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Review

An Update on Nutrients and Blood Pressure

Summary of INTERMAP Study Findings

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Adverse blood pressure (BP) is a major independent risk factor for epidemic cardiovascular diseases affecting almost one-quarter of the adult population worldwide. Dietary intake is a major determinant in the development and progression of high BP. Lifestyle modifications, including recommended dietary guidelines, are advocated by the American Society of Hypertension, the International Society of Hypertension, the Japanese Society of Hypertension, and many other organisations for treating all hypertensive people, prior to initiating drug therapy and as an adjunct to medication in persons already on drug therapy. Lifestyle modification can also reduce high BP and prevent development of hypertension. This review synthesizes results from the International Study of Macro/Micronutrients and Blood Pressure (INTERMAP), a cross-sectional epidemiological study of 4,680 men and women aged 40-59 years from Japan, the People's Republic of China, the United Kingdom, and the United States, published over the past few years on cross cultural BP differences. INTERMAP has previously reported that intakes of vegetable protein, glutamic acid, total and insoluble fibre, total polyunsaturated fatty acid and linoleic acid, total n-3 fatty acid and linolenic acid, phosphorus, calcium, magnesium, and non-heme iron were inversely related to BP. Direct associations of sugars (fructose, glucose, and sucrose) and sugar-sweetened beverages (especially combined with high sodium intake), cholesterol, glycine, alanine, and oleic acid from animal sources with BP were also reported by the INTERMAP Study.

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Introduction

Adverse blood pressure (BP), including prehypertensive [defined as systolic blood pressure (SBP) of 120 to 139 mmHg or a diastolic blood pressure (DBP) of 80 to 89 mmHg][1)] and hypertensive [defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or current use of antihypertensive medication] levels[1, 2)], is a key independent risk factor for major cardiovascular diseases (CVD), afflicting a high and growing proportion of the adult population worldwide[3-6)]. Overall, an estimated 26% of the world's adult population were hypertensive in 2000 and 29% are projected to have hypertension (HTN) by 2025[7)]. Health policies dependent on antihypertensive drugs alone are only partially successful as many persons with established HTN do not take medication or do not take enough medication to

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achieve control[8-10], while the large numbers of people with BP in the normal, but not optimal, and high-normal range go untreated. A challenge is how to set up an effective population-wide strategy to stem the BP rise with age and to reduce overall BP levels, and in turn, reduce cardiovascular morbidity and mortality. Lifestyle modification including adherence to evidence-based dietary guidelines is recommended in HTN management and included within prevention guidelines advocated by the American Society of Hypertension (ASH), the European Society of Hypertension, the International Society of Hypertension (ISH), and many other organisations for treatment of all hypertensive people and prevention among those with a strong family history of HTN[1, 2, 11-16].

Dietary intake is a major determinant in the development and progression of high BP[6]. Dietary factors identified as being associated with BP in the INTERnational study of MAcro/micronutrients and blood Pressure (INTERMAP) are reported here (surveyed 1996-1999) and placed in the context of the available literature.

Evidence Prior To the INTERMAP Study

Lifestyle modification offers the potential for preventing development of raised BP and frank HTN and can lower BP at little cost and with minimal risk[17]. The INTERSALT Study in 1988 reported that sodium (Na) intake, body mass index (BMI) and excessive alcohol intake were all directly associated with BP, while potassium (K) was inversely associated[18-21]. These findings were reflected in dietary recommendations for management and prevention of high BP[22]: reduction of Na intake[23] (<100 mmol/day); restriction of alcohol intake[24] (<30 ml/day ethanol for men and <15 ml/day ethanol for women); and maintenance of adequate K intake[25] (90 mmol/day). Other lifestyle modifications recommended included weight reduction (body mass index <27 kg/m^2), regular physical activity and tobacco avoidance[22]. There were no recommended intakes of calcium (Ca), magnesium (Mg), cholesterol or fatty acids (e.g. n-3 fatty acids) though favourable intakes of these nutrients may further contribute to lowering BP.

The INTERMAP Study–Design and Methods

The INTERMAP Study is a cross-sectional epidemiological study of 4,680 men and women aged 40-59 years from 17 population samples (**Fig. 1**) in Japan, the People's Republic of China, the United Kingdom and the United States (www.clinicaltrials.gov NCT00005271)[26]. Participants were selected randomly from population lists, stratified by age/sex. Staff were trained, standardized and certified for BP measurement on the basis of a common protocol[26]. Each participant attended four visits, visits 1 and 2 on consecutive days, visits 3 and 4 on consecutive days on average 3 weeks later. For BP measurement, each participant–having emptied his/her bladder–was seated comfortably for 5 min, with no physical activity in the preceding half hour. BP was measured twice at each visit with a random zero sphygmomanometer. Korotkoff sounds I and V were criteria for SBP and DBP. Measurements of height and weight were obtained at two visits, as were questionnaire data on daily alcohol consumption over the previous 7 days. Dietary data were collected at each visit by a trained certified interviewer with use of the in-depth multipass 24-h recall method[27]. All foods, beverages, and supplements consumed in the previous 24 hours, including preparation methods, were recorded. Each participant provided two 24-h urine collections, start and end timed at the research centre; measurements included urinary volume, Na, K, Mg, Ca, urea and creatinine[26], amino acids[28], and proton nuclear magnetic resonance (^{1}H NMR) spectroscopy[29]. For external estimation of laboratory precision, a random 10% of samples were split locally and sent to the laboratory with different identification numbers. Questionnaire data were obtained on demographic and other possible confounders, including education, occupation, physical activity, cigarette smoking, history of CVD, or diabetes mellitus (DM), current use of a special diet, and use of antihypertensive and lipid-lowering drugs. Individuals were excluded if they did not attend all four visits; diet data were considered unreliable; energy intake from any 24-h dietary recall was <500 kcal/day or >5000 kcal/day for women, >8000 kcal/day for men; two urine collections were not available; data on other variables were incomplete or indicated protocol violation (total exclusions: 215 people)[30]. The study received institutional ethics committee approval for each site; all participants gave written informed consent.

Individual Nutrients and Blood Pressure

The INTERMAP Study reported that intakes of vegetable (plant) protein[30], glutamic acid[31], total and insoluble fibre[32], total polyunsaturated fatty acid (PUFA) and linoleic acid[33], oleic acid from vegetable sources[34], total n-3 fatty acid and linolenic acid[35], phosphorus (P), Ca and Mg[36], non-heme iron (Fe) and total Fe[37], and starch[38] were inversely related to

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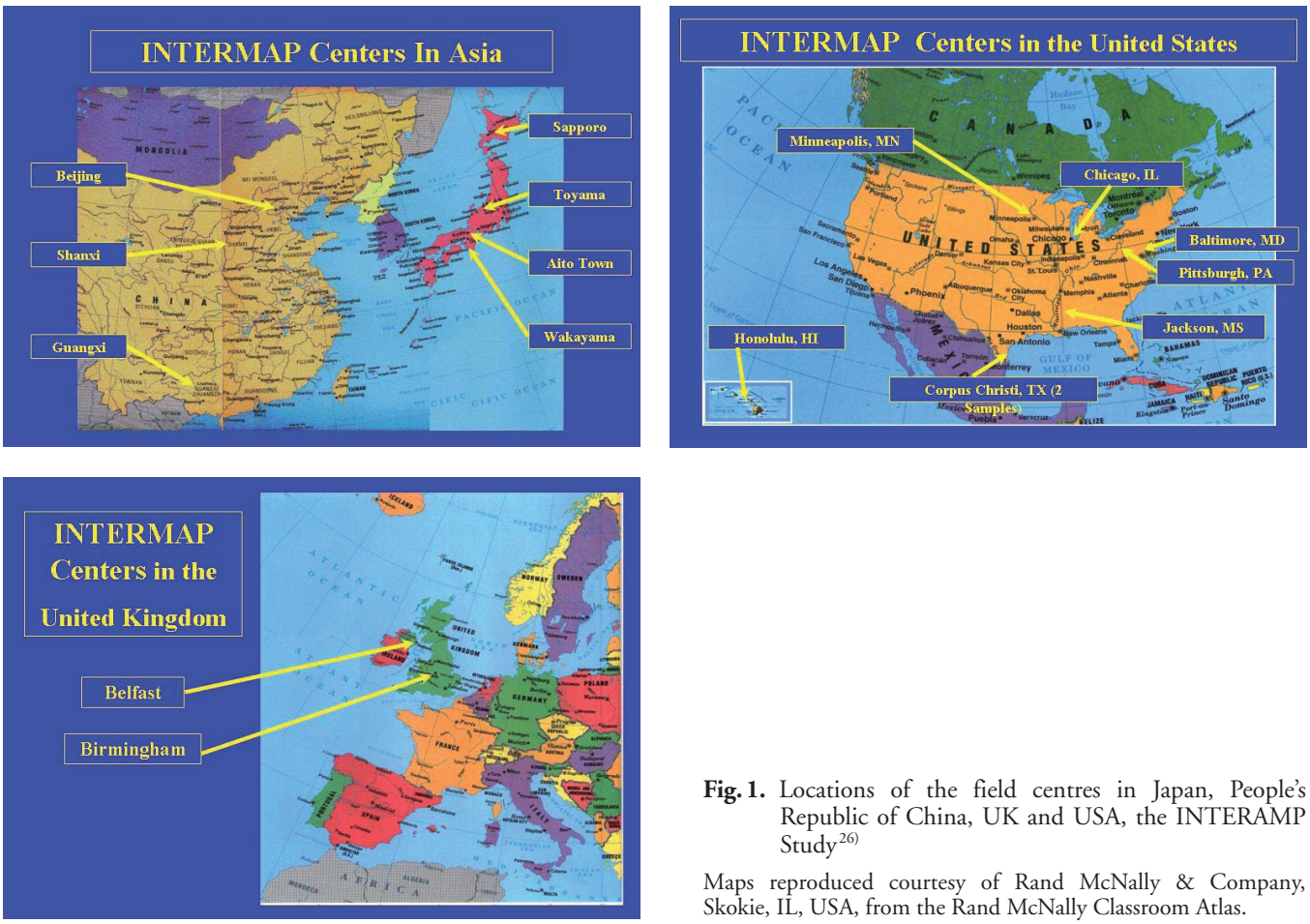


Fig. 1. Locations of the field centres in Japan, People's Republic of China, UK and USA, the INTERAMP Study[26]

Maps reproduced courtesy of Rand McNally & Company, Skokie, IL, USA, from the Rand McNally Classroom Atlas.

BP. Direct associations of sugars (fructose, glucose, and sucrose)[39], cholesterol[40], glycine and alanine[41], and oleic acid from animal sources[34] with BP were also reported by the INTERMAP Study. Findings of individual nutrients and BP of the INTERMAP Study are summarized in **Table 1** and in the following sections.

Protein and Amino Acids

As noted above, the relationship between individuals' vegetable protein intake and BP was inverse (SBP difference with 2 standard deviation (SD) higher vegetable protein intake was −1.1 mmHg, $P<0.01$); while for animal protein, there was significant direct associations with BP, which did not persist after adjustment for height and weight; there was no significant association between total protein intake and BP[30]. The INTERMAP Study subsequently reported that glutamic acid, the predominant dietary amino acid (especially in vegetable protein), was inversely associated with BP (SBP difference −1.1 mmHg for 2SD higher glutamic acid intake (4.72 %total protein), $P<0.05$)[31]. Dietary glycine and alanine levels (predominant in animal protein) had independent direct relations to BP: glycine intake higher by 2SD (0.89 %total protein) was associated with differences of 2.0 mmHg ($P<0.001$) for SBP[41]. Systematic reviews have suggested a small beneficial effect of protein on BP, especially for plant protein[42, 43]. A meta-analysis of randomized controlled trials (RCTs) with 32 comparisons between protein and carbohydrate found that dietary protein intake increased on average by 40 g/day lower mean SBP and DBP by −1.8 mmHg and −1.1 mmHg, respectively (both $P<0.001$), with no heterogeneity in BP reduction based on protein source[44]. A meta-analysis (2013) of observational studies and RCTs showed a small inverse association of total protein with BP, but a non-significant inverse association was found for plant protein[45]. The analysis reported a pooled estimate of −0.2 mmHg (95% confidence interval [CI] −0.4 to −0.01) systolic per 25 g of total protein intake in 6 cross-sectional studies; in 14 intervention studies using carbohydrate as a control treatment, the pooled BP effect was −2.1 mm systolic (−2.9 to −1.4) for a

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Table 1. Mean difference in blood pressure with dietary intakes higher by 2 standard derivations, regression model[§] for all INTERMAP participants (N=4,680)

Nutrient	2 SD difference	SBP difference (mmHg)	DBP difference (mmHg)	Note
Vegetable protein[30]	2.80 %kcal	−1.11**	−0.71*	
		−1.24*	−0.86*	(i)
Animal protein[30]	5.84 %kcal	0.20	−0.02	
Glutamic acid[31]	1.00 %kcal	−1.08*	−0.66*	(c)
Glycine[41]	0.89 % total protein	2.03***	0.89**	
	0.31 %kcal	0.42	0.15	(c)
Alanine[41]	0.85 % total protein	1.32*	0.38	
	0.34 %kcal	−0.18	−0.17	(c)
Total polyunsaturated fatty acid[33]	4.04 %kcal	−0.38	−0.34	
		−1.35*	−0.88*	(j)
Linoleic acid[33]	3.77 %kcal	−0.39	−0.31	(j)
		−1.36*	−0.83*	
Total n-3 fatty acid[35]	0.67 %kcal	−0.55	−0.57*	(a)
		−1.01	−0.98*	(a, j)
		−0.74*	−0.72*	(a, k)
Linolenic acid[35]	0.57 %kcal	−0.60	−0.50	
		−0.97	−0.87	(j)
		−0.77*	−0.61*	(k)
Monounsaturated fatty acid[34]	5.35 %kcal	0.05	−0.84*	(e)
		−1.22	−1.54*	(e,j)
Oleic acid from vegetable sources[34]	4.12 %kcal	−0.84*	−0.65*	(e)
		−1.28*	−1.01*	(e, j)
Oleic acid from animal sources[34]	3.86 %kcal	2.47***	0.94*	(j)
		1.80	1.22	(e, j)
Starch[38]	14.11 %kJ	−0.57	−0.52	
		−0.96	−0.92*	(b)
		−1.52	−1.23*	(b, j)
Fructose[39]	5.60 %kcal	0.73	0.44	(l)
		1.07	0.62	(c, l)
		2.50**	1.71**	(c, l, o)
Glucose[39]	5.10 %kcal	0.75	0.44	(l)
		1.08*	0.60	(c, l)
		2.69***	1.61**	(c, l, o)
Sucrose[39]	9.80 %kcal	0.21	0.71*	(l)
		0.33	0.74*	(c, l)
Total fibre[32]	6.80 g/1000 kcal	−1.01	−0.42	(f, m)
	6.90 g/1000 kcal	−1.69**	−1.15	(f, n)
Insoluble fibre[32]	4.60 g/1000 kcal	−1.81	−1.16*	(g, m)
	4.80 g/1000 kcal	−2.48**	−3.51**	(g, n)
Soluble fibre[32]	2.20 g/1000 kcal	0.88	0.68	(h, m)
	2.20 g/1000 kcal	0.89	−0.47	(h, n)
Cholesterol[40]	131.0 mg/1000 kcal	0.94*	0.24	
		1.42**	0.37	(d)
		1.46**	0.66*	(d, k)
Phosphorus[36]	232.0 mg/1000 kcal	−1.36**	−0.94**	
		−1.64*	−1.13*	(j)
Calcium[36]	240.2 mg/1000 kcal	−1.48***	−0.97**	
Magnesium[36]	75.6 mg/1000 kcal	−1.51**	−0.61	
Total Iron[37]	4.20 mg/4.2 MJ	−1.44***	−0.71**	
Non-haem Iron[37]	4.13 mg/4.2 MJ	−1.51***	−0.75**	
Haem Iron[37]	0.61 mg/4.2 MJ	0.19	0.10	

[§]Adjustment for population sample, age, sex, special diet, history of cardiovascular disease (CVD) or diabetes mellitus (DM), family history of hypertension, moderate or heavy physical activity (usual hours per day), dietary supplement intake, 24-h urinary sodium (Na) and potassium excretion and 7 day alcohol intake with either height and weight or body mass index *$p<0.05$; **$p<0.01$; ***$p<0.001$

(a) Regression model with additional adjustment for cholesterol, saturated fatty acid (SFA), calcium (Ca) and phosphorus (P)
(b) Regression model with additional adjustment for cholesterol, SFA, polyunsaturated fatty acid (PUFA) and Ca
(c) Regression model with additional adjustment for cholesterol, SFA and PUFA
(d) Regression model with additional adjustment for SFA, PUFA and P
(e) Regression model with additional adjustment for cholesterol, SFA, and Ca
(f) Regression model with additional adjustment for total energy, total protein, total fat, total sugar
(g) Regression model with additional adjustment for total energy, total protein, total fat, total sugar, soluble fibre
(h) Regression model with additional adjustment for total energy, total protein, total fat, total sugar, insoluble fibre
(i) Excluding persons taking hypertensive or cardiovascular disease medications (N=3,930)
(j) Non-intervened persons only (individuals not on a special diet, not consuming nutritional supplements, not with diagnosed CVD/diabetes, not taking medication for high BP/CVD/diabetes) and regressions not adjusted for special diet, supplement use, or CVD-DM (N=2,238)
(k) Non-hypertensive persons only (N=3,671) (l) UK and US participants only (N=2,696)
(m) US participants only (N=2,195) (n) Non-hypertensive US participants only (N=1,477)
(o) With Na excretion >median values: UK men, >155 mmol/24-h; UK women, >125 mmol/24-h; USA men, >174 mmol/24-h; USA women, >137 mmol/24-h (N=1,347)

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mean contrast in protein intake of 41 g/day. However, the associations of plant protein and animal protein with BP were broadly similar in prospective studies and RCTs. The BP effect of specific types of protein remains to be established.

Fatty Acids and Fish Oils

Participants in the INTERMAP Study who reported a higher intake of n-3 PUFA (rich in fish oil) had lower BP levels[35]. The study also reported an inverse association of linoleic acid (the main dietary PUFA) with BP[33]. Meta-analyses of RCTs on fish oil supplements reported significant BP reduction overall and in hypertensive participants[46, 47]. The analyses (1993) showed that, compared to control groups, pooled estimates of SBP and DBP change were −1.0 mmHg (95% CI −2.0 to 0.0) and −0.5 mmHg (−1.2 to 0.2) in normotensive individuals, and -5.5 mmHg (−8.1 to −2.9) and −3.5 mmHg (−5.0 to −2.1) in untreated hypertensive individuals with an average of >3 g/day n-3 PUFA supplementation[46]. Fish oil supplementation (median of 3.7 g/day) was reported to reduce SBP by 2.1 mmHg (95% CI 1.0 to 3.2) and DBP by 1.6 mmHg (1.0 to 2.2), compared to placebo, in meta-analysis of 36 RCTs (2002)[47]. A review (2006) of RCTs of linolenic acid supplementation showed no significant difference in BP changes between participants taking supplementation compared to placebo control groups[48]. Other INTERMAP Study findings include inverse associations of monounsaturated fatty acid (MUFA), total oleic acid (main MUFA) and oleic acid from vegetable sources with BP[34]. A review (2006) of studies conducted in the Mediterranean countries reported that MUFA was inversely associated with BP; this contrasts with earlier studies conducted mainly in the USA and Northern Europe[49]. This may due to the difference on food sources of MUFA: dairy, nut butter and meat for the western diet, and olives and olive oil for the traditional Mediterranean diet (MetDiet)[50]. A meta-analysis of 9 RCTs (2011) comparing a high MUFA diet to a low MUFA diet reported significant reduction on BP[51]. The pooled effect of a high-MUFA diet was −2.3 mmHg (95% CI −4.3 to −0.3) for SBP. Another meta-analysis of 13 RCTs (2014) reported studies examined effect of total amount of fat and the quality of fat (proportions of SFA, MUFA or total unsaturated fat) on BP but results were inconsistent and no conclusions could be drawn[52].

Starch and Sugars

Among the participants of the INTERMAP study, there were modest inverse associations of starch intake and BP, which were attenuated by control for vegetable protein[38]. Findings from the Multiple Risk Factor Intervention Trial (MRFIT) reported a direct association between dietary starch intake and BP[53]. A meta-analysis of 10 studies (2007) comparing the effects of high-carbohydrate versus high-MUFA diets indicated that the high-carbohydrate diets were associated with significantly higher BP (mean SBP difference 2.6 mmHg, $P=0.02$)[54].

The INTERMAP Study reported direct fructose- and glucose-BP associations, with significant sugar-sodium interactions: for individuals with above-median 24-h urinary Na excretion, fructose intake higher by 2SD (5.6% kcal) was associated with systolic/diastolic BP differences of 2.5/1.7 mmHg[39]. A meta-analysis of 13 RCTs of isocaloric diets (2012) with a median follow-up of 4 weeks found a significant DBP-lowering effect when fructose was substituted for other carbohydrates (mean difference −1.5 mmHg, 95% CI −2.8 to −0.3) but no significant effect on SBP[55]. A meta-analysis of 7 studies (2014) showed that fructose consumption was positively associated with elevated SBP (0.3 mmHg, $P=0.002$) and there was statistically significant heterogeneity among studies ($I^2=83.4\%$, $P=0.001$)[56]. Another review of 12 RCTs (2014) reported no significant effect of higher sugar intakes on SBP and a significantly greater DBP of 1.4 mmHg ($P=0.02$); a significant and positive association of sugar intake with BP was found in a subgroup of 3 trials >8 weeks in duration (mean difference: 6.9 mmHg for SBP, $P<0.0001$ and 5.6 mmHg for DBP, $P<0.001$)[57].

Fibre

The INTERMAP Study reported higher intake of total dietary fibre, especially insoluble, was associated with lower BP[32]. A meta-analysis (2005) of 25 RCTs demonstrated the hypotensive effects of dietary fibre in hypertensive persons (SBP −6.0 mmHg and DBP −4.2 mmHg per 10.7 g/day total fibre on average, both $P<0.001$) while in normotensive individuals, there was a smaller, non-significant reduction in BP[58]. Another meta-analysis in the same year investigating the effect of fibre supplementation (average dose of 11.5 g/day) on BP from 24 RCTs reported a small BP-lowering effect of −1.1 mmHg (95% CI −2.5 to 0.2) SBP and −1.3 mmHg (−2.0 to −0.5) DBP[59]. A recent review (2015) of RCTs of 7 types of fibre (e.g., arabinoxylan from wholegrain foods, beta-glucan from oats and barley) reported that higher consumption of fibre was associated with lower BP, and diets rich in beta-glucan reduced SBP by 2.9 mmHg (95% CI 0.2 to 2.7) and DBP by 1.5 mmHg (0.2 to

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2.7) for a median difference in beta-glucan of 4 g[60].

Phosphorus

The INTERMAP Study showed that higher P intake (per 2SD of 232.0 mg/1000 kcal), independently of other nutrients, was associated with lower BP levels (−1.4 mmHg for SBP, −0.9 mmHg for DBP, both $P<0.01$)[36]. A study using dietary data for 13,444 participants from Atherosclerosis Risk in Communities cohort and the Multi-Ethnic Study of Atherosclerosis reported *P* intake (per 500 mg/day higher) was inversely associated with SBP (−2.1 mmHg, 95% CI −1.1 to −3.0), after adjustment for confounders and highly correlated nutrients[61].

Calcium and Magnesium

Epidemiological data have shown that both dietary and supplemental Ca are associated with small reductions in BP. For all 4,680 INTERMAP participants, estimated BP differences for dietary Ca higher by 240.2 mg/1000 kcal (2SD) was −1.5 mmHg for SBP ($P<0.001$) and −1.0 mmHg for DBP ($P<0.01$)[36]. A meta-analysis of 22 RCTs (1996) reported an inverse relationship of Ca supplement on BP; overall pooled estimated of Ca supplementation were −0.9 mmHg (95% CI −1.74 to −0.05) for SBP and it was −1.7 mmHg (−3.2 to −0.2) for hypertensive persons[62]. Another pooled meta-analysis of RCTs of Ca supplements (1999) also reported a reduction in SBP of 1.4 mmHg and in DBP of 0.8 mmHg (both $P<0.001$)[63]. Similar results were reported in a meta-analysis of 40 RCTs (2006); mean daily dose of 1,200 mg Ca supplementation reduced SBP by −1.9 mmHg (95% CI, −2.9 to −0.8) and DBP by −1.0 mmHg (−1.6 to −0.4)[64]. A Cochrane review (2006) of 13 RCTs with between 8 and 15 weeks follow-up found that Ca supplementation was associated with a small statistically significant reduction in SBP (mean difference −2.5 mmHg) but had little effect on DBP[65].

The INTERMAP Study suggested an inverse association between dietary Mg and BP, for dietary Mg higher by 75.6 mg/1000 kcal (2SD), the estimated BP differences were −1.5 mmHg for SBP ($P<0.01$) and −0.6 mmHg for DBP[36]. An early meta-analysis (1998) of 29 studies reported a negative correlation between dietary Mg intake and BP[66]. Subsequently, a meta-analysis of 20 RCTs reported Mg supplementation resulted in only a small overall reduction in BP: estimates of BP change relative to placebo were −0.6 mmHg (95% CI −2.2 to 1.0) for SBP and −0.8 mmHg (−1.9 to 0.4) for DBP for average Mg increase of 367.6 mg/day[67]. There was a dose-dependent effect of Mg, with reduction of 4.3 mmHg SBP ($P<0.001$) and of 2.3 mmHg DBP ($P=0.09$) for each 238.7 mg/day increase in Mg. In 2006, a Cochrane review of 12 RCTs with 8 to 26 weeks follow-up reported that supplemental Mg and lowered DBP (though not SBP): mean difference −2.2 mmHg DBP (95% CI −3.4 to −0.9). However, there was marked heterogeneity between studies ($I^2=47.0\%$)[68].

A prospective study of >136,000 Chinese men and women reported that persons with Ca/Mg ratios above the median (>1.7), intakes of Ca (≥ 600 mg/day) and Mg (≥ 320 mg/day) were associated with reduced risks of total mortality, and mortality due to coronary heart disease; conversely, participants with a Ca/Mg ratio ≤ 1.7, intake of Mg was associated with increased risks of total mortality and mortality due to CVD[69]. The mean intake of Mg in Chinese population was similar to the US populations whereas the Ca/Mg intake ratio was significantly lower compared to US populations (3.0); the findings suggested that dietary Ca/Mg ratio, not Mg or Ca intake alone, might contribute to the different incidence and risks of mortality[69].

Iron

The INTERMAP Study suggested an inverse association of total Fe intake and non-heme Fe intake with BP[37]. Dietary total Fe intake higher by 4.20 mg/4.2 MJ (2SD) was associated with −1.4 mmHg ($P<0.001$) SBP and non-heme Fe intake higher by 4.1 mg/4.2 MJ (2SD) was associated with −1.5 mmHg ($P<0.001$) SBP. A follow-up study of 2,895 participants reported similar findings; low non-heme Fe intake at baseline was associated with a greater increase in SBP over time (*P*-trend=0.002) and participants in the top tertile of non-heme Fe intake at baseline had a significantly lower risk of HTN after 5.4 y of follow-up compared with those in the bottom tertile[70]. However, the relationship between Fe intake and raised BP or risk of CVD is not well established in the literature. A review of 55 studies (2013) suggested there was not a high level of evidence supporting the hypothesis that the Fe may be associated with CVD[71]. A recent meta-analysis (2015) of 13 prospective cohort studies showed higher dietary intake of heme Fe (1 mg/day) was associated with an increased risk of CVD (relative risk [RR]=1.07, 95% CI 1.01 to 1.14) and no association between CVD risk and dietary non-heme Fe (RR=0.98, 0.96 to 1.01) or total Fe (RR=1.00, 0.95 to 1.06)[72].

Multiple Nutrients

The INTERMAP Study reported the combined effects of multiple nutrients on BP by assessing multi-

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Table 2. Estimated population-wide lower average systolic blood pressure (mmHg) of more favourable diet, the INTERMAP Study

Variable	Improvement in level	Estimated lower average SBP (mmHg) Multivariate models with BMI[§]			
		Model 1: Ca, P, Vegetable Protein	Model 2: Ca, Non-heme Fe, Vegetable Protein	Model 3: Ca, P, Mg	Model 4: Ca, Mg, Non-heme Fe
Urinary sodium (mmol/24 h)	−110	−0.7[‡]	−0.7[‡]	−0.7	−0.7[‡]
Urinary potassium (mmol/24 h)	+60	−2.8***	−2.7***	−1.2[‡]	−2.8***
Calcium, Ca (mg/1000 kcal)	+240	−1.4*	−1.2**	−1.8**	−1.1
Phosphorus, P (mg/1000 kcal)	+232	−0.5	--	−0.2	--
Magnesium, Mg (mg/1000 kcal)	+76	--	--	−0.9[‡]	−1.3**
Non-heme Iron, Fe (mg/1000 kcal)	+4.1	--	−0.9[‡]	--	−1.3**
Vegetable protein (%kcal)	+2.8	−1.2**	−0.8[‡]	--	--
Polyunsaturated fatty acid (%kcal)	+4.1	−0.6	−0.6	−0.8	−0.7
Heavy alcohol intake Men >26 g/day; Women >13 g/day	Prevalence None	(−3.3***) −0.6[†]	(−3.3***) −0.5[†]	(−3.5***) −0.6[†]	(−3.4***) −0.6[†]
Body mass index (kg/m^2)	−4	−3.4***	−3.4***	−3.5***	−3.5***
Sum−All Variables	--	−11.2	−10.9	−10.4	−11.0
Sum−Na, K, Alcohol, BMI	--	−7.5	−7.4	−7.6	−7.7

[§]controlled for age, gender, sample, family history of high BP, physical activity, diagnosis of cardiovascular disease/diabetes, use of special diet, dietary supplement use
[‡]$p<0.10$; *$p<0.05$; **$p<0.01$; ***$p<0.001$

ple regression models involving various combinations of dietary vegetable protein, Ca, Mg, P, non-heme Fe, Na, K, PUFA and heavy alcohol consumption adjusted for BMI (**Table 2**)[73]. For all 4,680 INTERMAP participants, improved Na and K intakes and elimination of heavy alcohol consumption, gave a combined estimated effect of SBP lower by 7 mmHg; with the addition of other dietary variables, the estimated effect on SBP was 2-3 mmHg lower (about 10 mmHg).

Using a systematic nutrient-wide association study (NWAS) approach to evaluate multiple associations between a wide range of nutrients and BP, the INTERMAP Study reported inverse associations between BP and intake of B vitamins (folacin, riboflavin, and thiamin) which replicated in National Health And Nutrition Examination Survey data[74]. Associations of BP with B vitamins had previously been poorly studied or were not replicated. This systematic evaluation of multiple nutrients also found inverse associations of dietary P, Mg, and non-heme Fe intakes with SBP, and previously established direct associations of Na/K ratio and alcohol with BP.

In the Dietary Approaches to Stop Hypertension (DASH) trial, participants were randomly assigned to control diet (the average diet in the US), fruits-and-vegetables diet (a diet rich in fruits and vegetables), or combination diet (a diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat)[17]. The combination diet reduced SBP by −5.5 mmHg (95% CI −7.4 to −3.7) more than the control diet did ($P<0.001$)[17]. In the DASH-Na trial, participants were randomly assigned to a control diet or the DASH diet; and participants ate foods with 3 different levels of Na intake[75]. Reducing the Na intake from the high to the intermediate level reduced BP during both the control diet and the DASH diet. The Optimal Macronutrient Intake Trial for Heart Health (OMNIHEART) trial[76] reported BP benefits from replacing carbohydrate in the DASH-Na diet with either protein or MUFA. The INTERMAP Study investigated associations of three OMNIHEART-like nutrient profiles with a typical American nutrient profile, using two different statistical meth-

Advance Publication
Journal of Atherosclerosis and Thrombosis
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ods: regression of BP on a linear OMNIHEART nutrient score calculated for each individual and Bayesian profile regression[77]. After adjustment for potential confounders, an OMNIHEART score higher by 1 point was associated with differences of −1.0 mmHg for SBP and −0.5 mm Hg for DBP (both $P<0.001$). In the Bayesian analysis, mean systolic/diastolic BPs were 111.3/68.4 and 115.2/70.6 mmHg for OMNIHEART and Control profiles, respectively, after controlling for possible confounders, with BP differences of −3.9/−2.2 mmHg.

Foods and Drinks

Because people consume foods and beverages, not isolated nutrients, there is a fundamental interest in these associations. The INTERMAP Study collected data on foods, beverages and preparation methods derived from four 24-h dietary recalls provided by all participants. The study reported a significant and inverse relationship between total vegetable intake and BP; estimated average SBP differences associated with raw vegetable intake (68 g/1000 kcal) and cooked vegetable intake (92 g/1000 kcal) were −1.3 mmHg ($P=0.02$) and −0.9 mmHg ($P<0.1$)[78]. The commonly consumed individual vegetables, tomatoes, carrots, scallions, peas, and celery, were related significantly inversely to BP. Apples and pears, citrus fruit, and bananas were the most commonly consumed raw fruit among the INTERAMP participants in each country; fruit juice intake was negligible in East Asian samples[79]. Although there were no consistent associations between raw fruit and fruit juice intakes of individuals and BP, participants with higher raw fruit intakes had lower energy intake, and had lower BP than those with lower intakes. The higher raw fruit consumers in the UK and US had higher intakes of vegetables, low-fat dairy products, fiber-rich cereals and grains compared with lower raw fruit consumers. These INTERMAP findings on fruits and vegetables reinforce current dietary recommendations for HTN management and prevention[1, 2].

The INTERMAP study reported sugar-sweetened beverage (SSB) intake higher by 1 serving/day (355 ml/day) was associated with systolic/diastolic BP differences of 1.1/0.4 mmHg ($P<0.001/<0.05$)[39]. These direct SSB-BP associations were stronger for the INTERAMP US participants with higher 24-h urinary Na excretion with significant sugar-Na interactions in relation to higher BP. The associations of diet beverages with BPs were consistently inverse; diet beverages intake higher by 1 serving/day was associated with systolic/diastolic BP differences of −0.6/−0.4 mmHg (both $P<0.05$)[39]. A recent review (2014) of studies reported a positive relation between increased SSB intake and high BP; 5 reported an increase in mean BP whereas 7 reported an increase in the incidence of high BP. Dietary guidelines to reduce sugar intake and SSB consumption potentially will have major beneficial effects to prevent HTN[80] and CVD[81].

Dietary Guidelines for Management and Prevention of High Blood Pressure

The DASH-Na diet is a well-balanced approach to prevent and control HTN[17, 75]. It is recommended as part of the HTN guidelines from Canada[82], India[83], Japan[14], the UK[2] and the US[1]. It is also associated with lower risk of several types of cancer[84, 85], and reduced risk of developing type 2 diabetes[86]. The MedDiet has also been advocated as a means to reduce BP and risk of CVD[87]. It is characterized by a high intake of olive oil, fruit, nuts, and vegetables; a moderate intake of fish and poultry; low intake of dairy products, and red meat; and wine in moderation, consumed with meals[88]. This traditional dietary pattern was shown to be associated with reduced risk of CVD in the Seven Countries Study in 1950s[89], and in more recent studies[87, 90]. A meta-analysis (2011) of 10 RCTs reported that adherence to the MedDiet was associated with reduced BP: −2.4 mmHg (95% CI −3.5 to −1.2) for SBP and −1.6 mmHg (−2.0 to −1.1)[91]. MedDiet and DASH have in common greater intakes of fruit, vegetables, nuts and fish and low intake of meat, with the MedDiet including more olive oil but fewer dairy products compared to the DASH diet. The 2010 Dietary Guidelines Advisory Committee reviewed articles published between 2009 and 2010 concluded that moderate amounts of low-fat or reduced-fat dairy products improved BP and decreased HTN risk[92].

The guidelines of lifestyle modifications for management and prevention of HTN (2014, by ASH and the ISH)[93] remained unchanged compared to the 1995 guidelines:[22] healthy weight, salt reduction, moderate alcohol consumption, regular aerobic exercise and quit smoking. Most of the guidelines do recommend a healthy eating pattern: mainly plant-based foods such as fruits, vegetables, wholegrain foods; moderate amounts of low-fat or reduced-fat dairy products, moderate amounts of lean unprocessed meats, poultry and fish, moderate amounts of PUFA and MUFA (e.g. olive oil), and reduce amounts of SFA and cholesterol[1, 2, 11-14, 83]. Persons with HTN are also advised to increase the intake of fish in a few guidelines[13, 14]. Although the DASH-Na diet is often

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Journal of Atherosclerosis and Thrombosis
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recommended as part of the guidelines for management and prevention of HTN, it is not endorsed by many Asian countries, such as China, where populations consume fewer dairy products than in Western countries.

The 2002 China National Nutrition and Health Survey reported that a higher traditional southern pattern score (a diet characterized by high intakes of fruit, pork, poultry, rice, vegetables, fish and seafood, and nuts) was associated with a lower prevalence of HTN, independent of BMI (*P* for trend=0.01); odds ratio for the top vs bottom quartile of traditional southern pattern diet score was 0.8 (95% CI, 0.6-0.9)[94]. This southern Chinese diet has a similar combination of foods as the DASH diet, except dairy products. A pilot study, DASH for Koreans (K-DASH), developed culturally sensitive dietary guidelines by the adaptation of DASH-Na diet and demonstrated the efficacy of this K-DASH intervention in reducing HBP in Korean Americans[95]. The country-specific foods and beverages from the dietary recalls in the INTERMAP Study may provide information for developing culturally tailored dietary guidelines for management and prevention of HTN.

In summary, the INTERMAP findings on nutrients and foods associated with BP levels of individuals from four countries support current recommendations for a diet high in fruit and vegetables, whole grains, nuts and legumes, fish, lean meats, and poultry as well as low-fat dairy products, and low in Na and SFA, as part of comprehensive nutritional/lifestyle approaches to preventing and controlling major established cardiovascular risk factors and epidemic CVD.

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Conflicts of Interest

Paul Elliott is supported in part by the National Institute for Health Research (NIHR) Biomedical Research Centre, Imperial College Healthcare NHS Trust and Imperial College London.

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Advance Publication
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