Dietary Protein and Blood Pressure: A Systematic Review

Wieke Altorf – van der Kuil1,2, Mariëlle F. Engberink1,2, Elizabeth J. Brink1,3, Marleen A. van Baak1,4, Stephan J. L. Bakker1,5, Gerjan Navis1,5, Pieter van ‘t Veer2, Johanna M. Geleijnse1,2

1 Top Institute Food and Nutrition, Wageningen, The Netherlands, 2 Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands, 3 Human Studies Group, TNO Quality of Life, Zeist, The Netherlands, 4 Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands, 5 Kidney Center, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands

Abstract

Background: Elevated blood pressure (BP), which is a major risk factor for cardiovascular disease, is highly prevalent worldwide. Recently, interest has grown in the role of dietary protein in human BP. We performed a systematic review of all published scientific literature on dietary protein, including protein from various sources, in relation to human BP.

Methodology/Principal Findings: We performed a MEDLINE search and a manual search to identify English language studies on the association between protein and blood pressure, published before June 2010. A total of 46 papers met the inclusion criteria. Most observational studies showed no association or an inverse association between total dietary protein and BP or incident hypertension. Results of biomarker studies and randomized controlled trials indicated a beneficial effect of protein on BP. This beneficial effect may be mainly driven by plant protein, according to results in observational studies. Data on protein from specific sources (e.g. from fish, dairy, grain, soy, and nut) were scarce. There was some evidence that BP in people with elevated BP and/or older age could be more sensitive to dietary protein.

Conclusions/Significance: In conclusion, evidence suggests a small beneficial effect of protein on BP, especially for plant protein. A blood pressure lowering effect of protein may have important public health implications. However, this warrants further investigation in randomized controlled trials. Furthermore, more data are needed on protein from specific sources in relation to BP, and on the protein-BP relation in population subgroups.

Introduction

Elevated blood pressure (BP) is an independent risk factor for cardiovascular diseases (CVD) and renal impairment.[1] There is no evidence for a threshold effect: from systolic BP levels as low as 115 mmHg onward, risk of CVD doubles for each increment of 20 mmHg.[1] It has been estimated that, at population level, a 15 mmHg rise in systolic BP is associated with a doubling of the risk of CVD and renal impairment.[1,2] Further studies have shown that a 10 mmHg rise in systolic BP is associated with a doubling of the risk of fatal events.[1,2] It has been estimated that, at population level, a 10 mmHg rise in systolic BP is associated with a doubling of the risk of fatal events.[1,2]

Well-known dietary and lifestyle interventions to prevent hypertension include moderate physical activity, maintenance of normal body weight, low alcohol and salt intake, and a diet rich in fruits, vegetables, and low-fat dairy products.[2,3] More recently, interest has grown into dietary patterns and macronutrient intakes, including protein.[4,5] Whether protein content of the diet or type of protein is important for human BP is, however, unclear. We systematically reviewed all scientific literature, published before June 2010, on dietary protein in relation to human BP, with a focus on specific types of protein and possible interactions with age, gender, BP level, and overweight.

Methods

Ethical approval was not required for this review because only published data were included.

Search strategy

A systematic search was performed in MEDLINE (www.ncbi.nlm.nih.gov) to identify studies on the association between dietary protein and BP, published before June 2010. Search terms on dietary protein and BP or hypertension were used to search for words in title or abstract and Medical Subject Headings. The search was limited to studies in human adults and English-language literature. In addition, we performed a manual search using reference lists of original articles and previous reviews.[6–9] For all studies, we retrieved the original publication.

We selected any observational study or trial that examined the relationship between dietary protein and BP in humans. All titles, abstracts, and full papers of potentially relevant studies were assessed for eligibility based on predefined inclusion and exclusion criteria. Papers were excluded: 1) if data on exposure (dietary
protein) or outcome (BP, hypertension) was not reported, 2) if no data were reported on the relationship between exposure and outcome, 3) if the exclusive effect of protein could not be calculated (e.g., BP studies that focused on dietary patterns, or soy combined with isoflavones). Furthermore, review papers were excluded, as were drug trials and studies conducted in patient groups or pregnant women.

Data collection and data synthesis

From each included paper we extracted data on protein intake, source of protein, and BP values or estimated risk of hypertension according to a predefined standard form. In addition, we extracted data on design, place of study, number of participants, population characteristics (including initial BP, sex, and age), dietary assessment method (food frequency questionnaire (FFQ), 24-hour recall, food diary, biomarker), adjustment for confounders, and measures of variation.

To allow better comparison of results from observational studies we expressed associations in these studies by standard units of protein intake that correspond to approximately 1 SD of protein intake in the Dutch population, i.e. 25 g/d (3.5 en%) for total protein, 11 g/d (1.4 en%) for plant protein, and 23 g/d (2.9 en%) for animal protein.[10,11]

Results

The systematic search in MEDLINE resulted in 2,681 titles to be screened. Inclusion criteria were fulfilled by 40 papers, and the hand search yielded another 6 papers (Figure 1). In total, 15 observational studies, 13 biomarker studies and 20 trials were selected.

Total dietary protein and BP: observational data

Twelve observational studies focused on habitual total protein intake and BP or risk of hypertension (table 1). Most of these studies had a cross-sectional design and showed predominantly weak inverse associations.[12–20] However, although hypothesis-generating, a major drawback of a cross-sectional design is that protein intake and BP are assessed at the same moment in time, which makes it difficult to address the temporality of the association. Subjects with elevated BP, or otherwise at increased cardiovascular risk, may have changed their food intake (including protein intake) upon medical advice. Causality can, therefore, be better established in prospective studies.

So far, only three studies prospectively examined the association of total dietary protein with change in BP or incident hypertension. Total protein intake was not clearly associated with change in systolic BP after 8 years of follow up in 1714 US men (+0.16 mmHg per y per 3.5 en% systolic, p = 0.04) [21], and after 7 years of follow up in 4146 young US adults (+0.20 mmHg per year per 3.5 en% systolic, p > 0.05) [22]. It should be noted that in these two studies respondents using antihypertensive medication were not excluded from the analyses, which may have affected the associations. In 5880 university graduates of the prospective SUN cohort, not using antihypertensive medication, a non-significant 20% lower 2-year hypertension risk was found (p = 0.26).[23]
### Table 1. Observational studies of total protein intake and blood pressure.

| Author, year | respondents | Initial BP (mmHg) | Habitual protein intake | Dietary assessment | BP outcome (SBP/DBP) | BP outcome per 25 g/d or 3.5 en% (SBP/DBP) | P-value | Statistical adjustment |
|--------------|-------------|-------------------|-------------------------|-------------------|---------------------|---------------------------------------------|---------|------------------------|
| **Cross-sectional studies** | | | | | | | | |
| Pellum, 1983[16] | 61 normotensive US adults mean age ~24 | M: 119/73 F: 107/68 | M: 101 g/d; F: 65 g/d (=14 en%) | 3-d food record | ~0.13/… mmHg per g/d | ~ −3.33/… mmHg per 25 g/d | …/… | Sex, serum HDL, exercise, fat intake |
| Havlik, 1990[13] | 402 male US twins aged 42–56 y | 128/82 | 15 en% (= 75 g/d) | FFQ | …/+0.11 mmHg per g/d of energy adjusted protein | …/+2.75 mmHg per 25 g/d | NS/0.02 | Weight, serum cholesterol, triglycerides, total energy intake |
| Wang, 2008[20] (PRE-MIER) | 810 untreated pre- or mild hypertensives aged 25–79 y | 135/85 | 16 en% | 24 h recall | −0.08/+0.03 mmHg per en% | −2.08/~ +0.11 mmHg per 3.5 en% | 0.41/0.73 | |
| He, 1995[14] | 827 Chinese adults mean age ~38 | ~113/70 | ~12 en% (~93 g/d) | 3×24-h recall | −3.6/~ 2.2 mmHg per 5D (= 39 g/d) | −2.28/~ −1.38 mmHg per 25 g/d | <0.05/NS | Age, BMI, alcohol, urinary Na, enery intake, resident area |
| Reed, 1985[17] | 6496 Japanese men in Hawaii aged 46–69 y | … | … | 24-h recall | −3 mmHg/~1 mmHg for Q5 (~122) vs. Q1 (~67 g/d) | −0.85/~ −0.28 mmHg per 25 g/d | <0.001/0.03 | Age |
| Umesawa, 2009[19] | 7585 Japanese men and women aged 40–69 y | 137/83; F: 135/81 | M: 83 g/d; F: 65 g/d | Single 24 h recall | −0.29/~0.42 mmHg per 25 g/d | ~ −0.28/~ −0.41 mmHg per 25 g/d | NS/<0.05 | age, gender, BMI, smoking, alcohol, community, use of antihypertensive medication, intake of sodium, potassium, and calcium |
| Masala, 2008[15] (EPIC) | 7601 Italian women aged 35–64 y | 123/79 | … | FFQ | +0.38/~0.60 mmHg per log(g/d) | ~ +1.22/~ −1.93 mmHg per 25 g/d | 0.76/0.43 | Age, BMI, waist circumference, smoking, education, physical activity, energy intake |
| Garcia-Palmieri, 1984[12] | 7932 men from Puerto Rico aged 45–64 y | … | … | 24-h recall | SBP: between −0.03 and +0.03 mmHg per g/d depending on subgroup (urban/rural, middle-aged/old age); DBP: … | ~ +0.13/~ −0.93 mmHg per 25 g/d | NS/… | Age, smoking, weight, education, serum glucose, heart rate, intake of milk, fat, carbohydrates, coffee, alcohol |
| Stamler, 1980b[18] (MRFIT) | 11342 US men aged 35–57 y | 125/84 | 17 en% | 4–5×24-h recall | −0.06/~0.06 mmHg per en% | ~ −0.20/~ −0.21 mmHg per 3.5 en% | <0.01/<0.001 | Age, race, BMI, education, smoking, serum cholesterol, antihypertensive drugs, Na and K intake, alcohol and caffeine intake; corrected for regression dilution bias |
| **Prospective studies** | | | | | | | | |

Initial BP (mmHg)  Habitual dietary BP outcome  BP outcome per 25 g/d or 3.5 en% (SBP/DBP) P-value Statistical adjustment

135/87 15 en% FFQ + 0.05/2 0.02 mmHg +, 0.16/2, 0.05 0.04/0.16 Age, height, weight (change), education, alcohol, smoking 2002[21] 40–55 y 110/69 15 en% FFQ, 2 0.16/2 0.34 2, 0.20/2, 0.40 NS/NS Age, BMI, education, exercise, smoking, alcohol, hostility score, use of antihypertensive medication, intake of K and Ca 1996[22] whites aged 18–30 y

In 4,680 respondents from the INTERMAP study, 24 h urea nitrogen was inversely related to systolic BP (p = 0.01) per g of total 24-h urinary nitrogen was observed.[25] Also in 4,680 respondents from the INTERMAP study, 24 h urea nitrogen was inversely related to systolic BP (p = 0.01) per 5.34 g, although this was not statistically significant.[11] In the remaining studies, summarized in table 2, single spot or overnight urines were used to estimate protein intake.[26–28] Although these estimates are less reliable than estimates from 24-h urine, the results were in line with those of the studies mentioned above.

Protein and Blood Pressure

The association between total dietary protein and blood pressure was estimated using a variety of biomarkers. Among the 16 trials summarized in table 2, only one (n = 311 obese women) showed a decrease in systolic BP of 4.6 mmHg (p = 0.04) with 6 en% higher protein intake. Other large studies showed a decrease in BP on a high protein diet, although no clear dose-response relation could be distinguished.[5,42,43] In 100 obese participants with metabolic syndrome, systolic BP increased 6 mmHg (p < 0.05) with 6 en% higher protein intake [42], and in 141 obese adults 6 en% higher protein intake resulted in a BP change of −4.6 mmHg (p = 0.04) [43].

In almost all trials the high protein diet was compared with a high carbohydrate diet. The only study in which two different control diets were included was the OmniHeart trial.[3] In this 6 week, fully controlled cross-over feeding trial in 164 healthy US adults partial substitution of carbohydrates (10 en%) with protein significantly lowered systolic BP with −1.4 mmHg systolic (p = 0.002). No difference in BP response was observed when the protein-rich diet was compared with a diet high in mono-

Biomarkers of total dietary protein and BP: observational data

Daily urinary nitrogen excretion, about 85% excreted in the form of urea, correlates with dietary protein as calculated from weighed food records (r = 0.4–0.8) and reflects ~90% of total protein intake.[24] As shown in table 2, in five cross-sectional studies urinary total nitrogen [25] or urinary urea nitrogen [11,25–28] was used to estimate the association between total protein intake and BP. In the large INTERSALT-study, including 10,020 adults from 32 countries, an inverse association of −0.5 mmHg systolic (p < 0.05) with 3.5 en% was observed.[25] Also in 4,680 respondents from the INTERMAP study, 24 h urea nitrogen was inversely related to systolic BP (p < 0.05) per 5.34 g, although this was not statistically significant.[11] In the remaining studies, summarized in table 2, single spot or overnight urines were used to estimate protein intake.[26–28] Although these estimates are less reliable than estimates from 24-h urine, the results were in line with those of the studies mentioned above.

Concluding, in studies among participants that are in nitrogen balance, good agreement has been found between one or two 24-h urine collections and diet-history estimates of protein intake.[24] Findings from biomarker studies, therefore, suggest that protein intake may have a beneficial effect on BP.

Total dietary protein and BP: trial data

In 16 trials the BP effect of a high protein diet was assessed (table 3). Most trials were only small (number of participants per intervention group: n = 7 to n = 30), and the conflicting results may be due to chance findings.[29–39] In one of the larger trials, a parallel trial in which 121 type 2 diabetes patients received counseling on normal or reduced protein intake, an increase in BP was found (+5.4 mmHg systolic, p = 0.07).[40] However, the low range of intake may have influenced the results. Another large parallel trial among 311 obese women, in which different weight loss diets were compared, showed a decrease in systolic BP of −5.7 mmHg systolic (p value not given).[41] However, contrast in protein intake was low (2.3 en%), and BP decrease may be a result of exchange in carbohydrates and fat instead of increase in protein intake. Other large studies showed a decrease in BP on a high protein diet, although no clear dose-response relation could be distinguished.[5,42,43] In 100 obese participants with metabolic syndrome, systolic BP changed −6 mmHg (p < 0.05) with 6 en% higher protein intake [42], and in 141 obese adults 6 en% higher protein intake resulted in a BP change of −4.6 mmHg (p = 0.04) [43].
two macronutrients, and the answer to the question whether total protein intake versus the lowest quintile (p = 0.06) was found in 5880 year hypertension risk for the highest quintile of plant protein intake (p = 0.05) was found after a follow-up of 8 y.[21] It should be noted, however, that estimates were not adjusted for important potential confounders like sodium and potassium. In two other studies, in which estimates were adjusted for these confounders, a 21% reduction in hypertension risk per 50% lower 2 en% of plant protein intake (p = 0.08) was found.

In conclusion, the results of trials suggest that increased intake of protein may be beneficial to BP, although no clear dose – response association could be distinguished. From the results of the OmniHeart study, the only trial in which two different isocaloric control diets (high in carbohydrates and high in fat) were used, a conclusion can be drawn that both protein and dietary fat intake may affect blood pressure. In a trial in which only a high fat diet was included as control diet,[38] In this trial, however, the number of participants was conducted in which only a high fat diet was included as control diet.

Dietary plant protein and BP: observational data

The association between dietary plant protein and BP or hypertension was examined in 8 observational studies (Table 4). Most cross-sectional studies showed an inverse association [11,14,15,19,20,44], and this was confirmed in prospective studies [20,21,23]. In a prospective study among 1714 men a systolic BP difference of −0.34 mmHg per year per 1.4 en% (p < 0.01) was found after a follow-up of 8 y.[21] It should be noted, however, that estimates were not adjusted for important potential confounders like sodium and potassium. In two other studies, in which estimates were adjusted for these confounders, a 21% reduction in hypertension risk per 0.08 was found after 18 months of follow-up in 810 untreated pre- or mild hypertensives of the PREMIER study [20], and a 50% lower 2 year hypertension risk for the highest quintile of plant protein intake versus the lowest quintile (p = 0.06) was found in 3880 university graduates of the SUN cohort [23].
| Author, year         | Blinding | Participants                              | Initial BP (mmHg, Intervention vs. control) | Type of intervention                                                                 | Intake of protein in control group | Duration of intervention | ΔSBP/ΔDBP due to intervention | ΔBP due to intervention | P-value          |
|----------------------|----------|-------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|--------------------------|-------------------------------|--------------------------|------------------|
| Cross over trials    |          |                                           |                                             |                                                                                       |                                   |                          |                               |                          |                 |
| DeHaven, 1980[32]    | ...      | 7 healthy obese participants, aged 23–38 y | 114/69                                      | Pure prot (= boiled turkey), low caloric (400 Kcal) diet vs. mixed (turkey + grape juice) low caloric diet | “High”                             | 3 to 5.5 weeks for each diet | +5/1 mmHg*                     | ...                      |                 |
| Daniels, 1990[31]    | ...      | 7 normotensive healthy adults (6 M, 1 F), aged 22–49 y | .../...                                      | High prot vs. low prot diet                                                           | 0.55 g/kg/d                       | 4 days                   | +3/+2 mmHg NS/NS             | NS/NS                    |                 |
| Papakonstantinou, 2010[38] | sb     | 17 obese, newly diagnosed type 2 diabetes patients, aged 30–65 y | 134/86 vs. 134/80                          | Low caloric (~700 kcal) high protein low fat diet vs. low caloric low protein high fat diet. | 61 g/d ≈15 en%                     | 4 weeks per diet, 3 weeks wash out | −9/−5 mmHg NS/NS <0.001/0.001 | 0.001/0.001               |                 |
| Sacks, 1984[39]      | sb       | 23 US vegans, aged 22–41 y                | 112/74                                       | High prot supplement (60 g wheat prot + 40 g soy protein) vs. low prot supplement (rice prot) | 70 g                               | 6 weeks for each diet    | +1/+0.6 mmHg* NS/NS           | NS/NS                    |                 |
| Appel, 2005[5] (Omni—Heart) | db     | 164 US participants (55% African Americans), mean age 64 y | 131/77                                      | Prot rich diet (~50% plant prot) vs. CH rich diet                                       | 15 en%                             | 6 weeks for each diet    | −1.4/−1.2 mmHg 0.002/0.001 | 0.007/0.001               |                 |
| Ferrara, 2006[33]    | db       | 15 healthy men in exercise training project, aged 18–36 | 111/72 vs. 110/76                          | High vs. normal prot diet                                                            | 15 en% +7 en%                       | 6 months                | −2.1/+0.9 mmHg NS/NS          | NS/NS                    |                 |
| Hendler, 1988[34]    | ...      | 17 healthy obese participants, mean age ~31 | 120/79 vs. 121/79                          | Pure prot, low caloric (440 kcal) diet vs. mixed low caloric diet                     | 41 en% +54 en%                     | 3 weeks                 | −2/−8 mmHg NS/NS             | NS/NS                    |                 |
| Meckling, 2007[37]   | ...      | 30 overweight/obese women (premenopausal), aged 20–62 | 134/82 vs. 129/82                          | High prot low caloric (1383 kcal) diet vs. control low caloric (1391 kcal) diet       | −16 en% +8.2 en%                   | 12 weeks                | −3/−4 mmHg* .../...          | .../...                   |                 |

In prehypertensives: −0.9/−0.9 mmHg 0.047/0.01
In hypertensives: −3.5/−2.4 mmHg 0.006/0.008
In prehypertensives: 0.0/−0.4 mmHg 0.90/0.20
In hypertensives: −0.2/−0.5 mmHg 0.79/0.51

Table 3. Trials of total protein intake and blood pressure.
| Author, year | Blinding | Participants | Initial BP (mmHg, Intervention vs. control) | Type of intervention | Intake of protein in control group | Δ Protein | Δ CH | Δ Fat | Duration of intervention | ΔSBP/ΔDBP due to intervention | P-value |
|-------------|----------|--------------|--------------------------------------------|----------------------|-----------------------------------|-----------|-----|------|------------------------|-------------------------------|---------|
| Meckling, 2007 | ... | 30 overweight/obese women (premenopausal), aged 20–62 | 134/82 vs. 129/82 | High protein low caloric (1217 kcal) diet + exercise vs. control low caloric (1260 kcal) diet + exercise | -18 en% | +19.0 en% | -14.6 en% | -3.3 en% | 12 weeks | 0/0 mmHg* | .../... |
| Burke, 2001 | o | 41 Australian treated hypertensives, mean age ~57 y | 133/75 | Soy protein supplement vs. maltodextrin supplement (2×2 RCT with soluble fiber) | 12 en% | +11 en% | -13 en% | +2 en% | 8 weeks | -5.9 mmHg/ -2.6 mmHg | <0.01/<0.01 |
| Leidy, 2007 | o | 46 obese women (8 drop-outs), aged 28–80 | 109/69 vs. 113/73 | High protein (pork) low caloric (750 kcal) vs. normal protein (milk) low-caloric diet | 18 en% | +12 en% | -12 en% | 0 | 12 weeks | -2/+2 mmHg | NS/NS |
| Hodgson, 2006 | o | 60 Australian participants, mean age 57 y | 129/80 vs. 134/77 | CH replaced by lean red meat protein vs. maintaining normal diet | 18.6 en% | +5.2 en% | -4.3 en% | -0.6 en% | 8 weeks | -4.0/ -1.3 mmHg | 0.02/0.25 |
| Brinkworth, 2004 | ... | 64 obese type 2 diabetes patients, mean age ~62 y | 148/83 vs. 140/76 | High vs. low prot diet; Both groups 8 weeks energy restricted (~6.7 MJ/day) and 4 weeks energy balance | 15 en% | +15 en% | -15 en% | 0 | 12 weeks | -0.3/ -1.7 mmHg | NS/NS |
| Muzio, 2007 | sb | 100 obese participants with MetS, mean age ~52 y | 142/85 vs. 141/82 | Low vs. high CH diet. Both diets providing a deficit of (~500 kcal) | 13 en% | +6 en% | -17 en% | +11 en% | 5 months | -6/-1 mmHg* | <0.05/... |
| Pils, 1999 | sb | 121 type 2 diabetes patients, mean age ~63 y | 138/79 vs. 138/79 | Counseling by dietician; reduced SFA alone vs. reduced SFA + reduced prot (isocaloric) | 0.95 g/kg/d | +0.19 g/kg | +1 g/d | SFA: +2.9 g/d; UFA: +5 g/d | 6 months | +5.4/+4.6 mmHg | 0.07/0.01 |
| Delbridge, 2009 | ... | 141 obese (≥27 kg/m²) men and women aged 18–75 y | 135/85 vs. 131/83 | High protein diet vs. high CH diet after 12 weeks of low caloric diet (~500–550 kcal/d) | 22 en%* | +6 en%* | -12 en%* | +2 en%* | 12 months | -4.6/- 1.1 mmHg | 0.04/0.58 |
| Gardner, 2007 | sb | 311 obese women (premenopausal), aged 25–50 y | 116/75 | Comparison of several weight loss diets; Atkins (AT) vs. Zone (ZO) | 18 en% | 0.6 en% | -10.9 en% | 9.8 en% | 12 months | -4.3/- 2.3 mmHg | .../... |
| Atkins vs. LEARN (LE) | 18.5 en% | 2.5 en% | -12.7 en% | 11.4 en% | 12 months | -4.5/- 2.2 mmHg | .../... |
| Atkins vs. Ornish (OR) | 18.3 en% | +2.3 en% | -17.9 en% | +14.5 en% | 12 months | -5.7/- 3.7 mmHg | .../... |

* = open; sb = single-blind; db = double-blind; MetS = metabolic syndrome; SBP = systolic blood pressure, DBP = diastolic blood pressure, M = men, F = women, en% = energy percentage; CH = carbohydrates; prot = protein; SFA = saturated fat; UFA = unsaturated fat; NS = not statistically significant (p > 0.05); ... = value not given; *Best guess on basis of graph/implicit data in paper.

1 Users of anti-hypertensive medication were not excluded.

0 = open; sb = single-blind; db = double-blind; MetS = metabolic syndrome; SBP = systolic blood pressure, DBP = diastolic blood pressure, M = men, F = women, en% = energy percentage; CH = carbohydrates; prot = protein; SFA = saturated fat, UFA = unsaturated fat; NS = not statistically significant (p > 0.05); ... = value not given; *Best guess on basis of graph/implicit data in paper.

1 Users of anti-hypertensive medication were not excluded.

doi:10.1371/journal.pone.0012102.t003
Table 4. Observational studies of plant protein intake and blood pressure.

| Author, year | respondents | Initial BP (mmHg) | Habitual plant protein intake | Dietary assessment | BP outcome (SBP/DBP) | BP outcome per 11 g/d or 1.4 en% | P-value | Statistical adjustment |
|--------------|-------------|-------------------|-------------------------------|-------------------|---------------------|--------------------------------|---------|------------------------|
| Cross-sectional studies |
| Joffres, 1987[44] (Honolulu heart study) | 615 men of Japanese ancestry | ~130/... | ... | 24 h recall | ~4.5/1.8 mmHg for Q4 (36-78 g/d) vs. Q1 (4-21 g/d) | ~1.14/0.44 per 11 g/d | 0.006/0.02 | Age, BMI |
| Wang, 2008[20] (PRE-MIER) | 810 untreated pre- or mild hypertensives aged 25-79 y | 135/85 | 5 en% | 2×24 h recall | ~0.98/0.70 mmHg per en% | ~1.37/0.98 mmHg per 1.4 en% | <0.01/0.01 | Age, sex, race, weight, waist, exercise, education, income, antihypertensive drugs, study site, baseline BP, alcohol, energy intake, intake of Ca and K, urinary creatinine, urinary Na |
| He, 1995[14] | 827 Chinese adults mean age ~38 y | ~113/70 | ~9 en% (~76 g/d) | 3×24-h recall | ~1.6/1.3 mmHg per SD (=44 g/d) | ~0.41/0.32 mmHg per 11 g/d | NS/NS | age, BMI, alcohol, urinary Na, energy intake, residential area |
| Elliott, 2006[11] (INTER-MAP) | 4680 respondents from China, Japan, UK and USA aged 40-59 y | 119/74 | China: 10 en%; Other countries: 5-7 en% | 4×24-h recall | ~1.11/0.71 mmHg per 2.8 en% (2 SD) | ~0.50/0.48 mmHg per 1.4 en% | <0.01/0.05 | Age, sex, weight, height, exercise, alcohol, sample, history CVD or DM, family history of hypertension, special diet, supplement use, 24 h urinary Na, K |
| Umesawa, 2009[19] | 7585 Japanese men and women aged 40-69 y | M: 137/83; F: 135/81 | M: 40 g/d; F: 31 g/d | Single 24 h recall | +0.59/−0.31 mmHg per 13.1 g/d | +0.50/−0.26 mmHg per 11 g/d | <0.05/NS | age, gender, BMI, smoking, alcohol, community, use of antihypertensive medication, intake of sodium, potassium, and calcium |
| Masala, 2008[15] (EPIC) | 7601 Italian women aged 35-64 y | 123/79 | ... | FFQ | +1.18/−0.23 mmHg per log(g/d) | +3.79/−0.74 mmHg per 11 g/d | 0.28/0.73 | Age, BMI, waist circumference, smoking, education, physical activity, energy intake and intake of animal protein |
| Prospective studies |
| Waing 2008, (PRE-MIER) | 810 untreated pre- or mild hypertensives aged 25-79 y | 135/85 | 5 en% | 2×24 h recall | Change from baseline to 6 months: ~0.53/−0.37 mmHg per en% | ~0.74/−0.52 mmHg per 1.4 en% per 6 months | 0.08/0.09 | Age, sex, race, weight, waist, exercise, education, income, antihypertensive drugs, study site, baseline BP, alcohol, intake of Ca and K, urinary creatinine, urinary Na + 6-month changes in several variables |
| Wang 2008, (PRE-MIER) | 810 untreated pre- or mild hypertensives aged 25-79 y | 135/85 | 5 en% | 2×24 h recall | OR (95%-CI) for hypertension = 0.79 (0.60–1.02) per en% | NA | 0.08 | Age, sex, race, weight, waist, exercise, education, income, antihypertensive drugs, study site, baseline BP, alcohol, intake of Ca and K, urinary creatinine, urinary Na |
Dietary animal protein and BP: observational data

In 7 observational studies the relationship between dietary animal protein and BP was investigated (Table 5), with results from cross-sectional studies being inconclusive [11,15,19,20,45]. In studies with a prospective design no association or only weak associations were observed, with systolic BP differences of −0.06 mmHg per 2.9 en% (p = 0.84) after 6 months in 810 untreated pre- or mild hypertensives [20], and +0.16 mmHg per 2.9 en% per year (p < 0.01) in 1714 men [21]. Furthermore, no differences in hypertension risk with high intake of animal protein was observed in 5880 university graduates of the SUN cohort [23].

In conclusion, observational studies provide no evidence for an association of animal protein with BP. However, also for these studies, despite inclusion of many potential confounders in their multivariate model, residual confounding (e.g. by intake of other macronutrients or salt) cannot be excluded.

Biomarkers of dietary plant protein or animal protein and BP: observational data

We did not find any studies that used a biomarker specifically for plant protein intake. With regard to animal protein intake, urinary excretion of 3-methylhistidine (3-MH) has been suggested as marker of meat consumption because it is synthesized in the muscle of mammals and released and excreted in urine after intake of muscle protein [46]. Six cross-sectional studies included in this review used urinary 3-MH excretion to estimate animal protein intake in predominantly Asian populations (Table 6). Overlap between studies may exist, since all populations formed part of the study population of the World Health Organization Cardiovascular Disease and Dietary Comparison (CARDIAC) study, which is an international population-based cross-sectional study in more than 20 countries, among which are China and Japan. All studies showed inverse associations with BP. However, because studies were conducted mainly in Asian populations, results may not be generalizable to other populations. Furthermore, urinary 3-MH may partly reflect muscle catabolism in the human body itself, i.e., during starvation, cachexia, or heavy physical activity [52]. This phenomenon was not taken into account in the various studies, and overestimation of associations between animal protein and BP could have occurred. The findings of these biomarker studies, therefore, should not be overemphasized. A challenge for future protein research will be to find reliable biomarkers for plant and animal protein intake of protein from specific dietary sources.

Dietary plant protein or animal protein and BP: trial data

The BP response after protein intake from plant and animal sources was investigated in only 2 randomized controlled trials (Table 7). A systolic BP effect of +1 mmHg systolic (p = 0.90) was seen in 23 type 2 diabetics after a diet containing protein only from plant sources (from soy, vegetables, and legumes) compared to a diet in which 60% of the plant protein was replaced by animal protein (from beef, poultry, fish, and milk) [53]. However, the number of 23 participants is low, and this BP effect was not significant. Furthermore, these participants suffered from albuminuria, which may have influenced the results on BP. In 49
Table 5. Observational studies of animal protein intake and blood pressure.

| Author, year | respondents | Initial BP (mmHg) | Habitual animal protein intake | Dietary assessment | BP outcome (SBP/DBP) | Standardized BP outcome per 23 g/d or 2.9 en% (SBP/DBP) | P-value | Statistical adjustment |
|--------------|-------------|-------------------|------------------------------|-------------------|----------------------|--------------------------------------------------------|---------|------------------------|
| Cross-sectional studies |
| Zhou, 1994[45] | 705 rural Chinese aged 45–59 y | −117/75 | 0.1 to 5.3 en% | 24 h recall | Inverse association (only standardized regression coefficients presented in the paper) | ... | ... | Age, BMI, heart rate, alcohol |
| Wang, 2008[20] (PRE-MIER) | 810 untreated pre- or mild hypertensives aged 25–79 y | 135/85 | 11 en% | 2×24 h recall | +0.08/+0.03 mmHg per en% | −0.23/−0.09 mmHg per 2.9 en% | 0.42/0.71 | Age, sex, race, weight, waist, exercise, education, income, antihypertensive drugs, study site, BP, alcohol, energy intake, intake of Ca and K, urinary creatinine, urinary Na |
| Elliott, 2006[11] (INTER-MAP) | 4680 respondents from China, Japan, UK and USA aged 40–59 y | 119/74 | China: 2.5 en% Other countries: 9–10 en% | 4×24 h recall | +0.20/−0.02 mmHg per 5.8 en% (2 SD) | NS/NS | Age, sex, weight, height, exercise, alcohol, sample, history CVD or DM, family history of hypertension, special diet, supplement use, 24 h urinary Na, K |
| Umesa-wa, 2009 [19] | 7585 Japanese men and women aged 40–69 y | M: 137/83; F: 135/85 | M: 43 g/d; F: 35 g/d | 24 h recall | −0.56/−0.17 mmHg per 199 g/d | −0.64/−0.20 mmHg per 23 g/d | <0.05/NS | age, gender, BMI, smoking, alcohol, community use of antihypertensive medication, intake of sodium, potassium, and calcium |
| Masala, 2008 (15) (EPIC) | 7601 Italian women aged 35–64 y | 123/79 | ... | FFQ | +0.99/+0.58 mmHg per log(g/d) | ~3.18/~1.87 mmHg per 23 g/d | 0.21/0.23 | Age, BMI, waist circumference, smoking, education, physical activity, energy intake and intake of plant protein |
| Prospective studies |
| Wang 2008 (PREMIER) | 810 untreated pre- or mild hypertensives aged 25–79 y | 135/85 | 11 en% | 2×24 h recall | Change from baseline to 6 months: −0.02/+0.01 mmHg per en% | ~−0.06/−0.03 mmHg per 2.9 en% per 6 months | 0.84/0.97 | Age, sex, race, weight, waist, exercise, education, income, antihypertensive drugs, study site, baseline BP, alcohol, intake of Ca and K, urinary creatinine, urinary Na + 6-month changes in several variables |
| Wang 2008 (PREMIER) | 810 untreated pre- or mild hypertensives aged 25–79 y | 135/85 | 11 en% | 2×24 h recall | OR (95%-CI) for hypertension = 0.99 (0.93–1.07) per en% | NA | 0.90 | Age, sex, race, weight, waist, exercise, education, income, antihypertensive drugs, study site, baseline BP, alcohol, intake of Ca and K, urinary creatinine, urinary Na |
| Stamler 2002[21] | 1714 men, aged 40–55 | 135/87 | 11.5 en% | FFQ | +0.06/+0.002 mmHg per year per en% | ~+0.16/+−0.01 mmHg per 2.9 en% | <0.01/0.44 | Age, height, weight (+ change), education, alcohol, smoking |
| Alonso 2006[23] (SUN) | 5880 Hispanic, university graduates, mean age ~36 y | ... | ... | FFQ | HR for hypertension (95%-CI) = 1.1 (0.7; 1.6) for Q5 vs. Q1 of energy adjusted protein intake | NA | 0.84 | Age, sex |

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; en% = energy percentage; 95%-CI = 95% confidence interval; MUFA = monounsaturated fat; PUFA = polyunsaturated fat; SFA = saturated fat; Na = sodium; K = potassium; Ca = calcium; BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; Q = quintile; NS = not statistically significant (p>0.05); ... = value not given.

Users of anti-hypertensive medication were not excluded.

doi:10.1371/journal.pone.0012102.t005
Table 6. Observational studies of biomarkers of animal protein intake and blood pressure.

| Author, year | Respondents | Initial BP (mmHg) | Initial biomarker level | Biomarker assessment | BP outcome (SBP/DBP) | P-value | Statistical adjustment |
|--------------|-------------|-------------------|-------------------------|---------------------|----------------------|---------|------------------------|
| Cross-sectional studies |
| Liu, 2000b[78] (CARDIAC) | 619 Chinese subjects aged 48–56 y | 120/70 | 3MH = 211 μmol/d | 24 h urinary 3MH | BMI < 26 kg/m² (n = 497): | <0.01/ <0.01 | Age, sex, BMI, alcohol urinary Na, urinary K |
| | | | | | −2.39/ −2.24 mmHg/88 μmol/d | | |
| Zhou, 1994[45] | 705 rural Chinese aged 45–55 y | ~115/73 | ... | Overnight urinary 1MH | ... | Age, BMI, heart rate, ethnic group |
| Liu, 2002[48] (CARDIAC) | 1135 Chinese subjects aged 48–56 y | 122/73 | 3MH = 198 μmol/d | 24 h urinary 3MH | −0.02/ −0.02 mmHg/μmol/d | 0.048/0.01 | Age, sex, BMI, urinary Na/K, urinary Ca, urinary Mg |
| Liu, 2002 (CARDIAC) | 1135 Chinese subjects aged 48–56 y | 122/73 | 3MH:Cr = 191 μmol/mg | 24 h urinary 3MH:Cr (μmol/mg) | −0.02/ −0.02 mmHg/unit | 0.02/0.01 | Age, sex, BMI, urinary Na/K, urinary Ca, urinary Mg |
| Liu, 2000a | 1151 Chinese subjects aged 48–56 y | 120/71 | 3MH:Cr = 216 μmol/g | 24 h urinary 3MH:Cr ratio (μmol/g) | −0.046/ −0.039 mmHg/unit | 0.001/ <0.001 | Age, sex |
| Liu, 2001[79] (CARDIAC) | 1614 Chinese subjects from 4 different ethnic groups, aged 48–56 y | ~129/79 | 3MH:Cr = 142 to 258 μmol/mg | 24 h urinary 3MH:Cr ratio (μmol/mg) | −0.04 to −0.25/ −0.10 to −0.36 (Partial correlation coefficients) | <0.01/ <0.01 | Age, sex, urinary Na |
| Liu, 2000a[80] (CARDIAC) | 1681 Japanese subjects aged 48–56 y | 124/75 | 3MH:Cr = 206 μmol/g | 24 h urinary 3MH:Cr ratio (μmol/g) | .../ −0.008 mmHg/unit | NS/0.012 | Age, sex |
| Liu, 2002[48] (CARDIAC) | 1991 Chinese subjects aged 48–56 y | 123/73 | ... | 24 h urinary 3MH | OR for hypertension (95%-CI) = 0.60 (0.40; 0.90) for ≥253 vs. < 253 μmol/d | 0.01 | Age, sex, BMI, urinary Na/K, urinary Ca, urinary Mg |
| Liu, 2002 (CARDIAC) | 1991 Chinese subjects aged 48–56 y | 123/73 | ... | 24 h urinary 3MH:Cr (μmol/mg) | OR for hypertension (95%-CI) = 0.38 (0.24; 0.59) for ratio ≥224 vs. < 224 | <0.01 | Age, sex, BMI, urinary Na/K, urinary Ca, urinary Mg |
| Yamori, 1990[51] (CARDIAC) | 7334 subjects from 20 different countries aged 50–64 y | ... | ... | 24 h urinary 3MH:Cr ratio (mol/mol) | −568/ −339 mmHg/unit | <0.05/ <0.05 | Unadjusted |

cs = cross-sectional; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; Na = sodium; K = potassium; Ca = calcium; Mg = magnesium; BMI = body mass index; 1MH = 1-methylhistidine; 3MH = 3-methylhistidine; Cr = creatinine; NS = not statistically significant (p > 0.05).
doi:10.1371/journal.pone.0012102.t006
Table 7: Trials on intake of types of protein and blood pressure.

| Author, year | Study design | Participants | Type of intervention | Duration of intervention | Protein Design | Intake vs. animal protein intervention | Initial BP (plant protein) | MP due to intervention (SBP/DBP) | P-value |
|--------------|-------------|--------------|----------------------|-------------------------|----------------|--------------------------------------|--------------------------|-------------------------------|---------|
| Wheeler, 2002 | Randomized | 132/85 mmHg | Meals with only plant protein | 6 weeks for each diet | 0 | Soy prot isolate vs. casein prot isolate (2:1) | 123/69 mmHg vs. 124/70 mmHg | +0.6/0.3 mmHg | NS/NS |
| Brussaard, 1981 | Parallel | 120/69 mmHg | Soy prot isolate vs. casein prot isolate | 4 weeks | 0 | Soy prot isolate vs. casein prot isolate | 151/85 mmHg | +1/1 mmHg | 0.90/0.75 |

Users of anti-hypertensive medication were not excluded.

Dietary protein and BP

In several studies specific subgroup analyses were conducted to identify subgroups whose BP is more sensitive for protein intake. We explored, furthermore, whether differences in protein-BP associations could be identified in the results of studies among specific populations.

In the OmniHeart trial the effect of total dietary protein was more pronounced in hypertensives than in prehypertensives (−3.5 mmHg versus −0.9 mmHg for systolic BP). This difference of protein effect in subgroups of BP could not be recognized in observational studies. In trials, however, populations with, on average, elevated BP were more sensitive to the BP lowering effect of protein than populations with, on average, normal BP. Out of 9 trials in populations with elevated BP (5, 29, 30, 35, 37, 38, 40, 42, 43) only 2 trials showed a decrease in BP with high protein intake (3, 30, 33, 37, 38, 42, 43), whereas out of 7 trials in populations with normal BP (31–34, 36, 39, 41) only 2 trials (34, 41) showed a decrease.

With regard to age, in the INTERSALT study a stronger inverse association of urinary nitrogen with BP was observed in respondents aged 40–59 y than in respondents aged 20–39 y.
In a study on urinary 3-MH and BP, the inverse association was more pronounced in respondents with a BMI higher than 26 kg/m² than in respondents with a normal BMI (Δ systolic BP = −0.6 mmHg versus −2.39 mmHg per 88 µmol urinary 3-MH/d).[47] Among the other studies, however, only one study was explicitly conducted among normal weight respondents,[14], so no conclusion can be drawn on difference in sensitivity related to weight, although studies in overweight/obese participants often showed inverse associations (Out of 11 studies [5,18,20,29,32,34–37,41,42], 7 studies showed an inverse association or a decrease in BP with high protein intake [5,29,34,35,37,41,42]).

Finally, in two studies subgroup-analyses were conducted for men and women, but no effect modification was shown.[19,28] Also in studies that were specifically conducted in men [12,13,17,21,25,33] or women [36,37,41], no difference in sensitivity was seen.

In conclusion, the beneficial effect of protein intake on BP seems stronger in people with higher initial BP and, possibly, in studies that were specifically conducted in men,[12,13,17,21,25,33] and women,[36,37,41] but no effect modification was shown.[19,28] Also in studies that were specifically conducted in men [12,13,17,21,25,33] or women [36,37,41], no difference in sensitivity was seen.

Several other reviews on protein and BP have already been introduced, because awareness of BP may influence participants' lifestyle or other behavior.

The underlying mechanism for a potential beneficial effect of protein on BP has not yet been clarified. Several hypotheses have been put forward. First, dietary protein has been related to synthesis of cellular ion channels, which may indirectly influence the pathways in BP regulation.[25] High protein intake may improve insulin sensitivity and thereby BP.[26,65,72] Second, experiments suggest that dietary protein or protein fractions could induce natriuresis, leading to lower BP.[26,65,72] Second, experiments suggest that dietary protein or protein fractions could improve insulin sensitivity and thereby BP.[73–75] Third, dietary protein supplementation may result in a higher concentration of the amino acids tyrosine and tryptophan in regions of the brain or blood vessel wall, triggering a vasodilatory response.[76] The amino acid arginine, which is a substrate for nitric oxide, may play a role in vasodilatation, although it is unclear whether dietary intake of arginine is relevant in this respect.[75,77] Finally, as has already been stated in this review we cannot exclude that a lower BP is related to a lower carbohydrate intake instead of a higher protein intake.

In conclusion, evidence suggests a small beneficial effect of protein on BP, especially for plant protein. More data on protein from specific sources like dairy, grain or nuts and data in population subgroups should be obtained from epidemiological studies. Furthermore, there is a need for BP trials that focus on plant and animal protein and protein from specific sources. Preferably, these trials should be conducted in untreated (pre)hypertensive people. Finally, studies aimed at potential BP lowering mechanisms related to protein intake are warranted.

**Author Contributions**

Conceived and designed the experiments: MFE EJB MAvB SJB GN JMG. Performed the experiments: WAvdK MFE JMG. Analyzed the data: WAvdK MFE EJB MAvB SJB GN JMG. Wrote the paper: WAvdK MFE EJB MAvB SJB GN JMG.

---

**References**

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42: 1206–1252.
2. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, et al. (2002) Primary prevention of hypertension: Clinical and public health advisory from the National High Blood Pressure Education Program. Journal of the American Medical Association 288: 1822–1832.

3. Appel LJ, Beards MV, Daniels SR, Karanja N, Elmer PJ, et al. (2006) Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. Hypertension 47: 296–308.

4. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, et al. (1997) A clinical trial of the effects of dietary patterns on blood pressure. New England Journal of Medicine 336: 1117–1124.

5. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, et al. (2005) Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA 294: 2453–2464.

6. Appel LJ (2003) The effects of protein intake on blood pressure and cardiovascular disease. Current Opinion in Lipidology 14: 53–59.

7. He J, Whelton PK (1999) Effect of dietary fiber and protein intake on blood pressure: A review of epidemiologic evidence. Clinical and Experimental Hypertension 21: 785–796.

8. Myres VH, Champagne CM (2007) Nutritional effects on blood pressure. Current Opinion in Lipidology 18: 20–24.

9. Obarzanek E, Vollett EK, Cutler JA (1996) Dietary protein and blood pressure. JAMA 275: 1598–1603.

10. (1998) Zo ete Nederland, Resultaten van de voedselconsumptiepeiling 1997–1998 (Dutch food consumption survey of 1997–1998). Dutch nutrition center.

11. Ekhteraei P, Stendall-Dyer AR, Appel L, Dennis B, et al. (2006) Association between protein intake and blood pressure: the INTERMAP Study. Archives of internal medicine 166: 79–87.

12. Garcia-Palmieri MR, Cortes R, Jr., Cruz-Vidal M, Sorlie PD, Tilloston J, et al. (1984) Milk consumption, calcium intake, and increased hypertension: results in Puerto Rico. Puerto Rico Heart Health Program study. Hypertension 6: 322–329.

13. Havlik RJ, Fabris RK, Kaloupsidis S, Borhani NO, Christian JC (1990) Dietary protein and blood pressure in monozygotic twins. Preventive Medicine 19: 217–221.

14. He J, Klag MJ, Whelton PK, Chen JY, Qian MC, et al. (1995) Dietary macronutrients and blood pressure in southwestern China. Journal of hypertension 13: 1267–1274.

15. Musa G, Benfidi N, Versari D, Saieva C, Cerosi E, et al. (2008) Anthropometric and dietary determinants of blood pressure in over 7000 Mediterranean women: the European Prospective Investigation into Cancer and Nutrition-Florence cohort. J Hypertens 26: 2112–2120.

16. Pelleu LF, Meditrois DM (1983) Blood pressure in young adult normotensives: effect of protein, fat, and cholesterol intakes. Nutrition Reports International 27: 1277–1285.

17. Reed D, McGee D, Yano K, Hankin J (1995) Diet, blood pressure, and microalbuminuria. Hypertension 778–786.

18. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, Cutler JA (1996) Relationship between dietary protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). The American journal of clinical nutrition 39: 31–39.

19. Daniels BS, Hostetter TH (1990) Proteinuria and renal function in hypertension. Kidney international 37: 313–321.

20. Wang YF, Yancy Jr. WY, Yu D, Champagne C, Appel LJ, et al. (2008) The Dietary Approaches to Stop Hypertension (DASH) Study Cooperative Research Group. JAMA 299: 2143–2152.

21. Wang YF, Yancy Jr. WY, Yu D, Champagne C, Appel LJ, et al. (2008) The Dietary Approaches to Stop Hypertension (DASH) Study. JAMA 299: 2143–2152.

22. Daniels BS, Hostetter TH (1990) Proteinuria and renal function in hypertension. Kidney international 37: 313–321.

23. Daniels BS, Hostetter TH (1990) Proteinuria and renal function in hypertension. Kidney international 37: 313–321.

24. Daniels BS, Hostetter TH (1990) Proteinuria and renal function in hypertension. Kidney international 37: 313–321.

25. Daniels BS, Hostetter TH (1990) Proteinuria and renal function in hypertension. Kidney international 37: 313–321.
53. Wheeler ML, Fineberg SE, Fineberg NS, Gibson RG, Haggard LL (2002) Animal versus plant protein meals in individuals with type 2 diabetes and microalbuminuria: effects on renal, glycemic, and lipid parameters. Diabetes care 25: 1277–1282.

54. Brussaard JHL, van Raaij JM, Stasse-Wolthuis M, Katan MB, Hautvast JG (1981) Blood pressure and diet in normotensive volunteers: absence of an effect of dietary fiber, protein, or fat. American journal of clinical nutrition 34: 2023–2029.

55. Hekman PR, Bos AJ, Cunha RS, Moriyuchi Y (1990) Cardiovascular diseases and alimentary comparison study: preliminary analysis from Brazil. Journal of cardiovascular pharmacology 16 Suppl 8: S12–14.

56. Moran JP, Cohen L, Greene JM, Xu G, Feldman EB, et al. (1993) Plasma ascorbic acid concentrations relate inversely to blood pressure in human subjects. American Journal of Clinical Nutrition 57: 213–217.

57. Prescott SL, Jenner DA, Brillin LJ, Margrett BM, Vandongen R (1988) A randomized controlled trial of the effect on blood pressure of dietary non-meat protein versus meat protein in normotensive omnivores. Clinical science 74: 665–672.

58. Kestin M, Rouse IL, Correll RA, Nestel PJ (1989) Cardiovascular disease risk factors in free-living men: comparison of two prudent diets, one based on lactoovovegetarianism and the other allowing lean meat. American journal of clinical nutrition 50: 280–287.

59. Hooper L, Kroon PA, Cohn JS, Harvey I, et al. (2008) Flavonoids, flavonoid-rich foods, and cardiovascular risk: A meta-analysis of randomized controlled trials. American Journal of Clinical Nutrition 89: 38–50.

60. Azadbakht L, Kimaiger M, Mehrab Y, Esmaillzadeh A, Hu FB, et al. (2007) Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. Br J Nutr 99: 407–413.

61. Azadbakht L, Kimaiger M, Mehrab Y, Esmaillzadeh A, Hu FB, et al. (2007) Soy consumption, markers of inflammation, and endothelial function: a crossover study in postmenopausal women with the metabolic syndrome. Diabetes Care 30: 967–973.

62. Azadbakht L, Kimaiger M, Mehrab Y, Esmaillzadeh A, Pashah M, et al. (2007) Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. Am J Clin Nutr 85: 735–741.

63. Chan YH, Lau KK, Yiu KH, Li SW, Chan FT, et al. (2007) Isoflavone intake in persons at high risk of cardiovascular events: implications for vascular endothelial function and the carotid atherosclerotic burden. Am J Clin Nutr 86: 938–945.

64. Yang G, Shu XO, Jin F, Zhang X, Li HL, et al. (2005) Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. Am J Clin Nutr 81: 1012–1017.

65. He J, Gu D, Wu X, Chen J, Duan X, et al. (2005) Effect of soybean protein on blood pressure: a randomized, controlled trial. Ann Intern Med 143: 1–9.

66. Anderson JW, Fuller J, Patterson K, Blair R, Tahor A (2007) Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: randomized controlled trial. Metabolism 56: 280–288.

67. Harrison RA, Sagara M, Rajputra A, Armitage L, Birt N, et al. (2004) Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. Nutrition, Metabolism and Cardiovascular Diseases 14: 344–350.

68. Mathias NR, Dalbert SM, Aumain LM, Kuvin JT, Karas RH, et al. (2007) Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. Am J Clin Nutr 85: 960–966.

69. Sagara M, Kanda T, M NJ, Teramoto T, Armitage L, et al. (2004) Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. J Am Coll Nutr 23: 85–91.

70. Willett WC, Howe GR, Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. American Journal of Clinical Nutrition 65.

71. Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, et al. (2003) Structure of dietary measurement error: Results of the OPEN biomarker study. American Journal of Epidemiology 158: 14–21.

72. Kochel O (1998) Differential cathelicidin responses to protein intake in healthy and hypertensive subjects. American Journal of Physiology - Regulatory Integrative and Comparative Physiology 275.

73. Ruggenenti P, Cattaneo D, Loriga G, Ledda F, Motterlini N, et al. (2009) Ameliorating hypertension and insulin resistance in subjects at increased cardiovascular risk: effects of acetyl-L-carnitine therapy. Hypertension 54: 567–574.

74. Sowers JR (2004) Insulin resistance and hypertension. American Journal of Physiology - Heart and Circulatory Physiology 286.

75. Gokce N (2004) L-arginine and hypertension. Journal of Nutrition 134.

76. Anderson GH (1986) Proteins and amino acids: Effects on the sympathetic nervous system and blood pressure regulation. Canadian Journal of Physiology and Pharmacology 64: 863–870.

77. Palm F, Teerlink T, Hansell P (2009) Nitric oxide and kidney oxygenation. Current Opinion in Nephrology and Hypertension 18: 68–73.

78. Liu L, Ikeda K, Yamori Y (2000) Twenty-four hour urinary sodium and 3-methylhistidine excretion in relation to blood pressure in Chinese: results from the China-Japan cooperative research for the WHO-CARDIAC Study. Hypertension research: official journal of the Japanese Society of Hypertension 23: 151–157.

79. Liu L, Liu L, Ding Y, Huang Z, He B, et al. (2001) Ethnic and environmental differences in various markers of dietary intake and blood pressure among Chinese Han and three other minority peoples of China: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. Hypertension research: official journal of the Japanese Society of Hypertension 24: 315–322.

80. Liu L, Mizushima S, Ikeda K, Hatton H, Miura A, et al. (2000) Comparative studies of diet-related factors and blood pressure among Chinese and Japanese: results from the China-Japan Cooperative Research of the WHO-CARDIAC Study. Cardiovascular Disease and Alimentary Comparison. Hypertension research: official journal of the Japanese Society of Hypertension 23: 413–420.