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## Macronutrient Group Symposium on 'Protein intake and chronic disease'

# Protein intake and blood pressure in cardiovascular disease

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Raised blood pressure (BP) is a major cause of CHD and the leading cause of stroke. Although BP rises with age in most populations, there are remote populations around the world where BP does not rise with age and where the high prevalence of high BP and frank hypertension seen in the UK and other Western countries in the older age-groups is not found. However, when such populations migrate to urban settings, their BPs rise, indicating that the population-wide BP problem is largely environmental in origin. Thus, a substantial body of evidence has accumulated on the importance of dietary factors in BP (Na and alcohol intakes (direct relationship) and K intake (inverse relationship)) as well as body weight (direct relationship). More recently, attention has shifted to other dietary factors that might affect BP. Data from studies of vegetarians (who tend to have lower BP than meat-eating populations) as well as clinical data on the adverse effects of protein intake in patients with renal insufficiency led to the view in Western countries that dietary (animal or total) protein had an adverse effect on BP. By contrast, studies in Japan and China suggested that dietary protein might be protective of high BP and stroke. Recent epidemiological studies have found inverse associations between dietary protein intake and BP, consistent with this view, and supported by some evidence from animal studies. Recent controlled clinical trials of soyabean supplementation have also suggested a BP-lowering effect of protein intake. Results of further large-scale epidemiological studies of protein and BP are awaited.

**Blood pressure: Protein intake: Cardiovascular disease risk: Western lifestyle: Epidemiological data**

Raised blood pressure (BP) is a major risk factor for CHD and the major risk factor for stroke (Stamler, 1992). It is one of the most important underlying risk factors for cardiovascular and all-cause mortality in the world today, ranking alongside tobacco in estimates of the worldwide attributable burden of mortality (Murray & Lopez, 1996). The cardiovascular diseases are estimated to account for approximately 28 % of all deaths in the world, with more of such deaths occurring in the developing world than in the developed world (Appendix Table 6 of Murray & Lopez, 1996). Demographic changes in the poorer countries (the so-called 'epidemiological transition'), together with the adoption of a Western lifestyle, mean that the poorer countries are set to experience an epidemic of cardiovascular diseases, which has been the case in the last century in the developed countries (Pearson *et al*. 1993). The rise in BP with age leading to the development of unfavourable BP patterns in populations, along with smoking and unfavourable blood lipid profiles (related to diet), are the key factors underlying this worldwide epidemic.

### Risks associated with raised blood pressure in populations

Table 1 shows the risk of death from CHD at 11·6 years of follow-up among the 360000 men screened for entry into the Multiple Risk Factor Intervention Trial (Stamler *et al*. 1993). It gives the numbers of men in each 10 mmHg BP category at screening, ranging from < 110 to ≥ 180 mmHg, numbers of deaths (and adjusted mortality rate) at 11·6

**Abbreviation:** BP, blood pressure.

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**Table 1.** Baseline systolic blood pressure and adjusted CHD death rates for men screened for the Multiple Risk Factor Intervention Trial (from Stamler *et al.* 1993)

| Systolic blood pressure (mmHg) | *n* | No. of deaths | Rate† | Relative risk‡ | Excess deaths§ | Percentage of all excess deaths | |
|---|---|---|---|---|---|---|---|
| <110 | 21379 | 197 | 9·8 | 1·00 | 0 | 0·0 | |
| 110–119 | 66080 | 712 | 11·1 | 1·12 | 77 | 1·3 | |
| 120–129 | 98834 | 1349 | 12·9 | 1·32*** | 319 | 9·9 | 31·9 |
| 130–139 | 79308 | 1587 | 17·0 | 1·76*** | 669 | 20·7 | |
| 140–149 | 44388 | 1328 | 22·8 | 2·35*** | 755 | 23·4 | 42·9 |
| 150–159 | 21477 | 938 | 30·5 | 3·14*** | 631 | 19·5 | |
| 160–169 | 9308 | 470 | 34·0 | 3·41*** | 328 | 10·1 | |
| 170–179 | 4013 | 286 | 47·6 | 4·30*** | 221 | 8·8 | 24·1 |
| ≥180 | 3191 | 283 | 57·2 | 5·65*** | 232 | 7·2 | |

***$P < 0{\cdot}001$.

†Rate per 10000 person-years adjusted by direct method for age, race, serum cholesterol, cigarettes per d, use of medication for diabetes, and income; average follow-up was 11·6 years.

‡Adjusted by proportional hazards regression for age, race, serum cholesterol, cigarettes per d, use of medication for diabetes and income.

§Estimated number of excess deaths compared with the baseline systolic blood pressure category of < 110 mm Hg during 11·6 years of follow-up. Excess deaths were derived by first calculating expected number of deaths within deciles of a risk score based on age, race, serum cholesterol, cigarettes per d, use of medication for diabetes and income, then summing these estimates across risk score deciles within each blood pressure category and subtracting this number from the observed number of deaths.

years, together with estimates of both relative and attributable risk (excess deaths). As shown, the mortality rate increases in a graded and continuous fashion, from the lowest (< 110 mmHg systolic) to the highest BP levels, with no threshold; thus, men with stage 1 hypertension (140–159 mmHg), by systolic criteria as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (1997), had relative risk of 2·35–3·14, while those with stage 3 hypertension by systolic criteria (> 180 mmHg) had relative risk of 5·65. However, whilst the highest relative risk was found for men with the highest BP, in terms of attributable risk (excess deaths) approximately 32 % of these were found at systolic BP < 140 mmHg, i.e. at 'normal' or 'high normal' BP, and a further 43 % from 140 mmHg to 159 mmHg. This situation occurs because the majority of the population had BP in the 'normal' or 'high normal' range; a large number of individuals with a small excess risk have the potential to generate far more cases than a small number of individuals with a large excess risk (Rose, 1992).

In terms of prevention, pharmacological treatment of high BP is currently recommended for sustained systolic BP > 140 mmHg. Even if a campaign to lower BP in the community through pharmacological means were completely successful (implying a never-ending programme of screening and drug treatment, and assuming that anti-hypertensive drugs were 100 % effective and without side effects) approximately 32 % of the BP-related mortality (and associated morbidity) would still not be prevented. To address (at the least) this part of the population BP problem requires a non-pharmacological approach to run alongside drug treatment, in order to reduce the population burden of BP-related disease.

### *Populations with low blood pressure and the rise in blood pressure with age*

The data in Table 1 indicate that a substantial proportion of the population develops hypertension and, given the rise of BP with age, this outcome becomes particularly prevalent at older ages. For example, data from the Health Survey for England indicate that between 50 and 60 % of men and women have stage 1 hypertension by the age of 55–64 years (Fig. 1; Erens & Primatesta, 1999). However, a rise in BP with age is not a universal finding in all societies. There are populations around the world where BP remains low throughout the lifespan and hypertension is rare or absent.

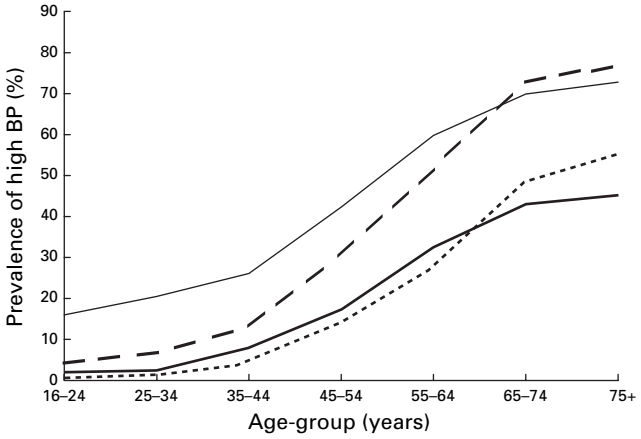


**Fig. 1.** Health Survey for England 1998: prevalence of high blood pressure (BP) by age. Systolic and diastolic BP of ≥140 and 90 mmHg respectively or on treatment: (————), men; (— —), women. Systolic and diastolic BP of ≥160 and 95 mmHg respectively or on treatment: (————), men; (- - - -), women. (From Erens & Primatesta, 1999; with permission.)

Fig. 2 compares the BP distribution of Kenyan nomads with that of London civil servants (Rose, 1985). While in both populations the BP distribution follows a familiar normal or log-normal curve, there is a striking shift to the right (towards higher BP levels) of the entire BP distribution for the London civil servants. The Kenyan population has much lower BP levels, and the prevalence of hypertension, even at older ages, is low.

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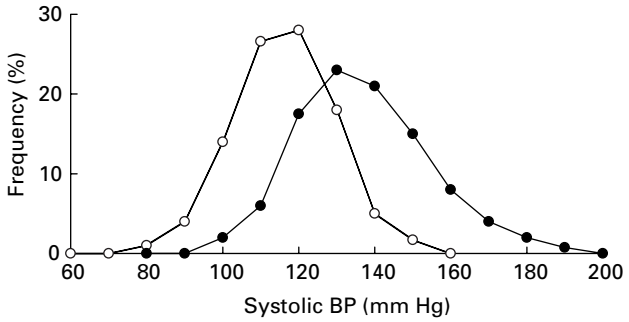


**Fig. 2.** Blood pressure (BP) distribution in London civil servants (●) and Kenyan nomads (○). (From Rose, 1985; with permission.)

Indeed, a number of populations around the world have been identified whose BP are low and there is no or only minimal rise in BP with age (Shaper, 1972; Carvalho *et al*. 1989). When individuals from low-BP populations migrate, however, their BP tend to increase. This outcome is illustrated by studies of the rural Luo in Kenya, whose BP were measured in their rural villages and then in an urban setting as men from the villages migrated to Nairobi (Poulter *et al*. 1990). Systolic BP were higher for the migrants compared with rural controls, with the BP difference becoming more marked by 24 months after migration. The differences in BP between the two groups correlated with a number of variables, including higher urinary Na:K and higher body weight among the migrants.

Studies of low BP populations and the rise in BP when they migrate indicate that the reasons for the large differences in the position of the BP distribution between populations (Fig. 2) are largely to be found among environmental factors rather than genetic factors. Thus, the key to prevention of the worldwide epidemic of BP-related morbidity and mortality is to identify and address those environmental factors (mainly dietary) that underlie the rise in BP with age and result in the high prevalence of high BP and frank hypertension at older ages.

## Dietary factors and blood pressure

### *Established risk factors for high blood pressure*

Four factors are considered established risk factors for high BP: high Na intake; low K intake; obesity; excessive alcohol drinking (National Research Council, 1989). Each of these factors was investigated as part of the International Study of Salt and Blood Pressure, an international epidemiological investigation carried out among over 10000 individuals in fifty-two centres and thirty-two countries worldwide (INTERSALT Cooperative Research Group, 1988; Elliott *et al*. 1996). Diet was assessed for Na and K intakes using 24 h urinary excretion as a biomarker; a random 8 % of participants provided two 24 h urine collections so that the reliability of Na and K excretion could be assessed and corrections made for unreliability of measurement (due to large day-to-day fluctuations in what participants eat; Dyer *et al*. 1994*a,b*). The study examined associations both across the fifty-two population samples and among the approximately 10000 individuals that took part. Across the samples, there was a highly significant ($P < 0{\cdot}001$) positive association between the slope of BP with age and urinary Na excretion, such that 100 mmol higher Na was associated with a rise in BP over a 30-year period (e.g. from age 25 years to 55 years) of 9–11 mmHg (Elliott *et al*. 1996).

**Table 2.** International Study of Salt and Blood Pressure (INTERSALT)*: individual-level regression estimates of differences in systolic (SBP) and diastolic (DBP) blood pressure (mmHg) for given differences in 24 h sodium and potassium excretion, BMI and alcohol intake

| | SBP | DBP |
|---|---|---|
| Na (/100 mmol): With BMI | 3·1 | 0·1 |
| Without BMI | 6·0 | 2·5 |
| K (/30 mmol) | –2·0 | –1·1 |
| BMI (per 2 units) | 1·6 | 1·2 |
| Alcohol (0 *v.* ≥300 ml/week†) | 3·3 | 2·0 |

*10074 men and women, fifty-two population samples. Adjusted for sample, age, gender and the other variables, except Na adjusted with and without BMI. Na and K corrected for reliability estimated from repeated measures on 8 %.

†Overall, 15 % of the population sample had an alcohol intake of ≥300 ml/week.

Results of the individual-level analysis for the four established risk factors for high BP are shown in Table 2. These data are the results of multiple regression models for each of the four factors, with estimated differences in BP for given differences in the four factors. For Na, the regression model was run with and without BMI, since Na and BMI are positively correlated and both are positively correlated with BP. However, whereas Na is poorly estimated by a single (24 h urine) measurement, BMI is highly reliably estimated from a single measure of height and weight. Thus, body mass will tend to dominate over Na in the regression models, even if the association between body mass and BP were working (at least in part) through their joint correlation with Na. Note also that the estimate for alcohol relates only to approximately 15 % of the participants, who were consuming > 300 ml absolute alcohol/week (so that at population level impact would be expected to be about one-sixth of these values).

The results indicate differences in BP of the order of < 1–6 mmHg for potentially-achievable differences in these dietary and lifestyle factors, indicating the potential for prevention of high BP through dietary and lifestyle means.

## Dietary protein

While favourable changes in population levels of the four established risk factors for high BP have the potential to have an important impact on the BP distribution (shifting the curve to the left toward more favourable BP values), it is clear that other dietary and nutritional factors must be involved (Appel & Elliott, 2003). Dietary protein is an important candidate (Burke *et al*. 1994; Obarzanek *et al*. 1996; He & Whelton 1999). Until the 1980s it was often assumed, especially by investigators from Western countries, that there was either no association (Meyer *et al*. 1983) or a direct association (Sacks *et al*. 1974; Armstrong *et al*. 1977; McCarron *et al*. 1982) between protein intake

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**Table 3.** International Study of Salt and Blood Pressure (INTERSALT): pooled regression estimates (B), standard errors and Z-scores for total nitrogen, urea-nitrogen, and sulfate (g/d) with blood pressure (mmHg) (from Stamler *et al.* 1996*b*, with permission)

| | Adjusted age–gender–sample | | | Multiple adjusted† | | |
|---|---|---|---|---|---|---|
| | Total N | Urea-N | Sulfate | Total N | Urea-N | Sulfate |
| SBP (*n* 10020) | | | | | | |
| B | +0·164 | +0·169 | +1·292 | –0·221 | –0·264 | –0·240 |
| SE | 0·046 | 0·054 | 0·238 | 0·064 | 0·074 | 0·326 |
| Z | +3·535*** | +3·128*** | +5·436*** | –3·439*** | –3·565*** | –0·736 |
| DBP (*n* 10009) | | | | | | |
| B | +0·062 | +0·059 | +0·587 | –0·165 | –0·195 | –0·363 |
| SE | 0·033 | 0·039 | 0·170 | 0·046 | 0·053 | 0·232 |
| Z | +1·859 | +1·530 | +3·451*** | –3·597*** | –3·695*** | –1·567 |

SBP, systolic blood pressure; DBP, diastolic blood pressure.
** $P<0·01$, *** $P<0·001$.
†Adjusted for age–gender–sample, 24 h Na, K, Ca, Mg and BMI, alcohol, men and women aged 20–59 years. Uncorrected for reliability.

(or intake of animal foods and protein of animal origin) and BP. For example, in individuals with protein malnutrition BP is often low (Viart, 1977), and diets low in protein improve the prognosis in renal insufficiency (Ihle *et al.* 1989), an important secondary cause of hypertension (Brod *et al.* 1983). Moreover, the rice diet, which was used to treat malignant hypertension in the 1940s, had a low protein content (20 g/d), as well as being low in Na and high in carbohydrate (Kempner, 1948; Watkin *et al.* 1950). Furthermore, the observation that vegetarians tend to have lower BP in comparison with meat eaters (Sacks *et al.* 1974) also seemed to suggest that low protein was protective of high BP (although vegetarians differ in other ways from non-vegetarians, including having lower body weight).

A different view of the protein–BP association emerged from observations in the 1970s and 1980s in Asian countries, especially Japan and China. Low protein intake was implicated as one of the factors underlying traditionally high rates of hypertension and high stroke rates in some regions of those countries (Yamori *et al.* 1984; Liu, 1989). In addition, experimental data indicated that protein-rich diets could slow the rise in BP and reduce stroke rates in response to Na load in salt-sensitive rats (Yamori *et al.* 1984).

Potentially, protein intake could influence BP through the actions of the constituent amino acids. Thus, tyrosine and phenylalanine affect the synthesis of catecholamines in the central nervous system (Anderson, 1986), and both tryptophan (Sved *et al.* 1982) and tyrosine (Sved *et al.* 1979) lower BP when injected intraperitoneally in animal models. Arginine is the metabolic precursor of NO, a potent vasodilator acting on the endothelium (Moncada & Higgs, 1993). Increased ingestion of arginine has been hypothesised to reverse vascular reactivity changes and reduce intimal thickness in atherosclerosis, and lower BP (Moncada & Higgs, 1993).

### *Epidemiological studies of protein intake and blood pressure*

Recently, a number of large epidemiological studies have reported on the association between protein and BP, finding inverse relationships in multiple adjusted analyses. The largest of these studies was the International Study of Salt and Blood Pressure (INTERSALT), which analysed the stored 24 h urinary samples for markers of protein intake, including total N excretion, urea-N and urinary sulfate (Stamler *et al.* 1996*b*). Results are summarized in Table 3. While positive associations with BP were found for all three markers in the age–gender–sample-adjusted analyses, these associations became inverse with additional adjustment for 24 h urinary Na, K, Ca and Mg excretion, BMI and alcohol intake (significantly inverse for both total N and urea-N $P<0·001$). Overall, the size of the coefficients indicated that differences in protein intake of 30 % above and below the group mean were associated with BP differences of 3·0 mmHg systolic BP and 2·5 mmHg diastolic BP. Inverse associations were also found in the analysis of the Multiple Risk Factor Intervention Trial cohort (Stamler *et al.* 1996*a*) and the Dietary and Nutritional Survey of British Adults, the latter based on protein intake estimated from 7 d weighed-diet records (Elliott *et al.* 1992).

Apart from these large recent studies, a number of other studies provided data on the relationship between protein intake and BP. Cross-sectional studies among adults are summarized in Table 4. The studies were identified from previous reviews (Burke *et al.* 1994; Obarzanek *et al.* 1996; He & Whelton, 1999), through bibliographic searches, reference lists from cited papers and author's own knowledge. Studies are listed by year of publication, except insofar that reports from the same study have been listed sequentially. Overall, twenty-six reports of cross-sectional analyses were identified from eighteen different studies. As can be seen from the data, most found a significant inverse association in at least one analysis, although in interpreting the data it should be noted that many of the studies were not designed to examine the diet–BP question, they varied in their design, dietary method and extent of control for confounding factors, and many included multiple significance testing (e.g. use of different protein markers, different end points such as BP or hypertension, different regression models for control of confounding factors, analysis of males and females separately or combined). In addition, several studies did not include control for energy intake, which (due to variable completeness of dietary reporting; Pryer *et al.* 1997) is an important potential source of bias (Willett & Stampfer, 1998). Since high BP is associated with overweight, and overweight individuals tend to under-report

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**Table 4.** Cross-sectional epidemiological studies of dietary protein and blood pressure in adults (adapted from Appel & Ellicott 2003; with permission)

| Reference | Study | Population | Dietary method | Confounders | Main findings* |
|---|---|---|---|---|---|
| Dawber *et al.* (1967) | Framingham Diet Study | 912 M and W, 37–69 years | Not specified | None | NS |
| Yamori *et al.* (1981) Kihara *et al.* (1984) | | 1120 M and W, > 30 years Japanese villagers | Spot urinary sulfate:urea-N | +++ | (–) SBP (M only) |
| Fehily *et al.* (1982) | Caerphilly Heart Study | 134 M, 44–60 years | 7 d weighed record | +++ | NS |
| Elliott *et al.* (1987) | Caerphilly Heart Study | 387 M, 45–59 years | 7 d weighed record | ++ | (–) HTN |
| Pellum & Madeiros (1983) | | 61 M and W, 22 and 25 years University students and staff | 3 d food record | + | (–) SBP and PP |
| McCarron *et al.* (1984) | NHANES I | 10 372 M and W, 18–74 years | 24 h recall | + | (–) HTN |
| Harlan *et al.* (1984) | NHANES I | 2055 M and W, 25–74 years | 24 h recall and 3 months FFQ | +++ | NS |
| Gruchow *et al.* (1985) | NHANES I | 9553 M and W, 18–74 years | 24 h recall | +++ | (–) HTN |
| Reed *et al.* (1985) | Honolulu Heart Program | 6496 M, 46–68 years Japanese ancestry | 24 h recall | ++ | (–) |
| Joffres *et al.* (1987) | Honolulu Heart Program | 615 M, 61–82 years Japanese ancestry | 24 h recall | ++ | (–) Vegetable protein |
| Slattery *et al.* (1988) | | 330 M and W, 22–66-year-old twins | FFQ | None | NS |
| Zhou *et al.* (1989) | Ten Chinese populations | 2672 M and W, 35–59 years Ecologic analysis | 3 × 24 h recall | +++ | (–) Animal protein, SBP |
| Havlik *et al.* (1990) | | 402 M, 42–56 years Monozygotic twins | FFQ | + | (+) DBP (twin-pair differences) |
| Elliott *et al.* (1992) | British Dietary and Nutritional Survey | 1922 M and W, 16–64 years | 7 d weighed record | +++ | (–) |
| Zhou *et al.* (1994) | | 705 M and W, 40–59 years Three Chinese populations | 3 × 24 h recall | +++ | (–) |
| He *et al.* (1995) | Yi Migrant Study | 827 M, Mean age 31·6–45·1 years Three Chinese populations | 3 × 24 h recall | +++ | (–) Total and vegetable protein |
| Stamler *et al.* (1996*a*) | MRFIT | 11 342 M, 35–57 years | 4–5 × 24 h recall | +++ | (–) |
| Stamler *et al.* (1996*b*) | INTERSALT | 10 020 M and W, 20–59 years Fifty-two population samples | 24 h urinary N, urea-N and sulfate | +++ | (–) Multiple adjusted (+) Age–gender–sample adjusted |
| Liu *et al.* (1996) | CARDIA | 4146 M and W, 18–30 years at baseline. Four race–gender groups (analysed separately) | FFQ at baseline and year 7 | +++ | (–) White W, DBP |
| Rafie *et al.* (1998) | | 950 M and W | FFQ | None | (+) Vegetable protein, HTN |
| Liu *et al.* (2000*a*) | CARDIAC Study | 619 M and W, Four Chinese population samples | 24 h urine | +++ | (–) Urinary 3-methyl histidine |
| Liu *et al.* (2000*b*) | CARDIAC Study | 1681 Japanese M and W 1151 Chinese M and W | 24 h urine | +++ | (–) Urinary 3-methyl histidine: creatinine Chinese (SBP, DBP) Japanese (DBP) |
| Liu *et al.* (2001) | CARDIAC Study | 1614 M and W, Four ethnic Chinese populations | 24 h urine | + | (–) Urinary 3-methyl histidine: creatinine three (of four) ethnic samples |
| He *et al.* (1998) | NHANES III | 13 977 M and W, ≥ 18 years Not on HBP medication | 24 h recall | + | NS |
| Hajjar *et al.* (2001) | NHANES III | 17 030 M and W, ≥ 20 years | 24 h recall | +++ | (+) SBP and PP |

M, men; W, women; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HBP, anti-hypertensive; HTN, hypertension (or hypertensive); FFQ, food-frequency questionnaire; NHANES, National Health and Nutrition Examination Survey; MRFIT, Multiple Risk Factor Intervention Trial; INTERSALT, International Study of Salt and Blood Pressure; CARDIAC, WHO Cardiovascular Diseases and Alimentary Comparison; +++, Adjusted for age, BMI (or body weight), (gender), and one or more other dietary factors; ++, adjusted for age, BMI (or body weight), (gender), alcohol; +, other adjustment. (–), inverse association; (+), direct association.

*Findings relate to total protein intake and to significant associations with both SBP and DBP in the most adjusted models unless otherwise stated.

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energy intake (Pryer *et al*. 1997), a spurious inverse association between low protein intake and BP might result. There was indication that such bias may potentially have been operating, for example, in the First National Health and Nutrition Examination Survey (McCarron *et al*. 1984; Gruchow *et al*. 1985) and the Honolulu Heart Program (Reed *et al*. 1985; Joffres *et al*. 1987), and to a lesser extent in the Caerphilly Heart Study (Elliott *et al*. 1987). Additionally, it is well known that dietary variables are poorly estimated in survey data, e.g. from a single 24 h dietary recall, which may lead to attenuation of regression estimates (so-called 'regression dilution'; Dyer *et al*. 1994*a*).

Table 5 gives findings from the five longitudinal studies (six reports) that have reported on dietary protein or change in dietary protein in relation to change in BP or incidence of hypertension. Results are inconclusive, with three reports finding no association, two finding an inverse association, and one finding an inverse association between vegetable protein and change in both systolic and diastolic BP, and a direct association between animal protein and change in systolic BP (Stamler *et al*. 2002). Again, there are differences in dietary method and extent of control for confounding factors between studies; in the Multiple Risk Factor Intervention Trial follow-up (Stamler *et al*. 1997) the regression dilution bias was addressed to some extent insofar as dietary assessment was based on the average of four to five 24 h dietary recalls over 6 years.

In addition to these studies in adults, four studies of protein and BP in children have been reported (Frank *et al*. 1978; Boulton, 1981; Jenner *et al*. 1988; Simons-Morton *et al*. 1997); weak inverse associations in two of the studies were no longer significant when energy (Jenner *et al*. 1988) or other dietary variables (Simons-Morton *et al*. 1997) were added to the regression models.

*Clinical trials of protein intake and blood pressure*

Trials of protein supplementation, protein restriction or substitution of meat for vegetarian products have given varying and inconsistent results (Sacks *et al*. 1974; Obarzanek *et al*. 1996). For example, in a series of randomized controlled studies Sacks *et al*. (1981, 1984*a,b*) and Sacks & Kass (1988) investigated the short-term (2–6 weeks) effects on BP of different combinations of added beef, low *v*. high protein, soyabean protein and addition of one egg daily to the diet. Apart from an increase in systolic BP with added beef in one trial (Sacks *et al*. 1981), these studies failed to find a significant effect of dietary protein manipulation on BP.

In contrast, recent trials of supplementation with soyabean protein have tended to demonstrate a BP-lowering effect, despite some inconsistencies (Table 6). For example, in a trial testing the effects on BP of both increased fibre and increased protein intake, Burke *et al*. (2001) reported marked reductions in systolic and diastolic BP of 5·9 and 2·6 mmHg respectively, following a supplement of 66 g soyabean protein/d, although most of this benefit was found in the high-fibre high-protein arm of the trial, with only a minor effect on BP in the low-fibre high-protein arm. He *et al*. (2000) and Teede *et al*. (2001) also reported falls in BP with soyabean supplements of 40 g/d. While in some of the studies intake of isoflavones was also increased, recent trials have reported that isoflavones alone, without soyabean supplementation, had no effect on BP (Nestel *et al*. 1997; Hodgson *et al*. 1999). Alteration of protein intake is also a feature of complex interventions such as vegetarian or lactovegetarian diets (Rouse *et al*. 1983; Sacks *et al*. 1984*b*; Margetts *et al*. 1986) and the Dietary Approaches to Stop Hypertension–combination diet. The Dietary Approaches to Stop Hypertension-diet is high in fruit and vegetables and

**Table 5.** Longitudinal epidemiological studies of dietary protein and blood pressure in adults (adapted from Appel & Elliott, 2003; with permission)

| Reference | Study | Population | Dietary method | Confounders | Main findings* |
|---|---|---|---|---|---|
| Stamler *et al.* (1997) | MRFIT | 11 342 M, 35–57 years<br>Years 1–6 *v.* baseline separately for SI and UC | 4–5 × 24 h recall | Age, race, education, smoking, special diet, baseline BP, HBP medication and Δ alcohol, wt, smoking | (–) Δ protein, Δ SBP (SI) and Δ DBP (UC) |
| Liu *et al.* (1996) | CARDIA | 4146 M and W, 18–30 years at baseline. 7-year follow up | FFQ, baseline and year 7 | Not specified | NS |
| Ludwig *et al.* (1999) | CARDIA | 2731 M and W, 18–30 years at baseline<br>10 years BP follow-up | FFQ, year 7 | Age, gender, centre, education, energy, vits, smoking, alcohol, physical activity +/– insulin | NS |
| Vupputuri *et al.* (1998) | NHANES I follow-up | 5727 M and W, mean age 47·9 years at baseline. Average 10 years follow-up | 24 h recall | Age, race, gender, BMI, energy, Na, K | (–) Incidence HTN (univariate) |
| Morris *et al.* (2001) | Calcium for Pre-eclampsia Prevention Study | 4157 pregnant W Intervention and control trial arms combined | 24 h recall | Energy | NS |
| Stamler *et al.* (2002) | Western Electric Study | 1714 men, 40–55 years at baseline<br>Up to 9 years follow-up | Usual intake (28 d) | Age, ht, education, smoking, alcohol, Δ wt +/– macro- and micronutrients | (–) Vegetable protein (+) Animal protein, Δ SBP |

MRFIT, Multiple Risk Factor Intervention Trial; NHANES, National Health and Nutrition Examination Survey; M, men; W, women; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; HBP, anti-hypertensive; FFQ, food-frequency questionnaire; vits, vitamin supplements; SI, special intervention, UC, usual care (MRFIT); Δ, change; +/– with and without; (–), inverse association; (+), direct association.

*Findings relate to total protein intake and to significant associations with both Δ SBP and Δ DBP unless otherwise stated.

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**Table 6.** Controlled clinical trials of soyabean-protein supplementation and blood pressure (BP, since 1999) (adapted from Appel & Elliott, 2003; with permission)

| Reference | *n* | Baseline BP | Design | Duration | Protein intervention (g soyabean/d) | Other intervention | Net Δ SBP (mmHg) | *P* | Net Δ DBP (mmHg) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| Washburn *et al.* (1999) | 51 W | 132/82 | Cross-over | 6 weeks | 20 (twice per d) | 34 mg phyto-oestrogens/d | −1·3 | NS | −4·9 | <0·01 |
| | | | | | 20 (once per d) | | −2·4 | NS | −2·3 | NS |
| Crouse *et al.* (1999) | 156 M and W | 127/71 | Parallel group | 9 weeks | 25 | 62, 37, 27 or 3 mg isoflavones/d | – | NS | −3 (W) (high *v.* low iso) | <0·04 (trend) |
| He *et al.* (2000) | 150 | 135/83 | Parallel group | 3 months | 40 | | −3 | 0·05 | −1·7 | 0.07 |
| Williams *et al.* (2000) | 22 M and W | 149/93 | Cross-over | 4 weeks | 38 (W) | 73 mg isoflavones/d | −0·4 | NS | +1 | NS |
| | | | | | 35 (M) | 162 mg isoflavones/d | | | | |
| Hermansen *et al.* (2001) | 20 M and W | 130/78 | Cross-over | 6 weeks | 50 | > 165 mg isoflavones/d, 20 g fibre/d | +1 | NS | 0 | NS |
| Teede *et al.* (2001) | 213 M and W | 130/76 | Parallel group | 3 months | 40 | 118 mg isoflavones | −3·9 | <0·05 | −2·4 | <0·05 |
| Burke *et al.* (2001) | 36 M and W | 134/77 | Parallel group | 8 weeks | 66 | | −5·9 | 0·001 | −2·6 | 0·006 |

Δ, change; M, men; W, women; SBP, systolic blood pressure; DBP, diastolic blood pressure.

low-fat dairy products and also includes a higher protein content than the usual US diet (17·9 *v.* 13·8 % energy from protein); it significantly lowers BP ($P < 0·001$) (Appel *et al.* 1997).

## Summary

Despite some inconsistencies, recent data from both epidemiological studies and clinical trials lend support to the concept that protein intake may be inversely associated with BP, although which component of dietary protein might be involved is at present uncertain. If confirmed, the new findings on protein and BP potentially have important implications for public health and clinical (non-pharmacological) recommendations for BP control at both individual and population level (Stamler *et al.* 1996*b*). Publication is awaited of the results of further studies on this issue, including those from the International Co-operative Study of Macronutrients, Other Factors and Blood Pressure (INTERMAP) of 4680 men and women from seventeen population samples in four countries (Japan, China, UK and USA; Stamler *et al.* 2003).

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