattern analysis was the subjective nature of decisions required during the process. This included grouping of food items, the number of factors to retain, factor loading cut-off values to identify food items contributing to the patterns, and labelling of the diets, which could affect interpretation of the diets [117]. Diets may be reflective of other factors that are integral in overall lifestyle. However, numerous lifestyle factors were adjusted for to address this issue. There are studies that show that lifestyle factors such as dietary intake are maintained overtime [271], suggesting this is less of an issue. Another limitation is the lack of information regarding the quantities of various foods consumed. A major strength of this study is the large sample of well-characterised non-Western participants that enabled control of a range of potential confounders, and stratification to address potential reverse causation.

3.5.5 Summary

In summary, this study incorporating several sensitivity analyses found the Non-nut and Non-cruciferous Vegetable diet was associated with increased risk of hyperglycaemia and T2DM. This could be due to a high glycaemic load in the diet. The High Protein-High Fat diet was associated with a lower risk of hyperglycaemia and T2DM. The Omnivorous diet was associated with a lower risk of hyperglycaemia but showed no association with T2DM. These findings need to be examined longitudinally and confirmed through interventional studies. The association, if causal, can inform public health approaches for tackling the emerging problem of diabetes in China.

Table 3.1 Baseline characteristics of 20,146 participants by tertile 1 and 3 of the dietary pattern scores.

	Non-nut and Non-cruciferous Vegetable diet			**High Protein-High Fat diet**			**Omnivorous diet**		
N	**Tertile 1 (6,709)**	**Tertile 3 (6,719)**	*p* value	**Tertile 1 (6,704)**	**Tertile 3 (6,726)**	*p* value	**Tertile 1 (6,744)**	**Tertile 3 (6,700)**	*p* value
Age, years [median (IQR)]	60 (55-67)	63 (58-68)	<0.001	64 (58-68)	61 (56-67)	<0.001	62 (57-67)	62 (56-67)	0.1
Sex (%)									
- Female	72.8	69.2	<0.001	76.6	66.1	<0.001	67.6	75.4	<0.001
Body Mass Index (kg/m^2)	23.8 (3.3)	23.7 (3.3)	0.6	23.6 (3.3)	23.9 (3.3)	<0.001	23.7 (3.3)	23.9 (3.3)	0.002
Waist Circumference (cm)	78.7 (8.7)	79.8 (9.1)	<0.001	79.0 (8.9)	79.5 (8.9)	0.005	79.6 (9.1)	79.0 (8.8)	<0.001
Blood pressure (mmHg)									
- Systolic blood pressure	131 (22.5)	131 (21.9)	0.2	133 (22.7)	130 (22.0)	<0.001	130 (22.2)	133 (22.4)	<0.001
- Diastolic blood pressure	74 (11.4)	74.1 (11.2)	0.1	73.8 (11.3)	74.1 (11.4)	0.1	73.8 (11.2)	74.4 (11.4)	<0.001
Fasting glucose, mmol/L [median (IQR)]	5.2 (4.8-5.8)	5.6 (5.1-6.1)	<0.001	5.5 (5.0-6.0)	5.3 (4.9-5.9)	<0.001	5.4 (4.9-6.0)	5.4 (4.9-6.0)	0.9
Cholesterol (mmol/L)									
- Total cholesterol	6.1 (1.2)	5.8 (1.2)	<0.001	5.9 (1.2)	6.0 (1.2)	<0.001	5.8 (1.2)	6.1 (1.2)	<0.001
- High-density lipoprotein	1.7 (0.4)	1.6 (0.4)	<0.001	1.7 (0.4)	1.7 (0.4)	0.008	1.6 (0.4)	1.8 (0.4)	<0.001
- Low density lipoprotein	3.3 (0.7)	3.1 (0.7)	<0.001	3.2 (0.7)	3.3 (0.7)	<0.001	3.1 (0.7)	3.3 (0.7)	<0.001
Education (%)			<0.001			<0.001			<0.001
- Primary or below	49.4	38.8		50.2	39.0		50.4	39.4	
- Secondary	25.8	24.9		25.3	28.8		23.6	29.0	
- Tertiary	24.8	36.3		24.5	32.2		26.0	31.6	
Occupation (%)			<0.001			<0.001			<0.001
- Manual	68.5	55.6		67.0	60.4		67.2	61.0	
- Non-manual	21.0	41.4		26.8	32.6		27.6	32.3	
- Other	10.5	3.0		6.2	7.0		5.2	6.7	
Smokers (%)			<0.001			<0.001			<0.001
- Never	74.2	76.6		79.4	71.2		71.8	78.5	
- Ex-smoker	11.6	14.0		11.6	14.1		14.0	12.3	
- Current	14.2	9.4		9.0	14.7		14.2	9.2	
Physical activity			<0.001			<0.001			<0.001
- Inactive	14.5	3.7		9.2	7.1		10.1	6.5	
- Minimally active	52.7	40.7		45.3	49.7		44.3	50.3	
- Very active	32.8	55.6		45.5	43.2		45.6	43.2	

Data are means (SD) and percentages unless indicated otherwise.
p values are for the significance of chi-square test for categorical variables and analysis of variance test for continuous variables.

Table 3.2 Multivariable RR (95% CI) for relationship between dietary pattern scores and hyperglycaemia (≥5.6mmol/L) and type 2 diabetes mellitus (≥7.0mmol/L) in middle-aged and older Chinese adults.

	Hyperglycaemia					**Type 2 Diabetes Mellitus**			
	Tertile 1	**Tertile 2**	**Tertile 3**	*P trend*		**Tertile 1**	**Tertile 2**	**Tertile 3**	*P trend*
Non-nut and Non-cruciferous Vegetable diet	***n* (2,127/6,709)**	***n* (2,563/6,718)**	***n* (3,175/6,719)**		**Non-nut and Non-cruciferous Vegetable diet**	***n* (807/5,389)**	***n* (903/5,058)**	***n* (1,081/4,625)**	
Model 1	1.00	1.20 (1.15-1.26)	1.49 (1.43-1.56)	<0.001	Model 1	1.00	1.19 (1.09-1.30)	1.56 (1.44-1.69)	<0.001
Model 2	1.00	1.18 (1.13-1.24)	1.43 (1.37-1.50)	<0.001	Model 2	1.00	1.16 (1.06-1.26)	1.46 (1.35-1.59)	<0.001
Model 3	1.00	1.15 (1.09-1.20)	1.37 (1.31-1.43)	<0.001	Model 3	1.00	1.14 (1.04-1.24)	1.43 (1.31-1.55)	<0.001
Model 4	1.00	1.15 (1.10-1.21)	1.36 (1.31-1.43)	<0.001	Model 4	1.00	1.14 (1.05-1.24)	1.42 (1.31-1.54)	<0.001
High Protein-High Fat diet	***n* (2,828/6,704)**	***n* (2,613/6,716)**	***n* (2,424/6,726)**		**High Protein-High Fat diet**	***n* (1,063/4,393)**	***n* (905/5,008)**	***n* (823/5,125)**	
Model 1	1.00	0.92 (0.89-0.96)	0.85 (0.82-0.89)	<0.001	Model 1	1.00	0.84 (0.78-0.91)	0.75 (0.69-0.81)	<0.001
Model 2	1.00	0.95 (0.91-0.99)	0.89 (0.85-0.93)	<0.001	Model 2	1.00	0.89 (0.82-0.96)	0.82 (0.75-0.88)	<0.001
Model 3	1.00	0.95 (0.91-0.99)	0.89 (0.85-0.93)	<0.001	Model 3	1.00	0.89 (0.82-0.96)	0.81 (0.74-0.88)	<0.001
Model 4	1.00	0.94 (0.91-0.98)	0.88 (0.85-0.92)	<0.001	Model 4	1.00	0.88 (0.82-0.96)	0.79 (0.73-0.86)	<0.001
Omnivorous diet	***n* (2,674/6,744)**	***n* (2,656/6,702)**	***n* (2,535/6,700)**		**Omnivorous diet**	***n* (907/4,977)**	***n* (951/4,997)**	***n* (933/5,098)**	
Model 1	1.00	1.00 (0.96-1.04)	0.95 (0.91-0.99)	0.031	Model 1	1.00	1.04 (0.96-1.13)	1.00 (0.92-1.09)	0.93
Model 2	1.00	1.00 (0.96-1.04)	0.96 (0.91-0.99)	0.023	Model 2	1.00	1.04 (0.96-1.13)	1.00 (0.92-1.09)	0.98
Model 3	1.00	1.00 (0.96-1.05)	0.96 (0.91-0.99)	0.029	Model 3	1.00	1.03 (0.95-1.12)	0.98 (0.91-1.07)	0.70
Model 4	1.00	1.01 (0.97-1.05)	0.95 (0.91-0.99)	0.008	Model 4	1.00	1.05 (0.97-1.13)	0.97 (0.89-1.05)	0.58

n = no of cases/participants.
Model 1: univariate.
Model 2: adjusted for age and gender.
Model 3: additionally adjusted for education, occupation, smoking, and physical activity.
Model 4: additionally adjusted for body mass index, waist circumference, systolic blood pressure, total cholesterol, and low-density lipoprotein cholesterol.
P for trend was estimated using generalised linear regression across tertiles of dietary pattern scores.

CHAPTER FOUR

4.0

THE ADVERSE ASSOCIATION BETWEEN THE "OMNIVOROUS" DIETARY PATTERN AND HYPERTENSION: THE GUANGZHOU BIOBANK COHORT STUDY

4.1 Abstract

Objective: The prevalence of hypertension, a key risk factor for cardiovascular disease, is high and increasing in China. Guidelines promote lifestyle approaches for the prevention and treatment of hypertension, yet dietary determinants of hypertension in the Chinese population remain unclear. This study empirically derived dietary patterns and examined their relationship with hypertension. **Research design and methods:** Cross-sectional analysis of data from 20,126 participants from the GBCS was carried out. Diet was assessed using a validated semi-quantitative food frequency questionnaire. Hypertension was classified as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg, treated with medication, or previous physician-diagnosed hypertension. Dietary patterns were extracted using PCFA. **Results:** PCFA identified "Omnivorous", "High Protein-High Fat", and "Non-nut and Non-cruciferous Vegetable" diets. In the fully adjusted model, the Omnivorous diet was associated with increased risk for hypertension (RR 1.11, 95%CI 1.07-1.15), independent of BMI and waist circumference. The High Protein-High Fat diet was associated with a lower risk (RR 0.96, 95%CI 0.93-0.99), including in those with good self-rated health and was independent of BMI and waist circumference. The Non-nut and Non-cruciferous Vegetable diet showed no association with hypertension (RR 0.98, 95%CI 0.94-1.01). **Conclusion:** The Omnivorous diet was associated with a greater risk of hypertension. The observed relationships need confirmation in prospective studies, but suggests that sodium contained in the meats may adversely impact blood pressure.

4.2 Introduction

Hypertension, a strong risk factor for stroke and CVD continues to be a growing challenge for health services worldwide [294]. A systematic analysis for the Global Burden of Disease Study identified that hypertension is responsible for 55% of CVD mortality [295]. In China, between 2002 and 2010, the prevalence of hypertension increased from 20% to 34% [296, 297]. In 2005, 20% of premature deaths in China were due to hypertension [54], in part resulting from sub-optimal management [294, 297, 298]. In China, less than 40% individuals with hypertension were aware of their condition, and less than 20% individuals were capable of managing their hypertension [297, 298]. Emerging evidence suggests that hypertension can be controlled at low cost even in poorly resourced settings [294, 299].

Dietary control is the first line approach in most guideline addressing prevention and management of hypertension. Intervention studies in Western populations have shown that combination diets that incorporate foods purported to promote health such as poultry, whole-grain, fruits, and vegetables, substantially lower blood pressure in high-risk hypertensive individuals [62]. Chinese food preparation differs considerably from those in the West, yet little is known about how this might contribute to hypertension [200, 300]. The complexity of preparation also means the value of conventional approaches to examine associations with individual components is limited. Using cross-sectional data from a large study of middle-aged and older residents of Guangzhou, China [241], this study aimed to identify dietary patterns of middle-aged and older Chinese and assess their relationship with hypertension.

4.3 Research design and methods

The GBCS, a collaboration between the Guangzhou Number 12 People's Hospital, (China), the University of Hong Kong, (China), and the University of Birmingham, (UK), is described elsewhere in detail [241]. Briefly, GBCS recruited 30,518 participants over three phases. Twenty thousand four hundred and thirty participants aged 50-93 years were enrolled in two phases. Recruitment was carried out during 2003-2004 for phase 1 and during 2005-2006 for phase 2. Recruitment for phase 3 was carried out during 2006-2007, which enrolled 10,088 participants.

The study obtained official ethical approval from the Guangzhou Medical Ethics Committee of the Chinese Medical Association and written informed consent was obtained from the participants before data collection. Participants were eligible to be included in the study if they were not receiving treatment for any life-threatening condition, were ambulatory, and able to provide informed consent. Via face-to-face interviews, participants completed a detailed questionnaire on demographics, lifestyle, physical activity levels, smoking status, medical history, and dietary intake. For the analyses conducted, participants from phase 1 and phase 2 were studied. Participants from phase 3 were excluded because of collection of incomparable dietary data.

4.3.1 Hypertension assessment

The participants attended the examination centre after an overnight fast and their blood pressure measured. Systolic and diastolic blood pressure was measured in a seated position following a 3-minute rest, and three measurements were recorded at 1-minute intervals. The last two measurements were used to derive the mean systolic and diastolic blood pressures [241]. Hypertension was classified as a systolic blood

pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg (≥140/90mmHg) or having physician-diagnosed hypertension, or receiving treatment for hypertension [52]. A systolic blood pressure ≥130-≤140mmHg and/or diastolic blood pressure ≥85-≤90mmHg without a previous diagnosis of hypertension was used to define pre-hypertension.

4.3.2 Dietary assessment

A 266-item validated SFFQ was used to collect dietary information for all phase 1 and 2 participants [243]. The SFFQ assessed the frequency of dietary items consumed over a week. Ten food groups were missing in the dietary data, as these were omitted in the collection in different study phases hence leaving information on 256-items. Dietary data were examined for outliers and eight implausible values on the frequency of consumption were detected. One food item had two outliers and six food items had one outlier each. These outliers were removed. No participant reported eating margarine, soft margarine, salad dressing, and butter. These items were therefore excluded. For dietary pattern analyses, the remaining 252 items were categorised into fifty-three predefined food groups [121].

4.3.3 Statistical analysis

PCFA was performed on the fifty-three food groups to extract the dietary patterns. An eigenvalue above one and the scree plot test were used to select the number of factors to retain. The eigenvalue threshold of 1.0 identified eighteen factors, but the scree plot showed an inflection point after the third factor, therefore the three first factors were retained [257]. Varimax (orthogonal) rotation was performed on the three factors to simplify the factor structure interpretation of the factors. The factors were interpreted

and labelled based on a ±0.30 factor loading cut-off criteria [122]. Summing up the food item weightings by the factor loadings of orthogonal transformed factors created a score for each factor and participant. This score determined how closely a participant followed each particular dietary pattern [192]. The participants' scores were then divided into tertiles. The participants' baseline characteristics were summarised across tertiles of dietary pattern, using mean (SD) or median [IQR] for continuous data, and as percentages for categorical variables. Comparison for baseline characteristics across tertiles of dietary patterns was estimated using chi-square test for categorical, and ANOVA for continuous variables.

The relationship between each dietary pattern and hypertension was assessed after excluding those with pre-hypertensive, using multivariable generalised linear Poisson regression model with robust standard errors [270]. RR and 95% CIs were estimated for each tertile with the first tertile used as the reference group. A hierarchical approach was taken with the first model being unadjusted. Model two adjusted for age (years) and gender. Model three additionally adjusted for education (primary or below/secondary/tertiary), occupation (manual/non-manual/other), physical activity (inactive/minimally active/active), smoking (never/ex-smoker/current smoker), total cholesterol (mmol/L), and glucose (mmol/L). The potential mediating factors such as BMI (kg/m^2), and waist circumference (cm) were added in model four. Alcohol was included in the dietary patterns and was thus not included additionally as a covariate. The P for trend was estimated using generalised linear Poisson regression across the tertiles of the dietary patterns.

Sensitivity analyses were used to address potential reverse causality in the results. We first evaluated the association by comparing normotensive with pre-hypertension after excluding those with newly and previously diagnosed hypertension. We then repeated the main and first sensitivity analyses after restricting the sample to just participants with good self-rated health. All models for sensitivity analyses were fully adjusted.

Three hundred and four (1.4%) participants of the 20,430 had missing information on potential confounders; therefore final analysis was restricted to 20,126 participants with complete information. Multiple imputations were not performed on the missing data because the number of missing values was not substantial. All statistical analyses were performed using STATA (version 13.1, Stata Corp, College Station, Texas).

4.4 Results

PCFA identified three dietary patterns based on the fifty-three food groups, for which twenty-five food groups contributed. Diet one, accounting for the most variance, was labelled the "Non-nut and Non-cruciferous Vegetable" because it included frequent consumption of red-orange vegetables, starchy vegetables, tomatoes, mushrooms, eggs, fruit, and soy. Diet two was labelled "High Protein-High Fat" because of the frequent consumption of seafood, beans & legumes, poultry, offal, red meat and high protein-high fat dishes. Diet three was labelled "Omnivorous" because of frequent consumption of cruciferous vegetables, citrus fruits, preserved meat, other meats, and nuts. Mean and SD of frequency intake of the food items was also summarised for each pattern.

Of the 20,126 participants, 8,870 (44.6%) participants were hypertensive and 2,290 (11.3%) had pre-hypertension. The participants' baseline characteristics stratified by dietary pattern scores are presented in Table 4.1. The third tertile of the Omnivorous diet had a greater representation of females and was associated with lower waist circumference, higher blood pressure, higher cholesterol levels, and less smoking. The third tertile of the High Protein-High Fat diet was associated with lower systolic blood pressure and lower fasting plasma glucose. The pattern with education and physical activity was unclear. The third tertile of Non-nut and Non-cruciferous Vegetable diet was associated with larger waist circumference, a higher fasting plasma glucose, lower total- and LDL-cholesterol. The third tertile was also associated less smoking and greater physical activity.

After controlling for potential confounders the Omnivorous diet was associated with an increased risk of hypertension (RR 1.11, 95%CI 1.07-1.15) (Table 4.2). To assess whether the association was mediated in part by waist circumference and BMI, we further adjusted for these factors. The association remained unchanged after adjustment for waist circumference and BMI. The High Protein-High Fat diet was associated with a lower risk of hypertension in the multivariable model controlling for potential confounders (RR 0.96, 95%CI 0.93-0.99). The Non-nut and Non-cruciferous Vegetable diet was not associated with hypertension after adjusting for potential confounder (RR 0.98, 95%CI 0.94-1.01).

In sensitivity analyses to address for potential reverse causation, the relationship with pre-hypertension was assessed after excluding those with newly and previously diagnosed hypertension. The Omnivorous diet showed an increased risk of pre-

hypertension after controlling for potential confounders (RR 1.13, 95%CI 1.03-1.24) and remained significantly associated with an increased risk after adjustment for waist circumference and BMI (RR 1.14, 95%CI 1.04-1.24) (Table 4.2). For the High Protein-High Fat diet, the effect sizes of association were similar with pre-hypertension after controlling for potential confounders, however, the reduction in study power in the stratified analysis meant these were no longer significant. As with hypertension, the Non-nut and Non-cruciferous Vegetable diet showed no association with pre-hypertension (RR 0.92, 95%CI 0.84-1.01) in the multivariable model adjusted for potential confounders.

Potential reverse causality was further assessed by restricting the sample to those with good self-rated health. Good self-rated health was reported by 16,688 participants, of whom, 1,988 (12%) were pre-hypertensive, and 7,142 (43%) hypertensive. In the multivariable model controlling for potential confounders, the Omnivorous diet was associated with an increased risk of hypertension both before (RR 1.12, 95%CI 1.08-1.16) and after additional adjustment for waist circumference and BMI (RR 1.12, 95%CI 1.07-1.16). The High Protein-High Fat diet was associated with a lower risk of hypertension after adjusting for potential confounder (RR 0.95, 95%CI 0.92-0.99). Lower risk of hypertension remained after further adjustment for waist circumference and BMI (RR 0.94, 95%CI 0.90-0.97). As with earlier analyses after controlling for potential confounders the Non-nut and Non-cruciferous Vegetable diet showed no association with hypertension (RR 0.98, 95%CI 0.94-1.02). For pre-hypertension in those with good self-rated health again the observed increased risk of pre-hypertension remained significant for the Omnivorous diet after adjusting for potential confounders before (RR 1.14, 95%CI 1.04-1.25) and after adjustment for

waist circumference and BMI (RR 1.15, 95%CI 1.04-1.26). The effect size of the association between the High Protein-High Fat diet and pre-hypertension was similar to those in the main analysis (RR 0.96, 95%CI 0.88-1.06) including after adjustment for waist circumference and BMI (RR 0.95, 95%CI 0.87-1.05), but did not reach significance. There was no association with the Non-nut and Non-cruciferous Vegetable diet (RR 0.92, 95%CI 0.83-1.02).

4.5 Discussion

This study identified three dietary patterns with which associations with hypertension were investigated, including the mediating effect of waist circumference and BMI in this large community-based study. The Omnivorous diet was consistently associated with an increased risk of having both hypertension and pre-hypertension, including in all sensitivity analyses. The High Protein-High Fat diet was associated with a lower risk of having hypertension, including in the main sensitivity analysis. For pre-hypertension, although effect sizes were similar to those for hypertension, they did not reach significance, most likely due to reduced study power following the stratification. The Non-nut and Non-cruciferous Vegetable diet showed no association with pre-hypertension or hypertension.

4.5.1 The Omnivorous Diet

This study found a clear adverse association between the Omnivorous diet and both hypertension and pre-hypertension in a manner that was independent of waist circumference and BMI.

The Omnivorous diet consists of food groups, for which, the evidence of an association with blood pressure is inconclusive. A recent systematic review and meta-analysis of 61 short-term RCTs lasting 3 to 26 weeks including 2,582 participants found no association between nuts and blood pressure [301]. There is limited evidence of the effects of citrus fruit on blood pressure. An 8 week trial of 22 adult participants found commercially available citrus juice to reduce systolic and diastolic blood pressure by 5.9% and 5.1%, but did not find natural citrus juice to significantly lower blood pressure [302]. The evidence on the effects of cruciferous vegetables on blood pressure is also limited. In the prospective analyses of the WHS [124] with a mean follow-up of 13 years involving 28,082 participants, cruciferous vegetables were found to increase the risk of hypertension by 14%. The increased risk of hypertension in our study may partly be attributed to preserved/processed meats. Recently, the prospective analyses of the Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale Study [303], with a follow-up of 15 years comprised of 44,616 participants examined the effects of preserved meat intake on incident hypertension. A higher intake was found to increase the risk of developing hypertension by 17%.

Mechanistically, the underlying mechanism explaining the harmful effects of cruciferous vegetables has not been clarified [124]. On the other hand, salt/sodium is added in preserved and processed meats [304]. A systematic review and meta-analysis identified that sodium content was 4-fold higher in processed meats than in unprocessed meats [114]. This suggests that the harmful effects of such meats on hypertension could potentially be due to the added sodium rather than the meat itself.

How sodium raises blood pressure has multiple explanations including vasoconstriction, volume dependent, and volume independent mechanisms [50].

4.5.2 The High Protein-High Fat Diet

The High Protein-High Fat pattern was inversely associated with hypertension. Other than the clear contribution of dietary salt to blood pressure, the most likely mediating factor is through differences in waist circumference and BMI. Increased obesity is associated with a range of changes that can promote increasing blood pressure. However, although tertile 3 of this diet showed statistically significant, though clinically marginal, higher BMI and waist circumference, blood pressure levels were mixed with slightly lower systolic but higher diastolic blood pressure. Adjustment for BMI and waist circumference highlighted that the effects of the diet were independent of them.

Our findings are in agreement with results of multiple RCTs. A systematic review and meta-analysis of 8 trials lasting 6 to 11 months, which included 753 participants found that a high protein and high fat diet reduced systolic and diastolic blood pressure by 5.19 mmHg and 3.53 mmHg, respectively [171].

The blood pressure-lowering effects of the High Protein-High Fat diet may be attributable to amino acids in the proteins. Seafood, poultry, meats, and beans/legumes are enriched with amino acids arginine, cysteine, and taurine [305-307]. Arginine and cysteine modulates the renin-angiotensin activity by inhibiting angiotensin-converting enzyme activity, which reduces levels of the vasoconstrictor angiotensin II and lowers blood pressure [306, 308]. Taurine reduces vasopressin

secretion by inhibiting the sympathetic nervous system activity and subsequently lowers blood pressure [308].

4.5.3 The Non-nut and Non-Cruciferous Vegetable Diet

Our finding of no association between the Non-nut and Non-cruciferous Vegetable diet and hypertension is supported by a prospective [309] and a cross-sectional study [300]. In the EPIC Potsdam Study [309] of 8,522 participants with 2 to 4 year follow-up, the "Fruit & Vegetable" diet consisting of raw vegetables, cooked vegetables, vegetable oil, and fruit showed no association with hypertension. A recent cross-sectional analyses of 2,518 Chinese participants living in Jiangsu Province also found no association with hypertension with their equivalent diet, which included pickled vegetables, fresh vegetables, fruit, eggs, fish, and whole-grains [300]. Although, the above-mentioned studies have detected no association with hypertension, vegetable intake has been shown to lower the risk of coronary heart disease and CVD [119].

An explanation for the lack of association between the Non-nut and Non-cruciferous Vegetable diet and hypertension could be added salt in the diet. Chinese prepared foods are frequently seasoned, pickled, and prepared with salt containing sauces such as soy, oyster, and vinegar [124, 300]. The added salt during food preparation may have offset any potential beneficial effects of this diet on blood pressure levels [124].

4.5.4 Strength and limitations

A major strength of our study is its large sample size in well-characterised non-Western population that enabled adjustment for a range of potential confounders. Stratified analyses to address potential reverse causation are another strength of the

study. Our study also has several limitations. Given the cross-sectional nature of this study, we are unable to infer causality. Although we adjusted for several potential confounders, the potential for residual confounding could not be excluded. Dietary information was gathered at baseline via a single SFFQ providing only a snapshot of the participants' dietary habits. This makes it difficult to assess prolonged dietary habits and dietary changes caused by hypertension diagnosis at baseline, which requires our findings to be confirmed prospectively. Another limitation is the inability to estimate and adjust for sodium. Furthermore, dietary pattern analysis often includes arbitrary decisions on the food groupings prior to PCFA, and decisions on the numbers of patterns to retain, the cut-off point used to identify food items, and labelling of the patterns, which can affect interpretation of the diets [147]. However, the advantage of the dietary patterns approach is that it enables analysis of whole diets that avoid the major pitfalls of analysis involving individual foods [310]. Diets may influence the risk of hypertension through alternative pathways other than obesity. Further work is required to determine these.

4.5.5 Summary

In summary, this study, incorporating several analyses, found the Omnivorous diet to be associated with an increased risk of hypertension independent of obesity. The High Protein-High Fat diet was associated with a lower risk of having hypertension but was no longer significant due to lower study power in sensitivity analyses. The Non-nut and Non-cruciferous Vegetable diet showed no association with hypertension. This study adds to the existing evidence that non-western dietary patterns are an important risk factor for hypertension. Our findings need to be examined prospectively and confirmed through interventional studies.

Table 4.1 Baseline characteristics of 20,126 participants by tertile 1 and 3 of dietary pattern scores.

	Non-nut and Non-cruciferous Vegetable diet			**High Protein-High Fat diet**			**Omnivorous diet**		
Characteristics	**Tertile 1 (6,705)**	**Tertile 3 (6,709)**	*p* value	**Tertile 1 (6,694)**	**Tertile 3 (6,719)**	*p* value	**Tertile 1 (6,737)**	**Tertile 3 (6,692)**	*p* value
Age, years [median (IQR)]	60 (55-67)	63 (58-68)	<0.001	63 (57-68)	61 (56-67)	<0.001	62 (57-67)	62 (56-67)	0.12
Sex (%)									
- Female	72.8	69.4	<0.001	76.7	65.7	<0.001	67.2	75.8	<0.001
Body Mass Index (kg/m^2)	23.8 (3.3)	23.8 (3.3)	0.3	23.6 (3.3)	23.9 (3.3)	<0.001	23.7 (3.3)	23.9 (3.3)	0.01
Waist Circumference (cm)	78.8 (8.8)	79.8 (9.1)	<0.001	79.3 (8.9)	79.5 (8.9)	0.001	79.6 (9.1)	78.9 (8.7)	<0.001
Blood pressure (mmHg)									
- Systolic blood pressure	131 (22.3)	131 (21.9)	0.2	132 (22.6)	130 (21.8)	<0.001	129 (22.1)	133 (22.1)	<0.001
- Diastolic blood pressure	74 (11.3)	74 (11.2)	0.1	73.6 (11.3)	74.1 (11.3)	0.02	73.8 (11.3)	74.3 (11.3)	0.001
Pre-hypertensive (%)	20.8	21.2	0.07	21.0	19.4	0.16	19.5	21.3	0.14
Hypertensive (%)	48.5	51.3	0.01	52.4	47.1	<0.001	47.0	52.5	<0.001
Fasting glucose, mmol/L [median (IQR)]	5.3 (4.8-5.8)	5.6 (5.1-6.1)	<0.001	5.5 (5.0-6.0)	5.3 (4.9-5.9)	<0.001	5.4 (4.9-6.0)	5.4 (4.9-6.0)	0.9
Cholesterol (mmol/L)									
- Total cholesterol	6.1 (1.2)	5.8 (1.1)	<0.001	5.9 (1.2)	6.0 (1.2)	<0.001	5.8 (1.2)	6.1 (1.2)	<0.001
- High-density lipoprotein	1.7 (0.4)	1.6 (0.4)	<0.001	1.7 (0.4)	1.7 (0.4)	0.05	1.6 (0.4)	1.8 (0.4)	<0.001
- Low density lipoprotein	3.3 (0.7)	3.1 (0.7)	<0.001	3.1 (0.7)	3.2 (0.7)	<0.001	3.1 (0.7)	3.3 (0.7)	<0.001
Education (%)			<0.001			<0.001			<0.001
- Primary or below	51.5	39.9		51.5	40.1		50.7	40.6	
- Secondary	25.5	25.5		23.9	28.0		24.1	28.1	
- Tertiary	23.0	34.6		24.6	31.9		25.2	31.3	
Occupation (%)			<0.001			<0.001			<0.001
- Manual	69.9	57.1		67.2	60.4		67.9	60.3	
- Non-manual	20.5	39.8		26.9	33.6		27.1	32.9	
- Other	9.6	3.1		5.9	6.0		5.0	6.8	
Smokers (%)			<0.001			<0.001			<0.001
- Never	74.1	76.8		79.6	70.8		71.4	79.0	
- Ex-smoker	11.7	13.9		11.5	14.5		14.2	12.3	
- Current	14.2	9.3		8.9	14.7		14.4	8.7	
Physical activity			<0.001			<0.001			<0.001
- Inactive	14.2	3.7		9.3	7.0		10.1	6.3	
- Minimally active	52.6	40.9		45.3	49.5		44.3	50.0	
- Very active	33.2	55.4		45.4	43.5		45.6	43.7	

Data are means (SD) and percentages unless indicated otherwise.
P values are for the significance of chi-square test for categorical variables and analysis of variance test for continuous variables.

Table 4.2 Multivariable RR (95% CI) for relationship between dietary pattern scores and hypertension (≥140/90mmHg) and pre-hypertension (≥130-<140/≥85-<90mmHg) in middle-aged and older Chinese adults.

	Hypertension					Pre-hypertension			
	Tertile 1	**Tertile 2**	**Tertile 3**	*P trend*		**Tertile 1**	**Tertile 2**	**Tertile 3**	*P trend*
Non-nut and Non-cruciferous Vegetable diet	***n* (2,867/5,908)**	***n* (2,962/5,995)**	***n* (3,041/5,933)**		**Non-nut and Non-cruciferous Vegetable diet**	***n* (797/3,838)**	***n* (717/3,750)**	***n* (776/3,668)**	
Model 1	1.00	1.02 (0.98-1.06)	1.06 (1.02-1.10)	0.003	Model 1	1.00	0.92 (0.84-1.00)	1.02 (0.93-1.11)	0.70
Model 2	1.00	0.99 (0.95-1.02)	0.99 (0.96-1.02)	0.55	Model 2	1.00	0.88 (0.81-0.96)	0.94 (0.86-1.02)	0.15
Model 3	1.00	0.98 (0.95-1.02)	0.98 (0.94-1.01)	0.21	Model 3	1.00	0.87 (0.80-0.95)	0.92 (0.84-1.01)	0.09
Model 4	1.00	0.98 (0.95-1.02)	0.98 (0.94-1.01)	0.13	Model 4	1.00	0.87 (0.80-0.95)	0.91 (0.83-1.00)	0.06
High Protein-High Fat diet	***n* (3,114/5,943)**	***n* (2,949/5,931)**	***n* (2,807/5,962)**		**High Protein-High Fat diet**	***n* (751/3,580)**	***n* (782/3,764)**	***n* (757/3,912)**	
Model 1	1.00	0.95 (0.92-0.98)	0.90 (0.87-0.93)	<0.001	Model 1	1.00	0.99 (0.91-1.08)	0.92 (0.84-1.00)	0.08
Model 2	1.00	0.99 (0.96-1.02)	0.96 (0.92-0.99)	0.01	Model 2	1.00	1.01 (0.93-1.11)	0.95 (0.87-1.04)	0.29
Model 3	1.00	0.99 (0.96-1.02)	0.96 (0.93-0.99)	0.04	Model 3	1.00	1.01 (0.93-1.11)	0.96 (0.88-1.05)	0.40
Model 4	1.00	0.98 (0.95-1.01)	0.94 (0.91-0.97)	<0.001	Model 4	1.00	1.00 (0.91-1.09)	0.94 (0.86-1.03)	0.22
Omnivorous diet	***n* (2,810/5,973)**	***n* (2,944/5,933)**	***n* (3,116/5,930)**		**Omnivorous diet**	***n* (764/3,927)**	***n* (764/3,753)**	***n* (762/3,576)**	
Model 1	1.00	1.05 (1.02-1.09)	1.12 (1.07-1.16)	<0.001	Model 1	1.00	1.05 (0.96-1.14)	1.10 (1.00-1.20)	0.04
Model 2	1.00	1.05 (1.01-1.09)	1.11 (1.07-1.16)	<0.001	Model 2	1.00	1.06 (0.97-1.16)	1.13 (1.03-1.23)	0.009
Model 3	1.00	1.05 (1.01-1.09)	1.11 (1.07-1.15)	<0.001	Model 3	1.00	1.07 (0.97-1.17)	1.13 (1.03-1.24)	0.007
Model 4	1.00	1.05 (1.01-1.09)	1.11 (1.07-1.15)	<0.001	Model 4	1.00	1.07 (0.98-1.17)	1.14 (1.04-1.24)	0.005

n = no of cases/participants.
Model 1: univariate.
Model 2: adjusted for age and sex.
Model 3: additionally adjusted for education, occupation, smoking, physical activity, total cholesterol, and glucose.
Model 4: additionally adjusted for body mass index, and waist circumference.
P for trend was estimated using generalised linear regression across tertiles of dietary pattern scores.

CHAPTER FIVE

5.0

EXPLORATION OF THE RELATIONSHIPS BETWEEN DIETARY PATTERNS AND THE METABOLIC SYNDROME IN MIDDLE-AGED AND OLDER CHINESE: THE GUANGZHOU BIOBANK COHORT STUDY

5.1 Abstract

Objective: The prevalence of the metabolic syndrome, a cluster of cardiovascular risk factors, is escalating in China. Data describing the effects of dietary patterns on the metabolic syndrome in Chinese are scarce. This study empirically extracted dietary patterns and examined the association with the metabolic syndrome in middle-aged and older Chinese. **Research design and methods:** Cross-sectional analysis of 20,121 participants in the Guangzhou Biobank Cohort Study. Diet was assessed using a 256-item semi-quantitative food frequency questionnaire. The metabolic syndrome was defined by the Joint Interim Statement guidelines as having three or more of enlarged waist circumference, hypertension, low HDL-cholesterol, high triglycerides, and hyperglycaemia. PCFA was used to identify the dietary patterns and the relationship with the metabolic syndrome was assessed using multivariable regression. **Results:** PCFA identified the Non-nut and Non-cruciferous Vegetable, Omnivorous, and High Protein-High Fat diets. In the fully adjusted model, the Non-nut and Non-cruciferous Vegetable diet was associated with increased risk of metabolic syndrome (RR 1.16, 95%CI 1.10-1.21). The Omnivorous diet was associated with a lower risk (RR 0.93, 95%CI 0.89-0.98). The results were similar in sensitivity analyses after excluding participants with T2DM, and further restricting the sample to those with good self-rated health. The association was not significant for the High Protein-High Fat diet. **Conclusion:** The Non-nut and Non-cruciferous Vegetable diet was associated with greater risk of metabolic syndrome while the Omnivorous diet was associated with a lower risk, and was unlikely the result of reverse causation. These associations, if confirmed to be causal, may help inform public health approaches for tackling the problem of the increasing burden of metabolic syndrome.

5.2 Introduction

The metabolic syndrome, a constellation of three or more of metabolic risk factors such as enlarged waist circumference, hyperglycaemia, hypertension, low HDL-cholesterol, and high triglycerides is a global public health issue [90]. The metabolic syndrome increases the risk of cardiovascular disease two-fold [311]. Once considered a disease of affluence or of western countries, the prevalence of the metabolic syndrome has dramatically increased in China with the development of rapid modernisation.

Between the 1940s and 1970s, Chinese authorities were concerned with food availability [312]. From the beginning of the 1980s, China started economic reform and underwent rapid modernisation, which spurred associated physical activity and nutritional transitions [12]. The classic Chinese diet, which was characterised by rice, wheat, and vegetables transitioned to more Westernised patterns by the 1990s, which included more calorie dense foods, with a particular emphasis on animal-based proteins [13].

Excess food intake and adverse diet compositions are purportedly among the main drivers of the metabolic syndrome epidemic [13]. As a result, dietary improvement is likely a key strategy for metabolic syndrome reduction either directly or indirectly through improvements in glycaemia, blood pressure, and lipids [313]. Studies of the Chinese diet in relation to metabolic syndrome risk are scarce, constituting to date only two studies [269, 314] investigating how dietary patterns are related to the condition. We therefore examined the effect of major dietary patterns on the risk for the metabolic syndrome in middle-aged and older Chinese.

5.3 Research design and methods

The GBCS, a collaboration among Guangzhou Number 12 People's Hospital, (China), the University of Hong Kong (China) and the University of Birmingham, (UK) is described in detail elsewhere [241]. Briefly, 30,518 middle-aged and older participants aged 50-93 years were recruited for the study in three phases from 2003-2007.

Participants were eligible for inclusion if they were ambulatory, able to give informed consent, and not undergoing treatment for life-threatening conditions. The participants completed a detailed computer-based questionnaire on demographic characteristics, medical history, diet, smoking habits, physical activity according to IPAQ, and other lifestyle factors via face-to-face interviews. The study obtained ethical approval from the Guangzhou Medical Ethics Committee of the Chinese Medical Association and also obtained written informed consent from the participants prior to data collection.

The participants attended the examination centre after an overnight fast. Prior to face-to-face interviews, the participant's anthropometric measurements and blood pressure was taken. They were also screened for biochemical parameters. Height, weight, and waist circumference was measured using the standardised protocol. Rested blood pressure was measured in a seated position. Three blood pressure readings were collected at one-minute intervals and an average of the last two readings was used to estimate the mean systolic and diastolic blood pressure value. Biochemical parameters measured included fasting plasma glucose, HDL-cholesterol and triglycerides [241].

5.3.1 Dietary assessment

A previously validated 266-item SFFQ was used to assess the dietary intake of participants enrolled in phases 1 and 2 [243]. Phase 3 data were not included because of lack of comparable dietary data due to the use of an abbreviated food frequency questionnaire. In the SFFQ the participants were asked to specify how frequently the participants consumed the foods and beverages over a week. Information on ten food items were omitted in the collection in different study phases. Therefore, information on 256-items was available and used for the analysis. The SFFQ data was examined for outliers and eight implausible values on the frequency of consumption were detected. One food item had two outliers and six food items had one outlier each. These outliers were removed. No participant reported eating margarine, soft margarine, salad dressing, or butter. These items were therefore excluded. Two clinical dietitians were consulted for their expertise on grouping of food items for dietary pattern analysis. Two hundred and fifty two items were categorised into 53 predefined food groups based on similarity [121]. For example, citrus fruit group was formed by combining oranges, grapefruit, lemons, and pomelo.

5.3.2 The metabolic syndrome

The metabolic syndrome was defined in accordance with the Joint Interim Statement [90] as having three or more of the following cardiovascular risk factors: (i) hyperglycaemia as fasting plasma glucose ≥5.6mmol/L, or having a physician-diagnosis of, or receiving treatment for, T2DM; (ii) hypertension as a systolic blood pressure ≥130mmHg and/or diastolic blood pressure ≥85mmHg, or having a physician-diagnosis of, or receiving treatment for, hypertension; (iii) high triglycerides as serum triglycerides ≥1.7mmol/L, or having a physician-diagnosis of,

or receiving treatment for, high triglycerides; (iv) low HDL-cholesterol (≤1.00mmol/L in males or ≤1.30mmol/L in females), or having a physician-diagnosis of, or receiving treatment for, low HDL-cholesterol; (v) a large waist circumference (≥90cm in males or ≥80cm in females).

5.3.3 Statistical analyses

PCFA was performed on the 53 food groups to extract dietary patterns. Dietary patterns were selected and retained on the basis of scree plot test and eigenvalues above 1.0. PCFA identified twenty-three patterns with eigenvalues above 1.0 but the scree plot showed an inflection point between the third and the fourth pattern therefore three patterns were retained [257]. Varimax or orthogonal rotation was performed on the three retained patterns to simplify their pattern structure and pattern interpretability [122]. The patterns were labelled and interpreted using the ±0.30 factor loading cut-off point [122]. Dietary pattern scores were created for each participant and for each pattern by summing up the food item weightings by the factor loadings of orthogonally rotated factors. The participants were then divided into tertiles based on each dietary pattern score.

The participant characteristics were summarised, stratified by tertiles of dietary patterns, using mean (SD) or median (IQR) for continuous variables and as percentages for categorical variables. Baseline characteristics were compared between tertiles of dietary patterns using chi square test for categorical variables and ANOVA for continuous variables.

The relationship between dietary patterns and metabolic syndrome was assessed using multivariable generalised linear Poisson regression with robust standard errors, which are more reliable and consistent standard errors that allow for the estimation of the risk in presence of heteroskedasticity [270]. RR and the corresponding 95%CIs were estimated for each tertile with the first tertile used as the reference group. Models were built to assess the confounding effects of potential confounders selected from the literature a priori. The first model was unadjusted. The second model adjusted for age (years) and gender. The third and main outcome model additionally adjusted for smoking (never/ex-smoker/current), physical activity (inactive/minimally active/very active), occupation (manual/non-manual/other), and education (primary or below/secondary/tertiary). Additionally, BMI (kg/m^2) was adjusted for in the fourth model. Regression analyses did not control for alcohol due to the fact that alcohol was incorporated as a food group in PCFA. P for trend was estimated using generalised Poisson regression across the tertiles of dietary pattern scores.

We performed sensitivity analyses to address potential reverse causality using two approaches. We assessed the association by comparing participants without the metabolic syndrome vs. participants with the metabolic syndrome after excluding those with newly and previously diagnosed T2DM. We then compared participants without the metabolic syndrome vs. participants with the metabolic syndrome after excluding those with newly and previously diagnosed T2DM after restricting the sample to participants with good self-rated health. All models for sensitivity analyses were fully adjusted. Additionally, we assessed the relationship between the dietary patterns and individual components of the metabolic syndrome.

Three hundred and nine participants out of the 20,430 participants had missing information on the potential confounders. The final analysis was restricted to 20,121 participants with full information. Statistical analyses were performed using STATA (version 13.1, STATA Corp, College Station, Texas).

5.4 Results

PCFA identified three dietary patterns. Only 25 food groups out of the 53 that contributed to the diets. The first dietary patterns showed a frequent intake of a vegetables (red and orange, starchy, dark yellow), mushrooms, tomatoes, fruit, soy, and eggs therefore this diet was labelled as the "Non-nut and Non-cruciferous Vegetable" diet. The second dietary pattern showed a frequent intake of poultry, seafood, offal, high protein-high fat dishes, red meat, beans and legumes, yellow-orange fruit, and beverages therefore this diet was labelled "High Protein-High Fat." The third dietary pattern showed a frequent intake of citrus fruits, cruciferous vegetables, preserved meats, and nuts therefore this diet was labelled as the "Omnivorous." The diets explained 11.3% of the variance, of which the Non-nut and Non-cruciferous Vegetable diet explained 5.8% variation.

Of the 20,121 participants, 6,733 (33%) participants had the metabolic syndrome. The characteristics of 20,121 participants stratified by dietary patterns are summarised in Table 5.1. The third tertile of Non-nut and Non-cruciferous Vegetable diet was associated with a larger waist circumference, higher fasting plasma glucose, lower total- and low-density lipoprotein-cholesterol, less smoking, and greater physical activity. The third tertile of the Omnivorous diet was associated with a smaller waist circumference, higher blood pressure, higher cholesterol levels, and non-smoking.

The third tertile of the High Protein-High Fat diet was associated with a larger waist circumference, lower systolic blood pressure, and lower fasting plasma glucose levels. The Non-nut and Non-cruciferous Vegetable diet was associated with an increased risk of the metabolic syndrome (RR 1.16, 95%CI 1.10-1.21) in the fully adjusted model (model 3, Table 5.2). We adjusted for BMI in model four to assess whether the association was mediated by it. The association remained unchanged after adjustment for BMI. The Omnivorous diet was associated with a lower risk of the metabolic syndrome after adjusting for potential confounders (RR 0.93, 95%CI 0.89-0.98) and the association remained significant after adjustment for BMI. In contrast, the High Protein-High Fat diet was not associated with the metabolic syndrome after adjusting for potential confounders (RR 1.00, 95%CI 0.96-1.05). The relationship became significant after adjusting for BMI (RR 0.95, 95%CI 0.91-0.99).

In sensitivity analyses to address the potential of reverse causation, we assessed the relationship with the metabolic syndrome after excluding participants with newly and previously diagnosed T2DM. The Non-nut and Non-cruciferous Vegetable diet continued to show an increased risk of metabolic syndrome in the fully adjusted model (RR 1.15, 95%CI 1.09-1.23) and remained associated with an increased risk after adjusting for BMI. The Omnivorous diet continued to show an association with a reduced risk of metabolic syndrome in the multivariable model controlling for potential confounders (RR 0.92, 95%CI 0.87-0.98) and after adjustment for BMI. The High Protein-High Fat diet was not associated with the metabolic syndrome in the fully adjusted model (RR 1.03, 95%CI 0.97-1.09) or after adjustment for BMI.

Potential for reverse causality was further assessed by comparing participants without the metabolic syndrome compared to participants with the metabolic syndrome after excluding participants with newly and previously diagnosed T2DM (*n* = 2,059) and restricting the sample to those with good self-rated health (*n* = 16,683), there were 14,624 participants (27% with metabolic syndrome). The Non-nut and Non-cruciferous Vegetable diet was associated with a similar increased risk of metabolic syndrome after controlling for potential confounders (RR 1.15, 95%CI 1.07-1.23) including after adjustment for BMI (RR 1.14, 95%CI 1.07-1.22). Likewise, the Omnivorous diet was still associated with a similar reduced risk of metabolic syndrome in the fully adjusted model before (RR 0.90, 95%CI 0.85-0.97) and after adjusting for BMI (RR 0.90, 95%CI 0.84-0.96). There was no association with High Protein-High Fat diet (RR 1.02, 95%CI 0.95-1.09).

Additionally, we assessed the relationship with the individual components of the metabolic syndrome. In the fully adjusted model including BMI, the Non-nut and Non-cruciferous Vegetable diet was associated with a 36% (95%CI 30-42)% increased risk of hyperglycaemia, 5% (95%CI 0-10)% of enlarged waist circumference, and 37% (95%CI 28-47)% of low HDL-cholesterol (Table 5.3). The Omnivorous diet was associated with a 5% (95%CI 1-9)% reduced risk of hyperglycaemia, 7% (95%CI 3-11)% of enlarged waist circumference, and 29% (95%CI 24-31)% of high triglycerides. In contrast, the Omnivorous diet was associated with an 8% (95%CI 5-11)% increased risk of hypertension. In the multivariable model including adjustment for BMI, the High Protein-High Fat diet was associated with a 13% (95%CI 9-16)% reduced risk of hyperglycaemia and 4%

(95%CI 2-7)% of hypertension. The High Protein-High Fat was associated with a 4% (95%CI 0-9)% increased risk of high triglycerides.

5.5 Discussion

In this study of middle-aged and older Chinese, three dietary patterns were extracted using PCFA. A frequent intake of the Non-nut and Non-cruciferous Vegetable diet pattern was associated with a 16% increased risk of the metabolic syndrome. This association was independent of relevant potential confounders and unaffected by sensitivity analyses addressing potential reverse causation. In contrast, the Omnivorous diet was associated with a 7% lower risk of the metabolic syndrome. The High Protein-High Fat diet was not associated with metabolic syndrome in the fully adjusted model.

5.5.1 The Non-nut and Non-Cruciferous Vegetable Diet

The harmful effects of the Non-nut and Non-cruciferous Vegetable diet on the metabolic syndrome could be due to high glycaemic load. This diet is associated with starchy vegetables such as sweet potatoes, potatoes, and sweet corn, which have a high glycaemic load [276]. A high glycaemic load has been found to be associated with several metabolic risk factors. In a systematic review of 17 prospective studies lasting 4-14 years, including 679,667 individuals showed that high glycaemic load was associated with 12% increased risk of hyperglycaemia [277]. In the 12 week trial including 163 participants, a high carbohydrate diet with high glycaemic index showed no association with triglycerides and systolic blood pressure [315]. Our results are consistent with this observation. Regarding the HDL-cholesterol, the Women's Health Initiative Study with average follow-up of 9 years found in 878

randomly selected participants found that HDL-cholesterol was reduced by 10% in those consuming a high glycaemic load diet [316]. Waist circumference is another component, which is negatively influenced by a high glycaemic load. In a cross-sectional analysis of the UK National Diet and Nutrition Survey involving 1,487 participants, per 50-unit increase in glycaemic load was associated with 2-fold increased risk of enlarged waist circumference [317].

Mechanistically, prolonged intake of high glycaemic load foods elevates postprandial glucose and insulin requirements, which in susceptible people over time could result in pancreatic beta-cell exhaustion through glucotoxicity [278]. The mechanism linking glycaemic load to obesity is inconsistent in the literature and remains to be clarified [317, 318]. The mechanism explaining the negative influence of high glycaemic load on HDL-cholesterol is not clarified [319]. Some have hypothesised that reduced HDL-cholesterol may be secondary to increased obesity [320]. We detected no association with hypertension. Any beneficial effects of the diet on blood pressure could have been offset by salt since salt-containing sauces like oyster and soy are used to pickle, season, and prepare foods in China [124].

5.5.2 The Omnivorous Diet

The Omnivorous diet was characterised by foods purported to promote health such as nuts, cruciferous vegetables, and citrus fruits. For instance, a systematic review and meta-analysis of 49 RCTs with median follow-up of 8 weeks totalling 2,226 participants assessed the effects of nuts on a range of metabolic risk factors [321]. Nuts showed no association with blood pressure, HDL-cholesterol, and waist circumference but reduced glucose and triglycerides by 0.08mmol/L and 0.06mmol/L.

Similar results have been observed for cruciferous vegetables. In a meta-analysis of five prospective studies lasting 4.6-24 years involving 307,723 participants, cruciferous vegetables reduced the risk of hyperglycaemia by 16% [322]. A 4 week trial, in which, 81 participants took part evaluated the effects of cruciferous vegetable extract (CV-E) on lipids [323]. CV-E lowered triglycerides by 0.44mmol/L but had no effect on HDL-cholesterol. CV-E was also found to have no impact on blood pressure in another 4 week trial of 40 participants [324]. Citrus fruit extract (CF-E) also have beneficial effects on some metabolic risk factors. In a 4 week trial involving 237 participants with metabolic syndrome, CF-E decreased glucose and triglycerides by 22.4% and 41% [325]. The relationship between citrus fruit and blood pressure is not well studied but in one small trial, 22 participants were randomised to consume commercial or natural citrus juice for 8 weeks [302]. Commercial citrus juice lowered systolic and diastolic blood pressure by 5.9% and 5.1% but natural citrus juice had no effect. It has been suggested that the flavonoid and pectin content of commercial citrus juice is higher because the grinding process uses entire fruit to produce citrus juice. The effects of citrus fruit on waist circumference have also been reported. A trial randomised 95 participants to CF-E or placebo for 12 weeks and at the end of the study, CF-E reduced waist circumference by 5.7% [326]. Furthermore, the diet Omnivorous diet was associated with preserved and processed meats. Such meats have been found to increase the risk of hypertension by 17% in a prospective study with 15 year follow-up involving 44,616 participants [303].

The mechanisms responsible for the observed associations are multiple and many elements of the diet may contribute to the reduced risk. Nuts have a low carbohydrate content; therefore, their ability to trigger post-prandial glycaemia is low [292]. They

are also high in phenolic compounds and unsaturated fatty acids, which lower post-prandial glucose by delaying digestion and absorption [292]. Unsaturated fatty acids are also involved in lowering triglycerides through lipoprotein lipase mechanism, which breaks down triglycerides and removes triglycerides remnants from the blood by the liver [327]. The protective effects of cruciferous vegetables are attributed to its isothiocyanates. In laboratory studies, isothiocyanates has been shown to lower glucose by reducing gluconeogenesis [328]. Isothiocyanates have also been shown to affect lipid metabolism and to reduce fat absorption by binding with bile acid in laboratory studies [329]. Flavanones in citrus fruit are also purported to have cardiovascular benefits. They increase glucose in the liver and muscles by enhancing AMP-activated protein kinase (AMPK) activity, and reduce triglycerides accumulation by influencing triglyceride synthetic enzymes [325]. Flavanones are also effective in reducing waist circumference by inhibiting fatty acid synthesis and increasing fatty acid oxidation [330]. These collectively could have reduced the risk of metabolic syndrome. On the other hand, preserved and processed meats have high sodium content, which may explain a higher risk of hypertension in this study [303].

5.5.3 The High Protein-High Fat Diet

The High Protein-High Fat diet was not associated with the metabolic syndrome after adjusting for potential confounders. The analyses were robust in sensitivity analyses indicating no relationship. The diet, however, was observed to be inversely associated with hyperglycaemia and hypertension but adversely associated with enlarged waist circumference and high triglycerides.

A systematic review of 17 trials lasting 3 to 36 months and comprising of 1,141 participants evaluated the effects of similar high protein and fat diets on a range of metabolic risk factors [171]. These diets lowered fasting plasma glucose by 0.06mmol/L and to reduced systolic and diastolic blood pressure by 4.81mmHg and 3.10mmHg. The review also found the diet to lower waist circumference (5.74cm), triglycerides (0.33mmol/L), and to increase HDL-cholesterol (0.4mmol/L). We found no association with HDL-cholesterol and detected adverse associated with enlarged waist circumference and triglycerides.

Few mechanisms may explain a reduced risk of hyperglycaemia and hypertension with the High Protein-High Fat diet. Reduced insulin demand from a lower carbohydrate intake is one potential mechanism. Reduced insulin demand reduces pancreatic beta-cell overload, and thereby enables better maintenance of glucose homeostasis [280]. Another potential mechanism is through the effects of amino acids leucine and arginine. Both have been postulated to improve beta-cell insulin secretion [281]. The effects on blood pressure are also via amino acids such as arginine, cysteine, and taurine. Arginine and cysteine modulate the renin-angiotensin activity by inhibiting angiotensin-converting enzyme activity, which reduces levels of the vasoconstrictor angiotensin II and lowers blood pressure [308]. Taurine reduces vasopressin secretion by inhibiting the sympathetic nervous system activity and subsequently lowers blood pressure [308].

Most trials evaluating the effects of high protein and fat diets on metabolic risk factors are short-term [171], and long-term effects are yet to be clarified. The downside of the High Protein-High Fat diet is the ad libitum intake of saturated fat in the expense of

carbohydrates [280]. A higher fat intake has been shown to be positively associated with obesity [331] and subsequent vascular disease [332]. Prolonged intake exacerbates obesity, which may have elevated triglycerides in this study and may eventually offset any beneficial effects of the diet on glycaemia and blood pressure.

5.5.4 Strength and limitations

The analysis performed in a large sample in a well-characterised non-western population is a major strength of this study. Dietary information was collected via a single SFFQ that provides a snapshot of the participant's dietary habits is the main limitation of the study, which unable us to infer causality. Another limitation is that with cross-sectional design we were unable to determine their dietary intake and its metabolic impact longitudinally. Prospective studies have demonstrated that dietary habits are maintained over time [121], which suggests that this is unlikely an issue. Diets may be reflective of other factors that are integral in overall lifestyle but several lifestyle factors were accounted for to address this, but residual confounding may still be present. Food patterns studies are inherently complex. The PCFA methodology relies on several subjective decisions and there is no gold standard for grouping the foods, selecting the number of pattern to keep, the factor loading cut-off point, and labelling of the diets are liable to different interpretations. This study is unable to conclude whether one specific mechanism or another, or unknown mechanisms are responsible for the effects on the metabolic syndrome. This suggests that there are several multiple pathways by which diet affects the metabolic syndrome.

5.5.5 Summary

This study found that the Non-nut and Non-cruciferous Vegetable diet was associated with increased risk of the metabolic syndrome. This may be due to the diet's high glycaemic load. The Omnivorous diet was associated with a lower risk of the metabolic syndrome. Prospective confirmation of these findings will identify approaches that can be implemented in public health programs to modify dietary intake to attenuate the emerging problem of the metabolic syndrome in China.

Table 5.1 Baseline characteristics of 20,121 participants by tertile 1 and 3 of the dietary pattern scores.

	Non-nut and Non-cruciferous Vegetable diet			**High Protein-High Fat diet**			**Omnivorous diet**		
N	**Tertile 1 (6,703)**	**Tertile 3 (6,708)**	*p* value	**Tertile 1 (6,691)**	**Tertile 3 (6,719)**	*p* value	**Tertile 1 (6,737)**	**Tertile 3 (6,688)**	*p* value
Age, years [median (IQR)]	60 (55-67)	63 (58-68)	<0.001	63 (57-68)	61 (56-67)	<0.001	62 (57-67)	62 (56-67)	0.1
Sex (%)									
- Female	72.8	69.4	<0.001	76.7	65.7	<0.001	67.2	75.8	<0.001
Body Mass Index (kg/m^2)	23.8 (3.3)	23.8 (3.3)	0.3	23.6 (3.3)	23.9 (3.3)	<0.001	23.7 (3.3)	23.9 (3.3)	0.01
Waist Circumference (cm)	78.8 (8.8)	79.8 (9.1)	<0.001	79.3 (8.9)	79.5 (8.9)	0.001	79.6 (9.1)	78.9 (8.7)	<0.001
Blood pressure (mmHg)									
- Systolic blood pressure	131 (22.3)	131 (21.9)	0.2	132 (22.6)	130 (21.8)	<0.001	129 (22.1)	133 (22.1)	<0.001
- Diastolic blood pressure	74 (11.3)	74 (11.2)	0.1	73.6 (11.3)	74.1 (11.3)	0.02	73.8 (11.3)	74.3 (11.3)	0.001
Fasting glucose, mmol/L [median (IQR)]	5.3 (4.8-5.8)	5.6 (5.1-6.1)	<0.001	5.5 (5.0-6.0)	5.3 (4.9-5.9)	<0.001	5.4 (4.9-6.0)	5.4 (4.9-6.0)	0.9
Cholesterol (mmol/L)									
- Total cholesterol	6.1 (1.2)	5.8 (1.1)	<0.001	5.9 (1.2)	6.0 (1.2)	<0.001	5.8 (1.2)	6.1 (1.2)	<0.001
- High-density lipoprotein	1.7 (0.4)	1.6 (0.4)	<0.001	1.7 (0.4)	1.7 (0.4)	0.05	1.6 (0.4)	1.8 (0.4)	<0.001
- Low density lipoprotein	3.3 (0.7)	3.1 (0.7)	<0.001	3.1 (0.7)	3.2 (0.7)	<0.001	3.1 (0.7)	3.3 (0.7)	<0.001
Education (%)			<0.001			<0.001			<0.001
- Primary or below	51.5	39.9		51.5	40.1		50.7	40.6	
- Secondary	25.5	25.5		23.9	28.0		24.1	28.1	
- Tertiary	23.0	34.6		24.6	31.9		25.2	31.3	
Occupation (%)			<0.001			<0.001			<0.001
- Manual	69.9	57.1		67.2	60.4		67.9	60.3	
- Non-manual	20.5	39.8		26.9	33.6		27.1	32.9	
- Other	9.6	3.1		5.9	6.0		5.0	6.8	
Smokers (%)			<0.001			<0.001			<0.001
- Never	74.1	76.8		79.6	70.8		71.4	79.0	
- Ex-smoker	11.7	13.9		11.5	14.5		14.2	12.3	
- Current	14.2	9.3		8.9	14.7		14.4	8.7	
Physical activity			<0.001			<0.001			<0.001
- Inactive	14.2	3.7		9.3	7.0		10.1	6.3	
- Minimally active	52.6	40.9		45.3	49.5		44.3	50.0	
- Very active	33.2	55.4		45.4	43.5		45.6	43.7	

Data are means (SD) and percentages unless indicated otherwise.
p values are for the significance of chi-square test for categorical variables and analysis of variance test for continuous variables.

Table 5.2 Multivariable RR (95% CI) for relationship between dietary pattern scores and the metabolic syndrome in middle-aged and older Chinese adults.

	Tertile 1	**Tertile 2**	**Tertile 3**	*P* trend
Non-nut and Non-cruciferous Vegetable diet	***n* (2,077/6,703)**	***n* (2,153/6,710)**	***n* (2,503/6,708)**	
Model 1	1.00	1.03 (0.99-1.09)	1.20 (1.15-1.26)	<0.001
Model 2	1.00	1.02 (0.97-1.07)	1.16 (1.11-1.22)	<0.001
Model 3	1.00	1.01 (0.96-1.01)	1.16 (1.10-1.21)	<0.001
Model 4	1.00	1.02 (0.97-1.07)	1.14 (1.09-1.20)	<0.001
High Protein-High Fat diet	***n* (2,358/6,691)**	***n* (2,204/6,711)**	***n* (2,171/6,719)**	
Model 1	1.00	0.93 (0.89-0.98)	0.92 (0.87-0.96)	<0.001
Model 2	1.00	0.98 (0.94-1.03)	1.00 (0.96-1.05)	0.95
Model 3	1.00	0.98 (0.94-1.03)	1.00 (0.96-1.05)	0.79
Model 4	1.00	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.03
Omnivorous diet	***n* (2,284/6,737)**	***n* (2,277/6,696)**	***n* (2,172/6,688)**	
Model 1	1.00	1.00 (0.96-1.05)	0.96 (0.91-1.01)	0.08
Model 2	1.00	0.99 (0.95-1.04)	0.93 (0.89-0.98)	0.003
Model 3	1.00	0.99 (0.95-1.04)	0.93 (0.89-0.98)	0.003
Model 4	1.00	1.00 (0.95-1.04)	0.92 (0.88-0.96)	<0.001

n = no of cases/participants.
Model 1: crude.
Model 2: adjusted for age and gender.
Model 3 (main analysis): additionally adjusted for education, occupation, smoking, physical activity.
Model 4: additionally adjusted for body mass index.
P for trend was estimated using generalised Poisson regression across tertiles of dietary patterns scores.

Table 5.3 Multivariable RR (95% CI) for relationship between dietary pattern scores and components of the metabolic syndrome in middle-aged and older Chinese adults.

	Non-nut and Non-cruciferous Vegetable Diet				High Protein-High Fat Diet				Omnivorous Diet			
	Tertile 1	Tertile 2	Tertile 3	*P*	Tertile 1	Tertile 2	Tertile 3	*P*	Tertile 1	Tertile 2	Tertile 3	*P*
n	**(6,703)**	**(6,710)**	**(6,708)**	**trend**	**(6,691)**	**(6,711)**	**(6,719)**	**trend**	**(6,737)**	**(6,696)**	**(6,688)**	**trend**
Metabolic syndrome components												
Hyperglycaemia												
Model 1	1.00	1.20 (1.15-1.26)	1.49 (1.43-1.56)	<0.001	1.00	0.92 (0.89-0.96)	0.85 (0.82-0.89)	<0.001	1.00	1.00 (0.95-1.04)	0.96 (0.92-0.99)	0.035
Model 2	1.00	1.18 (1.13-1.24)	1.44 (1.37-1.50)	<0.001	1.00	0.95 (0.91-0.99)	0.89 (0.85-0.83)	<0.001	1.00	1.00 (0.96-1.04)	0.95 (0.91-0.99)	0.025
Model 3	1.00	1.15 (1.09-1.20)	1.37 (1.31-1.43)	<0.001	1.00	0.95 (0.91-0.99)	0.89 (0.85-0.83)	<0.001	1.00	1.00 (0.96-1.05)	0.95 (0.91-0.99)	0.03
Model 4	1.00	1.15 (1.10-1.20)	1.36 (1.30-1.42)	<0.001	1.00	0.94 (0.90-0.98)	0.87 (0.84-0.91)	<0.001	1.00	1.00 (0.97-1.05)	0.95 (0.91-0.99)	0.01
Hypertension												
Model 1	1.00	1.00 (0.97-1.03)	1.04 (1.00-1.06)	0.016	1.00	0.92 (0.94-0.99)	0.93 (0.90-0.95)	<0.001	1.00	1.05 (1.01-1.08)	1.08 (1.06-1.12)	<0.001
Model 2	1.00	0.98 (0.95-1.00)	0.99 (0.96-1.01)	0.33	1.00	0.99 (0.97-1.02)	0.97 (0.94-0.99)	0.03	1.00	1.05 (1.02-1.08)	1.09 (1.06-1.12)	<0.001
Model 3	1.00	0.97 (0.94-1.00)	0.98 (0.95-1.01)	0.15	1.00	0.99 (0.97-1.02)	0.97 (0.95-1.00)	0.07	1.00	1.05 (1.02-1.08)	1.09 (1.06-1.12)	<0.001
Model 4	1.00	0.97 (0.95-1.00)	0.98 (0.95-1.00)	0.10	1.00	0.99 (0.96-1.01)	0.96 (0.93-0.98)	0.002	1.00	1.05 (1.02-1.08)	1.08 (1.05-1.11)	<0.001
Enlarged waist circumference												
Model 1	1.00	0.99 (0.95-1.04)	1.07 (1.02-1.11)	0.005	1.00	0.95 (0.90-0.99)	0.92 (0.88-0.97)	0.001	1.00	0.99 (0.94-1.03)	0.97 (0.93-1.02)	0.20
Model 2	1.00	0.98 (0.32-1.02)	1.04 (1.00-1.09)	0.05	1.00	1.01 (0.97-1.06)	1.05 (1.00-1.09)	0.04	1.00	0.96 (0.92-1.01)	0.92 (0.88-0.96)	<0.001
Model 3	1.00	0.98 (0.94-1.03)	1.07 (1.02-1.11)	0.004	1.00	1.02 (0.98-1.06)	1.06 (1.01-1.10)	0.008	1.00	0.98 (0.94-1.02)	0.94 (0.90-0.99)	0.009
Model 4	1.00	1.00 (0.95-1.04)	1.05 (1.00-1.10)	0.04	1.00	0.97 (0.92-1.00)	0.98 (0.94-1.02)	0.25	1.00	0.98 (0.94-1.02)	0.93 (0.89-0.97)	<0.001
Low HDL-cholesterol												
Model 1	1.00	1.10 (1.03-1.18)	1.32 (1.24-1.41)	<0.001	1.00	0.96 (0.90-1.02)	0.98 (0.92-1.05)	0.60	1.00	1.04 (0.99-1.08)	1.03 (0.99-1.08)	0.17
Model 2	1.00	1.11 (1.04-1.19)	1.35 (1.26-1.44)	<0.001	1.00	0.98 (0.92-1.04)	1.02 (0.95-1.08)	0.63	1.00	1.03 (0.99-1.08)	1.02 (0.98-1.06)	0.37
Model 3	1.00	1.13 (1.05-1.21)	1.38 (1.29-1.47)	<0.001	1.00	0.97 (0.91-1.04)	1.01 (0.94-1.07)	0.83	1.00	1.03 (0.98-1.07)	1.01 (0.97-1.06)	0.56
Model 4	1.00	1.13 (1.06-1.22)	1.37 (1.28-1.47)	<0.001	1.00	0.96 (0.90-1.02)	0.98 (0.91-1.04)	0.46	1.00	1.03 (0.99-1.08)	1.00 (0.96-1.05)	0.84
High triglycerides												
Model 1	1.00	0.94 (0.90-0.98)	0.97 (0.93-1.01)	0.12	1.00	0.99 (0.95-1.03)	1.05 (1.00-1.10)	0.02	1.00	0.88 (0.83-0.94)	0.77 (0.72-0.82)	<0.001
Model 2	1.00	0.94 (0.90-0.98)	0.96 (0.92-1.01)	0.09	1.00	1.00 (0.96-1.04)	1.08 (1.03-1.12)	0.001	1.00	0.87 (0.82-0.92)	0.74 (0.70-0.79)	<0.001
Model 3	1.00	0.94 (0.90-0.98)	0.96 (0.92-1.00)	0.11	1.00	1.00 (0.96-1.04)	1.08 (1.03-1.12)	0.001	1.00	0.85 (0.80-0.91)	0.72 (0.67-0.71)	<0.001
Model 4	1.00	0.94 (0.90-0.98)	0.96 (0.92-1.00)	0.08	1.00	0.99 (0.94-1.03)	1.04 (1.00-1.09)	0.046	1.00	0.86 (0.80-0.91)	0.71 (0.69-0.76)	<0.001

n = no of cases/participants.
Model 1: crude.
Model 2: adjusted for age and gender.
Model 3 (main analysis): additionally adjusted for age, gender, education, occupation, smoking, physical activity.
Model 4: additionally adjusted for body mass index.
P for trend was estimated using generalised Poisson regression across tertiles of dietary patterns scores.

CHAPTER SIX

6.0

EXPLORING THE PATHWAYS AND MECHANISMS MEDIATING THE ASSOCIATION BETWEEN THE HIGH PROTEIN-HIGH FAT DIET AND CARDIOVASCULAR RISK FACTORS USING STRUCTURAL EQUATION MODELLING

6.1 Abstract

Objective: To use the structural equation model to test a hypothesised model simultaneously examining pathways between High Protein-High Fat diet and major CVD risk factors (waist circumference, systolic blood pressure, triglyceride levels, HDL-cholesterol levels, and fasting plasma glucose levels). **Research design and methods:** Cross-sectional analysis of 19,995 participants in the Guangzhou Biobank Cohort Study. Participants' demographic and objectives measures such as waist circumference, systolic blood pressure, and levels of HDL-cholesterol, triglycerides, and fasting plasma glucose, and diet were collected at baseline visit. Diet was assessed using a 256-item SFFQ and the High Protein-High Fat diet was extracted using PCFA. Structural equation modelling was performed to examine the pathways between these factors. **Results:** In the fully adjusted model, the High Protein-High Fat diet was negatively associated with fasting plasma glucose (Standardised β -0.043, 95%CI -0.058 to -0.028), systolic blood pressure (β -0.019, 95%CI -0.032 to -0.006), and positively associated with HDL-cholesterol (β 0.018, 95%CI 0.004-0.031). In contrast, the High Protein-High Fat diet was positively associated with waist circumference (β 0.34, 95%CI 0.20-0.47) and triglyceride levels (β 0.21, 95%CI 0.07-0.35). **Conclusion:** The model showed that High Protein-High Fat diet was inversely associated with blood pressure, glucose, and positively associated with HDL-cholesterol. However, the diet was adversely associated with waist circumference. The long-term impact of the dietary pattern on CVD risk factors remains to be determined.

6.2 Introduction

Hyperglycaemia, hypertension, and dyslipidaemia are key risk factors for atherosclerosis and subsequent CVD, and are closely related to visceral fat [333-335]. A cluster of three or more of the above risk factors is associated with a 2- to 6-fold increased risk of cardiovascular mortality. Targeting CVD risk factors through understanding the underlying factors that influence them is essential for tackling CVD [336]. Lifestyle interventions, which include dietary modification, can alter the levels of CVD risk factors, and thus reduce the development and progression of CVD. However, there is insufficient information about the pathways and mechanisms mediating the association between diet and CVD risk factors. Based on previous work in the thesis, the High Protein-High Fat diet was observed to be associated with key CVD risk factors. Therefore, the objective of the work presented in this chapter was to assess the independent relevant pathways leading from the high protein fat diet to a range of CVD risk factors using structural equation modelling.

6.3 The hypothesised structural equation model

The model was developed to achieve the following aims:

- to document the known association between waist circumference, and systolic blood pressure, HDL-cholesterol, triglycerides, and fasting plasma glucose in the population studied.
- to help distinguish which risk factors could be causally associated, and which are non-causally associated with each other.
- to identify the effects of the High Protein-High Fat diet on key CVD risk factors and thus indirectly the underlying mechanisms of these effects.

6.3.1 Graphical model

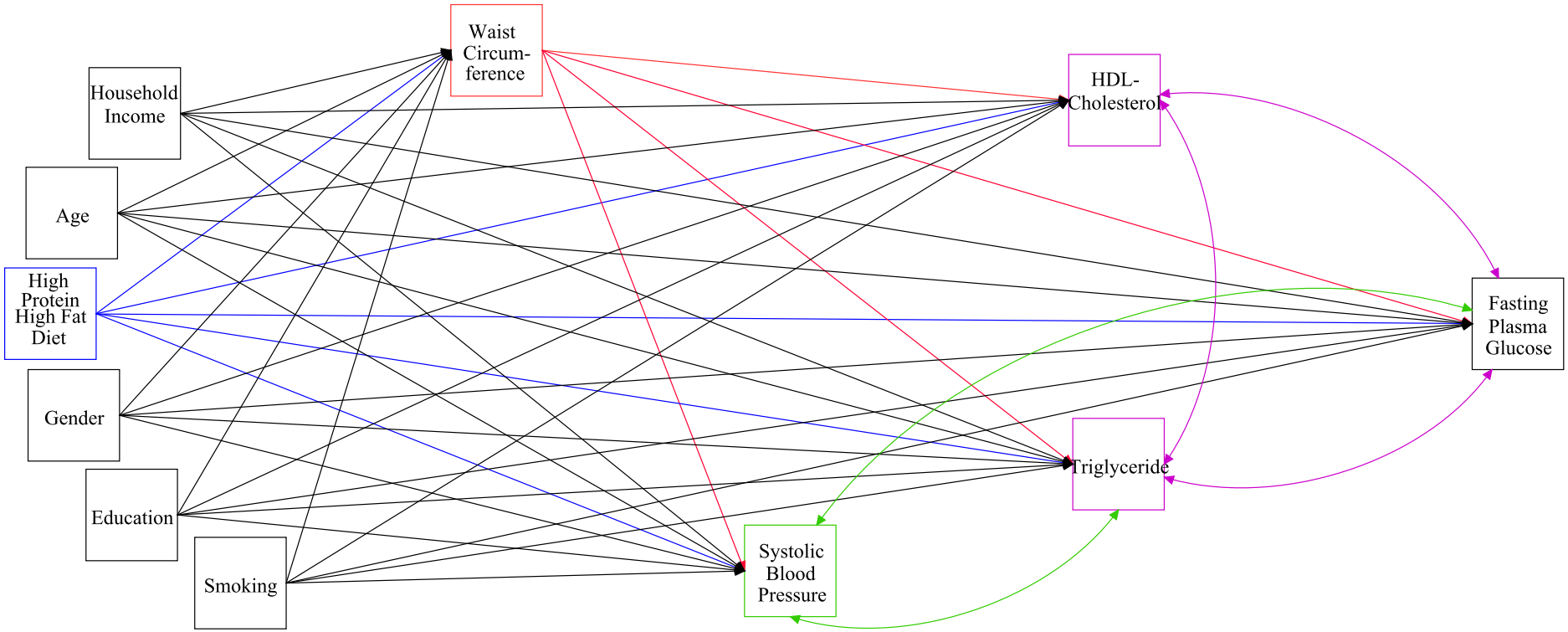
The conceptual structural equation model is illustrated in Figure 6.1. The figure shows that direct paths are specified from High Protein-High Fat diet to waist circumference, systolic blood pressure, HDL-cholesterol, triglycerides, and fasting plasma glucose. Additionally, direct paths are also specified from waist circumference to systolic blood pressure, HDL-cholesterol triglycerides, and fasting plasma glucose. The justification for these relationships is given below.

6.3.2 Associations between the diet and cardiovascular risk factors

Association between the High Protein-High Fat diet and waist circumference was assumed and we justify this assumption based on evidence from multiple clinical trials, which have shown that adherence to diet similar to the High Protein-High Fat can lead to changes in waist circumference [165, 337, 338].

Association between the High Protein-High Fat diet and systolic blood pressure was assumed and the justification for this assumption was that diets similar to the High-Protein-High Fat have a higher protein content, which has been correlated with a lower blood pressure [339, 340]. An RCT highlighted that a great majority of participants with hypertension were able to eliminate or reduce their anti-hypertension medication after following similar diets [340].

Association between the High Protein-High Fat diet and high-density lipoprotein cholesterol was assumed and the justification for this assumption was that several RCTs have shown that diets with a higher proportions of protein and fat increases certain amino acids and medium chain fatty acids. These nutrients have been shown to



Straight arrows represent direct paths/direct effects. **Double headed curved arrows** represent correlations. **Model adjusted for** age, gender, education, household income, and smoking.

Figure 6.1 A hypothesised structural equation model showing pathways leading from High Protein-High Fat diet to a range of cardiovascular risk factors in 19,995 middle-aged and older Chinese adults recruited in the Guangzhou Biobank Cohort Study.

to up-regulate HDL-cholesterol [341, 342].

Association between the High Protein-High Fat diet and triglycerides was specified and this assumption was based on evidence from series of RCTs, which have shown that compared to the conventional low-fat diet, the reduction in triglycerides is greatest with diets that have a high protein and high fat content [165, 339, 343-345].

Association between the High Protein-High Fat diet and fasting plasma glucose was assumed because the high protein and high fat intake was the primary therapy for abnormal glucose homeostasis before medical therapy was available [346]. RCTs performed in participants with abnormal glucose homeostasis have shown that participants who were randomised to similar diets compared to those randomised to control diets (usually low-fat) had significantly lower glucose levels post intervention [172, 344, 347]. An RCT also found that 95% of the participants in the study were able to taper off or discontinue their diabetes medication after increasing protein and fat in the diet [348].

6.3.3 Associations between waist circumference and systolic blood pressure, lipids, and fasting plasma glucose

Association between waist circumference and systolic blood pressure was assumed because several epidemiological studies have shown that obesity precedes high blood pressure and was accountable for over 60% of hypertension incidence [349-352]. Experimental studies conducted in animal models have demonstrated that increased obesity leads to arterial pressure increase [353, 354].

Association between waist circumference and high-density lipoprotein cholesterol was assumed. This assumption is based on ample evidence from epidemiological studies, which have highlighted that enlarged waist circumference results in increased catabolism of HDL-cholesterol particles [63, 94, 355-357].

Association between waist circumference and triglycerides was assumed and specified because epidemiological studies have suggested that enlarged waist circumference is positively associated with high triglyceride levels [132]. An intervention study involving over 3,000 obese participants showed that reduction in waist circumference reduced triglycerides levels by 13.2% [358].

Association between waist circumference and fasting plasma glucose was assumed because numerous epidemiological studies have supported this relationship [359-365]. Experimental studies performed in animal models have also shown that obesity leads to increased disturbance in glucose homeostasis [366], and reduction in visceral fat improves glucose homeostasis [367].

6.3.4 Correlations between cardiovascular risk factors

In the hypothesised model, besides specifying the direct paths, we also specified paths for which the direction is unknown in the literature and this amounts to a correlation.

A correlation between systolic blood pressure and triglycerides was assumed because the direction of the path between these two factors is not clarified in the literature. Longitudinal [368] and retrospective [369] studies have observed that a higher systolic blood pressure co-exists with high triglyceride levels. There is no

conclusive evidence that the relationship between these two is causal and temporality is difficult to establish. Isolating the effects of blood pressure and triglyceride levels on each other in observational studies is subject to confounding because a variety of factors alters them both.

A correlation between systolic blood pressure and fasting plasma glucose was assumed because the direction of the path between the two is unknown. Higher systolic blood pressure often co-exists with a higher fasting glucose [370, 371]. This correlation is expected because both risk factors share common etiological and environmental factors. The evidence from observational studies is inconclusive [372, 373] and it is uncertain whether the relationship between two is causal [374]. The evidence of high blood pressure preceding the development of hyperglycaemia is scarce [375]. Few have argued that insulin resistance antecedes the onset of hypertension [375, 376] and biological theories for this has been proposed, but the theories are contradictory and evidence is not compelling [377-380]. A Mendelian randomised study, which uses genetics to make inferences of causality about the impact of an exposure on an outcome in non-experimental studies [381], was performed to answer this. The study used 14 gene variants of fasting glucose and found that a genetically raised fasting glucose allele did not increase blood pressure [382].

A correlation between high-density lipoprotein cholesterol and triglyceride levels was assumed because the literature is yet to clarify the path between them. Higher triglyceride levels are seen to be inversely associated with HDL-cholesterol levels in epidemiological studies [383]. The negative correlation between the two has been

shown to be r = -0.21 to -0.61 [384]. Mechanisms that lower HDL-cholesterol are also involved in the elevation of triglycerides [385]. How triglycerides and HDL-cholesterol interact is complex and we are aware of no studies that have managed to ascertain whether the relationship between the two is causal. Mendelian randomised study are warranted to answer this.

A correlation between high-density lipoprotein cholesterol and fasting plasma glucose was assumed because reduced HDL-cholesterol co-exists with abnormal glucose homeostasis [386]. A 4-week trial involving 13 hyperglycaemic participants found that HDL-cholesterol administrated intravenously modulated glucose uptake in the skeletal muscle via activation of AMPK pathway mechanism [387]. This finding was not supported by a Mendelian randomised study, which was recently conducted to untangle causality [388]. The study used five genes related to HDL-cholesterol and found that a genetically reduced HDL-cholesterol allele was not causally associated with hyperglycaemia. At present, we are aware of no Mendelian randomised study observing that hyperglycaemia reduces HDL-cholesterol.

A correlation between triglycerides and fasting plasma glucose levels was assumed because studies have shown that individuals who have elevated triglyceride levels also have higher fasting glucose levels [389, 390]. A Mendelian randomised study tested 10 gene variants that were related to triglyceride levels in 12,497 normoglycaemic participants and determined whether genetically raised triglycerides levels increased fasting glucose [391]. Genetically raised triglycerides levels were not causally associated with glucose levels. This was later supported by another Mendelian RCT [392].

6.4 Research design and methods

The GBCS described in detail elsewhere [241] (Chapter 2) recruited 20,430 middle-aged and older adults aged 50-93 years between 2003 and 2006 from the GHHARE. Participants were recruited into the study if they were able to give written informed consent, not receiving treatment for life-threatening conditions, and ambulatory. Written informed consent was obtained from the participants before they completed a detailed computer-based questionnaire via face-to-face interviews. The GBCS obtained official ethical approval from the Guangzhou Medical Ethics Committee of the Chinese Medical Association in Guangzhou, China.

6.4.1 Dietary assessment

A previously validated 266-item SFFQ was used to obtain the dietary information of the participants [243]. Information on ten food groups were missing in the dietary data as these were omitted in the collection in different study phases. Therefore, information on 256-items was used. The participants specified in the SFFQ how frequently they consumed foods and beverages over a week. Dietary data was then examined for outliers. Six items with one outlier and one item with two outliers on the frequency of consumption were identified and excluded. The participants reported not eating butter, soft, margarine, margarine, and salad dressing therefore these food items were excluded. Two hundred and fifty two items were combined into 53 food groups [121, 205, 271], which were assessed in frequency per week [192].

6.4.2 Clinical measurements

The participants attended the examination centre after an overnight fast and their anthropometric measures, blood pressure, and blood samples were collected before

the interviews. Participant waist circumference in centimetres was measured at the smallest circumference between rib cage and iliac crest, or alternatively at the navel if not at natural waistline, using a standard tape measure. Blood pressure (systolic and diastolic) was measured in a seated position after 3-minute rest using a digital sphygmomanometer. Three measurements were recorded at 1-minute intervals and the mean value of the last two readings was used. Fasting blood samples were collected for the measurement of total, HDL- and LDL-cholesterol, triglycerides, and fasting plasma glucose levels [241].

6.4.3 Additional measures

Additional information collected during the baseline visit included age, education levels, household income, and smoking.

6.4.4 Statistical analysis

Diet scores for each participant were obtained from PCFA (Chapter 2, pages 82-88) for the High Protein-High Fat diet. A ±0.30 factor loading cut-off point criteria was used to identify food groups contributing to the diet. Varimax rotation was performed on the diet to simply its interpretation and summing up the food item weightings by the factor loadings created a diet score. A structural equation model was used to examine the hypothesised model. Age (years), gender, education (primary or below/secondary/tertiary), household income (<5,000 RMB/5,000 RMB/10,000 RMB/20,000 RMB/30,000 RMB/>50,000 RMB/ Don't know), and smoking (never/ex-smoker/current) were selected a priori from the literature as potential confounders and adjusted for in the model [393]. Physical activity could not be included as a confounder in the study. Inclusion of physical activity in the initial

model led to an ill fitted model and the parameters of the final model could not be identified therefore physical activity was excluded. Maximum likelihood was used for parameter estimation [394, 395]. The model fit was evaluated using the comparative fit index (CFI), Tucker-Lewis Index (TLI), and root mean square error of approximation (RMSEA) statistics [210, 394-396]. In agreement with the criteria of acceptable model fit previously used in epidemiological studies, the minimum cut-off for both CFI and TLI was set at 0.90 [393, 397]. The RMSEA value of <0.6 was also accepted as an acceptable indicator of good model fit [393, 398]. Beta coefficients and 95% CIs were estimated for each path. After estimating the model the non-significant paths, if any, were removed from the model to present a simpler model.

Descriptive statistics and PCFA were performed in STATA (version 13.1, Stata Corp, College Station, Texas). Structural equation model was analysed using Mplus version 7.3 (Muthén & Muthén, Los Angeles, CA, USA).

6.5 Results

Of the 20,430 participants, 435 had missing data on potential confounders; therefore the final analysis was restricted to 19,995 participants with complete data. The baseline characteristics of the 19,995 participants are summarised in Table 6.1.

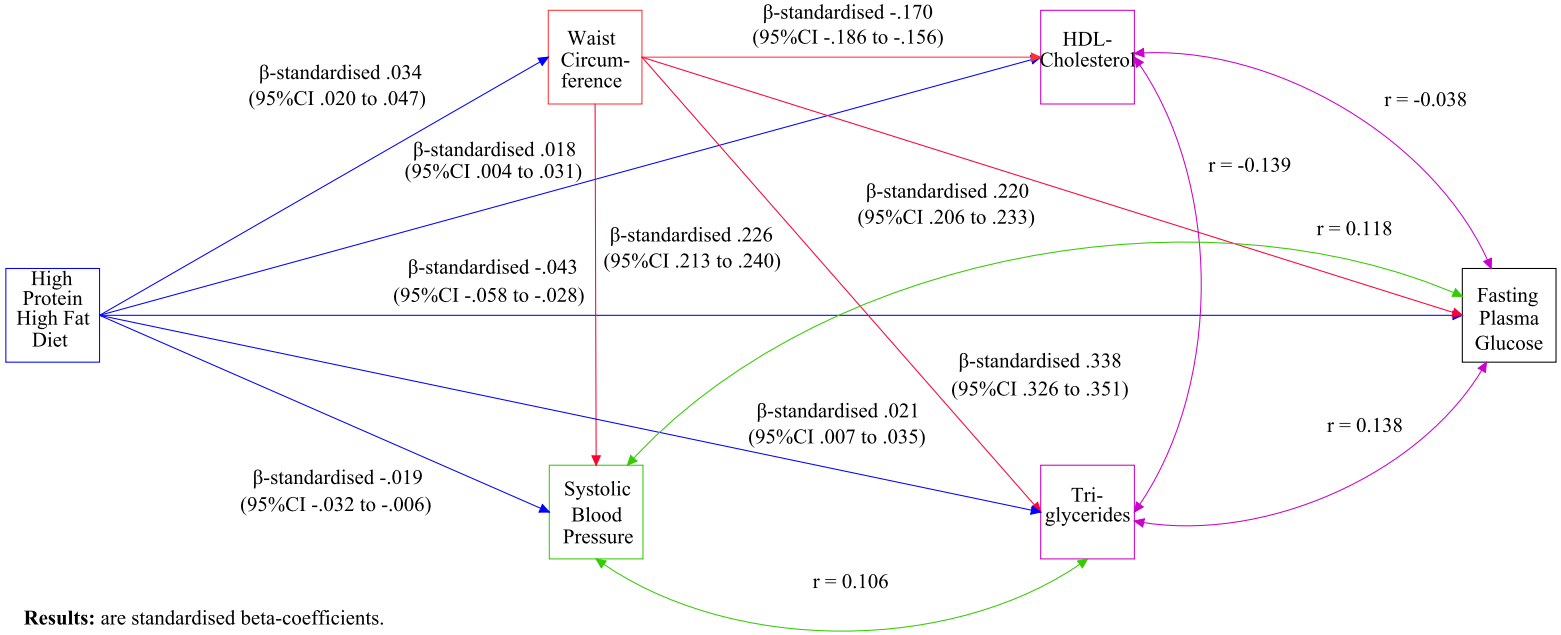
The High Protein-High Fat diet was identified by PCFA and represented frequent intake of seafood, fatty poultry, fatty red meat, high protein-high fat dishes, beans & legumes, offal, beverages, yellow and orange fruit, soups, and dessert.

The model fit estimates showed that the hypothesised structural equation model fitted

the data reasonably. Goodness of fit statistics showed that the CFI was 0.99, the TLI was 0.90, and the RMSEA was 0.04 (90%CI 0.03 to 0.05). These model fit statistics suggested an acceptable model fit.

The High Protein-High Fat diet was positively associated with waist circumference (standardised β .034, 95%CI .020-.047), HDL-cholesterol (β .018, 95%CI .004-.031), and triglyceride levels (β .021, 95%CI .007 to .035) after adjusting for potential confounders (Table 6.3). A significant and inverse association was found for High Protein-High Fat diet on systolic blood pressure (β -.019, 95%CI -.032 to -.006) and fasting plasma glucose levels (β -.043, 95%CI -.058 to -.028). A simplified model is presented in Figure 6.2.

The model results also showed weak correlations between cardiovascular risk factors. Systolic blood pressure was positively correlated with fasting plasma glucose (r = 0.12) and triglyceride levels (r = 0.11). Triglyceride levels were negatively correlated with HDL-cholesterol (r = -0.14) and positively correlated with fasting plasma glucose levels (r = 0.14). HDL-cholesterol was negatively correlated with fasting plasma glucose levels (r = -0.04) (Figure 6.2).



Results: are standardised beta-coefficients.

Straight arrows represent direct paths/direct effects. **Double headed curved arrows** represent correlations. **Model adjusted for** age, gender, education, household income, and smoking.

Figure 6.2 Simplified final structural equation model showing pathways leading from High Protein-High Fat diet to a range of cardiovascular risk factors in 19,995 middle-aged and older Chinese adults in the cross-sectional data of the Guangzhou Biobank Cohort Study.

6.6 Discussion

We developed and tested a hypothesised model incorporating the High Protein-High Fat diet and a range of cardiovascular risk factors using structural equation model. The model statistics showed that the model was a reasonable fit. The CFI, TLI, and RMSEA were within their acceptable values.

6.6.1 The association between waist circumference and systolic blood pressure

Waist circumference was found to have a strong positive association with systolic blood pressure. This corresponds with results of previously epidemiological studies. The ATTICA Study followed-up 3,042 participants for 5 years and found that 1cm increment in waist circumference increased the risk of hypertension by 2% [350]. The study also noted that older participants with enlarged waist circumference had a 2.18-fold higher risk of onset of hypertension compared to participants with normal waist circumference.

There has been considerable research into the plausible mechanisms explaining the relationship between obesity and blood pressure and research focusing on this is still ongoing [132, 399-403]. The renin-angiotensin system (RAS) and the sympathetic nervous system are the two mechanisms that have been well researched [132, 399]. It has been highlighted that angiotensinogen, a peptide hormone and an RAS component is expressed in the adipose tissue and secreted by adipocytes [404]. Angiotensinogen is converted into angiotensin I through the enzyme renin. Thereafter, angiotensin I is metabolised to angiotensin II via angiotensin converting enzyme. Angiotensin II constricts the blood vessels and increases blood pressure after stimulating sympathetic

nerves and releasing norepinephrine [405, 406]. Fatty acids have been shown to stimulate sympathetic nervous system [399, 407]. The stimulation of sympathetic nervous system increases blood pressure through the production of vasoconstriction of the blood vessels via baroreceptors [407]. Another important mechanism that explain the relationship between obesity and high blood pressure is the impact of obesity on the kidneys [408, 409]. The pressure associated with enlarged waist circumference leads to the stimulation of sodium reabsorption. An increase in renal sodium absorption impairs pressure natriuresis resulting in increased blood pressure [408, 409].

6.6.2 The association between waist circumference and high-density lipoprotein cholesterol

We found waist circumference to have a strong negative association with HDL-cholesterol, an observation consistent with previous studies [357, 410]. A 4 week trial intervention conducted in 3,045 participants with enlarged waist circumference and dyslipidaemia used pharmaceutical agent rimonabant to reduce waist circumference [358]. The study found that weight loss led to lower waist circumference and subsequently to 7.2% increase in HDL-cholesterol.

The mechanisms by which obesity reduces HDL-cholesterol are complex and the mediating role of adipose secreted cytokines and inflammatory markers such as Tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1) have been proposed [63, 411]. Firstly, these have been postulated to inhibit apolipoprotein A1 (Apo A1) production, an HDL-cholesterol synthesiser [412]. The independent effects of TNF-α on the reduction of ATP-binding cassette transporter A1 (ABCA1) may also partly explain some of the effects on HDL-cholesterol. ABCA1 has an essential function in

cellular cholesterol efflux, which is involved in HDL-cholesterol formation [413, 414]. Increased TNF-α levels impairs the ABCA1 function and cellular cholesterol efflux to HDL-cholesterol resulting in reduced HDL-cholesterol levels [413]. Secondly, obesity has been suggested to lower HDL-cholesterol through increased cholesteryl ester transferase protein [413, 415, 416]. The mediating role of adiponectin, a protein hormone, which is responsible for fatty acid oxidation is also of importance in the regulation of HDL-cholesterol. Obesity is associated with reduced adiponectin, which has been postulated to synthesise HDL-cholesterol by up-regulating ABCA1 pathway [413].

6.6.3 The association between waist circumference and triglycerides

The results of our model confirmed other observations in the literature that enlarged waist circumference is positively associated with triglycerides [63, 355].

The link between obesity and triglycerides is unclear and not well understood [132]. Despite ample research into the mechanisms, the exploration is still on going [417]. Past research has highlighted that obesity increases free fatty acids from the blood to the liver. Among the underlying mechanisms that explain the relationship between obesity and high triglycerides are the roles of cytokines TNF-α, IL-1, and interleukin-6 (IL-6) [418]. Increased production of these cytokines stimulates hepatic triglycerides synthesis that result in the overproduction of triglycerides and reduction in lipoprotein lipase activity, a regulatory enzyme which aids in the catabolism and clearance of triglycerides [132, 418]. Another contributing factors in the elevation of triglycerides is the reduced adiponectin activity. Adiponectin has also been hypothesised to lower triglycerides by enhancing lipoprotein lipase activity, which is

diminished in the state of hypoadiponectinaemia [418]. An up-to-date metabolic study has further helped in the clarification of the underlying mechanism [417]. The study recruited 28 participants with enlarged waist circumference and used stable isotope tracers to determine the secretion of triglycerides and further determine what triggers triglycerides in obesity. The study found that high triglycerides were caused by dual metabolic defects that included increased secretion and impaired clearance of enriched triglyceride very low-density lipoproteins.

6.6.4 The association between waist circumference and fasting plasma glucose

We detected a strong positive association with waist circumference on fasting plasma glucose. The DESIRE study [360] followed-up 979 disease free participants for 9 years. The study found that per 1 SD increase in waist circumference increased the risk of hyperglycaemia by 52%. An analysis of the Health Professional's Follow-Up Study [365], which involved 22,171 participants found that an increase of 14.6cm or more in waist lead to a 1.7-fold greater risk of incidence hyperglycaemia compared to those with stable waist.

A wealth of research has been conducted into the identification of mechanisms that link obesity to hyperglycaemia. The precise mechanism explaining this relationship was unclear in the past [419-421]. In 2011, an international working group of 32 professionals published a consensus statement and described reduced adiponectin, increased retinol binding protein 4 (RBP4) production, resistin, and TNF-α as the key underlying mechanisms in the pathogenesis of glycaemia [422]. A number of longitudinal studies have demonstrated a correlation between hypoadiponectinaemia and higher incidence of hyperglycaemia [423-425]. Adiponectin has been suggested

to regulate glucose metabolism and maintain glucose levels by increasing fatty acid oxidation and reducing hepatic glucose production [426-428]. RBP4 is a fat-derived adipokine and obesity is associated with higher RBP4 levels, which mediate the relationship between enlarged waist circumference and glucose. The mechanism explaining increased RBP4 in obesity is not clearly understood [429]. A metabolic study conducted in 154 participants found that enlarged waist circumference increased with plasma RBP4 levels [430]. This is due to increased hepatic glucose output because RBP4 up-regulates PEPCK expression, which is an important enzyme in hepatic gluconeogenesis in the liver. Resistin and TNF-α are fairly recent discoveries and a variety of different mechanism have been postulated [418, 420, 421, 431], but the precise putative mechanisms are yet to be disclosed by experimental and physiological studies.

6.6.5 The association between High Protein-High Fat diet and waist circumference

A systematic review of 15 clinical trials lasting 3-12 weeks involving 1,214 participants found the diet to reduce waist circumference by 0.43cm [432]. Our model results showed that the diet was adversely associated with waist circumference.

Usually, in short term RCTs the High Protein-High Fat diet has been shown to increase adiponectin and reduce RBP4 [433-435]. Mechanistically, adiponectin has been shown to stimulates AMPK phosphorylation activity in the liver and skeletal muscles. This process leads to increased fatty acid oxidation [426]. The High Protein-High Fat diet has been shown to lower RBP4 by 20% in a 12 week RCT involving 40 participants with enlarged waist circumference [435]. RBP4 was found to be correlated with carbohydrates but the underlying mechanism is not fully clarified.

Long-term RCTs evaluating the High Protein-High Fat on waist circumference are limited [171]. The drawback of this diet is the ad libitum intake of saturated fat at the expense of carbohydrates [280]. Intake of dietary fat overtime results in overconsumption of energy leading to weight gain and subsequently obesity [331], which may explain an adverse association with waist circumference in this study.

6.6.6 The association between High Protein-High Fat diet and systolic blood pressure

The High Protein-High Fat diet was inversely associated with blood pressure in this study. A systematic review and meta-analysis of 8 trials lasting 12-23 months, which included 753 participants found that High Protein-High Fat diet reduced systolic blood pressure by 5.19 mmHg [171].

The underlying mechanism for this improvement is increased amino acids from a high protein intake [436]. The amino acids in proteins affect blood pressure via different pathways. Beans, legumes, red, and white meats are enriched with amino acids arginine [308], taurine, and cysteine [305-308]. Arginine and cysteine have shown to modulate the renin-angiotensin activity by inhibiting angiotensin-converting enzyme activity, which reduces levels of the vasoconstrictor angiotensin II and lowers blood pressure [306, 308]. The effects of taurine on blood pressure are via the hypothalamus. Taurine has been postulated to reduce vasopressin secretion by inhibiting the sympathetic nervous system activity and subsequently lower blood pressure [308].

The beneficial influence of protein on blood pressure could potentially be offset if the diet is followed for a prolonged period. The relationship between dietary fat and blood

pressure is not well established, and a 12 week RCT conducted in 162 participants showed that saturated fat had no harmful effect on blood pressure [437].

6.6.7 The association between High Protein-High Fat diet and high-density lipoprotein cholesterol

The High Protein-High Fat diet was positively associated with HDL-cholesterol in this study. A systematic review of 19 RCTs lasting 6-24 month involving 1,305 participants found that the High Protein-High Fat diet increased HDL-cholesterol 0.09 mmol/L [279].

The precise mechanism linking the High Protein-High Fat diet to HDL-cholesterol is not well understood, but the diet composition of the High Protein-High Fat diet has been argued to be critical for HDL-cholesterol as such that dietary fats and the amino acid taurine up-regulate HDL-cholesterol [438, 439]. A meta-analysis of 60 RCTs including 1,672 participants concluded that dietary fats increased HDL-cholesterol by 0.010mmol/L when fat intake was increased at expense of carbohydrate [342]. It is hypothesised that this is due to lauric acid, a medium chain fatty acid considered to be a “healthier” saturated fatty acid; the mechanism by which lauric acid elevates HDL is yet to be clarified [342]. In animal model studies, the amino acid taurine has been shown to increase HDL-cholesterol [341].

6.6.8 The association between High Protein-High Fat diet and triglycerides

Our model found the High Protein-High Fat diet to be positively associated with triglycerides. This result was unexpected and because triglycerides have been shown to be reduced on a High Protein-High Fat diet. Our observation is consistent with an

RCT, in which 120 participants were randomised to follow the ad libitum High Protein-High Fat diet, low-fat diet, ad libitum moderate fat diet, and calorie controlled moderate fat diet for 12 months [440]. The High Protein-High Fat diet was found to increase triglycerides by 3.5% and 5.5% at 8 and 12 month intervals. The underlying mechanism explaining the adverse association between the High Protein-High Fat diet and triglycerides has not been adequately researched and is not well understood.

6.6.9 The association between High Protein-High Fat diet and fasting plasma glucose

The High Protein-High Fat diet was found to be inversely associated with fasting plasma glucose in this study. This finding is in agreement with results of a systematic review and meta-analysis of 17 RCTs, which assessed the effects of High Protein-High Fat diet on glycaemia in 1,141 participants [279]. The review found that High Protein-High Fat diet lowered glucose by 0.06 mmol/L.

Multiple mechanisms may explain the inverse relationship. The High Protein-High Fat diet is correlated with reduced carbohydrate intake and reduced insulin demand lowers pancreatic beta-cells overload thus reduces the risk of hyperglycaemia [280]. Additional mechanisms are increased adiponectin and reduced RBP4 levels with carbohydrate restriction [422, 426, 427]. Adiponectin through the stimulation of AMPK phosporylation has been found to result in glucose uptake [426, 441] whereas a reduction in RBP4 has been found to improve insulin signalling [435].

The satiating effects of the diet are also of interest. Protein and fat are both satiety inducing macronutrients but protein is by far the most satiating [442-445]. Increased satiety from increased dietary fats and protein help maintain blood sugar levels.

Furthermore, amino acid leucine also has an effect on glucose metabolism [281, 282, 446]. Leucine has been shown to improve beta-cell by stimulating insulin secretion through ATP and K_{ATP} mechanisms [282].

Just like with the blood pressure and the lipids, the main concern is that prolonged intake of the High Protein-High Fat diet may offset beneficial effects on glucose by exacerbating obesity although in this population that would have only occurred post 1960's when urbanisation set in.

6.6.10 Strengths and limitations

A major strength of this study is that this is the first study to examine pathways between the High Protein-High Fat diet and a range of cardiovascular risk factors using a novel approach like the structural equation model in well-characterised non-Western participants. The large sample size of the study and controlling for key factors such as age, gender, socioeconomic status, and smoking is another major strength of this study. Pre-specifying the model in the initial phase prevented us from modifying it later is also a major strength of the study. For instance, after estimating the hypothesised structural equation model, we performed no post-hoc analyses to try to strengthen our model fit. Post-hoc analyses uses modification indices and suggests improvements by providing information on non-estimated paths and correlations to be included in the model [210, 394]. Although this approach has its advantages such as contributing to theory building, the post-hoc technique within the structural equation model is an exploratory approach that capitalises on chance thus the final results will never be replicated in another sample [394]. This study has limitations that are typical of cross-sectional studies. Cross-sectional studies only offer a snapshot of the

participant's dietary habits therefore unable to verify causal relationships. These relationships also need to be studied longitudinally. Even though we adjusted for key confounders, the potential of residual confounding cannot be overlooked.

There are also limitations associated with the structural equation model approach. In the literature there are differences in opinions on what constitutes the structural equation model. For example, an earlier interpretation of the structural equation model was that it is a confirmatory factor analyses (CFA) followed by pathway analysis [397]. Another group of researchers later suggested that the structural equation model is a hybrid of CFA and pathway analysis [393]. It has also been suggested that CFA and pathway analysis are special forms or techniques of the structural equation model [447, 448]. The reason for this discrepancy is that the structural equation model methodology is still in the developmental phase and new capabilities are continuously being implemented in the structural equation model hence its terminology is also in a state of flux [449, 450]. Another limitation of the structural equation model is that there is no criterion on the number of paths required to estimate the model but it has been highlighted that few paths may lead to an ill fitted model [210, 447]. Another limitation of the structural equation model methodology is the model fit criteria. Although the objective of the model fit is to verify if the estimates of the data matches the estimates produced by the model [451], several model fit indices have been developed in the structural equation model methodology to achieve this. There is considerable disagreement in the literature about what constitutes a good model fit, which model fit indices to report, and the cut-off point of model fit indices to be used. This has intensified the debate on structural equation model fit methodology [210, 452, 453]. Furthermore, there are fundamental

difference between structural equation model and multivariable regression. A main difference is the parameter estimation target. The structural equation model uses a parameter estimator that best accounts for the analyses unlike multivariable regression, which uses ordinary least square to estimate regression coefficients, which may lead to different results [449].

6.6.11 Summary

This study developed a conceptual model to tease out and examine the pathways leading from the High Protein-High Fat diet to waist circumference, HDL-cholesterol, triglycerides, and fasting plasma glucose using structural equation modelling. This study also reviewed the underlying mechanisms of these effects. The High Protein-High Fat diet was found to affect CVD risk factors through multiple pathways, among which, increased adiponectin and reduced RBP4 were a few. The relationship with blood pressure, HDL-cholesterol, and glycaemia was independent of waist circumference. The diet was adversely associated with waist circumference. Since obesity exacerbates blood pressure, lipids, and glucose then its unlikely that the High Protein-High Fat diet would be beneficial overall, at least in long-term.

Table 6.1 Baseline characteristics of 19,995 participants.

Characteristics	Mean (SD)/Median [IQR]/Percentile
Age, years [median (IQR)]	62 [57-67]
Sex (%)	
- Female	71.3
Body Mass Index (kg/m^2)	23.8 (3.3)
Waist Circumference (cm)	79.2 (8.9)
Blood pressure (mmHg)	
- Systolic blood pressure	131.2 (22.1)
- Diastolic blood pressure	73.9 (11.3)
Fasting glucose, mmol/L [median (IQR)]	5.4 [5.0-6.0]
Cholesterol (mmol/L)	
- Total cholesterol	5.9 (1.2)
- High-density lipoprotein	1.7 (0.4)
- Low density lipoprotein	3.2 (0.7)
Triglycerides (mmol/L) [median (IQR)]	1.3 [1.0-1.9]
Education (%)	
- Primary or below	45.4
- Secondary	26.0
- Tertiary	28.6
Occupation (%)	
- Manual	63.9
- Non-manual	29.9
- Other	6.2
Household income (%)	
- <5,000 RMB	1.3
- 5,000 RMB	4.7
- 10,000 RMB	13.3
- 20,000 RMB	19.9
- 30,000 RMB	18.9
- >50,000 RMB	14.3
- Don’t know	27.6
Smokers (%)	
- Never	75.4
- Ex-smoker	13.0
- Current	11.6

Table 6.2 Unstandardised and standardised beta-coefficient (95%CI) of the direct effects of the diet on metabolic risk factors.

Direct effects of High Protein-High Fat Diet						
Paths	Unstandardised	Std. Errors	p value	Standardised	Std. Errors	p value
High Protein-High Fat diet → waist circumference	.300 (.180 to .420)	0.061	<0.001	.034 (.020 to .047)	0.007	<0.001
High Protein-High Fat diet → systolic blood pressure	-.425 (-.716 to -.134)	0.148	0.001	-.019 (-.032 to -.006)	0.007	0.001
High Protein-High Fat diet → HDL-cholesterol	.007 (.002 to .013)	0.003	0.015	.018 (.004 to .031)	0.007	0.015
High Protein-High Fat diet → triglycerides	.011 (.004 to .018)	0.004	0.001	.021 (.007 to .035)	0.007	<0.001
High Protein-High Fat diet → fasting plasma glucose	-.009 (-.013 to -.006)	0.002	<0.001	-.043 (-.058 to -.028)	0.008	<0.001

Adjusted for age, gender, education, household income, and smoking.

Table 6.3 Unstandardised and standardised beta-coefficient (95%CI) of the direct effects of waist circumference on blood pressure, lipids, glucose.

Direct effects of waist circumference						
Paths	Unstandardised	Std. Errors	p value	Standardised	Std. Errors	p value
Waist circumference → systolic blood pressure	.563 (.530 to .597)	0.017	<0.001	.226 (.213 to .240)	0.007	<0.001
Waist circumference → HDL-cholesterol	-.008 (-.008 to -.007)	0.001	<0.001	-.170 (-.185 to -.156)	0.007	<0.001
Waist circumference → triglycerides	.020 (.019 to .021)	0.001	<0.001	.338 (.326 to .351)	0.007	<0.001
Waist circumference → fasting plasma glucose	.005 (.005 to .006)	0.001	<0.001	.220 (.206 to .233)	0.007	<0.001

Adjusted for age, gender, education, household income, and smoking.

CHAPTER SEVEN

7.0

DISCUSSION

7.1 Overview

The majority of dietary pattern studies have been conducted in non-Asian populations. Less is known about the diets of the Chinese and how their diets affect CVD risk factors. There is also limited evidence on which food combinations should be recommended and which are to be avoided for the management of CVD risk in this population. This is where study one (chapter three), study two (chapter four), and study three (chapter five) are relevant.

7.2 Principal findings

This study performed PCFA on the frequency of 252 food items that the participants in the GBCS reported consuming and identified three dietary patterns. These were the Non-nut and Non-cruciferous Vegetable (variety of starchy vegetables), the High Protein-High Fat (variety of protein foods), and the Omnivorous (mixture of nuts, cruciferous vegetables, citrus fruit, and preserved meats) diets.

7.2.1 The relationship between dietary patterns and hyperglycaemia

7.2.1.1 The Non-nut and Non-cruciferous Vegetable diet and hyperglycaemia

Study one found a 37% increased risk of hyperglycaemia with the Non-nut and Non-cruciferous Vegetable diet. The cross-sectional analyses of the Shanghai Men's Health Study (SHMS) [272] and a study conducted in Jiangsu [454] supports our results. The SHMS showed a strong positive association with hyperglycaemia (OR 2.30, 95%CI 2.03-2.57) with an equivalent diet and a 2-fold (95%CI 1.35-3.62) risk was observed in the Jiangsu study with their equivalent diet. A strong dose-response relationship was present in our study, which was in agreement with the SHMS study.

As the diet intake increased so did the risk of hyperglycaemia (OR 1.0, 1.24, 1.59, 2.30). The dose-response was not clear in the Jiangsu study (OR 1.0, 2.10, 1.34, 2.21). None of the studies were able to establish temporality given their cross-sectional study design [455]. Longitudinal studies conducted in different populations confirming these results are lacking and are necessary. We noticed that increased intake of starchy vegetables (potatoes, sweet corn etc.) may be key to increased hyperglycaemia. These food have a high glycaemic load, which has been shown to lead to pancreatic beta-cell dysfunction [278] and experimental studies conducted in animals have demonstrated that a high glycaemic load can contribute to the development of hyperglycaemia [456]. A trial conducted in hyperglycaemic participants showed that lowering dietary glycaemic load reduced glucose levels [457].

7.2.1.2 The High-Protein-High Fat diet and hyperglycaemia

A novel finding of study one was that the High Protein-High Fat diet was found to lower the risk of hyperglycaemia by 11%. This finding is supported by multiple clinical trials. Most trials evaluating the relationship between the high protein high fat type diets and fasting plasma glucose have demonstrated that the diet lowers glucose levels. A systematic review of 7 clinical trials showed that adherence to similar type of diet lowered fasting plasma glucose by 0.12mmol/L, at least in short-term (6-11 months) [279]. An investigation into the mechanisms of the effects revealed that carbohydrate restriction and increase in amino acids were among the plausible explanations. For instance, carbohydrate restriction lowered insulin demand and thereby reduced pancreatic beta-cell overload [280, 348]. The amino acid leucine, found in high protein diets, is among the few amino acids that have been sufficiently

investigated [458, 459], and in several physiological studies was associated with improvements in beta-cell insulin release [281, 282]. Much remains to be learned about the other amino acids and future studies should focus on them.

7.2.1.3 The Omnivorous diet and hyperglycaemia

The Omnivorous dietary pattern was inversely associated with hyperglycaemia. No previous dietary pattern study was available for comparison therefore we looked into the food groups to explain the inverse relationship.

Several clinical trials have reported that nuts lower fasting plasma glucose. A systematic review of 12 trials found 56 grams of nuts per/day to lower glucose levels by 0.15mmol/L [286]. Biologically, the reduction in fasting plasma glucose was suggested to be associated with lower carbohydrate [291], sizeable amino acids, and essential fatty acids [460, 461], which have been shown to be beneficial for glucose homeostasis [292]. The evidence of citrus fruits in relation to hyperglycaemia and fasting plasma glucose is limited and inconsistent across studies. Three longitudinal studies found no association between citrus fruit and hyperglycaemia [123, 287, 462]. One short-term trial (4 weeks) reported reduction in glucose levels in hyperglycaemia participants who were provided citrus fruit supplementation [325]. The study showed glucose levels were reduced by 22.4% in the group receiving 1000mg of citrus fruit extract but more trials are needed to confirm this. A physiological study suggested that flavanones in citrus fruit increase glucose in the liver and muscles by enhancing AMPK activity [325]. For cruciferous vegetables, a 16% reduction in hyperglycaemia was reported in a meta-analysis of 4 longitudinal studies [322], but the results across individual cohorts are inconsistent such that one study reported an inverse association

[123] and others reported no relationship [462-464]. Furthermore, the dose-response relationship is not clear in the studies and temporality is yet to be adequately addressed by the cohorts. Some have hypothesised that sulforaphane, an antioxidant contained in cruciferous vegetable may lower fasting plasma glucose by lowering oxidative stress [288, 465], which downstream beta-cell impairment [289]. Clinical trials of cruciferous vegetables are warranted to show how they affect glucose levels.

7.2.2 The relationship between dietary patterns and hypertension

Very few studies had assessed how whole diets of the Chinese relate to hypertension [199, 200, 300, 466]. Therefore, study two aimed to explore this relationship.

7.2.2.1 The Non-nut and Non-cruciferous Vegetable diet and hypertension

Study two detected no relationship between the Non-nut and Non-cruciferous Vegetable diet and hypertension. The longitudinal analyses of the EPIC-Potsdam [309] and the cross-sectional analyses of a Chinese [300], and a Korean [224] study supported our results. We detected no biological gradient in our study, which also was in agreement with these studies (EPIC-Potsdam 1.0, 0.82, 1.01, 0.94; Jiangsu Study 1.0, 0.92, 0.88, 0.89; Korean Study 1.0, 0.86, 0.96, 0.99). The Chinese and the Korean studies were cross-sectional therefore they were unable to establish temporality. The EPIC-Potsdam study was unable to show temporality due to insufficient study duration. Moreover, the relationship between Non-nut and Non-cruciferous Vegetable type diets and hypertension in the literature is also inconsistent. Beside the aforementioned studies, two other cross-sectional studies conducted in the Chinese reported adverse associations between diet similar to Non-nut and Non-cruciferous Vegetable and hypertension [272, 454]. Epidemiological data is also inconsistent with

the evidence presented by clinical trials. Vegetable diets have been found to lower blood pressure in short-term (4-8 weeks) trials [62, 168]. Epidemiological studies have suggested that a plausible explanation for no relationship between vegetable diet and hypertension could be confounding by cooking methods, but this needs further investigation [124].

7.2.2.2 The High Protein-High Fat diet and hypertension

The High Protein-High Fat diet was associated with a 4% reduced risk of hypertension in our study. Multiple clinical trials support our finding [467]. Trials evaluating the relationship between the high protein high fat type diets and blood pressure showed that reduction in blood pressure with the diet was consistent across studies. High protein and high fat diets also resulted in greater reduction in blood pressure than controlled diets. These observations supported our results. A systematic review evaluated 8 trials and found that the high protein high fat diets significantly reduced systolic (-5.19mmHg) and diastolic blood pressure (-3.53mmHg) [171]. Blood pressure prevention also occurred after high protein high fat diet intervention. The literature suggested that the biological mechanism explaining this relationship was largely attributed to amino acids in dietary proteins. In mechanistic studies, they were found to modulate the renin-angiotensin activity by inhibiting angiotensin-converting enzyme activity, thereby reducing the levels of the vasoconstrictor angiotensin II and lowering blood pressure [306, 308]. These could be the reason for inverse relationship.

7.2.2.3 The Omnivorous diet and hypertension

The Omnivorous diet was associated with 11% increased risk of hypertension. We found that in the Physician's Health Study, a significant negative association (RR 0.82, 95%CI 0.71-0.94) was found for those who consumed nuts ≥7 times/week [468]. A biological-gradient was observed in the study, which demonstrated that as nut intake increased, the risk of hypertension decreased (OR 1.0, 0.97, 0.98, 0.96, 0.82). The authors found that besides reduction in the risk, there were fewer cases of hypertension during the follow-up. Unfortunately, the longitudinal data does not reconcile with the clinical trial data. A systematic review of 61 clinical trials demonstrated that nut consumption was not associated with blood pressure [301]. Blood pressure has usually been a secondary outcome in the trials and no trial has used the more accurate ambulatory blood pressure monitoring as the standard measurements [469]. It has been postulated that nuts may affect blood pressure via multiple pathways, which includes nitric oxide production, reduction in serum levels of the vasoconstrictor thromboxane 2, and modulation of the renin-angiotensin system activity [469]. Regarding citrus fruit intake, to date, only one longitudinal study has reported a relationship with hypertension. The WHS showed a negative association (RR 0.91, 95%CI 0.85-0.98) for ≥4 servings/week [124]. This study also demonstrated a biological gradient showing that as citrus fruit intake increased, the risk of hypertension decreased (RR 1.00, 0.98, 0.96, 0.95, 0.91). This study also met the criterion of temporality. This longitudinal study was supported by a 4-week clinical trial, in which, commercial citrus fruit juice reduced systolic and diastolic blood pressure by 5.9% and 5.1% [302]. There is suggestive evidence that pectin and flavonoids are responsible for this, but this needs to be further explored. Cruciferous vegetables represent another food group, for which, the evidence is scarce. There are

only two longitudinal studies (WHS and the NHS) that have evaluated the relationship with hypertension [124, 470]. The WHS demonstrated that cruciferous vegetables increased the risk of hypertension by 14% (95%CI 1.06-1.23) with ≥4 servings/week [124]. Prospective analyses of the NHS also confirmed that ≥4 servings/week of increased the risk of hypertension by 23% (95%CI 1.04-1.46) in their study [470]. The studies demonstrated that increasing the intake elevated the hypertension risk (WHS 1.0, 1.06, 1.05, 1.09, 1.14; NHS 1.0, 1.02, 1.04, 1.23). Besides, these cohorts were also able to support temporality. The prevailing mechanism responsible for the adverse relationship has not been clarified. Moreover, we are not aware of any trials that have examined the impact of cruciferous vegetables on blood pressure. Preserved meats have also been linked with hypertension in longitudinal studies. A longitudinal study established that ≥5 servings of preserved meats peer week had the potential of increasing the risk of hypertension by 17% (95%CI 1.09-1.26) [303]. A biological-gradient was observed in the study (RR 1.0, 1.14, 1.18, 1.25). The limitation of the literature is that the results of preserved meats and hypertension are inconsistent because the results from prospective studies have varied. A trial reported that lowering preserved meats in context of a diet that provides nuts, fruit, and vegetable lowers blood pressure [62]. An investigation into biological mechanisms showed that the precise underlying mechanisms explaining the adverse association with hypertension is yet to be clarified. Blood pressure raising effect of preserved meats is biologically plausible. A higher sodium content of such meats is a well-substantiated mechanism, by which, preserved meats increase blood pressure [303]. This could possibly explain the adverse relationship observed in our study.

7.2.3 The relationship between dietary pattern and metabolic syndrome

Study three attempted to clarify if the diets were predictors of the metabolic syndrome. Only three studies have examined how dietary patterns of the Chinese relates to the metabolic syndrome [199, 269, 454]. Therefore, it was important to determine if any of the three diets could delay the progression of the metabolic syndrome and CVD.

7.2.3.1 The Non-nut and Non-cruciferous Vegetable diet and metabolic syndrome

The results of study three showed that the Non-nut and Non-cruciferous Vegetable diet was associated with an increased risk of metabolic syndrome by 16%. We also evaluated the association with the individual components and found that diet pattern to adversely affect waist circumference and HDL-cholesterol, but detected no relationship with triglyceride levels. The effects of the diets on hyperglycaemia and hypertension have been discussed in section 7.2.1 and 7.2.2. A study conducted in the Chinese also found that a similar vegetable diet increased the risk of the metabolic syndrome by 54% (95%CI 1.13-2.10) [454]. The same diet was also associated with 31% (95%CI 1.11-1.54) increased risk of enlarged waist circumference [274]. In a study of Koreans, their equivalent vegetable diet lowered HDL-cholesterol by 22% (95%CI 1.01-1.46) [224]. No relationship with triglyceride levels was detected in either study. We detected a dose-response relationship only with the metabolic syndrome and low HDL-cholesterol but not for waist circumference. Others have reported no clear dose-response association with the metabolic syndrome (1.0, 1.43, 1.21, 1.54) [454], low HDL-cholesterol (1.0, 0.97, 0.98, 1.22) [224], but found a clear dose-response relationship with waist circumference (1.0, 1.14, 1.17, 1.31) [274]. The

aforementioned studies were all cross-sectional and therefore were unable to answer whether vegetable diets influenced the risk of the metabolic syndrome, dyslipidaemia, and obesity. The relationship between vegetable diets and the metabolic syndrome is also inconsistent in the literature. Two studies reported an adverse association [454, 471], one study reported no association [224], and one reported an inverse association [472]. Plausible mechanisms, by which, vegetables may impact CVD risk factors was suggested in the literature. We found supporting evidence from few epidemiological studies that a high glycaemic load could potentially be the reason. Glycaemic load has no relationship with blood pressure and triglycerides in clinical trials [315]. The effects on glycaemia are highlighted in section 7.2.1. We also found that high glycaemic load was linked to increased waist circumference [317, 318] and low HDL-cholesterol [319], but the underlying mechanisms is yet to be clarified.

7.2.3.2 The High Protein-High Fat diet and metabolic syndrome

The High Protein-High Fat diet showed no association with the metabolic syndrome but was associated with few of its components. To our knowledge, no longitudinal study has evaluated the relationship between similar diets and the metabolic syndrome and the evidence is mostly available from trials. Beside the improvements in glycaemia (section 7.2.1) and blood pressure (section 7.2.2), the diet, in a systematic review of 17 trials, was efficient in reducing waist circumference (-5.74cm), triglycerides (-0.33mmol/L), and increasing HDL-cholesterol (0.044mmol/L) [171]. Our results were inconsistent with these observations. We detected no relationship with HDL-cholesterol but found an adverse relationship with waist circumference and triglycerides. The magnitude of summary estimates for waist circumference and triglycerides were weak in our study. The reason for this discrepancy needs to be

further studied, but it is plausible that an increase in waist circumference could perhaps be a consequence of high fatty acid intake on this eating pattern, which in turn could be elevating triglycerides and offsetting the benefits on HDL-cholesterol.

7.2.3.3 The Omnivorous diet and metabolic syndrome

The Omnivorous diet was associated with 7% reduced risk of the metabolic syndrome. The direct prospective association between the intake of nuts and the metabolic syndrome is limited to longitudinal analyses of the Atherosclerosis Risk in Communities (ARIC) Study [203], in which, no association between the two was observed. For the individual components, longitudinal data of nuts is restricted to hyperglycaemia (section 7.2.1), and hypertension (7.2.2). Short-term experimental studies have reported no benefits of nut consumption on waist circumference and HDL-cholesterol, but the potential of lowering triglycerides up to 0.06mmol/L has been highlighted [321]. We are aware of no studies that have assessed prospective association between citrus fruit intake and the metabolic syndrome or between cruciferous vegetable intake and the metabolic syndrome. Longitudinal studies of citrus fruit consumption have reported no benefits on glycaemia (section 7.2.1) and there is suggestive evidence of benefits on blood pressure (section 7.2.2) and longitudinal studies assessing the relationship with waist circumference and lipids are lacking. The trial data is limited to few short-term studies (4-8 weeks maximum), in which, citrus fruits and cruciferous vegetables have been provided to participants in supplemental form or as juice. In trials, citrus fruit supplementation reduced obesity and triglycerides, whereas cruciferous vegetable supplementation was found to lower triglycerides. The long-term effects are unknown and the information pertaining to the dose-response association is also lacking. We found multiple plausible mechanisms in

the literature, which included a lower carbohydrate, higher phenolic, and an unsaturated fatty acid content of nuts [292, 327]. Physiological studies showed that isothiocyanates was found in higher quantities in cruciferous vegetables supplementation, which favourably impact lipid metabolism [329]. Flavanones in citrus fruits were found to lower triglycerides, [325], and waist circumference [330]. These could have contributed to lower risk of the metabolic syndrome in our study.

7.2.4 Structural equation model of relationships between diet and cardiovascular risk factors

Study four teased out these individual effects of the High Protein-High Fat diet and assessed the pathways, by which, the dietary pattern was associated with waist circumference, systolic blood pressure, HDL-cholesterol, triglycerides, and fasting plasma glucose. It also assessed the pathways, by which, waist circumference impacted blood pressure, HDL-cholesterol, triglycerides, and glucose. This was done to better understand the putative mechanisms of these effects. The novelty of study four is that it is the first study to explore the complex pathways and mechanisms of the high protein high fat type diet and CVD risk factors in a conceptual framework using the structural equation model.

The structural equation model estimated fourteen relationships based on available theoretical background. This helped ensuring that our hypothesised model had theoretical and statistical validation [210, 394, 447, 449]. Our results agreed with previous epidemiological and physiological reports highlighting that waist circumference was the major determinant and central core in dyslipidemia [63, 357], hypertension [349, 350, 352], and hyperglycemia [359, 360, 362]. Several

biologically plausible explanations for these effects were found. Obesity has been found to reduce adiponectin [422, 426] and increase RBP4 [422, 429], resistin [422], and TNF-α [405], which were among the main central mechanisms responsible for increasing blood pressure, triglyceride levels, fasting plasma glucose, and lowering HDL-cholesterol. Experiments conducted in animal models also support this. Available evidence suggests that the High Protein-High Fat diet affects CVD risk factors through multiple pathways, among which, increased adiponectin and reduced RBP4 are a few [433, 435]. However, the diet was adversely associated with obesity. Since obesity exacerbates blood pressure, and lipid and glucose levels, we determined that it is unlikely that the High Protein-High Fat diet would be beneficial overall, at least in the long-term.

7.2.5 Formulating health messages

Results from our studies show that dietary patterns themselves are very complex. This is reflected by Table 7.1, which gives an overview of the results of the all diets side by side. It shows that the High Protein-High Fat diet may be associated with improvements in glycaemia and blood pressure, but in some ways it may be detrimental for waist circumference and triglyceride levels. The same is for the Omnivorous diet, which may potentially improve glycaemia, triglyceride levels, and waist circumference, but may be harmful for blood pressure. Therefore, formulating health recommendations based on these results is a challenge and it is very challenging to recommend a specific diet for the management and prevention of CVD. There are key limitations to the analyses conducted, which further complicate developing a key health message.

Table 7.1 Overview of results of the relationship between the three dietary patterns and cardiovascular risk factors.

Diet *Risk factor*	**Non-nut & Non-cruciferous Vegetable Diet**	*p* value	**High Protein-High Fat Diet**	*p* value	**Omnivorous Diet**	*p* value	**Structural equation model: High Protein-High Fat Diet**	*p value*
	Increases hyperglycaemia		Reduces hyperglycaemia		Reduces hyperglycaemia		Reduces fasting plasma glucose	
*Hyperglycaemia	1.37 (1.31-1.43)	<0.001	0.89 (0.85-0.93)	<0.001	0.96 (0.91-0.99)	0.01	-0.043 (-0.058 to -0.028)	<0.001
	No relationship with hypertension		Reduces hypertension		Increases hypertension		Reduces blood pressure	
*Hypertension	0.98 (0.94-1.01)	0.21	0.96 (0.93-0.99)	0.04	1.11 (1.07-1.15)	<0.001	-0.019 (-0.032 to -0.006)	<0.001
	Increases risk of low HDL-cholesterol		No relationship with low HDL-cholesterol		No relationship with low HDL-cholesterol		Increases HDL-cholesterol	
*Low HDL-cholesterol	1.38 (1.29-1.47)	<0.001	1.01 (0.94-1.07)	0.83	1.01 (0.97-1.06)	0.56	0.018 (0.004 to 0.031)	0.015
	No relationship with hypertriglyceridaemia		Increases hypertriglyceridaemia		Reduces hypertriglyceridaemia		Increases triglycerides	
*Triglycerides	0.96 (0.92-1.00)	0.08	1.08 (1.03-1.12)	<0.001	0.72 (0.67-0.71)	<0.001	0.021 (0.007 to 0.035)	<0.001
	Increases waist circumference		Increases waist circumference		Lowers waist circumference		Increases waist circumference	
*Enlarged waist circumference	1.07 (1.02-1.11)	0.004	1.06 (1.01-1.10)	0.008	0.94 (0.90-0.99)	0.009	0.034 (0.020 to 0.047)	<0001
	Increased risk of metabolic syndrome		No relationship with metabolic syndrome		Reduced risk of metabolic syndrome			
*Metabolic syndrome	1.16 (1.10-1.21)	<0.001	1.00 (0.96-1.05)	0.79	0.93 (0.89-0.98)	<0.001	-	-

* Adjusted for age, gender, education, occupation, smoking, and physical activity.

7.3 Percentage variance in dietary pattern studies

An overlooked aspect in diet research is the total amount or percentage variance explained by dietary patterns within a dietary dataset. Most studies using the PCFA methodology have briefly described total percent variance explained by each pattern but have not highlighted the relevance of it.

We discovered the three dietary patterns in our study to account for 11.3% of total percentage variance. This number is similar in magnitude to what has been reported by some investigations [473, 474]. However, our figure contrasts with figures reported by the UK [475], Chinese [314], and Australian [205] studies where 28.4%, 37.4%, and 68.3% total percentage variance was detected. At present, there is no gold standard criteria on what the acceptable percentage in dietary pattern analysis is but researchers [121, 267, 476] are acknowledging that percentage variance may not be as prudent as other aspects such as diet interpretability and greater detail in food use for reasons discussed below.

Percentage variance has been argued to be influenced by total numbers of food items used in the PCFA [477]. Each food item used in the PCFA contributes one unit of variance to the total variance in the dietary data [147]. Hu et al. [122] used 40 items in PCFA and retained two patterns. The percentage variance explained by both patterns was 17% altogether. In comparison, Sun et al. [314] used 34 items in PCFA and retained four patterns. The percentage variance for the two first patterns was 27% altogether, which was 10% more than what was detected by Hu et al. [122]. This showed that when fewer food item are used in PCFA, the percentage variance increases. However, comparison of the results published by Yu et al. [136] and Hodge

et al. [205] showed the opposite. Yu et al. [136] used 31 items in PCFA and retained four patterns. They found that the total variance for the four patterns was 50.8% with the first pattern explaining 18% of total variance. Hodge et al. [205] used 121 items in PCFA and also extracted four patterns that explained 68.3% of total variance with the first pattern explaining 27.9%, which is higher than what was detected by Yu et al. [136]. This shows that how percentage variance may behave in relation to the number of food items is difficult to determine.

Some suggest that if dietary patterns fail to explain greater percentage variance then their use in epidemiological research is limited [478]. Others have argued that it is more appropriate to assess the performance of dietary patterns in the same study and make decisions accordingly [473]. This was done by McCann et al. [267]. They generated PCFA patterns by using three methods of classifying food use (168 single items; items categorised into 56 groups; items categorised into 36 groups) to assess how the pattern performed and the influence of percentage variance associated with each classification method. They found that classification method did not affect the numbers nor the character of the patterns. The percentage variance, however, increased from 8% to 13% to 17%. They also noticed that when foods were categorised into fewer food groups then the level of detail in the patterns were reduced. Subsequently, when the team assessed the relationship with chronic diseases they discovered wider 95%CIs that indicated uncertainty of the results. The performance of dietary patterns with a lower percentage variance was stronger compared to the performance of patterns with the higher percent variance.

7.4 Limitations

This thesis has several limitations. The major limitation is the cross-sectional study design limiting inference of causal relationships. Another major limitation is the degree of subjectivity that was involved in dietary pattern analyses as described in Chapter 2. There is no gold standard criterion on food grouping and on the numbers of food groups to be included in dietary pattern analyses using data-driven methods. Epidemiological studies have suggested that food groups should neither be few or too many [477]. A systematic review of dietary patterns showed that most studies used between 15 and 69 food groups [253]. This shows that the number of food groups in our study was within this range.

Another limitation is that there is no a gold standard criterion on the identification of dietary patterns using PCFA. This relates to the eigenvalue cut-point, which identifies the number of dietary patterns to keep and the use of factor loading cut-points that identifies the food groups that are correlated with the dietary patterns. This has been highlighted extensively in Appendix 2. These aspects can make comparisons between the studies very difficult. Furthermore, in dietary pattern analyses, the individual effects of foods are difficult/impossible to separate out [115], which makes it more difficult to pinpoint which food groups in the diets are responsible for the health outcome [106]. Dietary patterns were constructed on the basis of self-reported information. The participants' food intake may have differed from that reported in the SFFQ. Therefore, potential bias due to inaccurate food intake reporting could have occurred.

The SFFQ used in this study could have had an impact on the findings of this study. The SFFQ used in this study is more prone to measurement error than methods such as weighted records and 24-hour recalls. In older populations, non-response to SFFQ questions could have led to underreporting. Misreporting may have affected dietary pattern analysis, especially since underreporting can be more prevalent for some specific food groups. Underreporting could have biased the relative risk towards the null. The SFFQ was not compared to the 24-hour recall in our study group. This is crucial when assessing the diet-disease relationship and results of comparison between the two could have helped with better ranking of the participants. A very important limitation of the study was that dietary patterns were also based on the frequency of intake and not on quantity or portion sizes. It is plausible that the use of reference portions for foods in the SFFQ could have been vague and the participants could have found it difficult in judging their portions size in relation to the reference portion given hence the participants could have skipped portion size questions after fulfilling the frequency of consumption. Longitudinal analyses should estimate the portion sizes, which will enable the study to take into account the confounding effects of energy intake and enable it to also estimate the glycaemic load, protein, and sodium contents of the diets. Caution is warranted when extrapolating the results of our studies to other population groups.

Another potential limitation of this study is that it was unable to use PCFA in conjunction with RRR. As described in chapter 1, RRR analysis is dependent on intermediate variables that are in the causal pathway of a disease and a clinical endpoint. This study had the relevant information on intermediates variables in the

causal pathway of CVD but information clinical endpoint was not available therefore RRR methodology could not be utilised.

7.5 Recommendations for future work

The GBCS is a large-scale study that is following up the participants longitudinally every four years [241]. Following-up the participants longitudinally would subsequently allow us to determine if the diets identified in this thesis have changed overtime or are maintained. Longitudinal analyses will also enable us to assess if the High Protein-High fat diet predicts the risk of enlarged waist circumference like we observed in studies three and four. Ideally, if feasible we also recommend conducting a long-term trial, which would allow us to determine the magnitude of the reduction in CVD risk factors and assess whether the diet pattern of interest offers long-term benefits and if the benefits, if any, can be maintained.

Despite the growing body of literature on dietary patterns, there are only a few studies reporting the relationship between vegetable diets and hyperglycaemia especially in Chinese adults, and all are limited to cross-sectional analyses. We also need longitudinal evidence to show consistency in this population group, which will strengthen our confidence in the results. Specificity is also very difficult to establish in dietary pattern studies, especially for diseases with multifactorial influences. Future studies should explore how to best address this issue.

There are several short-term trials of high protein high fat diets, but the long-term benefits have not been well documented. Studies of how the diet performs in long-

term is warranted and there is no evidence on the safety and efficacy of high protein high fat diets [479], which also needs to be tested by clinical trials.

Glycaemic load is a much-debated topic in nutritional epidemiology but much remains to be learned about how it affects CVD risk factors. It has been shown to adversely influence waist circumference and HDL-cholesterol but the precise underlying mechanism for these effects are yet to be clarified. Physiological and metabolic studies pinpointing these are strongly recommended.

At present, there is insufficient evidence on the effects of citrus fruit and cruciferous vegetables on CVD risk factors. Paucity in the evidence limits the understanding of underlying mechanisms.

Very few studies have associated dietary patterns with different definitions of the metabolic syndrome and studied how the results obtained with one definition differ from another. A study conducted in the Chinese assessed the relationship between the "Vegetable diet" similar to the Non-nut and Non-cruciferous Vegetable diet and metabolic syndrome using the modified ATP III criteria (a definition similar to the Joint Interim Statement) and the IDF criteria [454]. The study found that the Vegetable diet was associated with 54% increased risk of metabolic syndrome using the modified ATP III criteria in the fully adjusted model but the risk of metabolic syndrome was greater (63%) when the study used the IDF criteria. In another study conducted in the Chinese, the relationship between the "animal protein food pattern", which had similarities to the High Protein-High Fat diet and the metabolic syndrome defined by the Join Interim Statement criteria was explored [269]. The study detected

no association an observation consistent with our results. In an updated analyses, the research team further evaluated the relationship between the animal protein pattern and metabolic syndrome using the IDF criteria [480]. The diet was associated with 36% increased risk of metabolic syndrome. These results suggest that the presence of waist circumference in the IDF criteria leads to a stronger estimate for the association between the diets and the metabolic syndrome. These results needs to be assessed and confirmed in our study population. Furthermore, future research is also needed along with an understanding of the direction and magnitude of the effects of Omnivorous diet pattern on metabolic syndrome defined by the IDF criteria. With the Joint Interim Statement criteria, we observed protective effect of the Omnivorous diet on the metabolic syndrome but the association was borderline significant. It is plausible that the relationship between the two may weaken or be attenuated.

7.6 New knowledge generated about diet and cardiovascular risk factors

This thesis aimed to provide an understanding of how the cardiovascular function could be influenced by dietary factors in Chinese, a population where understanding of diet-disease relationship is limited. The novel findings from this work regarding the relationship between diet and cardiovascular risk are:

- It is among the first to support that a High Protein-High Fat diet has the potential to lower major cardiovascular disease risk factors like hyperglycaemia, hypertension, and the metabolic syndrome in the Chinese. Diets similar to High Protein-High Fat diet have usually been inversely associated with a range of cardiovascular disease risk factors in the Caucasians.

- It also demonstrated the complexity of dietary patterns in relation to cardiovascular disease risk factors. Diets identified in this research are presumably palatable and acceptable to follow for individuals in the GBCS. Diets based on certain types of foods influenced biological pathways related to blood pressure, lipid, waist, and glucose homeostasis differently in this group. For instance, certain dietary patterns were found to impair blood pressure and glucose homeostasis pathway whereas other patterns had relatively neutral and/or positive effects. Clinicians may use this knowledge and adjust these dietary patterns accordingly in order to reduce the risk of CVD in this population group.

- It explored and discussed potential up-to-date underlying mechanisms in the causal pathway between dietary patterns and CVD risk factors. It was discovered that dietary patterns influence CVD risk factors through multiple pathways and despite ample research, complex physiological mechanisms are still being elucidated.

- The work further supports that a whole diet based approach in more appropriate in facilitating public health messages in relation to CVD than isolated food items that result in paradoxical dietary choices.

7.7 Final conclusion

This doctoral thesis has made a contribution to the limited body of literature on the dietary patterns of Chinese adults. The thesis has demonstrated three different diets consumed by a sample of middle-aged and older people living in Guangzhou, and has helped enhanced the understanding of how those diets may impact cardiovascular function. The results of this thesis are significantly adding information to existing

evidence and the work has also suggested recommendations where more research is needed. Those recommendations will aid in the interpretations of diet-disease relationships and will lead to an understanding of the underlying mechanisms, which will subsequently improve dietary approaches for prevention, delay, and treatment of CVD.

APPENDICES

Appendix 1. Description of a priori dietary indices and scores developed from 2004 and modified by authors.

Year	Index or Score	Criteria of the original index/score	Developed by	Modified by
1994	Diet Quality Index	8 components	Patterson et al. [481]	Drewnowski et al. [482] Drewnowski et al. [483] Lowik et al. [484] Seymour et al. [485] Dubois et al. [486]
1995	Healthy Eating Index	10 components	Kennedy et al. [487]	McCullough et al [488] McCullough et al. [489] Dubois et al. [486] Kennedy et al. [490] Hann et al. [491] McCullough et al. [492] Weinstein et al. [493] Fung et al. [494]
1995	Mediterranean Diet Score	8 items	Trichopoulou et al. [177]	Osler & Schroll [495] Kouris-Blazos et al. [496] Lasheras et al. [497] Woo et al. [498] Haveman-Nies et al. [499] Bosetti et al. [500] Mantzoros et al. [501] Lagiou et al. [502] Panagiotakos et al. [503]
1996	Diet Quality	8 selected nutrients: (nutrient based diet quality in accordance with 2/3 of 1989 Recommended Dietary Allowance)	Murphy et al. [504]	-

Appendix 1 cont.

Year	Index or Score	Criteria of the original index/score	Developed by	Modified by
1996	Total and specific food group diversity, and diet composition	Via unique foods consumed in past year with variety of 6 food groups	Fernandez et al. [505]	-
1997	Healthy Diet Indicator	9 items	Huijbregts et al. [506, 507]	Huijbregts et al. [508] Dubois et al. [486] Haveman-Nies et al. [499] Knoops et al. [509]
1999	Food Based Quality Index	7 items	Lowik et al. [484]	-
1999	Diet Quality Index Revised	10 items	Haines et al. [510]	Newby et al. [511] Fung et al. [494]
2000	Mediterranean Diet Quality Index	9 items (mixture of nutrients and foods groups)	Gerber et al. [512]	Scali et al. [513]
2000	Recommended Food Score	Sums food items eaten in the past week	Kant et al. [514]	McCullough et al. [492] Mai et al. [515]
2000	Healthy Eating Index from Food Frequency Score	10 items (mixture of nutrients and food groups)	McCullough et al. [488, 489]	-
2000	Diet Quality Index	9 nutrients	Gerber et al. [512]	Seymour et al. [485]
2001/2002	Healthy Food Index	4 items	Osler et al. [516, 517]	-
2002	Mediterranean Diet Index (based on MDS)	10 items	Haveman-Nies et al. [518]	Schroder et al. [519] Fung et al. [494] Pitsavos et al. [520]

Appendix 1 cont.

Year	Index or Score	Criteria of the original index/score	Developed by	Modified by
2002	Alternative Healthy Eating Index	10 items (combination of nutrients and food groups)	McCullough et al. [492]	Fung et al. [494]
2002	Modified Recommended Food Score	Sums healthy food items eaten monthly (juices, poultry and potatoes excluded)	Michels and Wolk [521]	Fung et al. [522]
2002	Diet Quality Score	Focuses on grams of specific foods and energy percentage	Fitzgerald et al. [523]	Toft et al. [524]
2002	Not Recommended Food Score (NRFS)	Sums unhealthy foods eaten monthly (juices, poultry, potatoes excluded and meat; chips; butter; white bread; cheese included)	Michels and Wolk [521]	-
2002	Dietary Guidelines Index	9 items	Harnack et al. [525]	-
2003	Modified Mediterranean Diet Score	9 items + fish added	Trichopoulou et al. [526]	Knoops et al. [527] Trichopoulou et al. [528]
2003	Diet Quality Index International	17 components with emphasis on variation, moderation, and balance	Kim et al. [529]	-
2003	Dietary Approach to Stop Hypertension	3 components	Schulze et al. [309]	Folsom et al. [151] Fung et al. [189] Gunther et al. [530] Harrington et al. [531]

Appendix 1 cont.

Year	Index or Score	Criteria of the original index/score	Developed by	Modified by
2003	Dietary Approach to Stop Hypertension	3 components	Schulze et al. [309]	Levitan et al. [159] Lin et al. [532] Bertoia et al. [533]
2005	Canadian Healthy Eating Index	Focuses on 9 items (foods and variety)	Shatenstein et al. [534]	-
2006	Healthy Food and Nutrient Index	Focuses on 8 items (foods and nutrients)	Bazelmans et al. [535]	-
2006	Mediterranean Adequacy Index	Mediterranean items divided by non-Mediterranean items	Knoops et al. [509]	-
2006	Alternative Mediterranean Diet Score	Mediterranean foods divided into subgroups (potatoes excluded, meat groups modified, alcohol intake assigned)	Fung et al. [522]	-
2006	Low Carbohydrate Diet Score	11 strata of carbohydrate, protein, and fat	Halton et al. [536]	Trichopolou et al. [537] Lagiou et al. [538] Sjogren et al. [539] Nilsson et al. [540]

Appendix 2. Studies post 2004 examining association between a posteriori dietary patterns and cardiovascular risk factors in adults.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2004	Newby et al. [541]	American (n = 459) (longitudinal)	PCA	Eigenvalue >1	6	>0.20	1) Low fat, dairy, fruit	Waist Circumference	beta -1.04 (0.42) cm
							2) Protein and alcohol	Waist Circumference	beta 0.61 (0.40) cm
							3) Sweets	Waist Circumference	beta 0.95 (0.39) cm
							4) Veg fat and veg	Waist Circumference	Not reported
							5) Fatty meats	Waist Circumference	Not reported
							6) Egg, bread, soup	Waist Circumference	Not reported
2004	Villegas et al. [228]	Irish (n =1,018) (cross-sectional)	CA	K-means	3	NA	1) Trad Irish	Insulin Resistance	Reference diet
							2) Prudent	Type 2 Diabetes Mellitus	OR 0.53 (0.33 to 0.85)
							3) Other	Type 2 Diabetes Mellitus	OR 0.49 (0.16 to 1.49)
2004	Fung et al. [137]	American (n = 69,554) (longitudinal)	PCFA	Eigenvalue >1	2	>0.15	1) Prudent	Type 2 Diabetes Mellitus	RR 0.89 (0.78 to 1.02)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Result (fully adjusted)
2004	Fung et al. [137]	American (n = 69,554) (longitudinal)	PCFA	Eigenvalue >1	2	>0.15	2) Western	Type 2 Diabetes Mellitus	RR 1.49 (1.26 to 1.76)
2004	Liese et al. [542]	American (n = 980) (cross-sectional)	CA	K-means	6	NA	1) Fries, whole milk, soft drinks, pastry, sweets	Insulin Sensitivity Fasting Insulin Waist Circumference	*Mean SE* 1·88 (0·10) 12·2 (0·74) 89·5 (0·97)
							2) White bread, tomatoes, cheese, beans, meat, beer	Insulin Sensitivity Fasting Insulin Waist Circumference	1·74 (0·16) 13·4 (1·55) 91·9 (1·62)
							3) Low-frequency eaters	Insulin Sensitivity Fasting Insulin Waist Circumference	1·55 (0·06) 13·2 (0·59) 91·4 (0·73)
							4) Fruit, fruit juice, poultry	Insulin Sensitivity Fasting Insulin Waist Circumference	1·78 (0·07) 13·0 (0·61) 90·5 (0·74)
							5) Wine, mixed drink	Insulin Sensitivity Fasting Insulin Waist Circumference	2·17 (0·24) 10·5 (1·30) 25·9 (1·99)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Result (fully adjusted)
2004	Liese et al. [542]	American (n = 980) (cross-sectional)	CA	K-means	6	NA	6) Dark bread, rice and pasta, veg	Insulin Sensitivity Fasting Insulin Waist Circumference	1·75 (0·35) 9·4 (2·23) 85·1 (3·93)
2005	Montonen et al. [206]	Finnish (n = 4304) (longitudinal)	PCFA	Eigenvalue >2.5	2	>0.20	1) Prudent	Type 2 Diabetes Mellitus	OR 0.72 (0.53 to 0.97)
							2) Conser-vative	Type 2 Diabetes Mellitus	OR 1.49 (1.11 to 2.00)
2005	Schulze et al. [543]	American (n = 89,311) (longitudinal)	RRR	Not reported	1	NA	1) No label	Type 2 Diabetes Mellitus	NHS I RR 2.56 (2.38 to 0.67)
								Type 2 Diabetes Mellitus	NHS II RR 2.93 (2.18 to 3.92)
2005	Heidemann et al. [544]	German (n = 574) (case-control)	RRR	Not reported	1	>0.20	1) No label	Type 2 Diabetes Mellitus	OR 0.27 (0.13 to 0.64)
2006	Mizoue et al. [192]	Japanese (n = 2,106) (cross-sectional)	PCFA	Scree plot	3	>0.15	1) DFSA	Glucose Tolerance Abnormality	OR 0.51 (0.38 to 0.67)
							2) Animal	Glucose Tolerance Abnormality	OR 0.97 (0.74 to 1.27)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Result (fully adjusted)
2006	Mizoue et al. [192]	Japanese (n = 2,106) (cross-sectional)	PCFA	Scree plot	3	>0.15	3) Japanese	Glucose Tolerance Abnormality	OR 1.20 (0.91 to 1.58)
2006	Chen et al. [545]	Bangladeshi (n = 11,116) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.20	1) Balanced	Hypertension	POR 0.79 (0.62 to 0.99)
							2) Animal protein	Hypertension	POR 0.96 (0.56 to 1.23)
							3) Root vegetable	Hypertension	POR 1.13 (0.93 to 1.37)
2007	Hodge et al. [205]	Australian (n = 31,641) (longitudinal)	PCFA	Eigenvalue >2	4	>0.20	1) No label	Type 2 Diabetes Mellitus	OR 1.12 (0.71 to 1.77)
							2) No label	Type 2 Diabetes Mellitus	OR 0.83 (0.56 to 1.23)
							3) No label	Type 2 Diabetes Mellitus	OR 1.65 (1.03 to 2.63)
							4) No label	Type 2 Diabetes Mellitus	OR 1.18 (0.81 to 1.71)
2007	Esmaill-zadeh et al. [222]	Tehrani (n = 486) (cross-sectional)	PCFA	Eigenvalue >1	3	>0.20	1) Healthy	Metabolic Syndrome	OR 0.69 (0.36 to 0.92)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2007	Esmaill-zadeh et al. [222]	Tehrani (n = 486) (cross-sectional)	PCFA	Eigenvalue >1	3	>0.20	1) Healthy	Insulin Resistance	OR 0.55 (0.28 to 0.85)
								Waist Circumference	OR 0.61 (0.46 to 0.83)
								Triglycerol	OR 0.78 (0.60 to 0.91)
								Hypertension	OR 0.50 (0.22 to 0.64)
								Hyperglycaemia	OR 0.83 (0.49 to 0.97)
								Low HDL-Cholesterol	OR 0.82 (0.63 to 0.91)
							2) Western	Metabolic Syndrome	OR 1.60 (1.06 to 1.88)
								Insulin Resistance	OR 1.15 (0.93 to 1.74)
								Waist Circumference	OR 1.34 (1.16 to 1.58)
								Triglycerol	OR 1.83 (1.61 to 1.99)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2007	Esmaill-zadeh et al. [222]	Tehrani (n = 486) (cross-sectional)	PCFA	Eigenvalue >1	3	>0.20	2) Western	Hypertension	OR 2.17 (1.96 to 2.42)
								Hyperglycaemia	OR 1.11 (0.95 to 1.46)
								Low HDL-Cholesterol	OR 1.28 (1.14 to 1.55)
							3) Traditional	Metabolic Syndrome	OR 1.07 (0.86 to 1.22)
								Insulin Resistance	OR 1.04 (0.65 to 1.20)
								Waist Circumference	OR 1.06 (0.90 to 1.19)
								Triglycerol	OR 1.09 (0.98 to 1.25)
								Hypertension	OR 1.03 (0.95 to 1.16)
								Hyperglycaemia	OR 1.19 (1.04 to 1.59)
								Low HDL-Cholesterol	OR 1.08 (0.97 to 1.32)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2007	Panagio-takos et al. [546]	Greek (n = 3,042) (cross-sectional)	PCA	Eigenvalue >1	6	>0.20	1) Fish, veg, legume, cereals...	Metabolic Syndrome	OR 0.87 (0.79 to 0.97)
							2) Potatoes, red or white meats	Metabolic Syndrome	OR 1.13 (1.05 to 1.21)
							3) Bread, pasta	Metabolic Syndrome	OR 0.97 (0.87 to 1.08)
							4) Dairy and eggs	Metabolic Syndrome	OR 1.04 (0.93 to 1.15)
							5) Sweet	Metabolic Syndrome	OR 1.06 (0.96 to 1.18)
							6) Alcohol beverages	Metabolic Syndrome	OR 1.26 (1.21 to 1.33)
2007	Cai et al. [272]	Chinese (n = 61,582) (cross-sectional)	PCFA	Not reported	3	>0.30	1) Vegetable rich	Type 2 Diabetes Mellitus	OR 2.30 (2.07 to 2.56)
								Hypertension	OR 1.33 (1.26 to 1.41)
							2) Fruit rich	Type 2 Diabetes Mellitus	OR 0.39 (0.35 to 0.44)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2007	Cai et al. [272]	Chinese (n = 61,582) (cross-sectional)	PCFA	Not reported	3	>0.30	2) Fruit rich	Hypertension	OR 0.83 (0.78 to 0.88)
							3) Meat	Type 2 Diabetes Mellitus	OR 1.57 (1.40 to 1.76)
								Hypertension	OR 0.70 (0.66 to 0.74)
2007	McNaughton et al. [263]	English (n = 1,265) (cross-sectional)	FA	Not reported	3	>0.25			- Females
							1) Ethnic food & alcohol	Waist	4.83 (4.60 to 5.10)
								Hypertension	5.20 (4.90 to 5.50)
							2) Fruit, veg, dairy	Waist	4.10 (3.60 to 4.50)
								Hypertension	4.10 (3.70 to 4.50)
							3) Meat, potato, sweet	Waist	Not reported
								Hypertension	Not reported
									- Males
							1) Ethnic food & alcohol	HDL-Cholesterol	1.80 (1.40 to 2.20)
							2) Fruit, veg, dairy	Not assessed	-
							3) Meat, potato, sweet	Not assessed	-

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									- Males
2008	Nanri et al. [256]	Japanese (n = 7,910) (cross-sectional)	PCA	Eigenvalue >1	4	>0.15	1) Healthy	Haemoglobin A1C	OR 0.84 (0.59 to 1.20)
							2) High fat	Haemoglobin A1C	OR 0.74 (0.53 to 1.04)
							3) Seafood	Haemoglobin A1C	OR 1.34 (0.95 to 1.89)
							4) Western breakfast	Haemoglobin A1C	OR 0.60 (0.43 to 0.84)
									- Females
							1) Healthy	Haemoglobin A1C	OR 1.38 (1.00 to 1.91)
							2) High fat	Haemoglobin A1C	OR 0.95 (0.70 to 1.30)
							3) Seafood	Haemoglobin A1C	OR 0.86 (0.63 to 1.18)
							4) Western breakfast	Haemoglobin A1C	OR 0.64 (0.46 to 0.90)
2008	Esmaill-zadeh & Azadbakht [547]	Iranian (n = 486) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	1) Healthy	Waist Circumference	OR 0.48 (0.27 to 0.67)
							2) Western	Waist Circumference	OR 5.33 (2.85 to 10.6)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Esmaill-zadeh & Azadbakht [547]	Iranian (n = 486) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	3) Iranian	Waist Circumference	OR 1.61 (0.94 to 2.61)
2008	Esmaill-zadeh & Azadbakht [548]	Iranian (n = 486) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	1) Healthy	Type 2 Diabetes Mellitus	OR 0.29 (0.11 to 1.07)
								Hypertension	OR 0.33 (0.17 to 0.60)
								Dyslipidaemia	OR 0.36 (0.14 to 0.53)
							2) Western	Type 2 Diabetes Mellitus	OR 3.42 (0.88 to 13.3)
								Hypertension	OR 2.61 (1.27 to 5.19)
								Dyslipidaemia	OR 2.59 (1.41 to 4.76)
							3) Iranian	Type 2 Diabetes Mellitus	OR 2.11 (0.66 to 7.12)
								Hypertension	OR 1.35 (0.73 to 2.41)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Esmaill-zadeh & Azadbakht [548]	Iranian (n = 486) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	3) Iranian	Dyslipidaemia	OR 1.73 (1.02 to 2.99)
2008	Nettleton et al. [549]	American (n = 5,011) (longitudinal)	PCA	Not reported	4	>0.30	1) Fats & processed meat	Type 2 Diabetes Mellitus	Not reported
							2) Veg and fish	Type 2 Diabetes Mellitus	Not reported
							3) Beans, tomato, refined grain	Type 2 Diabetes Mellitus	HR 1.28 (0.88 to 1.84)
							4) Whole-grain & fruit	Type 2 Diabetes Mellitus	HR 0.73 (0.52 to 1.04)
2008	Shi et al. [274]	Chinese (n = 2,849) (cross-sectional)	PCFA	Eigenvalue >1	4	>0.20	1) Macho	Not reported	Not reported
							2) Traditional	Nor reported	Not reported
							3) Sweet tooth	Not reported	Not reported
							4) Vegetable rich	Waist Circumference	PR 1.31 (1.11 to 1.54)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									Mean values (male)
2008	Sadakane et al. [264]	Japanese (n = 6,886 for blood pressure & 7,641 for lipids) (cross-sectional)	PCA	Scree plot	3	>0.40	1) Vegetable	Systolic BP	No association
								Diastolic BP	No association
								Pulse Pressure	No association
								Total Cholesterol	No association
								HDL-Cholesterol	No association
								LDL-Cholesterol	No association
							2) Meat	Systolic BP	No association
								Diastolic BP	No association
								Pulse Pressure	No association
								Total Cholesterol	Adverse association
								HDL-Cholesterol	Inverse association
								LDL-Cholesterol	Adverse association
							3) Western	Systolic BP	No association
								Diastolic BP	No association
								Pulse Pressure	No association
								Total Cholesterol	Adverse association
								HDL-Cholesterol	No association
								LDL-Cholesterol	Adverse association
									Mean values (female)
							1) Vegetable	Systolic BP	Inverse association
								Diastolic BP	Inverse association
								Pulse Pressure	Inverse association
								Total Cholesterol	No association
								HDL-Cholesterol	Inverse association
								LDL-Cholesterol	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Sadakane et al. [264]	Japanese (n = 6,886 for blood pressure & 7,641 for lipids) (cross-sectional)	PCA	Scree plot	3	>0.40	2) Meat	Systolic BP	No association
								Diastolic BP	No association
								Pulse Pressure	No association
								Total Cholesterol	Adverse association
								HDL-Cholesterol	Inverse association
								LDL-Cholesterol	Adverse association
							3) Western	Systolic BP	Inverse association
								Diastolic BP	No association
								Pulse Pressure	Inverse association
								Total Cholesterol	Adverse association
								HDL-Cholesterol	Inverse association
								LDL-Cholesterol	Adverse association
2008	Lutsey et al. [203]	American (n = 9,514) (longitudinal)	PCFA	Scree plot & Eigenvalue >2	2	>0.20	1) Western	Metabolic Syndrome	HR 1.18 (1.03 to 1.37)
							2) Prudent	Metabolic Syndrome	HR 1.07 (0.95 to 1.20)
2008	Brunner et al. [229]	English (n = 7,731) (longitudinal)	CA	K-means	4	NA	1) Unhealthy	-	Reference diet
							2) Mediterr-anean-like	Type 2 Diabetes Mellitus	HR 1.04 (0.75 to 1.43)
							3) Healthy	Type 2 Diabetes Mellitus	HR 0.74 (0.58 to 0.94)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Brunner et al. [229]	English (n = 7,731) (longitudinal)	CA	K-means	4	NA	4) Sweet	Type 2 Diabetes Mellitus	HR 1.16 (0.83 to 1.61)
2008	Berg et al. [550]	Swedish (n = 3,452) (cross-sectional)	CA	K-means	5	NA	1) Healthy	-	Age adjusted (male) Reference diet
							2) Sweet	Metabolic Syndrome	OR 2.20 (1.00 to 4.90)
								Waist Circumference	OR 0.60 (0.20 to 1.60)
								High Triglycerides	OR 2.40 (1.30 to 4.50)
								Hypertension	OR 0.80 (0.40 to 1.50)
								Hyperglycaemia	OR 3.00 (1.00 to 9.00)
								Low HDL-Cholesterol	OR 2.60 (1.30 to 5.20)
							3) Coffee	Metabolic Syndrome	OR 1.30 (0.70 to 2.20)
								Waist Circumference	OR 1.30 (0.80 to 2.10)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Berg et al. [550]	Swedish (n = 3,452) (cross-sectional)	CA	K-means	5	NA	3) Coffee	Hypertension	OR 1.02 (0.80 to 1.70)
								Low HDL-Cholesterol	OR 0.80 (0.50 to 1.30)
								Hyperglycaemia	OR 1.00 (0.40 to 2.10)
								High Triglycerides	OR 1.10 (0.80 to 1.70)
							4) Traditional	Metabolic Syndrome	OR 0.90 (0.40 to 1.90)
								Waist Circumference	OR 1.50 (0.90 to 2.70)
								Hypertension	OR 1.00 (0.70 to 1.70)
								Low HDL-Cholesterol	OR 1.00 (0.50 to 1.70)
								Hyperglycaemia	OR 1.20 (0.50 to 3.40)
								High Triglycerides	OR 1.30 (0.80 to 2.20)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Berg et al. [550]	Swedish (n = 3,452) (cross-sectional)	CA	K-means	5	NA	5) Fast energy	Metabolic Syndrome	OR 1.30 (0.80 to 2.20)
								Waist Circumference	OR 2.00 (1.10 to 3.60)
								Low HDL-Cholesterol	OR 0.80 (0.50 to 1.30)
								Hyperglycaemia	OR 1.00 (0.40 to 2.10)
								High Triglycerides	OR 1.10 (0.80 to 1.70)
							1) Healthy	-	Age adjust (female) Reference diet
							2) Sweet	Metabolic Syndrome	OR 1.10 (0.40 to 3.40)
								Waist Circumference	OR 0.70 (0.30 to 1.60)
								Hypertension	OR 1.00 (0.50 to 2.10)
								Low HDL-Cholesterol	OR 1.10 (0.50 to 2.40)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Berg et al. [550]	Swedish (n = 3,452) (cross-sectional)	CA	K-means	5	NA	2) Sweet	Hyperglycaemia	OR 15.1 (2.2 to 103.7)
								High Triglycerides	OR 0.80 (0.50 to 1.30)
							3) Coffee	Metabolic Syndrome	OR 1.40 (0.70 to 2.50)
								Waist Circumference	OR 0.80 (0.60 to 1.00)
								Hypertension	OR 1.10 (0.90 to 1.50)
								Low HDL-Cholesterol	OR 0.60 (0.40 to 0.80)
								Hyperglycaemia	OR 2.40 (0.90 to 9.60)
								High Triglycerides	OR 0.60 (0.40 to 1.00)
							4) Traditional	Metabolic Syndrome	OR 1.40 (0.70 to 2.50)
								Waist Circumference	OR 1.20 (0.80 to 1.90)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	Berg et al. [550]	Swedish (n = 3,452) (cross-sectional)	CA	K-means	5	NA	4) Traditional	Hypertension	OR 1.50 (1.00 to 2.20)
								Low HDL-Cholesterol	OR 1.20 (0.80 to 1.90)
								Hyperglycaemia	OR 2.70 (0.50 to 14.3)
								High Triglycerides	OR 1.30 (0.80 to 2.10)
							5) Fast energy	Metabolic Syndrome	OR 2.50 (1.30 to 4.80)
								Waist Circumference	OR 1.40 (0.90 to 2.40)
								Hypertension	OR 1.90 (1.20 to 3.00)
								Low HDL-Cholesterol	OR 1.30 (0.80 to 2.10)
								Hyperglycaemia	OR 3.10 (0.30 to 31.8)
								High Triglycerides	OR 1.60 (0.90 to 2.90)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2008	McNaughton et al. [551]	English (n = 6,699) (longitudinal)	RRR	Not reported	1	>0.20	1) No label	Type 2 Diabetes Mellitus	RR 1.51 (1.10 to 2.09)
2008	Okubo et al. [552]	Japanese (n = 3,760) (cross-sectional)	PCFA	Eigenvalue >1	4	>0.30	1) Healthy	General Obesity	OR 0.57 (0.37 to 0.87)
							2) Japanese	General Obesity	OR 0.77 (1.17 to 2.67)
							3) Western	General Obesity	OR 1.56 (1.01 to 2.40)
							4) Coffee/ dairy	General Obesity	OR 0.82 (0.54 to 1.23)
2008	Kim et al. [207]	Multi-ethnic (n = 1,257) (cross-sectional)	PCFA	Scree plot & Eigenvalue >3	3	Not identi-fied	1) No label	Type 2 Diabetes Mellitus	OR 0.99 (0.74 to 1.34)
							2) No label	Type 2 Diabetes Mellitus	OR 1.34 (0.93 to 1.83)
							3) No label	Type 2 Diabetes Mellitus	OR 1.09 (0.80 to 1.49)
2009	Qi et al. [231]	American (n = 1,196) (longitudinal)	PCFA	Scree plot & Eigenvalue >1	2	>0.30	1) Prudent	Type 2 Diabetes Mellitus	OR 0.81 (0.59 to 1.13)
							2) Western	Type 2 Diabetes Mellitus	OR 2.06 (1.48 to 2.88)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2009	Kim [553]	Korean (n = 1,869) (cross-sectional)	FA	Scree plot & Eigenvalue >1.6	3	>0.25	1) Traditional	Hypertension	OR 1.03 (0.70 to 1.50)
							2) Western	Hypertension	OR 0.94 (0.66 to 1.34)
							3) Drinker	Hypertension	OR 1.30 (0.88 to 1.91)
2009	Dugee et al. [554]	Mongolian (n = 418) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.25	3	>0.5	1) Transitional	General Obesity	OR 2.47 (1.04 to 5.86)
							2) Traditional	General Obesity	OR 1.12 (0.47 to 2.69)
							3) Healthy	General Obesity	OR 0.49 (0.25 to 0.95)
									- Male
							1) Transitional	Waist Circumference	OR 4.08 (1.11 to 14.97)
							2) Traditional	Waist Circumference	OR 0.33 (0.08 to 1.35)
							3) Healthy	Waist Circumference	OR 0.64 (0.21 to 1.99)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									- Female
2009	Dugee et al. [554]	Mongolian (n = 418) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.25	3	>0.5	1) Transitional	Waist Circumference	OR 1.03 (0.27 to 3.87)
							2) Traditional	Waist Circumference	OR 3.74 (0.92 to 15.20)
							3) Healthy	Waist Circumference	OR 0.47 (0.18 to 1.23)
2009	Deshmukh-Taskar et al. [555]	American (n = 995) (cross-sectional)	PCFA	Scree plot & Eigenvalue >2	2	>0.30	1) Western	Metabolic Syndrome	OR 0.93 (0.80 to 1.07)
							2) Prudent	Metabolic Syndrome	OR 0.93 (0.80 to 1.07)
2009	He et al. [193]	Chinese (n = 20,210) (cross-sectional)	CA based on PCFA	Not reported	4	NA	1) Green water	-	Reference diet
							2) Yellow earth	Glucose Tolerance Abnormality	PR 1.12 (0.93 to 1.15)
							3) New affluence	Glucose Tolerance Abnormality	PR 1.24 (1.04 to 1.49)
							4) Western adopters	Glucose Tolerance Abnormality	PR 0.99 (0.78 to 1.26)
2009	Liese et al. [556]	American (n = 880) (longitudinal)	RRR	Not reported	1	>0.20	1) No label	Type 2 Diabetes Mellitus	OR 4.51 (1.60 to 12.69)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2009	Noel et al. [557]	American (n = 1,167) (cross-sectional)	PCFA	Scree plot & Eigenvalue (cut off not reported)	3	>0.20	1) Meat, processed meat, french fries	Metabolic Syndrome	OR 1.20 (0.76 to 2.00)
							2) Rice, beans, oil	Metabolic Syndrome	OR 1.70 (1.04 to 2.70)
							3) Sweet, sugary beverages, and dairy	Metabolic Syndrome	OR 1.30 (0.83 to 2.10)
2009	DiBello et al. [558]	American (n = 1,508) (cross-sectional)	Partial Least Square	-	2	Not reported	1) Modern	Metabolic Syndrome	- American Samoa PR 1.13 (0.93 to 1.38)
								Waist Circumference	PR 1.02 (0.91 to 1.15)
								Hyperglycaemia	PR 0.99 (0.77 to 1.29)
								Low HDL-Cholesterol	PR 0.98 (0.84 to 1.13)
								High Triglycerides	PR 1.27 (0.88 to 1.84)
								Hypertension	PR 0.89 (0.66 to 1.15)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2009	DiBello et al. [558]	American (n = 1,508) (cross-sectional)	Partial Least Square	-	2	Not reported	2) Neo-Traditional	Metabolic Syndrome	PR 0.89 (0.72 to 1.06)
								Waist Circumference	PR 0.90 (0.80 to 1.02)
								Hyperglycaemia	PR 1.05 (0.79 to 1.39)
								Low HDL-Cholesterol	PR 0.83 (0.70 to 0.98)
								High Triglycerides	PR 0.82 (0.57 to 1.18)
								Hypertension	PR 1.08 (0.81 to 1.44)
									- Samoa
							1) Modern	Metabolic Syndrome	PR 1.21 (0.93 to 1.57)
								Waist Circumference	PR 0.74 (0.54 to 1.01)
								Hyperglycaemia	PR 0.89 (0.77 to 1.02)
								Low HDL-Cholesterol	PR 1.02 (0.80 to 1.29)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2009	DiBello et al. [558]	American (n = 1,508) (cross-sectional)	Partial Least Square	-	2	Not reported	1) Modern	High Triglycerides	PR 1.41 (0.94 to 2.13)
								Hypertension	PR 1.14 (0.80 to 1.63)
							2) Neo-Traditional	Metabolic Syndrome	PR 0.74 (0.54 to 1.01)
								Waist Circumference	PR 0.87 (0.76 to 1.00)
								Hyperglycaemia	PR 0.74 (0.51 to 1.06)
								Low HDL-Cholesterol	PR 0.81 (0.62 to 1.06)
								High Triglycerides	PR 1.13 (0.73 to 1.76)
								Hypertension	PR 0.98 (0.63 to 1.50)
2009	Centritto et al. [238]	Italian (n = 7,646) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	PCFA: 3	>0.15	PCFA Diets 1) Olive oil and vegetables	Systolic BP	*Reported in means* Inverse association
								Diastolic BP	Inverse association
			&					Triglycerides	Inverse association
			RRR	Not reported	RRR: 1	>0.15		Fasting Glucose	Inverse association
								HDL-Cholesterol	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2009	Centritto et al. [238]	Italian (n = 7,646) (cross-sectional)	PCFA & RRR	Scree plot & Eigenvalue >1 Not reported	PCFA: 3 RRR: 1	>0.15 >0.15	PCFA Diets 1) Olive oil and vegetables	LDL-Cholesterol Total Cholesterol	Inverse association Inverse association
							2) Pasta and meat	Systolic BP Diastolic BP Triglycerides Fasting Glucose HDL-Cholesterol LDL-Cholesterol Total Cholesterol	No association No association Adverse association Adverse association Adverse association Adverse association Adverse association
							3) Eggs and sweet	Systolic BP Diastolic BP Triglycerides Fasting Glucose HDL-Cholesterol LDL-Cholesterol Total Cholesterol	No association No association Inverse association No association No association No association No association
							RRR Diet - No label	Systolic BP Diastolic BP Triglycerides Fasting Glucose HDL-cholesterol LDL-cholesterol Total Cholesterol	 HR/OR/RR and 95%CI not reported

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2009	Leite et al. [559]	Italian (n =1,052) (cross-sectional)	CA	K-means	5	NA	1) Common	-	Reference diet
							2) Animal product	Metabolic Syndrome	OR 1.40 (0.90 to 2.00)
							3) Starch	Metabolic Syndrome	OR 1.80 (1.00 to 3.04)
							4) Vegetable/ fat	Metabolic Syndrome	OR 0.80 (0.50 to 1.20)
							5) Vitamin/ fibre	Metabolic Syndrome	OR 0.80 (0.50 to 1.30)
2010	Erber et al. [202]	Multi-ethnic (n = 75,512) (longitudinal)	FA	Scree plot & Eigenvalue >1.25	3	>0.60	1) Fat and meat	Type 2 Diabetes Mellitus	HR 1.40 (1.23 to 1.60)
							2) Vegetable	Type 2 Diabetes Mellitus	HR 0.86 (0.77 to 0.95)
							3) Fruit & milk	Type 2 Diabetes Mellitus	HR 0.92 (0.83 to 1.02)
2010	Villegas et al. [273]	Chinese (n = 64,191) (longitudinal)	CA	K-means	3	NA	1) No label	-	Reference diet
							2) No label	Type 2 Diabetes Mellitus	RR 0.78 (0.71 to 0.86)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Villegas et al. [273]	Chinese (n = 64,191) (longitudinal)	CA	K-means	3	NA	3) No label	Type 2 Diabetes Mellitus	RR 1.05 (0.81 to 1.35)
2010	Cunha et al. [560]	Brazilian (n = 1,009) (cross-sectional)	PCFA	Not reported	3	>0.30	1) Mixed	Waist Circumference	*Reported in probability values only*
							2) Western	Waist Circumference	
							3) Traditional	Waist Circumference	
2010	Sherafat-Kazemzade et al. [561]	Iranian (n = 141) (longitudinal)	RRR	Not reported	5	>0.17	1) Traditional	Waist Circumference	*Reported in mean* No association
								General Obesity	Adverse association
							2) Fibre & PUFA	Waist Circumference	No association
								General Obesity	No association
							3) Fibre & dairy	Waist Circumference	No association
								General Obesity	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Sherafat-Kazemzade et al. [561]	Iranian (n = 141) (longitudinal)	RRR	Not reported	5	>0.17	4) Dairy	Waist Circumference	No association
								General Obesity	No association
							5) Egg	Waist Circumference	No association
								General Obesity	Adverse association
2010	Hydrie et al. [562]	Pakistani (n = 871) (cross-sectional)	CA	K-means	5	NA	Diets - not labelled	Metabolic Syndrome	HR/OR/RR & 95% CI not reported
2010	Becquey et al. [563]	African (n = 1,072) (cross-sectional)	PCA	Eigenvalue >2	2	>0.40	1) Snacking	General Obesity	OR 1.04 (0.95 to 1.13)
							2) Modernity	General Obesity	OR 1.19 (1.03 to 1.36)
2010	Hamer et al. [473]	English (n = 2,931) (cross-sectional)	PCFA	Not reported	4	>0.30	1) Fast food	Systolic BP HDL-Cholesterol Total Cholesterol Triglycerides	Not reported Not reported Not reported Not reported
							2) Health aware	Systolic BP HDL-Cholesterol Total Cholesterol	b -1.0 (-3.0 to 0.1) b 0.1 (0.03 to 0.1) b -0.1 (-0.3 to 0.04)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Hamer et al. [473]	English (n = 2,931) (cross-sectional)	PCFA	Not reported	4	>0.30	2) Health aware	Triglycerides	b -0.1 (-0.3 to 0.1)
							3) Traditional	-	Not reported
							4) Sweet	-	Not reported
2010	Denova-Gutierrez et al. [227]	Mexican (n = 5,240) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.30	1) Prudent	Metabolic Syndrome	OR 0.99 (0.85 to 1.17)
								Hyperglycaemia	OR 0.98 (0.80 to 1.20)
								High Triglycerides	OR 0.95 (0.82 to 1.10)
								Low HDL-Cholesterol	OR 0.95 (0.80 to 1.13)
								Waist Circumference	OR 0.90 (0.77 to 1.05)
								Hypertension	OR 0.97 (0.82 to 1.16)
							2) Western	Metabolic Syndrome	OR 1.58 (1.35 to 1.85)
								Hyperglycaemia	OR 1.71 (1.40 to 2.10)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Denova-Gutierrez et al. [227]	Mexican (n = 5,240) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.30	2) Western	High Triglycerides	OR 1.42 (1.22 to 1.65)
								Low HDL-Cholesterol	OR 1.37 (1.16 to 1.63)
								Waist Circumference	OR 1.43 (1.23 to 1.67)
								Hypertension	OR 1.20 (1.01 to 1.41)
							3) High protein/high fat	Metabolic Syndrome	OR 1.18 (1.01 to 1.39)
								Hyperglycaemia	OR 1.17 (0.96 to 1.43)
								High Triglycerides	OR 0.94 (0.81 to 1.09)
								Low HDL-Cholesterol	OR 1.17 (0.99 to 1.39)
								Waist Circumference	OR 1.17 (1.01 to 1.37)
								Hypertension	OR 1.03 (0.87 to 1.22)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Shi et al. [454]	Chinese (n = 2,849) (cross-sectional)	PCFA	Eigenvalue >1	4	>0.20	1) Diet 1, 2, 3	Metabolic Syndrome	Not reported
							4) Vegetable rich	Metabolic Syndrome	OR 1.54 (1.13 to 2.10)
2010	Lee et al. [564]	Chinese (n = 39,252) (cross-sectional)	PCFA	Scree plot Eigenvalue (cut-off not reported)	3	Not reported	1) Vegetable	Hypertension	OR 1.15 (1.07 to 1.24)
							2) Fruit & milk	Hypertension	OR 0.74 (0.68 to 0.80)
							3) Meat	Hypertension	OR 1.28 (1.19 to 1.38)
2010	Amini et al. [204]	Iranian (n = 425) (cross-sectional)	PCA	Eigenvalue >1.5	5	>0.20	1) Western	Metabolic Syndrome	OR 2.32 (1.27 to 4.21)
								Hyperglycaemia	OR 0.81 (0.44 to 1.47)
								High Triglycerides	OR 1.76 (1.01 to 3.07)
								Low HDL-Cholesterol	OR 1.16 (0.67 to 2.00)
								Waist Circumference	OR 1.71 (0.97 to 3.03)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Amini et al. [204]	Iranian (n = 425) (cross-sectional)	PCA	Eigenvalue >1.5	5	>0.20	1) Western	Hypertension	OR 2.62 (1.32 to 5.23)
							2) Prudent	Metabolic Syndrome	OR 0.58 (0.32 to 1.04)
								Hyperglycaemia	OR 0.73 (0.39 to 1.37)
								High Triglycerides	OR 0.78 (0.45 to 1.35)
								Low HDL-Cholesterol	OR 0.55 (0.31 to 0.96)
								Waist Circumference	OR 0.74 (0.42 to 1.32)
								Hypertension	OR 1.29 (0.69 to 2.41)
							3) Chicken & plants	Metabolic Syndrome	OR 1.05 (0.60 to 1.84)
								Hyperglycaemia	OR 0.89 (0.51 to 1.58)
								High Triglycerides	OR 1.65 (0.97 to 2.80)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Amini et al. [204]	Iranian (n = 425) (cross-sectional)	PCA	Eigenvalue >1.5	5	>0.20	3) Chicken & plants	Low HDL-Cholesterol	OR 0.90 (0.53 to 1.52)
								Waist Circumference	OR 1.18 (0.68 to 2.04)
								Hypertension	OR 1.09 (0.59 to 2.00)
							4) Vegetarian	Metabolic Syndrome	OR 1.36 (0.78 to 2.38)
								Hyperglycaemia	OR 0.97 (0.51 to 1.82)
								High Triglycerides	OR 0.72 (0.43 to 1.23)
								Low HDL-Cholesterol	OR 1.19 (0.70 to 2.02)
								Waist Circumference	OR 1.11 (0.64 to 1.91)
								Hypertension	OR 0.97 (0.51 to 1.82)
							5) High-fat dairy	Metabolic Syndrome	OR 1.25 (0.71 to 2.29)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2010	Amini et al. [204]	Iranian (n = 425) (cross-sectional)	PCA	Eigenvalue >1.5	5	>0.20	5) High-fat dairy	Hyperglycaemia	OR 0.78 (0.43 to 1.38)
								High Triglycerides	OR 1.65 (0.97 to 2.81)
								Low HDL-Cholesterol	OR 1.22 (0.72 to 2.07)
								Waist Circumference	OR 0.94 (0.54 to 1.62)
								Hypertension	OR 0.99 (0.52 to 1.89)
2010	Rezazadeh and Rashidkhani [565]	Tehrani (n = 460) (cross-sectional)	PCA	Scree plot & Eigenvalue >1	2	>0.20	1) Healthy	General Obesity	OR 0.38 (0.15 to 0.98)
								Waist Circumference	OR 0.33 (0.16 to 0.71)
							2) Unhealthy	General Obesity	OR 7.33 (2.39 to 22.51)
								Waist Circumference	OR 4.99 (2.08 to 11.94)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									Never-smokers
2011	Odegaard et al. [223]	Chinese (n = 43,176) (longitudinal)	PCA	Scree plot & Eigenvalue (cut-off not reported)	2	>0.20	1) Veg, fruit, soy	Type 2 Diabetes Mellitus	HR 0.77 (0.65 to 0.92)
							2) Dim sum & meat	Type 2 Diabetes Mellitus	HR 1.38 (1.14 to 1.66)
									Ever smokers
							1) Veg, fruit, soy	Type 2 Diabetes Mellitus	HR 1.17 (0.91 to 1.51)
							2) Dim sum & meat	Type 2 Diabetes Mellitus	HR 0.98 (0.72 to 1.35)
2011	Heidemann et al. [566]	German (n = 4,025) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	2	>0.15	1) Processed	Metabolic Syndrome	OR 1.64 (1.10 to 2.43)
								Hyperglycaemia	OR 1.50 (0.85 to 2.67)
								High Triglycerides	OR 1.59 (1.11 to 2.28)
								Low HDL-Cholesterol	OR 0.95 (0.67 to 1.35)
								Waist Circumference	OR 1.88 (1.31 to 2.69)
								Hypertension	OR 1.34 (0.96 to 1.86)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Heidemann et al. [566]	German (n = 4,025) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	2	>0.15	2) Health-conscious	Metabolic Syndrome	OR 0.98 (0.72 to 1.34)
								Hyperglycaemia	OR 0.81 (0.52 to 1.25)
								High Triglycerides	OR 1.05 (0.79 to 1.38)
								Low HDL-Cholesterol	OR 1.01 (0.77 to 1.32)
								Waist Circumference	OR 1.12 (0.85 to 1.48)
								Hypertension	OR 0.70 (0.54 to 0.90)
2011	Cho et al. [224]	Korean (n = 4,984) (cross-sectional)	PCFA	Scree plot & Eigenvalue (cut-off not reported)	3	>0.20	1) Western	Metabolic Syndrome	Age-adjusted OR 0.87 (0.54 to 1.20)
								Waist Circumference	OR 1.07 (0.87 to 1.31)
								Hypertension	OR 0.96 (0.78 to 1.18)
								High Triglycerides	OR 0.84 (0.63 to 1.13)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Cho et al. [224]	Korean (n = 4,984) (cross-sectional)	PCFA	Scree plot & Eigenvalue (cut-off not reported)	3	>0.20	1) Western	Hyperglycaemia	OR 0.77 (0.52 to 1.13)
								Low HDL-Cholesterol	OR 0.74 (0.61 to 0.90)
							2) Healthy	Metabolic Syndrome	OR 0.58 (0.50 to 0.91)
								Hyperglycaemia	OR 0.78 (0.64 to 0.94)
								High Triglycerides	OR 0.75 (0.62 to 0.91)
								Low HDL-Cholesterol	OR 0.70 (0.53 to 0.93)
								Waist Circumference	OR 0.80 (0.57 to 1.13)
								Hypertension	OR 0.85 (0.71 to 1.03)
							3) Traditional	Metabolic Syndrome	OR 1.05 (0.79 to 1.40)
								Waist Circumference	OR 1.01 (0.92 to 1.34)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Cho et al. [224]	Korean (n = 4,984) (cross-sectional)	PCFA	Scree plot & Eigenvalue (cut-off not reported)	3	>0.20	3) Traditional	Hypertension	OR 0.99 (0.83 to 1.20)
								High Triglycerides	OR 1.03 (0.79 to 1.34)
								Hyperglycaemia	OR 0.74 (0.52 to 1.06)
								Low HDL-Cholesterol	OR 1.22 (1.01 to 1.46)
2011	Wang et al. [200]	Chinese (n = 23,671) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	3	>0.30	1) Western	Hypertension	OR 1.04 (0.83 to 1.31)
							2) Northern	Hypertension	OR 1.06 (0.90 to 1.24)
							3) Southern	Hypertension	OR 0.75 (0.60 to 0.92)
2011	Yu et al. [136]	Chinese (n = 1,010) (longitudinal)	PCA	Eigenvalue >1.14	4	>0.10	1) Snack & drink	Type 2 Diabetes Mellitus	OR 0.86 (0.67 to 1.11)
							2) Veg, fruit, and fish	Type 2 Diabetes Mellitus	OR 0.76 (0.58 to 0.99)
							3) Meat & milk	Type 2 Diabetes Mellitus	OR 1.39 (1.04 to 1.88)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Yu et al. [136]	Chinese (n = 1,010) (longitudinal)	PCA	Eigenvalue >1.14	4	>0.10	4) Refined grain	Type 2 Diabetes Mellitus	OR 1.02 (0.80 to 1.29)
									Mean changes
2011	Lim et al. [567]	Korean (n = 680) (cross-sectional)	PCFA	Not identified	4	>0.20	1) Bread and meat	General Obesity	No association
								Waist	No association
								Fasting Glucose	No association
								Triglycerides	No association
								HDL-cholesterol	Inverse association
								Systolic BP	No association
								Diastolic BP	No association
							2) Noodle and seafood	General Obesity	No association
								Waist	No association
								Fasting Glucose	No association
								Triglycerides	No association
								HDL-cholesterol	No association
								Systolic BP	No association
								Diastolic BP	No association
							3) Rice and vegetables	General Obesity	No association
								Waist	No association
								Fasting Glucose	No association
								Triglycerides	No association
								HDL-cholesterol	No association
								Systolic BP	No association
								Diastolic BP	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Lim et al. [567]	Korean (n = 680) (cross-sectional)	PCFA	Not identified	4	>0.20	4) Korean healthy	Waist Fasting Glucose Triglycerides HDL-cholesterol Systolic BP Diastolic BP	No association No association Inverse association No association No association No association
2011	Cho et al. [568]	Korean (n = 1,118) (cross-sectional)	PCA	Scree plot & Eigenvalue >1	3	Not identi-fied	1) Vegetable-seafood	General Obesity	OR 0.79 (0.45 to 1.36)
							2) Meat-fat	General Obesity	OR 2.78 (1.43 to 5.42)
							3) Snack	General Obesity	OR 0.85 (0.49 to 1.50)
2011	Kim et al. [472]	Korean (n = 9,850) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.3	4	Not identi-fied	1) White rice and kimchi	Metabolic Syndrome	OR 0.97 (0.85 to 1.11)
								Waist Circumference	OR 0.96 (0.81 to 1.14)
								Hyperglycaemia	OR 1.01 (0.89 to 1.14)
								High Triglycerides	OR 0.96 (0.85 to 1.08)
								Low HDL-Cholesterol	OR 1.03 (0.92 to 1.15)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Kim et al. [472]	Korean (n = 9,850) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.3	4	Not identi-fied	1) White rice and kimchi	Hypertension	OR 1.04 (0.91 to 1.18)
							2) Meat and alcohol	Metabolic Syndrome	OR 1.04 (0.91 to 1.19)
								Waist Circumference	OR 0.95 (0.80 to 1.12)
								Hyperglycaemia	OR 1.06 (0.94 to 1.19)
								High Triglycerides	OR 1.19 (1.05 to 1.34)
								Low HDL-Cholesterol	OR 0.95 (0.85 to 1.08)
								Hypertension	OR 1.19 (1.05 to 1.35)
							3) High fat, sweet, and coffee	Metabolic Syndrome	OR 1.04 (0.93 to 1.14)
								Waist Circumference	OR 1.10 (0.98 to 1.23)
								Hyperglycaemia	OR 1.06 (0.94 to 1.18)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Kim et al. [472]	Korean (n = 9,850) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.3	4	Not identi-fied	3) High fat, sweet, and coffee	High Triglycerides	OR 0.93 (0.83 to 1.04)
								Low HDL-Cholesterol	OR 1.02 (0.92 to 1.13)
								Hypertension	OR 1.03 (0.91 to 1.16)
							4) Grains, veg, fish	Metabolic Syndrome	OR 0.86 (0.76 to 0.98)
								Waist Circumference	OR 0.94 (0.80 to 1.10)
								Hyperglycaemia	OR 0.96 (0.86 to 1.08)
								High Triglycerides	OR 0.80 (0.72 to 0.90)
								Low HDL-Cholesterol	OR 0.97 (0.87 to 1.08)
								Hypertension	OR 0.99 (0.88 to 1.12)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Naja et al. [569]	Lebanese (n = 2,048) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	4	>0.40	1) Western	General Obesity	beta 0.49 (0.21 to 0.76)
								Waist Circumference	beta 1.08 (0.39 to 1.76)
							2) Traditional Lebanese	General Obesity	beta 0.14 (-0.12 to 0.40)
								Waist Circumference	beta 0.40 (-0.25 to 1.05)
							3) Prudent	General Obesity	beta 0.23 (-0.02 to 0.48)
								Waist Circumference	beta 0.59 (-0.02 to 1.21)
							4) Fish and alcohol	General Obesity	beta 0.24 (-0.02 to 0.50)
								Waist Circumference	beta 0.39 (-0.27 to 1.04)
2011	Marsola et al. [570]	Brazilian (n = 237) (cross-sectional)	PCFA	Not reported	3	>0.40	1) Western	Metabolic Syndrome	OR 1.30 (0.77 to 2.18)
								Waist Circumference	OR 0.88 (0.60 to 1.28)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Marsola et al. [570]	Brazilian (n = 237) (cross-sectional)	PCFA	Not reported	3	>0.40	1) Western	Hyperglycaemia	OR 1.57 (0.87 to 2.86)
								High Triglycerides	OR 1.29 (0.77 to 2.16)
								Low HDL-Cholesterol	OR 0.89 (0.53 to 1.51)
								Hypertension	OR 1.17 (0.77 to 1.79)
								Metabolic Syndrome	OR 0.73 (0.44 to 1.23)
								Waist Circumference	OR 0.91 (0.66 to 1.24)
							2) Traditional	Hyperglycaemia	OR 0.80 (0.45 to 1.44)
								High Triglycerides	OR 1.00 (0.60 to 1.65)
								Low HDL-Cholesterol	OR 0.73 (0.43 to 1.23)
								Hypertension	OR 1.10 (0.80 to 1.50)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Marsola et al. [570]	Brazilian (n = 237) (cross-sectional)	PCFA	Not reported	3	>0.40	3) Healthy	Metabolic Syndrome	OR 0.82 (0.57 to 1.16)
								Waist Circumference	OR 0.61 (0.42 to 0.89)
								Hyperglycaemia	OR 0.72 (0.39 to 1.34)
								High Triglycerides	OR 1.00 (0.67 to 1.51)
								Low HDL-Cholesterol	OR 0.76 (0.48 to 1.21)
								Hypertension	OR 1.02 (0.70 to 1.49)
2011	Li et al. [466]	Chinese (n 26,276) (cross-sectional)	CA based on PCFA	Not reported	3	NA	1) Traditional Southern	Hypertension	OR 3.78 (2.24 to 6.37)
								Hyperglycaemia	OR 2.10 (1.15 to 3.84)
								Dyslipidaemia	OR 1.73 (1.08 to 2.77)
								General Obesity	OR 2.60 (1.66 to 4.08)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Li et al. [466]	Chinese (n 26,276) (cross-sectional)	CA based on PCFA	Not reported	3	NA	2) Traditional Northern	Hypertension	OR 4.31 (2.62 to 7.08)
								Hyperglycaemia	OR 2.76 (1.85 to 4.13)
								Dyslipidaemia	OR 2.27 (1.51 to 3.42)
								General Obesity	OR 2.98 (2.02 to 4.42)
							3) Western	Hypertension	OR 5.98 (3.61 to 9.90)
								Hyperglycaemia	OR 4.21 (2.55 to 6.94)
								Dyslipidaemia	OR 2.84 (1.85 to 4.37)
								General Obesity	OR 3.51 (2.32 to 5.30)
2011	Ganguli et al. [571]	Indian (n = 701) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.30	1) Veg, fruit, pulses	Type 2 Diabetes Mellitus	OR 0.50 (0.26 to 0.95)
								Hypertension	OR 0.82 (0.49 to 1.36)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Ganguli et al. [571]	Indian (n = 701) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.30	1) Veg, fruit, pulses	Dyslipidaemia	OR 0.90 (0.54 to 1.49)
							2) Hydrogen fat, saturated fat, & veg oil	Type 2 Diabetes Mellitus	OR 1.25 (0.65 to 2.41)
								Hypertension	OR 1.07 (0.64 to 1.80)
								Dyslipidaemia	OR 0.65 (0.38 to 1.11)
							3) Red meat, high fat dairy	Type 2 Diabetes Mellitus	OR 1.18 (0.65 to 2.13)
								Hypertension	OR 0.71 (0.43 to 1.17)
								Dyslipidaemia	OR 1.30 (0.79 to 2.14)
2011	Lee et al. [572]	Korean (n = 3,581) (cross-sectional)	PCFA	Eigenvalue >1.25	3	>0.15	1) Animal food	General Obesity	OR 1.59 (1.24 to 2.04)
								Waist Circumference	OR 1.06 (0.78 to 1.42)
								Hypertension	OR 0.69 (0.48 to 1.00)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Lee et al. [572]	Korean (n = 3,581) (cross-sectional)	PCFA	Eigenvalue >1.25	3	>0.15	1) Animal food	High Triglycerides	OR 1.00 (0.76 to 1.31)
								High Cholesterol	OR 1.92 (1.22 to 2.78)
							2) Rice-vegetable	General Obesity	OR 1.06 (0.85 to 1.33)
								Waist Circumference	OR 1.07 (0.81 to 1.40)
								Hypertension	OR 1.47 (1.05 to 2.07)
								High Triglycerides	OR 1.08 (0.84 to 1.37)
								High Cholesterol	OR 0.90 (0.64 to 1.25)
							3) Noodle-bread	General Obesity	OR 1.20 (0.96 to 1.50)
								Waist Circumference	OR 1.38 (1.05 to 1.81)
								Hypertension	OR 0.82 (0.60 to 1.12)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Lee et al. [572]	Korean (n = 3,581) (cross-sectional)	PCFA	Eigenvalue >1.25	3	>0.15	3) Noodle-bread	High Triglycerides	OR 1.48 (1.07 to 2.05)
								High Cholesterol	OR 1.00 (0.76 to 1.31)
2011	Denova-Gutierrez et al. [573]	Mexican (n = 6,070) (cross-sectional)	FA	Scree plot & Eigenvalue >1.5	3	>0.30	1) Prudent	General Obesity	OR 0.93 (0.78 to 1.10)
							2) Western	Waist Circumference	OR 0.91 (0.76 to 1.09)
							3) High animal/ protein fat	General Obesity	OR 1.46 (1.23 to 1.73)
								Waist Circumference	OR 1.64 (1.37 to 1.96)
								General Obesity	OR 1.23 (1.06 to 1.42)
								Waist Circumference	OR 1.35 (1.12 to 1.62)
2011	Oliveira et al. [261]	Portuguese (n = 2,182) (case-control)	CA	Not identified	4	NA	1) Healthy	Systolic BP	- Females
							2) Low fruit/veg	Diastolic BP Fasting Glucose Triglycerides	*Reported in adjusted mean only*

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2011	Oliveira et al. [261]	Portuguese (n = 2,182) (case-control)	CA	Not identified	4	NA	3) Red meat, alcohol		*Reported in adjusted mean only*
							4) Transition to fast food		
							1) Healthy		- Males
							2) Fish		*Reported in adjusted mean only*
							3) Red meat, alcohol	Systolic BP Diastolic BP Fasting Glucose Triglycerides	
							4) Inter-mediate		
2011	Naja et al. [569]	Lebanese (n = 116) (case-control)	PCFA	Scree plot & Eigenvalue >1	4	>0.40	1) Refined grain & dessert	Type 2 Diabetes Mellitus	OR 3.85 (1.31 to 11.23)
							2) Lebanese	Type 2 Diabetes Mellitus	OR 0.46 (0.22 to 0.97)
							3) Fast food	Type 2 Diabetes Mellitus	OR 2.80 (1.41 to 5.59)
							4) Meat/ alcohol	Type 2 Diabetes Mellitus	OR 1.41 (0.83 to 2.46)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Song and Joung [232]	Korean (n = 4,730) (cross-sectional)	CA	K-means	3	NA	1) Traditional	-	Reference diet
							2) Meat and alcohol	Metabolic Syndrome	OR 1.21 (0.92 to 1.58)
								Waist Circumference	OR 1.14 (0.94 to 1.38)
								High Triglycerides	OR 1.21 (1.00 to 1.47)
								Low HDL-Cholesterol	OR 0.77 (0.65 to 0.92)
								Hyperglycaemia	OR 1.33 (0.92 to 1.58)
								Hypertension	OR 1.21 (0.99 to 1.47)
							3) Korean healthy	Metabolic Syndrome	OR 0.92 (0.75 to 1.13)
								Waist Circumference	OR 1.02 (0.88 to 1.18)
								High Triglycerides	OR 1.06 (0.91 to 1.24)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Song and Joung [232]	Korean (n = 4,730) (cross-sectional)	CA	K-means	3	NA	3) Korean healthy	Low HDL-Cholesterol	OR 0.87 (0.76 to 1.00)
								Hyperglycaemia	OR 0.94 (0.81 to 1.11)
								Hypertension	OR 1.02 (0.81 to 1.28)
2012	Duffey et al. [230]	American (n = 4,161) (longitudinal)	CA	K-means	2	NA	1) Prudent	Metabolic Syndrome	HR 0.64 (0.50 to 0.82)
								Hypertension	HR 0.92 (0.72 to 1.19)
								High Triglycerides	HR 0.72 (0.56 to 0.93)
								Low HDL-Cholesterol	HR 0.81 (0.65 to 1.01)
								Hyperglycaemia	HR 0.92 (0.73 to 1.18)
								Waist Circumference	HR 0.78 (0.62 to 0.97)
							2) Western	Metabolic Syndrome	HR 0.85 (0.69 to 1.07)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Duffey et al. [230]	American (n = 4,161) (longitudinal)	CA	K-means	2	NA	2) Western	Hypertension	HR 1.21 (0.97 to 1.53)
								High Triglycerides	HR 0.93 (0.74 to 1.18)
								Low HDL-Cholesterol	HR 0.85 (0.70 to 1.05)
								Hyperglycaemia	HR 0.92 (0.74 to 1.16)
								Waist Circumference	HR 0.85 (0.70 to 1.04)
2012	Kim et al. [574]	Korean (n = 10,089) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.3	4	NA	1) White rice, kimchi	General Obesity	OR 1.19 (1.06 to 1.33)
							2) Meat and alcohol	General Obesity	OR 1.04 (0.94 to 1.16)
							3) High fat, sweet, coffee	General Obesity	OR 1.17 (1.05 to 1.31)
							4) Grains, veg, fish	General Obesity	OR 1.02 (0.91 to 1.13)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									- Male
2012	Song et al. [575]	Korean (n = 9,725) (cross-sectional)	RRR	Not reported	2	>0.20	1) Balanced	Type 2 Diabetes Mellitus	OR 0.55 (0.26 to 1.20)
								High Triglycerides	OR 0.89 (0.68 to 1.17)
								Low HDL-Cholesterol	OR 1.04 (0.83 to 1.31)
							2) Rice oriented	Type 2 Diabetes Mellitus	OR 1.28 (0.65 to 2.52)
								High Triglycerides	OR 1.58 (1.20 to 2.09)
								Low HDL-Cholesterol	OR 1.43 (1.12 to 1.82)
									- Female
							1) Balanced	Type 2 Diabetes Mellitus	OR 1.33 (0.63 to 2.78)
								High Triglycerides	OR 0.91 (0.66 to 1.24)
								Low HDL-Cholesterol	OR 0.99 (0.83 to 1.17)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Song et al. [575]	Korean (n = 9,725) (cross-sectional)	RRR	Not reported	2	>0.20	2) Rice oriented	Type 2 Diabetes Mellitus	OR 0.79 (0.32 to 1.95)
								High Triglycerides	OR 1.10 (0.78 to 1.55)
								Low HDL-Cholesterol	OR 1.29 (1.08 to 1.55)
2012	Olinto et al. [576]	Brazilian (n = 4,202) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	2	>0.30	1) Common Brazilian		- Male
								General Obesity	beta -1.8 (-2.4 to -1.2)
								Waist Circumference	beta -3.8 (-5.4 to -2.2)
								Systolic BP	beta -0.7 (-2.9 to 1.6)
								Diastolic BP	beta -0.7 (-2.5 to 1.10)
								LDL-Cholesterol	beta -3.4 (-8.9 to 2.2)
								HDL-Cholesterol	beta -1.8 (-3.7 to 0.06)
								Total Cholesterol	beta -5.7 (-12.4 to 1.00)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									- Male
2012	Olinto et al. [576]	Brazilian (n = 4,202) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	2	>0.30	1) Common Brazilian	General Obesity	beta -1.8 (-2.4 to -1.2)
								Waist Circumference	beta -3.8 (-5.4 to -2.2)
								Systolic BP	beta -0.7 (-2.9 to 1.6)
								Diastolic BP	beta -0.7 (-2.5 to 1.10)
								LDL-Cholesterol	beta -3.4 (-8.9 to 2.2)
								HDL-Cholesterol	beta -1.8 (-3.7 to 0.06)
								Total Cholesterol	beta -5.7 (-12.4 to 1.00)
							2) Processed	General Obesity	beta 1.00 (0.39 to 1.6)
								Waist Circumference	beta 2.7 (1.2 to 4.2)
								Systolic BP	beta -1.4 (-3.6 to 0.70)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Olinto et al. [576]	Brazilian (n = 4,202) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	2	>0.30	2) Processed	Diastolic BP	beta -0.5 (-2.2 to 1.3)
								LDL-Cholesterol	beta 5.0 (-0.3 to 10.3)
								HDL-Cholesterol	beta 2.6 (0.8 to 4.4)
								Total Cholesterol	beta 10.5 (3.9 to 16.6)
									- Females
							1) Common Brazilian	General Obesity	beta -0.5 (-1.2 to 0.2)
								Waist Circumference	beta -0.1 (-1.8 to 1.6)
								Systolic BP	beta -2.6 (-4.6 to -0.6)
								Diastolic BP	beta -1.9 (-3.6 to -0.2)
								LDL-Cholesterol	beta -7.6 (-13.5 to -1.7)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									- Female
2012	Fonseca et al. [262]	Portuguese (n = 2,167) (cross-sectional)	CA	Not identified	4	NA	1) Healthy	-	Reference diet
							2) Low fruit & veg	Metabolic Syndrome	OR 1.06 (0.59 to 1.91)
								Waist Circumference	OR 1.95 (0.94 to 4.06)
								High Triglycerides	OR 0.82 (0.46 to 1.46)
								Low HDL-Cholesterol	OR 1.47 (0.90 to 2.41)
								Hypertension	OR 1.62 (0.84 to 3.12)
								Hyperglycaemia	OR 0.77 (0.42 to 1.43)
							3) Red meat & alcohol	Metabolic Syndrome	OR 1.19 (0.76 to 1.87)
								Waist Circumference	OR 1.12 (0.64 to 1.96)
								High Triglycerides	OR 0.97 (0.62 to 1.51)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Fonseca et al. [262]	Portuguese (n = 2,167) (cross-sectional)	CA	Not identified	4	NA	3) Red meat & alcohol	Low HDL-Cholesterol	OR 1.13 (0.76 to 1.68)
								Hypertension	OR 0.98 (0.62 to 1.56)
								Hyperglycaemia	OR 1.03 (0.66 to 1.63)
							4) Transition to fast food	Metabolic Syndrome	OR 0.97 (0.65 to 1.44)
								Waist Circumference	OR 1.08 (0.67 to 1.73)
								High Triglycerides	OR 1.00 (0.68 to 1.47)
								Low HDL-Cholesterol	OR 1.30 (0.92 to 1.82)
								Hypertension	OR 0.94 (0.64 to 1.39)
								Hyperglycaemia	OR 0.92 (0.62 to 1.37)
							1) Healthy	-	- Male Reference diet

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Fonseca et al. [262]	Portuguese (n = 2,167) (cross-sectional)	CA	Not identified	4	NA	2) Fish	Metabolic Syndrome	OR 0.84 (0.48 to 1.45)
								Waist Circumference	OR 1.10 (0.46 to 2.65)
								High Triglycerides	OR 1.29 (0.78 to 2.14)
								Low HDL-Cholesterol	OR 0.95 (0.57 to 1.57)
								Hypertension	OR 0.59 (0.32 to 1.08)
								Hyperglycaemia	OR 1.06 (0.64 to 1.75)
							3) Red meat & alcohol	Metabolic Syndrome	OR 0.91 (0.49 to 1.69)
								Waist Circumference	OR 1.51 (0.55 to 4.20)
								High Triglycerides	OR 1.10 (0.63 to 1.94)
								Low HDL-Cholesterol	OR 0.88 (0.49 to 1.56)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Fonseca et al. [262]	Portuguese (n = 2,167) (cross-sectional)	CA	Not identified	4	NA	3) Red meat & alcohol	Hypertension	OR 0.76 (0.39 to 1.46)
								Hyperglycaemia	OR 1.05 (0.60 to 1.85)
							4) Inter-mediate	Metabolic Syndrome	OR 1.52 (0.83 to 2.78)
								Waist Circumference	OR 2.78 (0.96 to 8.01)
								High Triglycerides	OR 1.07 (0.60 to 1.88)
								Low HDL-Cholesterol	OR 1.26 (0.73 to 2.18)
								Hypertension	OR 1.77 (0.88 to 3.59)
								Hyperglycaemia	OR 0.96 (0.54 to 1.71)
2012	Hong et al. [471]	Korean (n = 406) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	4	>0.20	1) Korean traditional	Hyperglycaemia	OR 1.46 (0.79 to 2.70)
								Hypertension	OR 1.17 (0.63 to 2.18)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Hong et al. [471]	Korean (n = 406) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	4	>0.20	1) Korean traditional	Low HDL-Cholesterol	OR 1.75 (0.96 to 3.20)
								High Triglycerides	OR 1.30 (0.72 to 2.37)
								Waist Circumference	OR 0.94 (0.47 to 1.88)
								Metabolic Syndrome	OR 2.03 (1.05 to 3.92)
							2) Alcohol and meat	Hyperglycaemia	OR 0.46 (0.23 to 0.92)
								Hypertension	OR 0.95 (0.47 to 1.90)
								Low HDL-Cholesterol	OR 1.09 (0.56 to 2.09)
								High Triglycerides	OR 1.51 (0.79 to 2.91)
								Waist Circumference	OR 1.13 (0.53 to 2.41)
								Metabolic Syndrome	OR 1.16 (0.58 to 2.34)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Hong et al. [471]	Korean (n = 406) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	4	>0.20	3) Sweet and fast food	Hyperglycaemia	OR 0.70 (0.36 to 1.36)
								Hypertension	OR 0.98 (0.50 to 1.90)
								Low HDL-Cholesterol	OR 0.72 (0.38 to 1.37)
								High Triglycerides	OR 0.57 (0.30 to 1.06)
								Waist Circumference	OR 1.16 (0.55 to 2.44)
								Metabolic Syndrome	OR 0.81 (0.41 to 1.61)
							4) Fruit and dairy	Hyperglycaemia	OR 0.42 (0.20 to 0.84)
								Hypertension	OR 0.72 (0.36 to 1.43)
								Low HDL-Cholesterol	OR 0.97 (0.50 to 1.87)
								High Triglycerides	OR 0.39 (0.20 to 0.76)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Hong et al. [471]	Korean (n = 406) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	4	>0.20	4) Fruit and dairy	Waist Circumference	OR 1.68 (0.78 to 3.59)
								Metabolic Syndrome	OR 0.46 (0.22 to 0.95)
2012	Morimoto et al. [225]	Japanese (n = 5,665) (longitudinal)	PCFA	Scree plot & Eigenvalue >2.5	3	>0.06	1) Healthy	Type 2 Diabetes Mellitus	HR 0.78 (0.61 to 0.95)
							2) No label	Type 2 Diabetes Mellitus	Not reported
							3) No label	Type 2 Diabetes Mellitus	Not reported
2012	Kim et al. [577]	Korean (n = 3,742) (cross-sectional)	PCFA	Eigenvalue >1.25	4	>0.20	1) Animal food	General Obesity	OR 0.98 (0.92 to 1.04)
								Waist Circumference	OR 0.98 (0.02 to 1.05)
							2) Rice-vegetable	General Obesity	OR 1.00 (0.94 to 1.07)
								Waist Circumference	OR 1.07 (1.01 to 1.16)
							3) Bread-dairy	General Obesity	OR 0.98 (0.92 to 1.04)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Kim et al. [577]	Korean (n = 3,742) (cross-sectional)	PCFA	Eigenvalue >1.25	4	>0.20	3) Bread-dairy	General Obesity	OR 0.98 (0.92 to 1.04)
								Waist Circumference	OR 0.88 (0.82 to 0.94)
							4) Noodle	General Obesity	OR 1.02 (0.97 to 1.08)
								Waist Circumference	OR 1.08 (1.02 to 1.15)
2012	Nyholm et al. [578]	Swedish (n = 6,545) (longitudinal)	CA	K-means	4	NA	1) High fat	General Obesity	Not reported
							2) Tea & ice cream	General Obesity	Not reported
							3) Coffee & sandwich	General Obesity	Not reported
							4) Fruit & vegetable	General Obesity	OR 1.30 (0.89 to 1.91)
2012	Fialkowski et al. [579]	Native American (n = 418) (cross-sectional)	RRR	Not reported	3	>0.20	1) Fruit & sweet drink	General Obesity	- Total group Not reported
							2) Veg, fruit, whole-grain	General Obesity	Not reported

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Fialkowski et al. [579]	Native American (n = 418) (cross-sectional)	RRR	Not reported	3	>0.20	3) High fat & sugar	General Obesity	Not reported
									- Plausible group
							1) Vegetarian, grain	General Obesity	Not reported
							2) Healthy	General Obesity	Not reported
							3) Sweet drinks	General Obesity	Not reported
2012	Song et al. [580]	Korean (n = 3,871) (cross-sectional)	PCFA	Scree plot & Eigenvalue (Cut-off not reported)	5	>0.20	1) Diverse	Insulin Resistance	OR 1.09 (0.84 to 1.81)
							2) Western	Insulin Resistance	OR 1.17 (0.89 to 1.55)
							3) Whole-grain, bean	Insulin Resistance	OR 0.80 (0.61 to 1.03)
							4) White rice, kimchi	Insulin Resistance	OR 0.92 (0.71 to 1.18)
							5) Alcohol coffee	Insulin Resistance	OR 1.01 (0.75 to 1.35)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Min et al. [581]	Korean (n = 371) (cross-sectional)	PCFA	Not reported	3	>0.20	1) Rice, kimchi, veg	Hyperglycaemia	OR 0.87 (0.43 to 1.75)
								Hypertension	OR 1.51 (0.85 to 2.69)
								Low HDL-Cholesterol	OR 1.41 (0.71 to 2.77)
								High Triglycerides	OR 1.87 (0.97 to 3.60)
								Waist Circumference	OR 1.22 (0.60 to 2.49)
								Metabolic Syndrome	OR 1.09 (0.40 to 2.98)
							2) Potato, fruits, nuts	Hyperglycaemia	OR 0.51 (0.26 to 1.00)
								Hypertension	OR 0.49 (0.28 to 0.88)
								Low HDL-Cholesterol	OR 0.72 (0.38 to 1.38)
								High Triglycerides	OR 1.39 (0.74 to 2.62)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Min et al. [581]	Korean (n = 371) (cross-sectional)	PCFA	Not reported	3	>0.20	2) Potato, fruits, nuts	Waist Circumference	OR 0.74 (0.37 to 1.52)
								Metabolic Syndrome	OR 0.48 (0.17 to 1.36)
								Hyperglycaemia	OR 0.97 (0.51 to 1.84)
								Hypertension	OR 0.92 (0.52 to 1.61)
								Low HDL-Cholesterol	OR 1.13 (0.58 to 2.24)
								High Triglycerides	OR 2.06 (1.06 to 3.98)
							3) Eggs, breads, processed meat	Waist Circumference	OR 0.72 (0.36 to 1.43)
								Metabolic Syndrome	OR 0.69 (0.26 to 1.79)
2012	Anderson et al. [582]	American (n = 1,751) (cross-sectional)	CA	K-means	6	NA	1) Healthy	Fasting Glucose	*Reported in mean changes only*
							2) Breakfast cereal	Fasting Glucose	

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2012	Anderson et al. [582]	American (n = 1,751) (cross-sectional)	CA	K-means	6	NA	3) Meat and alcohol	Fasting Glucose	*Reported in mean changes only*
							4) Sweets and dessert	Fasting Glucose	
							5) Refined grain	Fasting Glucose	
							6) High fat dairy	Fasting Glucose	
2013	Sahay et al. [583]	Croatian (n = 1,442) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	3	>0.20	1) Meat, alcohol, and fish	Metabolic Syndrome	HR/OR/RR & 95%CI not reported Adverse association
								Hyperglycaemia	Adverse association
								Hypertension	No association
								Low HDL-Cholesterol	No association
								High Triglycerides	No association
								Waist Circumference	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Sahay et al. [583]	Croatian (n = 1,442) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	3	>0.20	2) Sweets, grain, and fat	Metabolic Syndrome	No association
								Hyperglycaemia	No association
								Hypertension	No association
								Low HDL-Cholesterol	No association
								High Triglycerides	No association
								Waist Circumference	No association
							3) Olive oil, veg, and fruit	Metabolic Syndrome	No association
								Hyperglycaemia	No association
								Hypertension	No association
								Low HDL-Cholesterol	No association
								High Triglycerides	No association
								Waist Circumference	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Bauer et al. [584]	Dutch (n = 20,385) (longitudinal)	PCFA	Scree plot & Eigenvalue >1	2	>0.25	1) No label	Type 2 Diabetes Mellitus	HR 1.00 (0.81 to 1.23)
							2) No label	Type 2 Diabetes Mellitus	HR 1.56 (1.20 to 2.02)
2013	Garduno-Diaz and Khokar [585]	South Asian (n = 100) (cross-sectional)	PCA	Eigenvalue >1	3	>0.30	1) Eastern	Hypertension Dyslipidaemia Waist Circumference	HR/OR/RR and 95%CI not reported
							2) Mixed	Hypertension Dyslipidaemia Waist Circumference	HR/OR/RR and 95%CI not reported
							3) Western	Hypertension Dyslipidaemia Waist Circumference	HR/OR/RR and 95%CI not reported
2013	Shin et al. [586]	Korean (n = 11,883) (cross-sectional)	PCFA	Eigenvalue >1.6	3	>0.20	1) Traditional	Hypertension	OR 0.99 (0.86 to 1.14)
							2) Western	Hypertension	OR 1.24 (1.04 to 1.46)
							3) Dairy & carbohydrates	Hypertension	OR 0.65 (0.55 to 0.75)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Eilat-Adar et al. [587]	American (n = 3,172) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	4	>0.30	1) Western 2) Traditional 3) Healthy 4) Unhealthy	Systolic BP HDL-Cholesterol LDL-Cholesterol Triglycerides General Obesity	*Reported in adjusted mean only*
2013	Zuo et al. [588]	Chinese (n = 1070) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.25	4	>0.20	1) Western	Insulin Resistance	OR 1.89 (1.12 to 3.19)
							2) High-wheat	Insulin Resistance	OR 1.48 (0.91 to 2.39)
							3) Traditional	Insulin Resistance	OR 1.05 (0.62 to 1.76)
							4) Hedonic	Insulin Resistance	OR 0.58 (0.34 to 0.99)
2013	Baik et al. [226]	Korean (n = 5,251) (longitudinal)	PCFA	Scree plot & Eigenvalue >2	2	Not reported	1) Healthy	Hyperglycaemia	RR 0.67 (0.45 to 0.99)
								Hypertension	RR 0.82 (0.61 to 1.09)
								Low HDL-Cholesterol	RR 0.73 (0.56 to 0.95)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Baik et al. [226]	Korean (n = 5,251) (longitudinal)	PCFA	Scree plot & Eigenvalue >2	2	Not reported	1) Healthy	High Triglycerides	RR 0.84 (0.63 to 1.12)
								Waist Circumference	RR 0.61 (0.45 to 0.81)
								Metabolic Syndrome	RR 0.76 (0.60 to 0.97)
							2) Unhealthy	Hyperglycaemia	RR 1.06 (0.77 to 1.45)
								Hypertension	RR 1.05 (0.82 to 1.33)
								Low HDL-Cholesterol	RR 1.10 (0.88 to 1.37)
								High Triglycerides	RR 1.08 (0.86 to 1.37)
								Waist Circumference	RR 1.48 (1.16 to 1.90)
								Metabolic Syndrome	RR 1.12 (0.92 to 1.37)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Hsiao et al. [589]	American (n = 449) (cross-sectional)	CA	K-means	3	NA	1) Sweets & dairy	Metabolic Syndrome	OR 1.24 (0.69 to 2.26)
								Type 2 Diabetes Mellitus	OR 0.80 (0.41 to 1.59)
								Hypertension	OR 2.18 (1.11 to 4.30)
							2) Western	Metabolic Syndrome	OR 0.92 (0.46 to 1.85)
								Type 2 Diabetes Mellitus	OR 0.79 (0.35 to 1.80)
								Hypertension	OR 1.95 (0.87 to 4.35)
							3) Health-conscious	-	Reference diet
2013	Nanri et al. [590]	Japanese (n = 89,037) (longitudinal)	PCFA	Scree plot & Eigenvalue (Cut-off not reported)	3	>0.15	1) Prudent	Type 2 Diabetes Mellitus	- Males OR 0.93 (0.74 to 1.16)
							2) Western	Type 2 Diabetes Mellitus	OR 1.15 (0.90 to 1.46)
							3) Traditional	Type 2 Diabetes Mellitus	OR 0.97 (0.74 to 1.27)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									Females
2013	Nanri et al. [590]	Japanese (n = 89,037) (longitudinal)	PCFA	Scree plot & Eigenvalue (Cut-off not reported)	3	>0.15	1) Prudent	Type 2 Diabetes Mellitus	OR 0.90 (0.69 to 1.16)
							2) Western	Type 2 Diabetes Mellitus	OR 0.81 (0.61 to 1.08)
							3) Traditional	Type 2 Diabetes Mellitus	OR 0.87 (0.66 to 1.15)
2013	Sun et al. [314]	Chinese (n = 750) (cross-sectional)	FA	Not reported	4	Not reported	1) Traditional		
							2) Fast & processed food	General Obesity Systolic BP Diastolic BP Serum Cholesterol Waist Triglycerides HDL-cholesterol Fasting Glucose	*Univariate adjusted means only*
							3) Soybeans, grain & flower		
							4) Animal liver & animal meats		
2013	He et al. [269]	Chinese (n = 20,827) (cross-sectional)	CA based on PCFA	Not reported	4	NA	1) Green water	-	Reference diet
							2) Yellow earth	Metabolic Syndrome	OR 1.12 (0.93 to 1.05)
								Hypertension	OR 1.04 (0.90 to 1.20)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	He et al. [269]	Chinese (n = 20,827) (cross-sectional)	CA based on PCFA	Not reported	4	NA	2) Yellow earth	High Triglycerides	OR 0.80 (0.66 to 0.97)
								Low HDL-Cholesterol	OR 1.46 (1.25 to 1.70)
								Hyperglycaemia	OR 0.97 (0.80 to 1.18)
								Waist Circumference	OR 1.30 (1.06 to 1.60)
								Metabolic Syndrome	OR 1.03 (0.82 to 1.30)
							3 & 4) Western/new affluence	Hypertension	OR 0.88 (0.75 to 1.04)
								High Triglycerides	OR 0.82 (0.66 to 1.01)
								Low HDL-Cholesterol	OR 1.26 (1.05 to 1.50)
								Hyperglycaemia	OR 1.47 (1.18 to 1.84)
								Waist Circumference	OR 1.71 (1.36 to 2.16)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Akter et al. [591]	Japanese (n = 460) (cross-sectional)	PCFA	Scree plot & Eigenvalue (Cut-off not reported)	3	>0.15	1) Healthy Japanese	Metabolic Syndrome	OR 1.35 (0.55 to 3.30)
								General Obesity	OR 1.20 (0.63 to 2.31)
								High Triglycerides	OR 0.37 (0.14 to 0.98)
								Low HDL-Cholesterol	OR 1.20 (0.43 to 3.37)
								Hypertension	OR 1.37 (0.69 to 2.74)
								Hyperglycaemia	OR 0.67 (0.31 to 1.45)
							2) Animal food	Metabolic Syndrome	OR 1.54 (0.73 to 3.24)
								General Obesity	OR 0.94 (0.54 to 1.63)
								High Triglycerides	OR 1.45 (0.74 to 2.83)
								Low HDL-Cholesterol	OR 0.93 (0.42 to 2.07)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Akter et al. [591]	Japanese (n = 460) (cross-sectional)	PCFA	Scree plot & Eigenvalue (Cut-off not reported)	3	>0.15	2) Animal food	Hypertension	OR 1.78 (1.01 to 3.17)
								Hyperglycaemia	OR 2.08 (1.09 to 3.98)
								Metabolic Syndrome	OR 0.39 (0.16 to 0.95)
								General Obesity	OR 0.89 (0.49 to 1.63)
								High Triglycerides	OR 0.65 (0.30 to 1.39)
								Low HDL-Cholesterol	OR 1.77 (0.67 to 4.69)
							3) Western-nised break-fast	Hypertension	OR 0.54 (0.31 to 0.99)
								Hyperglycaemia	OR 0.58 (0.30 to 1.21)
2013	Naja et al. [592]	Lebanese (n = 323) (cross-sectional)	FA	Not reported	3	>0.40	1) Fast food/dessert	Metabolic Syndrome	OR 3.13 (1.36 to 7.22)
								Waist Circumference	OR 1.70 (0.31 to 2.58)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Naja et al. [592]	Lebanese (n = 323) (cross-sectional)	FA	Not reported	3	>0.40	1) Fast food/dessert	High Triglycerides	OR 2.01 (0.84 to 4.74)
								Low HDL-Cholesterol	OR 1.32 (0.56 to 3.12)
								Hypertension	OR 1.40 (0.62 to 3.17)
								Hyperglycaemia	OR 3.81 (1.59 to 9.14)
							2) Traditional Lebanese	Metabolic Syndrome	OR 1.96 (0.82 to 4.34)
								Waist Circumference	OR 1.07 (0.51 to 2.24)
								High Triglycerides	OR 1.28 (0.59 to 2.79)
								Low HDL-Cholesterol	OR 1.77 (0.80 to 3.93)
								Hypertension	OR 2.31 (0.91 to 6.74)
								Hyperglycaemia	OR 1.44 (0.67 to 3.08)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Naja et al. [592]	Lebanese (n = 323) (cross-sectional)	FA	Not reported	3	>0.40	3) High protein	Metabolic Syndrome	OR 1.22 (0.54 to 2.77)
								Waist Circumference	OR 1.74 (0.79 to 3.85)
								High Triglycerides	OR 1.02 (0.46 to 2.27)
								Low HDL-Cholesterol	OR 0.60 (0.30 to 1.38)
								Hypertension	OR 2.98 (1.26 to 7.02)
								Hyperglycaemia	OR 1.60 (0.70 to 3.62)
2013	Wang et al. [480]	Chinese (n = 13,511) (cross-sectional)	CA based on PCA	Not reported	4	NA	1) Green water	-	Reference diet
							2) Yellow earth	Metabolic Syndrome	OR 1.22 (1.01 to 1.48)
								Waist Circumference	OR 1.24 (1.05 to 1.47)
								Hypertension	OR 1.18 (0.70 to 1.31)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Wang et al. [480]	Chinese (n = 13,511) (cross-sectional)	CA based on PCA	Not reported	4	NA	2) Yellow earth	Hyperglycaemia	OR 1.01 (0.79 to 0.28)
								High Triglycerides	OR 0.91 (0.79 to 1.04)
								Low HDL-C	OR 1.61 (1.44 to 1.80)
							3) Western adopters	Metabolic Syndrome	OR 1.38 (1.12 to 1.70)
								Waist Circumference	OR 1.23 (1.02 to 1.49)
								Hypertension	OR 1.04 (0.91 to 1.18)
								Hyperglycaemia	OR 1.05 (0.80 to 1.39)
								High Triglycerides	OR 1.09 (0.92 to 1.27)
								Low HDL-C	OR 1.36 (1.18 to 1.57)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2013	Wang et al. [480]	Chinese (n = 13,511) (cross-sectional)	CA based on PCA	Not reported	4	NA	4) New affluent	Metabolic Syndrome	OR 1.36 (1.13 to 0.64)
								Waist Circumference	OR 1.00 (0.85 to 1.18)
								Hypertension	OR 1.31 (1.17 to 1.37)
								Hyperglycaemia	OR 1.38 (1.10 to 1.73)
								High Triglycerides	OR 0.86 (0.75 to 1.00)
								Low HDL-Cholesterol	OR 1.38 (1.22 to 1.57)
2014	Sugawara et al. [593]	Japanese (n = 338) (cross-sectional)	PCA	Not reported	3	>0.15	1) Healthy	General Obesity	OR 0.29 (0.13 to 0.62)
							2) Processed	General Obesity	OR 0.44 (0.22 to 0.89)
							3) Alcohol and accomp-anying	General Obesity	OR 1.80 (0.90 to 3.59)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Qin et al. [300]	Chinese (n = 2,518) (cross-sectional)	PCFA	Not reported	3	>0.20	1) Traditional	Hypertension	PR 1.47 (1.18 to 1.82)
							2) Macho	Hypertension	PR 0.78 (0.65 to 0.94)
							3) Sweet tooth	Hypertension	PR 0.71 (0.58 to 0.86)
							4) Healthy	Hypertension	PR 0.89 (0.74 to 1.07)
2014	Woo et al. [594]	Korean (n = 1,257) (cross-sectional)	PCFA	Eigenvalue (cut-off not reported)	3	>0.20	1) Traditional	Metabolic Syndrome	PR 1.08 (0.71 to 1.63)
							2) Meat	Metabolic Syndrome	PR 1.47 (1.00 to 2.15)
							3) Snack	Metabolic Syndrome	PR 0.93 (0.66 to 1.32)
2014	Sun et al. [199]	Chinese (n = 1,219) (cross-sectional)	CA based on PCFA	Scree plot & Eigenvalue >1	3	>0.30	1) Healthy	-	Reference diet
							2) Western	Metabolic Syndrome	RR 1.60 (1.09 to 2.68)
								Waist Circumference	RR 0.95 (0.50 to 1.81)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Sun et al. [199]	Chinese (n = 1,219) (cross-sectional)	CA based on PCFA	Scree plot & Eigenvalue >1	3	>0.30	2) Western	High Triglycerides	RR 1.80 (1.05 to 3.44)
								Dyslipidaemia	RR 1.10 (0.55 to 2.18)
								Hypertension	RR 1.95 (1.15 to 1.31)
								Hyperglycaemia	RR 0.23 (0.12 to 0.46)
							3) Balanced	Metabolic Syndrome	RR 0.55 (0.26 to 1.16)
								Waist Circumference	RR 0.83 (0.28 to 2.50)
								High Triglycerides	RR 0.87 (0.43 to 1.79)
								Dyslipidaemia	RR 0.92 (0.44 to 1.94)
								Hypertension	RR 1.06 (0.61 to 1.85)
								Hyperglycaemia	RR 0.73 (0.35 to 1.49)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Frank et al. [595]	Ghanaian (n = 1,217) (case-control)	PCFA	Scree plot & Eigenvalue >1	2	>0.20	1) Purchase	Type 2 Diabetes Mellitus	OR 1.11 (0.06 to 0.21)
							2) Traditional	Type 2 Diabetes Mellitus	OR 3.20 (1.96 to 5.22)
2014	Yoo et al. [596]	Korean (n = 16,734) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	2	>0.20	1) Traditional Korean	Metabolic Syndrome	OR 0.83 (0.68 to 1.02)
							2) Dairy-cereal	Metabolic Syndrome	OR 0.73 (0.58 to 0.93)
2014	Park et al. [597]	Korean (n = 5,308) (cross-sectional)	FA	Scree plot & Eigenvalue >1.5	3	>0.30	1) Whole food	Hypertension	OR 0.80 (0.56 to 1.15)
							2) Western	Hypertension	OR 1.30 (0.88 to 1.94)
							3) Drinking	Hypertension	OR 3.05 (2.12 to 4.40)
2014	Labonte et al. [598]	Canadian (n = 666) (cross-sectional)	PCA	Scree plot & Eigenvalue >1	4	>0.30	1) Traditional		*Reported in mean*
								Total Cholesterol	Adverse association
								HDL-Cholesterol	Adverse association
								LDL-Cholesterol	No association
								Triglycerides	No association
							2) Western	Total Cholesterol	No association

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									Reported in mean
2014	Labonte et al. [598]	Canadian (n = 666) (cross-sectional)	PCA	Scree plot & Eigenvalue >1	4	>0.30	2) Western	HDL-cholesterol	No association
								LDL-cholesterol	No association
								Triglycerides	No association
							3) Nutrient-poor food	Total Cholesterol	No association
								HDL-Cholesterol	No association
								LDL-Cholesterol	No association
								Triglycerides	No association
							4) Healthy	Total Cholesterol	No association
								HDL-Cholesterol	No association
								LDL-Cholesterol	Adverse association
								Triglycerides	No association
2014	Batis et al. [599]	Chinese (n = 4,096) (longitudinal)	RRR diet used in LCTA	Not reported	1	-	1) No label	Type 2 Diabetes Mellitus	OR 0.60 (0.26 to 1.40)
2014	Arisawa et al. [198]	Japanese (n = 513) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	1) Prudent	Metabolic Syndrome	OR 0.77 (0.56 to 1.03)
								Waist Circumference	OR 0.85 (0.68 to 1.05)
								High Triglyceride	OR 0.91 (0.69 to 1.18)
								Low HDL-Cholesterol	OR 0.69 (0.47 to 0.99)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Arisawa et al. [198]	Japanese (n = 513) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	1) Prudent	Metabolic Syndrome	OR 0.77 (0.56 to 1.03)
								Waist Circumference	OR 0.85 (0.68 to 1.05)
								High Triglyceride	OR 0.91 (0.69 to 1.18)
								Low HDL-Cholesterol	OR 0.69 (0.47 to 0.99)
								Hypertension	OR 0.79 (0.61 to 1.00)
								Hyperglycaemia	OR 0.84 (0.66 to 1.05)
							2) High fat/Western	Metabolic Syndrome	OR 1.08 (0.83 to 1.42)
								Waist Circumference	OR 1.20 (0.97 to 1.49)
								High Triglyceride	OR 1.14 (0.89 to 1.46)
								Low HDL-Cholesterol	OR 0.99 (0.72 to 1.34)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Arisawa et al. [198]	Japanese (n = 513) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	2) High fat/Western	Hypertension	OR 1.04 (0.81 to 1.32)
								Hyperglycaemia	OR 0.84 (0.67 to 1.06)
							3) Bread and dairy products	Metabolic Syndrome	OR 1.08 (0.83 to 1.42)
								Waist Circumference	OR 1.20 (0.97 to 1.49)
								High Triglycerides	OR 0.82 (0.64 to 1.04)
								Low HDL-Cholesterol	OR 1.05 (0.79 to 1.39)
								Hypertension	OR 0.89 (0.71 to 1.11)
								Hyperglycaemia	OR 0.80 (0.65 to 1.00)
							4) Seafood	Metabolic Syndrome	OR 1.14 (0.91 to 1.44)
								Waist Circumference	OR 1.03 (0.85 to 1.25)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Arisawa et al. [198]	Japanese (n = 513) (cross-sectional)	PCA	Eigenvalue >1	3	>0.20	4) Seafood	High Triglycerides	OR 1.17 (0.95 to 1.47)
								Low HDL-Cholesterol	OR 0.99 (0.75 to 1.27)
								Hypertension	OR 1.07 (0.87 to 1.31)
								Hyperglycaemia	OR 1.02 (0.83 to 1.25)
									- Males
2014	Lyu et al. [600]	Chinese (n = 8,392) (cross-sectional)	FA	Scree plot & Eigenvalue (Cut-off not reported)	4	>0.20	1) Meat	High Triglycerides/ HDL ratio	OR 0.63 (0.49 to 0.82)
							2) Healthy	High Triglycerides/ HDL ratio	OR 0.78 (0.63 to 0.97)
							3) High-energy	High Triglycerides/ HDL ratio	OR 0.77 (0.63 to 0.96)
							4) Traditional Chinese	High Triglycerides/ HDL ratio	OR 0.77 (0.62 to 0.95)
									- Females
							1) Meat	High Triglycerides/ HDL ratio	OR 0.93 (0.71 to 1.22)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Lyu et al. [600]	Chinese (n = 8,392) (cross-sectional)	FA	Scree plot & Eigenvalue (Cut-off not reported)	4	>0.20	2) Healthy	High Triglycerides/ HDL ratio	OR 0.75 (0.60 to 0.94)
							3) High-energy	High Triglycerides/ HDL ratio	OR 0.65 (0.52 to 0.81)
							4) Traditional Chinese	High Triglycerides/ HDL ratio	OR 0.86 (0.69 to 1.07)
2014	Dipnall et al. [601]	American (n = 4,588) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1	5	>0.30	1) Healthy diet	Depression with Type 2 Diabetes	OR 0.68 (0.52 to 0.88)
							2) Unhealthy diet	Depression with Type 2 Diabetes	Not reported
							3) Sweets diet	Depression with Type 2 Diabetes	OR 1.17 (0.77 to 1.79)
							4) Mexican diet	Depression with Type 2 Diabetes	Not reported
							5) Breakfast diet	Depression with Type 2 Diabetes	Not reported
2014	Eshriqui et al. [602]	Brazilian (n = 191) (longitudinal)	PCA	Scree plot & Eigenvalue >1.5	3	>0.20	1) Healthy	Systolic BP	beta -0.2 (-1.3 to 0.1)
								Diastolic BP	beta -0.7 (-1.6 to 0.2)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2014	Eshriqui et al. [602]	Brazilian (n = 191) (longitudinal)	PCA	Scree plot & Eigenvalue >1.5	3	>0.20	2) Common Brazilian	Systolic BP	beta -0.3 (-1.4 to 0.8)
								Diastolic BP	beta -0.4 (-1.3 to 0.5)
							3) Processed	Systolic BP	beta -0.3 (-1.7 to 1.1)
								Diastolic BP	beta -0.03 (-1.2 to 1.1)
2014	Barbaresko et al. [237]	German (n = 905) (cross-sectional)	PCFA &	Scree plot	1	>0.20	PCFA diet – no label	Metabolic Syndrome	OR 1.92 (1.21 to 3.03)
			RRR	Not reported	1	>0.20	RRR diet – no label	Metabolic Syndrome	OR 2.18 (1.25 to 3.81)
2014	Silva Bdel et al. [603]	Brazilian (n = 1,026) (cross-sectional)	RRR	Not reported	3	>0.20	1) No label	Hypertension	OR 1.30 (0.89 to 1.90)
							2) No label	Hypertension	OR 0.88 (0.61 to 1.28)
							3) Not label	Hypertension	OR 0.95 (0.66 to 1.37)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2015	Jaacks et al. [604]	Chinese (n = 99) (cross-sectional)	RRR	Not reported	2	>0.25	1) No label	Haemoglobin A1c	OR and 95%CI not reported
							2) No label	LDL-Cholesterol	- Males
2015	Aekplakorn et al. [605]	Thai (n = 5,872) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.20	1) Meat	Metabolic Syndrome	OR 1.01 (0.82 to 1.22)
								Waist Circumference	OR 1.40 (1.10 to 1.83)
								High Triglycerides	OR 0.92 (0.74 to 1.14)
								Low HDL-Cholesterol	OR 0.80 (0.64 to 0.99)
								Hypertension	OR 1.56 (1.24 to 1.97)
								Hyperglycaemia	OR 1.78 (1.32 to 2.41)
							2) Carbo-hydrate	Metabolic Syndrome	OR 1.82 (1.31 to 2.55)
								Waist Circumference	OR 0.60 (0.46 to 0.79)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2015	Aekplakorn et al. [605]	Thai (n = 5,872) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.20	2) Carbo-hydrate	High Triglycerides	OR 2.26 (1.69 to 3.03)
								Low HDL-Cholesterol	OR 1.93 (1.50 to 2.47)
								Hypertension	OR 0.79 (0.62 to 1.00)
								Hyperglycaemia	OR 0.52 (0.36 to 0.75)
							3) Healthy	Metabolic Syndrome	OR 0.91 (0.67 to 1.23)
								Waist Circumference	OR 1.03 (0.79 to 1.33)
								High Triglycerides	OR 0.92 (0.74 to 1.15)
								Low HDL-Cholesterol	OR 0.88 (0.75 to 1.02)
								Hypertension	OR 0.91 (0.71 to 1.17)
								Hyperglycaemia	OR 1.03 (0.76 to 1.39)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
									- Female
2015	Aekplakorn et al. [605]	Thai (n = 5,872) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.20	1) Meat	Metabolic Syndrome	OR 0.94 (0.72 to 1.21)
								Waist Circumference	OR 1.17 (0.98 to 1.41)
								High Triglycerides	OR 1.01 (0.88 to 1.49)
								Low HDL-Cholesterol	OR 0.86 (0.70 to 1.05)
								Hypertension	OR 1.03 (0.79 to 1.35)
								Hyperglycaemia	OR 1.96 (1.30 to 2.96)
							2) Carbo-hydrate	Metabolic Syndrome	OR 1.60 (1.24 to 2.08)
								Waist Circumference	OR 1.11 (0.88 to 1.40)
								High Triglycerides	OR 2.12 (1.62 to 2.77)
								Low HDL-Cholesterol	OR 2.03 (1.63 to 2.54)

Appendix 2 cont.

Year	Author	Participants & study design	Extraction method	Identification method	No of patterns retained	Variable cut-off point	Diet label	Outcome	Results (fully adjusted)
2015	Aekplakorn et al. [605]	Thai (n = 5,872) (cross-sectional)	PCFA	Scree plot & Eigenvalue >1.5	3	>0.20	2) Carbo-hydrate	Hypertension	OR 0.85 (0.66 to 1.09)
								Hyperglycaemia	OR 0.63 (0.39 to 1.02)
							3) Healthy	Metabolic Syndrome	OR 0.72 (0.52 to 0.99)
								Waist Circumference	OR 0.67 (0.57 to 0.79)
								High Triglycerides	OR 0.74 (0.59 to 0.92)
								Low HDL-Cholesterol	OR 0.97 (0.82 to 1.15)
								Hypertension	OR 0.89 (0.67 to 1.18)
								Hyperglycaemia	OR 0.86 (0.54 to 1.37)
2015	Johns et al. [606]	Swedish (n = 2,037) (longitudinal)	RRR	Not reported	1	>0.40	1) Energy dense, high-saturated fat, and low-fibre	Obesity Triglycerides HDL-cholesterol Systolic BP Diastolic BP Fasting Glucose	OR/HR/RR & 95%CI not reported for CVD risk factors

Abbreviations: PCFA = principal component factor analysis; PCA = principal component analysis; CA = cluster analysis; RRR = reduced rank regression; OR = odds ratio; HR = hazard ratio; RR = relative risk; 95%CI = 95% confidence intervals; HDL = high-density lipoprotein cholesterol; LDL; low-density lipoprotein cholesterol; BP = blood pressure; POR = prevalence odds ratio; LCTA = latent class trajectory analysis.

Appendix 3. Nutrition food frequency questionnaire

Please put a "tick" before foods that you have consumed over last week. Then write down the portion and frequency over a week in the space provided (It is important that we can calculate the total amount of food you consume last week).

1 Grain/ Cereal

Code	Food item	Portion size	No of portion	Times/week
1001	Cooked rice	1 bowl = 200g		
1002	Soft rice	1 bowl = 200g		
1003	Congee	1 bowl = 200g		
1004	Mixed rice congee, sweetened	1 bowl = 200g		
1005	Wheat noodle	1 bowl = 200g		
1006	Instant noodle	1 bowl = 200g		
1007	Flattened rice noodle	1 bowl = 200g		
1010	Porridge	1 bowl = 200g		
1011	Corn flakes	1 box = 25g		
1013	Mann-Tau	1 piece = 50g		
1014	Plain roll	1 piece = 70g		
1015	Bread	1 piece = 50g		
1016	Whole wheat bread	1 piece = 50g		
1017	Sweet roll	1 piece = 70g		
1020	Croissant	1 piece = 75g		
1022	Others	1 piece = 40g		

2 Vegetable/ Nuts

Code	Food item	Portion size	No of portion	Times/week
2001	Chinese flowering cabbage	1 plate = 100g		
2002	Chinese white cabbage	1 plate = 100g		
2003	Chinese kale	1 plate = 100g		
2004	Broccoli	1 plate = 50g		
2005	Lettuce	1 plate = 100g		
2006	Chinese spinach	1 plate = 100g		
2007	Chinese chives	1 plate = 100g		
2008	Cabbage	1 plate = 100g		
2010	Watercress	1 plate = 100g		
2011	Water spinach	1 plate = 100g		
2012	Asparagus	1 plate = 100g		
2013	Celery	1 plate = 50g		
2014	Spinach	1 plate = 100g		
2015	Cauliflower	1 plate = 50g		
2016	Pea shoot	1 plate = 100g		

2017	Mustard green	1 plate = 100g		
2018	Hairy melon/squash	1 portion = 100g		
2019	Cucumber	1 portion = 100g		
2020	Bitter	1 portion = 100g		
2021	Winter melon	1 portion = 100g		
2022	Angled loofah	1 portion = 100g		
2023	Egg plant	1 portion = 100g		
2024	Pumpkin	1 portion = 100g		
2025	Onion	1 portion = 50g		
2026	Carrots	1 portion = 50g		
2027	Turnips, green	1 portion = 50g		
2028	Radish	1 portion = 50g		
2029	Sweet potato	1 portion = 50g		
2030	Potato (baked/boiled)	1 portion = 50g		
2031	Water chestnut	7 pieces = 50g		
2032	Lotus root	1 portion = 50g		
	Bamboo shoot	1 portion = 50g		
2033	Tomatoes	1 portion = 50g		
2034	Red pepper/red capsicum	1 portion = 50g		
2035	Green pepper/green capsicum	1 portion = 100g		
2036	Sweet corn	1 portion = 50g		
2037	Canned Sweet corn	1 portion = 50g		
2038	Fresh soybean	1 portion = 50g		
2039	Tofu	1 cube = 300g		
2040	Tofu sheet	1 portion = 50g		
2041	Fried Tofu	2 pieces = 120g		
2042	Tofu-pop	3piece = 50g		
2043	Tofu-skin	1 portion = 50g		
2044	Wheat gluten	1 portion = 50g		
2045	Vegetarian chicken	3 pieces = 50g		
2046	Mungbean thread	1portion = 10g		
2047	Sprout mungbean	1 plate = 100g		
2048	Soybean sprout	1 plate = 100g		
2051	Red bean	1 portion = 25g		
2052	Brow bean	1 portion = 50g		
2053	Lentils	1 portion = 50g		
2054	Snap bean	1 plate = 100g		
2055	Snow bean	1 plate = 100g		
2056	Peas	1 portion = 50g		
2058	String beans	1 portion = 50g		
2059	Fresh mushroom	10 pieces = 100g		
2060	Dried mushroom	1 pieces = 25g		
2061	Canned mushroom	1 pieces = 100g		
2062	White fungus	1 portion = 10g		
2063	Wood fungus	1 portion = 10g		
2065	Preserved radish	6 slice = 50g		
	White melon	1 portion = 100g		
2066	Others			

3 Fruit (fresh & dried)

Code	Food item	Portion size	No of portion	Times/week
3001	Orange	1 piece = 150g		
3002	Grape fruit	1 piece = 200g		
3003	Apple	1 piece = 150g		
3004	Pear	1 piece = 180g		
3005	Banana	1 piece = 200g		
3006	Strawberry	4 piece = 100g		
3007	Honeydew melon	1 portion = 100g		
3008	Watermelon	1 portion = 100g		
3009	Peach	1 piece = 200g		
3010	Prune	2 piece = 200g		
3011	Mango	1 piece = 200g		
3012	Apricot	1 piece = 35g		
3013	Grapes	10 piece = 100g		
3014	Papaya	1 small pc = 400g		
3015	Lychee	10 piece = 100g		
3016	Logan	10 piece = 30g		
3017	Pineapple	1 slice = 100g		
3019	Lemon	1 piece = 100g		
3020	Pomelo	1 slice = 70g		
3021	Cherry	10 piece = 100g		
3022	Persimmon	1 piece = 100g		
3023	Kiwifruit	1 piece = 75g		
3025	Raspberries	1 cup = 123 g		
3027	Dried apricot	10 piece = 20g		
3028	Dried raisins	1 small box = 40g		
3029	Dried date	15 pieces = 20g		
3030	Others			

4 (1) Meat

Code	Food item	Portion size	No of portion	Times/week
4-1001	Lean pork	6 slice = 50g		
4-1002	Lean & fat pork	5 slice = 50g		
4-1003	Lean sparerib	4 slice = 50g		
4-1004	Lean & fat sparerib	4 slice = 50g		
4-1005	Lean roasted pork	2 slice = 50g		
4-1008	Fried steak	2 slice = 50g		
4-1010	Ox belly	4 slice = 50g		
4-1013	Chicken with skin	1 portion = 100g		
4-1014	Chicken without skin	1 portion = 100g		
4-1015	Chicken meat	1 slice = 50g		
4-1017	Chicken wing quarter	1 slice = 100g		
4-1018	Chicken leg quarter	1 slice = 100g		

4-1019	Roast goose with skin	1 portion = 100g		
4-1020	Roast goose without skin	1 portion = 100g		
4-1021	Roast dusk with skin	1 portion = 100g		
4-1022	Roast dusk without skin	1 portion = 100g		
4-1023	Lamp	1 slice = 50g		
4-1024	Roast pigeon	¼ slice = 50g		
4-1026	Chicken heart	slice = 50g		
4-1027	Chicken kidney	slice = 50g		
4-1028	Pig liver	slice = 50g		
4-1029	Pig heart	slice = 50g		
4-1030	Pig kidney	slice = 50g		
4-1031	Beef oval	slice = 50g		
4-1034	Chinese sausage	1 roll = 30g		
	Liver sausage	1 roll = 30g		
4-1036	Preserved pork	1 portion = 25g		
4-1037	Ham	2 slice = 50g		
4-1038	Luncheon meat	2 slice = 50g		
4-1039	Bacon	1 slice = 7g		
4-1042	Others			

4 (2) Fish

Code	Food item	Portion size	No of portion	Times/week
4-2001	Grass fish	1 portion = 200g		
4-2002	Big head fish	1 portion = 100g		
4-2003	Mud carp dace fish	1 portion = 100g		
4-2004	Eel	10 slice = 50g		
4-2005	Japanese eel	10 slice = 50g		
4-2006	Blace	1 portion = 200g		
4-2007	Golden thread fish	1 portion = 100g		
4-2008	Snakehead fish	10 slice = 50g		
4-2009	Carp	1 portion = 100g		
4-2010	Cat fish	1 portion = 100g		
4-2011	Garouper	1 portion = 100g		
4-2012	Mackerel	1 portion = 100g		
4-2013	Ribbon fish	1 portion = 100g		
4-2014	Big eye fish	1 portion = 100g		
4-2015	Squid	7 slice = 50g		
4-2016	Oyster	slice = 50g		
4-2017	Dried Oyster	slice = 50g		
4-2018	Prawns	1 portion = 25g		
4-2019	Crab	1 portion = 50g		
4-2020	Lobster	1 portion = 50g		
4-2021	Scallops	3 pieces = 20g		
4-2022	Sea cucumber	1 portion = 5g		
4-2023	Fish ball	pieces = 100g		
4-2024	Fish Cake	4 slice = 50g		

4-2025	Ink fish	slice = 50g		
4-2026	Mud carp ball	2 pieces = 50g		
4-2027	Sardines	1 portion = 50g		
4-2028	Fried dace	1 portion = 50g		
4-2030	Salted fish	1 slice = 5g		
4-2031	Jelly fish	1 portion = 50g		
4-2032	Salmon (smoked)	1 portion = 100g		
4-2036	Cod fish	1 portion = 100g		
	Crucian carp	1 portion = 100g		
4-2037	Others			

4 (3) Egg

Code	Food item	Portion size	No of portion	Times/week
4-3001	Boiled egg	pieces = 0g		
4-3002	Fried egg	pieces = 0g		
4-3003	Limed duck egg	pieces = 0g		
4-3004	Salted duck egg	pieces = 0g		
4-3005	Quail egg	pieces = 10g		
4-3006	Egg white	pieces = 35g		
4-3007	Egg yolk	pieces = 15g		
4-3008	Others			

4 (4) Milk/ Drink

Code	Food item	Portion size	No of portion	Times/week
4-4002	Cow milk	1 Glass = 250ml		
4-4003	Skim milk	1 Glass = 250ml		
4-4004	Chocolate milk	1 Glass = 250ml		
4-4005	Dried whole milk	1 Tas = 7g		
4-4006	Dried skimmed milk	1 Tas = 7g		
4-4007	Sweetened condensed milk	1 Tas = 20g		
4-4011	Ice cream 1	1 Cup = 150ml		
4-4012	Ice cream 2	1 Cup = 250ml		
4-4013	Ice cream 3	1 Piece = 60ml		
4-4014	Milk shake	1 Cup = 300ml		
4-4019	Coca-Cola	1 Glass = 250ml		
4-4020	Sprite	1 Glass = 250ml		
4-4021	Vitasoy	1 Box = 250ml		
4-4022	Soy drink	1 Glass = 250ml		
4-4023	Fresh fruit juice	1 Glass = 250ml		
4-4024	Squash	1 Box = 250ml		
4-4025	Chrysanthemum tea	1 Box = 250ml		
4-4026	Chinese tea	1 Cup = 150ml		
4-4027	Green tea	1 Cup = 150ml		
	Olong tea	1 Cup = 150ml		

	Other tea (Chinese tea)	1 Cup = 150ml		
4-4028	Ginseng tea	1 Cup = 250ml		
4-4030	Coffee	1 Cup = 250ml		
4-4031	Wine	1 Cup = 250ml		
4-4032	Spirit	1 Cup = 250ml		
4-4033	Beer	1 Cup = 250ml		
4-4034	Mineral water	1 Cup = 150ml		
4-4035	Plain water	1 Cup = 150ml		
	Acidophilus milk	1 Cup = 250ml		
	Calcarious milk (whole milk)	1 Cup = 250ml		
	Calcarious milk (low fat milk)	1 Cup = 250ml		
4-4036	Others			

5 Dim Sum/ Snack

Code	Food item	Portion size	No of portion	Times/week
5001	Wan tonne	1 Piece = 20g		
5002	Barbeque pork bun	1 Piece = 75g		
5003	Egg yolk & lotus seed bun	1 Piece = 40g		
5004	Steamed dim sum	1 Piece = 20g		
5005	Deep fried dim sum	1 Piece = 35g		
5006	Steamed cheung fan	1 Roll = 60g		
5001	Chinese turnip pudding	1 Piece = 40g		
5002	Chicken paw	1 Plate = 100g		
5003	Sticky rice dumpling	1 Piece = 275g		
5004	Yau-char-kwai	1 Roll = 70g		
5005	Hot Dog	1 Piece = 140g		
5006	Hamburger	1 Piece = 100g		
5015	Filet-o-fish-McDonald	1 Piece = 140g		
5016	Chicken Nuggets-McDonald	1 Piece = 20g		
5017	Hash Brown	1 Piece = 50g		
5018	Pork pie	1 Piece = 100g		
5019	Apple pie	1 Piece = 100g		
5020	Dry beef/ beef jerky	3 slices = 100g		
5021	Pork stick	3 slices = 100g		
5022	Beef floss	1 Pack = 25g		
5023	Pork floss	1 Pack = 25g		
5024	Squid thread	1 Pack = 20g		
5025	Red bean tong sui	1 Bowl = 200g		
5026	Cream crackers	3 Pieces = 25g		
5027	Semi sweet biscuit	2 Pieces = 20g		
5028	Chocolate coated biscuit	3 Pieces = 45g		
5029	Cookies	3 Pieces = 45g		
5031	Walnut short cake	1 Piece = 150g		
5033	Egg tart	1 Piece = 60g		
5034	Potato chips	1 Portion = 100g		
5035	Potato crisps	1 s Pack = 35g		

5036	Pop corn	1 Cup = 9g		
5038	Spongy cake	1 Piece = 70g		
5039	Madeira cake	1 slice = 80g		
5041	Chocolate 1	1 Piece = 8g		
5042	Chocolate 2	1 Piece = 12g		
5043	Candy	2 Piece = 10g		
5044	Honey	1 Tas = 20g		
5045	Jam	1 Tas = 20g		
5046	Peanut butter	1 Tas = 15g		
5047	Syrup	1 Tas = 20g		
5048	White Sugar	1 Tas = 10g		
5049	Chestnut	1 Piece = 10g		
5050	Cashew nut	1 Portion/pack = 35g		
5051	Peanut	1 Portion = 25g		
5052	Walnut	1 Plate-s = 50g		
5053	Almonds	1 Portion = 25g		
5054	Others			

6 Soups

Code	Food item	Portion size	No of portion	Times/week
6001	Vegetable soup	1 Bowl = 200ml		
6002	Melon soup	1 Bowl = 200ml		
6003	Fish soup	1 Bowl = 200ml		
6004	Chicken soup	1 Bowl = 200ml		
6005	Meat Pork soup	1 Bowl = 200ml		
6007	Tonic soup	1 Bowl = 200ml		
	Bone (Pork) soup	1 Bowl = 200ml		
6008	Others			

7 Fat/ Oil

Code	Food item	Portion size	No of portion	Times/week
7001	Corn oil/ Vegetable Oil	1 Tas = 14ml		
7002	Olive Oil	1 Tas = 14ml		
7003	Canola Oil	1 Tas = 14ml		
7004	Lard	1 Tas = 14ml		
7006	Butter	1 piece = 10g		
7007	Margarine Hard	1 piece = 10g		
7008	Margarine Soft	1 piece = 10g		
	Mixed Oil	1 Tas = 14ml		
7009	Salad Dressing	1 Tas = 14ml		
7010	Others			

Appendix 4. Food groups used in dietary analysis.

Food groups or foods	Food items
Whole grain	Porridge, whole wheat bread, wheat gluten, corn flakes, pop corn
Rice	Rice, soft rice, congee, rice noodle, mixed rice congee, steamed cheung fan
Noodles	Wheat noodles, instant noodles
Breads	Bread, sweet roll, plain roll, croissant
High protein high fat Chinese dishes	Egg yolk lotus seed bun, deep fried dim sum, Chinese turnip pudding, sticky rice dumpling, yau char kwai
High protein low fat Chinese dishes	Mann tau, wan ton, barbeque pork bun, steamed dim sum, chicken paw
Eggs	Boiled eggs, fried eggs, duck lime egg, salted duck eggs, quail egg, Egg white, egg yolk
Red meat, lean	Lean pork, lean sparerib, lean roasted pork
Red meat, fatty	Fatty pork, fatty sparerib, fried steak, lamb
Poultry, lean	Chicken without skin, chicken meat, chicken leg, roasted goose without skin, roasted duck without skin, roasted pigeon
Poultry, fatty	Chicken with skin, chicken wing, roasted goose with skin, roasted duck with skin
Offal	Ox belly, chicken heart, chicken kidney, pig liver, pig heart, pig kidney, beef offal
Meat, preserved	Beef jerky, pork stick, beef floss, pork floss, preserved pork, ham
Meat, other	Chinese sausage, luncheon meat, bacon, hamburger, pork pie, hotdogs, McDonald's chicken Nuggets
Mushrooms & fungi	Fresh mushroom, dried mushroom, canned mushroom, white fungus, wood fungus
Soy	Tofu, tofu sheet, fried tofu, tofu pop, tofu skin, vita soy, fresh soya bean, soya drink
Beans and legumes	Sprout mungbean, red beans, brow beans, lentils, snap beans, snow beans, string beans, mungbean thread, water chestnut, soybean sprout, peas
Vegetable, cruciferous	Flower cabbage, white cabbage, Chinese kale, broccoli, Chinese chives, cabbage, watercress, cauliflower
Vegetable, green	Spinach, Chinese spinach, water spinach, mustard green, green turnip, lettuce, pea shoot
Vegetable, dark yellow	Bitter melon, winter melon
Vegetable, red and orange	Melon squash, pumpkin, carrot, red pepper

Appendix 4 cont.

Food groups or foods	Food items
Vegetable, stem	Asparagus, celery, lotus root
Vegetable, other	Egg plant, green pepper, cucumber, angled loofah, vegetarian chicken
Vegetable, starch and tuber	Potato, sweet corn, canned sweet corn, sweet potato
Vegetable, onion and radish	Onions, radishes, preserved radish
Tomatoes	Tomato
Nuts	Chest nut, walnut, almonds
Nuts, other	Peanut butter, peanuts, cashew nuts
Fish, fatty	Eel, Japanese eel, mackerel, sardines, fried dace, smoked salmon
Fish, other	Grass fish, big head fish, mud carp dace fish, blace, golden thread fish, snake head fish, carp, cat fish, garouper, ribbon fish, big eye fish, cod
Fish, processed	Fish ball, fish cake, cuttle fish, mud carp ball, McDonald's fish fillet
Fish, salty	Salted fish, squid thread
Seafood	Squid, oyster, dried oyster, prawns, crab, lobster, scallops, sea cucumber, jelly fish
Fruit, citrus	Oranges, grape fruit, lemons, pomelo
Fruit, berries	Strawberries, raspberries
Fruit, yellow and orange	Peach, mango, apricot, papaya, pineapple, honeydew melon, watermelon
Fruit, red and purple	Prune, grapes, cherry
Fruit, other	Apples, pear, banana, lychee, longan, persimmon, kiwi
Fruit, dried	Dried apricot, dried raisins, dried date
Soups	Vegetable soup, melon soup, fish soup, chicken soup, pork soup
Desserts	Madeira cake, Apple pie, Spongy cake, Red bean tong sui, walnut short biscuit, egg tart, ice cream, ice cream cone, ice lollies
Biscuits and cookies	Cream crackers, semi sweet biscuits, chocolate biscuits, cookies
Sweets and sugary spread	Chocolate, Cadbury chocolate, candy, honey, jam, syrup, sugar
Salty snacks	Potato chips, crisps, hash brown
Desserts	Madeira cake, Apple pie, Spongy cake, Red bean tong sui, walnut short biscuit, egg tart, ice cream, ice cream cone, ice lollies
Sweets and sugary spread	Chocolate, Cadbury chocolate, candy, honey, jam, syrup, sugar

Appendix 4 cont.

Food groups or foods	Food items
Salty snacks	Potato chips, crisps, hash brown
Milk, sweet	Chocolate milk, sweet condensed milk, milk shake
Milk, skimmed	Skimmed milk, dried skimmed milk
Milk, whole	Cow's milk, dried whole milk
Beverages	Coca cola, sprite, fruit juice, squash drink
Tea	Chrysanthemum tea, Chinese tea, green tea, ginseng tea
Coffee	Coffee
Alcohol	Wine, spirit, beer
Fats and oils	Lard, vegetable oil, peanut oil, olive oil, canola oil
Water	Mineral water, plain water

Appendix 5. Absolute factor loading values for dietary patterns.

Non-nut and Non-cruciferous Vegetable diet	factor loading	**High Protein-High Fat diet**	factor loading	**Omnivorous diet**	factor loading
Vegetables, red and orange	**0.62**	Seafood	**0.47**	Fruits, citrus	**0.56**
Vegetables, starch and tuber	**0.60**	Poultry, fatty	**0.45**	Vegetables, cruciferous	**0.51**
Tomatoes	**0.59**	Beverages	**0.39**	Meats, other	**0.46**
Vegetables, other	**0.50**	High protein-high fat dishes	**0.39**	Meats, preserved	**0.36**
Vegetables, dark yellow	**0.43**	Desserts	**0.37**	Nuts, other	**0.32**
Mushrooms and fungi	**0.42**	Fruit, yellow and orange	**0.36**	Nuts	**0.31**
Eggs	**0.38**	Offal	**0.35**	Vegetables, dark yellow	**-0.40**
Soy products	**0.34**	Beans and legumes	**0.33**		
Fruits, other	**0.34**	Red meat, fatty	**0.31**		
		Soups	**0.31**		

Factor loading ±0.30 are shown for simplicity.
Food items with factor loadings less than ±0.30 for all dietary patterns are omitted in the table.

Appendix 6. Mean and SD of frequency (times per week) of food groups by tertiles of dietary patterns.

Non-nut and Non-cruciferous Vegetable diet	Tertile 1	Tertile 2	Tertile 3	**High Protein-High Fat diet**	Tertile 1	Tertile 2	Tertile 3	**Omnivorous diet**	Tertile 1	Tertile 2	Tertile 3
Vegetables, red and orange	0.55 (0.92)	1.42 (1.45)	3.30 (2.73)	**Seafood**	0.10 (0.39)	0.33 (0.69)	1.04 (1.49)	**Fruits, citrus**	0.15 (0.60)	0.64 (1.27)	2.40 (2.63)
Vegetables, starch and tuber	0.08 (0.34)	0.38 (0.75)	1.57 (1.78)	**Poultry, fatty**	0.97 (1.18)	1.67 (1.51)	2.61 (2.20)	**Vegetables, cruciferous**	2.94 (2.34)	4.87 (2.95)	6.94 (3.69)
Tomatoes	0.06 (0.30)	0.29 (0.65)	1.31 (1.56)	**Beverages**	0.01 (0.10)	0.04 (0.24)	0.33 (0.99)	**Meats, other**	0.09 (0.35)	0.30 (0.62)	0.99 (1.24)
Vegetables, other	0.46 (0.84)	1.00 (1.25)	2.17 (2.38)	**High protein-high fat dishes**	0.25 (0.65)	0.61 (1.05)	1.25 (1.85)	**Meats, preserved**	0.03 (0.22)	0.13 (0.43)	0.69 (1.17)
Vegetables, dark yellow	0.40 (0.82)	0.90 (1.20)	1.70 (1.92)	**Desserts**	0.27 (0.64)	0.57 (1.01)	1.06 (1.47)	**Nuts, other**	0.45 (1.07)	0.80 (1.43)	1.56 (2.09)
Mushrooms and fungi	1.13 (1.36)	1.83 (1.77)	3.02 (2.92)	**Fruits, yellow and orange**	0.26 (0.77)	0.69 (1.25)	1.55 (2.15)	**Nuts**	0.06 (0.35)	0.21 (0.71)	0.71 (1.59)
Eggs	1.66 (1.58)	2.48 (2.02)	3.49 (2.56)	**Offal**	0.06 (0.30)	0.18 (0.55)	0.54 (1.20)	**Vegetables, dark yellow**	1.77 (1.88)	0.79 (1.16)	0.43 (0.90)
Soy products	0.76 (0.99)	1.07 (1.25)	1.65 (1.94)	**Red meat, fatty**	0.79 (1.35)	1.30 (1.75)	2.05 (2.46)				
Fruits, other	3.0 (2.77)	4.25 (3.27)	5.61 (4.08)	**Beans and legumes**	0.94 (1.32)	1.60 (1.79)	2.48 (2.57)				
				Soups	1.86 (1.81)	2.56 (2.12)	3.51 (2.71)				

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