ASSOCIATION OF EATING PATTERNS WITH BLOOD PRESSURE AND BODY MASS INDEX: THE INTERMAP STUDY

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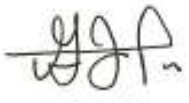
Statement of Personal Contribution

I declare that this dissertation is my own work and that where any material could be construed as the work of others, it is fully cited and referenced, and/or with appropriate acknowledgement given. The author was responsible of all data processing, data handling, and data analyses. The author validated and calculated the dietary glycaemic index values for the United Kingdom participants. All critical appraisal and interpretation was the opinion of the author.

Work based on this thesis was presented by the author at The American Heart Association Cardiovascular Disease Epidemiology and Prevention Scientific Sessions (2012, 2013, and 2014) entitled 'Association of Number of Eating Episodes per Day with Blood Pressure: INTERMAP Study'; 'Relation of nutrient-rich diet to blood pressure and BMI: The INTERMAP Study'; 'Relation to Blood Pressure of Total and Individual Components of Dietary Fibre and Sugar: The INTERMAP Study' and the International Society of Hypertension Annual Meeting (2013) entitled 'Eating frequency, time of energy intake in relation to BMI: INTERMAP Study'.

Signature  Date: 26/08/2014

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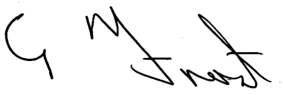
Signature  Date: 26/08/2014

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Copyright Declaration

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Abstract

Background

Epidemiologic evidence is sparse on the role of dietary patterns that may be important drivers of high blood pressure (BP) and body mass index (BMI) levels. Additionally, dietary fibre intake in association with BP and BMI yielded inconsistent results.

Objective

Investigate the relationships of eating frequency, dietary energy density, diet quality, evening energy intake, GI, GL, and dietary fibre to BP, BMI using cross-sectional data from the INTERnational study on MAcro/micronutrients and blood Pressure (INTERMAP) of 4680 men and women aged 40–59 y from Japan, China, the United Kingdom, and the United States of America.

Methods

During 4 visits, eight BP, four weight and height measures, four 24-hour dietary recalls, and two 24-hour urine samples were collected. Consumption of all solid foods was aggregated into eating occasions. Nutrient density is expressed using the Nutrient Rich Food index. Multivariable adjusted linear regression models were used to estimate BP and BMI differences per 2SD higher intakes of eating occasions, dietary energy density, Nutrient Rich Food index, evening energy intake, GI, GL, and dietary fibre.

Results

Compared to participants with <4 eating occasions/24-hours, those with ≥6 eating occasions/24-hours had lower average: systolic BP: 116.4 vs. 121.4 mm Hg; BMI: 27.3 vs. 29.0 kg/m^2; total energy: 2127 vs. 2521 kcal/24-hours; dietary energy density: 1.5 vs. 2.2 kcal/g; and higher Nutrient Rich Food index score: 35.1 vs. 26.8. Additionally,

insoluble fibre higher by 4 g/1000 was inversely associated with systolic BP (p<0.05), while soluble fibre and GI, GL showed no associations with BP and BMI.

Conclusions

Results suggest that higher meal frequency may be associated with improved diet quality and lower BP and BMI. Higher intakes of insoluble fibre may contribute to lower BP and BMI. This may have implications for behavioural approaches to controlling high BP levels and the obesity epidemic.

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Abbreviations

AUC	Area Under the blood glucose response Curve
BMI	Body mass index
BP	Blood pressure
CARDIA	The Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
CHO	Carbohydrate
CI	Confidence interval
CVD	Cardiovascular diseases
DASH	Dietary Approaches to Stop Hypertension
DM	Diabetes mellitus
EPIC	European Prospective Investigation into Cancer and nutrition
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FFQ	Food frequency questionnaires
GI	Glycaemic index
GIANT	Genetic Investigation of ANthropometric Traits
GL	Glycaemic load
HDL	High density lipoprotein
HPFS	Health Professional's Follow-up Study
HSE	Health survey for England
INTERMAP	INTERnational collaborative study of MAcronutrients, micronutrients and blood pressure
INTERSALT	International Co-operative Study of Electrolyte Excretion and Blood Pressure
IRAS	Insulin resistance atherosclerosis study
JNC	Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure
LDL	Low density lipoprotein

MDC	Malmo Diet and Cancer
MFA	Mono-unsaturated fatty acid
NDNS	National Diet and Nutritional Survey
NEFA	Non-essential fatty acids
NEMS	The Nurses and Midwives' e-cohort Study
NGHS	National heart, lung, and blood institute Growth and Health Study
NHANES	National Health and Nutrition Examination Survey
NHS	National health service
NHSII	The Nurses' Health Study II
PFA	Poly-unsaturated fatty acid
PREDIMED	Prevención con Dieta Mediterránea trial
PYY	Peptide YY
RCT	Randomised controlled trial
RDA	Recommended dietary allowance
SCFA	Short-chain fatty acids
SD	Standard deviation
SEASONS	The Seasonal Variation of Blood Cholesterol Study
SFA	Saturated fatty acid
SUVIMAX	SUpplementation en VItamines et Mineraux AntioXydants
TAG	Triacylglyceride
UK	United Kingdom
USA	United States of America
USDA	USA department of agriculture
WGHS	Women's genome health study
WHI	Women's health initiative
WHO	World health organisation
WHR	Waist-hip ratio
WHS	Women's health study

CHAPTER I

Background

1. BACKGROUND

1.1. Definition and prevalence of high blood pressure

High Blood Pressure (BP) is defined as systolic BP of ≥140 mm Hg and diastolic BP of ≥ 90 mm Hg, or the use of anti-hypertensive medication [1]. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) classified hypertension into: Stage 1 (systolic and diastolic BP: 140-159 and 90-99 mm Hg) and Stage 2 (systolic and diastolic BP: 160-179 and 100-109 mm Hg and systolic and diastolic BP: ≥180 and ≥110 mm Hg) [2]. The JNC 7 introduced the term "pre-hypertension" to include those with systolic BP of 120–139 mm Hg and/or diastolic BP of 80–89 mm Hg. This new classification aims to identify those who can benefit from early lifestyle intervention for BP reduction (Table 1.1) [3].

The relationship between BP and cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is graded and continuous [4]. This positive correlation is stronger for systolic BP than it is for diastolic BP [5]. According to a meta-analysis of over one million adults from the Prospective Study Collaboration (2002), the risk of CVD doubled for increases in systolic and diastolic BP of 20 and 10 mm Hg, respectively [4]. Their analyses were based on 286,000 repeated BP measurements over several years of follow up [4]. In 2004, the INTERHEART study, a global case-control study of risk factors contributing to acute myocardial infarction, reported that nearly 22% of heart attacks in Western Europe, and 25% of heart attacks in Central and Eastern Europe could be attributed to raised BP [6].

Table 1.1. Blood pressure classification

JNC 7 Category	Systolic and diastolic BP, mm Hg
Normal	<120 and 80
Pre-hypertension	120-129 and 80-84
	130–139 and 85-89
Hypertension	
Stage 1	140–159 and 90–99
Stage 2	160–179 and 100–109
	≥180 and 110

JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
Source: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003; 289:2560–71.

In the United States of America (USA), the age adjusted prevalence of hypertension in 2009-2010 was 28.6%, similar to the 2007-2008 reports (29.7%) [7]. The prevalence, however, was higher in women, older adults, and non-Hispanic blacks [8]. The National Health and Nutrition Examination Survey (NHANES) data showed increased rates of hypertension from 24% in 1988-1994 to 29% in 1999-2000, which remained unchanged in the 2007-2008 report [8]. Although efforts have been focused on hypertension awareness, treatment, and control, more than 50% of individuals had uncontrolled BP levels in 2007-2008 [9]. Prediction models demonstrated that 14,000 deaths per year could be prevented in adults with every 10% increase in hypertension treatment and control [10].

In England, the 2011 Health Survey for England (HSE) reported the prevalence of hypertension remained unchanged since the 2003 report (31.7% of men and 29.5% of women were hypertensive). More than 50% of men and women with hypertension remained untreated. The report also stated that two fifths of men and women who are on treatment for hypertension failed to reduce their BP levels to <140/90 mm Hg [11].

1.1.1. Pathophysiology

Environmental factors like age and diet, as well as genetic factors, were found to affect the BP regulation process [12]. Studies on families with similar trends in BP provide evidence that genetic mutations may be linked to high BP levels [13,14]. Arterial pressure is determined by cardiac output and peripheral resistance. Heart rate and stroke volume are two determinants of cardiac output, while peripheral resistance is associated with changes in small arteries and arterioles [15]. The autonomic nervous system regulates the functions of the kidneys, which in turn play a role in the regulation of cardiac output, fluid retention, and vascular resistance, thus in the onset of hypertension [16]. When kidneys require elevated BP to sustain extracellular fluid volume in the normal range, BP starts to escalate [17]. Therefore, any degree of impairment in renal function (fluid balance) causes hypertension. This mechanism is supported by animal [18] and human studies [19], showing an improvement in BP levels following a kidney transplant. Peripheral resistance and extracellular fluid volume are also regulated by the renin-angiotensin-aldosterone system. Arterial vasoconstriction and extracellular volume are affected by the level of circulating enzyme Renin. Renin breaks down angiotensinogen into angiotensin I, playing a major role in BP regulation. Angiotensin I is further hydrolysed into angiotensin II, which enhances the production of the hormone Aldosterone, which in turns stimulates reabsorption of salt and water [20].

1.1.2. Risk factors for high blood pressure

Observational studies and clinical trial data indicate that causes of elevated BP are mainly environmental. This includes dietary and lifestyle factors such as: sodium, potassium, alcohol consumption, body mass index (BMI) level, physical activity, socioeconomic status, and genetic factors - all discussed briefly below.

Dietary sodium

Dietary sodium intake has been directly associated with elevated BP in several observational and clinical trial studies [21-24]. The most widely known trial is the Dietary Approaches to Stop Hypertension - Sodium Trial (DASH) [21]. The crossover trial included 412 participants with slightly increased BP levels (systolic BP of 120 to 159 mm Hg, diastolic BP of 80 to 95 mm Hg). The participants were randomised to receive either a DASH diet (rich in fruits, vegetables, and low-fat dairy foods; includes whole grains, poultry, fish, and nuts; with less amounts of red meat, sweets, and sugar-sweetened beverages compared to a typical diet) or a common, typical western diet for 3 months. Different levels of sodium were provided to trial and control groups; high, intermediate, and low: 144, 107 and 67 mmol/24-hours otherwise, all diets were similar in nutritional content. The reduction of sodium intake from the high to the intermediate level resulted in a reduction in systolic BP by 2.1 (p<0.001) and 1.3 mm Hg (p=0.03) in the control and DASH diet periods, respectively. In addition, the reduction in sodium intake from the intermediate to the low level further reduced systolic BP by 4.6 mm Hg in the control diet period (p<0.001) and by 1.7 mm Hg in the DASH diet period (p<0.01). The DASH diet was associated with a significantly lower systolic BP at each sodium level [21]. Evidence from large epidemiologic studies, like the International Co-operative Study of Electrolyte Excretion and Blood Pressure (INTERSALT), supports the direct association between sodium intake and BP [25]. In 1996, a reanalyses of the INTERSALT study confirmed a direct and consistent association between urinary sodium and systolic BP in multivariate analyses with and without adjustment for BMI. The INTERSALT study included 10074 men and women 20 to 59 years of age from 52 samples in 32 countries. Higher urinary sodium excretion by 100 mmol was associated

with systolic BP higher by 5-7 mm Hg. These findings provide evidence that the reduction of sodium intake protects against adverse BP levels [25].

Dietary potassium

The INTERSALT study provides evidence that dietary potassium is inversely associated with BP [26]. In 1997, Whelton *et al.* conducted a meta-analyses of 32 randomised controlled trials (RCT) and concluded that supplementation with an average of 75 mmol/24-hours of potassium chloride was associated with average reductions in systolic and diastolic BP of 3.1 and 1.9 mm Hg, respectively [27]. These results support the hypothesis that raising potassium intake will help in the prevention of high BP level. Potassium affects cell uptake of norepinephrine, increasing blood flow and relaxing vascular smooth muscle [28]. Infusion of an iso-osmotic solution of potassium chloride into the brachial artery of dogs lead to a rise in blood flow, making it a vasodilator [29], while reducing potassium to 1 meq/L causes vasoconstriction [30].

Alcohol

Consumption of alcohol (ethanol), especially in excessive drinking, has been consistently associated with hypertension and elevated BP level in prospective cohort [31] and cross-sectional [32] studies. Intervention studies have also reported favourable effects on BP level through the reduction of alcohol consumption [33,34]. A meta-analysis of 15 trials assessed the effects of reduced alcohol consumption on BP level, showing significant reductions in systolic and diastolic BP of (−3.3, 95% confidence interval (CI): −2.5, −4.1 mm Hg) and (−2.0, 95% CI: −1.5, −2.6 mm Hg) with reduced alcohol intake [35]. In Japan, a 7-year follow up study including metal workers was conducted to investigate the association between ethanol consumption and BP [36]. In comparison to non-drinkers, consumption of 300 g or above of ethanol per week was found to increase

systolic BP by 0.44 mm Hg per year [36]. The proposed mechanism by which ethanol raises BP is complex. The sympathetic nervous system plays a key role in elevating BP after alcohol consumption [37]. It has been proposed that ethanol consumption inhibits nitric oxide (atheroprotective), alters calcium–magnesium balance, affects renin-angiotensin-aldosterone system, and causes insulin resistance, all of which are contributory factors in raising BP level [38].

Body weight

Obesity and CVD are interlinked. This is illustrated by the unfavourable cardiovascular risk profile in obese individuals including hypertension, hyperlipidaemia, and type 2 diabetes mellitus (DM) [39-41]. There are several proposed mechanisms by which obesity may cause hypertension. One is attributed to the activation of the sympathetic nervous system in those who are obese [42]. The sympathetic nervous system is stimulated by high caloric intake, especially of dietary carbohydrate and fat, particularly free-fatty acids [43], which stimulate adrenergic receptors. This eventually increases norepinephrine in peripheral tissues and plasma, increasing vascular tone [44]. Elevated BP associated with obesity may be also be related to the rise in angiotensinogen, a precursor of angiotensin, which is released from adipocytes. In addition, larger body mass is accompanied by increased blood volume, along with a rise in blood thickness [45]. Obese individuals typically manifest increased arterial thickness, especially excessive adiposity over an extended period, which eventually raises BP level. Obesity has also been consistently linked to insulin resistance [46-48]. Experimental trials and cohort studies showed that both hyperglycaemia and hyperinsulinemia were linked to elevated BP levels [49-52]. This link occurs through the stimulation of the rennin-angiotensin system, promotion of vascular smooth muscle cell proliferation and release of prothrombotic factors. Both the kidneys and the arterial wall are damaged due to

increased blood sugar levels which causes the deposition of advanced glycation end products; reduction in nitric oxide and the production of oxygen radicals [53-55].

Physical activity

Physical activity has been shown to be protective against CVD [56]. Regular physical activity was also associated with lower risk of hypertension [57]. Longitudinal intervention studies have supported the inverse association between physical activity and BP level [58,59]. A meta-analysis in the year 2007, including 72 trials and 105 study groups, on the effect of different exercise methods on BP control showed overall net reductions in systolic and diastolic BP of 3.0 and 2.4 mm Hg associated with training [59]. There were also significant reductions in systemic vascular resistance, plasma renin activity, and plasma norepinephrine, all of which were shown to be favourable to BP level. Other measurements were also reduced: body weight, waist circumference, body fat percent, and insulin resistance, all of which affect BP level [59]. An RCT comparing the DASH diet alone or in combination with exercise and body weight management was conducted for 4 months in 144 overweight and obese adults with elevated BP [60]. Results showed that those following the DASH diet had a BP reduction of 11.2/7.5 mm Hg, while those on the DASH diet plus exercise had a reduction of 16.1/9.9 mm Hg. The control group (following a weight reduction diet) had a BP reduction of 3.4/3.8 mm Hg ($p< 0.001$) [60]. It has been proposed that exercise decreases the production of catecholamines (epinephrine and norepinephrine) and improves insulin sensitivity, therefore decreases BP level [57]. Decreases in cardiac output and peripheral resistance were also documented post exercise treatment, especially in individuals with increased peripheral resistance [61].

Socioeconomic status

Indicators of socioeconomic status-including education, income, and occupation-were inversely associated with BP levels in a number of cross-sectional studies [62-64]. Also, the Women's Health Study (WHS), a randomised trial on the effects of using aspirin, vitamin E, and beta-carotene to prevent CVD and cancer, assessed the association between socioeconomic status and hypertension in 39876 female health professionals [65]. Results showed an independent association of socioeconomic status with incident hypertension after 10 years of follow up. Across quintiles of income, those in the highest quintile (quintile 5) had an 11-16% lower risk of developing high BP compared to those in the lowest income quintile (quintile 1). Across categories of education, the relative risk for BP development was lower in those in the highest category of education (p for trend <0.0001) [65]. The relation between low socioeconomic status and higher risk of hypertension may be related to several factors, like access to quality medical care [66], dietary habits [67,68], and the condition of residential area [61]. With limited financial and living means, diets may be low in fruits and vegetables and high in fat and sodium, leading to an increased risk of developing hypertension [68]. In addition, emotional distress caused by financial limitations and increased job strain may elevate neuro-hormonal activity, leading to hypertension [69].

Genetic factors

Both genetic and environmental factors influence the BP regulation process. With advances in genetic approaches, there is a clearer understanding of the biological pathways that explain inter-individual variations in BP [12]. The genome-wide association study of systolic and diastolic BP included 200,000 European participants in a multi-stage designed study aimed to identify genetic variants that influence BP and other outcomes [70]. A total of 16 loci with genes related to BP were identified, where six

of them include genes known to regulate BP (*GUCY1A3–GUCY1B3*, *NPR3–C5orf23*, *ADM*, *FURIN–FES*, *GOSR2*, *GNAS–EDN3*). Association of hypertension, left ventricular wall thickness, stroke and coronary artery disease with a genetic risk score based on 29 genomes was significant. Those in the highest quintile of the genetic risk score had higher systolic and diastolic BP levels by 4.6 and 3.0 mm Hg compared to those in the lowest quintile [70]. In the Women's Genome Health Study (WGHS) sample of 23294 women, an increase of one standard deviation (SD) in the genetic risk score was associated with a 23% increase in odds of hypertension (95% CI: 19, 28%) [71]. Across deciles of the genetic risk score, those in the highest category had a higher prevalence of hypertension compared to those in the lowest category (29% *vs.* 16%; OR 2.09, 95% CI: 1.9, 2.4) [71].

1.2. Definition and prevalence of overweight and obesity

Adiposity is commonly approximated by BMI (kg/m^2): body weight (kg) divided by the square of height (m). Adiposity, expressed by an elevated BMI level (≥25 kg/m^2) [72], is an established risk factor for mortality and morbidity, primarily of CVD [73], liver cirrhosis [74], cancer [75], diabetes [76], and adult-onset asthma [77].

Long term analyses of trends in BMI level have shown that adiposity has increased globally in both genders between 1980 and 2008 [78]. Male BMI has increased by 1.1 kg/m^2 per decade since the early 1980's; with similar increases observed in the United Kingdom (UK) and Australia. Women in the USA had an average increase of 1.2 kg/m^2 per decade. The age-standardized prevalence of obesity around the world was 9.8% (95% CI: 9.2, 10.4) in men and 13.8% (95% CI: 13.1, 14.7) in women in 2008. These values are twice the 1980 levels for men and for women [78]. The 2007–2008 NHANES reported that approximately 34.2% of all adults in the USA were overweight (≥25

kg/m^2) [79], 33.8% were obese (BMI ≥ 30 kg/m^2) [79], and 5.7% were morbidly obese (BMI ≥ 40 kg/m^2) [79] compared to 33.1%, 22.9%, and 2.9%, respectively, in the age adjusted data from 1988–1994 [80]. Data from the HSE show that the percentage of adults with optimum BMI (between 18.5 to 24.9 kg/m^2) [79] decreased from 41% to 32% between 1993 and 2005. The prevalence of obesity increased over the same period from 13.2% to 23.1% in men, and 16.4% to 24.8% in women [81]. The 2011 HSE reported an increase in the prevalence of obesity in men and women compared to 2006 (24% and 26% respectively). A higher proportion of men than women were overweight (41% compared with 33%); therefore, 65% of men and 58% of women were overweight or obese [82].

1.2.1. Risk factors for overweight and obesity

Obesity generally results from excess energy intake compared to energy expenditure [83]. Obesity is a multifactorial health issue that can be attributed to environmental and genetic factors. Due to the rising prevalence of obesity worldwide, it can be argued that environmental and behavioural factors are likely to play the major role in its epidemic. Some of the most important risk factors associated with obesity are briefly discussed below: diet, physical activity, socioeconomic status, and genetic factors.

Diet

There is substantial evidence on the impact of increased dietary intake on body weight [84-86]. Rapid urbanisation and westernization in different parts of the world have changed local diets, often coinciding with increased obesity [87,88]. The Western diet was generally described as high in fat and in energy density [72,89]. With the expansion of food-manufactures, available diets are now high in energy, protein, and fat and low in fibre. A recent systematic review and meta-analyses of 15 RCTs found that both diet and

exercise interventions over 6 months resulted in body weight reduction and favourable metabolic profile including: high density lipoprotein cholesterol (3.86, 95% CI: 2.70, 4.63 mg/dL), fasting glucose (-2.16, 95% CI: -3.78, -0.72 mg/dL), and fasting insulin (-2.75, 95% CI: -4.50, -1.00 μIU/mL) [90].

Physical activity

Regular exercise contributes to body weight loss and stability [45]. Physical inactivity has long been associated with body weight gain [91-93]. Individuals with the lowest activity level have the highest risk for CVD [94]. Data suggest that the decline in physical activity correlates to an increase in hours spent watching television, increase in using household devices (e.g. dishwasher), decrease in the time spent walking among children, with these changes occurring simultaneously with increases in obesity [95]. Evidence from a longitudinal cohort study on school children show that a sedentary lifestyle in adolescence strongly predicts obesity (OR 3.9, 95% CI: 1.4, 10.9). It was suggested that increasing physical activity during adolescent years may support the prevention of obesity, especially in the abdomen [93].

Socioeconomic status

Evidence suggests that low socioeconomic status is strongly correlated with obesity [96]. Previously, Sobal *et al.* reviewed published literature on the relation between socioeconomic status and obesity between the 1960s and 1980s and concluded that socioeconomic status is generally inversely related to obesity in the developed world. Women of lower socioeconomic status in developed countries were most likely to be obese. In contrast, in developing countries, those in higher socioeconomic status were likely to be obese [97]. Following the Sobal *et al.* review, this trend was supported in an updated review of epidemiologic studies, primarily cross-sectional, including data from

1988–2004 [98]. Women of lower socioeconomic status were more overweight in highly developed countries, whereas women in developing countries had lower body weight [98]. The link between socioeconomic status and obesity in developed countries may be attributed to the lack of education among individuals of low income who generally do not perceive themselves as being overweight compared to those of high income [99]. In addition, limited access to healthy foods, consumption of energy dense foods, and lack of motivation to participate in physical activity were all associated with low income [100]. Areas of poor economic status have a higher number of fast-food restaurants [101], with less activity and sports centres [102,103].

Genetic factors

It has been hypothesised in the early 1960s that obesity observed in populations suffering from starvation could be related to certain genes. It was suggested that this relation may explain the tendency of some individuals who possess those genes to gain far more body weight than those who do not [104]. Since then, a large body of research aimed to identify predisposing genes that may explain familial general obesity and fat distribution [13,105-108]. The Quebec Family Study, a prospective cohort study investigating the role of genetics in the aetiology of obesity, provides evidence that fat mass is affected by a recessive major gene responsible for 40-45% of variations and distribution of fat [109]. At this time, more than 250 genes, markers, or chromosomal regions associated with obesity have been identified [110]. The Genetic Investigation of ANthropometric Traits (GIANT) consortium is an international collaboration that aims to identify genetic loci associated with measures of obesity and other outcomes. Two loci (*FTO* and *MC4R*) were initially reported to be associated with BMI. Six additional loci were recently identified (*TMEM18*, *KCTD15*, *GNPDA2*, *SH2B1*, *MTCH2* and *NEGR),* confirming their role in the predisposition of monogenetic forms of obesity [107].

1.3. Eating frequency

Meals and snacking patterns, i.e., eating frequency, have been linked to body weight and the development of chronic disease [111]. However, data are sparse on the association between the number of eating occasions per day and BP. Previous cross-sectional and prospective cohort studies on associations between eating frequency and body weight have yielded inconsistent results, with several reporting that more frequent meal intake throughout the day is associated with lower BMI [112-114], and others finding no association [115,116]. This gap in knowledge has been identified by the 2010 Dietary Guidelines Advisory Report that called for future research in this field [117].

1.3.1. Eating frequency and blood pressure

The association between eating frequency and BP has not been thoroughly investigated in observational and intervention studies [118,119]. Even on those occasions, BP level was seldom the primary outcome in studies of food frequency. For example, Arnold *et al.* examined the metabolic effect of grazing in 19 healthy free-living normo-cholesterolemic individuals, in a 4-week experimental design [120]. Participants received either 3 or 9 meals per day for 14 days, with a one and seven-day washout period between the two diet regimens. Results showed no significant differences were observed in either body weight or systolic BP, however, total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) were significantly lower in the 9 meals per day regimen. The 24-hour insulin and insulin-glucose output was lower in the grazing diet than the 3-meal diet, although this difference was not significant. It should be noted that a short trial and washout period makes differences in systolic BP and other markers difficult to obtain [120].

Forslund *et al.* studied the effect of two diet treatments (3 meals and 3 meals plus 3 snacks per day) in a randomised one-year body weight loss trial including 180 participants [121]. Body weight loss was found to be greater in the 3 meals plus 3 snacks group, although the difference was not significant. Additionally, BP, glucose, insulin, LDL, HDL, and triacylglyceride TAG did not differ between the two groups. It is noteworthy that body weight, waist and hip circumference, BP, blood samples were all measured once at baseline and after one year [121]. Poston *et al.* conducted a similar prospective 24-week randomised weight reduction trial in 100 over-weight participants [122]. Participants were divided into snackers (≥4.5 meals/day) and non-snackers (≤ 5.5 meals/day), based on data from the USA NHANES database. These groups were randomised to receive a meal replacement or a meal replacement plus snack. Although body weight and systolic BP declined in all groups, no significant difference was observed across all four groups (non-snackers meal replacement only, non-snackers meal replacement plus snacks, snackers meal replacement only, snackers meal replacement plus snacks) [122].

In contrast, Stote *et al.* conducted a randomised crossover design for 8 weeks to examine the relation between eating frequency and BP level in healthy adults with a BMI between 18 and 25 kg/m^2 [119]. Participants were given either one or three meals per day, consumed under the supervision of a registered dietician, with an 11-week washout period. Findings indicated that systolic and diastolic BP were significantly lower (6%) among those consuming 3 meals/day in comparison to those consuming one meal/day. The long washout period (11 weeks) ensured the effects of one diet regimen did not last up to the alternative regimen. In this study, meal frequency was the only change between the two diets, and no caloric restriction was applied [119].

1.3.2. Eating frequency and body weight

The association between the number of eating occasions per day and body weight has been the focus of a number of prospective cohort, cross-sectional, and intervention studies [113,123-128]. However, the findings of this literature reveal inconsistencies despite similar study designs, all of which include different levels of adjustments for key confounding variables, such as under-reporting, physical activity, energy intake, dieting, and smoking [126,127]. A number of cross-sectional and longitudinal studies have found that more frequent meal intake throughout the day was associated with lower BMI [112-114,127,129-132], while others reported no significant findings [115,116,128,133-137].

One of the earliest trials exploring the association between eating frequency and body weight found an inverse association between the number of meals consumed in a day and body weight [126]. A total of 379 male participants were divided into: those having ≤3, 3-4 meals, 3-4 meals with snacks, 3-4 meals with one bedtime snack, and ≥5 meals. In comparisons of the five groups, the percentages of overweight and mean skin fold thickness were significantly higher in those consuming three or less meals per day [126].

A cross-sectional analysis of the Tecumseh Community Health Study, a prospective epidemiologic study of a community's health and disease status in Michigan, USA, included 2000 men and women [131]. A single 24-hour dietary recall and an adiposity index computed from body weight and skin-fold thickness measures were used. In order to quantify meal frequency, Metzner *et al.* combined meals if they were less than 30 minutes apart and were consumed within an hour; the combined intake was counted as a meal when it provided 40 calories or more. After adjustment for energy intake, the mean adiposity index was inversely and significantly associated with the number of meals consumed. This study, however, did not address confounding factors like under

reporters or physical activity level [131]. Similar results were reported using data from The Seasonal Variation of Blood Cholesterol Study (SEASONS), a prospective study where 499 USA men and women were followed up for one year [113]. The risk of obesity, adjusted for known confounders, was found to be 45% lower (95% CI: 0.33, 0.91) in those consuming ≥4 meals per day, in comparison to those consuming ≤3 meals per day. In this study, data were gathered from 5 body weight measurements and 15 24-hour dietary recalls. A meal was defined as that providing 50 kcal or more, with a 15 minute time interval or more between each meal [113]. Another study supporting the inverse association between eating frequency and BMI is a longitudinal study by Franko *et al.,* where a sample of 1209 black and 1166 white adolescent girls (9-19 y) were followed up over a period of 10 years [112]. The study used data from a 3-day food record obtained during annual visits, in conjunction with height and body weight measurements and self-reported levels of physical activity. Results indicate that meal frequency was inversely and consistently associated with BMI, adjusted for demographic and energy expenditure variables [112].

The aforementioned studies found an inverse association between eating frequency and body weight, however a likely source of error may be under-reporting. Ruidavets *et al.* addressed this issue in their cross-sectional study in 330 free living middle-aged men [132]. A 3 day food record was used, as in the work of Franko *et al.* [112]. These records were then validated by home visits of certified dieticians. Ruidavets *et al.* adopted the same definition by Metzner *et al.* of an interval of 30 min used to separate meals from one another [131]. After under reporters and dieters had been excluded, waist-hip ratio (WHR) and BMI were found to be significantly and inversely associated with the number of meals. These results remained consistent after adjustment for confounders, such as total caloric intake, age, physical activity, and smoking. Based on these

findings, it was suggested that the observed inverse association between BMI and eating frequency may be attributable to the reduction in insulin production and lipogenesis which can be associated with higher eating frequency [132]. A similar study design was conducted by Drummond *et al.*, in which under-reporters were excluded in a cross-sectional study of a sample of 48 men and 47 women with a wide BMI range of 18 and 30 kg/m^2 [127]. A seven-day food record was used to determine eating frequency. This was supplemented by the measurement of skin-fold thickness and physical activity level. The definition of eating occasions was based upon that offered by De Castro, in which eating occasions are combined when they occur within 15 minutes of each other [138]. This approach attempts to avoid misconceptions in describing eating occasions as meals or snacks, or discriminating against those with high daily eating frequencies. The relationship between eating frequency and body weight was found to be significantly inverse in men. An inverse association was also observed between eating frequency and BMI [127].

A prospective cohort study by Ritchie examined the relation between frequency of eating and adiposity in 2372 adolescent black and white girls (9–10 to 19–20 years) from 3 USA centres. The study sample was derived from the 10 years National Heart, Lung, and Blood Institute Growth and Health Study (NGHS). Dietary data were obtained from a 3-day food record; where annual information on dietary patterns was provided and records were examined in association with BMI and waist circumference changes over 10 years. Results show that eating frequency was higher in white girls (p<0.0001). Black girls had lower eating frequencies and higher increases in BMI (p=0.02) and waist circumference (p=0.01). In addition, lower snacking and eating frequency, adjusted for known confounders, was associated with a higher increase in BMI (p=0.01) and waist circumference (p=0.03) over the 10 year period [114].

A cross-sectional analysis of the Malmo Diet and Cancer (MDC) study, a prospective population study in Sweden, included a sub-sample of 3009 adults aged 47 to 68 years. Using a 7-day diet record, self-reported daily eating occasions were inversely associated with BMI and waist circumference ($p<0.05$) in normal weight men, adjusted for potential confounders. In addition, those having higher eating occasions per day had higher intake of total dietary fibre ($p<0.0001$), smoked less, and were more active ($p<0.01$) compared to those having lower eating occasions per day [130].

In contrast to the above findings, a number of studies did not support the hypothesis that greater daily eating frequency is associated with lower BMI. Dreon *et al.* found no significant association between eating frequency and body weight or percent body fat [133]. While their cross-sectional study of 155 sedentary overweight men used a 7-day food record, regression models did not adjust for other possible confounding factors. It should also be noted that the sample population was extremely homogeneous in terms of body weight, body fat composition, and eating patterns, with minimal deviation in either the number of eating occasions or in the amount of calories consumed during each eating occasion [133]. The NHANES I epidemiologic follow up study of the association between frequency of eating occasions and body weight also did not support the hypothesis that eating frequency is inversely associated with BMI [128]. Data in this study were based upon a single 24-hour dietary recall administered in 1971-1975, in which interviewers estimated the number of eating occasions based on time of food consumption. The frequency of eating occasions and BMI were inversely related at baseline in multiple covariate adjusted regression models. At follow up in 1982–1984, participants were asked to report the number of meals and snacks per day, with under-reporters and dieters being excluded from the final analysis. After adjustment for multiple confounding factors, no significant association was shown between body

weight change and number of eating occasions. Key methodological issues are that only a single 24-hour dietary recall was used, and that the method by which eating occasions were quantified was different at baseline from follow up [128]. The larger data set of the European Prospective Investigation into Cancer and Nutrition (EPIC) in 14,666 men and women also found a weak inverse association between eating frequency and body weight [137]. Data, however, were derived from a single food frequency questionnaire (FFQ), in which a single question asked participants to quantify the number of times they ate in a day, suggesting that the findings are not necessarily representative.

The aforementioned studies have not compared frequency of meal intake in different body weight groups (i.e. obese *vs.* normal) individuals. This type of comparison was considered in a few prospective cohort, case-control and cross-sectional studies [115,134,136]. The longitudinal study, Gustaf study, presented more representative data on meal intake by using twelve telephone-administered 24-hour recalls over a period of three months [115]. The study sample included obese and normal men from Sweden. No significant differences were observed in meal patterns and trends between the two groups, which may be attributed to a high level of under-reporters in the obese sample (73%) [115].

The eating behaviour and activity levels of 19 weight-gaining men and women and of weight-stable, matched control subjects were compared with the use of a 7-day diet diary (weight gain of ≥ 5% in the previous 6 months as reported by participants). Results show that weight-gaining individuals consumed more total energy and have more food in their stomachs after each meal than the weight stable group. However, meal frequency was not significantly different between the 2 groups. Their findings

may have been biased by under-reporters of energy intake, especially overweight participants [136].

The work of Howarth *et al.* differed slightly from the previous studies, as it included a sample of younger and older adults from the USA Department of Agriculture (USDA) Continuing Survey of Food Intake by Individuals [135]. After adjustment for possible confounders, eating frequency was shown to be positively associated with energy intake and BMI. However, their investigation was based on the use of self-reported body weight and height, plus one 24-hour dietary recall [135]. It is worth noting that self-reported body weight and height and a single 24-hour dietary recall were shown to reduce the reliability of findings [139,140].

Based on the above findings, it is important to consider methods of dietary assessment [141], presence of under-reporters of energy [142], adjustment for physical activity level, and the definition of what constitutes an eating occasion [141,143].

Studies included were based on data from FFQ, 24-hour dietary recall method and food diary records. By way of illustration, the work of Metzner *et al.* used a single 24-hour dietary recall and found an inverse association between eating frequency and markers of adiposity (using an adiposity index based on 4 skin-fold measures) in their cross-sectional study [131]. Cross-sectional studies by Burley *et al.* and Drummond *et al.* recorded similar results utilising a 4-day food diary, while Yannakoulia *et al.* found no association with the use of a 3-day food diary [125,127,144].

The validity and reliability of dietary assessment methods is important to consider in epidemiologic studies that collect data through self-reported dietary intake approaches (e.g. food record and FFQ). Under-reporting is the most common problem encountered in data collection, especially among overweight individuals [145,146] or among older

participants [147]. A review of epidemiologic studies on meal frequency and body weight from 1964 to 1997 by Bellisle *et al.* states that results may be misinterpreted due to the presence of under-reporters of energy [148]. Prospective cohort and cross-sectional studies have generally found that respondents with a higher level of education and intrinsic motivation tend to provide more reliable data on energy intake and are less likely to under-report their intake [149-151]. Furthermore, female participants generally show a higher degree of under-reporting compared to male participants [150,152-154]. The association between under-reporting and BMI may be largely dependent on the method of dietary assessment [154-156]. When comparing dietary assessment methods, De Vries *et al.* found that food records have higher precision in reflecting actual intake compared to other methods [152]. A number of studies have suggested that the use of multiple 24-hour dietary recalls tends to be more representative of typical intake than the use of both FFQs and 24-hour dietary records, and can minimise the effect of random error caused by day to day variability in intake [157,158].

In longitudinal studies investigating the influence of meal frequency on body weight there may also be an issue of "reverse causality", in which people tend to skip meals in hopes of losing weight. This could result in a lower meal frequency being associated with over-weight, therefore potentially altering the results. It is therefore important to consider both the method of dietary assessment and the presence of under-reporters in order to minimise the potential of error in interpreting findings [142,148].

Another confounding factor in the association between eating frequency and BMI is physical activity [148,159]. Duval *et al.* used a 7-day food diary in their prospective cohort study to measure dietary intake. Results showed that eating frequency was inversely correlated with BMI, waist circumference, and fat mass. However, once adjustments had been made for physical activity and oxygen consumption the relationship between

eating frequency and adiposity was no longer significant. This suggests that those with higher eating frequency also had greater physical activity, and that physical activity is therefore potentially a confounder that should be adjusted for in regression models examining the association between eating frequency and BMI [159].

Finally, an important major factor to consider in studies of meal frequency is the absence of a common definition of what constitutes an eating occasion [118,148,160]. This issue has been addressed in a number of critical reviews [123,161,162]. These reviews explain that as definitions are often notably different, it can be difficult to compare results of studies on meal frequency [123], and to generalize findings [143]. This means that a common, consistent definition is required in order for the association between eating frequency and health to be objectively studied [141,162].

1.4. Dietary energy density

Dietary energy density is a relatively new concept that can be utilised for BP level control and body weight reduction [163]. Dietary energy density is defined as energy of food and/or beverage divided by the weight of food and/or beverage (kcal/gram). This value is affected by a number of nutrients, such as fibre, water and the fat content of food [164]. This is because fibre and water provide a considerable amount of weight but little or no energy, and so are low in dietary energy density. In contrast, fat has an increased amount of energy per gram, and is therefore high in dietary energy density. There are several methods for the calculation of dietary energy density, for example; excluding all beverages and using food only, excluding energy-containing-beverages and using food and non-caloric beverages, and using all foods and beverages [165]. In 2010, the Dietary Guidelines Advisory committee published a systematic review acknowledging the association between dietary energy density and body weight, and

concluded that low dietary energy density is strongly associated with body weight loss and maintenance in adults [166]. The review also concluded that cohort studies including children and adolescents support the hypothesis that dietary energy density is positively associated with adiposity [166].

The association between dietary energy density and total energy intake in feeding trials shows that the consumption of low dietary energy density leads to overall reduction in energy intake and increased satiety among adults [167,168]. With the available evidence over the years supporting low dietary energy density intake or low fat intake, the food industry responded with the production of low fat meals and foods [169,170]. Despite this approach, the average population energy intake and prevalence of obesity has increased in Western population in the last decade [171]. It may be that some foods that are marketed as low in fat are actually high in dietary energy density [172]. Evidence suggests that total energy intake is less when people are provided with low energy density foods compared to similar foods with high energy density [167,173-178]. A few intervention trials have compared energy intake between high fat foods that are energy dense and high fat foods that are low in energy density [179,180]. Results show that high fat foods, which are energy dense, promote overall energy intake. It was therefore concluded that dietary energy density is the major factor in energy intake in Western diets. The extensive work of Drewnowski on energy density of food supports the above conclusion, focusing on the fact that "Energy density as opposed to the macronutrient content of foods, is currently thought to be the key factor in the regulation of food intake" [181]. This suggests that changes in dietary energy density are the main determinants of energy intake.

1.4.1. Dietary energy density and blood pressure

Intervention and cohort studies on the relationship between dietary energy density and BP are limited [182]. Ledikwe *et al.* was the first to assess the influence of dietary energy density changes on BP. Data were analysed from the PREMIER study, a multicentre randomised trial investigating the effects of 3 interventions to reduce BP in participants with pre-hypertension and hypertension in 6 months [183]. Participants were assigned to either: an established group educated on weight loss, sodium reduction, and physical activity; an established plus DASH-diet educated group; and the advice group educated once on these topics. Participants assigned to the established plus DASH-diet educated group had the greatest dietary energy density reduction and the greatest increase in the weight of food consumed. Participants in the highest tertile (i.e., largest dietary energy density reduction) had greater weight loss (5.9 kg) than those in the middle (4.0 kg) or lowest (2.4 kg) tertile.[183]. A cross-sectional study assessed the relationship between dietary energy density and the metabolic syndrome in 489 Iranian female teachers using a single FFQ [184]. No significant difference was observed in systolic and diastolic BP across quartiles of dietary energy density. Those in the highest quartile of dietary energy density showed higher levels of serum TAG, total cholesterol and LDL-C and lower levels of serum HDL-C compared to those in the lowest quartile. It is worth noting that a single use of FFQ may be considered a limitation, in addition of including a sample of highly educated women [184]. A Japanese cross-sectional study examined the association between dietary energy density and the metabolic syndrome [185]. A total of 1136 female dietetic students aged 18-22 years were provided with a self-administered diet history questionnaire. No significant association between dietary energy density and BP was found [185]. Findings may be biased by sample characteristic (young

dietetics) with an average BMI level of 21.3 kg/m^2, making it difficult to observe differences in BP levels.

1.4.2. Dietary energy density and body weight

In review of the available literature, RCTs have examined the association between dietary energy density and body weight reduction in particular [186-190]. The majority of trials concluded that low dietary energy density contributes to body weight loss [186,188,190,191] with the exception of two RCTs reporting no change in body weight loss with low dietary energy density [187,192].

A USA trial by Ello-Martin *et al.* compared two body weight reduction diets, one of low fat content and the other of low fat content in addition to low energy density foods, such as fruit and vegetables [190]. After one year, the group assigned to the low fat and low energy density diet showed more body weight loss and reported higher satiety level than the group assigned to the low fat diet only (−7.9, *SD*=0.9 kg *vs.* −6.4, *SD*=0.9 kg; $p<0.01$) [190]. A randomised trial by Rolls *et al.* compared body weight loss among participants instructed to consume an energy restricted diet that was supplemented with one or two portions of low energy density soup, two portions of high energy density snacks, or no particular food group (control). After one year, those consuming two portions of soup had greater body weight loss (7.2, *SD*=0.9 kg) than those consuming two portions of high energy density snacks (4.8, *SD*=0.7 kg, $p=0.03$) [188].

However, a few trials comparing low and high dietary energy density intake do not support the above findings [187,192]. Lowe *et al.* reported no significant difference in body weight loss during weight maintenance period for those participants following reduced dietary energy density intake when compared to intervention groups [187]. Song *et al.* also reported that comparisons of a group following a low dietary energy density plus

exercise against a group following a high dietary energy density plus exercise showed no significant difference in body weight loss [192].

In cohort studies, the main outcomes on the association between dietary energy density and body weight included: changes in body weight or BMI [193-196]; maintenance of body weight [183,197,198]; or changes in waist circumference [199,200]. The Nurses' Health Study (NHSII), a prospective cohort study of 116671 female USA nurses, examined the long-term effect of dietary energy density on body weight gain [193]. A total of 50026 women were followed up for 8 years; dietary energy density was assessed at 3 time points with 4-year intervals. Results show that in a multivariate adjusted model, those in the highest quintile of increases in dietary energy density had significantly higher average body weight gain than those in the lowest quintile of dietary energy density (quintile 5, 3.94, *SE*=0.06 kg *vs.* quintile 1, 2.80, *SE*=0.06 kg, $p<0.001$). Overweight and obese participants showed a stronger positive association between changes in dietary energy density and body weight increase when compared to normal weight participants [193]. Similar results were found in other cohort studies, such as the work of Savage *et al.* including 186 USA women [195]. Using three telephoned 24-hour recalls, body weight gain and increases in BMI over 6 years were positively associated with dietary energy density, with no changes in dietary energy density being recorded over time for each participant. Body weight gain was highest for those in the highest tertile of dietary energy density (6.4, *SE*=6.5 kg) compared to those in the lowest tertile (2.5, *SE*=6.8 kg, $p<0.01$). Those consuming low dietary energy density had a generally higher intake of vegetables, fruit, and cereal, with less fried vegetables and baked goods [195].

Fewer prospective studies have investigated the association between dietary energy density and waist circumference. Analyses of data from the EPIC study (n=89432 men and women) showed annual body weight change was not significantly associated with

dietary energy density over 6.5 years, however dietary energy density was significantly and directly associated with waist circumference change (0.1, 95% CI: 0.01, 0.18 cm/year) [199].

A cross-sectional analyses (n=7356) of data from the 1994–1996 Continuing Survey of Food Intakes by Individuals—a 2-day survey conducted by the USDA investigated the association between dietary energy density and total energy intake, weight of food, and body weight [201]. Results show that a diet with low energy density is associated with lower total energy intake than with high energy density diets (≈425 and 275 kcal/day less, in men and women). Further analyses into food choices showed that those with the lowest dietary energy density had the highest fruit and vegetable intake (>9 servings/day) (p<0.05). The study concluded that the consumption of a diet with low energy density is associated with higher food weight (≈400 and 300 g/day more, in men and women), thus a more profound feeling of fullness [201]. This was supported by the work of Rolls; low energy density foods such as fruits, vegetables, and grains result in the consumption of a greater weight of food relative to total energy, which may lead to a feeling of fullness and thereby prevents overeating [202].

The above RCT, prospective, and cross-sectional studies support a strong association between dietary energy density and body weight. The mechanism behind this association has not been thoroughly investigated; however a leading hypothesis is that the enhanced satiety level of low energy density diets leads to lower overall energy intake [167,168]. A recent RCT suggests that lower dietary energy density is related to a decrease of the hunger-stimulating hormone, ghrelin, and an increase in peptide YY (PYY), a satiety hormone [203]. Another proposed mechanism is that people tend to consume a consistent weight of food [179,204,205], therefore low energy density food choices may reduce overall energy intake [168,206].

1.5. Nutrient density

Obesity has been associated with high fat and sugar intake and low vitamin and mineral intake [207,208]. In previous reports, the 2005 Dietary Guidelines Advisory called attention to the low intakes of many nutrients among USA adults. These include fibre, vitamins A and C, calcium, magnesium, and potassium [209]. An updated 2010 Dietary Guidelines Advisory report stated that Americans are consuming excess amounts of sodium, fat, added sugars, and refined grains. The 2010 report emphasized on encouraging the consumption of nutrient-dense foods and limiting the intake of sodium, fat, added sugars, and refined grains [117].

The term "poor diet quality" was often used to describe diets that are high in energy density and low in nutrient density, which therefore result in adiposity [85]. As a result of this, the incorporation of nutrient rich foods into the diet is necessary to augment diet quality, i.e. improve nutrient density [210]. Early efforts to define nutrient density suggested ranking the nutrient content of food with words like fair, adequate, good, or excellent based on the recommended dietary allowance (RDA) [211]. In 2005, the Dietary Guidelines Advisory and the USDA MyPyramid distinguished between energy dense and nutrient dense foods in an attempt to help consumers make nutrient-rich food choices without surpassing the recommended daily energy intake [209,212]. The USA Food and Drug Administration (FDA) define healthy food as that which contains sufficient amounts of protein, fibre, vitamins A and C, calcium, and iron [213]. Because of different forms of interpretation, a unified definition of nutrient density is currently unavailable and was not made clear in the 2005 or 2010 Dietary Guidelines Advisory. A nutrient-rich diet may be described as having "more" of the recommended nutrients as opposed to calorie content [209,214].

The concept of nutrient profiling describes the attempt to compute the percentage of suggested intakes of selected nutrients in foods with respect to the energy provided by that food [215]. Scores are appointed to each food item in order to provide an overall assessment of its nutrient quality. Ranking of scores according to key nutrients is then applied [215]. Some model algorithms include selected "recommended" nutrients like vitamins and minerals, or nutrients to limit like fat and sugar, or both [216-218]. A positive score is appointed to selected nutrients in a food, depending on the percentage of daily values available. The sum of nutrients to limit is subtracted from recommended nutrients, if the appointed algorithm includes both indexes [219]. Recently, the Nutrient Rich Food index score has been promoted as a comprehensive, simple tool for use by the general public to make sound decisions about the food they choose. The Nutrient Rich Food approach is unique because of its applicability to individual food items, and to the diet as a whole. This means that it can be used as a guide to nutritious food rather than a rating or numbering method [219]. The selection of nutrients included in the Nutrient Rich Food index score was based on the 2005 Dietary Guidelines Advisory, which reported a low intake of specific nutrients among adults and children [209], selection of nutrients to be limited is based on the guidelines of the FDA and the regulations of the European Union [213]. The family of Nutrient Rich Food scores has evolved gradually. At first, there was the nutrient rich sub-score which included desirable nutrients that ranged from 6 to 15 nutrients [215,220]. The nutrient rich model included the 6 nutrients to encourage as per FDA recommendations (protein, fibre, vitamins A and C, calcium, and iron). With consideration to the Dietary Guidelines Advisory report, the nutrient rich model was revised to include 3 additional nutrients (vitamin E, magnesium, and potassium). Next, the nutrient rich model included 2 more nutrients (vitamin B12, and zinc). Models for undesirable nutrients or nutrients to limit

score include (saturated fat, added sugar and sodium), and (total fat, total sugar, and sodium) [221]. Percent daily values are computed based on the amount of food and are then capped at 100% to avoid disproportionate values [215]. The maximum values for daily intake of saturated fat, total sugar, added sugar and sodium are used as reference in a 2000 kcal diet (20 g, 125 g, 50 g, and 2400 mg, respectively) [221]. The Nutrient Rich Food score algorithm is based on either 100 g or 100 kcal of food [221,222].

Other indexes for diet quality are available, for example, the Australian Nutritious Food Index [223], the Ratio of Recommended to Restricted food components [224], the Diet Quality Index which is based on the percentage of dietary recommendations met [225], and the Healthy Eating Index. The Healthy Eating Index is a measure of diet quality in compliance with the 2005 Dietary Guidelines Advisory and MyPyramid including (saturated fat intake, total fat intake, cholesterol intake, sodium intake, grain intake, fruit intake, dairy intake, meat intake, vegetable intake, and dietary variety) [209]. It uses a scale of a maximum of 100-points with awards points to classify nutrients and foods as being adequately or moderately consumed. Following extensive analyses, the Healthy Eating Index score has been validated and established as a measure of diet quality [226,227]. A limitation of the Healthy Eating Index score method is that it does not distinguish between whole and processed grains; it is also mostly useful for retrospective analyses of diet quality and identifying changes over time.

It is essential to objectively consider the validation of the chosen method and the main nutrients included in the algorithm [214]. For the current study, the Nutrient Rich Food 9.3 index score is used. The Nutrient Rich Food 9.3 index score has been validated against the Healthy Eating Index score [228]. The validity of the Nutrient Rich Food family score was tested using data from the NHANES 1999-2002. The Nutrient Rich Food scores were significantly related to the Healthy Eating Index score, with the strongest

correlation between the Nutrient Rich Food 9.3 index score and the Healthy Eating Index score (r=0.5) compared to other Nutrient Rich Food family scores [228].

1.5.1. Nutrient density and blood pressure

Review of the available literature indicates that observational and experimental studies exploring the association between nutrient density and BP are limited [229]. A retrospective case series pilot study explored the effectiveness of a high nutrient density diet on glycaemic control and risk factors of CVD, including BP [230]. The high nutrient density diet was rich in micronutrients from fruits, vegetables, nuts, beans, and legumes rich in fibre. The small study sample included 13 women with type II DM from the USA aged 30-80 years. After 7 months on the high nutrient density diet plan, both systolic and diastolic BP dropped significantly by 18% and 15.2%, respectively, compared to pre-intervention levels (p=0.0004 and p=0.01). This study, however, did not explain method and frequency of BP measurement and did not clarify the amount of total energy for the specified diets, all of which are considered limitations [230]. A recent cross-sectional study in Iran on 9568 men and women explored the association between the Healthy Eating Index score and CVD risk factors [231]. Across quintiles of the Healthy Eating Index score, women in the highest quintile had lower systolic BP compared to the lowest quintile (quintile 1: 112.7, *SD*=20.2 *vs.* quintile 5: 110.6, *SD*=19.5 mm Hg; p=0.001). A limitation of this study is using a single FFQ with only 48 food items [231]. A cross-sectional analysis of the NHANES 2001–2008 investigated the association between the Healthy Eating Index score and CVD risk factors in 18,988 adults [232]. A single 24-hour dietary recall was used, and the averages of 3 to 4 BP readings were utilized. Across quartiles of the Healthy Eating Index score, average adjusted BMI and diastolic BP were significantly lower in the highest quartile compared to the lowest (p<0.0001 and p=0.0002), while systolic BP showed no

significance (p=0.08). It worth noting that under-reporting may be an issue in this sample, especially among obese and overweight participants. Another limitation is that a single 24-hour recall was used for dietary analyses [232]. The Coronary Artery Risk Development in Young Adults (CARDIA) study, a multi-centre population based cohort of the change in CVD risk factors over 10 years, study examined the relation between Diet Quality Index and CVD risk factors prospectively in 5115 black and white young adults from the USA. With the use of 3 diet history questionnaires, participants in the highest quartile of the Diet Quality Index had less increases in systolic and diastolic BP (estimated 13 year change) (p=0.03 and p=0.01) [233].

1.5.2. Nutrient density and body weight

Studies investigating the association between diet quality and BMI have been generally focused on dietary patterns [234,235]. Currently, only one study has investigated the association between the Nutrient Rich Food 9.3 index score and BMI, as well as total energy intake [236]. This was a cross-sectional sample from the Rotterdam study, a cohort of 7983 Dutch adults, using a semi-quantitative FFQ. Results show that those in the highest quintile of the Nutrient Rich Food 9.3 index score had the lowest total energy intake (1631, *SE*=372 kcal) compared to those in the lowest quintile of the Nutrient Rich Food 9.3 index score (2289, *SE*=550 kcal) [236].

Other studies have examined the relationship between other available measures of diet quality, e.g., the Healthy Eating Index score and BMI [229,237,238]. The work of Tande *et al.* explored the association between the Healthy Eating Index score and obesity using data from the third NHANES in 15658 USA adults [237]. In their analyses of a single 24-hour dietary recall, each 10 unit increase in total Healthy Eating Index score was associated with 8.3% (95% CI: 1.8, 14.9%, p<0.05) lower abdominal obesity waist

circumference in women and 14.5% lower in men (95% CI: 6.8, 21.9 %, p<0.001). Abdominal obesity waist circumference is defined as ≥ 102 cm for men and ≥ 88 cm for women. A higher Healthy Eating Index score was shown to be associated with lower risk of abdominal obesity [237].

Studies using dietary pattern analyses explored the association between healthy pattern and BMI or waist circumference. For example, the on-going Baltimore longitudinal study of aging, a prospective study in 459 adults, used cluster analyses to obtain 5 dietary patterns [234]. Participants in the healthy eating cluster (rich in fruit, vegetables, reduced-fat dairy, and whole grains and low in red and processed meat, fast food, and soda) had less annual increases in BMI (0.05, SE=0.06 kg/m^2) compared to participants in the meat-and-potatoes cluster (0.30, SE=0.06 kg/m^2, p<0.01). Those in the healthy cluster were also found to have smaller annual change in waist circumference (0.43, SE=0.27 cm) in comparison to those in the white bread cluster (1.32, SE=0.29 cm, p<0.05) [234].

1.6. Time of meals and blood pressure, body weight

1.6.1. Studies on shift work

Prospective cohort and cross-sectional studies on shift workers provide evidence that time of energy intake may be associated with health [175,239-242]. Shift work is defined as work after the usual 8-hour daytime. It may disrupt the diurnal biological rhythm and affect dietary behaviour [243]. A number of epidemiologic studies found direct associations between night shift work and the risk of developing CVD [240,244]. A meta-analyses of prospective cohort and cross-sectional studies suggests that shift workers are at 1.4 relative risk of developing CVD compared to regular day workers [239]. A cross-sectional study in France divided 2610 white-collar workers into 3 types of shift

and day work to examine the relationship between shift work and cardiovascular risk factors [245]. In univariate analyses, systolic BP was higher (132.7, *SE*=17.4 mm Hg) among the 3 categories of shift workers compared to day workers (126.9, *SE*=15.1 mm Hg, $p<0.05$). Night workers also had higher plasma TG (1.6, *SE*=0.8 g/L) compared to day workers (1.3, *SE*=0.8 g/L). The adjusted risk of hypertension was also twice the number of times higher in night workers compared to day workers (OR: 2.1, 95% CI: 1.4, 3.2) [245]. Epidemiologic studies reporting no association between shift work and CVD may potentially be attributed to differences in definitions of shift-work [246,247].

Intervention studies found that the adoption of a better shift schedule was associated with improved biomarkers of heart disease (LDL, HDL) [248], while night shift work was typically associated with body weight gain and the worsening of cardiovascular parameters [249]. Morgan *et al.* studied the effects of time of meal intake and carbohydrate quality on glucose control and insulin secretion through the use of four different types of diets [250]. In their cross-over design, participants were randomly assigned to: a low glycaemic index (GI) diet with the majority of the energy consumed in the morning; a low GI diet with the majority of the energy consumed in the evening; a high GI diet with the majority of the energy consumed in the morning; and a high GI diet with the majority of the energy consumed in the evening. Results show that when a higher GI diet was consumed during the evening, a higher level of glucose response and lower insulin sensitivity were observed compared to the other 3 diets ($p<0.05$) [250].

The association between BMI and shift work was investigated in a cross-sectional study of 319 men aged 35-60 years randomly selected from a production company in Italy [251]. Shift workers had a rotating schedule (working 2 nights, 2 afternoons, and 2 mornings with 3 days of rest), while day-workers only worked during daytime. Of the total sample, 74% of obese were shift workers ($p<0.05$), in models adjusted for known

confounders [251]. The Nurses and Midwives' e-cohort study (NMeS), a longitudinal population-based study, examined factors associated with health outcomes in nurses and midwives of Australia, New Zealand, and the UK. A cross-sectional analyses of NMeS compared 1259 day and 1235 night workers and showed that night workers had a higher prevalence of overweight and obesity (1.15 times) compared to day workers (95% CI: 1.03, 1.28, p=0.01; 95% CI: 1.02, 1.30, p=0.02, respectively), using adjusted BMI measures [252]. A cohort study in Japan investigated changes in parameters related to metabolic disturbances by dividing 1529 factory workers into 4 categories followed up for 10 years: daytime workers (day–day), those who switched from shift work to daytime work (shift–day), those who switched from daytime work to shift work (day–shift), and those doing shift work only (shift–shift) [253]. For day–shift workers, age adjusted average BMI increase was 1.0 kg/m^2, significantly higher than day-day and shift-day workers. For those in the shift-shift and day–shift group, increase in cholesterol was higher compared to other groups but not significant [253].

The adverse health effects associated with night work may be attributed to meal intake late in the night that may cause changes in glucose tolerance and insulin response, including reduction in insulin sensitivity later in the day and increased glucose production in night shift workers [254-256]. An increase in TAG level observed in night shift workers suggests insulin resistance [257]. Night shifts were associated with a decrease in non-essential fatty acids (NEFA) levels in plasma, which require a longer time to return to basal level compared to day-shifts. Plasma NEFA results from the breakdown of TAG in adipose tissue by lipase. Therefore, as lipase is inhibited by insulin, low NEFA levels coincide with high postprandial insulin in night shift workers [257]. Elevated TAG level is also an independent risk factor for CVD [258]. With disruption of the circadian rhythm associated with night work, degree of stress is also

elevated [259]. Sleep deprivation associated with shift work may alter the endocrine leading to a disruption in carbohydrate metabolism [260]. Poor dietary habits are also associated with night work. A cross-sectional sample of nurses aged 25-63 reported their preference for fast food and food high in sugar due to ease of access compared to healthy meals [261]. Spiegel *et al.* also reported that night shift workers tend to feel hungry and consume foods that are energy-dense and rich in carbohydrates compared to daytime workers, with adjustment for total energy intake ($p<0.05$) [262]. Lack of exercise and engagement in physical activity are also common behaviours among night shift workers [263,264].

1.7. Glycaemic index, glycaemic load, and dietary fibre

Introduction

Given that dietary fibre is a major determinant of dietary energy density [205], the role of GI, GL and dietary fibre in relation to BP and BMI is explored.

The World Health Organisation (WHO) and the Food and Agriculture Organization of the United Nations (FAO) classified carbohydrates based on the degree of polymerization (DP), i.e., the number of linked saccharide units. Sugars (monosaccharaides, disaccharides) have a DP of 1-2, while oligosaccharides (Malto-oligosaccharides [x-glucans]) and polysaccharides (starch and non-starch) have a DP of 3-9, and 9 or above, respectively [265].

Sugars, in general, can improve the texture and viscosity of food, and are thus used in baked goods to improve dough yield and to prevent the finished products from drying out. Monosaccharaides including glucose, fructose and galactose are considered a single saccharide unit, which is the building block of disaccharides. Both glucose and fructose can be found in honey and fruit, especially berries, and can be used for food

preservation and as sweeteners, the latter is also found in vegetables [266]. Galactose, on the other hand, is primarily found in cultured dairy products, with minimal amounts identified in specific fruits and vegetables (apples, bananas, onions, and tomatoes) [266]. The other class of sugars—disaccharides—includes lactose, maltose, and sucrose, all of which contain two saccharide units [267]. Lactose can be found in dairy products, maltose in barley and wheat, and sucrose is the most widely used type of sugar, due to its natural presence in most fruits and vegetables and its prevalence in processed foods [268]. Finally, starch, a mixture of amylose and amylopectin, is found in cereals, legumes, and root vegetables [269].

In terms of digestion, carbohydrates can be divided into available carbohydrates (e.g., glucose, fructose, lactose, etc.) and resistant carbohydrates (e.g., dietary fibre and starch). The name "available" or "glycaemic" carbohydrates stems from the fact that these are easily absorbed in the small intestine [270], whereas resistant carbohydrates, or non-glycaemic carbohydrates, are not [271]. Dietary fibre is most resistant and cannot be hydrolysed in the small bowel. Instead, its total or partial fermentation, if present, takes place in the colon. Consequently, dietary fibre acts as a bulking agent, both directly and through the water it absorbs. If fermentation occurs, it is achieved by micro flora in the colon, thus stimulating its growth and contributing to faecal bulk. Following fermentation, dietary fibre is metabolized to hydrogen, methane, carbon dioxide, and short-chain fatty acids (SCFAs), which are further digested in the colonocytes. The energy released by the fermented but non-digestible carbohydrates is estimated at 1.5-2 kcal/g, while the unfermented and non-digestible carbohydrates have no caloric value [272].

The amount and type of carbohydrate is important to consider in relation to insulin response and postprandial glycaemia. Given today's excessive intake of refined sugar

[273,274], combined with the dietary fibre intake at its lowest point since the 1970s [275], it is essential to develop cost-effective strategies that can be implemented to modify dietary choices and behaviours. Such efforts would play a significant role in management and prevention of many diseases.

Glycaemic index and glycaemic load

The term 'glycaemic index' was first introduced by Jenkins *et al*. [276], who classified carbohydrates based on the glycaemic response following a meal. In this context, GI applies to foods rich in available carbohydrates (e.g., rice, potatoes). Foods that have a low glycaemic response and are digested and absorbed slowly have low GI, whereas high GI foods have a high glycaemic response and are absorbed more rapidly [277]. In their study involving 16 participants, Crapo *et al*.[278] tested the hypothesis that 'simple' sugars are absorbed more rapidly than 'complex' carbohydrates. The authors assessed the effects of dextrose, rice, potato, corn, and bread on post-meal glucose and insulin responses using a 50 g test load of glucose. Their findings revealed that glucose and potato produced higher glucose responses (peaking at 136 and 138 mg/100 ml, respectively), compared to rice and bread (with their respective peaks of 119 and 122 mg/100 ml, $p<0.01$, 0.05). This was in contrast to the previously reported hypothesis that the speed of carbohydrate absorption is solely determined by the degree of polymerisation. Jenkins *et al.* first conducted their trial on a sample of 5-10 healthy individuals [276]. In this study, the participants were given glucose tolerance tests, whereby their blood glucose was measured at 15-minute intervals during the first hour, and every 30 minutes thereafter. Glucose response was identified as the percentage of the incremental area under the blood glucose response curve (AUC) resulting from the ingestion of equal amounts of carbohydrates as glucose [276].

The importance of GI and its relation to various health issues has since been recognised by the FAO and WHO [265], the European Association for the Study of Diabetes [279], and Diabetes UK [280], among other important organisations supporting the hypothesis that a low GI diet contributes to better glycaemic control in diabetics. Evidence suggests that the rate of glucose absorption and the length of time blood glucose remains high may adversely affect health through stimulation of hormonal and metabolic changes, both of which play an important role in the development of these chronic diseases [277]. However, knowledge about the relation of GI to health is still limited, and there is a need to standardise the GI values found in various foods as well as recommended daily allowances for different populations.

As previously noted, GI is defined as the incremental AUC after the intake of a specific amount of carbohydrate. After consuming 50 g of available carbohydrates, blood glucose levels increase and are measured over the period of two hours, after which the values are expressed as a percent of the glucose response. More specifically, to obtain the GI of the test food, its AUC is divided by the AUC of a standard reference food (glucose or bread). According to this classification, high GI foods have a value of 70 or above, whereas low GI foods have a value of 55 or less. Wolever *et al.* expanded this classification to include the "GI of meals", which is helpful for assessing the GI intake after consuming a variety of foods with different carbohydrate content. This composite GI is calculated by determining the average GI value of all constituent food items, weighted by the available carbohydrates provided by each food, using the following calculation:

$$\text{Meal GI} = \sum_{i=1}^{n} \text{GI}i \times \text{CHO}i \div \sum_{i=1}^{n} \text{CHO}i$$

Where GIi is the GI for the food i, CHOi is the amount of carbohydrate provided by food i (g/day), and n is the number of food items consumed [281]. When calculating the final GI of the meal, other contributing factors that may influence absorption and affect the GI were considered, such as grinding, degree of ripening, heat treatment, added acids, etc. [282].

Another term associated with GI and dietary intake is glycaemic load (GL), which is calculated by multiplying the GI of a specific food by the amount of available carbohydrates in that food. It is differentiated from GI, which only describes the quality, but not the quantity of carbohydrates [277]. Some foods, such as carrots, have a high GI but a low GL (GI=35, GL=2), as they contain only a small percentage of carbohydrates (6 g per recommended serving of 80 g).

1.7.1. Glycaemic index, glycaemic load and blood pressure

A low GI, GL diet has been linked to improved blood lipids and insulin sensitivity, and can result in the modification of BP levels [283,284]. However, research in this field is limited, leaving the association between GI, GL and BP insufficiently explored.

Recently, the relation between GI, GL and CHD was assessed in a meta-analysis of eight prospective studies conducted from 2000 to 2011, involving 220,050 patients in total [285,286-293]. The reported findings indicated that the risk of CHD was significantly associated with GI; pooled relative risk was 0.99 (95% CI: 0.84, 1.16) in women [286,287,290,292] and 1.26 (95% CI: 1.12, 1.43) in men [287,288,291-293]. For GL, the relative risk was 1.69 (95% CI: 1.32, 2.16) in women [287,290,292], whereas no association between GL and CHD incidence was detected in men (relative risk= 1.08, 95% CI: 0.92, 1.27) [287,288,291-293]. Similarly, another meta-analysis including prospective studies conducted in the period ending in 2011 assessed the relationship between GI, GL and the risk of

developing CVD [294]. In fourteen reviewed studies [286,288,289,291-293,295-302], including a total of 229,213 participants, risk of CVD in the highest *vs*. the lowest quintile of GI and GL was 1.13 (95% CI: 1.04, 1.22) and 1.23 (95% CI: 1.11, 1.36), respectively. Moreover, the findings indicated that women consuming food with higher GI and GL were at a greater risk of developing CVD (GI: relative risk=1.19, 95% CI: 1.06, 1.34; GL: relative risk=1.35, 95% CI: 1.18, 1.55), than men (GI: relative risk=1.05, 95% CI: 0.94, 1.17; GL: relative risk=1.10, 95% CI: 0.95, 1.28) [294]. Thus, these results [285,294] indicate that women whose intake of high GI, GI foods is greater, especially overweight and obese women, are potentially at risk of developing CVD.

Intervention studies on the effect of low GI, GL diets on BP have produced inconsistent results, with some showing no effect [303] and others showing reductions in systolic and diastolic BP [304,305]. One of the few intervention studies is a pilot study involving 38 men with at least one CHD risk [306]. The participants were randomly assigned to two groups, receiving healthy diets, one rich in low and the other in high GI foods. After six months, the reduction in ambulatory 24-hour systolic BP was greater in the low GI diet group (M=13 mm Hg, SD=17) compared to the high GI diet group (M=3 mm Hg, SD=18, $p<0.05$) [306]. On the other hand, among men and women that took part in the PREMIER trial (n=756), the changes in GI and GL were not associated with BP at 6-month or 18-month follow-up [307].

A few observational and cross-sectional studies have investigated the association between GI, GL and BP, showing inconsistent results as well [308-310]. In the Women's Health Initiative (WHI) study, an observational study of CVD and other chronic diseases in postmenopausal women (n=878), average systolic BP from two readings was surprisingly lower in the highest quartile of GL in White women (p=0.03),

irrespective of their BMI [310]. On the other hand, a similar study involving 858 Australian adolescents, the association between GI, GL and the changes in BP level (reported as the mean of three readings) was assessed over a 5-year period. In multivariate adjusted models, dietary GI higher by 3.5 (*SD* =1) was associated with 1.81 mm Hg higher systolic BP (p=0.001) in girls aged 12 years at baseline [308]. However, the National Diet and Nutritional Survey (NDNS) involving 1152 adults revealed non-significant associations between GI and BP in a cross-sectional analysis using multivariate adjusted models [309].

The mechanism by which high GI diets affect BP level has been linked to elevated blood sugar, which can damage arterial walls by decreasing the production of nitric oxide, inducing oxidative stress, and enhancing the activity of protein kinase C [311]. In addition, hyperglycaemia may stimulate renal sodium retention, therefore elevating BP [312].

1.7.2. Glycaemic index, glycaemic load and body weight

The GI concept was first introduced to help control the glycaemic response in diabetics, and the associated benefit is well established. Because hyperinsulinemia promotes lipogenesis, a low GI, GL diet that produces low insulin response may also promote body weight loss [313]. While low GI, GL diets have recently been linked to satiety and metabolism in intervention studies, evidence supporting these benefits is inconsistent [314-317]. Thus far, 22 trials have investigated the effect of low GI, GL diets on body weight in adults, where body weight loss was the primary outcome [303,305,318-337]. The majority of these studies were based on controlled parallel designed trials. In six trials [303,318,319,321,325,335], significant differences in body weight loss were reported when low GI, GL diets were compared to either high GI, GL diets [318,325], a low fat diet

[303], or an energy restricted diet [335]. The reported body weight reductions from baseline ranged from 1 to 7 kg, $p<0.05$; with individuals participating in these trials being either overweight [325] or obese [303,318,335]. Thus, it cannot be established whether similar effects would be produced in normal-weight individuals. In contrast, 12 trials reported non-significant body weight reductions in the group that followed low GI, GL diets, compared to controls [305,322-324,326-328,330-332,334,336].

Other outcomes, including fat mass, body fat percentage, lean muscle, energy intake, and satiety, were also investigated. Several trials comparing body fat percentage in study participants following a low GI or low GL diet reported non-significant reductions compared to controls [303,305,318,320,323-327,329,331,336,337]. Despite inconsistent findings, the prevalent view is that low GI, GL diets can be beneficial in certain population samples. In a study on individuals diagnosed with high postprandial insulin levels, Ebbeling *et al.* reported significant body weight and fat percentage reductions following a low GI or low GL diet, in comparison to those who were placed on a low fat diet (5.8 kg *vs*. 1.2 kg; $p=0.004$ and 2.6% *vs*. 0.9%; $p=0.03$, respectively) [326].

The above evidence indicates that a low GI, GL diet is as effective in reducing body weight as other dietary interventions. Following a meta-analysis of 6 RCTs conducted in 2007, the authors concluded that low GI, GL diets were beneficial in reducing body weight by an average total body weight loss of 1 kg, fat mass reduction of 1 kg, and BMI decrease of 1.3 units compared to other diets ($p<0.05$) [317].

Several epidemiological studies reported inconsistent results on the association between GI, GL and body weight. For example, findings of the EURODIAB IDDM Complications Study [338]—a cross-sectional study including 3250 participants with type 1 diabetes from 31 European centres—suggest direct associations between GI and waist

to hip ratio in men (p=0.005), but not women. The findings of the Insulin Resistance Atherosclerosis Study (IRAS), a cross-sectional study, revealed significant direct associations between GL and BMI, but not GI, in models adjusted for potential confounders. However, these associations were no longer statistically significant after adjusting for total energy intake from non-carbohydrate sources [339]. More recently, results from the EPIC study indicate that a diet based on foods with GI higher by 10 units was associated with a 34 g increase in body weight (95% CI: −47, 115 g) and 0.2 cm increase in waist circumference per year. The increase in GL by 50 units was associated with a 10 g increase in body weight (95% CI: -65, 85 g) and a 0.1 cm increase in waist circumference per year [340].

Several limitations should be noted however with the above intervention trials. For example, in some of the aforementioned trials, caloric intake was not restricted to induce body weight loss [320,321,325,326]. Moreover, in a number of trials [322,332,335,336], GI and GL values of the foods included in the participants' diets were not reported, and there was no consensus on the low and/or high GI and GL. More specifically, Aston *et al.*[320] considered 55.5 a low GI, while in the study by Sloth *et al.* [336] the upper limit was set at 79. In addition, short trial duration and difficulties in adhering to treatment diets may be considered limitations in intervention studies related to body weight loss. Furthermore, the inconsistency between findings of intervention and epidemiological studies may be due to the GI values of foods. In cohort studies, the GI distribution is mostly centred at the higher level. For example, in the IRAS study [339], the median GI was 58, while this value was considered a high GI in several intervention trials [341,342]. In addition, the lowest GI value in the IRAS study was 45 [339], while it ranged between 48 and 50 in other cohort studies [343,344], all of which were significantly higher than permitted in low GI intervention diets [345-347].

Dietary fibre

The American Association of Cereal Chemists defines dietary fibre as "The edible part of plants or analogous carbohydrates that is resistant to digestion and absorption in the human small intestine, with complete or partial fermentation in the large intestine. Dietary fibre includes polysaccharides, oligosaccharides, lignin and associated plant substances. Dietary fibre promotes beneficial physiological effects including laxation, and/or blood cholesterol attenuation, and/or blood glucose attenuation" [348]. More recently, the international Codex Alimentarius Commission stated that "Dietary fibre means carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine" [349].

Dietary fibres can be divided into insoluble and soluble fibre depending upon their solubility in water. Insoluble fibre (cellulose, lignin) increases faecal bulk, thus accelerating its passage through the intestine. Dietary sources of insoluble fibre include wheat bran, vegetables, and whole grains [350]. Soluble fibre (pectin, gum) increases viscosity and turns to gel during digestion, and has lowering effects on plasma cholesterol and glycaemic response [351]. Dietary sources of soluble fibre include oat bran, barley, nuts, seeds, beans, lentils, peas, and some fruits and vegetables. Insoluble resistant starch, oligosaccharides (i.e., cellulose and hemicelluloses) and soluble fibre (i.e., pectin, inulin, and b-glucans) have a higher fermentation rate compared to cereal fibre [352]. When all parts of the kernel (i.e., bran, germ, and endosperm) are available in a food, it is considered to be whole grain. In the market, whole grain food products consist of 12% of total dietary fibre, mainly insoluble cereal, and some bran-rich products contain 25% of dietary fibre [353]. In the USA, the main source of whole grain and bran products are from corn and wheat [354]. The average American consumes about 15 g of fibre per day, which is about 50% of the fibre intake suggested by the American

Heart Association [350].

Meta-analyses of prospective cohort studies showed that higher intake of total fibre is associated with a lower risk of incident coronary events [355], stroke [356] and DM. The extensive review of available literature revealed inconclusive epidemiological evidence to the contributions of total, insoluble, and soluble fibre to BP and BMI.

1.7.3. Dietary fibre and blood pressure

Cross-sectional studies investigating the relationship between dietary total fibre intake and BP in vegetarian population samples found significant inverse associations [357-359]. Vegetarians often consume a diet that is relatively low in salt, rich in potassium, magnesium, and PUFA; therefore, it was difficult to assess the independent association between fibre intake and BP in these populations [358,359]. A number of cross-sectional studies involving the general population reported inverse associations between total fibre and BP [360-365], with some results significant for diastolic BP only [366,367], while others found no association [363,366,368,369], despite similar study design. It is worth noting that regression models used in data analyses of these studies were mainly adjusted for lifestyle confounders only [360-363,366,368], or a *limited* number of dietary confounders [363,366,368]. More recently, a cross-sectional analysis of the Prevención con Dieta Mediterránea trial (PREDIMED) —a multicentre, randomised trial including 457 men and women, indicated that systolic and diastolic BP were significantly lower in quintile 5 of total fibre intake (>31 g/day) compared to quintile 1 (<21 g/day), after adjusting for age, sex, and sample (*p for trend*=0.01 and 0.001). These findings were based on two BP readings and the use of a single FFQ [370]. In contrast, a cross-sectional analysis of the EPIC-Florence sample of 7601 participants showed no significant association

between dietary total fibre and systolic and diastolic BP. Similar to the PREDIMED, the average of two BP readings was used, and only one FFQ was analysed [368].

There have been few prospective cohort studies that found inverse relationships between total fibre intake and BP change [346], or risk of developing hypertension [364,365]. For example, in the CARDIA study, compared to the lowest quintile of fibre intake, those in the highest quintile had lower systolic and diastolic BP levels in year ten after adjusting for baseline BP and other lifestyle confounders (p=0.01, p<0.001). These results, however, were only significant for White men and women. Similar to previous cross-sectional studies, the regression models did not adjust for dietary confounders [346]. Additionally, the UK National Health Service (NHS) reported a lower relative risk of hypertension (0.76) among women with high total fibre intake (≥ 25 g/day) compared to women with low total fibre intake (<10 g/day, p=0.002). However, the association was no longer significant after further adjustment for calcium, magnesium, and potassium intake [365]. In contrast, the Health Professional's Follow-up Study (HPFS), including 30,000 male participants, found the relative risk of hypertension was 1.46 (95% CI: 1.09, 1.96) for those whose total fibre intake was < 12.0 g/day, while relative risk was lower (1.11, 95% CI: 0.94, 1.31) when the total fibre intake was greater (20.0-23.9 g/day), after adjusting for dietary potassium, magnesium, and total energy intake [364]. It is worth noting that, in both studies [364,365], BP was self-reported, and the population samples were highly selective.

With regard to types of fibre, a recent systematic review and meta-analyses of cohort studies assessed the association between risk of CVD, CHD and total, insoluble, and soluble fibre intakes [371]. Pooled estimates including 15 studies showed that, for CVD, the risk ratio was 0.91 with a 7 g/day increase in total fibre intake (95% CI: 0.87, 0.94), with similar findings reported for CHD. For insoluble fibre intake, five studies [372-376]

showed that a 7-g/day increase in insoluble fibre intake was associated with similar risk ratios for CVD and CHD (0.82, 95% CI: 0.70, 0.96). However, for soluble fibre intake, six [372-377] studies included in the meta-analyses showed non-significant associations with CHD [371]. The French SUpplementation en VItamines et Mineraux AntioXydants (SU.VI.MAX) study, an on-going randomized, double-blind, placebo-controlled, primary-prevention trial was, to the author's knowledge, the only study that investigated the relation between insoluble and soluble fibre intake and the risk of high BP [378]. Their cross-sectional analysis included 5961 men and women with at least six 24-hour dietary recalls and two BP measures. The results reported by quintiles of total, insoluble, and soluble fibre intakes showed: OR 0.71 (95% CI: 0.54, 0.93; *p* for trend=0.02) for total fibre, and 0.68 (95% CI: 0.52, 0.89; *p* for trend=0.01) for insoluble fibre, while soluble fibre showed no significant association 0.86 (95% CI: 0.68, 1.10; *p* for trend=0.10), adjusted for BMI. It is worth noting that participants were receiving daily antioxidant supplementation of vitamin C, vitamin E, β-carotene, selenium, and zinc as part of the study [378].

Based on the findings of the aforementioned epidemiologic evidence, inconsistent findings may be explained by methodological issues including the validity of dietary assessment methods [363-365,368], absent or limited adjustment for dietary and lifestyle confounders [363,366,368], inadequate frequency of BP measurements [363,368,369], or by differences in study design [379-383].

Most intervention trials investigating the effect of fibre supplementation on BP found that it had a non-significant lowering reduction on both systolic and diastolic BP. Based on a meta-analysis conducted by Streppel *et al*. of randomised placebo controlled trials from 1966 to 2003, the overall effect of fibre supplementation (average dose of 11.5 g/day) on systolic and diastolic BP was -1.13 and -1.26 mm Hg [384]. These findings also

suggest that the reduction in BP level was greater in older individuals (> 40 years) compared to younger (significant for systolic BP only), and in hypertensive participants (significant for systolic and diastolic BP) compared to normotensive [384]. Based on the same meta-analysis [384], insoluble fibre supplementation in six trials reduced systolic and diastolic BP by an average of -0.2 and -0.6 mm Hg [379,382,385-388]. Additionally, the effect of soluble fibre intake on BP was assessed in 10 trials, revealing a non-significant reduction in systolic and diastolic BP (by an average of -1.3 and -0.8 mm Hg) following soluble fibre supplementation [380,381,383,385,389-394].

Several methodological issues are also present in trials investigating the effect of insoluble, soluble fibre on BP, including small sample size, short trial period, BP not being the main outcome, inadequate methods and frequency of BP measurement, short wash-out periods in cross-over trials, and inclusion of a body weight reduction plan. Additionally, BP responses to fibre intake in these trials may also depend on its type (insoluble and soluble), dose, and if its form of consumption is as supplement or as a part of a fibre-rich diet [384].

1.7.4. Dietary fibre and body weight

The relationship between total fibre intake and body weight has been investigated in several observational studies, some of which have found inverse associations between total fibre intake and body weight or BMI [339,346,395,396]. However, some large-scale studies reported no association [397,398].

Howarth *et al*. used data from the USDA Continuing Survey of Food Intakes by Individuals (n=4539) to investigate associations between fibre intake and fat and excessive body weight gain [396]. While inverse associations between total fibre and BMI were reported in women (p=0.001), this was not the case for men (p=0.4). Although

possible under-reporters of energy intake were excluded from data analyses, the study was still subject to several limitations; notably, the use of one or two 24-hour dietary recalls and self-reported body weight and height [396]. Results from IRAS, involving 979 participants indicate that fibre intake higher by 10 g/day was associated with a 0.80 kg/m^2 lower BMI level in cross-sectional analysis, using FFQs. It is worth noting that Pearson correlation coefficients between FFQ and 24-hour dietary recalls were low (r=0.2), and differed considerably between samples and ethnic groups [339].

More recent studies have attempted to identify the relationship between consumption of specific foods high in fibre (e.g., whole grain, cereal) and health outcomes [397,399-401]. Results from the UK NHS reported inverse associations between body weight gain and whole grain intake, as well as direct associations with refined grain intakes including 74091 individuals. In a 12-year follow-up, those who had the greatest increase in total fibre intake had gained 1.5 kg less body weight compared to those who had the smallest increase in total fibre (p=0.0001), after adjusting for lifestyle and dietary confounders [402]. In contrast, Cheng *et al*. reported no association between total fibre or whole grain intake and BMI per *SD* increase in fibre and whole-grain intake (p=0.5). This prospective study included 215 adolescents, all of whom were followed-up over a 4-year period. At each visit, a 3-day food record was analysed. However, it is worth noting that, as the dietary method used was not validated against other methods, energy intake under-reporting may be a potential confounder [397].

Literature review conducted as a part of this study revealed paucity of epidemiological investigations into the link between the types of fibre and BMI. Findings of the French SU.VI.MAX cohort indicate that the highest total and insoluble fibre intakes were associated with lower risk of being overweight: quintile 5 *vs*. quintile 1, OR 0.70 (95% CI: 0.54, 0.91, p for trend=0.01) was reported for total fibre, and 0.69 (95% CI: 0.53,

0.90; *p* for trend=0.01) for insoluble fibre, while soluble fibre showed no significant association 0.96 (95% CI: 0.76, 1.22; *p* for trend=0.27). Models used in this study were adjusted for lifestyle and dietary factors, with the exception of protein intake [378].

Intervention studies have suggested that total dietary fibre is beneficial for body weight loss [379,403,404]. However, it is possible that the form of food, type and dose of fibre provided, and dietary energy density may have affected the reported results [404,405]. The effect of type of fibre included in the diet on body weight loss was noted when additions of up to 30 g/day of total fibre lead to surprisingly small reductions in body weight [403,404], which may be attributed to the different effects of types of fibre (insoluble and soluble) [404]. In a randomised crossover trial, lasting 4 weeks, with a 2-week washout period, Rave *et al*. examined the effect of a calorie-restricted whole grain cereal diet on body weight of their participants, all of whom were obese [406]. The sample was randomly split into two groups, a nutrient-dense meal replacement product or a whole-grain based dietary product. Body weight decreased in both treatment groups, (22.5, *SD*=2.0 *vs*. 23.2, *SD*=1.6 kg, with no significant difference between the two treatments, except for an improvement in insulin sensitivity in the whole grain cereal diet. These findings were attributed by the authors to the short trial period. In addition, it is likely that the participants may have under-reported their intake of other foods eaten at home [406]. Melanson *et al*. conducted a controlled trial over a period of 24 weeks, where participants were randomly assigned to two groups, and received either a diet rich in whole-grain cereal, or a conventional low calorie, low cereal diet [407]. The diet prescribed to the first group consisted of two meals of whole-grain cereal for 12 weeks, which was reduced to one meal during the remaining 12 weeks. Their food intake was assessed via 3-day food records. The authors reported no difference in body weight loss achieved by the two groups. This may be explained by the fact that, in the

second 12-week period, the participants in the treatment group reduced their fibre intake to 21 g/day, a value close to that received by the conventional group (17 g/day) [407]. A similar trial found no difference in body weight reduction when obese adults were asked to follow either a diet rich in whole grains, or a diet that excluded whole grains for 12 weeks. The whole grain diet group, however, had lower body fat percentage (p=0.001) and 38% lower high-sensitivity C-reactive protein compared to controls, independent of body weight loss [401].

Hypotheses and Objectives

The following hypotheses are tested: 1. There is an inverse association between frequency of daily eating occasions and BP and BMI of the UK and the USA INTERMAP study participants. 2. Dietary energy density is directly associated with BP and BMI, while nutrient density is inversely associated with BP and BMI. 3. Higher evening relative to morning energy intake is directly associated with BP and BMI. 3. Higher GI and GL are directly associated with BP and BMI. 4. Dietary fibre intake, including insoluble and soluble fibre, is inversely associated with BP and BMI. 5. A diet low in GI, GL and high in dietary fibre is associated with lower BP and BMI.

The objectives of this thesis are to: 1. Examine the associations of daily eating occasions, dietary energy density, and nutrient density with BP and BMI. 2. Explore the impact of time of energy intake on BP and BMI. 3. Investigate the associations of GI, GL to BP and BMI. 3. Determine relations to BP and BMI of total dietary fibre and its individual-components (insoluble and soluble fibre).

CHAPTER II

Methods

2. METHODS

The INTERnational study on MAcro/micronutrients and blood Pressure (INTERMAP) is a cross-sectional epidemiologic investigation on associations between dietary factors and BP in middle-aged and older adults. There are several publications using the INTERMAP data investigating different dietary and non-dietary aspects and BP [408-414]

2.1. INTERMAP methods

2.1.1. Study design

The INTERMAP study surveyed 4680 men and women ages 40-59 years from 17 population samples in four countries (Japan, the People's Republic of China, the UK, and the USA) [415]. The study protocol was established in two International Coordinating Centres (ICC) led by principal investigators (Jeremiah Stamler, Chicago, USA; Paul Elliott, London, UK). The principal investigators developed the study design, data collection, and analyses of data. Protocols for nutrition data processing were established by two USA centres: the International Nutrition Coordinator and the Nutrition Coordinating Centre. The study sample was chosen assuming a power of 90% that would detect a correlation of 0.06 between a nutrient and BP with alpha=0.01 [415].

2.1.2. Study sample

Study samples were recruited randomly from community and workforce populations[415]. Age and gender stratifications of participants were applied to ensure that equal numbers of persons were obtained in each group (four 10 year age and gender categories). Recruiting staff was trained in the appropriate data collection and processing protocols, as per the *Manuals of Operations*. All staff was certified in study methods. A total of 110 participants were excluded: either they did not attend all four clinic visits (5

people), their dietary interviews were declared as unreliable by the interviewing dietician and site nutritionist (7 people), their total dietary intake was less than 500 kcal/24-hours or more than 5000 kcal/24-hours (37 people), their two 24-hour urine collections were not available (37 people), or missing or incomplete data (24 people). For every participant that was excluded, a replacement was made from the same age and/or sex group. For this thesis, further exclusion was done of possible under-reporter's of energy (explained in section 2.1.5), therefore, a total of 2385 participants were included from two population samples in the UK and eight population samples in the USA. Country specific metabolic phenotype of the INTERMAP study had been investigated using Proton Nuclear Magnetic Resonance (^{1}H NMR) spectroscopy [416]. This approach aimed to objectively identify metabonomic profiles that discriminate across populations. Hierarchical cluster analysis of NMR spectra showed urinary metabolite excretion patterns of e.g., alanine, formate, hippurate and *N*-methylnicotinate to be similar for Western samples, suggesting participants from the UK and the USA had similar dietary intakes [416].

2.1.3. Clinic visits

A total of four visits were documented for each participant. Two visits were on consecutive days, with the following two visits occurring 2-3 weeks later. Whenever possible, the visits were scheduled at the convenience of participants. On each of the four visits, BP was measured twice. Twenty-four hour dietary recall was performed once on each visit. Collection of 24-hour urine was performed on visit 1 and completed on visit 2; the second collection was on visit 3 and completed on visit 4. Height and body weight were measured twice (on visits 1 and 3). A health history questionnaire was collected on the first visit-gathering information on medical history, medication

intake, smoking, and physical activity. On all four visits, participants provided information on their vitamin and supplement intake.

2.1.4. Training of observers

Blood pressure collection

For BP measurements, INTERMAP observers were extensively trained in practice and then certified in accordance with INTERMAP protocols. Certification required trainees to pass a two phase evaluation test: phase one was a film to assess their recognition of Korotkoff sounds for systolic and diastolic BP measures within ±4 mm Hg. Phase two included assessment of measurement technique by a certified BP observer.

Measurement of blood pressure

A total of 8 systolic and diastolic BP readings were available for each participant: BP was measured twice on all four visits. A random zero mercury sphygmomanometer was used to measure BP by trained personnel, as explained above. Participants were instructed to abstain from eating, drinking, smoking, and physical activity for 30 minutes before BP measures were conducted. After 5 minutes of rest with the instrument cuff placed, the device was inflated. Cuff sizes were provided to cater to the needs of all participants [415]. A time interval of 30 seconds was allotted between measurements to ensure that participants were comfortable, and to minimise any unexpected rise in BP due to BP measurement effect [417]. In order to minimise measuring error, all centres used the Mark II Hawksley random zero sphygmomanometer, a replica of the standard mercury sphygmomanometer. Measuring error was also minimised through the addition of a random mercury measure to the manometer prior to measurement, in order to 'blind' the observer to the reading [418].

Anthropometric measurements and health questionnaire

On visits 1 and 3, height and body weight were measured twice. Methods of measurements were standardised for all sites to ensure proper comparability. A stadiometer was used to measure height. A calibrated scale was used to measure body weight, without shoes or heavy clothes. Measurements were repeated if consecutive readings differed by more than 2 cm or 1 kg. Socioeconomic and lifestyle data were collected on visits 1 and 3 including: age, employment (yes/no), on a special diet at the time of the study (yes/no), physical activity (hours per day engaged in moderate and heavy physical activity during leisure time as reported by participants), dietary supplement use (yes/no), years of education (years completed), smoking (yes/no), family medical history, and current medication intake. Information about physical activity included questions about the intensity of activity (heavy, moderate, light, no activity) and frequency. The questions were designed to be simple and straightforward[415].

Dietary recalls

The International Nutrition Coordinator ran a 4-day workshop to train interviewers. The workshop was designed to introduce trainees to the aims and objectives of INTERMAP, and to explain the dietary assessment method through lectures and written exercises. Trainees were required to do the following: code four 24-hour dietary recalls with <6% line errors, practice dietary collection and coding on 5 tape-recorded 24-hour recalls, and tape an evaluation procedure to assess the performance of their peers. Extensive training was provided for 24-hour urine collection to ensure an understanding of participants' experience. Training included all aspects of the study: administration of medical questionnaire and dietary recall, data input, coding, and the handling of urine samples. After the training period, practice was conducted on ten

volunteers to ensure study protocol was followed. The country nutritionist and the International Nutrition Coordinator continued to monitor and observe the training process [419].

2.1.5. Dietary data

Dietary assessment and coding

The 24-hour dietary recall method was used to collect data on dietary intake. Interviews were conducted by trained and certified dieticians, following a structured format. Intakes of all food, drinks, and supplements were recorded. Food and drink models and photographs were used to help estimate food portion, and as memory aids. Each study site had a nutritionist, and each country had a national nutritionist responsible for monitoring data collection and processing. All interviews were taped to enable rechecking of details and to ensure that protocol was followed correctly. The dietary data collection of the INTERMAP study followed standard methods [419]. First participants were instructed on the importance of accuracy and detailed information on all dietary data, followed by how the food models work. Afterwards, individual interviews were structured in 3 phases: participants generally explained their energy intake in the last 24 hours, along with the time and place of energy intake. Meal locations included home, work, school, restaurant, friend's home, during travel, and other. Participants were asked on the first and third visit whether or not they were following a specific diet plan (weight reduction, low salt diet, etc.). Second, the open-question technique was used to obtain details on food items (brand, portion size, additions to food and drink). This involved the use of visual aid and food models to help provide details on the particular food and/or drink consumed. A list of commonly forgotten foods was consulted to ensure that all consumed food and drink had been

reported. Finally, the interviewer repeated the contents of the report to give the participant an opportunity to edit the recall. Detailed information on alcohol consumption over the previous 7 days was recorded on the first and third visits [415].

In the UK, data were first recorded manually, after which they were coded and computerized [409]. In the USA, dietary data were transferred to the software (the Nutrition Data System, version 2.9, 1996, University of Minnesota, Minneapolis) for on-screen coding during an interview [419]. The Nutrition Data System allows for automatic coding and calculation of nutrient content. Country-specific nutrient databases were consulted to estimate nutrient content of all reported foods and beverages by the country nutritionist. On the occasions that food and/or drink product information was missing or incomplete, the site nutritionist and country nutritionist cooperated to complete the data, by contacting food manufacturers or consulting product labels. When nutrient values were unusually low or high, recalls were consulted for any abnormal intakes. The site nutritionist then decided whether or not the intake was valid. Nutrient databases considered different intakes for each country [419]. Tables were then standardized across countries and validated by the Nutrition Coordinating Centre [419,420]. All nutrient data here are exclusive of supplement intake.

Quality control

The site nutritionist and country nutritionist worked together to ensure the quality of data collected and to rate the performance of interviewers. Dietary recalls were reviewed by site nutritionists to ensure all information was available and no data were missing. A random sample was occasionally withdrawn for revision by site nutritionists, to ensure continued accuracy and quality. The country nutritionist then selected a sub-sample of these for monitoring. A rating score from 1 to 4 was assigned

for interviewers, where 1 indicated “retrain” and 4 “excellent”. Interviewers with low scores (1 or 2) were educated and monitored by site and country nutritionists until a score of 3 was achieved. In addition, the site nutritionist would randomly select one out of ten recalls and code it blindly. If 6% or more of the coded lines appeared inaccurate, the recall would be sent back to the person who had coded it for revision, after which the site nutritionist would recheck. The site nutritionist would then send off recalls to the country nutritionist for a final review, with 3 recalls out of each batch of 30 being coded blindly. Again, if 6% or more of the coded lines appeared inaccurate, the recall would be sent back to the site nutritionist for revision.

In order to assess the validity of dietary recalls, sample and gender-controlled correlations were calculated between dietary and urinary total protein, sodium, and potassium. Correlation coefficients were 0.48, 0.36, 0.51 for the UK and 0.52, 0.46, 0.58 for the USA, respectively [419].

Under-reporting

Under-reporting of energy intake was defined by the author as a ratio of energy intake to estimated energy expenditure lower than the 95% confidence limit [421]. Schofield equations [422] were used to determine the basal metabolic rate of participants, with energy expenditure calculated at ‘low’ physical activity level [1.3] for adults [83]. On this basis, 311 participants were excluded as possibly having under-reported their energy intake. All analyses in this report are therefore based on data from 2385 UK and USA participants (1232 men and 1153 women).

2.2. Eating occasions

An eating occasion is defined by the author as any instance in which participants reported the consumption of solid meals and snacks, with a minimum time gap of 15 minutes between occasions. This time gap was adopted from previous studies on eating frequency [113,141], as it allows the capture of main meal intakes as well as snacks. All beverages, including water, fruit juice, soda, alcoholic beverages, tea and coffee, were excluded from the eating occasion counts to avoid over-estimation of the total number of eating occasions per day. This was noticeable when the data set was first dealt with, where initially beverages were considered as eating occasions. Beverages, especially tea and coffee, were consumed a lot during the day, which exaggerated the total number of eating occasions per day. Therefore, in this report, the eating occasion number analysed was confined to solid intake only. Thus, if a participant had for example a cup of tea between meals, that would not be considered an eating occasion. To achieve the 15-minute time gap specified, it was necessary to convert the time of energy intake to minutes of the day, which was conveniently read by the statistical software (SAS). Each line of food intake was checked to ensure that the 15-minute rule was applied, and to ensure the number of each eating occasion is in order of time of energy intake. Missing data on eating occasions were manually recorded; this was observed for intakes at exactly 12:00 noon or 12:00 midnight. For the UK data set, manual recording of the time of energy intake for each food item was done for a total of 2004 paper-recalls (4 recalls for 501 UK participants). To ensure accuracy, 100 paper-recalls were selected where the time of energy intake was checked against the electronic version. After the input of eating occasions was made available for both the UK and USA data

sets, the two data sets were combined. Eating occasions were classified into the following categories: <4, ≥4 to <5, ≥5 to <6, and ≥6 per 24-hours.

2.3. Dietary energy density

Dietary energy density in this report was calculated by the author in two steps. First, solid foods and beverages were coded separately for each of the UK and USA data sets using food codes and food descriptions, to determine which are solid foods and which are beverages. Items that were considered beverages are: tea, coffee, juices, alcohol drinks, and milk. After separate codes were generated for solid foods and beverages, their weights and energy were calculated. From this, two variables were generated: (1) dietary energy density of solid food: calculated by dividing energy of solid food by weight of solid food, and (2) dietary energy density of solid food and beverages (combined): calculated by dividing energy of solid food and beverages by weight of solid food and beverages. The UK and USA data sets were then combined and both dietary energy density variables were averaged over four visits.

Studies have previously concluded that beverages should be excluded when calculating dietary energy density, therefore using the dietary energy density of solid food [165,423]. The lower density of liquids compared to solid food may result in disproportionate individual dietary energy density values. These values can vary greatly between intake assessment methods and may therefore affect the associations of health outcomes with the dietary energy density variable. Also, dietary energy density from food only yielded intraindividual-to-interindividual coefficient of variation ratios that were relatively lower than other methods (e.g., energy density from food and energy-containing beverages) [165,423].

2.4. Nutrient density

For the purpose of this study, the Nutrient Rich Food 9.3 index score was chosen to define nutrient density. This index includes the sum of daily values of nine nutrients to encourage: (protein; dietary fibre; vitamins A, C and E; calcium; iron; potassium and magnesium) minus the sum daily values of three nutrients to limit based on 100 kcal: (saturated fat, added sugar and sodium). For example: Nutrient Rich Food 9.3 index score = [(protein g÷50 g + fibre g÷25 g + vitamin A IU÷5000 IU + vitamin C mg÷60 mg + vitamin E IU÷30 IU + calcium mg÷1000 mg + iron mg÷18 mg + magnesium mg÷400 mg + potassium mg÷3500 mg) – (saturated fat g÷20 g + added sugars g÷50 g + sodium mg÷2400 mg)] × 100.

All components of the Nutrient Rich Food 9.3 index score algorithm were available in the INTERMAP data set for both the UK and the USA, except for added sugar. Therefore, it was necessary to generate a separate code for added sugar. This included: white sugar, brown sugar, caster sugar, and sweeteners of all kinds. The algorithm also included either added sodium or total sodium. Because dietary recalls of added sodium are generally less accurate than total sodium, thus total sodium was used in the algorithm. After the components were coded, the nutrient rich score was firstly calculated for each visit and then the average nutrient rich score of 4 visits. The nutrients to limit score was then calculated for each visit, and the average computed for 4 visits. For each visit, the Nutrient Rich Food 9.3 index score was calculated by subtracting the nutrients to limit score from the nutrient rich score. The average Nutrient Rich Food 9.3 index score over 4 visits was used for the final analyses. Participants were classified into gender-specific quintiles of the Nutrient Rich Food 9.3 index score (quintile 1 to quintile 5).

2.5. Time of energy intake

For the UK data set, electronic coding of the time of food intake was not available. Therefore, it was necessary for the author to revisit all the UK dietary recalls and code the time of intake for each food item. A total of 2004 recalls were revisited, with a total of 67883 lines being coded for the time of food intake. For the USA data set, the time of food intake was already available electronically.

The time of energy intake was expressed as a ratio of evening to morning energy intake. Morning intake was defined as the average energy intake from 6:00 am to 11:55 am, while evening intake was defined as average energy intake from 6:00 pm to 11:55 pm:

$$\textit{The ratio of evening to morning energy intake} = \frac{\text{evening energy intake}}{24-\text{hour energy intake}} \div \frac{\text{morning energy intake}}{24-\text{hour energy intake}}$$

These times were selected based on when the majority (97%) of the UK and USA INTERMAP participants consumed their morning and evening meals. Participants were classified into gender-specific quartiles of the ratio of evening to morning energy intake (<1.0, ≥1.0 to <1.5, ≥1.5 to <2.0, ≥2.0).

2.6. Food groups

Available food descriptions for the INTERMAP UK and USA data were reviewed by the author to generate new food groups using the food-group definitions provided by the American Dietetic Association as reference. Each food line in the UK and USA data sets was therefore assigned to a new food group. Mean food group per day was computed in grams, and averaged over four days. The average grams/1000 kcal for each food group was used for the final analyses. Food groups generated include: dairy

products (whole and low or medium-fat), meat (beef, veal, lamb, poultry, and pork), fish (including shellfish), raw vegetables, cooked vegetables, potatoes, cakes and pies, raw fruit (excluded were avocado, coconut, sugar cane, plantains, and tamarind, because their nutritional value differs substantially from that of most fruit. Fruit nectars, fruit drinks, lemonades, and soft drinks were not considered fruit juice, because these beverages contain minimal fruit content and are often sweetened).

2.7. Macro and micro nutrients

Estimated nutrient intakes were calculated using country-specific, national nutrient databases. Databases differed in types and number of foods used and methods for deriving values. The Nutrition Coordinating Centre modified available databases to make data comparable for the UK and USA by adding new food and preparation methods prior to and during fieldwork. Intakes of macro and micronutrients were calculated as (g/day), (%) of total kcal intake; or g/1000 kcal, and averaged over 4 visits.

2.8. Glycaemic index and glycaemic load

The GI was calculated using available carbohydrates of each food item. The first step was to sum available carbohydrates of all food items, next; the proportion of available carbohydrates is calculated: (available carbohydrates of each food item ÷ total available carbohydrates of the day). The third step is to calculate proportional GI: (proportion of available carbohydrates × GI of the food item). Lastly, we sum the proportional GI values to obtain food GI [277]. For each person, average GI and GL of four values was used. Glucose was used as the reference food to assign GI values.

For the UK dataset, GI and GL values were not available, and were assigned by previous INTERMAP researcher, Ian Brown, and were then validated by the author. The steps for assigning GI and GL values were as follows: use of the online reference of the University of Sydney (www.glycemicindex.com); when more than one value was available, the average value of GI was used. Where GI values were not available in the literature for some foods, GI was either estimated from similar foods, or estimated by Professor Tom Wolever (University of Toronto). The present researcher validated GI values by updating GI values for all food items in the UK dataset.

For the USA dataset, the Nutrition Coordinating Centre provided values of both GI and GL, using the above calculation method. They followed the same process for assigning GI values: for foods where measured GI data were unavailable in the literature, GI was either estimated from similar foods, calculated from available carbohydrate amounts and the GI of ingredients within the food, or given a default GI.

For GL calculation, the first step is to multiply food available carbohydrates by food GI, divided by 100. Next, the values are summed up to obtain food GL [277]. Lastly, the UK and USA datasets were combined for further analyses. Participants were classified into gender-specific quintiles of GI, GL (quintile 1 to quintile 5).

2.9. Statistical methods

Analyses were performed using SAS (Statistical Analysis System version 9.3; SAS Institute Inc., Cary NC, USA). Initially, descriptive analyses were performed, followed by correlation and multivariable linear regression analyses. All statistical tests were two-sided, with p values ($p<0.05$) considered significant.

2.9.1. Descriptive analysis

Mean and *SD* were calculated for all continuous study variables, averaged over four visits for each participant, and presented by gender, country, and in total. These variables include: BP, BMI, dietary and lifestyle factors, macro and micronutrients. The means of macro and micronutrients are described as (% total intake) or (amount/1000 kcal) where appropriate, to adjust for individual differences in total energy intake. Average alcohol intake over 14 days was expressed in g/24-hours. Urinary excretion of sodium, potassium, magnesium, and calcium are expressed as mmol/24-hours. Mean and *SD* were calculated for glycaemic index and glycaemic load including UK and USA samples, while mean and *SD* of total, insoluble, and soluble fibre included USA samples only; all were averaged over four visits for each participant, and presented by gender and in total. Dichotomous variables include: cigarette smoking, adherence to a special diet, dietary supplement use, family history of hypertension in any 1st degree relative, medical history of CVD or DM, use of antihypertensive and/or CVD treatment, employment, marital status.

Across categories of eating occasions, Chi square tests were used to examine differences in the prevalence of normal weight, overweight, and obesity. In addition, Chi square tests were used to examine differences in meal location and the use of antihypertensive and/or CVD treatment across eating occasion categories.

2.9.2. Reliability

Reliability of BP and BMI and eating occasions, dietary energy density, nutrient density, and the ratio of evening to morning energy intake were estimated from the formula 1 ÷ [1+ (ratio ÷ 4)] x100, where the ratio is intra-individual variance ÷ inter-individual variance, estimated separately by gender, and for women and men

combined; mean across four visits. This was calculated from the means of the first two and second two visits in order to account for a higher correlation between values on consecutive days. The reliability of eating occasions for example, gives a first approximation of the effect of random error (day-to-day variability) on the size of eating occasion associations with BP and BMI; the statistic is the estimated size of an observed coefficient as a percent of the theoretical coefficient in univariate regression analysis. The percentage demonstrates the reduction in regression dilution bias gained from the repeated measures [424,425].

2.9.3. Correlations between specific variables

Strongly correlated explanatory variables were identified (r>0.05), since high correlation suggests collinearity. The presence of strongly correlated variables in a multivariable linear regression model may potentially lead to misleading results and the overestimation of standard errors of the coefficients. Initially, a correlation model was used for continuous variables, adjusted for age, gender, and population sample. Model outputs were monitored for indications of multicollinearity.

2.9.4. Multivariable regression analysis

Regression analyses were performed after combining the UK and USA data sets. Generalized linear models and multivariable linear regression models were used. For generalized linear models, variables are presented as adjusted means and SE, where cross-adjusted sum of squares (SS, or Type III SS in SAS) is used to test the null hypothesis that the model does not explain the variance of the response variable.

To examine the associations between BP, BMI and eating occasions, dietary energy density, nutrient density, the ratio of evening to morning energy intake, GI, GL, and total, insoluble, and soluble fibre intakes, sequential adjustments for confounders were

applied. Each model includes additional variables over the previous model. The selection of covariates for inclusion in the model was drawn from published literature on potential variables that correlate with BP and BMI. This includes dietary and lifestyle factors associated with high BP and BMI levels. The multivariable linear regression analyses were used to examine associations between the variable of interest (per 2SD of eating occasions, dietary energy density, nutrient density, the ratio of evening to morning energy intake, GI, GL, and total, insoluble, and soluble fibre intakes) and BP and BMI. Differences in BMI (kg/m^2) are also presented in text as differences in weight (kg), using the average height of INTERMAP UK and USA participants (1.7 meter). The following calculation was used:

$$Difference\ in\ weight\ (kg) = \text{difference in BMI} \times (\text{height in m})^2$$

The potential for age and sex interactions were assessed through the inclusion of a separate interaction term in each regression model. Where significant interaction was detected ($p<0.05$), age- or sex-specific regression models are reported. The degree of multicollinearity present in each regression model was measured from the regressions of the variable of interest against all covariates.

The models for the (eating occasions, dietary energy density, nutrient density, the ratio of evening to morning energy intake) and BP associations are as follows (with and without BMI): **Model 1** adjusted for gender, age and population sample (Table 2.1). **Model 1a** adjusted for variables in Model 1 plus total energy intake (kcal/24-hours). **Model 2** adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity, dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP. **Model 3** adjusted for variables in Model 2 plus 24-hour urinary excretion of sodium

and potassium (mmol/24-hours). **Model 3a** adjusted for variables in Model 3 plus total fibre intake (g/1000 kcal). **Model 4** adjusted for variables in Model 3 plus alcohol intake (g/24-hours).

The models for the (eating occasions, dietary energy density, nutrient density, the ratio of evening to morning energy intake) and BMI associations are as follows: **Model 1** adjusted for gender, age and population sample (Table 2.2). **Model 1a** adjusted for variables in Model 1 plus total energy intake (kcal/24-hours). **Model 2** adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity, dietary supplement use, smoking, and years of education (years completed). **Model 2a** adjusted for variables in Model 2 plus total fibre intake (g/1000 kcal). **Model 3** adjusted for variables in Model 2 plus alcohol intake (g/24-hours).

Sensitivity analyses were conducted using model 4 where BP was the outcome (Table 2.3) and model 3 where BMI was the outcome (Table 2.4). These include: gender sub-cohort analyses, the exclusion of certain sub-cohorts (individuals with high variability in their diet, those following a special diet, those diagnosed with CVD or DM). Individuals with high variability in their diet were classified by a series of nutrient, BP, and BMI coefficient of variation criteria and urinary to dietary ratios. They were defined by senior INTERMAP researchers prior to data analyses, so that individuals with unreliable dietary recalls or fluctuating BPs or BMIs could be flagged. Additionally censored regression analyses was applied for those on antihypertensive medication [426]. The effects on the magnitude and direction of regression coefficients of the various sub-cohort and sensitivity analyses were assessed.

Multivariable models adjusted extensively for lifestyle and dietary factors were used to assess relations of GI, GL, total, insoluble, and soluble fibre to BP and BMI (Tables 2.5

and 2.6). This method (the nutrient density method) is one of several available approaches in epidemiologic analyses to adjust for total energy intake when addressing the relations of specific nutrient intakes with total energy intake [427]. Other methods include: energy-adjusted (residual), the standard multivariable, and the energy decomposition method. The multivariable nutrient density model used in the present report is an isocaloric analysis that allows for interpretation of the relation of the nutrient composition of the diet with the outcome, i.e., BP, BMI while controlling for total energy intake; thus avoiding statistical problems presented by other nutrient density models that do not control for total energy. The coefficient for total energy intake will be therefore interpreted as the effect of the "biological value of energy" because nutrient densities (nutrient/total energy) are not part of/or highly correlated with total energy intake. Example of a multivariable nutrient density model: outcome (disease) = (nutrient/total energy) (%) + total calories (kcal/24-hours) [428]. Therefore, nutrient densities were computed as percentages of total energy (total protein, total fat, total sugar %) or as g/1000 kcal (total fibre, insoluble and soluble fibre), then both the densities and total energy intake were used in multivariable regression models.

The multivariable nutrient density models for the GI, GL, fibre (total, insoluble, soluble) and BP associations are as follows (with and without BMI): **Model 1** adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample (Table 2.5). **Model 2** adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity, dietary supplement use, smoking, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, and 24-hour urinary excretion of sodium (mmol/24-hours). Additional models for total, insoluble, soluble fibre and BP associations were used to adjust for nutrients known to be high in fibre-

rich foods: **Model 3** was adjusted for variables in model 2 plus 24-hour urinary excretion of magnesium (mmol/24-hours). **Model 4** was adjusted for variables in model 2 plus 24-hour urinary excretion of potassium (mmol/24-hours). **Model 5** was adjusted for variables in model 2 plus 24-hour urinary excretion of calcium (mmol/24-hours).

The multivariable nutrient density models for the GI, GL, fibre (total, insoluble, soluble) and BMI associations are as follows: **Model 1** adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample (Table 2.6). **Model 2** adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity, dietary supplement use, smoking, years of education (years completed), and alcohol intake (g/24-hours). Additional models for total, insoluble, soluble fibre and BMI associations were used to adjust for nutrients known to be high in fibre-rich foods: **Model 3** was adjusted for variables in model 2 plus 24-hour urinary excretion of magnesium (mmol/24-hours). **Model 4** was adjusted for variables in model 2 plus 24-hour urinary excretion of potassium (mmol/24-hours). **Model 5** was adjusted for variables in model 2 plus 24-hour urinary excretion of calcium (mmol/24-hours).

For the combined effect of GI and fibre intake on BP, BMI, UK and USA participants were cross-classified by GI and total fibre intake using model 1 to examine the relation.

Table 2.1. Model variables in multivariable linear regression of blood pressure against eating occasions, dietary energy density, nutrient density, and the ratio of evening to morning energy intake

Model number	Description
Model 1	Adjusted for gender, age and population sample.
Model 1a	Adjusted for variables in Model 1 plus total energy intake (kcal/24-hours).
Model 2	Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24-hours), dietary supplement use [1], smoking, years of education (years completed), DM or CVD diagnosis [2], and family history of high BP.
Model 3	Adjusted for variables in Model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 3a	Adjusted for variables in Model 3 plus total fibre intake (g/1000 kcal) [3].
Model 4	Adjusted for variables in Model 3 plus alcohol intake (g/24-hours) [4].

[1] Taking dietary supplements at time of study.
[2] Medical history of diabetes mellitus or cardiovascular disease (heart attack, other heart disease, stroke).
[3] For eating occasions and blood pressure associations.
[4] Alcohol intake over the previous 7 days was recorded on the first and third visits; average alcohol intake over 14 days is used.

Table 2.2. Model variables in multivariable linear regression of body mass index against eating occasions, dietary energy density, nutrient density, and the ratio of evening to morning energy intake

Model number	Description
Model 1	Adjusted for gender, age and population sample.
Model 1a	Adjusted for variables in Model 1 plus total energy intake (kcal/24-hours).
Model 2	Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24-hours), dietary supplement use [1], smoking, and years of education (years completed).
Model 2a	Adjusted for variables in Model 2 plus total fibre intake (g/1000 kcal) [2].
Model 3	Adjusted for variables in Model 2 plus alcohol intake (g/24-hours) [3].

[1] Taking dietary supplements at time of study.
[2] For eating occasions and body mass index associations only.
[3] Alcohol intake over the previous 7 days was recorded on the first and third visits; average alcohol intake over 14 days is used.

Table 2.3. Sub-cohort, exclusions and other sensitivity analyses where blood pressure is the outcome.

Sex: men and women separately
Censored regression for antihypertensive medication use
Excluding participants with a highly variable diet
Excluding those following a special diet
Excluding individuals with a medical history of CVD or DM

Table 2.4. Sub-cohort, exclusions and other sensitivity analyses where body mass index is the outcome

Sex: men and women separately
Excluding participants with a highly variable diet
Excluding those following a special diet
Excluding individuals with a medical history of CVD or DM

Table 2.5. Model variables in multivariable nutrient density models of blood pressure against glycaemic index, glycaemic load, dietary fibre and its components

Model number	Description
Model 1	Adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2	Adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24-hours), dietary supplement use [1], smoking, years of education (years completed), alcohol intake (g/24-hours) [2], DM or CVD diagnosis [3], family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
Model 3	Adjusted for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24-hours).
Model 4	Adjusted for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24-hours).
Model 5	Adjusted for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24-hours).

[1] Taking dietary supplements at time of study.
[2] Alcohol intake over the previous 7 days was recorded on the first and third visits; average alcohol intake over 14 days is used.
[3] Medical history of diabetes mellitus or cardiovascular disease (heart attack, other heart disease, stroke).

Table 2.6. Model variables in multivariable nutrient density models of body mass index against glycaemic index, glycaemic load, dietary fibre and its components

Model number	Description
Model 1	Adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2	Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24-hours), dietary supplement use [1], smoking, years of education (years completed), and alcohol intake (g/24-hours) [2].
Model 3	Adjusted for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24-hours).
Model 4	Adjusted for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24-hours).
Model 5	Adjusted for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24-hours).

[1] Taking dietary supplements at time of study.
[2] Alcohol intake over the previous 7 days was recorded on the first and third visits; average alcohol intake over 14 days is used.

CHAPTER III

Results Part I

3. RESULTS PART I

The first part of the results presents associations of eating occasions, dietary energy density, nutrient density, and the ratio of evening to morning energy intake to BP and BMI.

3.1. Descriptive statistics

The following analyses are based on data from 2385 UK and USA INTERMAP participants (1232 men and 1153 women). Gender and country specific dietary and lifestyle characteristics are presented in (Table 3.1).

Average systolic BP was higher in the UK (120.2 mm Hg) than in the USA (118.4 mm Hg), with a similar trend for diastolic BP (77.3 mm Hg in the UK and 73.3 mm Hg in the USA). Average systolic and diastolic BP were higher in men than in women in both countries. Average BMI was lower in the UK (27.1 kg/m^2) than in the USA (28.6 kg/m^2). Men in the UK and the USA had higher average BMI compared to women (27.4 *vs.* 26.8 kg/m^2; 28.8 kg.m^2 *vs.* 28.3 kg/m^2). The percentage of participants receiving drug treatment for high BP or CVD was higher in the USA (21.8%) than in the UK (14.2%). In the UK, men were more likely to be receiving drug treatment for high BP or CVD than women (15.7% *vs.* 12.4%), while the proportion of men and women receiving treatment in the USA was similar (21.8%). Average eating occasions/24-hours were higher in the UK compared to the USA (5.4 *vs.* 4.6). Men in both countries had slightly lower average eating occasions/24-hours compared to women. Average dietary energy density from food only was similar across countries and between genders (1.8 kcal/g). Nutrient density expressed by the Nutrient Rich Food 9.3 index score was slightly lower in the UK than in the USA (28.8 *vs.* 31.4). Women in the UK had higher Nutrient Rich Food 9.3 index score compared to men (30.8 *vs.* 27.1) with a similar trend in the USA (33.4 *vs.* 29.5). The average ratio of evening to morning energy intake was higher in the USA than the UK (3.5 *vs.* 3.0). Women had lower ratio of evening to morning

energy intake in both countries compared to men (2.8 *vs.* 3.2 in the UK; 3.2 *vs.* 3.5 in the USA).

3.2. Reliability estimates

Univariate estimates of the reliability of systolic and diastolic BP based on mean values from the four 24-hour recalls per participant were 96% in the UK and slightly lower in the USA (96%, 95%) (Table 3.2). The reliability estimate for BMI was 99.9% overall. The reliability estimates for eating occasions ranged from about 83% to 86% of the theoretical coefficient. The reliability estimate for dietary energy density was slightly lower in the UK than in the USA (75% *vs.* 76%). The reliability estimate for nutrient density was 95% overall. For the ratio of evening to morning energy intake, the reliability estimate ranged from about 87% to 88%. Estimates were similar across population samples and by gender.

3.3. Correlations

Partial Pearson correlations between dietary, lifestyle variables and outcome variables for the UK and USA participants are presented in (Table 3.3). Gender specific correlations between dietary, lifestyle variables and outcome variables are presented in [Tables A.1 (men) and A.2 (women)].

Average years of education correlated negatively with BP and BMI (r=-0.10). Hours of engagement in moderate and heavy physical activity, smoking and supplement use were not correlated with BP, and correlated inversely but only in low order with BMI (r=-0.05 to -0.07). Following a special diet did not correlate with BP and only in low order with BMI (r=0.05). Total energy intake per day correlated positively with systolic BP and BMI (r=0.10 and 0.20, respectively). Average eating occasions/24-hours was inversely correlated with systolic BP and BMI (r=-0.06 and -0.08). Dietary energy density was positively correlated

with systolic BP and BMI (r=0.10). Nutrient density was inversely correlated with systolic BP and BMI (r=-0.12 and -0.16), and slightly higher in women compared to men (Tables A.1 and A.2.). The average ratio of evening to morning energy intake was positively correlated with systolic BP, diastolic BP, and BMI, but only low order (r=0.04 to 0.03), while the correlation was slightly higher for men than women. For nutrient intakes, total carbohydrate and total fibre correlated inversely with systolic BP and BMI (r=-0.13 to -0.19). Total fat, saturated fatty acid (SFA), mono-unsaturated fatty acid (MFA), and poly-unsaturated fatty acid (PFA) all correlated positively with systolic and diastolic BP and BMI. The 24-hour urinary excretion of sodium correlated positively with systolic BP and BMI (r=0.12 and 0.33, respectively). The 24-hour urinary excretion of potassium correlated inversely with systolic and diastolic BP (r=-0.04), and positively with BMI (r=0.10). The 24-hour urinary excretion of magnesium did not correlate with systolic BP (r=0.02), and correlated positively with BMI (r=0.05). The 24-hour urinary excretion of calcium was positively correlated with systolic BP and BMI (r=0.10 and 0.12).

Table 3.4 shows correlation coefficients between dietary macro and micro nutrients for UK and USA participants. Total carbohydrates correlated positively with total fibre (r=0.33), and negatively with total protein (r=-0.33), fat (r=-0.75), alcohol, (r=-0.33), 24-hour urinary excretion of sodium (r=-0.17), and 24-hour urinary excretion of calcium (r=-0.13). Total protein did not correlate with total fat (r=-0.02). Total fibre correlated inversely with SFA (r=-0.48) and positively with vegetable protein (r=0.77). The 24-hour urinary excretion of sodium correlated positively with 24-hour urinary excretion of potassium (r=0.35) and 24-hour urinary excretion of magnesium and calcium (r=0.30).

Gender specific correlations between dietary macro and micro nutrients are presented in [Tables A.3 (men) and A.4 (women)].

3.4. Eating occasions

Compared to participants with <4 eating occasions/24-hours, those with ≥6 eating occasions/24-hours were more educated (14.8 *vs*. 14.2 y), had lower average: systolic BP: 116.4 *vs.* 121.4 mm Hg; diastolic BP: 73.0 *vs.* 75.5 mm Hg; BMI: 27.3 *vs.* 29.0 kg/m^2; total energy intake: 2127 *vs.* 2521 kcal/24-hours; dietary energy density: 1.4 *vs.* 2.2 kcal/g; and higher Nutrient Rich Food index score: 35.1 *vs.* 26.8 (*p for trend*<0.0001) (Table 3.5). In addition, participants with ≥6 eating occasions/24-hours had greater intakes of low or medium-fat dairy products (*p for trend*<0.0001), raw vegetables (*p for trend*=0.02), cooked vegetables (*p for trend*=0.02), and fruits (*p for trend*<0.0001) and lower intakes of meats (*p for trend*<0.0001) and potatoes (*p for trend*<0.004) compared to those with <4 eating occasions/24-hours. Individuals with ≥6 eating occasions/24-hours also had significantly more intakes of total carbohydrate (*p for trend*<0.0001), total fibre (*p for trend*<0.0001), vegetable protein (*p for trend*<0.0001), and lower GI (*p for trend*=0.0005), GL (*p for trend*<0.0001), total fat (*p for trend*=0.0002), SFA (*p for trend*=0.005), MFA (*p for trend*=0.0002), cholesterol (*p for trend*<0.0001), and alcohol (*p for trend*<0.0001) compared to those with <4 eating occasions/24-hours. Those with ≥6 eating occasions/24-hours had lower 24-hour urinary excretion of sodium (*p for trend*<0.0001), and higher 24-hour urinary excretion of potassium, magnesium, and calcium (*p for trend*<0.0001) compared to those with <4 eating occasions/24-hours. Furthermore, information on meal location show that 26%, 33%, 25%, and 16% of participants with <4, ≥4 to <5, ≥5 to <6, and ≥6 eating occasions/24-hours, respectively, were having their evening meals at restaurants or cafeterias.

3.4.1. Eating occasions and blood pressure

In 2385 UK and USA INTERMAP participants, adjustment of for lifestyle, dietary and urinary risk factors for high BP level (model 3) showed eating occasions higher by 2.6 eating

occasions/24-hours (2SD) were associated with systolic and diastolic BP differences of -2.5 mm Hg (95% CI: -3.7, -1.4 mm Hg, $p<0.0001$) and -1.2 mm Hg (95% CI: -2.1, -0.4 mm Hg, $p=0.004$) (Table 3.6). Further adjustment for BMI showed lower coefficients: (-1.9, 95% CI: -3.0, -0.8 mm Hg, $p<0.001$) for systolic BP and (-0.9, 95% CI: -1.7, -0.1 mm Hg, $p=0.03$) for diastolic BP. Additional adjustment for dietary fibre (model 3a) showed (with BMI: -1.8, 95% CI: -2.9, -0.7 mm Hg, $p=0.002$) for systolic BP and (with BMI: -0.9, 95% CI: -1.7, -0.03 mm Hg, $p=0.04$) for diastolic BP. Further adjustment for alcohol intake (model 4) showed eating occasions higher by 2.6 eating occasions/24-hours were associated with systolic and diastolic BP differences of -1.6 mm Hg (with BMI: 95% CI: -2.7, -0.5 mm Hg, $p<0.01$) and -0.1 mm Hg (with BMI: 95% CI: -1.5, 0.1 mm Hg, $p=0.09$), respectively, where results did not remain statistically significant.

Using model 4 for censored regression for those on antihypertensive medication use, 487 participants were right censored and results were compatible to (model 4): systolic BP differences were -2.3 mm Hg (95% CI: -3.7, -1.0 mm Hg, $p<0.001$) and diastolic BP -1.1 mm Hg (95% CI: -2.0, -0.1 mm Hg, $p=0.03$). Further adjustment for BMI lowered differences to -1.4 mm Hg (95% CI: -2.7, -0.2 mm Hg, $p=0.03$) for systolic BP, and to -0.5 mm Hg (95% CI: -1.4, 0.4 mm Hg, $p=0.27$) for diastolic BP where results were no longer statistically significant. With the exclusion of participants with high variability in their diet, systolic BP difference associated with 2SD higher intake in eating occasions was compatible to that of (model 4) (with BMI, -1.7, 95% CI: -3.0, -0.4 mm Hg, $p<0.01$) and diastolic BP (-0.8, 95% CI: -1.7, 0.1 mm Hg, $p=0.09$). Excluding individuals following a special diet at the time of the study showed similar results to (model 4). Further sub-cohort analyses excluded those diagnosed with DM and/or CVD, where differences in systolic and diastolic BP associated with 2SD higher intake in eating occasions were similar to the aforementioned

sub-cohort analyses, but with significant results for diastolic BP (with BMI: 95% CI: -1.8, -0.1 mm Hg, p=0.04).

Gender-specific regressions showed that associations of eating occasions with systolic and diastolic BP were similarly inverse for men and women, with higher differences in systolic and diastolic BP among women (Table A.5).

3.4.2. Eating occasions and body mass index

Participants with ≥6 eating occasions/24-hours had the highest percentage of those normal weight (36%) and lowest percentage of those obese (23%), while participants with <4 eating occasions/24-hours had the lowest percentage of normal weight (25%) and highest percentage of obese (36%) (Table 3.5).

In 2385 UK and USA INTERMAP participants, adjustment of for lifestyle and dietary risk factors for high BMI level (model 2) showed eating occasions higher by 2.6 eating occasions/24-hours (2SD) were associated with BMI differences of -1.1 kg/m^2 (95% CI: -1.6, -0.6 kg/m^2) [equivalent to -3.2 kg in weight] (Table 3.7). Additional adjustment for dietary fibre (model 2a) showed BMI (-0.8, 95% CI: -1.3, -0.4 kg/m^2) [equivalent to -2.3 kg in weight], while adjustment for alcohol intake showed similar results as (model 2).

With the exclusion of participants with high variability in their diet, results were compatible to (model 3) (-1.3, 95% CI: -1.8, -0.8 kg/m^2) [equivalent to -3.8 kg in weight]. Excluding individuals following a special diet at the time of the study showed similar results to (model 3). Further sub-cohort analyses excluded those diagnosed with DM and/or CVD, where differences in BMI associated with 2SD higher intakes in eating occasions were smaller compared to (model 3) (-0.8, 95% CI: -1.3, -0.3 kg/m^2) [equivalent to -2.3 kg in weight].

Gender-specific regressions showed eating occasions were similarly inversely associated with BMI in men and women, with a higher difference in BMI among women (Table A.6). No significant interactions with age or gender were detected.

3.5. Dietary energy density

3.5.1. Dietary energy density and blood pressure

Adjustment of for lifestyle, dietary and urinary risk factors for high BP level in model 4 showed dietary energy density (from food only) higher by 0.8 kcal/g (2SD) was associated with systolic and diastolic BP differences of 3.2 mm Hg (95% CI: 2.1, 4.4 mm Hg, $p<0.0001$) and 1.9 mm Hg (95% CI: 1.0, 2.7 mm Hg, $p<0.0001$) (Table 3.8). Further adjustment for BMI showed lower coefficients: 2.2 mm Hg (95% CI: 1.1, 3.3 mm Hg, $p=0.0001$) for systolic BP and 1.3 mm Hg (95% CI: 0.5, 2.1 mm Hg, $p<0.01$) for diastolic BP.

Using model 4 for censored regression for those on antihypertensive medication use, results were compatible to (model 4): systolic BP differences were 3.3 mm Hg (95% CI: 2.0, 4.6 mm Hg, $p<0.0001$) and diastolic BP 1.9 mm Hg (95% CI: 1.0, 2.9 mm Hg, $p<0.0001$). Further adjustment for BMI lowered differences to 1.9 mm Hg (95% CI: 0.7, 3.2 mm Hg, $p=0.003$) for systolic BP, and to 1.1 mm Hg (95% CI: 0.2, 2.0 mm Hg, $p=0.02$) for diastolic BP. With the exclusion of participants with high variability in their diet, systolic and diastolic BP differences associated with 2SD difference in dietary energy density were slightly lower than that of (model 4) (with BMI, 1.5, 95% CI: 0.2, 2.7 mm Hg, $p=0.02$ for systolic BP) and (with BMI, 0.8, 95% CI: -0.1, 1.7 mm Hg, $p=0.09$ for diastolic BP), where results were no longer statistically significant. Excluding individuals following a special diet at the time of the study showed similar systolic and diastolic BP differences to that of (model 4). Further sub-cohort analyses excluded those diagnosed with DM and/or CVD, where differences in systolic and

diastolic BP associated with 2SD higher eating occasions were similar to the aforementioned sub-cohort analyses (with BMI, 2.1, 95% CI: 0.9, 3.3 mm Hg, $p<0.001$) for systolic BP and (1.0, 95% CI: 0.2, 1.9 mm Hg, $p=0.02$) for diastolic BP.

Gender-specific regressions showed that associations of dietary energy density with systolic and diastolic BP were similarly positive for men and women (Table A.7). No significant interactions with gender and age and gender were detected.

3.5.2. Dietary energy density and body mass index

Adjustment of for lifestyle and dietary risk factors for high BMI level in model 3 showed dietary energy density (from food only) higher by 0.8 kcal/g (2SD) was associated with BMI differences of 1.9 kg/m^2 (95% CI: 1.4, 2.3 kg/m^2) [equivalent to 5.5 kg in weight] (Table 3.9).

With the exclusion of participants with high variability in their diet, BMI difference associated with 2SD higher dietary energy density was similar to that of (model 3): (1.9, 95% CI: 1.4, 2.4 kg/m^2, $p<0.0001$). Excluding individuals following a special diet at the time of the study showed compatible results to (model 3): (1.8, 95% CI: 1.3, 2.3 kg/m^2, $p<0.0001$) [equivalent to 5.2 kg in weight]. Furthermore, excluding those diagnosed with DM and/or CVD, showed similar results (1.7, 95% CI: 1.3, 2.2 kg/m^2, $p<0.0001$) [equivalent to 4.9 kg in weight].

Gender-specific regressions showed that associations of dietary energy density with BMI were similarly positive for men and women (Table A.8). No significant interactions with gender or age were detected.

3.6. Nutrient density

Participants in the highest Nutrient Rich Food 9.3 index score quintile (quintile 5, median=52.6) were more educated (*p for trend*<0.0001), had significantly lower systolic BP (*p for trend*<0.0001), diastolic BP (*p for trend*=0.01), BMI (*p for trend*<0.0001), total energy intake per day (*p for trend*<0.0001), dietary energy density from food only and from food and beverages (*p for trend*<0.0001) compared to (quintile 1, median=15) (Table 3.10). Those in the highest quintile also consumed higher amounts of solid foods (*p for trend*<0.0001), had significantly greater intakes of low or medium-fat dairy products (*p for trend*<0.0001), fish (*p for trend*<0.0001), raw vegetables (*p for trend*<0.0001), cooked vegetables (*p for trend*<0.0001), fruits (*p for trend*<0.0001) and lower intakes of meats (*p for trend*<0.0001) and cakes and pies (*p for trend*=0.004) compared to those in the lowest quintile. Those in the highest quintile had significantly higher intakes of total carbohydrate (*p for trend*<0.0001), total fibre (*p for trend*<0.0001), total protein (*p for trend*<0.0001), and lower intakes of total fat (*p for trend*<0.0001), SFA (*p for trend*<0.0001), MFA (*p for trend*<0.0001), PFA (*p for trend*<0.0001), and cholesterol (*p for trend*<0.0001) compared to those in the lowest quintile. Compared to quintile 1, those in quintile 5 showed lower 24-hour urinary excretion of sodium, calcium (*p for trend*<0.01) and potassium (*p for trend*<0.0001), while 24-hour urinary excretion of magnesium was higher in quintile 5 (*p for trend*<0.0001).

3.6.1. Nutrient density and blood pressure

In model 4, nutrient density (expressed by Nutrient Rich Food 9.3 index score) higher by 28.2 (2SD) was associated with systolic and diastolic BP differences of -1.5 mm Hg (95% CI: -2.8, -0.3, *p*<0.001) and -1.2 mm Hg (95% CI: -2.0, -0.3, *p*<0.01) (Table 3.11). Further adjustment for BMI showed lower coefficients: -1.3 mm Hg (95% CI: -2.5, -0.1, *p*=0.03) for

systolic BP and -0.7 mm Hg (95% CI: -1.7, 0.1, p=0.09) for diastolic BP, where results did not remain statistically significant.

Gender-specific regressions showed that associations of nutrient density with systolic and diastolic BP were similarly inverse for men and women (Tables 3.12 and 3.13); however associations of nutrient density with systolic and diastolic BP were not significant in women. No significant interactions with age were detected, however significant interaction with gender was observed. In men (Table 3.12), using model 4 for censored regression for those on antihypertensive medication use, results showed systolic BP differences were (with BMI, -2.8 mm Hg 95% CI: -4.7, -0.9, p<0.01), however associations with diastolic BP were no longer statistically significant after adjustment for BMI (p=0.11). With the exclusion of men with high variability in their diet, systolic BP difference associated with 2SD higher in nutrient density was (with BMI, -3.2 mm Hg, p=0.001), while diastolic BP associations were not significant (with BMI, -1.3 mm Hg, p=0.09). Excluding individuals following a special diet at the time of the study showed smaller differences in systolic BP (with BMI, -2.2 mm Hg, p=0.01), while diastolic BP associations were not significant (with BMI, -0.7 mm Hg, p=0.33). Further sub-cohort analyses excluded those diagnosed with DM and/or CVD, where differences in systolic and diastolic BP associated with 2SD higher nutrient density were lower than the aforementioned sub-cohort analyses (with BMI, -2.0 mm Hg, p=0.03) and (-0.8 mm Hg for diastolic BP, p=0.23). No significant associations between nutrient density and systolic and diastolic BP were observed in women (Table 3.13).

3.6.2. Nutrient density and body mass index

Participants in quintile 5 had the highest percentage of those normal weight (40%) and lowest percentage of those obese (21%), while participants in quintile 1 and quintile 2 had the lowest

percentage of normal weight (26% and 22%, respectively) and the highest percentage of obese (37% and 36%, respectively) (Table 3.10).

In model 3, adjustment of for lifestyle and dietary risk factors for high BMI level showed nutrient density higher by 28.2 (2SD) was associated with BMI difference of -1.6 kg/m^2 (95% CI: -2.1, -1.1 kg/m^2, p<0.0001) [equivalent to -4.7 kg in weight] (Table 3.14).

Excluding participants with high variability in their diet showed BMI differences associated with 2SD higher nutrient density to be (-1.7, 95% CI: -2.2, -1.2 kg/m^2) [equivalent to -4.9 kg in weight], similar to that of (model 3). Excluding individuals following a special diet at the time of the study showed lower difference in BMI compared to (model 3) (-1.5, 95% CI: -1.9, -1.1 kg/m^2) [equivalent to -4.4 kg in weight]. Furthermore, excluding those diagnosed with DM and/or CVD showed a lower difference in BMI associated with 2SD difference in nutrient density compared to (model 3) (-1.3, 95% CI: -1.8, -0.9 kg/m^2) [equivalent to -3.8 kg in weight].

Gender-specific regressions showed that associations of nutrient density with BMI were similarly inverse for men and women (Table A.9). No significant interactions with gender or age were detected.

3.7. The ratio of evening to morning energy intake

By dividing the ratio of evening to morning energy intake into quartiles, no significant differences in systolic BP, BMI or total energy were observed across quartiles (Table 3.15). Those in the highest quartile (≥2.0) had higher BMI (*p for trend*=0.07), diastolic BP (*p for trend*=0.004), dietary energy density from food (*p for trend*<0.01), and from food and beverages (*p for trend*=0.03), and lower nutrient density (*p for trend*<0.0001) compared to those in the lowest quartile (<1.0). Significant differences in food group intake were observed

for some food groups. Participants in the lower ratio of evening to morning energy intake had greater intakes of low or medium-fat dairy products (*p for trend*<0.0001) and fruits (*p for trend*=0.02) and lower intakes of meats (*p for trend*<0.0001) compared to those in the higher ratio of evening to morning energy intake. Macro and micro nutrient intakes were different among quartiles; those in the highest quartile (≥2.0) had significantly less intakes of total carbohydrate (*p for trend*<0.0001), total fibre (*p for trend*<0.0001), vegetable protein (*p for trend*<0.0001) and higher intakes of total fat (*p for trend*=0.004), cholesterol (*p for trend*<0.0001), and alcohol (*p for trend*<0.0001) compared to those lowest quartile (<1.0). Those in the highest quartile also showed lower 24-hour urinary excretion of magnesium (*p for trend*=0.03) compared to those in the lowest quartile.

3.7.1. The ratio of evening to morning energy intake and blood pressure

In 2385 UK and USA INTERMAP participants, adjustment of for lifestyle, dietary and urinary risk factors for high BP showed no significant association of the ratio of evening to morning energy intake with systolic BP (Table 3.16). However, the ratio of evening to morning energy intake was significantly related to diastolic BP (without BMI, 0.1 mm Hg, p=0.03) and was attenuated with adjustment for BMI (0.1 mm Hg, p=0.06).

In sub-cohort analyses, significant associations were observed for diastolic BP in some models: in censored regression, the ratio of evening to morning energy intake higher by 3.6 (2SD) was associated with diastolic BP differences of (without BMI, 0.1 mm Hg, p=0.06 and with BMI, 0.1, p=0.09); with the exclusion of those with high variability in their diet, diastolic BP differences were (without BMI, 0.1 mm Hg, p=0.02 and with BMI, 0.1 mm Hg, p=0.03); with the exclusion of those following a special diet, diastolic BP differences were (without BMI, 0.1 mm Hg, p=0.02 and with BMI, 0.1 mm Hg, p=0.05); with the exclusion

of those with DM and/or CVD, diastolic BP differences were (without BMI, 0.1 mm Hg, p=0.04 and with BMI, 0.1, p=0.03).

Gender-specific regressions showed no significant associations of the ratio of evening to morning energy intake with systolic and diastolic BP in all sub-cohort analyses, however the ratio of evening to morning energy intake was significantly and positively associated with diastolic BP in women (without BMI, 0.1 mm Hg, p=0.02) (Table A. 10).

3.7.2. The ratio of evening to morning energy intake and body mass index

Adjusting for lifestyle and dietary risk factors for high BMI level (model 3) showed a positive association of BMI with the ratio of evening to morning energy intake (BMI differences of 0.1, 95% CI: -0.03, 0.1 kg/m^2, p=0.07) [equivalent to 0.3 kg in weight] (Table 3.17).

With the exclusion of participants with high variability in their diet, the association was attenuated compared to (model 3) (0.1 kg/m^2, p=0.09). Excluding individuals following a special diet at the time of the study showed BMI differences associated with 2SD higher ratio of evening to morning energy intake to be similar to (model 3) (0.04 kg/m^2, p=0.06) [equivalent to 0.1 kg in weight]. Furthermore, excluding those diagnosed with DM and/or CVD also showed similar results to the (model 3) (0.04 kg/m^2, p=0.08).

Gender-specific regressions showed that associations of the ratio of evening to morning energy intake with BMI were similarly direct for men and women. No significant interactions with gender or age were detected (Table A.11).

3.7.3. Eating occasions and the ratio of evening to morning energy intake

Table 3.18 shows the combined association of eating occasions and the ratio of evening to morning energy intake. Participants who ate more frequently and consumed most of their energy earlier in the day (≥6 eating occasions/24-hours and the ratio of evening to morning energy intake ≤1.8) had lower systolic BP (116.2 *vs.* 120.6 mm Hg, *p* for T-test=0.001); diastolic BP (72.7 *vs.* 75.3 mm Hg, *p* for T-test=0.004); BMI (27.6 *vs.* 28.9 kg/m^2, *p* for T-test=0.02); total energy intake (*p* for T-test<0.0001); dietary energy density (*p* for T-test=0.004); alcohol intake (*p* for T-test<0.0001); and higher nutrient density (*p* for T-test<0.0001); food weight (*p* for T-test <0.0001); and fruit intake (*p* for T-test<0.0001) compared to those who ate fewer eating occasions/24-hours and consumed most of their food later in the day (<4 eating occasions/24-hours and the ratio of evening to morning energy intake >1.8).

Table 3.1. Baseline characteristics of UK and USA INTERMAP participants, *n*=2385 [1]

	UK			USA			
Variable	Men	Women	UK all	Men	Women	USA all	UK and USA
n	235	209	444	997	944	1941	2385
Age (y)	49.3 (5.7)	48.3 (5.5)	48.8 (5.6)	48.9 (5.3)	49.0 (5.4)	49.0 (5.4)	48.9 (5.4)
Education (y)	13.4 (3.1)	12.3 (2.9)	12.9 (3.0)	15.0 (3.1)	14.6 (2.9)	15.0 (3.0)	14.6 (3.1)
Engagement in moderate and heavy physical activity (h/24 h)	2.4 (2.7)	2.0 (2.0)	2.2 (2.4)	3.6 (3.3)	3.0 (3.0)	3.3 (3.2)	3.1 (3.1)
Weight (kg)	83.6 (12.6)	70.2 (14.0)	77.3 (14.9)	88.6 (17.1)	74.1 (17.9)	81.5 (18.9)	80.7 (18.3)
Height (m)	1.8 (0.1)	1.6 (0.1)	1.7 (0.1)	1.8 (0.1)	1.6 (0.1)	1.7 (0.1)	1.7 (0.1)
Systolic BP (mm Hg)	123.8 (14.1)	116.2 (13.8)	120.2 (14.4)	120.2 (12.4)	116.5 (14.6)	118.4 (13.6)	118.7 (13.8)
Diastolic BP (mm Hg)	80.8 (9.2)	73.3 (9.4)	77.3 (10.0)	75.6 (9.5)	71.0 (9.2)	73.3 (9.6)	74.1 (9.8)
Body mass index (kg/m^2)	27.4 (3.8)	26.8 (5.1)	27.1 (4.4)	28.8 (4.9)	28.3 (6.5)	28.6 (5.7)	28.3 (5.5)
Total energy intake (kcal/24 h)	2603 (546)	1899 (382)	2271 (591)	2714 (640)	1978 (422)	2356 (658)	2340 (647)
Eating occasions per 24 h	5.3 (1.5)	5.6 (1.3)	5.4 (1.4)	4.5 (1.2)	4.8 (1.2)	4.6 (1.2)	4.8 (1.3)
Dietary energy density							
Food only (kcal/g)	1.9 (0.3)	1.8 (0.4)	1.8 (0.4)	1.9 (0.4)	1.8 (0.4)	1.8 (0.4)	1.8 (0.4)
Food and beverages (kcal/g)	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.7 (0.2)	0.7 (0.2)	0.9 (0.2)	0.9 (0.2)
Nutrient density (Nutrient Rich Food 9.3 index score) [2]	27.1 (9.2)	30.8 (11.1)	28.8 (10.3)	29.5 (13.4)	33.4 (15.9)	31.4 (14.8)	30.9 (14.1)
Nutrients to encourage score	41.1 (8.2)	44.8 (9.9)	42.9 (9.2)	43.5 (12.8)	47.6 (15.1)	45.5 (14.1)	45.0 (13.4)
Percent protein	7.9 (1.7)	8.2 (1.8)	8.0 (1.7)	7.9 (1.9)	7.8 (1.8)	7.9 (1.8)	7.9 (1.8)
Percent dietary fibre	4.7 (1.3)	4.7 (1.3)	4.7 (1.3)	3.4 (1.3)	3.7 (1.3)	3.5 (1.3)	3.8 (1.4)
Percent vitamin A	4.7 (2.8)	5.2 (2.8)	4.9 (2.8)	6.9 (5.5)	8.8 (7.4)	7.8 (6.6)	7.3 (6.1)
Percent vitamin E	2.3 (0.8)	2.2 (0.8)	2.2 (0.8)	2.2 (0.9)	2.3 (0.9)	2.2 (0.9)	2.2 (0.9)
Percent vitamin C	6.1 (3.8)	7.9 (4.9)	6.9 (4.4)	8.1 (5.6)	9.2 (6.1)	8.7 (5.9)	8.3 (5.7)
Percent calcium	4.1 (1.0)	4.7 (1.2)	4.4 (1.1)	3.4 (1.3)	3.8 (1.4)	3.6 (1.4)	3.8 (1.4)

Percent magnesium	3.6 (0.7)	3.8 (0.8)	3.7 (0.8)	3.6 (0.9)	3.7 (1.0)	3.7 (1.0)	3.7 (0.9)
Percent iron	3.3 (0.7)	3.4 (0.8)	3.4 (0.8)	4.2 (1.6)	4.3 (1.4)	4.3 (1.5)	4.1 (1.4)
Percent potassium	4.3 (0.8)	4.7 (0.9)	4.5 (0.9)	3.7 (0.9)	3.9 (1.1)	3.8 (1.0)	3.9 (1.0)
Nutrients to limit score	14.0 (2.3)	14.0 (2.2)	14.0 (2.2)	14.0 (2.4)	14.2 (2.3)	14.1 (2.4)	14.1 (2.3)
Percent saturated fat	6.8 (1.8)	6.9 (1.8)	6.8 (1.8)	6.1 (1.5)	6.0 (1.6)	6.1 (1.6)	6.2 (1.6)
Percent added sugar	0.7 (1.0)	0.4 (0.9)	0.6 (1.0)	1.0 (0.9)	1.2 (1.0)	1.1 (1.0)	1.0 (1.0)
Percent sodium	6.6 (1.4)	6.7 (1.5)	6.6 (1.4)	6.8 (1.6)	7.0 (1.6)	6.9 (1.6)	6.8 (1.6)
Morning proportion of energy [3]	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Evening proportion of energy [4]	0.6 (0.1)	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)	0.5 (0.1)	0.6 (0.1)	0.5 (0.1)
Ratio of evening to morning energy intake [5]	3.2 (2.1)	2.8 (2.2)	3.0 (2.2)	3.5 (1.8)	3.4 (1.6)	3.5 (1.9)	3.4 (1.8)
Total carbohydrate (%kcal)	43.5 (6.5)	45.0 (6.4)	44.2 (6.5)	48.4 (8.0)	50.5 (7.7)	49.4 (7.9)	48.5 (7.9)
Total sugar (%kcal)	19.2 (5.4)	21.5 (6.1)	20.3 (5.9)	26.1 (8.3)	27.4 (7.5)	26.7 (7.9)	25.5 (8.0)
Fructose (%kcal)	3.0 (1.7)	3.6 (1.8)	3.3 (1.8)	5.1 (2.9)	4.9 (2.6)	5.0 (2.8)	4.7 (2.7)
Galactose (%kcal)	0.1 (0.1)	0.1 (0.1)	0.1 (1.8)	0.03 (0.1)	0.1 (0.1)	0.04 (0.1)	0.04 (0.1)
Glucose (%kcal)	3.1 (1.5)	3.7 (1.5)	3.4 (1.6)	5.4 (2.7)	5.3 (2.4)	5.4 (2.6)	5.0 (2.5)
Lactose (%kcal)	2.7 (1.3)	3.5 (1.8)	3.1 (1.6)	2.1 (1.7)	2.4 (1.8)	2.3 (1.8)	2.4 (1.8)
Maltose (%kcal)	1.2 (1.5)	0.6 (0.7)	0.9 (1.2)	0.6 (0.4)	0.7 (0.5)	0.6 (0.4)	0.7 (0.7)
Sucrose (%kcal)	9.2 (4.1)	10.0 (4.1)	9.6 (4.1)	10.3 (5.2)	11.3 (4.8)	10.8 (5.1)	10.6 (4.9)
Glycaemic index	63.0 (4.0)	60.9 (3.3)	62.0 (3.8)	64.3 (8.5)	66.5 (10.3)	65.4 (9.5)	64.7 (8.8)
Glycaemic load	203.8 (50.6)	148.4 (33.2)	177.7 (51.4)	208.5 (64.7)	163.2 (47.9)	186.5 (61.5)	184.8 (59.8)
Total fibre (g/1000 kcal)	11.8 (3.3)	11.9 (3.3)	11.8 (3.3)	8.5 (3.1)	9.2 (3.3)	8.8 (3.3)	9.4 (3.5)
Insoluble fibre (g/1000 kcal) [6]	--	--	--	5.1 (2.2)	5.5 (2.2)	5.3 (2.2)	--
Soluble fibre (g/1000 kcal) [6]	--	--	--	2.7 (1.0)	3.0 (1.1)	2.8 (1.0)	--
Total protein (%kcal)	15.3(2.9)	15.8 (2.9)	15.5 (2.9)	15.2 (3.0)	15.3 (3.0)	15.3 (3.0)	15.3 (3.0)
Total fat (%kcal)	33.4 (6.2)	33.1 (6.2)	33.3 6.2)	33.4 (6.5)	32.9 (6.9)	33.2 (6.7)	33.2 (6.6)
Cholesterol (mg/1000 kcal)	120.5 (46.8)	120.5 (49.1)	120.5 (47.9)	131.7 (56.9)	128.8 (56.3)	130.3 (56.6)	128.5 (55.2)

Dietary alcohol (g/24 h)	21.0 (23.0)	8.8 (11.6)	15.3 (19.5)	10.9 (17.5)	3.4 (7.4)	7.2 (14.0)	8.7 (15.5)
24-hour urinary excretion data (mmol/24 h)							
Sodium	160.5 (50.8)	128.9 (39.8)	145.6 (48.5)	183.4 (62.8)	144.1 (48.5)	164.3 (59.6)	160.8 (58.1)
Potassium	75.7 (21.6)	61.2 (15.1)	68.9 (20.1)	64.9 (21.3)	51.3 (18.0)	58.3 (20.9)	60.3 (21.1)
Magnesium	4.1 (1.2)	3.4 (0.8)	3.7 (1.1)	4.8 (1.6)	3.8 (1.4)	4.3 (1.6)	4.2 (1.5)
Calcium	4.3 (2.1)	3.7 (1.7)	4.1 (1.9)	4.6 (2.3)	3.9 (2.0)	4.3 (2.2)	4.2 (2.1)
Cigarette smoker (%)	37 (15.7)	37 (17.7)	74 (16.7)	193 (19.4)	139 (14.7)	332 (17.1)	406 (17.0)
Adhering to a special diet (%)	10 (4.3)	16 (7.7)	26 (5.9)	37 (3.7)	79 (8.4)	116 (6.0)	142 (6.0)
Dietary supplement use (%)	71 (30.2)	108 (51.7)	179 (40.3)	468 (47)	533 (56.5)	1001 (51.6)	1180 (49.5)
Family history of hypertension in any 1st degree relative (%)	106 (45.1)	109 (52.2)	215 (48.4)	613 (61.5)	690 (73.1)	1303 (67.1)	1518 (63.7)
History of CVD or DM (%)	24 (10.2)	16 (7.7)	40 (9.0)	148 (14.8)	143 (15.2)	291 (15.0)	331 (13.9)
Use of antihypertensive and/or CVD treatment (%)	37 (15.7)	26 (12.4)	63 (14.2)	217 (21.8)	207 (21.9)	424 (21.8)	487 (20.4)
Employed (%)	208 (88.5)	180 (84.7)	388 (87.4)	907 (90.9)	795 (84.2)	1702 (87.7)	2090 (87.6)
Married (%)	188 (80)	159 (76.1)	347 (78.2)	763 (76.5)	584 (61.9)	1347 (69.4)	1694 (71.0)

[1] Presented as mean (SD) or percent (%).
[2] Nutrient Rich Food 9.3 index score was calculated as the sum of the daily values of nutrients to encourage, subtracting the daily values of nutrients to limit based on 100 kcal:
Example; Nutrient Rich Food 9.3 index score = [(protein g÷50 g + fibre g÷25 g + vitamin A IU÷5000 IU + vitamin C mg÷60 mg + vitamin E IU÷30 IU + calcium mg÷1000 mg + iron mg÷18 mg + magnesium mg÷400 mg + potassium mg÷3500 mg) – (saturated fat g÷20 g + added sugars g÷50 g + sodium mg÷2400 mg)] × 100.
[3] Morning proportion of energy= (average energy intake from 6:00 am to 11:55 am) ÷ (24 h energy intake).
[4] Evening proportion of energy= (average energy intake from 6:00 pm to 11:55 pm) ÷ (24 h energy intake).
[5] Ratio of evening to morning energy intake = (evening proportion of energy) ÷ (morning proportion of energy).
[6] Data for insoluble and soluble fibre intake are available for the USA samples only.

Table 3.2. Ratio of within-to-between person variance for BP, BMI, eating occasions, dietary energy density, nutrient density, and the ratio of evening to morning energy intake

	Ratio of within to between variance [1]	Mean of 4 measurements: observed regression coefficient as a % of true coefficient [2]
UK		
Systolic BP (mm Hg)	0.2	96.2
Diastolic BP (mm Hg)	0.2	95.7
Body mass index (kg/m^2)	0.004	99.9
Eating occasions per 24 h	0.6	86.0
Dietary energy density	0.9	75.2
Nutrient density (Nutrient Rich Food 9.3 index score)	0.2	95.7
Ratio of evening to morning energy intake	0.5	88.2
USA		
Systolic BP (mm Hg)	0.2	95.5
Diastolic BP (mm Hg)	0.2	95.1
Body mass index (kg/m^2)	0.003	99.9
Eating occasions per 24 h	0.7	82.8
Dietary energy density	0.8	76.1
Nutrient density (Nutrient Rich Food 9.3 index score)	0.2	95.1
Ratio of evening to morning energy intake	0.6	87.0

[1] Ratio of within: between person variance calculated by ANOVA.
[2] 1 ÷ [1+ (ratio ÷ 4)] x100.

Table 3.3. Partial Pearson correlation coefficients between dietary, lifestyle variables and outcome measures of UK and USA INTERMAP participants, *n*=2385 [1,2]

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Body mass index (kg/m^2)
Education (y)	-0.11	-0.07	-0.10
Engagement in moderate and heavy physical activity (h/24 h)	-0.03	-0.04	-0.05
Current smokers (%)	0.02	-0.03	-0.06
Adhering to a special diet (%)	0.01	-0.01	0.05
Dietary supplement use (%)	-0.04	-0.04	-0.07
History of CVD or DM (%)	0.09	-0.04	0.11
Total energy intake (kcal/24 h)	0.09	0.05	0.20
Eating occasions per 24 h	-0.06	-0.05	-0.08
Dietary energy density-food only (kcal/g)	0.11	0.06	0.14
Dietary energy density-food and beverages (kcal/g)	0.04	0.05	0.07
Nutrient density (Nutrient Rich Food 9.3 index score)	-0.12	-0.07	-0.16
Ratio of evening to morning energy intake	0.03	0.04	0.03
Total carbohydrate (%kcal)	-0.13	-0.07	-0.15
Total fibre (g/1000 kcal)	-0.14	-0.10	-0.19
Total protein (%kcal)	0.001	-0.02	0.08
Animal protein (%kcal)	0.07	0.03	0.16
Vegetable protein (%kcal)	-0.13	-0.11	-0.15
Total fat (%kcal)	0.10	0.06	0.19
Total SFA (%kcal)	0.08	0.06	0.15
Total MFA (%kcal)	0.12	0.06	0.20
Total PFA (%kcal)	0.02	0.00	0.08
Cholesterol (mg/1000 kcal)	0.11	0.05	0.16
Dietary alcohol (g/24 h)	0.08	0.06	-0.05
24-hour urinary excretion data (mmol/24 h)			
Sodium	0.12	0.07	0.33
Potassium	-0.04	-0.04	0.10
Magnesium	-0.02	-0.05	0.05
Calcium	0.10	0.06	0.12

[1] Adjusted for age, gender, and population sample.
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table 3.4. Partial Pearson correlation coefficients for dietary macro and micro nutrients of UK and USA INTERMAP participants, *n*=2385 [1,2]

	Total carbohydrate (%kcal)	Total fibre (g/1000 kcal)	Total protein (%kcal)	Animal protein (%kcal)	Vegetable protein (%kcal)	Total fat (%kcal)	Total SFA (%kcal)	Total MFA (%kcal)	Total PFA (%kcal)	Cholesterol (mg/1000 kcal)	Dietary alcohol (g/24 h)	Urinary sodium (mmol/24 h)	Urinary potassium (mmol/24 h)	Urinary magnesium (mmol/24 h)	Urinary calcium (mmol/24 h)
Total carbohydrate (%kcal)		0.33	-0.33	-0.45	0.30	-0.75	-0.59	-0.71	-0.42	-0.49	-0.33	-0.17	0.06	-0.02	-0.13
Total fibre (g/1000 kcal)	0.33		0.15	-0.23	0.77	-0.40	-0.48	-0.39	-0.08	-0.34	-0.06	-0.04	0.34	0.22	-0.04
Total protein (%kcal)	-0.33	0.15		0.88	0.15	-0.02	-0.05	-0.01	-0.09	0.37	-0.05	0.16	0.24	0.13	0.12
Animal protein (%kcal)	-0.45	-0.23	0.88		-0.33	0.14	0.16	0.14	-0.09	0.52	0.00	0.15	0.12	0.03	0.12
Vegetable protein (%kcal)	0.30	0.77	0.15	-0.33		-0.31	-0.43	-0.31	0.02	-0.35	-0.14	0.02	0.21	0.19	-0.02
Total fat (%kcal)	-0.75	-0.40	-0.02	0.14	-0.31		0.81	0.93	0.60	0.41	-0.14	0.20	-0.16	-0.02	0.12
Total SFA (%kcal)	-0.59	-0.48	-0.05	0.16	-0.43	0.81		0.68	0.12	0.41	-0.11	0.14	-0.15	-0.04	0.14
Total MFA (%kcal)	-0.71	-0.39	-0.01	0.14	-0.31	0.93	0.68		0.47	0.39	-0.12	0.18	-0.15	-0.02	0.09
Total PFA (%kcal)	-0.42	-0.08	-0.09	-0.09	0.02	0.60	0.12	0.47		0.06	-0.11	0.12	-0.08	0.03	0.02
Cholesterol (mg/1000 kcal)	-0.49	-0.34	0.37	0.52	-0.35	0.41	0.41	0.39	0.06		0.02	0.16	-0.11	-0.07	0.11
Dietary alcohol (g/24 h)	-0.33	-0.06	-0.05	0.01	-0.14	-0.14	-0.11	-0.12	-0.11	0.02		-0.05	0.02	-0.01	0.01
Urinary sodium (mmol/24 h)	-0.17	-0.04	0.16	0.15	0.02	0.20	0.14	0.18	0.12	0.16	-0.05		0.35	0.30	0.31
Urinary potassium (mmol/24 h)	0.06	0.34	0.24	0.12	0.21	-0.16	-0.15	-0.15	-0.08	-0.11	0.02	0.35		0.46	0.24
Urinary magnesium (mmol/24 h)	-0.02	0.22	0.13	0.03	0.19	-0.02	-0.04	-0.02	0.03	-0.07	-0.01	0.30	0.46		0.42
Urinary calcium (mmol/24 h)	-0.13	-0.04	0.12	0.12	-0.02	0.12	0.14	0.09	0.02	0.11	0.01	0.31	0.24	0.42	

[1] Adjusted for age, gender, and population sample.

[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table 3.5. Variables by category of eating occasions per day for UK and USA INTERMAP participants, *n*=2385[1,2]

Variable	Number of eating occasions/24 h								
	<4		≥4 to <5		≥5 to <6		≥6		
	Mean	*SE*	Mean	*SE*	Mean	*SE*	Mean	*SE*	*P for trend*
n	577		795		601		412		
Men (%)	64		52		45		43		
Education (y) [3]	14.2	0.1	14.6	0.1	14.7	0.1	14.8	0.1	0.002
Engagement in moderate and heavy physical activity (h/24 h) [3]	3.1	0.1	3.0	0.1	3.2	0.1	3.0	0.1	0.59
Systolic BP (mm Hg) [3]	121.4	0.6	118.3	0.5	118.8	0.5	116.4	0.7	2.83×10^{-07}
Diastolic BP (mm Hg) [3]	75.5	0.4	73.8	0.3	74.3	0.4	73.0	0.5	0.0003
Body mass index (kg/m^2) [3]	29.0	0.2	28.4	0.2	28.1	0.2	27.3	0.3	0.0001
Total energy intake (kcal/24 h)	2520.6	25.9	2398.5	21.2	2286.8	18.4	2126.7	22.3	1.07×10^{-17}
Food energy (kcal/24 h)	2083.7	22.8	1986.3	18.7	1910.7	16.2	1730.2	19.6	1.91×10^{-31}
Beverage energy (kcal/24 h)	436.9	10.3	412.2	8.5	376.1	9.8	396.5	12.0	0.0003
Food weight (g/24 h)	961.2	13.4	1084.3	11.0	1146.0	12.7	1227.5	15.6	1.76×10^{-37}
Beverage weight (g/24 h) [4]	1606.6	31.2	1566.7	25.7	1573.9	29.7	1684.7	36.3	0.05
Dietary energy density									
Food only (kcal/g)	2.2	0.01	1.8	0.01	1.7	0.02	1.4	0.02	0.0004
Food and beverages (kcal/g)	1.0	0.01	0.9	0.01	0.8	0.01	0.7	0.01	0.08
Nutrient density (Nutrient Rich Food 9.3 index score)[3]	26.8	0.6	30.1	0.5	32.4	0.5	35.1	0.7	2.79×10^{-20}
Morning proportion of energy [5]	0.2	0.01	0.2	0.01	0.2	0.01	0.2	0.01	5.86×10^{-05}
Evening proportion of energy [6]	0.7	0.01	0.5	0.01	0.4	0.01	0.4	0.01	0.06
Ratio of evening to morning energy intake [7]	4.5	0.9	3.0	0.7	2.1	0.8	2.4	0.9	0.09
Food Groups (g/1000 kcal)									
Whole fat dairy	27.3	1.7	26.3	1.4	27.3	1.6	21.8	2.0	0.13
Low or medium-fat dairy	66.6	3.6	83.0	3.0	95.1	3.5	110.4	4.2	5.14×10^{-14}
Meat	32.2	0.9	26.8	0.8	26.1	0.9	20.9	1.1	1.87×10^{-13}
Fish	7.4	0.5	8.0	0.4	6.8	0.5	7.4	0.6	0.37
Raw vegetables	22.8	1.2	25.1	1.0	28.6	1.2	31.6	1.4	0.02
Cooked vegetables	41.6	1.7	45.1	1.4	50.0	1.6	56.7	2.0	0.02
Potatoes	40.9	1.3	37.5	1.1	36.4	1.2	33.9	1.5	0.05×10^{-01}
Fruit	31.0	2.5	47.4	2.1	59.7	2.4	74.6	2.9	3.13×10^{-29}
Cakes and pies	6.5	0.5	6.1	0.4	5.4	0.5	5.3	0.6	0.32
Nutrients									
Total carbohydrate (%kcal)	46.4	0.3	48.3	0.3	48.8	0.3	50.7	0.4	2.32×10^{-16}
Glycaemic index	65.4	0.4	65.1	0.4	65.0	0.3	63.3	0.4	0.05×10^{-03}
Glycaemic load	197.4	1.9	188.0	1.5	184.9	1.3	172.2	1.6	8.49×10^{-22}

Total fibre (g/1000 kcal)	8.6	0.1	9.2	0.1	9.9	0.1	10.3	0.2	1.07×10^{-16}
Insoluble fibre (g/1000 kcal)	4.7	0.1	5.2	0.1	5.7	0.1	5.9	0.1	3.71×10^{-18}
Soluble fibre (g/1000 kcal)	2.6	0.04	2.8	0.04	3.0	0.05	3.1	0.06	2.72×10^{-15}
Total protein (%kcal)	15.5	0.1	15.4	0.1	15.2	0.1	15.0	0.1	0.06
Animal protein (%kcal)	10.4	0.1	10.0	0.1	9.6	0.1	9.4	0.2	4.84×10^{-07}
Vegetable protein (%kcal)	4.9	0.1	5.3	0.1	5.5	0.1	5.5	0.1	1.06×10^{-11}
Total fat (%kcal)	33.7	0.3	33.4	0.2	33.5	0.3	31.9	0.3	0.0002
Total SFA (%kcal)	11.3	0.1	11.1	0.1	11.2	0.1	10.6	0.1	0.05×10^{-01}
Total MFA (%kcal)	12.3	0.1	12.1	0.1	12.2	0.1	11.5	0.1	0.0002
Total PFA (%kcal)	6.8	0.1	7.0	0.1	6.9	0.1	6.7	0.1	0.29
Cholesterol (mg/1000 kcal)	139.6	2.3	130.9	1.9	123.7	2.2	114.5	2.6	6.74×10^{-12}
Dietary alcohol (g/24 h) [3]	11.8	0.6	8.7	0.5	7.4	0.6	6.4	0.7	3.98×10^{-08}
24-hour urinary excretion data (mmol/24 h) [3]									
Sodium	160.7	2.7	163.7	1.9	161.8	2.2	151.7	2.3	6.86×10^{-04}
Potassium	53.7	0.8	58.5	0.6	62.5	0.7	68.3	0.9	2.22×10^{-32}
Magnesium	3.9	0.1	4.1	0.1	4.3	0.1	4.6	0.1	2.87×10^{-16}
Calcium	3.9	0.1	4.1	0.1	4.5	0.1	4.5	0.1	5.14×10^{-07}
Weight status (%) [8]									
Normal weight	147 (25%)		225 (28%)		192 (32%)		147 (36%)		
Overweight	225 (39%)		321 (41%)		229 (38%)		167 (41%)		
Obese	205 (36%)		249 (31%)		180 (30%)		98 (23%)		0.002
Evening meal location (%) [8]									
Restaurants or cafeterias	150 (26%)		262 (33%)		150 (25%)		66 (16%)		0.0002
Use of antihypertensive and/or CVD treatment [8]	117 (20.3%)		173 (22%)		119 (20%)		78 (19%)		0.66

[1] Presented as mean and *SE*.
[2] Model 1 adjusted for gender, age, and population sample.
[3] Model 1a adjusted for variables in Model 1 plus total energy intake.
[4] Drinking water excluded.
[5] Morning proportion of energy= (average energy intake from 6:00 am to 11:55 am) ÷ (24 h energy intake).
[6] Evening proportion of energy= (average energy intake from 6:00 pm to 11:55 pm) ÷ (24 h energy intake).
[7] Ratio of evening to morning energy intake =(evening proportion of energy) ÷ (morning proportion of energy).
[8] Chi square.

Table 3.6. Estimated mean systolic and diastolic BP differences per 2SD higher intake of eating occasions in UK and USA INTERMAP participants [1]

Models	*n*	Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
		Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 1a	2385	-3.3	-4.4, -2.2	2.43×10^{-08}	-2.4	-3.5, -1.3	1.33×10^{-05}	-1.5	-2.3, -0.7	0.0004	-1.0	-1.8, -0.2	0.01
Model 2	2385	-2.9	-4.0, -1.8	6.43×10^{-07}	-2.2	-3.3, -1.1	7.73×10^{-05}	-1.3	-2.1, -0.5	0.002	-0.9	-1.7, -0.1	0.03
Model 3	2385	-2.5	-3.7, -1.4	2.04×10^{-05}	-1.9	-3.0, -0.8	0.08×10^{-02}	-1.2	-2.1, -0.4	0.004	-0.9	-1.7, -0.1	0.03
Model 3a	2385	-2.3	-3.4, -1.1	0.0001	-1.8	-2.9, -0.7	0.002	-1.1	-2.0, -0.3	0.09×10^{-01}	-0.9	-1.7, -0.03	0.04
Model 4	2385	-2.2	-3.4, -1.1	0.0002	-1.6	-2.7, -0.5	0.06×10^{-01}	-1.1	-1.9, -0.2	0.01	-0.1	-1.5, 0.1	0.09
Sensitivity analyses using model 4													
Censored regression [2]	1898	-2.3	-3.7, -1.0	0.07×10^{-02}	-1.4	-2.7, -0.2	0.03	-1.1	-2.0, -0.1	0.03	-0.5	-1.4, 0.4	0.27
Excluding those with high variability in their diet [2]	1870	-2.4	-3.6, -1.2	2.28×10^{-05}	-1.7	-3.0, -0.4	0.08×10^{-01}	-1.3	-2.2, -0.4	0.01	-0.8	-1.7, 0.1	0.09
Excluding those following a special diet [2]	2243	-2.4	-3.6, -1.2	6.87×10^{-08}	-1.7	-2.8, -0.5	0.004	-1.2	-2.1, -0.4	0.06×10^{-01}	-0.8	-1.7, 0.01	0.05
Excluding those diagnosed with DM and/or CVD [3]	2054	-2.5	-3.7, -1.2	2.33×10^{-08}	-1.9	-3.1, -0.8	0.001	-1.2	-2.1, -0.3	0.08×10^{-01}	-0.9	-1.8, -0.1	0.04

Model 1a adjusted for total energy intake, gender, age, and population sample.
Model 2 Adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 3a adjusted for variables in model 3 plus total fibre intake (g/1000 kcal).
Model 4 adjusted for variables in model 3 plus alcohol intake (g/24 h).
[1] 2SD of eating occasions=2.6.
[2] 2SD of eating occasions=2.5.
[3] Not adjusted for DM or CVD diagnosis.

Table 3.7. Estimated mean BMI difference per 2SD higher intake of eating occasions in UK and USA INTERMAP participants [1]

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 1a	2385	-1.1	-1.5, -0.6	5.73×10^{-06}
Model 2	2385	-1.1	-1.6, -0.6	3.28×10^{-06}
Model 2a	2385	-0.8	-1.3, -0.4	0.0004
Model 3	2385	-1.1	-1.6, -0.7	2.71×10^{-06}
Sensitivity analyses using model 3				
Excluding those with high variability in their diet [2]	1870	-1.3	-1.8, -0.8	5.87×10^{-07}
Excluding those following a special diet [2]	2243	-1.1	-1.6, -0.7	5.03×10^{-06}
Excluding those diagnosed with DM and/or CVD	2054	-0.8	-1.3, -0.3	0.001

Model 1a adjusted for total energy intake, gender, age, and population sample.
Model 2 adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 2a adjusted for variables in Model 2 plus total fibre intake (g/1000 kcal).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of eating occasions=2.6.
[2] 2SD of eating occasions=2.5.

Table 3.8. Estimated mean systolic and diastolic BP differences per 2SD higher dietary energy density in UK and USA INTERMAP participants [1]

Models	*n*	Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
		Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 1	2385	4.1	2.9, 5.2	1.52×10^{-12}	2.6	1.5, 3.6	2.92×10^{-06}	1.8	1.1, 2.6	5.46×10^{-06}	1.1	0.3, 1.9	0.07×10^{-01}
Model 2	2385	3.6	2.5, 4.7	6.95×10^{-10}	2.4	1.3, 3.5	2.56×10^{-05}	1.8	1.0, 2.6	9.45×10^{-06}	1.2	0.4, 2.0	0.004
Model 3	2385	3.1	1.9, 4.2	2.58×10^{-07}	2.0	0.9, 3.1	0.05×10^{-02}	1.8	0.9, 2.6	3.39×10^{-05}	1.2	0.4, 2.0	0.05×10^{-01}
Model 4	2385	3.2	2.1, 4.4	4.09×10^{-08}	2.2	1.1, 3.3	0.0001	1.9	1.0, 2.7	1.04×10^{-05}	1.3	0.5, 2.1	0.002
Sensitivity analyses using model 4													
Censored regression	1898	3.3	2.0, 4.6	1.38×10^{-06}	1.9	0.7, 3.2	0.003	1.9	1.0, 2.9	5.56×10^{-05}	1.1	0.2, 2.0	0.02
Excluding those with high variability in their diet	1870	3.2	2.0, 4.3	0.0001	1.5	0.2, 2.7	0.02	1.7	0.4, 2.3	0.004	0.8	-0.1, 1.7	0.09
Excluding those following a special diet	2243	3.2	2.0, 4.3	1.13×10^{-06}	2.1	0.9, 3.2	0.0004	1.8	1.0, 2.7	8.53×10^{-05}	1.3	0.4, 2.1	0.004
Excluding those diagnosed with DM and/or CVD [2]	2054	3.2	2.0, 4.4	2.62×10^{-07}	2.1	0.9, 3.3	0.05×10^{-02}	1.7	0.8, 2.5	0.0002	1.0	0.2, 1.9	0.02

Model 1 adjusted for gender, age, and population sample.
Model 2 Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of dietary energy density (kcal/g)=0.8.
[2] Not adjusted for DM or CVD diagnosis.

Table 3.9. Estimated mean BMI difference per 2SD higher dietary energy density in UK and USA INTERMAP participants [1]

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 1	2385	1.9	1.5, 2.4	5.82×10^{-16}
Model 2	2385	1.8	1.4, 2.3	9.73×10^{-15}
Model 3	2385	1.9	1.4, 2.3	1.00×10^{-14}
Sensitivity analyses using model 3				
Excluding those with high variability in their diet	1870	1.9	1.4, 2.4	3.03×10^{-12}
Excluding those following a special diet	2243	1.8	1.3, 2.3	9.41×10^{-13}
Excluding those diagnosed with DM and/or CVD	2054	1.7	1.3, 2.2	2.33×10^{-12}

Model 1 adjusted for gender, age, and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of dietary energy density (kcal/g)=0.8.

Table 3.10. Variables by quintiles of nutrient density (Nutrient Rich Food 9.3 index score) in UK and USA INTERMAP participants, *n*=2385 [1,2]

	Nutrient Rich Food 9.3 index score										
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5		
Variable	Mean	*SE*	Mean	*SE*	Mean	*SE*	Mean	*SE*	Mean	*SE*	*P for trend*
n	477		477		477		477		477		
Nutrient Rich Food 9.3 index score (median)	15.0		22.5		28.5		36.0		52.6		
Education (y) [3]	13.7	0.1	14.1	0.1	14.7	0.1	15.1	0.1	15.2	0.1	5.32×10^{-21}
Engagement in moderate and heavy physical activity (h/24 h) [3]	3.3	0.1	3.1	0.1	3.0	0.1	2.9	0.1	2.9	0.1	0.19
Systolic BP (mm Hg) [3]	121.0	0.6	120.0	0.6	117.4	0.6	118.7	0.6	117.0	0.6	8.56×10^{-06}
Diastolic BP (mm Hg) [3]	74.8	0.4	75.1	0.4	73.4	0.4	74.3	0.4	73.2	0.4	0.05×10^{-01}
BMI (kg/m^2) [3]	28.7	0.2	28.8	0.2	28.6	0.2	28.0	0.2	27.2	0.2	1.22×10^{-05}
Total energy (kcal/24 h)	2507.0	24.0	2371.1	23.5	2350.2	23.6	2206.2	23.6	2178.7	24.0	3.76×10^{-25}
Food energy (kcal/24 h)	2014.2	21.7	1956.7	21.2	1970.9	21.3	1837.7	21.3	1803.3	21.7	8.05×10^{-14}
Beverage energy (kcal/24 h)	492.8	11.0	414.4	10.8	379.2	10.8	368.5	10.9	375.4	11.0	2.32×10^{-17}
Food weight (g/24 h)	952.5	14.3	1014.1	14.0	1110.9	14.0	1131.8	14.0	1269.7	14.3	5.44×10^{-56}
Beverage weight (g/24 h) [4]	1736.4	33.8	1615.9	33.1	1540.7	33.2	1531.8	33.3	1567.5	33.8	7.70×10^{-05}
Dietary energy density											
Food only (kcal/g)	2.1	0.01	2.0	0.01	1.8	0.01	1.7	0.01	1.5	0.01	4.65×10^{-288}
Food and beverages (kcal/g)	1.0	0.01	1.0	0.01	1.0	0.01	0.9	0.01	0.8	0.01	2.74×10^{-39}
Food Groups (g/1000 kcal)											
Whole fat dairy	34.6	1.8	28.4	1.8	23.9	1.8	22.8	1.8	20.2	1.8	2.76×10^{-07}
Low or medium-fat dairy	53.1	3.8	68.6	3.8	85.4	3.8	106.0	3.8	121.9	3.8	2.09×10^{-40}
Meat	29.9	1.0	29.5	1.0	28.5	1.0	25.1	1.0	21.4	1.0	5.03×10^{-10}
Fish	5.3	0.6	6.7	0.6	6.6	0.6	8.2	0.6	10.5	0.6	1.33×10^{-09}
Raw vegetables	16.5	1.2	18.7	1.2	26.3	1.2	33.9	1.2	44.9	1.2	6.57×10^{-68}
Cooked vegetables	27.8	1.7	38.4	1.6	46.8	1.7	56.5	1.7	76.8	1.7	2.46×10^{-92}
Fruit	17.7	2.5	29.6	2.4	46.0	2.4	64.9	2.4	98.9	2.5	1.44×10^{-121}
Cakes and pies	7.3	0.6	5.8	0.6	6.3	0.6	5.2	0.6	4.3	0.6	0.004
Nutrients											
Total carbohydrate (%kcal)	46.3	0.3	46.3	0.3	47.5	0.3	49.5	0.3	52.4	0.3	3.97×10^{-46}
Total fibre (g/1000 kcal)	6.6	0.1	8.0	0.1	9.0	0.1	10.5	0.1	13.0	0.1	1.50×10^{-281}
Total protein (%kcal)	13.8	0.1	14.9	0.1	15.5	0.1	16.0	0.1	16.4	0.1	2.12×10^{-48}
Animal protein (%kcal)	9.4	0.1	9.9	0.1	10.1	0.1	10.2	0.1	9.9	0.1	0.001
Vegetable protein (%kcal)	4.3	0.1	4.8	0.1	5.3	0.1	5.7	0.1	6.4	0.1	4.12×10^{-137}

Total fat (%kcal)	36.7	0.3	35.6	0.3	34.2	0.3	31.4	0.3	28.3	0.3	1.65×10^{-111}
Total SFA (%kcal)	12.9	0.1	12.1	0.1	11.3	0.1	10.2	0.1	8.8	0.1	7.69×10^{-135}
Total MFA (%kcal)	13.4	0.1	13.0	0.1	12.4	0.1	11.3	0.1	10.1	0.1	2.80×10^{-98}
Total PFA (%kcal)	7.1	0.1	7.2	0.1	7.1	0.1	6.7	0.1	6.3	0.1	6.48×10^{-11}
Cholesterol (mg/1000 kcal)	141.0	2.4	137.3	2.4	131.3	2.4	121.4	2.4	110.4	2.5	2.96×10^{-20}
Dietary alcohol (g/24 h) [3]	8.9	0.7	9.1	0.7	8.5	0.7	8.5	0.7	8.6	0.7	0.96
24-hour urinary excretion data (mmol/24 h) [3]											
Sodium	159.9	2.5	164.4	2.5	164.6	2.5	156.2	2.5	154.1	2.5	0.07×10^{-01}
Potassium	72.0	0.8	64.2	0.8	60.8	0.8	54.0	0.8	49.6	0.8	1.73×10^{-87}
Magnesium	3.8	0.1	4.0	0.1	4.2	0.1	4.2	0.1	4.6	0.1	5.05×10^{-16}
Calcium	4.2	0.1	4.2	0.1	4.3	0.1	4.2	0.1	4.1	0.1	5.51×10^{-01}
Weight status (%) [5]											
Normal weight	122 (26%)		106 (22%)		141(30%)		151(31%)		191(40%)		
Overweight	176 (37%)		201(42%)		182(38%)		198(42%)		185(39%)		
Obese	179 (37%)		170 (36%)		154(32%)		128(27%)		101(21%)		<0.0001

[1] Presented as mean and *SE*.
[2] Model 1 adjusted for gender, age, and population sample.
[3] Model 1a adjusted for variables in Model 1 plus total energy intake.
[4] Drinking water excluded.
[5] Chi square.

Table 3.11. Estimated mean systolic and diastolic BP differences per 2SD higher nutrient density (Nutrient Rich Food 9.3 index score) in UK and USA INTERMAP participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 1a	2385	-2.9	-4.0, -1.7	7.69×10^{-10}	-2.3	-3.4, -1.3	0.001	-1.4	-2.2, -0.6	0.05×10^{-02}	-0.8	-1.6, -0.01	0.05
Model 2	2385	-2.4	-3.6, -1.3	7.34×10^{-07}	-2.0	-3.1, -0.8	0.09×10^{-01}	-1.3	-2.1, -0.5	0.002	-0.8	-1.6, 0.04	0.06
Model 3	2385	-1.6	-2.8, -0.3	0.07×10^{-02}	-1.4	-2.5, -0.2	0.02	-1.2	-2.1, -0.3	0.08×10^{-01}	-0.8	-1.6, 0.1	0.08
Model 4	2385	-1.5	-2.8, -0.3	0.08×10^{-02}	-1.3	-2.5, -0.1	0.03	-1.2	-2.0, -0.3	0.09×10^{-01}	-0.7	-1.7, 0.1	0.09
Sensitivity analyses using model 4													
Censored regression [2]	1898	-2.4	-3.8, -1.0	0.001	-1.4	-2.7, -0.1	0.04	-1.5	-2.5, -0.5	0.003	-0.9	-1.8, 0.1	0.07
Excluding those with high variability in their diet [2]	1870	-2.1	-3.3, -0.8	0.001	-1.5	-2.9, -0.2	0.02	-1.3	-2.4, -0.2	0.09×10^{-01}	-0.9	-2.0, 0.2	0.06
Excluding those following a special diet [3]	2243	-2.1	-3.3, -0.8	0.001	-1.3	-2.5, -0.1	0.04	-1.2	-2.1, -0.3	0.09×10^{-01}	-0.8	-1.7, 0.1	0.08
Excluding those diagnosed with DM and/or CVD [4,5]	2054	-2.1	-3.4, -0.9	0.001	-1.4	-2.5, -0.3	0.03	-1.2	-2.1, -0.3	0.01	-0.7	-1.6, 0.1	0.10

Model 1a adjusted for total energy intake, gender, age, and population sample.
Model 2 Adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of Nutrient Rich Food 9.3 index score=28.2.
[2] 2SD of Nutrient Rich Food 9.3 index score=28.0.
[3] 2SD of Nutrient Rich Food 9.3 index score=27.6.
[4] 2SD of Nutrient Rich Food 9.3 index score=28.5.
[5] Not adjusted for DM or CVD diagnosis.

Table 3.12. Estimated mean systolic and diastolic BP differences per 2SD higher nutrient density (Nutrient Rich Food 9.3 index score) in UK and USA INTERMAP men participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 1a	1232	-4.3	-5.9, -2.7	1.94×10^{-07}	-3.4	-4.9, -1.9	1.62×10^{-05}	-1.4	-2.6, -0.2	0.02	-0.8	-2.0, 0.4	0.17
Model 2	1232	-3.7	-5.3, -2.0	1.70×10^{-05}	-2.9	-4.5, -1.3	0.0004	-1.3	-2.5, -0.02	0.05	-0.7	-2.0, 0.5	0.23
Model 3	1232	-2.5	-4.1, -0.8	0.004	-3.3	-5.0, -1.5	0.0003	-1.2	-2.5, 0.1	0.08	-0.7	-2.0, 0.6	0.31
Model 4	1232	-2.3	-4.0, -0.7	0.06×10^{-02}	-3.2	-4.9, -1.4	0.0004	-1.2	-2.5, 0.2	0.09	-0.02	-0.9, 0.4	0.35
Sensitivity analyses using model 4													
Censored regression	1898	-3.7	-5.7, -1.7	0.0002	-2.8	-4.7, -0.9	0.05×10^{-01}	-2.0	-3.5, -0.5	0.01	-1.1	-2.6, 0.3	0.11
Excluding those with high variability in their diet	956	-3.9	-5.8, -1.9	0.0001	-3.2	-5.1, -1.3	0.001	-1.8	-3.3, -0.3	0.02	-1.3	-2.7, 0.2	0.09
Excluding those following a special diet [2]	1185	-3.2	-4.9, -1.4	0.05×10^{-02}	-2.2	-3.9, -0.5	0.01	-1.3	-2.7, 0.1	0.06	-0.7	-2.0, 0.7	0.33
Excluding those diagnosed with DM and/or CVD [3,4]	1060	-2.8	-4.6, -1.0	0.003	-2.0	-3.7, -0.2	0.03	-1.4	-2.8, -0.03	0.05	-0.8	-2.2, 0.5	0.23

Model 1a adjusted for total energy intake, age, and population sample.
Model 2 Adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of Nutrient Rich Food 9.3 index score=25.4.
[2] 2SD of Nutrient Rich Food 9.3 index score=25.2.
[3] 2SD of Nutrient Rich Food 9.3 index score=25.8.
[4] Not adjusted for DM or CVD diagnosis.

Table 3.13. Estimated mean systolic and diastolic BP differences per 2SD higher nutrient density (Nutrient Rich Food 9.3 index score) in UK and USA INTERMAP women participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 1a	1232	-2.7	-4.3, -1.2	0.06×10^{-02}	-1.5	-3.0, -0.04	0.04	-1.2	-2.2, -0.2	0.02	-0.7	-1.7, 0.3	0.17
Model 2	1232	-1.2	-2.7, -0.4	0.01	-2.1	-3.7, 0.5	0.14	-1.1	-2.2, -0.02	0.05	-0.7	-1.7, 0.4	0.22
Model 3	1232	-0.3	-1.9, 1.4	0.34	-0.8	-2.5, 0.9	0.74	-0.9	-2.1, 0.2	0.12	-0.7	-1.8, 0.5	0.25
Model 4	1232	-0.8	-2.5, 0.9	0.34	-0.3	-1.9, 1.4	0.74	-0.9	-2.1, 0.2	0.11	-0.7	-1.8, 0.5	0.25
Sensitivity analyses using model 4													
Censored regression [2]	1898	-0.8	-2.8, 1.1	0.43	-0.3	-2.2, 1.7	0.89	-0.8	-2.2, 0.5	0.19	-0.6	-1.9, 0.7	0.42
Excluding those with high variability in their diet [2]	914	-0.8	-2.7, 1.2	0.44	-0.3	-2.1, 1.5	0.89	-0.8	-2.1, 0.5	0.21	-0.5	-1.8, 0.7	0.41
Excluding those following a special diet [3]	1058	-0.8	-2.6, 1.0	0.36	-0.4	-2.1, 1.4	0.66	-0.9	-2.2, 0.3	0.14	-0.7	-1.9, 0.5	0.24
Excluding those diagnosed with DM and/or CVD [4,5]	994	-1.4	-3.1, 0.4	0.13	-0.8	-2.5, 0.9	0.37	-0.9	-2.1, 0.3	0.15	-0.6	-1.8, 0.6	0.32

Model 1a adjusted for total energy intake, age, and population sample.
Model 2 Adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of Nutrient Rich Food 9.3 index score=30.4.
[2] 2SD of Nutrient Rich Food 9.3 index score=30.1.
[3] 2SD of Nutrient Rich Food 9.3 index score=29.7.
[4] 2SD of Nutrient Rich Food 9.3 index score=30.6.
[5] Not adjusted for DM or CVD diagnosis.

Table 3.14. Estimated mean BMI difference per 2SD higher nutrient density (Nutrient Rich Food 9.3 index score) in UK and USA INTERMAP participants [1]

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 1a	2385	-1.5	-2.0, -1.1	3.31×10^{-11}
Model 2	2385	-1.5	-2.0, -1.1	9.26×10^{-11}
Model 3	2385	-1.6	-2.1, -1.1	2.88×10^{-11}
Sensitivity analyses using model 3				
High variability in their diet [2]	1870	-1.7	-2.2, -1.2	1.01×10^{-09}
Excluding those following a special diet [3]	2243	-1.5	-1.9, -1.1	1.81×10^{-09}
Excluding those diagnosed with DM and/or CVD [4]	2054	-1.3	-1.8, -0.9	5.93×10^{-08}

Model 1a adjusted for total energy intake, gender, age, and population sample.
Model 2 adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of Nutrient Rich Food 9.3 index score=28.2.
[2] 2SD of Nutrient Rich Food 9.3 index score=28.0.
[3] 2SD of Nutrient Rich Food 9.3 index score=27.6.
[4] 2SD of Nutrient Rich Food 9.3 index score=28.5.

Table 3.15. Variables by quartiles of the ratio of evening to morning energy intake in UK and USA INTERMAP participants, *n*=2385 [1,2]

	The ratio of evening to morning energy intake								
	<1.0		≥1.0 to <1.5		≥1.5 to <2.0		≥2.0		
Variable	Mean	*SE*	Mean	*SE*	Mean	*SE*	Mean	*SE*	*P for trend*
n	594		595		595		595		
Men (%)	47		51		49		59		
Education (y) [3]	14.3	0.1	14.6	0.1	14.7	0.1	14.7	0.1	0.09
Engagement in moderate and heavy physical activity (h/24 h) [3]	3.2	0.1	3.1	0.1	2.9	0.1	3.0	0.1	0.34
Systolic BP (mm Hg) [3]	118.1	0.5	119.6	0.5	118.2	0.5	119.3	0.5	0.12
Diastolic BP (mm Hg) [3]	73.4	0.4	74.4	0.4	73.7	0.4	75.2	0.4	0.004
BMI (kg/m^2) [3]	28.0	0.2	28.0	0.2	28.1	0.2	28.5	0.2	0.07
Total energy (kcal/24 h)	2304.0	21.8	2322.4	21.7	2333.0	21.6	2332.4	21.7	0.76
Food energy (kcal/24 h)	1913.3	19.4	1931.1	19.4	1917.6	19.3	1905.6	19.4	0.82
Beverage energy (kcal/24 h)	390.7	9.9	391.3	9.9	415.4	9.8	426.8	9.9	0.02
Food weight (g/24 h)	1103.0	13.3	1124.0	13.2	1104.0	13.2	1067.0	13.3	0.17×10^{-01}
Beverage weight (g/24 h) [4]	1575.3	30.0	1568.4	29.9	1649.2	29.8	1600.6	30.0	0.22
Dietary energy density									
Food only (kcal/g)	1.7	0.02	1.7	0.02	1.7	0.02	1.8	0.02	0.05×10^{-01}
Food and beverages (kcal/g)	0.9	0.01	0.9	0.01	0.9	0.01	0.9	0.01	0.03
Nutrient density (Nutrient Rich Food 9.3 index score) [3]	31.5	0.5	31.8	0.5	31.6	0.5	28.4	0.5	1.25×10^{-05}
Food Groups (g/1000 kcal)									
Whole fat dairy	28.3	1.6	24.6	1.6	23.8	1.6	27.4	1.6	0.15
Low or medium-fat dairy	91.0	3.5	88.8	3.5	94.4	3.5	73.2	3.5	9.14×10^{-05}
Meat	25.3	0.9	25.4	0.9	27.5	0.9	29.2	0.9	4.60×10^{-03}
Fish	7.3	0.5	6.7	0.5	7.3	0.5	8.4	0.5	0.15
Raw vegetables	26.4	1.2	28.0	1.2	30.1	1.2	27.6	1.2	0.15
Cooked vegetables	48.6	1.6	51.7	1.6	48.3	1.6	48.4	1.6	0.38
Potatoes	37.9	1.2	37.9	1.2	39.1	1.2	34.7	1.2	0.07
Fruit	54.4	2.5	54.1	2.5	51.2	2.5	44.7	2.5	0.19×10^{-01}
Cakes and pies	5.7	0.5	5.6	0.5	5.6	0.5	6.2	0.5	0.85
Nutrients									
Total carbohydrate (%kcal)	49.3	0.3	49.0	0.3	48.6	0.3	46.7	0.3	8.81×10^{-09}
Total fibre (g/1000 kcal)	9.7	0.1	9.7	0.1	9.5	0.1	8.8	0.1	3.21×10^{-06}
Total protein (%kcal)	15.4	0.1	15.3	0.1	15.3	0.1	15.3	0.1	0.93
Animal protein (%kcal)	9.8	0.1	9.7	0.1	9.9	0.1	10.1	0.1	0.20
Vegetable protein (%kcal)	5.4	0.1	5.4	0.1	5.3	0.1	5.0	0.1	7.75×10^{-07}
Total fat (%kcal)	33.1	0.3	33.0	0.3	32.8	0.3	34.1	0.3	0.004
Total SFA (%kcal)	11.0	0.1	10.9	0.1	11.0	0.1	11.3	0.1	0.13

Total MFA (%kcal)	12.0	0.1	11.9	0.1	11.9	0.1	12.4	0.1	0.003
Total PFA (%kcal)	6.9	0.1	6.9	0.1	6.7	0.1	7.1	0.1	0.004
Cholesterol (mg/1000 kcal)	123.6	2.2	124.4	2.2	130.4	2.2	135.2	2.2	3.93×10^{-04}
Dietary alcohol (g/24 h) [3]	7.1	0.6	7.9	0.6	8.8	0.6	11.1	0.6	1.19×10^{-05}
24-hour urinary excretion data (mmol/24 h) [3]									
Sodium	160.7	2.2	161.6	2.2	160.3	2.2	156.9	2.2	0.46
Potassium	60.3	0.8	59.7	0.8	61.3	0.8	59.0	0.8	0.18
Magnesium	4.2	0.1	4.1	0.1	4.3	0.1	4.0	0.1	0.03
Calcium	4.2	0.1	4.2	0.1	4.4	0.1	4.1	0.1	0.25
Weight status (%) [5]									
Normal weight	174 (30%)		180 (30%)		194 (32%)		162 (27%)		
Overweight	219 (37%)		248 (42%)		234 (39%)		240 (40%)		
Obese	201 (33%)		167 (29%)		167 (28%)		193 (33%)		0.12

[1] Presented as mean and *SE*.
[2] Model 1 adjusted for gender, age, and population sample.
[3] Model 1a adjusted for variables in Model 1 plus total energy intake.
[4] Drinking water excluded.
[5] Chi square.

Table 3.16. Estimated mean systolic and diastolic BP differences per 2SD higher ratio of evening to morning energy intake in UK and USA INTERMAP participants [1]

Models	*n*	Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
		Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 1	2385	0.06	-0.01, 0.1	0.08	0.1	-0.02, 0.1	0.20	0.1	0.01, 0.1	0.03	0.1	-0.01, 0.1	0.07
Model 2	2385	0.06	-0.01, 0.1	0.09	0.1	-0.03, 0.1	0.20	0.1	0.01, 0.1	0.03	0.1	-0.01, 0.1	0.07
Model 3	2385	0.06	-0.01, 0.1	0.09	0.1	-0.03, 0.1	0.21	0.1	0.01, 0.1	0.03	0.1	-1.0, 0.9	0.06
Model 4	2385	0.06	-0.01, 0.1	0.09	0.1	-0.03, 0.1	0.20	0.02	0.01, 0.1	0.03	0.1	-1.0, 0.1	0.06
Sensitivity analyses using model 4													
Censored regression [2]	1898	0.1	-0.04, 0.2	0.20	0.1	-0.1, 0.2	0.35	0.1	-0.01, 0.2	0.06	0.1	-0.01, 0.2	0.09
Excluding those with high variability in their diet [2]	1870	0.1	-0.1, 0.2	0.06	0.1	0.2, 0.04	0.23	0.1	0.02, 0.2	0.03	0.1	0.02, 0.2	0.02
Excluding those following a special diet [3]	2243	0.1	-0.1, 0.2	0.06	0.1	-0.03, 0.2	0.18	0.1	0.01, 0.2	0.02	0.1	0.01, 0.1	0.05
Excluding those diagnosed with DM and/or CVD [3,4]	2054	0.1	-0.04, 0.2	0.23	0.1	-0.04, 0.1	0.19	0.1	0.01, 0.2	0.04	0.1	0.01, 0.2	0.03

Model 1 adjusted for gender, age, and population sample.
Model 2 Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of ratio of evening to morning energy intake=3.6.
[2] 2SD of ratio of evening to morning energy intake=3.4.
[3] 2SD of ratio of evening to morning energy intake=3.5.
[4] Not adjusted for DM or CVD diagnosis.

Table 3.17. Estimated mean BMI difference per 2SD higher ratio of evening to morning energy intake in UK and USA INTERMAP participants [1]

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 1	2385	0.1	-0.01, 0.1	0.08
Model 2	2385	0.1	-0.01, 0.1	0.08
Model 3	2385	0.1	-0.03, 0.1	0.07
Sensitivity analyses using model 3				
Excluding those with high variability in their diet [2]	1870	0.1	-0.03, 0.1	0.09
Excluding those following a special diet [3]	2243	0.04	-0.02, 0.1	0.06
Excluding those diagnosed with DM and/or CVD [3]	2054	0.04	-0.01, 0.1	0.08

Model 1 adjusted for gender, age, and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of ratio of evening to morning energy intake=3.6.
[2] 2SD of ratio of evening to morning energy intake=3.4.
[3] 2SD of ratio of evening to morning energy intake=3.5.

Table 3.18. Comparison between extreme low and high eating occasions by the ratio of evening to morning energy intake in UK and USA INTERMAP participants, *n*=520 [1, 2]

Variables/ eating occasions and the ratio of evening to morning energy intake	<4 eating occasions/24 h and >1.8		≥6 eating occasions/24 h and ≤1.8		
	Mean	*SE*	Mean	*SE*	*P for T-test*
n	317		203		
Men (%)	68		41		
Education (y) [3]	14.4	0.2	14.8	0.2	0.13
Engagement in moderate and heavy physical activity (h/24 h) [3]	2.9	0.2	3.3	0.2	0.20
Systolic BP (mm Hg) [3]	120.6	0.8	116.2	1.0	0.001
Diastolic BP (mm Hg) [3]	75.3	0.6	72.7	0.6	0.004
BMI (kg/m^2) [3]	28.9	0.3	27.6	0.4	0.18×10^{-01}
Total energy (kcal/24 h)	2528.9	39.0	2283.3	32.5	5.23×10^{-06}
Food energy (kcal/24 h)	2121.4	35.3	1829.9	30.3	2.49×10^{-15}
Beverage energy (kcal/24 h)	407.5	20.1	453.4	17.2	0.09
Food weight (g/24 h)	952.1	20.5	1152.9	23.9	5.00×10^{-19}
Beverage weight (g/24 h) [4]	1612.7	51.4	1710.4	60.0	0.23
Dietary energy density					
Food only (kcal/g)	2.2	0.02	1.6	0.03	0.004
Food and beverages (kcal/g)	0.9	0.02	0.8	0.02	0.58
Nutrient density (Nutrient Rich Food 9.3 index score) [3]	26.9	0.8	35.8	1.0	9.02×10^{-11}
Food Groups (g/1000 kcal)					
Whole fat dairy	28.3	2.5	22.1	2.9	0.11
Low or medium-fat dairy	61.7	5.2	110.5	6.0	4.37×10^{-09}
Meat	33.4	1.4	21.8	1.6	1.92×10^{-07}
Fish	7.9	0.7	6.4	0.8	0.20
Raw vegetables	26.1	1.7	26.7	1.9	0.81
Cooked vegetables	40.6	2.4	55.8	2.8	0.05
Potatoes	40.9	1.8	31.1	2.1	0.06×10^{-02}
Fruit	31.1	3.5	84.2	4.1	8.03×10^{-20}
Cakes and pies	5.7	0.7	5.9	0.8	0.86
Dietary alcohol (g/24 h) [3]	12.3	1.1	5.6	1.3	1.21×10^{-04}

[1] Presented as mean and *SE*.
[2] Model 1 adjusted for gender, age, and population sample.
[3] Model 1a adjusted for variables in Model 1 plus total energy intake.
[4] Drinking water excluded.

CHAPTER IV

Results Part II

4. RESULTS PART II

The second part of the results presents associations of glycaemic index, glycaemic load, and dietary fibre and its individual components to BP and BMI separately.

4.1. Descriptive statistics

Descriptive characteristics of study samples are available in detail in (section 3.1, Table 3.1). Average (*SD*) GI was lower in the UK compared to the USA [62.0 (3.8) *vs.* 65.4 (9.5)]. GI was lower in women than in men in the UK [60.9 (3.3) *vs.* 63.0 (4.0)], while in the USA GI was higher for women compared to men [66.5 (10.3) *vs.* 64.3(8.5)]. A similar trend was observed for GL, lower in the UK compared to the USA: 177.7 (51.4) *vs.* 186.5 (61.5). However, GL was lower in women of both countries compared to men; UK: 148.4 (33.2) *vs.* 203.8 (50.6); USA: 163.2 (47.9) *vs.* 208.5 (64.7). Average intake (*SD*; %kcal) of total sugar was lower in the UK than in the USA [20.3 (5.9) *vs.* 26.7 (7.9)], and was lower for men in both countries compared to women.

Average intake (*SD*; g/1000 kcal) of total fibre was higher in the UK compared to the USA [11.8 (3.3) *vs.* 8.8 (3.3)]. In the UK, men and women had similar intakes, while in the USA, women had slightly higher intakes [9.2 (3.3) *vs.* 8.5 (3.1)]. In the USA, average insoluble fibre intake was 5.3 (2.2); higher in women than in men [5.5 (2.2) *vs.* 5.1 (2.2)]. Average soluble fibre intake was 2.8 (1.0); higher in women [3.0 (1.1)] than in men [2.7 (1.0)].

4.2. Correlations

In the USA samples, partial Pearson correlation coefficients adjusted for age, sex, and population sample shows GI was not correlated with total sugar (r=-0.01), total fibre (r=-0.03), insoluble fibre (r=-0.03), soluble fibre (r=-0.01), and correlated positively

with total fat (r=0.05) and total carbohydrate (r=0.07), and inversely with total protein (r=-0.05) (Table 4.1). In gender specific correlations, similar findings were observed for men and women [Tables A.12 (men) and A.13 (women)].

GL was positively correlated with total carbohydrate (r=0.44), total sugar (r=0.39), inversely with total protein (r=-0.31), total fat (r=-0.21), and total fibre (r=-0.04) (Table 4.1). Similar correlations were observed for men and women separately (Tables A.12 and A.13).

Total dietary fibre was positively correlated with insoluble (r=0.96) and soluble (r=0.89) fibre, with similar findings for men and women separately. The intake of insoluble fibre was positively correlated with soluble fibre (r=0.80), and similarly for men and women separately. The intake of total fibre correlated positively with total carbohydrate (r=0.30), slightly less in men (r=0.27) than women (r=0.33). The intake of total fibre did not correlate with total sugar (r=0.02), with similar findings in men and women separately.

The intake of total fibre was positively correlated with total protein (r=0.16), 24-hour urinary excretion of magnesium (r=0.24), 24-hour urinary excretion of potassium (r=0.35), and negatively with total fat (r=-0.38), alcohol (r=-0.05), 24-hour urinary excretion of sodium (r=-0.04), but not with 24-hour urinary excretion of calcium (r=-0.02) (Table 4.1), with similar correlation coefficients in men and women separately (Tables A.12 and A.13).

4.3. Glycaemic index and glycaemic load

Across gender-specific quintiles of GI in (Table 4.2), systolic BP, diastolic BP, and BMI were not significantly different across groups. However, there was a positive

association with quintile of GI and total energy intake (*p for trend*=0.0002), energy from food (*p for trend*<0.0001), dietary energy density from food and from food and beverages (*p for trend*<0.0001), and an inverse association with energy from beverages (*p for trend*=0.0001), food weight (*p for trend*=0.003), beverage weight (*p for trend*=0.005), and nutrient density (*p for trend*<0.0001).

Those in the highest quintile had less intakes of low or medium-fat dairy products (*p for trend*<0.0001), raw vegetables (*p for trend*=0.005), cooked vegetables (*p for trend*<0.0001), and fruits (*p for trend*<0.0001) compared to those in the lowest quintiles.

For macro and micro nutrient intakes, individuals in the highest quintile of GI had significantly greater intakes of total carbohydrate (*p for trend*=0.01), starch (*p for trend*<0.0001), total fat (*p for trend*<0.0001), SFA (*p for trend*=0.001), MFA (*p for trend*=0.0001), PFA (*p for trend*=0.002), and cholesterol (*p for trend*=0.04). There was an inverse association with quintile of GI and total protein (*p for trend*<0.0001), 24-hour urinary excretion of potassium (*p for trend*<0.0001) and magnesium (*p for trend*=0.001), and a positive association with 24-hour urinary excretion of sodium (*p for trend*=0.0002).

4.3.1. Glycaemic index, glycaemic load and blood pressure

In multivariable regression analyses, there was no significant association between GI and BP (model 2) (Table 4.3). Sensitivity analyses including of censored regression adjusted for BMI showed a significant difference in systolic BP (0.01, 95% CI: 0.01, 0.02 mm Hg, *p*=0.01), and diastolic BP (0.02, 95% CI: 0.01, 0.03 mm Hg, *p*=0.001). Further analyses showed small differences in diastolic BP only in the sub-cohort

excluding those following a special diet (with BMI, 0.8, 95% CI: 0.1, 1.5 mm Hg, p=0.04).

Similarly, GL was not significantly associated with BP (model 2) (Table 4.4). Sensitivity analyses of censored regression adjusted for BMI showed a small, but significant difference in diastolic BP only (0.04, 95% CI: 0.02, 0.06 mm Hg, p=0.03). Further analyses showed small and significant differences in diastolic BP only in the sub-cohort excluding those following a special diet (without BMI, 1.7, 95% CI: 0.1, 3.3 mm Hg, p=0.04).

Gender-specific regressions showed similar findings, as both GI, GL were not associated with BP (Tables A.14 and A.15). No significant interactions with age or gender were detected.

4.3.2. Glycaemic index, glycaemic load and body mass index

In multivariable regression analyses, GI was positively associated with BMI, although the results were not statistically significant (model 2) (Table 4.5). In sub-cohort analyses, associations were similarly non-significant for the three sub-cohorts under investigation: (excluding those with high variability in their diet, excluding those following a special diet, and excluding those diagnosed with DM and/or CVD).

A similar trend was found for the regression of GL against BMI where non-significant associations were observed (model 2) (Table 4.6). Further sub-cohort analyses showed no change in any of the three sub-cohorts under investigation: (excluding those with high variability in their diet, excluding those following a special diet, and excluding those diagnosed with DM and/or CVD).

Gender-specific regressions showed similar findings, both GI, GL were not associated with BMI (Tables A.16 and A.17). No significant interactions with age or gender were detected.

4.4. Total and individual components of fibre

4.4.1. Total and individual components of fibre and blood pressure

Total fibre intake higher by 7 g/1000 kcal was associated with systolic BP lower by 3.0, 95% CI: -4.3, -1.6 mm Hg, $p<0.0001$ and diastolic BP lower by 1.5, 95% CI: -2.4, -0.5 mm Hg, $p=0.003$ (model 2), additionally adjusted for total sugar (%) (Table 4.7). Further adjustment for BMI slightly reduced the association for systolic BP: -1.7, 95% CI: -3.0, -0.4 mm Hg, $p=0.01$, while the association of total fibre with diastolic BP was no longer statistically significant: -0.7, 95% CI: -1.7, 0.2 mm Hg, $p=0.14$. Further adjustments for nutrients high in fibre-rich foods showed different results for different nutrients (with adjustment for BMI): additional adjustment for 24-hour urinary excretion of magnesium excretion (model 3) showed total fibre intake higher by 7 g/1000 kcal was associated with a systolic BP difference similar to (model 2): (-1.7, 95% CI: -3.0, -0.3 mm Hg, $p=0.02$); additional adjustment for 24-hour urinary excretion of potassium excretion (model 4) attenuated the association between total fibre and systolic BP and was no longer statistically significant; additional adjustment for 24-hour urinary excretion of calcium excretion (model 5) resulted in a systolic BP difference similar to that of (model 2): (-1.8, 95% CI: -3.1, -0.4 mm Hg, $p=0.01$). Further regression analyses on sub-cohorts (adjusted for BMI) showed inverse associations held constant, but reduced with censored regression (systolic BP: -0.5; 95% CI: -0.6, -0.1 mm Hg, $p=0.001$), and in a sub-cohort excluding individuals with

high variability in their diet (systolic BP: -1.4, 95% CI: -2.9, 0.04 mm Hg, *p*=0.06). Regression analyses including a sub-cohort (excluding those following a special diet) and a sub-cohort (excluding those diagnosed with DM and/or CVD) showed compatible results to (model 2): (systolic BP: -1.7 and -1.8, 95% CI: -3.2, -0.5 mm Hg, *p*=0.02, 0.009, respectively).

In gender-specific regression analysis, total fibre was inversely associated with systolic BP, with and without BMI adjustment. The association in women was stronger compared to men [adjusted for BMI, 95% CI: -4.2, -0.2 mm Hg, *p*=0.03 vs. 95% CI: -3.2, -0.1 mm Hg, *p*=0.04] (Table A.18)

Insoluble fibre higher by 4.4 g/1000 kcal was associated with systolic BP lower by 2.0 mm Hg (95% CI: –3.9, -0.1 mm Hg, *p*=0.04), additionally adjusted for BMI, total sugar (%) and soluble fibre (Table 4.8). Further adjustments for nutrients high in fibre-rich foods showed different results for different nutrients (with adjustment for BMI): additional adjustment for 24-hour urinary excretion of magnesium excretion (model 3) showed insoluble fibre intake higher by 4.4 g/1000 kcal was associated with a systolic BP difference similar to (model 2): (-1.9, 95% CI: -3.8, -0.1 mm Hg, *p*=0.04); additional adjustment for 24-hour urinary excretion of potassium excretion (model 4) attenuated the association between insoluble fibre and systolic BP (systolic BP: -1.8, 95% CI: -3.7, 0.1 mm Hg, *p*=0.06); additional adjustment for 24-hour urinary excretion of calcium (model 5) resulted in a systolic BP difference similar to that of (model 2): (-2.0, 95% CI: -3.8, -0.1 mm Hg, *p*=0.04). Further regression analyses on sub-cohorts (adjusted for BMI) showed inverse associations held constant, but was reduced with censored regression (systolic BP: -0.3; 95% CI: -0.5, -0.1 mm Hg, *p*=0.002), and was no longer statistically significant in sub-cohort analyses: (a sub-cohort excluding

individuals with high variability in their diet, a sub-cohort excluding those following a special diet).

In gender-specific regression analysis, insoluble fibre was inversely associated with systolic BP, with and without BMI adjustment. The association in women was stronger compared to men [adjusted for BMI, 95% CI: -5.5, -0.2 mm Hg, p=0.04 vs. 95% CI: -3.7, -0.1 mm Hg, p=0.05] (Table A.19).

Soluble fibre was not significantly associated with BP in any of the models, additionally adjusted for insoluble fibre (Table 4.9). Further censored regression and sub-cohort analyses showed no change in association. Gender-specific regressions showed compatible findings (Table A.20).

4.4.2. Total and individual components of fibre and body mass index

Total fibre intake higher by 7 g/1000 kcal (2SD) was inversely associated with BMI in all models (model 2: -1.7, 95% CI: -2.3, -1.2 kg/m^2, p<0.0001) [equivalent to -4.9 kg in weight], additionally adjusted for total sugar (%) (Table 4.10). Analyses with adjustments for nutrients high in fibre-rich foods showed compatible results to (model 2): additional adjustment for 24-hour urinary excretion of magnesium excretion (model 3) showed total fibre intake higher by 7 g/1000 kcal was associated with BMI difference of (-1.9, 95% CI: -2.5, -1.3 kg/m^2, p<0.0001) [equivalent to -5.5 kg in weight]; additional adjustment for 24-hour urinary excretion of potassium excretion (model 4) resulted in BMI difference of (-2.3, 95% CI: -2.9, -1.7 kg/m^2, p<0.0001) [equivalent to -6.7 kg in weight]; additional adjustment for 24-hour urinary excretion of calcium excretion (model 5) resulted in BMI difference of (-1.7, 95% CI: -2.3, -1.2 kg/m^2, p<0.0001) [equivalent to -4.9 kg in weight]. Further sub-cohort analyses showed

inverse associations held constant and compatible to (model 2): (BMI differences ranging between -1.5 to -1.7 kg/m^2, p<0.0001; equivalent to -4.4 to -4.9 kg in weight).

In gender-specific regressions, 7 g/1000 kcal of total fibre intake was similarly inversely associated with BMI, with a higher average difference in BMI among women than men [95% CI: -2.9, -1.2 kg/m^2, p<0.0001 *vs*. 95%CI: -2.0, -0.6 kg/m^2, p=0.0003] (Table A.21). No significant interactions with age or gender were detected.

Insoluble fibre higher by 4.4 g/1000 kcal was associated with BMI (model 2) lower by 1.7, 95% CI: -2.5, -0.9 kg/m^2, p<0.0001 [equivalent to -4.9 kg in weight], additionally adjusted for total sugar and soluble fibre (Table 4.11). Analyses with adjustments for nutrients high in fibre-rich foods showed compatible results to (model 2): additional adjustment for 24-hour urinary excretion of magnesium excretion (model 3) showed insoluble fibre intake higher by 4.4 g/1000 kcal was associated with BMI difference of (-1.8, 95% CI: -2.6, -1.0 kg/m^2, p<0.0001) [equivalent to -5.2 kg in weight]; additional adjustment for 24-hour urinary excretion of potassium excretion (model 4) resulted in BMI difference of (-1.9, 95% CI: -2.7, -1.1 kg/m^2, p<0.0001) [equivalent to -5.5 kg in weight]; additional adjustment for 24-hour urinary excretion of calcium excretion (model 5) resulted in BMI difference of (-1.7, 95% CI: -2.5, -0.9 kg/m^2, p<0.0001) [equivalent to -4.9 kg in weight]. Further sub-cohort analyses showed inverse associations held constant and compatible to (model 2): (BMI differences ranging between -1.5 to -1.8 kg/m^2, p<0.001; equivalent to -4.4 to -5.2 kg in weight).

In gender-specific regressions, 4.4 g/1000 kcal of insoluble fibre intake was similarly inversely associated with BMI in men and women separately (Table A.22). No significant interactions with age or gender were detected.

Association of soluble fibre with BMI was not statistically significantly in any of the models, additionally adjusted for total sugar and insoluble fibre (Table 4.12). Further sub-cohort analyses showed similar results. Gender-specific regressions showed compatible findings (Table A.23).

4.4.3. Glycaemic index and total fibre combined

Because dietary fibre is inversely associated with BP and BMI, UK and USA participants were classified jointly by GI and total fibre intake. Participants were cross-classified by both variables into quartiles, with the following median values (GI: 57.4, 61.8, 65.0, 73.0; total fibre: 6.0, 8.1, 10.1, 13.5) (Figure 4.1, Figure 4.2, and Figure 4.3). After adjustment for age, gender, total energy (kcal/24-hours), protein (%), total fat (%), and population sample (model 1), results showed that there was an inverse association between systolic BP and total fibre intake by GI groups; i.e., compared to participants with the lowest GI and highest fibre intake, those with the highest GI and lowest fibre intake had the highest systolic BP level (p for T-test=0.05) (Figure 4.1). There was also an inverse association between diastolic BP and total fibre intake by GI groups; where those with the highest GI and lowest fibre intake had the highest diastolic BP level (p for T-test=0.02) compared to participants with the lowest GI and highest fibre intake (Figure 4.2). Finally, there was an inverse association between BMI and total fibre intake by GI groups; where those with the highest GI and lowest fibre intake had the highest BMI level (p for T-test =0.05) compared to participants with the lowest GI and highest fibre intake (Figure 4.3).

Gender-specific analyses showed no significant difference in systolic BP, diastolic BP, or BMI between the lowest GI and highest fibre intake and the highest GI and lowest fibre intake (Figures A.1, A.2, A.3, A.4, A.5, A.6).

Table 4.1. Partial Pearson correlation coefficients for dietary macro and micro nutrients of USA INTERMAP participants, *n*=1941 [1,2]

	Total carbohydrate (%kcal)	Starch (%kcal)	Total sugar (%kcal)	Fructose (%kcal)	Galactose (%kcal)	Glucose (%kcal)	Lactose (%kcal)	Maltose (%kcal)	Sucrose (%kcal)	Glycaemic index	Glycaemic load	Total fibre (g/1000 kcal)	Insoluble fibre (g/1000 kcal)	Soluble fibre (g/1000 kcal)	Total protein (%kcal)	Animal protein (%kcal)	Vegetable protein (%kcal)	Total fat (%kcal)	Total SFA (%kcal)	Total PFA (%kcal)	Total MFA (%kcal)	Dietary alcohol (g/24 h)	Urinary sodium (mmol/24 h)	Urinary potassium (mmol/24 h)	Urinary magnesium (mmol/24 h)	Urinary calcium (mmol/24 h)
Total carbohydrate (%kcal)		0.36	0.78	0.52	0.16	0.53	0.09	0.23	0.54	0.07	0.44	0.30	0.31	0.31	-0.37	-0.47	0.28	-0.78	-0.62	-0.73	-0.45	-0.30	-0.18	0.03	-0.03	-0.13
Starch (%kcal)	0.36		-0.31	-0.26	0.06	-0.27	-0.07	0.03	-0.24	0.12	0.10	0.42	0.40	0.41	0.04	-0.27	0.64	-0.35	-0.39	-0.35	-0.12	-0.09	0.04	0.05	0.06	-0.03
Total sugar (%kcal)	0.78	-0.31		0.70	0.12	0.72	0.14	0.21	0.71	-0.01	0.39	0.02	0.04	0.03	-0.40	-0.30	-0.15	-0.55	-0.37	-0.50	-0.38	-0.24	-0.21	-0.01	-0.07	-0.12
Fructose (%kcal)	0.52	-0.26	0.70		0.03	0.93	-0.13	0.11	0.10	-0.09	0.22	0.03	0.04	0.03	-0.28	-0.21	-0.08	-0.40	-0.35	-0.35	-0.21	-0.13	-0.18	-0.06	-0.10	-0.12
Galactose (%kcal)	0.16	0.06	0.12	0.03		0.04	0.12	0.09	0.04	-0.06	0.01	0.14	0.13	0.14	0.02	-0.03	0.10	-0.18	-0.14	-0.18	-0.11	-0.02	-0.07	0.09	0.10	0.03
Glucose (%kcal)	0.53	-0.27	0.72	0.93	0.04		-0.13	0.20	0.12	-0.04	0.25	-0.03	-0.01	-0.02	-0.32	-0.24	-0.12	-0.42	-0.35	-0.36	-0.23	-0.10	-0.16	-0.07	-0.10	-0.13
Lactose (%kcal)	0.09	-0.07	0.14	-0.13	0.12	-0.13		0.03	-0.02	-0.01	0.07	0.04	0.07	0.01	0.22	0.23	-0.03	-0.13	0.04	-0.17	-0.18	-0.10	-0.04	0.32	0.14	0.18
Maltose (%kcal)	0.23	0.03	0.21	0.11	0.09	0.20	0.03		0.05	0.11	0.14	0.10	0.07	0.10	-0.15	-0.15	0.02	-0.20	-0.12	-0.20	-0.13	0.02	-0.08	0.03	0.03	-0.06
Sucrose (%kcal)	0.54	-0.24	0.71	0.10	0.04	0.12	-0.02	0.05		0.06	0.32	-0.12	-0.09	-0.09	-0.40	-0.27	-0.21	-0.28	-0.13	-0.25	-0.24	-0.23	-0.13	-0.12	-0.10	-0.11
Glycaemic index	0.07	0.12	-0.01	-0.09	-0.06	-0.04	-0.01	0.11	0.06		0.47	-0.03	-0.03	-0.01	-0.05	-0.05	0.03	0.05	0.04	0.06	0.05	-0.18	0.06	-0.02	0.02	0.02
Glycaemic load	0.44	0.10	0.39	0.22	0.01	0.25	0.07	0.14	0.32	0.47		-0.04	0.04	0.01	-0.31	-0.30	0.03	-0.21	-0.13	-0.18	-0.14	-0.18	0.15	0.15	0.08	0.09
Total fibre (g/1000 kcal)	0.30	0.42	0.02	0.03	0.14	-0.03	0.04	0.10	-0.12	-0.03	-0.04		0.96	0.89	0.16	-0.22	0.76	-0.38	-0.47	-0.37	-0.08	-0.05	-0.04	0.35	0.24	-0.02
Insoluble fibre (g/1000 kcal)	0.31	0.40	0.04	0.04	0.13	-0.01	0.07	0.07	-0.09	-0.03	0.04	0.96		0.80	0.14	-0.22	0.75	-0.34	-0.44	-0.33	-0.05	-0.12	-0.03	0.33	0.23	-0.02
Soluble fibre (g/1000 kcal)	0.31	0.41	0.03	0.03	0.14	-0.02	0.01	0.10	-0.09	-0.01	0.01	0.89	0.80		0.18	-0.18	0.72	-0.36	-0.45	-0.34	-0.10	-0.10	-0.02	0.34	0.21	-0.01
Total protein (%kcal)	-0.37	0.04	-0.40	-0.28	0.02	-0.32	0.22	-0.15	-0.40	-0.05	-0.31	0.16	0.14	0.18		0.88	0.17	0.02	-0.02	0.02	-0.07	-0.03	0.15	0.26	0.14	0.13
Animal protein (%kcal)	-0.47	-0.27	-0.30	-0.21	-0.03	-0.24	0.23	-0.15	-0.27	-0.05	-0.30	-0.22	-0.22	-0.18	0.88		-0.32	0.17	0.20	0.17	-0.07	-0.01	0.14	0.14	0.03	0.12
Vegetable protein (%kcal)	0.28	0.64	-0.15	-0.08	0.10	-0.12	-0.03	0.02	-0.21	0.03	0.03	0.76	0.75	0.72	0.17	-0.32		-0.30	-0.43	-0.30	0.02	-0.13	0.01	0.22	0.20	-0.01

Total fat (%kcal)	-0.78	-0.35	-0.55	-0.40	-0.18	-0.42	-0.13	-0.20	-0.28	0.05	-0.21	-0.38	-0.34	-0.36	0.02	0.17	-0.30	1.00	0.81	0.93	0.63	-0.13	0.22	-0.14	-0.01	0.12
Total SFA (%kcal)	-0.62	-0.39	-0.37	-0.35	-0.14	-0.35	0.04	-0.12	-0.13	0.04	-0.13	-0.47	-0.44	-0.45	-0.02	0.20	-0.43	0.81		0.70	0.17	-0.11	0.16	-0.13	-0.03	0.15
Total PFA (%kcal)	-0.73	-0.35	-0.50	-0.35	-0.18	-0.36	-0.17	-0.20	-0.25	0.06	-0.18	-0.37	-0.33	-0.34	0.02	0.17	-0.30	0.93	0.70		0.47	-0.11	0.21	-0.14	-0.02	0.10
Total MFA (%kcal)	-0.45	-0.12	-0.38	-0.21	-0.11	-0.23	-0.18	-0.13	-0.24	0.05	-0.14	-0.08	-0.05	-0.10	-0.07	-0.07	0.02	0.63	0.17	0.47		-0.10	0.13	-0.07	0.02	0.01
Dietary alcohol (g/24 h)	-0.30	-0.09	-0.24	-0.13	-0.02	-0.10	-0.10	0.02	-0.23	-0.18	-0.18	-0.05	-0.12	-0.10	-0.03	-0.01	-0.13	-0.13	-0.11	-0.11	-0.10		-0.06	0.01	-0.01	0.01
Urinary sodium (mmol/24 h)	-0.18	0.04	-0.21	-0.18	-0.07	-0.16	-0.04	-0.08	-0.13	0.06	0.15	-0.04	-0.03	-0.02	0.15	0.14	0.01	0.22	0.16	0.21	0.13	-0.06		0.37	0.31	0.32
Urinary potassium (mmol/24 h)	0.03	0.05	-0.01	-0.06	0.09	-0.07	0.32	0.03	-0.12	-0.02	0.15	0.35	0.33	0.34	0.26	0.14	0.22	-0.14	-0.13	-0.14	-0.07	0.01	0.37		0.48	0.25
Urinary magnesium (mmol/24 h)	-0.03	0.06	-0.07	-0.10	0.10	-0.10	0.14	0.03	-0.10	0.02	0.08	0.24	0.23	0.21	0.14	0.03	0.20	-0.01	-0.03	-0.02	0.02	-0.01	0.31	0.48		0.43
Urinary calcium (mmol/24 h)	-0.13	-0.03	-0.12	-0.12	0.03	-0.13	0.18	-0.06	-0.11	0.02	0.09	-0.02	-0.02	-0.01	0.13	0.12	-0.01	0.12	0.15	0.10	0.01	0.01	0.32	0.25	0.43	

[1] Adjusted for age, gender, and population sample.
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table 4.2. Variables by quintiles of glycaemic index in UK and USA INTERMAP participants, *n*=2385 [1,2]

	Glycaemic index										
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5		
Variable	mean	*SE*	mean	*SE*	mean	*SE*	mean	*SE*	mean	*SE*	*P for trend*
n	594		595		595		595				
Median	56.7		60.8		63.3		66.4		74.4		
Men (%)	41		42		41		42		41		
Education (y) [3]	14.7	0.1	14.6	0.1	14.4	0.1	14.5	0.1	14.6	0.1	0.50
Engagement in moderate and heavy physical activity (h/24 h) [3]	3.1	0.1	3.0	0.1	3.0	0.1	3.1	0.1	3.0	0.1	0.99
Systolic BP (mm Hg) [3]	117.9	0.6	119.0	0.6	119.2	0.6	119.2	0.6	118.8	0.6	0.55
Diastolic BP (mm Hg) [3]	73.8	0.4	74.8	0.4	74.2	0.4	74.2	0.4	73.9	0.4	0.52
Body mass index (kg/m^2) [3]	27.7	0.2	28.5	0.2	28.5	0.2	28.3	0.2	28.4	0.2	0.15
Total energy (kcal/24 h)	2239.0	24.1	2365.4	24.1	2341.1	24.1	2383.0	24.1	2313.4	24.6	0.0002
Food energy (kcal/24 h)	1788.4	21.4	1947.5	21.4	1936.6	21.4	1976.8	21.4	1935.0	21.8	1.65×10^{-09}
Beverage energy (kcal/24 h)	445.7	11.0	414.2	11.0	397.6	11.0	399.8	11.0	372.8	11.2	0.0001
Food weight (g/24 h)	1112.3	14.8	1136.6	14.8	1081.6	14.8	1088.7	14.8	1056.4	15.1	0.003
Beverage weight (g/24 h) [4]	1707.0	33.3	1571.8	33.3	1554.2	33.3	1553.4	33.3	1607.4	34.0	0.05×10^{-01}
Dietary energy density											
Food only (kcal/g)	1.7	0.02	1.8	0.02	1.8	0.02	1.9	0.02	1.9	0.02	4.14×10^{-21}
Food and beverages (kcal/g)	0.8	0.01	0.9	0.01	1.0	0.01	1.0	0.01	0.9	0.01	2.75×10^{-15}
Nutrient density (Nutrient Rich Food 9.3 index score)[3]	36.0	0.6	31.3	0.6	28.4	0.6	28.4	0.6	29.9	0.6	3.73×10^{-22}

Food Groups (g/1000 kcal)											
Whole fat dairy	24.9	1.8	28.5	1.8	25.7	1.8	25.2	1.8	25.8	1.9	0.64
Low or medium-fat dairy	110.4	3.9	94.0	3.9	76.9	3.9	70.6	3.9	82.4	4.0	4.37×10^{-13}
Meat	25.6	1.0	27.0	1.0	27.8	1.0	28.8	1.0	25.0	1.0	0.05
Fish	7.8	0.6	8.2	0.6	7.6	0.6	7.2	0.6	6.5	0.6	0.33
Raw vegetables	32.4	1.3	27.8	1.3	27.3	1.3	26.4	1.3	26.1	1.3	0.05×10^{-01}
Cooked vegetables	58.0	1.8	52.8	1.8	45.8	1.8	45.5	1.8	43.7	1.8	6.90×10^{-09}
Potatoes	30.7	1.4	36.9	1.4	40.6	1.4	40.6	1.4	38.4	1.4	6.70×10^{-07}
Fruit	68.7	2.7	54.3	2.7	43.8	2.7	43.4	2.7	46.3	2.8	2.38×10^{-12}
Cakes and pies	5.1	0.6	6.1	0.6	7.1	0.6	5.4	0.6	5.2	0.6	0.08
Nutrients											
Total Carbohydrate (%kcal)	47.3	0.3	48.9	0.3	48.7	0.3	48.5	0.3	48.7	0.4	0.01
Starch (%kcal)	22.5	0.2	22.9	0.2	22.9	0.2	23.5	0.2	24.2	0.2	8.30×10^{-06}
Estimated Total Sugar (%kcal)	25.1	0.3	26.2	0.3	26.0	0.3	25.3	0.3	24.7	0.3	0.09×10^{-01}
Fructose (%kcal)	5.0	0.1	5.0	0.1	4.8	0.1	4.6	0.1	4.1	0.1	1.13×10^{-07}
Galactose (%kcal)	0.1	0.02	0.04	0.01	0.03	0.01	0.04	0.01	0.04	0.01	5.46×10^{-12}
Glucose (%kcal)	5.0	0.1	5.1	0.1	5.1	0.1	5.0	0.1	4.6	0.1	0.01
Lactose (%kcal)	2.8	0.1	2.6	0.1	2.2	0.1	2.1	0.1	2.4	0.1	2.24×10^{-11}
Maltose (%kcal)	0.6	0.03	0.6	0.03	0.6	0.03	0.8	0.03	0.9	0.03	6.49×10^{-20}
Sucrose (%kcal)	9.4	0.2	10.9	0.2	11.3	0.2	10.9	0.2	10.6	0.2	2.83×10^{-08}
Total fibre (g/1000 kcal)	10.7	0.1	9.3	0.1	8.6	0.1	8.8	0.1	9.6	0.1	2.82×10^{-27}
Total protein (%kcal)	15.8	0.1	15.5	0.1	15.1	0.1	15.0	0.1	15.1	0.1	1.21×10^{-05}
Animal protein (%kcal)	10.1	0.1	10.1	0.1	9.9	0.1	9.7	0.1	9.5	0.1	0.01
Vegetable protein (%kcal)	5.5	0.1	5.2	0.1	5.1	0.1	5.2	0.1	5.4	0.1	3.48×10^{-06}

Total fat (%kcal)	32.0	0.3	33.2	0.3	33.9	0.3	33.8	0.3	33.2	0.3	4.91×10^{-05}
Total SFA (%kcal)	10.6	0.1	11.1	0.1	11.4	0.1	11.1	0.1	11.1	0.1	0.001
Total MFA (%kcal)	11.6	0.1	12.0	0.1	12.3	0.1	12.3	0.1	12.1	0.1	0.0001
Total PFA (%kcal)	6.6	0.1	6.9	0.1	7.0	0.1	7.1	0.1	6.9	0.1	0.002
Cholesterol (mg/1000 kcal)	121.5	2.5	128.5	2.5	129.5	2.5	131.9	2.5	130.1	2.5	0.04
24-hour urinary excretion data (mmol/24 h) [3]											
Sodium	151.1	2.5	162.5	2.5	158.4	2.5	167.1	2.5	160.3	2.5	0.0002
Potassium	63.2	0.9	62.0	0.9	57.5	0.9	57.4	0.9	60.3	0.9	2.19×10^{-07}
Magnesium	4.3	0.1	4.2	0.1	4.0	0.1	4.1	0.1	4.3	0.1	0.001
Calcium	4.2	0.1	4.3	0.1	4.1	0.1	4.2	0.1	4.4	0.1	0.18
Weight status (%) [5]											
Normal weight	149	31.3	138	28.9	141	29.6	148	31.0	135	28.3	
Overweight	207	43.5	187	39.1	185	38.9	174	36.4	189	39.6	
Obese	120	25.2	153	32.0	150	31.5	156	32.6	153	32.1	0.26

[1] Presented as mean and *SE*.
[2] Model 1 adjusted for gender, age, and population sample.
[3] Model 1a adjusted for variables in Model 1 plus total energy intake.
[4] Drinking water excluded.
[5] Chi square.

Table 4.3. Estimated mean systolic and diastolic BP differences per 2SD higher glycaemic index in UK and USA INTERMAP participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Model	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Glycaemic index													
Model 1	2385	0.04	-1.0, 1.1	0.95	0.3	-0.7, 1.4	0.52	0.5	-0.2, 1.3	0.16	0.7	0.1, 1.4	0.05
Model 2	2385	0.4	-0.7, 1.4	0.50	0.2	-0.8, 1.2	0.66	0.7	-0.04, 1.5	0.06	0.6	-0.6, 1.4	0.08
Sensitivity analyses using model 2													
Censored regression	1898	0.01	0.02, 0.01	0.02	0.01	0.01, 0.02	0.01	0.02	0.01, 0.03	0.002	0.02	0.01, 0.03	0.001
Excluding those with high variability in their diet	1870	0.7	-0.5, 1.8	0.29	0.4	-0.8, 1.5	0.54	0.8	-0.01, 1.6	0.05	0.6	-0.2, 1.4	0.11
Excluding those following a special diet	2243	0.3	-0.8, 1.4	0.58	0.02	-0.8, 1.3	0.60	0.8	0.05, 1.6	0.04	0.8	0.1, 1.5	0.04
Excluding those diagnosed with DM and/or CVD [2,3]	2054	0.3	-0.9, 1.5	0.61	0.2	-0.8, 1.9	0.69	0.8	-0.01, 1.5	0.07	0.7	-0.01, 1.5	0.07

Model 1 adjusted f for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] 2SD of GI=17.6.
[2] 2SD of GI=16.7.
[3] Not adjusted for DM or CVD diagnosis.

Table 4.4. Estimated mean systolic and diastolic BP differences per 2SD higher glycaemic load in UK and USA INTERMAP participant [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Model	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Glycaemic load													
Model 1	2385	0.3	-2.2, 2.8	0.82	3.0	1.1, 4.9	0.002	0.9	-0.8, 2.7	0.30	2.3	0.9, 3.6	0.001
Model 2	2385	0.6	-1.7, 2.9	0.62	0.2	-2.2, 2.6	0.87	1.4	-0.2, 3.0	0.09	1.1	-2.7, 0.6	0.22
Sensitivity analyses using model 2													
Censored regression [2]	1898	0.01	-0.02, 0.02	0.23	0.01	-0.02, 0.04	0.28	0.04	0.02, 0.1	0.03	0.04	0.02, 0.06	0.03
Excluding those with high variability in their diet [2]	1870	0.6	-3.4, 2.3	0.69	0.3	-2.5, 3.0	0.85	1.5	-3.3, 0.3	0.10	1.4	-0.5, 3.2	0.16
Excluding those following a special diet [3]	2243	0.6	-2.9, 1.8	0.65	0.2	-2.2, 2.6	0.86	1.7	0.1, 3.3	0.04	1.3	-0.4, 3.0	0.13
Excluding those diagnosed with DM and/or CVD [4,5]	2054	0.5	-2.0, 3.0	0.66	0.5	-1.9, 2.9	0.66	1.6	-0.1, 3.4	0.06	1.6	-0.03, 3.3	0.05

Model 1 adjusted f for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] 2SD of GL=119.6.
[2] 2SD of GL=114.4.
[3] 2SD of GL=120.3.
[4] 2SD of GL=119.4.
[5] Not adjusted for DM or CVD diagnosis.

Table 4.5. Estimated mean BMI difference per 2SD higher glycaemic index in UK and USA INTERMAP participants [1]

Model	*n*	BMI Difference, kg/m^2	95% CI	*p*
Glycaemic index				
Model 1	2385	0.1	-0.4, 0.5	0.82
Model 2	2385	0.01	-0.4, 0.4	0.96
Sensitivity analyses using model 2				
Excluding those with high variability in their diet	1870	-0.3	-0.7, 0.2	0.29
Excluding those following a special diet	2243	0.1	-0.4, 0.5	0.78
Excluding those diagnosed with DM and/or CVD [2]	2054	0.01	-0.5, 0.5	0.95

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] 2SD of GI=17.6.
[2] 2SD of GI=16.7.

Table 4.6. Estimated mean BMI difference per 2SD higher glycaemic load in UK and USA INTERMAP participants [1]

Model	*n*	BMI Difference, kg/m^2	95% CI	*p*
Glycaemic load				
Model 1	2385	0.1	-0.9, 1.2	0.78
Model 2	2385	0.1	-0.9, 1.1	0.88
Sensitivity analyses using model 2				
Excluding those with high variability in their diet [2]	1870	-0.002	-1.3, 0.9	0.75
Excluding those following a special diet [3]	2243	0.02	-1.0, 1.0	0.97
Excluding those diagnosed with DM and/or CVD [4]	2054	0.2	-0.9, 1.2	0.74

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] 2SD of GL=119.6.
[2] 2SD of GL=114.4.
[3] 2SD of GL=120.3.
[4] 2SD of GL=119.4.

Table 4.7. Estimated mean systolic and diastolic BP differences per 2SD higher intakes of total fibre in USA INTERMAP participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Model	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Total fibre [2]													
Model 1	1941	-3.5	-4.8, -2.2	3.23×10^{-07}	-2.4	-3.7, -1.1	0.0002	-1.7	-2.7, -0.8	0.0003	-1.1	-2.0, -0.2	0.02
Model 2	1941	-3.0	-4.3, -1.6	2.79×10^{-05}	-1.7	-3.0, -0.4	0.01	-1.5	-2.4, -0.5	0.003	-0.7	-1.7, 0.2	0.14
Model 3	1941	-3.0	-4.3, -1.7	2.99×10^{-05}	-1.7	-3.0, -0.3	0.02	-1.4	-2.4, -0.4	0.06×10^{-01}	-0.6	-1.5, 0.4	0.26
Model 4	1941	-2.8	-4.4, -1.6	0.0001	-1.1	-2.6, 0.3	0.12	-1.3	-2.3, -0.2	0.02	-0.2	-1.2, 0.8	0.67
Model 5	1941	-3.0	-4.2, -1.4	2.32×10^{-05}	-1.8	-3.1, -0.4	0.01	-1.5	-2.4, -0.5	0.003	-0.7	-1.7, 0.2	0.12
Sensitivity analyses using model 2													
Censored regression [3]	1517	-0.7	-0.9, -0.2	1.45×10^{-06}	-0.5	-0.6, -0.1	0.001	-0.3	-0.4, -0.1	0.0003	-0.2	-0.3, -0.1	0.04
Excluding those with high variability in their diet [3]	1506	-2.5	-4.0, -0.9	0.002	-1.4	-2.9, 0.04	0.06	-1.3	-2.3, -0.3	0.01	-0.7	-1.7, 0.3	0.17
Excluding those following a special diet [4]	1825	-2.9	-4.2, -1.5	6.32×10^{-05}	-1.7	-3.0, -0.3	0.02	-1.5	-2.5, -0.5	0.003	-0.8	-1.7, 0.2	0.10
Excluding those diagnosed with DM and/or CVD [5]	1650	-3.1	-4.5, -1.7	2.52×10^{-05}	-1.8	-3.2, -0.5	0.09×10^{-01}	-1.7	-2.7, -0.7	0.001	-0.9	-1.9, 0.1	0.08

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
Model 3 for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24 h).
Model 4 for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24 h).
Model 5 for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24 h).
[1] 2SD of total fibre (g/1000 kcal)=6.6.
[2] Additionally adjusted for total sugar (%).
[3] 2SD of total fibre (g/1000 kcal)=6.3.
[4] 2SD of total fibre (g/1000 kcal)=6.4.
[5] Not adjusted for DM or CVD diagnosis.

Table 4.8. Estimated mean systolic and diastolic BP differences per 2SD higher intake of insoluble fibre in USA INTERMAP participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Model	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Insoluble fibre [2]													
Model 1	1941	-3.3	-5.2, -1.3	0.001	-2.1	-4.0, -0.3	0.03	-1.9	-3.2, -0.5	0.08×10^{-01}	-1.2	-2.5, 0.1	0.08
Model 2	1941	-3.2	-5.1, -1.2	0.002	-2.0	-3.9, -0.1	0.04	-1.7	-3.1, -0.4	0.01	-1.0	-2.4, 0.3	0.12
Model 3	1941	-3.2	-5.1, -1.2	0.001	-1.9	-3.8, -0.1	0.04	-1.7	-3.0, -0.3	0.02	-0.9	-2.2, 0.4	0.17
Model 4	1941	-3.1	-5.0, -1.1	0.002	-1.8	-3.7, 0.1	0.06	-1.7	-3.0, -0.3	0.02	-0.8	-2.1, 0.5	0.21
Model 5	1941	-1.7	-3.1, -0.4	0.01	-2.0	-3.8, -0.1	0.04	-1.7	-3.1, -0.4	0.01	-1.0	-2.3, 0.3	0.12
Sensitivity analyses using model 2													
Censored regression [3]	1517	-0.4	-0.6, -0.2	2.53×10^{-05}	-0.3	-0.5, -0.1	0.002	-0.3	-0.5, -0.2	0.0004	-0.2	-0.4, -0.1	0.02
Excluding those with high variability in their diet [3]	1506	-2.8	-5.0, -0.6	0.01	-1.9	-3.9, 0.2	0.08	-1.3	-2.8, 0.1	0.08	-0.8	-2.2, 0.7	0.31
Excluding those following a special diet	1825	-3.2	-5.3, -1.2	0.002	-1.9	-3.9, 0.1	0.06	-2.1	-3.5, -0.6	0.05×10^{-01}	-1.2	-2.6, 0.2	0.08
Excluding those diagnosed with DM and/or CVD [4,5]	1650	-3.2	-5.2, -1.1	0.003	-2.0	-3.9, 0.1	0.06	-1.9	-3.3, -0.4	0.01	-1.1	-2.5, 0.3	0.13

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
Model 3 for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24 h).
Model 4 for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24 h).
Model 5 for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24 h).
[1] 2SD of insoluble fibres (g/1000 kcal)=4.4.
[2] Additionally adjusted for total sugar (%) and soluble fibre (g/1000 kcal).
[3] 2SD of insoluble fibres (g/1000 kcal)=4.3.
[4] 2SD of insoluble fibres (g/1000 kcal)=4.5.
[5] Not adjusted for DM or CVD diagnosis.

Table 4.9. Estimated mean systolic and diastolic BP difference per 2SD higher intake of soluble fibre in USA INTERMAP participants [1]

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Variable	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Soluble fibre [2]													
Model 1	1941	-0.2	-2.3, 1.9	0.86	-0.5	-2.5, 1.6	0.66	0.1	-1.4, 1.5	0.94	-0.1	-1.5, 1.3	0.89
Model 2	1941	0.1	-2.0, 2.2	0.94	-0.02	-2.0, 2.0	0.99	0.1	-1.4, 1.6	0.92	0.02	-1.4, 1.4	0.98
Model 3	1941	0.1	-2.1, 2.2	0.96	-0.03	-2.3, 1.7	0.99	0.1	-1.4, 1.6	0.90	0.1	-1.4, 1.5	0.95
Model 4	1941	0.2	-1.9, 2.3	0.86	0.3	-2.0, 2.1	0.76	0.2	-1.3, 1.7	0.79	0.3	-1.2, 1.7	0.97
Model 5	1941	0.02	-2.1, 2.1	0.98	-0.1	-2.1, 1.9	0.94	0.1	-1.4, 1.5	0.95	-0.02	-1.4, 1.4	0.98
Sensitivity analyses using model 2													
Censored regression [3]	1517	0.01	-0.01, 0.03	0.53	0.01	-0.01, 0.03	0.35	0.01	-0.02, 0.03	0.52	0.01	-0.02, 0.03	0.28
Excluding those with high variability in their diet [3]	1506	0.1	-2.1, 2.2	0.95	0.01	-2.1, 2.1	0.99	-0.1	-1.5, 1.4	0.92	-0.1	-1.5, 1.3	0.88
Excluding those following a special diet [4]	1825	0.5	-1.6, 2.6	0.65	0.2	-1.8, 2.3	0.82	0.5	-1.0, 1.8	0.51	0.3	-1.1, 1.8	0.64
Excluding those diagnosed with DM and/or CVD [4,5]	1650	0.1	-2.1, 2.3	0.96	0.01	-2.1, 2.1	0.98	0.2	-1.4, 1.7	0.85	0.1	-1.4, 1.6	0.87

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
Model 3 for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24 h).
Model 4 for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24 h).
Model 5 for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24 h).
[1] 2SD of soluble fibres (g/1000 kcal)=2.2.
[2] Additionally adjusted for total sugar (%) and insoluble fibre (g/1000 kcal).
[3] 2SD of soluble fibres (g/1000 kcal)=2.0.
[4] 2SD of soluble fibres (g/1000 kcal)=2.1.
[5] Not adjusted for DM or CVD diagnosis. 2SD

Table 4.10. Estimated mean BMI difference per 2SD higher intake of total fibre in USA INTERMAP participant [1]

Model	*n*	BMI Difference, kg/m^2	95% CI	*p*
Total fibre (g/1000 kcal) [2]				
Model 1	1941	-1.5	-2.0, -0.9	2.02×10^{-07}
Model 2	1941	-1.7	-2.3, -1.2	2.45×10^{-09}
Model 3	1941	-1.9	-2.5, -1.3	1.25×10^{-10}
Model 4	1941	-2.3	-2.9, -1.7	2.64×10^{-14}
Model 5	1941	-1.7	-2.3, -1.2	3.53×10^{-09}
Sensitivity analyses using model 2				
Excluding those with high variability in their diet [3]	1506	-1.5	-2.2, -0.9	3.82×10^{-06}
Excluding those following a special diet [4]	1825	-1.7	-2.3, -1.1	2.18×10^{-08}
Excluding those diagnosed with DM and/or CVD	1650	-1.7	-2.2, -1.1	4.03×10^{-08}

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
Model 3 for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24 h).
Model 4 for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24 h).
Model 5 for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24 h).
[1] 2SD of total fibre (g/1000 kcal)=6.6.
[2] Additionally adjusted for total sugar (%).
[3] 2SD of total fibre (g/1000 kcal)=6.3.
[4] 2SD of total fibre (g/1000 kcal)=6.4.

Table 4.11. Estimated mean BMI difference per 2SD higher intake of insoluble fibre in USA INTERMAP participants [1]

Model	*n*	BMI Difference, kg/m^2	95% CI	*p*
Insoluble fibre (g/1000 kcal) [2]				
Model 1	1941	-1.6	-2.4, -0.8	0.0002
Model 2	1941	-1.7	-2.5, -0.9	3.75×10^{-05}
Model 3	1941	-1.8	-2.6, -1.0	8.95×10^{-06}
Model 4	1941	-1.9	-2.7, -1.1	2.19×10^{-06}
Model 5	1941	-1.7	-2.5, -0.9	4.06×10^{-05}
Sensitivity analyses using model 2				
Excluding those with high variability in their diet [3]	1506	-1.5	-2.4, -0.6	0.002
Excluding those following a special diet	1825	-1.8	-2.7, -1.0	6.10×10^{-07}
Excluding those diagnosed with DM and/or CVD [4]	1650	-1.7	-2.4, -0.7	0.0003

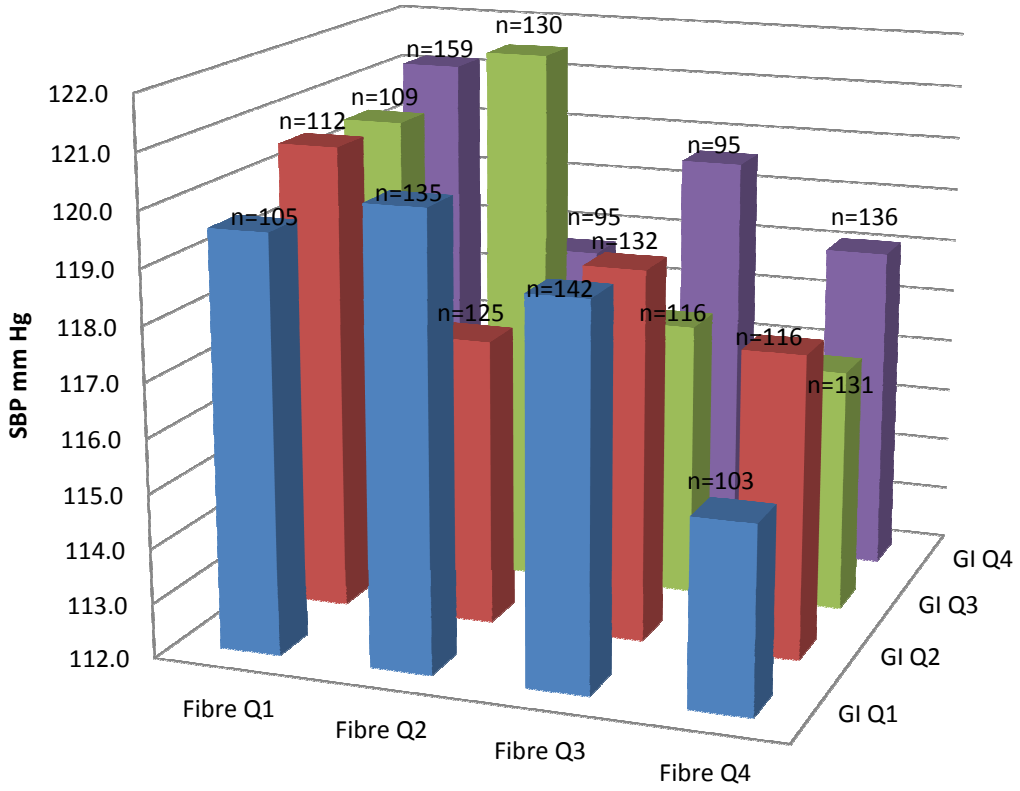
Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
Model 3 for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24 h).
Model 4 for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24 h).
Model 5 for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24 h).
[1] 2SD of insoluble fibres (g/1000 kcal)=4.4.
[2] Additionally adjusted for total sugar (%) and soluble fibre (g/1000 kcal).
[3] 2SD of insoluble fibres (g/1000 kcal)=4.3.
[4] 2SD of insoluble fibres (g/1000 kcal)=4.5.

Table 4.12. Estimated mean BMI difference per 2SD higher intake of soluble fibre in USA INTERMAP participants [1]

Model	*n*	BMI Difference, kg/m^2	95% CI	*p*
Soluble fibre (g/1000 kcal) [2]				
Model 1	1941	0.3	-0.5, 1.2	0.45
Model 2	1941	0.1	-0.8, 1.0	0.80
Model 3	1941	0.1	-0.8, 1.0	0.86
Model 4	1941	-0.2	-1.1, 0.7	0.62
Model 5	1941	0.1	-0.7, 1.0	0.78
Sensitivity analyses using model 2				
Excluding those with high variability in their diet [3]	1506	-0.1	-1.1, 0.8	0.77
Excluding those following a special diet [4]	1825	0.02	0.9, 1.0	0.93
Excluding those diagnosed with DM and/or CVD [4]	1650	-0.3	-1.2, 0.6	0.54

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
Model 3 for variables in Model 2 plus 24-hour urinary excretion of magnesium (mmol/24 h).
Model 4 for variables in Model 2 plus 24-hour urinary excretion of potassium (mmol/24 h).
Model 5 for variables in Model 2 plus 24-hour urinary excretion of calcium (mmol/24 h).
[1] 2SD of soluble fibres (g/1000 kcal)=2.2.
[2] Additionally adjusted for total sugar (%) and insoluble fibre (g/1000 kcal).
[3] 2SD of soluble fibres (g/1000 kcal)=2.0.
[4] 2SD of soluble fibres (g/1000 kcal)=2.1.

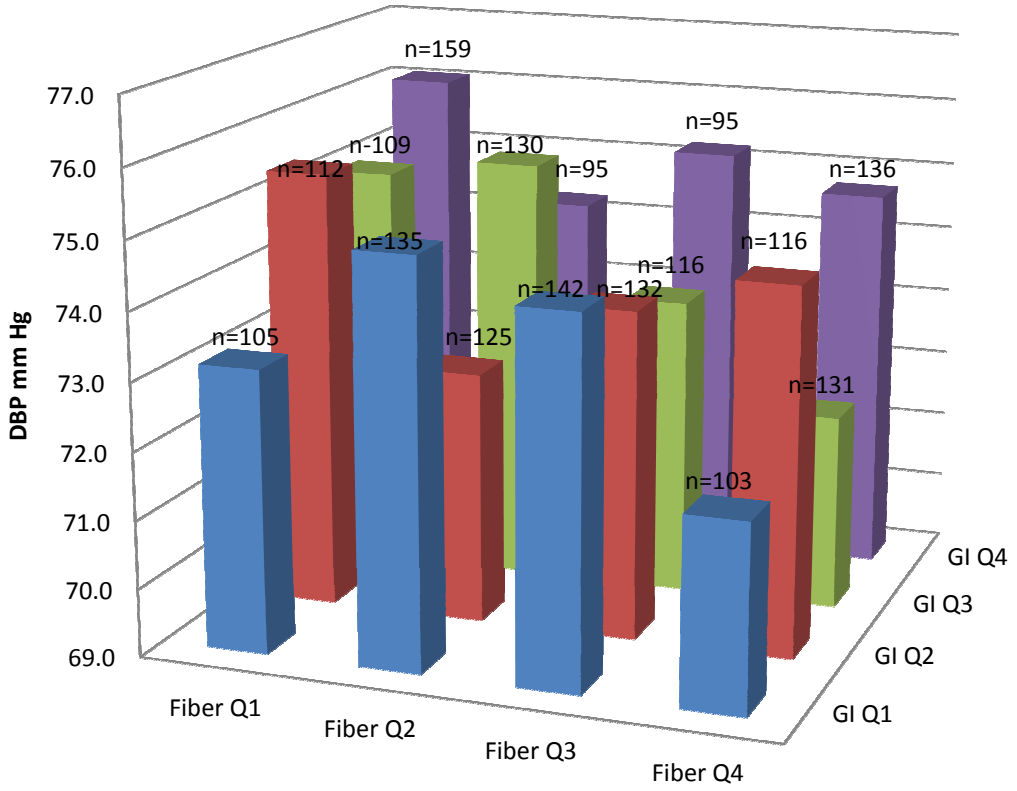
Figure 4.1. Glycaemic index and total fibre intake in relation to systolic BP in UK and USA INTERMAP participants, *n*=2385



	Fibre Q1	Fibre Q2	Fibre Q3	Fibre Q4
GI Q1	119.6	120.2	118.9	115.4
GI Q2	120.6	117.2	118.8	117.5
GI Q3	120.5	121.9	117.1	116.5
GI Q4	121.2	117.6	119.6	118.1

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

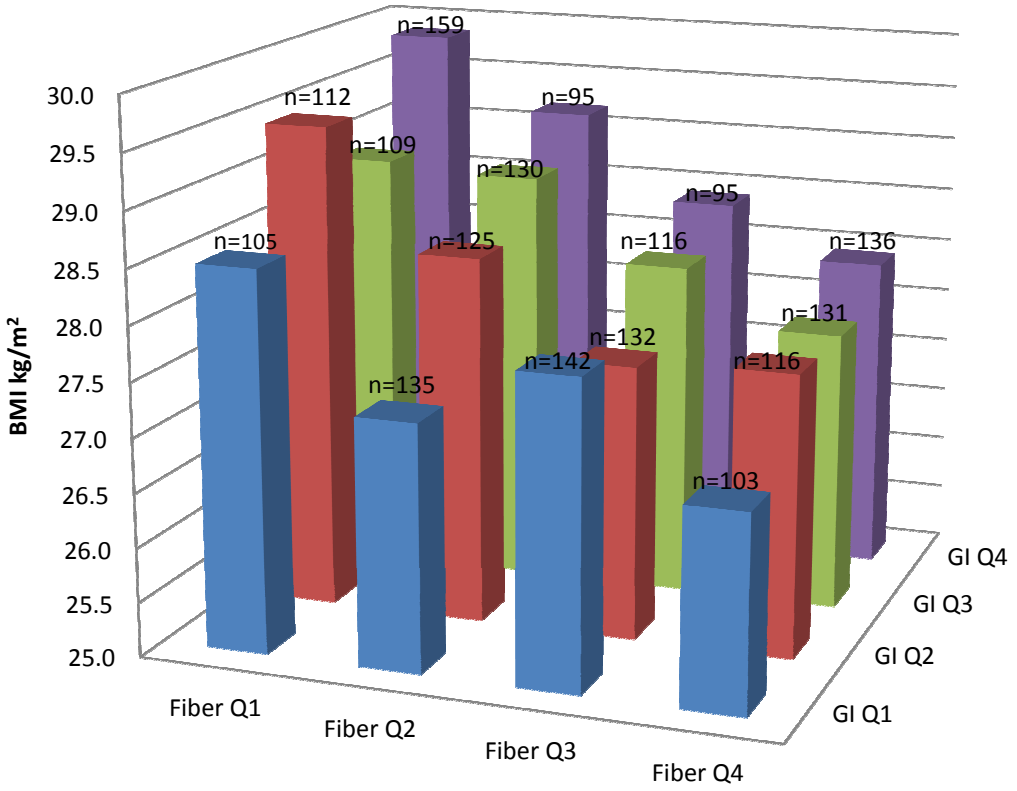
Figure 4.2. Glycaemic index and total fibre intake in relation to diastolic BP in UK and USA INTERMAP participants, *n*=2385



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	73.2	75.0	74.4	71.7
GI Q2	75.5	72.7	73.8	74.4
GI Q3	75.0	75.3	73.4	71.9
GI Q4	76.1	74.3	75.2	74.7

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

Figure 4.3. Glycaemic index and total fibre intake in relation to body mass index in UK and USA INTERMAP participants, *n*=2385



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	28.5	27.3	27.8	26.8
GI Q2	29.5	28.4	27.5	27.6
GI Q3	28.9	28.8	28.1	27.6
GI Q4	29.9	29.2	28.4	27.9

Model 1 adjusted for age, gender, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

CHAPTER V

Discussion

5. DISCUSSION

5.1. Main findings

- A higher number of eating occasions per day was associated with lower BP and BMI, as well as lower dietary energy density and higher nutrient density.
- Higher evening relative to morning energy intake was directly associated with BMI.
- Glycaemic index and glycaemic load were not associated with BP or BMI.
- Total and insoluble fibre intakes were inversely associated with BP and BMI.
- Soluble fibre was not associated with BP or BMI.
- Participants with the highest GI and lowest fibre intake had the highest BP and BMI levels compared to participants with the lowest GI and highest fibre intake.

This study has demonstrated that frequent consumption of meals was associated with lower BP and BMI, which maybe due to a lower dietary energy density and a higher nutritional quality eating pattern. The inverse association between eating frequency and systolic BP was independent of BMI. In multivariable regression analysis adjusted for lifestyle and dietary confounders, eating occasions higher by 2SD were associated with systolic BP lower by 1.6 mm Hg, and the adjustment for BMI only slightly reduced the regression coefficient values (Table 3.6). In addition, eating occasions higher by 2SD were associated with BMI lower by 1.1 kg/m^2 [equivalent to -3.2 kg in weight], adjusted for lifestyle and dietary confounders (Table 3.7). These findings support the first and second hypotheses: an inverse association between the number of eating occasions, nutrient density and BP, BMI; a direct association of dietary energy density and both BP and BMI.

Multivariable regression analysis showed that the ratio of evening to morning energy intake was directly associated with BMI, whereas this consumption pattern was not associated with BP level. These findings support the hypothesis that a direct association exists between the ratio of evening to morning energy intake and BMI, however not BP. In gender-specific analysis, the ratio of evening to morning energy intake was significantly and directly associated with BMI in women (Table A.11).

When the association of GI, GL and BP, BMI was analysed, the results showed no evidence of a direct association in any of the models (Table 4.3, 4.4, 4.5, and 4.6). These findings do no support the hypothesis of a direct association between GI, GL and BP, BMI. Only the results of censored regression for antihypertensive medication use revealed a direct and significant association between GI, GL and systolic and diastolic BP, independent of BMI. However, differences in systolic and diastolic BP associated with 2SD higher GI, GL were small (ranging from 0.01 mm Hg for systolic BP to 0.04 mm Hg for diastolic BP).

Total fibre intake higher by 7 g/1000 kcal was associated with systolic and diastolic BP lower by 1.7 and 0.7 mm Hg, respectively, independent of BMI. The findings obtained for insoluble fibre were similar to total fibre, with an inverse association with systolic BP, independent of soluble fibre intake and BMI (Table 4.8). Finally, no evidence in support of an inverse association between soluble fibre and BP was found (Table 4.9).

Total and insoluble fibre intakes were inversely associated with BMI and were independent of the intake of nutrients known to be present in high quantities in fibre-rich foods. Total fibre intake higher by 7 g/1000 kcal was associated with BMI lower by 1.7 kg/m^2 [equivalent to -4.9 kg in weight], with multivariable adjustment (Table 4.10). Similarly, insoluble fibre intake higher by 4 g/1000 kcal was associated with

BMI lower by 1.7 kg/m^2 (Table 4.11). However, there was no evidence supporting an inverse association between soluble fibre intake and BMI (Table 4.12). These findings support the hypothesis that an inverse association exists between dietary fibre and BP, BMI, however not with soluble fibre.

5.1.1. Eating behaviour

A limited number of intervention studies have included BP in their outcome measure when investigating the relation between eating frequency and health, reporting lower BP level with high number of meals/day compared to fewer number of meals/day [119]. Improvements in risk factors related to CVD, such as lower LDL, total cholesterol, 24-hour insulin and insulin-glucose output were reported when participants were provided with small-frequent meals compared to large-less frequent meals/day [120]. However, other similar trials found no difference in lipid profile or BP between groups assigned to low and high meal frequency treatments [121,122]. These differences may potentially be attributed to inconsistencies in trial length, frequency of BP measurements, and participants' dietary compliance.

The findings of the INTERMAP study demonstrate that frequent eating is associated with lower BMI. This outcome is in accordance with eight population studies[112-114,127,129-132], four of which were conducted on large samples and have revealed similar relationships [112,114,130,131]. However, in another eight studies, no evidence of an inverse relationship between eating frequency and body weight was found [115,116,128,133-137].

Inconsistencies in findings reported in published studies may be attributed to studies being of small sample size with low statistical power [429], differences in dietary assessment methods [141], presence of under-reporters of energy [142], and the lack of a unified definition of what constitutes an eating occasion [118,141,143,148,160], especially

when the number of meals is self-reported [137]. Thus, it is essential that epidemiologic studies employ consistent and rigorously validated assessment methods, as energy intake under-reporting is common, especially among women [150,152-154], overweight, obese [145,146], or older participants [147]. As multiple 24-hour dietary recalls are more representative of typical food intake, they reduce the effect of random error due to day-to-day variability in food intake [157,158]. Another limitation typically affecting studies of eating frequency and body weight stems from the absence of an adjustment for physical activity level [116,128], which has been reported as a potential confounder in the association between eating frequency and body weight [159].

Possible mechanisms through which eating frequency is associated with BP and BMI

The biological basis of the putative beneficial effect on BP and BMI and total energy intake of greater eating frequency is likely to be multifactorial. Findings of several clinical feeding trials suggest that eating on only a few occasions during the day may have a negative effect on appetite control [119,430]. Evidence indicates that, when meal frequency is increased, a number of hormonal and nutritional signals may enhance appetite suppression (e.g., ghrelin). This, in turn, may result in a reduction in energy intake [431], as well as delayed gastric emptying, leading to a decreased feeling of hunger [432]. Similarly, research findings indicate that isocaloric increase in meal frequency in the morning may lead to a decrease in subjective feelings of hunger, possibly due to a complex interaction of anoretic signals from an increase in glucagon-like peptide 1(GLP-1) and a decrease in ghrelin [433]. Results of a randomised cross-over trial involving 12 men revealed that higher plasma free-fatty acids (p=0.01), and lower plasma GLP-1 (p=0.01) were reported in individuals who ate later in the day and in

large portions, compared to those that had regular breakfast and several smaller meals throughout the day prior to preload [434].

The findings of the INTERMAP study also demonstrate an inverse association between eating frequency and dietary energy density. This is in line with the findings of a recent systematic review of cohort studies and RCTs, which indicated that most research in this field supports an inverse association between body weight and dietary energy density [166]. Having fewer meals in a 24-hour period that consist of large portions of energy-dense food may promote overeating [435], which may be explained by the increase in ghrelin and the decrease in PYY associated with higher dietary energy density [203], especially that people tend to consume a consistent weight of food [179,204,205].

Increased frequency of eating occasions has also been linked to improvements in glucose homeostasis in both prospective cohort studies [436] and clinical trials [437-440]. Impaired glucose homeostasis has been associated with high BP level and obesity in adults [441]. In a randomised cross-over pilot study, a causal relationship between breakfast frequency and quality and both appetite control and glycaemic control was established [442]. Having fewer, larger meals a day resulted in a larger AUC of insulin response (p=0.01), higher fasting total cholesterol (3.43 vs. 3.14 mmol/l) and higher LDL (1.82 vs. 1.55 mmol/l), compared to those who consumed breakfast and generally ate smaller meals (p=0.001) [443].

In the INTERMAP study, the consumption of a larger amount of food in the evening, compared to what is ingested in the morning, was directly associated with BMI. Furthermore, when participants were classified jointly by frequency of eating occasions and the ratio of evening to morning energy intake, individuals whose diets are characterised by a higher ratio of evening to morning energy intake were found to, on

average, consume their overall food intake on fewer eating occasions. It is possible that those individuals generally consumed larger servings, with the larger portion of their diet consumed in the evening. Evidence from studies on shift work provides more insight into the association between the time of energy intake and being overweight. Shift workers, particularly those that often work during the night, tend to have higher night-time food intake and consume larger quantities of energy dense foods [251,444], and are thus at risk of body weight gain [241]. The observed direct association between evening relative to morning energy intake and BMI in the INTERMAP study may be linked to the possible decline in insulin sensitivity during the evening, which is caused by an elevation in NEFA [254]. Findings suggest that lifestyle and dietary behaviours play a key role in managing healthy body weight. Participants whose total food intake is consumed through fewer eating occasions may typically have a lifestyle associated with dining out in the evening, with the meals consumed consisting of energy-dense foods with lower nutrient density (e.g., deep-fried foods), along with excessive alcohol consumption. In addition, there may be limited access to low energy-dense foods of high nutrient density (e.g., fruit and vegetables).

In addition, fibre intake may have played a role in the observed inverse associations between BP, BMI and eating occasions, since associations were reduced when dietary fibre was adjusted for. This lead to further investigation into the association between dietary fibre, GI, GL and BP, BMI.

5.1.2. Glycaemic index, glycaemic load and dietary fibre

The analyses conducted as part of this study did not establish a direct association between GI, GL and BP or BMI. Only a few observational and cross-sectional studies investigated the association between GI, GL and BP, and showed inconsistent

findings [308-310], with some findings significantly inverse in White women only [310], or non-significant [309]. Randomised feeding trials showed inconsistent findings as well, with some showing significant reductions in BP level following a low GI diet [306], and similar trials showing non-significant reductions in BP [307]. For the association with body weight, prospective cohort studies showed that a high GI, GL was related to a small change in body weight, and GI, GL was inversely but non significantly related to body weight [340,445]. Intervention trials examining the effect of a low GI, GL diet on BMI found non-significant reductions in BMI or body weight [305,322-324,326-328,330-332,334,336], while only a few revealed significant reductions [303,318,319,321,325,335]. These inconsistencies may be attributed to differences in reported GI, GL values, absence of caloric restriction, short trial duration, and participants' adherence to the prescribed diet treatments [320,321,325,327,336]. While low glycaemic diets have been linked to increased satiety, affecting subsequent food intake [446-448], and improved blood lipids and insulin sensitivity, these findings were only reported in one prospective cohort and one RCT study [283,284].

One particular large cross-sectional study [339], the IRAS study, did not support the hypothesis that low GI, GL diets are associated with lower BP and BMI levels. Their findings indicate that increased fibre intake is more associated with lower fasting insulin level, waist circumference, and BMI compared to GI, GL [339], thus further investigation into the role of dietary fibre was conducted for the present study.

Results of the INTERMAP study, involving USA participants only, revealed significant inverse relationships between total and insoluble dietary fibre and BP, BMI when data were analysed using models controlling for a wide range of potential lifestyle and dietary confounders. However, there was no evidence to support an inverse association between soluble fibre and BP, BMI. To the author's knowledge, the present study is the

first to use multivariable models adjusted extensively for lifestyle and dietary confounders to examine the associations between total, insoluble, and soluble fibre intake and BP, BMI, while controlling mutually for the other types of fibre.

Previous cross-sectional studies reported inverse associations between total fibre and BP [360-365], while others found no association [363,366,368,369]. There have been few prospective cohort studies that found inverse relations between total fibre intake and BP change [346], or risk of developing hypertension [364,365]. Some findings were significant in white men and women only [346] or findings were attenuated after adjustment for dietary confounders [365]. It is worth noting that in these studies, results were based on models adjusted mainly for lifestyle factors, with less emphasis on dietary confounders. More specifically, in several studies, the models used adjusted for non-dietary confounders only [360-363,366,368], with only a few including *some* dietary confounders [363,366,368]. The INTERMAP study used multivariable nutrient density models, adjusted for total energy intake and for objective measures of dietary intake from urinary data, which are not available in most studies. In addition, in studies examining the association of fibre and BP, BP was generally not the main outcome; thus, the BP measurement frequency was typically low, including one [369] or two [363,368], and was, in some cases, self-reported [364,365]. Additionally, the majority of these studies used data based on single [363,368] or self-reported FFQs [364,365], or alternatively single 24-hour dietary recalls [363,369]. In the INTERMAP study, however, results were derived from high quality dietary data collected over four visits, with higher correlations between dietary and urinary variables in comparison to previously reported values [449]. Meta-analysis of randomized placebo-controlled trials measuring the effect of total fibre supplementation on BP concluded non-significant reductions in BP [384]. The variability in the results obtained in different trials may be attributed to the dose and type of fibre

(dietary, supplementary), the length of trial, and the washout period [380,381,383,385,389,392] (especially when change in BP level is the primary study outcome), as well as the age of participants, sample size [380,381,383,385,392], and the inclusion of a body weight reduction plan [379,380,382,388,392].

For the association between total fibre intake and body weight, some cross-sectional [339,395] and prospective cohort studies [346,402] showed invers associations with BMI, while other cross-sectional [396,398] and prospective cohort [397] studies reported no association. Intervention studies revealed small [403,404] or non-significant reductions in body weight with fibre intake [401,406,407]

The independent association between different types of fibre and BP, BMI has been less thoroughly explored, as an extensive literature review conducted as a part of this study revealed only one cross-sectional analysis (the SU.VI.MAX) exploring different types of fibre in relation to risk of high BP and high BMI [378]. This study explored the association between total, insoluble, and soluble fibre and CVD risk factors, while adjusting for some dietary confounders (saturated fat, carbohydrates, and alcohol) [378]. The reported findings were compatible with those of the INTERMAP study, in that they revealed significant associations between total and insoluble dietary fibre and both BP and BMI, but not with soluble fibre [378].

The mechanism by which fibre intake affects BP may be attributed to a variety of factors, including increase in nitric oxide release (a vasodilator) [450]; improvement in endothelial function by inhibiting sodium absorption [451], although inconclusive [452]; and improvement in CVD risk factors [453]. Moreover, higher fibre intake was linked to the improvements in insulin sensitivity and hyperglycaemia, which resulted in more optimal BP levels and body weight status [454,455]. Insoluble and soluble fibre cause lower

postprandial glucose responses and LDL cholesterol levels [456]. Additionally, in large population-based studies, insoluble fibre has been strongly linked to a lower risk of type 2 diabetes [456,457]. A recent meta-analysis including 328,212 individuals found inverse associations between high cereal fibre and risk of developing diabetes, but fruit or vegetable intakes were not associated [353]. The reduction in the risk of developing diabetes can be attributed to the mechanisms of both insoluble and soluble dietary fibre, which act in tandem to achieve optimal effects, including improvements in insulin sensitivity, reduced levels of inflammatory markers (C-reactive protein), and hormonal response (i.e., increased satiety). While it can be hypothesised that improvement in insulin sensitivity is likely to be the factor behind the ability of insoluble fibre to lower diabetes risk, the exact mechanism is yet to be identified [458]. Health benefits of insoluble fibre include an increase in faecal bulk, consequently accelerating transit time through the intestine [350]. Some evidence suggests that soluble fibre can increase satiety, thus decreasing overall energy intake [459]; however, this mechanism is controversial [403,404].

Furthermore, differences in gut microbial population have been observed in relation to fibre intake; fewer Bacteroidetes and more Firmicutes were found in obese individuals, resulting from low fibre intake [460]. In addition, when participants were classified jointly by GI and dietary total fibre intake, lower BP and BMI levels were associated with diets low in GI and high in dietary fibre. Diets with a high GI and low in dietary fibre (e.g., white rice, refined bread, potato) may lead to higher demand for insulin, aggravated by insulin resistance [461,462]. Pancreas exhaustion may occur when it fails to meet the demand for more insulin. It may occur in relation to glucose toxicity in beta cells, however, this condition is reversible [463,464].

Based on the aforementioned evidence, it can be posited that the inverse associations between insoluble fibre and BP observed in the INTERMAP study may be driven by potassium present in fibre-rich foods, as the identified association was no longer statistically significant after adjusting for potassium. Potassium is one of the key electrolytes in the human body and is essential for acid-electrolyte balance, cell function, muscle contraction, and many more physiological functions, including BP regulation [465,466]. Two meta-analyses of RCTs revealed that potassium intake could be effective in reducing BP in normotensive and hypertensive individuals [27,467]. Similarly, a recent meta-analysis of RCTs and cohort studies concluded that higher potassium intake showed overall reductions in systolic and diastolic BP of 3.49 (95% CI: 1.82, 5.15 mm Hg) and 1.96 (95% CI: 0.86, 3.06 mm Hg), respectively [468]. A low potassium level may disrupt the renin-angiotensin-aldosterone system, causing elevation in BP level in rats [469].

5.2. Study strengths and limitations

The INTERMAP study aimed to identify the role of macro and micronutrients in the aetiology of high BP. Its quality and contribution to the academic research and clinical practice are best exemplified by its unique characteristics, which include the large and diverse population samples (four in Japan, three in China, two in the UK, and eight in the US), highly standardised multiple measures of dietary intake, urinary excretion, and BP (four 24-hour dietary recalls, two 24-hour urine collections, eight BP measurements), and the ability to successfully control for a wide range of known confounders.

Moreover, extensive measures were applied to increase the precision and accuracy of the data collection process. The staff responsible for this part of the study underwent

rigorous training with local, national, and international checks on completeness and accuracy. The importance of complete and accurate information was also explained to the study participants to minimise observer and participant bias. Measures of body weight, height, BP, and urinary data were repeated to better reflect dietary intake and average BP and BMI levels. Also, in order to improve the result precision, data relating to any possible under-reporters of dietary energy intake were excluded from the analyses. Regression models were adjusted extensively for dietary and non-dietary factors sequentially, allowing the model to account for their possible effect on BP and/or BMI. Consequently, the correlations between dietary and urinary variables in INTERMAP were higher than those previously reported from other population-wide studies[449].

As previously noted, the inconsistencies between the findings reported from the INTERMAP study and those of previous studies, in particular those related to the relationship between eating frequency and body weight, may be attributed to methodological issues that affected the previous outcomes. These most likely include, but are not limited to, under-reporting of energy, variations in definitions of eating occasions, and validity and reliability of dietary assessment methods [118,160]. The present study addressed these limitations by the use of multiple highly standardised 24-hour dietary recalls and refraining from the inclusion of participants who potentially may have under-reported their energy intake. In addition, exclusion of beverages from the eating occasion count is believed to have ensured that findings were not influenced by consumption of beverages.

As with any research, the current study is subject to several limitations. For example, the cross-sectional design does not allow for the inference of causal relationships. Thus, findings of cross-sectional studies should be confirmed prospectively, or by a RCT.

Owing to this limitation, age-related rise in BP, for example, could be underestimated due to the study design.

As an ideal measure of dietary intake is currently unavailable, it is possible that the study findings are affected by systematic and random errors. Systematic errors are associated with observer bias (e.g., leading questions), energy under-reporting, and errors in food composition tables as ingredients change over time [470,471]. Systematic error leads to consistent under- or over-estimation of intakes. Random errors, on the other hand, stem from the expected variability in the day-to-day food intake, instrument error in estimating portion size, and differences in food composition tables, as nutrient content varies with factors including variety, size, growing conditions, maturity, storage and cooking [472]. This has important implications for regression analysis: if random measurement error is present in the independent variable of a simple linear regression analysis, the gradient of the regression slope will be attenuated. This effect, known as regression dilution bias occurs because compared with the true intake, a greater number of extreme high and low values are observed in the predictor variable and as a result the gradient of the association is attenuated [472]. Potential for these errors can be minimised by repeated measurements, extensive observer training, standardised methods, open-ended questions, and on-going quality control measures [473]. However, despite including as many error prevention methods as practically possible, misreporting is inevitable, and the effects of regression dilution bias cannot be fully eliminated [474]. It has been documented that participants in population-wide studies, especially those who are classed as obese, have a tendency to omit from their food intake diary items that are considered 'unhealthy' [475].

An additional limitation is that the average eating event over a four-day period may not be representative of long-term dietary habits, which are subject to seasonal and festive changes. It is also possible that study participants would, even if inadvertently, change their food intake during the study, as they become more aware of what foods they consume, due to the need to record every eating event at the clinic interview.

Further limitation arises in interpretation of the results for eating frequency and BMI because of possible reverse causality, as participants may skip meals in order to lose body weight.

Even the BP measurement is a source of several limitations, despite extensive measures being applied to increase data precision. The key limitations arise from the potential increased anxiety with the discomfort of cuff placement [476] and observer bias in collecting second readings [477]. Reverse causality may also be an issue affecting the measured BP levels, where individuals may have altered their dietary intake towards a 'healthier' diet, following diagnosis with elevated BP levels.

Finally, it should be noted that multicollinearity may introduce type I or type II errors in multivariable regression models. Multicollinearity is of concern when highly correlated variables are included together in regression analysis. As the effects of collinearity can lead to inflation or attenuation of the coefficients, excluding highly correlated variables from the regression model is necessary, and sequential adjustment is required [478,479].

5.3. Future work

To understand the implications of these findings on the public health management of adverse BP levels and obesity, there is need for further research. A randomized

controlled feeding trial, addressing all previous limitations, is suggested. The aim is to examine the impact of a low meal frequency that is high in dietary energy density and a high meal frequency that is low in dietary energy density on BP and body weight.

The scarcity of information available on the separate effects of insoluble and soluble fibre on BP leads to a necessity to conduct RCTs. However, given the discrepancy in the findings reported by previous RCTs, it is necessary for future studies of this type to account for all the recognised limitations. For example, in a crossover design, participants should be assigned to a diet high in insoluble or soluble dietary fibre, with a long lasting treatment for each diet. Another future plan is to further analyse food groups based on their insoluble-soluble fibre content using the INTERMAP data set.

5.4. Conclusions

Having more frequent meals of low dietary energy density and high nutrient quality may be effective in managing high BP levels and the obesity epidemic in industrialised countries. Findings of this study show that 2 to 3 additional eating occasions per day are associated with systolic BP lower by 3 mm Hg and BMI lower by 1.1 kg/m^2 (equivalent to -3.2 kg in weight). High BP levels and obesity are a growing concern in the developing world, and thus, the findings of this and similar studies may help identify globally applicable strategies in combating unhealthy lifestyles and eating habits.

Additionally, intakes of dietary fibre higher by 7 g/1000 kcal (about 1 cup of raspberries), may contribute to a systolic BP level lower by 3 mm Hg and a BMI level lower by 1.7 kg/m^2 (equivalent to -5.0 kg in weight). Moreover, increasing the intake of food sources rich in insoluble fibre and potassium may be beneficial for BP control.

In sum, eating more frequent meals throughout the day, especially in the morning, may also be an effective way to reduce the risk of developing diseases related to excess body weight and unhealthy lifestyle. Our findings support the notion that consuming a diet rich in fibre and low in GI values is a valuable approach to bettering one's health.

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Appendix A: gender specific tables and figures

Table A. 1. Partial Pearson correlation coefficients between dietary, lifestyle variables and outcome measures of UK and USA INTERMAP men, n=1232 [1,2]

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Body mass index (kg/m^2)
Education (y)	-0.12	-0.07	-0.06
Engagement in moderate and heavy physical activity (h/24 h)	0.01	-0.03	-0.07
Current smokers (%)	0.04	-0.04	-0.11
Adhering to a special diet (%)	0.05	0.01	0.04
Taking dietary supplements (%)	-0.05	-0.05	-0.03
History of CVD or DM (%)	0.06	-0.04	0.10
Total energy intake (kcal/24 h)	0.05	0.01	0.14
Eating occasions per 24 h	-0.09	-0.05	-0.03
Dietary energy density-food only (kcal/g)	0.10	0.05	0.12
Dietary energy density-food and beverages (kcal/g)	-0.01	0.00	0.04
Nutrient density (Nutrient Rich Food 9.3 index score)	-0.13	-0.05	-0.12
Ratio of evening to morning energy intake	0.01	0.01	0.06
Total carbohydrate (%kcal)	-0.11	-0.04	-0.15
Total fibre (g/1000 kcal)	-0.13	-0.08	-0.16
Total protein (%kcal)	-0.03	-0.04	0.10
Animal protein (%kcal)	0.03	0.01	0.16
Vegetable protein (%kcal)	-0.14	-0.11	-0.13
Total fat (%kcal)	0.06	0.01	0.21
Total SFA (%kcal)	0.06	0.03	0.16
Total MFA (%kcal)	0.08	0.02	0.21
Total PFA (%kcal)	-0.03	-0.02	0.10
Cholesterol (mg/1000 kcal)	0.06	0.01	0.15
Dietary alcohol (g/24 h)	0.13	0.07	-0.05
24-hour urinary excretion data (mmol/24 h)			
Sodium	0.08	0.05	0.31
Potassium	-0.05	-0.05	0.15
Magnesium	-0.01	-0.08	0.07
Calcium	0.08	0.06	0.15

[1] Adjusted for age and population sample
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03

Table A. 2. Partial Pearson correlation coefficients between dietary, lifestyle variables and outcome measures of UK and USA INTERMAP women, n=1150 [1,2]

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Body mass index (kg/m^2)
Education (y)	-0.10	-0.08	-0.13
Engagement in moderate and heavy physical activity (h/24 h)	-0.07	-0.05	-0.04
Current smokers (%)	0.00	-0.03	-0.02
Adhering to a special diet (%)	-0.01	-0.04	0.06
Taking dietary supplements (%)	-0.03	-0.01	-0.10
History of CVD or DM (%)	0.12	-0.04	0.13
Total energy intake (kcal/24 h)	0.15	0.11	0.31
Eating occasions per 24 h	-0.08	-0.08	-0.07
Dietary energy density-food only (kcal/g)	0.14	0.09	0.17
Dietary energy density-food and beverages (kcal/g)	0.09	0.07	0.16
Nutrient density (Nutrient Rich Food 9.3 index score)	-0.11	-0.09	-0.19
Ratio of evening to morning energy intake	0.04	0.06	0.06
Total carbohydrate (%kcal)	-0.15	-0.11	-0.15
Total fibre (g/1000 kcal)	-0.15	-0.12	-0.21
Total protein (%kcal)	0.03	0.01	0.06
Animal protein (%kcal)	0.10	0.06	0.15
Vegetable protein (%kcal)	-0.14	-0.12	-0.18
Total fat (%kcal)	0.13	0.10	0.18
Total SFA (%kcal)	0.09	0.09	0.14
Total MFA (%kcal)	0.14	0.10	0.19
Total PFA (%kcal)	0.06	0.03	0.06
Cholesterol (mg/1000 kcal)	0.15	0.09	0.18
Dietary alcohol (g/24 h)	0.01	0.04	-0.06
24-hour urinary excretion data (mmol/24 h)			
Sodium	0.18	0.10	0.36
Potassium	-0.04	-0.04	0.06
Magnesium	-0.02	-0.01	0.04
Calcium	0.11	0.06	0.09

[1] Adjusted for age and population sample
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table A. 3. Partial Pearson correlation coefficients for dietary macro and micro nutrients of UK and USA INTERMAP men, *n*=1232 [1,2]

	Total carbohydrate (%kcal)	Total fibre (g/1000 kcal)	Total protein (%kcal)	Animal protein (%kcal)	Vegetable protein (%kcal)	Total fat (%kcal)	Total SFA (%kcal)	Total MFA (%kcal)	Total PFA (%kcal)	Cholesterol (mg/1000 kcal)	Dietary alcohol (g/24 h)	Urinary sodium (mmol/24 h)	Urinary potassium (mmol/24 h)	Urinary magnesium (mmol/24 h)	Urinary calcium (mmol/24 h)
Total carbohydrate (%kcal)		0.31	-0.35	-0.47	0.32	-0.70	-0.56	-0.66	-0.35	-0.49	-0.39	-0.13	0.05	-0.03	-0.11
Total fibre (g/1000 kcal)	0.31		0.11	-0.25	0.76	-0.37	-0.48	-0.36	-0.02	-0.34	-0.09	-0.05	0.28	0.17	-0.09
Total protein (%kcal)	-0.35	0.11		0.88	0.13	0.02	-0.01	0.03	-0.06	0.37	-0.04	0.16	0.23	0.11	0.10
Animal protein (%kcal)	-0.47	-0.25	0.88		-0.34	0.16	0.20	0.16	-0.08	0.52	0.02	0.15	0.14	0.04	0.13
Vegetable protein (%kcal)	0.32	0.76	0.13	-0.34		-0.29	-0.43	-0.28	0.06	-0.35	-0.19	0.01	0.17	0.13	-0.07
Total fat (%kcal)	-0.70	-0.37	0.02	0.16	-0.29		0.81	0.93	0.58	0.42	-0.16	0.21	-0.12	0.01	0.12
Total SFA (%kcal)	-0.56	-0.48	-0.01	0.20	-0.43	0.81		0.70	0.09	0.43	-0.12	0.16	-0.11	-0.01	0.17
Total MFA (%kcal)	-0.66	-0.36	0.03	0.16	-0.28	0.93	0.70		0.43	0.39	-0.14	0.19	-0.12	0.01	0.08
Total PFA (%kcal)	-0.35	-0.02	-0.06	-0.08	0.06	0.58	0.09	0.43		0.05	-0.13	0.13	-0.07	0.04	0.02
Cholesterol (mg/1000 kcal)	-0.49	-0.34	0.37	0.52	-0.35	0.42	0.43	0.39	0.05		0.03	0.14	-0.08	-0.05	0.12
Dietary alcohol (g/24 h)	-0.39	-0.09	-0.04	0.02	-0.19	-0.16	-0.12	-0.14	-0.13	0.03		-0.07	0.00	-0.01	0.01
Urinary sodium (mmol/24 h)	-0.13	-0.05	0.16	0.15	0.01	0.21	0.16	0.19	0.13	0.14	-0.07		0.36	0.30	0.32
Urinary potassium (mmol/24 h)	0.05	0.28	0.23	0.14	0.17	-0.12	-0.11	-0.12	-0.07	-0.08	0.00	0.36		0.45	0.21
Urinary magnesium (mmol/24 h)	-0.03	0.17	0.11	0.04	0.13	0.01	-0.01	0.01	0.04	-0.05	-0.01	0.30	0.45		0.40
Urinary calcium (mmol/24 h)	-0.11	-0.09	0.10	0.13	-0.07	0.12	0.17	0.08	0.02	0.12	0.01	0.32	0.21	0.40	

[1] Adjusted for age and population sample.
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table A. 4. Partial Pearson correlation coefficients for dietary macro and micro nutrients of UK and USA INTERMAP women, *n*=1152 [1,2]

	Total carbohydrate (%kcal)	Total fibre (g/1000 kcal)	Total protein (%kcal)	Animal protein (%kcal)	Vegetable protein (%kcal)	Total fat (%kcal)	Total SFA (%kcal)	Total MFA (%kcal)	Total PFA (%kcal)	Cholesterol (mg/1000 kcal)	Dietary alcohol (g/24 h)	Urinary sodium (mmol/24 h)	Urinary potassium (mmol/24 h)	Urinary magnesium (mmol/24 h)	Urinary calcium (mmol/24 h)
Total carbohydrate (%kcal)		0.35	-0.31	-0.43	0.28	-0.81	-0.63	-0.76	-0.49	-0.50	-0.25	-0.21	0.07	-0.01	-0.15
Total fibre (g/1000 kcal)	0.35		0.18	-0.20	0.78	-0.44	-0.48	-0.42	-0.15	-0.34	-0.03	-0.04	0.42	0.28	0.02
Total protein (%kcal)	-0.31	0.18		0.88	0.17	-0.06	-0.09	-0.04	-0.11	0.38	-0.06	0.17	0.25	0.13	0.13
Animal protein (%kcal)	-0.43	-0.20	0.88		-0.32	0.11	0.12	0.13	-0.09	0.54	-0.05	0.15	0.11	0.00	0.11
Vegetable protein (%kcal)	0.28	0.78	0.17	-0.32		-0.34	-0.43	-0.34	-0.03	-0.36	-0.04	0.03	0.27	0.25	0.04
Total fat (%kcal)	-0.81	-0.44	-0.06	0.11	-0.34		0.81	0.93	0.62	0.40	-0.11	0.18	-0.21	-0.05	0.11
Total SFA (%kcal)	-0.63	-0.48	-0.09	0.12	-0.43	0.81		0.67	0.16	0.38	-0.10	0.12	-0.21	-0.06	0.11
Total MFA (%kcal)	-0.76	-0.42	-0.04	0.13	-0.34	0.93	0.67		0.50	0.40	-0.08	0.17	-0.20	-0.06	0.11
Total PFA (%kcal)	-0.49	-0.15	-0.11	-0.09	-0.03	0.62	0.16	0.50		0.07	-0.07	0.11	-0.10	0.01	0.02
Cholesterol (mg/1000 kcal)	-0.50	-0.34	0.38	0.54	-0.36	0.40	0.38	0.40	0.07		-0.01	0.18	-0.13	-0.08	0.09
Dietary alcohol (g/24 h)	-0.25	-0.03	-0.06	-0.05	-0.04	-0.11	-0.10	-0.08	-0.07	-0.01		0.02	0.07	0.00	0.02
Urinary sodium (mmol/24 h)	-0.21	-0.04	0.17	0.15	0.03	0.18	0.12	0.17	0.11	0.18	0.02		0.32	0.30	0.32
Urinary potassium (mmol/24 h)	0.07	0.42	0.25	0.11	0.27	-0.21	-0.21	-0.20	-0.10	-0.13	0.07	0.32		0.49	0.28
Urinary magnesium (mmol/24 h)	-0.01	0.28	0.13	0.00	0.25	-0.05	-0.06	-0.06	0.01	-0.08	0.00	0.30	0.49		0.45
Urinary calcium (mmol/24 h)	-0.15	0.02	0.13	0.11	0.04	0.11	0.11	0.11	0.02	0.09	0.02	0.32	0.28	0.45	

[1] Adjusted for age and population sample.
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table A. 5. Estimated systolic and diastolic BP difference per 2SD higher differences of eating occasions, UK and USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 4													
Men [1]	1232	-1.9	-3.4, -0.5	0.01	-1.4	-2.9, -0.2	0.05	-0.7	-1.8, 0.5	0.27	-0.3	-1.5, 0.8	0.56
Women [2]	1153	-2.6	-4.4, -0.8	0.004	-1.7	-3.1, -0.3	0.04	-1.6	-2.8, -0.5	0.07×10^{-01}	-1.2	-2.4,- 0.1	0.04

Model 1a adjusted for total energy intake, age, and population sample.
Model 2 Adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 3a adjusted for variables in model 3 plus total fibre intake (g/1000 kcal).
Model 4 adjusted for variables in model 3 plus alcohol intake (g/24 h).
[1] 2SD of eating occasions=2.6.
[2] 2SD of eating occasions=2.5.

Table A. 6. Estimated BMI difference per 2SD higher differences of eating occasions, UK and USA men and women separately

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 3				
Men [1]	1232	-0.7	-1.2, -0.2	0.02
Women [2]	1153	-1.7	-2.4, -1.0	4.81×10^{-06}

Model 1a adjusted for total energy intake, age, and population sample.
Model 2 adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of eating occasions=2.6.
[2] 2SD of eating occasions=2.5.

Table A. 7. Estimated systolic and diastolic BP difference per 2SD higher differences of dietary energy density, UK and USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 4													
Men [1]	1232	3.0	1.5, 4.5	9.05×10^{-05}	2.5	0.6, 3.5	0.06×10^{-01}	1.8	0.6, 2.9	0.003	1.1	-0.01, 2.2	0.05
Women [1]	1153	3.3	1.5, 5.1	0.004	2.1	0.4, 3.8	0.02	2.0	0.7, 3.2	0.002	1.4	0.2, 2.6	0.02

Model 1 adjusted for age, and population sample.
Model 2 Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of dietary energy density (kcal/g)=0.8.

Table A. 8. Estimated BMI difference per 2SD higher differences of dietary energy density, UK and USA men and women separately

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 3				
Men [1]	1232	1.4	0.8, 1.9	1.29×10^{-06}
Women [1]	1153	2.4	1.6, 3.1	1.18×10^{-09}

Model 1 adjusted for age, and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of dietary energy density (kcal/g)=0.8.

Table A. 9. Estimated BMI difference per 2SD higher differences of nutrient density, UK and USA men and women separately

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 3				
Men [1]	1232	-1.3	-1.9, -0.7	3.30×10^{-05}
Women [2]	1153	-1.6	-2.3, -0.9	4.72×10^{-06}

Model 1a adjusted for total energy intake, age, and population sample.
Model 2 adjusted for variables in Model 1a plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of Nutrient Rich Food 9.3 index score=25.5.
[2] 2SD of Nutrient Rich Food 9.3 index score=30.4.

Table A. 10. Estimated systolic and diastolic BP difference per 2SD higher differences of the ratio of evening to morning energy intake, UK and USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 4													
Men [1]	1232	0.01	-0.2, 0.2	0.91	0.04	-0.2, 0.3	0.68	0.02	-0.2, 0.2	0.85	0.1	-0.2, 0.3	0.51
Women [2]	1153	0.1	-0.5, 0.2	0.11	0.04	-0.03, 0.1	0.32	0.1	0.01, 0.2	0.02	0.1	-0.01, 0.1	0.06

Model 1 adjusted for age, and population sample.
Model 2 Adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, years of education (years completed), DM or CVD diagnosis, and family history of high BP.
Model 3 adjusted for variables in model 2 plus 24-hour urinary excretion of sodium and potassium (mmol/24-hours).
Model 4 adjusted for variables in Model 3 plus alcohol intake (g/24 h).
[1] 2SD of ratio of evening to morning energy intake=3.6
[2] 2SD of ratio of evening to morning energy intake=3.4.

Table A. 11. Estimated BMI difference per 2SD higher differences of the ratio of evening to morning energy intake, UK and USA men and women separately

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 3				
Men [1]	1232	0.1	-0.03, 0.1	0.08
Women [2]	1153	0.1	0.03, 0.1	0.03

Model 1 adjusted for age, and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), dietary supplement use, smoking, and years of education (years completed).
Model 3 adjusted for variables in Model 2 plus alcohol intake (g/24 h).
[1] 2SD of ratio of evening to morning energy intake=3.6
[2] 2SD of ratio of evening to morning energy intake=3.4.

Table A. 12. Partial Pearson correlation coefficients for dietary macro and micro nutrients of USA INTERMAP men participants, *n*=997 [1,2]

	Total carbohydrate (%kcal)	Starch (%kcal)	Total sugar (%kcal)	Fructose (%kcal)	Galactose (%kcal)	Glucose (%kcal)	Lactose (%kcal)	Maltose (%kcal)	Sucrose (%kcal)	Glycaemic index	Glycaemic load	Total fibre (g/1000 kcal)	Insoluble fibre (g/1000 kcal)	Soluble fibre (g/1000 kcal)	Total protein (%kcal)	Animal protein (%kcal)	Vegetable protein (%kcal)	Total fat (%kcal)	Total SFA (%kcal)	Total PFA (%kcal)	Total MFA (%kcal)	Dietary alcohol (g/24 h)	Urinary sodium (mmol/24 h)	Urinary potassium (mmol/24 h)	Urinary magnesium (mmol/24 h)	Urinary calcium (mmol/24 h)
Total carbohydrate (%kcal)		0.32	0.79	0.56	0.14	0.56	0.08	0.19	0.55	0.09	0.46	0.27	0.30	0.28	-0.39	-0.49	0.29	-0.73	-0.59	-0.38	-0.69	-0.37	-0.15	0.01	-0.05	-0.11
Starch (%kcal)	0.32		-0.33	-0.26	0.07	-0.28	-0.10	-0.01	-0.25	0.10	0.08	0.44	0.41	0.42	0.02	-0.29	0.64	-0.30	-0.39	-0.02	-0.31	-0.12	0.04	0.04	0.01	-0.07
Total sugar (%kcal)	0.79	-0.33		0.73	0.10	0.74	0.15	0.19	0.71	0.03	0.41	-0.02	0.04	0.01	-0.40	-0.30	-0.13	-0.53	-0.33	-0.37	-0.48	-0.29	-0.18	-0.02	-0.06	-0.06
Fructose (%kcal)	0.56	-0.26	0.73		0.05	0.94	-0.10	0.11	0.12	-0.07	0.24	0.02	0.05	0.03	-0.31	-0.24	-0.07	-0.42	-0.34	-0.23	-0.37	-0.15	-0.16	-0.06	-0.08	-0.08
Galactose (%kcal)	0.14	0.07	0.10	0.05		0.05	0.06	0.12	0.02	-0.01	0.04	0.14	0.16	0.13	0.01	-0.04	0.13	-0.16	-0.12	-0.07	-0.17	-0.01	-0.07	0.08	0.05	-0.01
Glucose (%kcal)	0.56	-0.28	0.74	0.94	0.05		-0.10	0.20	0.14	-0.02	0.28	-0.05	-0.01	-0.04	-0.35	-0.26	-0.11	-0.42	-0.33	-0.24	-0.36	-0.12	-0.14	-0.07	-0.08	-0.08
Lactose (%kcal)	0.08	-0.10	0.15	-0.10	0.06	-0.10		0.03	-0.01	0.02	0.09	0.004	0.04	-0.03	0.23	0.25	-0.05	-0.09	0.07	-0.14	-0.14	-0.13	0.004	0.31	0.15	0.20
Maltose (%kcal)	0.19	-0.01	0.19	0.11	0.12	0.20	0.03		0.03	0.06	0.14	0.08	0.06	0.05	-0.15	-0.15	-0.01	-0.20	-0.10	-0.15	-0.19	0.06	-0.07	0.02	0.06	-0.02
Sucrose (%kcal)	0.55	-0.25	0.71	0.12	0.02	0.14	-0.01	0.03		0.08	0.33	-0.12	-0.07	-0.08	-0.36	-0.25	-0.18	-0.28	-0.12	-0.25	-0.25	-0.26	-0.11	-0.13	-0.09	-0.08
Glycaemic index	0.09	0.10	0.03	-0.07	-0.01	-0.02	0.02	0.06	0.08		0.45	-0.01	0.05	0.05	-0.02	-0.05	0.08	0.09	0.07	0.08	0.09	-0.25	0.06	0.04	0.04	0.02
Glycaemic load	0.46	0.08	0.41	0.24	0.04	0.28	0.09	0.14	0.33	0.45		-0.03	0.03	0.01	-0.31	-0.30	0.05	-0.21	-0.11	-0.15	-0.18	-0.20	0.16	0.17	0.10	0.12
Total fibre (g/1000 kcal)	0.27	0.44	-0.02	0.02	0.14	-0.05	0.004	0.08	-0.12	-0.01	-0.03		0.95	0.87	0.14	-0.24	0.76	-0.33	-0.47	-0.02	-0.33	-0.08	-0.04	0.29	0.18	-0.08
Insoluble fibre (g/1000 kcal)	0.30	0.41	0.04	0.05	0.16	-0.01	0.04	0.06	-0.07	0.05	0.03	0.95		0.79	0.12	-0.25	0.76	-0.29	-0.44	0.02	-0.28	-0.16	-0.02	0.27	0.18	-0.07
Soluble fibre (g/1000 kcal)	0.28	0.42	0.01	0.03	0.13	-0.04	-0.03	0.05	-0.08	0.05	0.01	0.87	0.79		0.17	-0.18	0.71	-0.30	-0.43	-0.03	-0.28	-0.14	-0.02	0.28	0.15	-0.07
Total protein (%kcal)	-0.39	0.02	-0.40	-0.31	0.01	-0.35	0.23	-0.15	-0.36	-0.02	-0.31	0.14	0.12	0.17		0.88	0.15	0.06	0.01	-0.05	0.05	-0.03	0.14	0.26	0.13	0.10
Animal protein (%kcal)	-0.49	-0.29	-0.30	-0.24	-0.04	-0.26	0.25	-0.15	-0.25	-0.05	-0.30	-0.24	-0.25	-0.18	0.88		-0.34	0.19	0.23	-0.07	0.18	0.03	0.13	0.17	0.06	0.13

Vegetable protein (%kcal)	0.29	0.64	-0.13	-0.07	0.13	-0.11	-0.05	-0.01	-0.18	0.08	0.05	0.76	0.76	0.71	0.15	-0.34		-0.26	-0.43	0.07	-0.26	-0.18	0.005	0.17	0.13	-0.06
Total fat (%kcal)	-0.73	-0.30	-0.53	-0.42	-0.16	-0.42	-0.09	-0.20	-0.28	0.09	-0.21	-0.33	-0.29	-0.30	0.06	0.19	-0.26		0.82	0.61	0.93	-0.15	0.23	-0.09	0.02	0.11
Total SFA (%kcal)	-0.59	-0.39	-0.33	-0.34	-0.12	-0.33	0.07	-0.10	-0.12	0.07	-0.11	-0.47	-0.44	-0.43	0.01	0.23	-0.43	0.82		0.15	0.73	-0.12	0.19	-0.08	-0.01	0.17
Total PFA (%kcal)	-0.38	-0.02	-0.37	-0.23	-0.07	-0.24	-0.14	-0.15	-0.25	0.08	-0.15	-0.02	0.02	-0.03	-0.05	-0.07	0.07	0.61	0.15		0.44	-0.12	0.14	-0.06	0.04	0.002
Total MFA (%kcal)	-0.69	-0.31	-0.48	-0.37	-0.17	-0.36	-0.14	-0.19	-0.25	0.09	-0.18	-0.33	-0.28	-0.28	0.05	0.18	-0.26	0.93	0.73	0.44		-0.13	0.21	-0.10	0.02	0.07
Dietary alcohol (g/24 h)	-0.37	-0.12	-0.29	-0.15	-0.01	-0.12	-0.13	0.06	-0.26	-0.25	-0.20	-0.08	-0.16	-0.14	-0.03	0.03	-0.18	-0.15	-0.12	-0.12	-0.13		-0.07	-0.01	0.001	0.02
Urinary sodium (mmol/24 h)	-0.15	0.04	-0.18	-0.16	-0.07	-0.14	0.004	-0.07	-0.11	0.06	0.16	-0.04	-0.02	-0.02	0.14	0.13	0.005	0.23	0.19	0.14	0.21	-0.07		0.39	0.31	0.32
Urinary potassium (mmol/24 h)	0.01	0.04	-0.02	-0.06	0.08	-0.07	0.31	0.02	-0.13	0.04	0.17	0.29	0.27	0.28	0.26	0.17	0.17	-0.09	-0.08	-0.06	-0.10	-0.01	0.39		0.46	0.21
Urinary magnesium (mmol/24 h)	-0.05	0.01	-0.06	-0.08	0.05	-0.08	0.15	0.06	-0.09	0.04	0.10	0.18	0.18	0.15	0.13	0.06	0.13	0.02	-0.01	0.04	0.02	0.001	0.31	0.46		0.40
Urinary calcium (mmol/24 h)	-0.11	-0.07	-0.06	-0.08	-0.01	-0.08	0.20	-0.02	-0.08	0.02	0.12	-0.08	-0.07	-0.07	0.10	0.13	-0.06	0.11	0.17	0.002	0.07	0.02	0.32	0.21	0.40	

[1] Adjusted for age and population sample.
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table A. 13. Partial Pearson correlation coefficients for dietary macro and micro nutrients of USA INTERMAP women participants, *n*=944 [1,2]

	Total carbohydrate (%kcal)	Starch (%kcal)	Total sugar (%kcal)	Fructose (%kcal)	Galactose (%kcal)	Glucose (%kcal)	Lactose (%kcal)	Maltose (%kcal)	Sucrose (%kcal)	Glycaemic index	Glycaemic load	Total fibre (g/1000 kcal)	Insoluble fibre (g/1000 kcal)	Soluble fibre (g/1000 kcal)	Total protein (%kcal)	Animal protein (%kcal)	Vegetable protein (%kcal)	Total fat (%kcal)	Total SFA (%kcal)	Total PFA (%kcal)	Total MFA (%kcal)	Dietary alcohol (g/24 h)	Urinary sodium (mmol/24 h)	Urinary potassium (mmol/24 h)	Urinary magnesium (mmol/24 h)	Urinary calcium (mmol/24 h)
Total carbohydrate (%kcal)		0.32	0.79	0.56	0.14	0.56	0.08	0.19	0.55	0.09	0.46	0.27	0.30	0.28	-0.39	-0.49	0.29	-0.73	-0.59	-0.38	-0.69	-0.37	-0.15	0.01	-0.05	-0.11
Starch (%kcal)	0.40		-0.33	-0.26	0.07	-0.28	-0.10	-0.01	-0.25	0.10	0.08	0.44	0.41	0.42	0.02	-0.29	0.64	-0.30	-0.39	-0.02	-0.31	-0.12	0.04	0.04	0.01	-0.07
Total sugar (%kcal)	0.76	-0.33		0.73	0.10	0.74	0.15	0.19	0.71	0.03	0.41	-0.02	0.04	0.01	-0.40	-0.30	-0.13	-0.53	-0.33	-0.37	-0.48	-0.29	-0.18	-0.02	-0.06	-0.06
Fructose (%kcal)	0.47	-0.26	0.73		0.05	0.94	-0.10	0.11	0.12	-0.07	0.24	0.02	0.05	0.03	-0.31	-0.24	-0.07	-0.42	-0.34	-0.23	-0.37	-0.15	-0.16	-0.06	-0.08	-0.08
Galactose (%kcal)	0.18	0.07	0.10	0.05		0.05	0.06	0.12	0.02	-0.01	0.04	0.14	0.16	0.13	0.01	-0.04	0.13	-0.16	-0.12	-0.07	-0.17	-0.01	-0.07	0.08	0.05	-0.01
Glucose (%kcal)	0.50	-0.28	0.74	0.94	0.05		-0.10	0.20	0.14	-0.02	0.28	-0.05	-0.01	-0.04	-0.35	-0.26	-0.11	-0.42	-0.33	-0.24	-0.36	-0.12	-0.14	-0.07	-0.08	-0.08
Lactose (%kcal)	0.10	-0.10	0.15	-0.10	0.06	-0.10		0.03	-0.01	0.02	0.09	0.004	0.04	-0.03	0.23	0.25	-0.05	-0.09	0.07	-0.14	-0.14	-0.13	0.004	0.31	0.15	0.20
Maltose (%kcal)	0.26	-0.01	0.19	0.11	0.12	0.20	0.03		0.03	0.06	0.14	0.08	0.06	0.05	-0.15	-0.15	-0.01	-0.20	-0.10	-0.15	-0.19	0.06	-0.07	0.02	0.06	-0.02
Sucrose (%kcal)	0.52	-0.25	0.71	0.12	0.02	0.14	-0.01	0.03		0.08	0.33	-0.12	-0.07	-0.08	-0.36	-0.25	-0.18	-0.28	-0.12	-0.25	-0.25	-0.26	-0.11	-0.13	-0.09	-0.08
Glycaemic index	0.05	0.10	0.03	-0.07	-0.01	-0.02	0.02	0.06	0.08		0.45	-0.01	0.05	0.05	-0.02	-0.05	0.08	0.09	0.07	0.08	0.09	-0.25	0.06	0.04	0.04	0.02
Glycaemic load	0.42	0.08	0.41	0.24	0.04	0.28	0.09	0.14	0.33	0.45		-0.03	0.03	0.01	-0.31	-0.30	0.05	-0.21	-0.11	-0.15	-0.18	-0.20	0.16	0.17	0.10	0.12
Total fibre (g/1000 kcal)	0.33	0.44	-0.02	0.02	0.14	-0.05	0.004	0.08	-0.12	-0.01	-0.03		0.95	0.87	0.14	-0.24	0.76	-0.33	-0.47	-0.02	-0.33	-0.08	-0.04	0.29	0.18	-0.08
Insoluble fibre (g/1000 kcal)	0.31	0.41	0.04	0.05	0.16	-0.01	0.04	0.06	-0.07	0.05	0.03	0.95		0.79	0.12	-0.25	0.76	-0.29	-0.44	0.02	-0.28	-0.16	-0.02	0.27	0.18	-0.07
Soluble fibre (g/1000 kcal)	0.34	0.42	0.01	0.03	0.13	-0.04	-0.03	0.05	-0.08	0.05	0.01	0.87	0.79		0.17	-0.18	0.71	-0.30	-0.43	-0.03	-0.28	-0.14	-0.02	0.28	0.15	-0.07
Total protein (%kcal)	-0.35	0.02	-0.40	-0.31	0.01	-0.35	0.23	-0.15	-0.36	-0.02	-0.31	0.14	0.12	0.17		0.88	0.15	0.06	0.01	-0.05	0.05	-0.03	0.14	0.26	0.13	0.10
Animal protein (%kcal)	-0.46	-0.29	-0.30	-0.24	-0.04	-0.26	0.25	-0.15	-0.25	-0.05	-0.30	-0.24	-0.25	-0.18	0.88		-0.34	0.19	0.23	-0.07	0.18	0.03	0.13	0.17	0.06	0.13

Vegetable protein (%kcal)	0.27	0.64	-0.13	-0.07	0.13	-0.11	-0.05	-0.01	-0.18	0.08	0.05	0.76	0.76	0.71	0.15	-0.34		-0.26	-0.43	0.07	-0.26	-0.18	0.005	0.17	0.13	-0.06
Total fat (%kcal)	-0.83	-0.30	-0.53	-0.42	-0.16	-0.42	-0.09	-0.20	-0.28	0.09	-0.21	-0.33	-0.29	-0.30	0.06	0.19	-0.26		0.82	0.61	0.93	-0.15	0.23	-0.09	0.02	0.11
Total SFA (%kcal)	-0.65	-0.39	-0.33	-0.34	-0.12	-0.33	0.07	-0.10	-0.12	0.07	-0.11	-0.47	-0.44	-0.43	0.01	0.23	-0.43	0.82		0.15	0.73	-0.12	0.19	-0.08	-0.01	0.17
Total PFA (%kcal)	-0.52	-0.02	-0.37	-0.23	-0.07	-0.24	-0.14	-0.15	-0.25	0.08	-0.15	-0.02	0.02	-0.03	-0.05	-0.07	0.07	0.61	0.15		0.44	-0.12	0.14	-0.06	0.04	0.002
Total MFA (%kcal)	-0.78	-0.31	-0.48	-0.37	-0.17	-0.36	-0.14	-0.19	-0.25	0.09	-0.18	-0.33	-0.28	-0.28	0.05	0.18	-0.26	0.93	0.73	0.44		-0.13	0.21	-0.10	0.02	0.07
Dietary alcohol (g/24 h)	-0.20	-0.12	-0.29	-0.15	-0.01	-0.12	-0.13	0.06	-0.26	-0.25	-0.20	-0.08	-0.16	-0.14	-0.03	0.03	-0.18	-0.15	-0.12	-0.12	-0.13		-0.07	-0.01	0.001	0.02
Urinary sodium (mmol/24 h)	-0.23	0.04	-0.18	-0.16	-0.07	-0.14	0.004	-0.07	-0.11	0.06	0.16	-0.04	-0.02	-0.02	0.14	0.13	0.005	0.23	0.19	0.14	0.21	-0.07		0.39	0.31	0.32
Urinary potassium (mmol/24 h)	0.07	0.04	-0.02	-0.06	0.08	-0.07	0.31	0.02	-0.13	0.04	0.17	0.29	0.27	0.28	0.26	0.17	0.17	-0.09	-0.08	-0.06	-0.10	-0.01	0.39		0.46	0.21
Urinary magnesium (mmol/24 h)	-0.01	0.01	-0.06	-0.08	0.05	-0.08	0.15	0.06	-0.09	0.04	0.10	0.18	0.18	0.15	0.13	0.06	0.13	0.02	-0.01	0.04	0.02	0.001	0.31	0.46		0.40
Urinary calcium (mmol/24 h)	-0.16	-0.07	-0.06	-0.08	-0.01	-0.08	0.20	-0.02	-0.08	0.02	0.12	-0.08	-0.07	-0.07	0.10	0.13	-0.06	0.11	0.17	0.002	0.07	0.02	0.32	0.21	0.40	

[1] Adjusted for age and population sample.
[2] Correlation coefficients are statistically significant, except those ranging from -0.03 to 0.03.

Table A. 14. Estimated systolic and diastolic BP difference per 2SD higher differences of glycaemic index in UK and USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 2													
Men [1]	1232	0.3	-1.3, 1.9	0.71	0.4	-1.1, 1.9	0.62	0.6	-0.6, 1.7	0.35	0.5	-0.6, 1.6	0.39
Women [2]	1153	1.0	-0.5, 2.5	0.17	0.8	-0.6, 2.2	0.25	0.9	-0.1, 1.9	0.08	0.8	-0.2, 1.7	0.12

Model 1 adjusted f for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] 2SD of GI=15.7.
[2] 2SD of GI=19.64.

Table A. 15. Estimated systolic and diastolic BP difference per 2SD higher differences of glycaemic load in UK and USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 2													
Men [1]	1232	0.4	-2.5, 3.4	0.77	0.8	-2.0, 3.5	0.59	1.3	-0.9, 3.4	0.25	1.1	-1.0, 3.1	0.32
Women [2]	1153	3.2	-0.7, 7.1	0.11	3.0	-0.7, 6.8	0.11	2.5	-0.1, 5.1	0.06	2.4	-0.2, 4.9	0.07

Model 1 adjusted f for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] 2SD of GL=124.6.
[2] 2SD of GL=91.9.

Table A. 16. Estimated BMI difference per 2SD higher differences of glycaemic index in UK and USA men and women separately

		BMI		
Models	*n*	Difference, kg/m^2	95% CI	*p*
Model 2				
Men [1]	1232	0.03	-0.6, 0.6	0.92
Women [2]	1153	0.1	-0.5, 0.7	0.82

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] 2SD of GI=15.7.
[2] 2SD of GI=19.64.

Table A. 17. Estimated BMI difference per 2SD higher differences of glycaemic load in UK and USA men and women separately

		BMI		
Models	*n*	Difference, kg/m^2	95% CI	*p*
Model 2				
Men [1]	1232	0.3	-0.7, 1.4	0.54
Women [2]	1153	0.01	-1.5, 1.7	0.89

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] 2SD of GL=124.6.
[2] 2SD of GL=91.9.

Table A. 18. Estimated systolic and diastolic BP difference per 2SD higher differences of total fibre in USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 2 [1]													
Men [2]	997	-2.5	-4.3, -0.6	0.08×10^{-01}	-1.4	-3.2, -0.1	0.04	-1.3	-2.7, 0.1	0.07	-0.5	-1.9, 0.8	0.45
Women [3]	944	-3.6	-5.6, -1.5	0.001	-2.2	-4.2, -0.2	0.03	-1.6	-2.9, -0.2	0.02	-0.9	-2.2, 0.4	0.18

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] Additionally adjusted for total sugar (%).
[2] 2SD fibres (g/1000 kcal) =6.3.
[3] 2SD fibres (g/1000 kcal) =6.7.

Table A. 19. Estimated systolic and diastolic BP difference per 2SD higher differences of insoluble fibre in USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 2 [1]													
Men [2]	997	-2.3	-4.8, -0.2	0.04	-1.3	-3.7, -0.1	0.05	-1.2	-3.1, 0.7	0.20	-0.5	-2.3, 1.4	0.62
Women [3]	944	-3.8	-6.8, -0.8	0.01	-2.5	-5.5, -0.2	0.04	-2.3	-4.3, -0.4	0.02	-1.7	-3.6, 0.2	0.08

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] Additionally adjusted for total sugar (%) and soluble fibre (g/1000 kcal).
[2] 2SD insoluble fibres (g/1000 kcal)=4.4.
[3] 2SD insoluble fibres (g/1000 kcal)=4.5.

Table A. 20. Estimated systolic and diastolic BP difference per 2SD higher differences of soluble fibre in USA men and women separately

		Systolic BP						Diastolic BP					
		Not adjusted for BMI			Adjusted for BMI			Not adjusted for BMI			Adjusted for BMI		
Models	*n*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*	Difference, mm Hg	95% CI	*p*
Model 2 [1]													
Men [2]	997	-0.4	-3.2, 2.4	0.79	-0.5	-3.2, 2.2	0.72	-0.4	-2.5, 1.8	0.72	-0.5	-2.5, 1.6	0.65
Women [3]	944	0.2	-2.9, 3.4	0.88	0.2	-2.9, 3.2	0.92	0.3	-1.3, 2.8	0.50	0.7	-1.3, 2.7	0.52

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 2 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), alcohol intake (g/24-hours), DM or CVD diagnosis, family history of high BP, 24-hour urinary excretion of sodium (mmol/24-hours).
[1] Additionally adjusted for total sugar (%) and insoluble fibre (g/1000 kcal).
[2] 2SD soluble fibres (g/1000 kcal)=2.0.
[3] 2SD soluble fibres (g/1000 kcal)=2.2.

Table A. 21. Estimated BMI difference per 2SD higher differences of total fibre in USA men and women separately

		BMI		
Models	*n*	Difference, kg/m^2	95% CI	*p*
Model 2 [1]				
Men [2]	997	-1.3	-2.0, -0.6	0.0003
Women [3]	944	-2.0	-2.9, -1.2	5.34×10^{-06}

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] Additionally adjusted for total sugar (%).
[2] 2SD total fibre (g/1000 kcal)=6.3.
[3] 2SD total fibre (g/1000 kcal)=6.7.

Table A. 22. Estimated BMI difference per 2SD higher differences of insoluble fibre in USA men and women separately

		BMI		
Models	*n*	Difference, kg/m^2	95% CI	*p*
Model 2 [1]				
Men [2]	997	-1.3	-2.3, -0.3	0.08×10^{-01}
Women [3]	944	-1.9	-3.2, -0.7	0.003

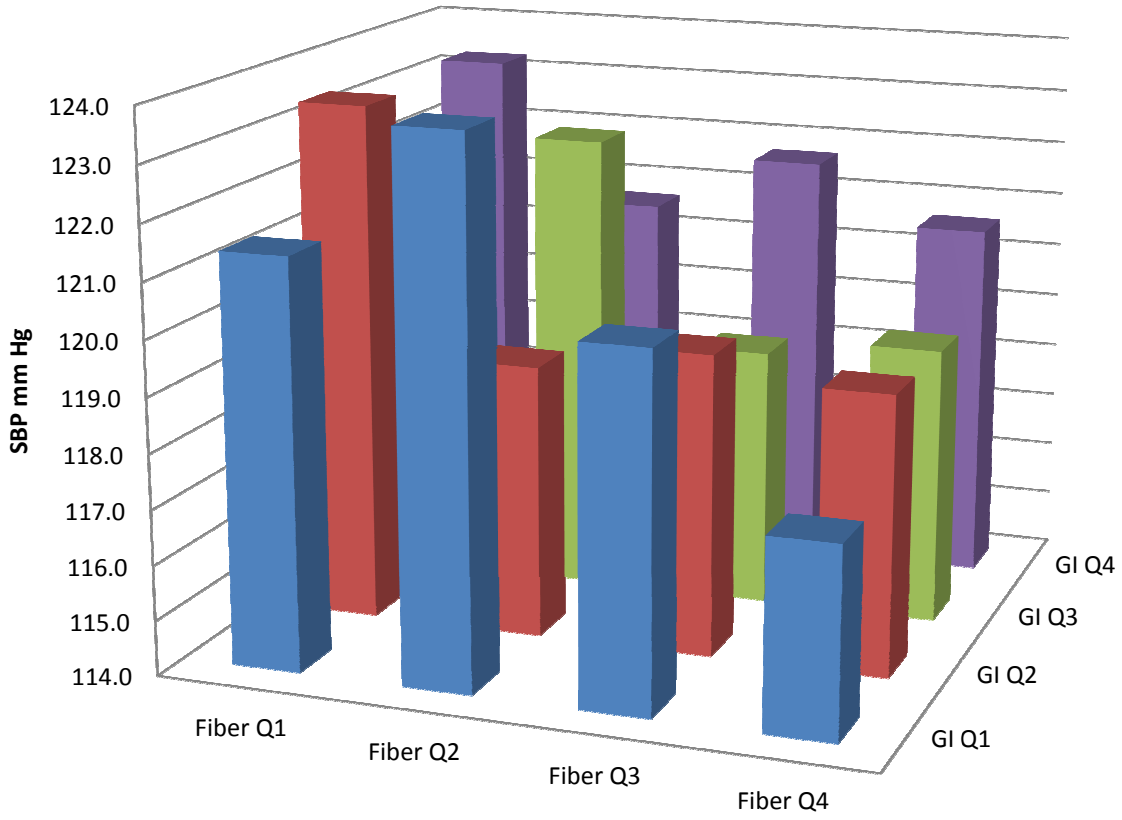
Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] Additionally adjusted for total sugar (%) and soluble fibre (g/1000 kcal).
[2] 2SD insoluble fibre (g/1000 kcal)=4.4.
[3] 2SD insoluble fibre (g/1000 kcal)=4.5.

Table A. 23 Estimated BMI difference per 2SD higher differences of soluble fibre in USA men and women separately

Models	*n*	BMI Difference, kg/m^2	95% CI	*p*
Model 2 [1]				
Men [2]	997	0.1	-1.0, 1.2	0.85
Women [3]	944	0.1	-1.2, 1.4	0.87

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.
Model 2 adjusted for variables in Model 1 plus adherence to a special diet, engagement in moderate and heavy physical activity (h/24 h), smoking, dietary supplement use, years of education (years completed), and alcohol intake (g/24-hours).
[1] Additionally adjusted for total sugar (%) and insoluble fibre (g/1000 kcal).
[2] 2SD soluble fibre (g/1000 kcal)=2.0.
[3] 2SD soluble fibre (g/1000 kcal)=2.2.

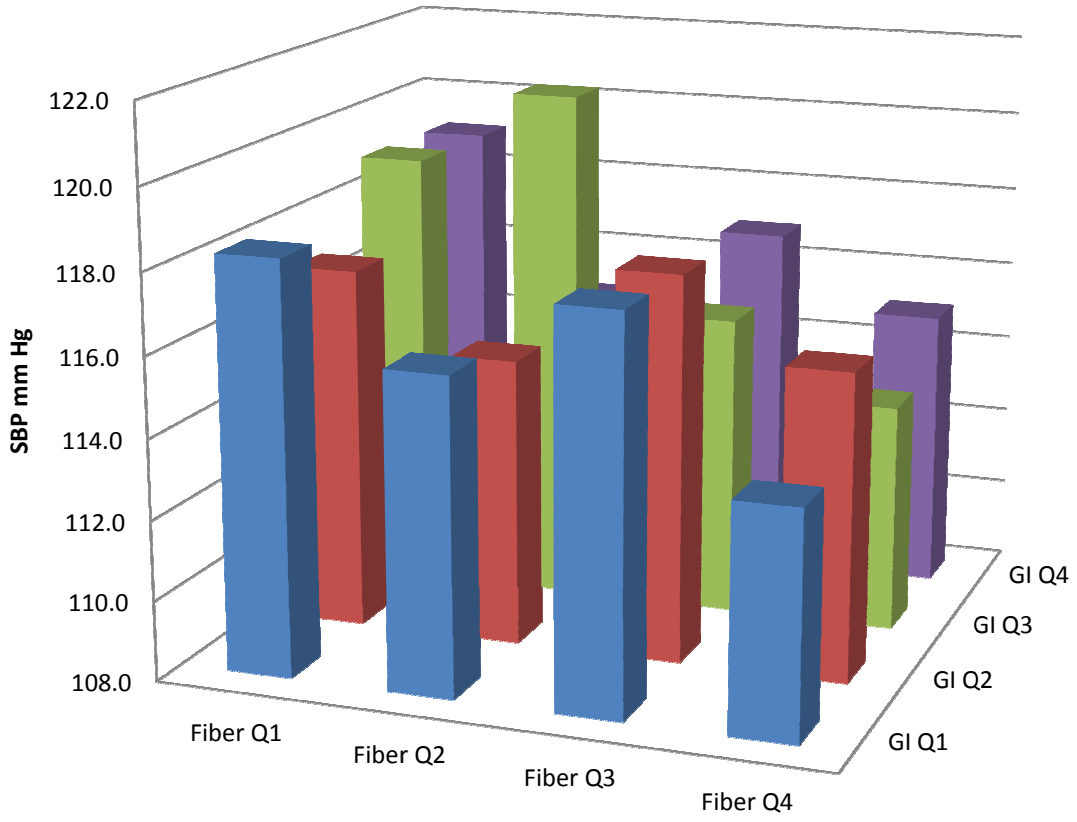
Figure A. 1. Glycaemic index and total fibre intake in relation to systolic BP in UK and USA INTERMAP men participants, *n*=1232



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	121.4	123.8	120.4	117.4
GI Q2	123.4	119.0	119.5	119.1
GI Q3	122.0	122.5	118.7	119.1
GI Q4	123.3	120.6	121.7	120.6

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

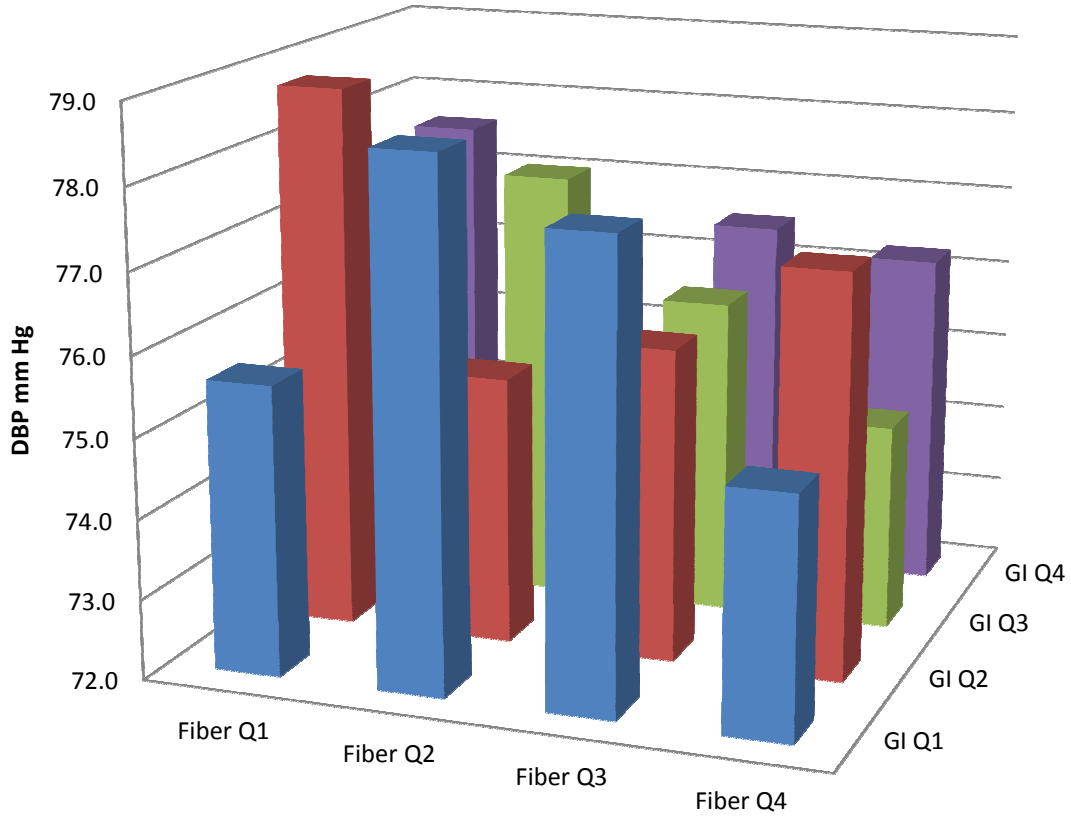
Figure A. 2. Glycaemic index and total fibre intake in relation to systolic BP in UK and USA INTERMAP women participants, *n*=1153



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	118.3	115.9	117.7	113.6
GI Q2	117.1	115.2	117.6	115.7
GI Q3	119.1	121.0	115.6	113.7
GI Q4	119.0	114.8	116.9	115.0

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

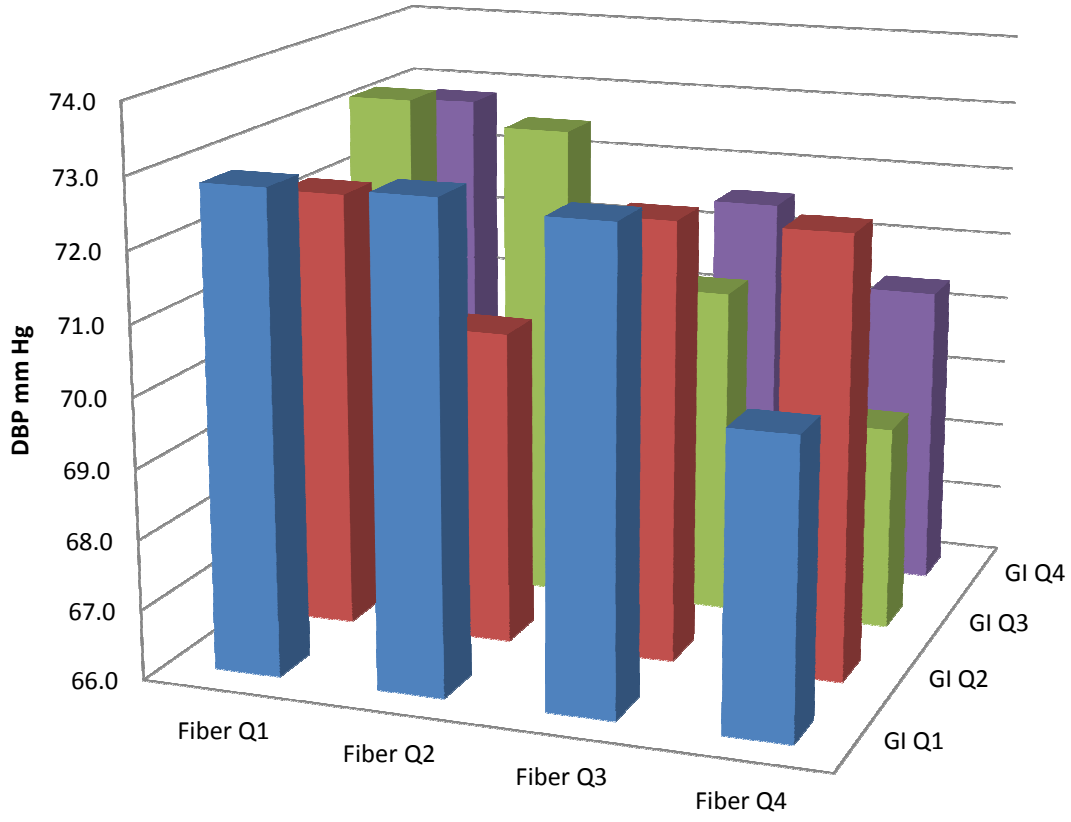
Figure A. 3. Glycaemic index and total fibre intake in relation to diastolic BP in UK and USA INTERMAP men participants, *n*=1232



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	75.6	78.5	77.7	75.0
GI Q2	78.8	75.3	75.9	77.0
GI Q3	76.7	77.4	76.0	74.6
GI Q4	77.6	76.3	76.5	76.2

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

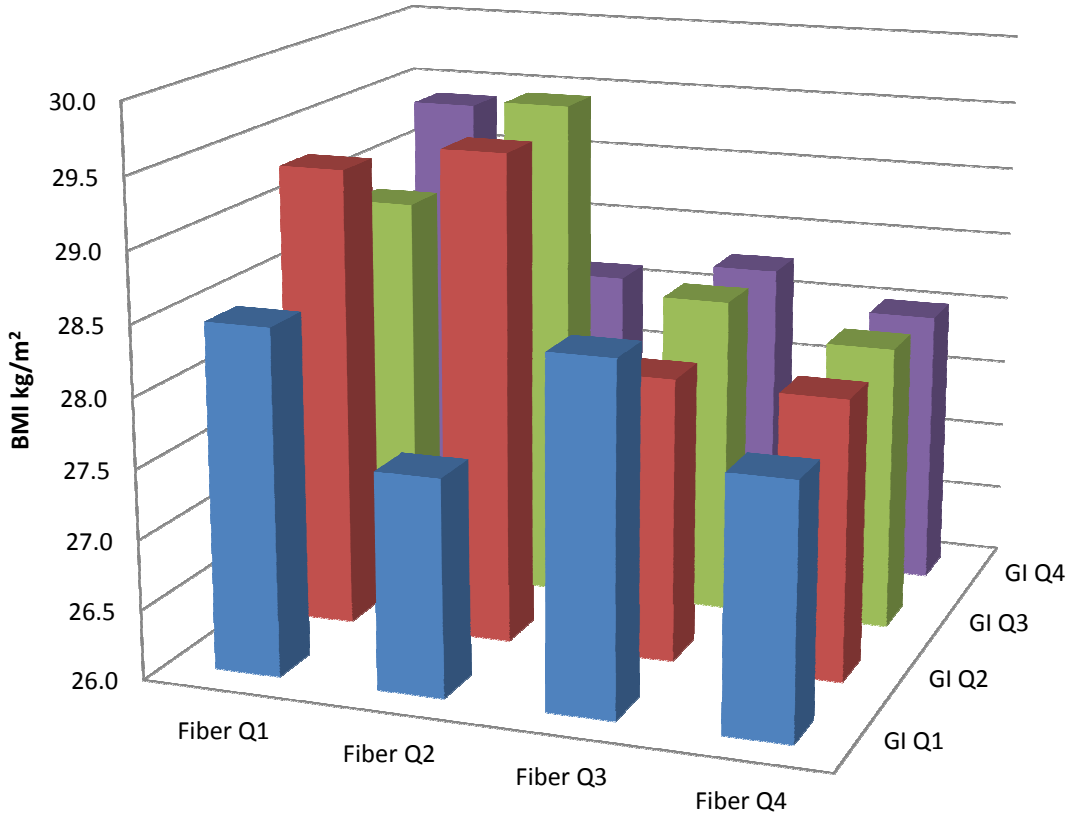
Figure A. 4. Glycaemic index and total fibre intake in relation to diastolic BP in UK and USA INTERMAP women participants, *n*=1153



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	72.8	72.9	72.7	70.2
GI Q2	72.3	70.5	72.2	72.3
GI Q3	73.2	72.9	70.7	68.9
GI Q4	72.8	70.5	71.5	70.4

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

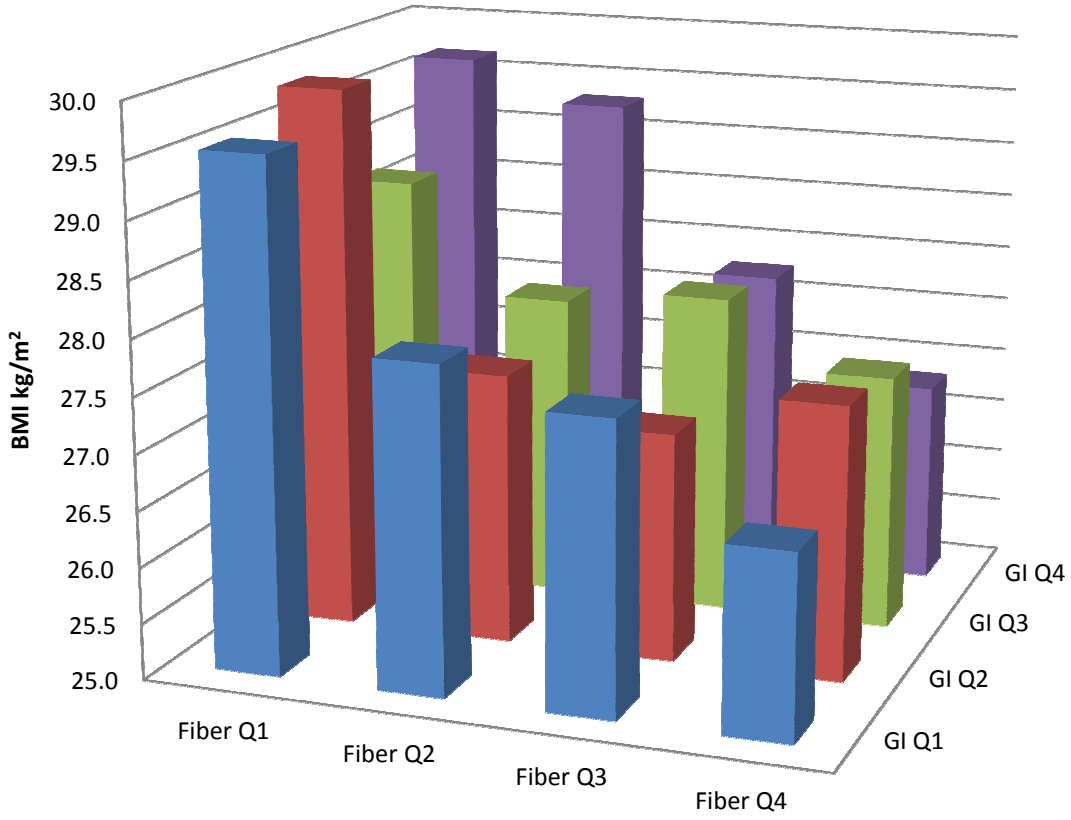
Figure A. 5. Glycaemic index and total fibre intake in relation to body mass index in UK and USA INTERMAP men participants, *n*=1232



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	28.5	27.5	28.5	27.8
GI Q2	29.3	29.5	28.0	28.0
GI Q3	28.8	29.6	28.3	28.1
GI Q4	29.4	28.1	28.3	28.0

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.

Figure A. 6. Glycaemic index and total fibre intake in relation to body mass index in UK and USA INTERMAP women participants, *n*=1153



	Fiber Q1	Fiber Q2	Fiber Q3	Fiber Q4
GI Q1	29.5	27.9	27.6	26.6
GI Q2	29.8	27.4	27.0	27.4
GI Q3	28.7	27.7	27.9	27.3
GI Q4	29.7	29.3	27.8	26.8

Model 1 adjusted for age, total energy intake (kcal/24-hours), total protein (%kcal), total fat (%kcal), and population sample.