

How effective are current dietary guidelines for cardiovascular disease prevention in healthy middle-aged and older men and women? A randomized controlled trial^{1–4}

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ABSTRACT

Background: Controversy surrounds the effectiveness of dietary guidelines for cardiovascular disease (CVD) prevention in healthy middle-aged and older men and women.

Objective: The objective was to compare effects on vascular and lipid CVD risk factors of following the United Kingdom dietary guidelines with a traditional British diet (control).

Design: With the use of a parallel-designed randomized controlled trial in 165 healthy nonsmoking men and women (aged 40–70 y), we measured ambulatory blood pressure (BP) on 5 occasions, vascular function, and CVD risk factors at baseline and during 12 wk after random assignment to treatment. The primary outcomes were differences between treatments in daytime ambulatory systolic BP, flow-mediated dilation, and total cholesterol/HDL cholesterol. Secondary outcomes were differences between treatment in carotid-to-femoral pulse wave velocity, high-sensitivity C-reactive protein, and a measure of insulin sensitivity (Revised Quantitative Insulin Sensitivity Check Index).

Results: Data were available on 162 participants, and adherence to the dietary advice was confirmed from dietary records and biomarkers of compliance. In the dietary guidelines group ($n = 80$) compared with control ($n = 82$), daytime systolic BP was 4.2 mm Hg (95% CI: 1.7, 6.6 mm Hg; $P < 0.001$) lower, the treatment effect on flow-mediated dilation [-0.62% (95% CI: -1.48% , 0.24%)] was not significant, the total cholesterol:HDL cholesterol ratio was 0.13 (95% CI: 0, 0.26; $P = 0.044$) lower, pulse wave velocity was 0.29 m/s (95% CI: 0.07, 0.52 m/s; $P = 0.011$) lower, high-sensitivity C-reactive protein was 36% (95% CI: 7%, 48%; $P = 0.017$) lower, the treatment effect on the Revised Quantitative Insulin Sensitivity Check Index [2% (95% CI: -2% , 5%)] was not significant, and body weight was 1.9 kg (95% CI: 1.3, 2.5 kg; $P < 0.001$) lower. Causal mediated effects analysis based on urinary sodium excretion indicated that sodium reduction explained 2.4 mm Hg (95% CI: 1.0, 3.9 mm Hg) of the fall in blood pressure.

Conclusion: Selecting a diet consistent with current dietary guidelines lowers BP and lipids, which would be expected to reduce the risk of CVD by one-third in healthy middle-aged and older men and women. This study is registered at www.isrctn.com as 92382106. *Am J Clin Nutr* 2015;101:922–30.

Keywords: blood pressure, endothelial function, lipids, arterial stiffness, dietary pattern

INTRODUCTION

Population-based strategies to prevent cardiovascular disease (CVD)⁵ focus on diet and lifestyle modification (1). There is general

agreement regarding smoking cessation and prevention of obesity, but reductions in sodium intake (2) in normotensive persons and the replacement of SFAs with n-6 PUFAs (3, 4) remain contentious. Cohort studies suggest that the replacement of SFAs with carbohydrates, especially refined carbohydrates (5), but not those with a low glycemic index, particularly those from whole grains (6), might increase CVD risk or may have no effect (7). A possible explanation may be that although some SFA-rich foods such as red and fatty meat are associated with increased risk, others such as nuts, oily fish, milk, and dairy foods are associated with a lower risk (8).

Dietary guidelines for CVD prevention are broadly similar in the United Kingdom (9), Western Europe, and United States (10) and focus on modifying the overall dietary pattern so that food

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² Supported by funding from the UK Food Standards Agency and Department of Health and by the National Institute for Health Research (NIHR) Clinical Research Facility at Guy's and St Thomas' NHS Foundation Trust and NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. Archer Daniel Mills PLC, Veetee Rice, Heinz PLC, Almond Board of California, and the Southern African Macadamia Growers Association supplied some foods for the study. Donor companies were not involved in the trial design, data collection, data analysis, or reporting of the results. This is a free access article, distributed under terms (<http://www.nutrition.org/publications/guidelines-and-policies/license/>) that permit unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

³ Supplemental Figures 1 and 2 and Supplemental Table 1 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

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⁵ Abbreviations used: ABP, ambulatory blood pressure; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DG, dietary guideline; FMD, flow-mediated dilation; hsCRP, high-sensitivity C-reactive protein; PABA, para-amino benzoic acid; PWV_{c-f}, carotid-to-femoral pulse wave velocity; SBP, systolic blood pressure; TC, total cholesterol.

Received August 6, 2014. Accepted for publication February 9, 2015.

First published online March 18, 2015; doi: 10.3945/ajcn.114.097352.

and nutrient targets are met. Supporting evidence is derived from observational data from prospective cohort studies as well as the effects of individual dietary components on surrogate risk markers [i.e., blood pressure (BP), serum cholesterol] for CVD rather than from controlled trials with clinical endpoints. The nutrient targets for reduced sodium (salt), added sugar, and SFA and *trans* fatty acid intakes, as well as increased intakes of potassium and fiber, have been translated to food-based guidelines: these include replacement of fats rich in SFAs with unsaturated fatty acids (mainly MUFAs); the selection of low-fat dairy products and whole-grain cereals; an increased consumption of fruit, vegetables, and fish; and the avoidance of fatty meat, meat products, salt, and added sugar. The Dietary Approaches to Stop Hypertension (11, 12) and Optimal Macronutrient Intake Trial to Prevent Heart Disease (13) studies demonstrated that global changes in diet were more effective than focusing on individual components in lowering BP in participants with mildly or moderately elevated BP who were at above average risk of CVD. However, most CVD events occur in those at average risk (14). The present study was designed to test whether conforming to the United Kingdom dietary guidelines lowers the risk of CVD in participants judged to be at average risk, with a particular focus on vascular function. Key features of this study are that the participants were free living and empowered to modify their dietary pattern, and evidence of compliance to the intervention was provided by monitoring objective biomarkers of intake.

METHODS

Study design

CRESSIDA (Cardiovascular disease risk REduction Study), registered at www.isrctn.com as 92382106, was a 12-wk parallel-designed randomized controlled trial that compared United Kingdom dietary guidelines (DGs) (15) with a control diet based on a traditional British dietary pattern. The study was approved by the South London Research Ethics Committee (ref: 10/H0802/24). Participants gave informed written consent and received a small remuneration for taking part. Outcome measurements were made at baseline and after randomization to their respective diets.

Participant selection and randomization

Nonsmoking healthy men and women [aged 40–70 y; BMI (in kg/m^2) ≥ 18.5 and ≤ 35] were recruited (August 2010–July 2012) by newspaper (*London Metro*) and electronic advertisement (e-mail from the university and website). Respondents, who appeared suitable from a questionnaire, attended a clinic in the fasting state for measurement of height, weight, waist circumference, and seated BP and collection of urine and blood samples to assess liver function, glucose, lipids, hematology, and nonsmoking status by urinary cotinine measurement. Seated BP was measured in triplicate at 2-min intervals after a 10-min rest by using an upper-arm blood pressure monitor (Omron 705CP; Omron Health Care). The first reading was discarded and the mean for the 2 following readings taken; if the readings were more than 10% different, further readings were obtained. Exclusion criteria included diagnosis of CVD or $>20\%$ 10-y risk of CVD by using the QRISK-2 (14), which includes age; ethnicity; systolic BP (SBP); total cholesterol:HDL cholesterol

ratio; BMI; angina or heart attack in a first-degree relative aged <60 y in the algorithm; cancer (excluding basal cell carcinoma) in the previous 5 y; diabetes mellitus; chronic renal, liver, or inflammatory bowel disease; history of substance abuse or alcoholism; pregnancy; or weight change of >3 kg in preceding 2 mo. Before randomization to treatment, eligible participants were required to complete two 24-h ambulatory BP (ABP) measurements and urine collections, a 4-d food record, and validated food-frequency (16) and physical activity questionnaires (17). Treatment was allocated by minimization for age, sex, ethnicity, and BMI by using a custom-designed computer database (MedSciNet AB). Where 2 participants cohabited, both were allocated to the same treatment group (17 couples).

Participants attended the clinical research facility at St Thomas' Hospital, London, United Kingdom, in the fasting state for measurements of vascular function and to provide blood samples; procedures were repeated after 12 wk. The mean of the 2 preintervention 24-h ABP measurements was used as the baseline. Three 24-h ABP measurements and urine collections were made at wk 4–6, 8, and 12 during treatment; and a 4-d food record and food-frequency and physical activity questionnaires were completed toward the end of the study. The timeline for the study is shown in **Supplemental Figure 1**.

Interventions and measurements

The key dietary targets for the DG diet were to reduce sodium intake to <100 mmol/d; to reduce total fat, saturated fatty acids, and nonmilk extrinsic sugars to $<35\%$, $<11\%$, and $<11\%$ energy, respectively; and to increase the consumption of oily fish to at least 1 serving/wk, fruit and vegetables to at least 5 servings/d, and whole grains to at least 2 servings/d. These targets were achieved by dietary advice, which aimed to ensure that weight stability was provided by a dietitian (DR) after baseline measurements, and reinforced by face-to-face meetings (week 4) or by e-mail/phone call (weeks 6 and 8). Participants allocated to DG were provided with a margarine low in SFAs (16 g/100 g) and *trans* fatty acids (<0.5 g/100 g) and a liquid vegetable oil (high-oleic sunflower oil; 9 g SFAs/100 g). They were advised to choose low-fat dairy products and select lean cuts of meat and to avoid meat products (ham, sausages, hamburgers), sugar-sweetened beverages, and added salt at the table and during food preparation. Instructions were given on interpreting food labels to select foods with a lower salt and SFA content and on selecting foods eaten outside the home.

The control diet was a nutritionally balanced traditional British diet without restriction on salt and sugar intake. It was based around refined cereals (white bread, pasta, breakfast cereals, white rice) and potatoes with meat (red meat, meat products, or poultry) but with a limited intake of oily fish (less than once a month) and whole-grain cereals. Participants allocated to the control diet were supplied with a butter-based spread (35.3 g SFAs/100 g and 2.4 g *trans* fatty acids/100 g) and a liquid unhydrogenated vegetable oil (palm olein) that contained 40% SFAs. They were advised to consume 3 servings of full-fat dairy products (milk, yogurt, and cheese) and at least 1 serving of fruit and 2 servings of vegetables each day.

Both groups were given advice to limit consumption of confectionery and snack foods (chips, cake, cookies) and to drink alcohol within safe limits. Participants were provided with



a choice of breakfast cereals (whole grain or refined), rice (brown or white), some snack foods (nuts/cereal bars or chocolate cookies/crackers), and tinned fish (mackerel/sardines or tuna). Both groups were given baked beans; the DG group received the reduced sugar and salt product, whereas the control group received the standard product. In addition, the DG group was offered reduced salt condiments. Nutrient intakes were calculated from 4-d records by using Weighed Intake analysis Software Package (version 3.0; Tinuviel Software) before randomization and toward the end of the intervention phase.

Compliance with the dietary advice was further verified by the use of biomarkers of intake: 24-h urinary sodium (salt) and potassium (fruit and vegetables) (18); sucrose and fructose excretion (added sugars) (19); the $n-3$ index, which is the sum proportions of eicosapentaenoic acid and docosahexaenoic acid in erythrocyte lipids (oily fish) (20); and plasma alkylresorcinol concentrations (whole grains) (21). Completeness of urine collection was assessed by using para-aminobenzoic acid (PABA) (22) as well as creatinine because 3 participants declined to take PABA.

Clinic visits

Participants abstained from alcohol and strenuous activity 24 h before the clinic visits and were provided with a low-fat ready meal (10 g fat, 3 MJ) to consume in the evening (before 2100) and thus fasted overnight consuming no fluid other than water until attending the facility between 0800 and 1000. Height, weight, waist circumference, and seated BP were measured and a venous blood sample collected for determination (23) of lipids, lipoproteins, glucose, insulin, nonesterified fatty acids, erythrocyte lipids, high-sensitivity C-reactive protein (hsCRP), and biomarkers of intake (18–21). After 30 min of supine rest in a temperature-controlled room (23°C), measurements were made of supine BP in triplicate at 5-min intervals by using the Omron 705CP device (Omron Health Care) and arterial stiffness (23) as pulse wave velocity (PWV_{c-f}) determined by carotid and femoral tonometry by using a SphygmoCor VW device and software version 7.01 (AtCor Medical Pty). Central blood pressure was estimated from supine BP measurement and the carotid-radial pulse wave form by using the SphygmoCor software. After a further 15 min of supine rest, measurements were made of endothelium-dependent and endothelium-independent vasodilation of the brachial artery by using the flow-mediated dilation (FMD) technique as previously described (23), and scans were evaluated by using the Brachial Analyzer (Medical Imaging Applications LLC). Personnel who made the vascular and biochemical measurements were not informed of the treatment allocation.

Outcomes

Specified primary outcomes were a 4-mm Hg change in daytime SBP and a 5% change in the ratio of total cholesterol (TC):HDL cholesterol as being important (24, 25) and biologically plausible and a 1% change in FMD as being clinically significant. A sample size of 78/group had 90% power to detect a 4-mm Hg effect of diet on daytime systolic ABP at $P < 0.05$, assuming at least one useful measurement at baseline and 3 on treatment (26). An SD of 13 and correlations between mea-

surements of 0.68 (baseline to follow-up) and 0.72 (follow-up) were assumed on the basis of earlier data (18); the same data suggested that a sample size of 64 was sufficient to detect a change in FMD from 6.7% to 7.7% at $P < 0.05$ with 80% power, assuming an SD of 2%. Secondary outcomes were changes in PWV_{c-f} , hsCRP, and insulin sensitivity by using the Revised Quantitative Insulin Sensitivity Check Index (27). Further analysis of 24-h urinary C-peptide excretion was conducted post hoc as an indicator of insulin secretion on baseline, midpoint, and endpoint samples. Post hoc analyses of plasma 25-hydroxyvitamin D, homocysteine, endothelin, and ferritin were made on baseline and follow-up samples.

Statistical analysis

STATA version 11.1 (StataCorp LP) was used for the statistical analysis. Comparison between randomized groups was based on an intention-to-treat basis with regression analysis. Subjects, once randomly allocated, continued to be analyzed as far as possible in their original randomized groups. Treatment effects are shown as the comparisons between diets at the end of the study adjusted for baseline values. Corrections were made by using multiple linear regression with robust standard errors for the baseline values and the minimization variables used in the randomization: sex, age group (40–49, 50–59, and 60–70 y), ethnicity (white, black, and other), and BMI group (18.5–24.9, 25–29.9, and 30.0–35.0). The intervention effect was the coefficient for the DG group compared with the control group in the regression analysis. The quantiles of each variable were plotted against the quantiles of the normal distribution, and $\log_e$ transformations were used where substantial deviations from normality were revealed, and in these cases, the treatment effect is shown as the percent change. The contribution of changes in sodium intake and BMI to BP reduction was estimated by using average causal mediated effects modeling (28).

RESULTS

Baseline characteristics of the study participants

Of 227 potential eligible participants, 165 were randomly allocated to treatment and 162 completed the study. Reasons for noncompletion were withdrawal of consent before receiving the intervention, family bereavement, and unwillingness to follow dietary advice (see **Supplemental Figure 2** for the Consolidated Standards of Reporting Trials diagram). The details of the participants are shown in **Table 1**. There were more women than men, and around one-fifth of the participants were ethnic minorities; estimated risk of a CVD event by using QRISK-2 over the next 10 y was about 8% in the men and 4% in the women and typical for their age group in the United Kingdom population (14).

Compliance to the dietary advice

The composition of the participants' usual diets at baseline is shown with both groups combined because there were no between-group differences (**Table 2**). Neither food records nor physical activity records indicated any change in energy intake or expenditure following allocation to their respective diets. The within-subject SD for measures of body weight was 1.4 kg, indicating that weight was relatively stable. However, mean

TABLE 1Details of the study participants by randomized treatment group¹

	Dietary guidelines (<i>n</i> = 82)	Control (<i>n</i> = 83)
Age, y	53 ± 8 ²	52 ± 8
Sex, M/F, <i>n</i>	32/49	33/50
Postmenopausal, <i>n</i> (%)	25 (50%)	28 (56%)
White/black/Asian, <i>n</i>	71/6/5	66/10/7
BMI, kg/m ²	25.5 ± 3.7	26.8 ± 3.9
Waist circumference, M/F, cm	98 ± 10/88 ± 12	97 ± 12/91 ± 10
Seated SBP/DBP, mm Hg	119 ± 14/77 ± 8	120 ± 14/79 ± 9
24-h SBP/DBP, mm Hg	120.4 ± 12.6/73.3 ± 7.1	122.7 ± 13.3/74.4 ± 7.0
Glucose, mmol/L	5.3 ± 0.5	5.2 ± 0.5
Total cholesterol, mmol/L	5.31 ± 1.04	5.35 ± 0.95
TC:HDL cholesterol ratio	3.5 ± 1.0	3.7 ± 1.0
10-y CVD risk, M/F, %	7.7 ± 5.2/3.3 ± 3.0	7.6 ± 5.7/4.5 ± 3.5

¹No significant differences between groups: 2-sample test or Mann-Whitney *U* test. CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol.

²Mean ± SD (all such values).

body weight fell by 1.3 kg (95% CI: 1.8, 0.9) in the DG group and increased in the control group by 0.6 kg (95% CI: 0.2, 1.0) over the 12-wk study period (**Figure 1A**), showing significant treatment-associated differences in weight of 1.9 kg (95% CI: 1.3, 2.5; *P* < 0.001) and BMI of 0.7 (95% CI: 0.5, 0.9; *P* < 0.001) in the DG compared with control group. Both diets were well accepted and did not differ in cost. Changes in dietary intake in the control group were minimal (except for an additional 8 g SFAs/d) compared with their usual diet. In contrast, there were marked changes after DG. In the DG group compared with the control group, protein and dietary fiber intakes were 2.1% energy and 7.6 g/d higher, respectively; nonmilk extrinsic sugar, fat, and SFA and *trans* fatty acid intakes

were 2.6%, 3.4%, 7.2%, and 0.6% energy lower, respectively, and those of MUFAs and PUFAs were 3.4% and 1.9% higher; the intake of long-chain n-3 PUFAs was 1.3 g/d higher; sodium intake was 65 mmol/d lower; and potassium intake was 12 mmol/d greater.

At baseline, total fat and SFAs supplied 35% and 12% of energy intake, respectively, and salt intakes (8 g/d) estimated from 4-d records and 24-h urine sodium excretion were similar to those reported in the National Diet and Nutrition Survey, a nationally representative survey of men and women in the United Kingdom population (29, 30) (**Table 3**). Most participants allocated to the DG group met the target for SFAs and total fat. Self-reported intakes of sugar from sugar-sweetened beverages

TABLE 2Nutrient intakes estimated from 4-d food diaries and BMI at baseline and changes after the DG and control diets¹

	Baseline (<i>n</i> = 162) ²	DG (<i>n</i> = 80) ³	Control (<i>n</i> = 82) ³	Main comparison ⁴ between groups	<i>P</i> value ⁵
Energy intake, MJ/d	9.77 ± 2.08	-0.18 (-0.65, 0.31)	0.47 (-0.2, 0.97)	-0.59 (-1.18, 0.01)	0.052
Physical activity level ⁷	1.30 ± 0.16	0.05 (-0.02, 0.13)	-0.03 (-0.10, 0.05)	0.08 (-0.02, 0.19)	0.125
BMI, kg/m ²	26.1 ± 3.9	-0.4 (-0.6, -0.3)	0.2 (0.1, 0.3)	-0.7 (-0.9, -0.5)	<0.001
Protein, % of energy	15.9 ± 3.0	1.8 (1.0, 2.4)	-0.2 (-0.9, 0.4)	2.1 (1.3, 2.9)	<0.001
Carbohydrate, % of energy	44.9 ± 7.0	0.3 (-1.8, 1.1)	-1.8 (-3.2, 0.4)	0.5 (-1.2, 2.2)	0.578
Dietary fiber, g/d	23.9 ± 9.0	7.1 (5.1, 9.0)	-0.2 (-0.18, 1.5)	7.6 (5.2, 9.9)	<0.001
Sugars, % of energy	20.7 ± 5.9	0.5 (-1.1, 2.2)	-0.6 (-2.0, 0.8)	0.9 (-1.1, 2.8)	0.385
NMESs, % of energy	9.8 ± 4.5	-2.5 (-3.7, -1.4)	-0.4 (-1.4, 0.6)	-2.6 (-3.7, -1.4)	<0.001
Fat, % of energy	35.4 ± 6.1	-2.3 (-3.8, -0.8)	2.4 (0.8, 4.0)	-3.4 (-5.1, -1.7)	<0.001
SFAs, % of energy	12.0 ± 3.3	-4.7 (-5.5, -3.8)	3.2 (2.4, 4.0)	-7.2 (-7.9, -6.4)	<0.001
<i>trans</i> Fatty acids, % of energy	0.6 ± 0.3	-0.4 (-0.4, -0.3)	0.2 (0.1, 0.3)	-0.6 (-0.7, -0.5)	<0.001
MUFAs, % of energy	11.8 ± 2.6	3.5 (2.7, 4.4)	0.5 (-0.2, 1.2)	3.3 (2.4, 4.3)	<0.001
PUFAs, % of energy	6.4 ± 2.0	0.6 (0.1, 1.2)	-0.8 (1.2, -0.3)	1.9 (1.3, 2.4)	<0.001
n-3 LCP, g/d	0.3 ± 0.7	1.2 (0.8, 1.5)	-0.3 (-0.5, -0.1)	1.3 (0.9, 1.7)	<0.001
Sodium, mmol/d	139 ± 53	-56 (-67, -45)	9 (-3, 22)	-65 (-78, -51)	<0.001
Potassium, mmol/d	91 ± 26	15 (10, 20)	1 (-3, 6)	12 (7, 20)	0.009

¹DG, dietary guideline; LCP, long-chain PUFAs; NMES, nonmilk extrinsic sugar.

²Means ± SDs, no significant difference between groups at baseline.

³Mean changes from baseline; 95% CIs in parentheses.

⁴Mean treatment effects; 95% CIs in parentheses.

⁵Probability based on analysis of covariance with value on treatment regressed against the baseline value, age group, sex, ethnicity, and BMI category.

⁶Participants recording energy intake <1.2 × basal metabolic rate were excluded from estimates of energy intake: baseline DGs (*n* = 18), control (*n* = 25); follow-up DG (*n* = 23), control (*n* = 20).

⁷Physical activity level is the ratio of activity in relation to the resting metabolic rate.

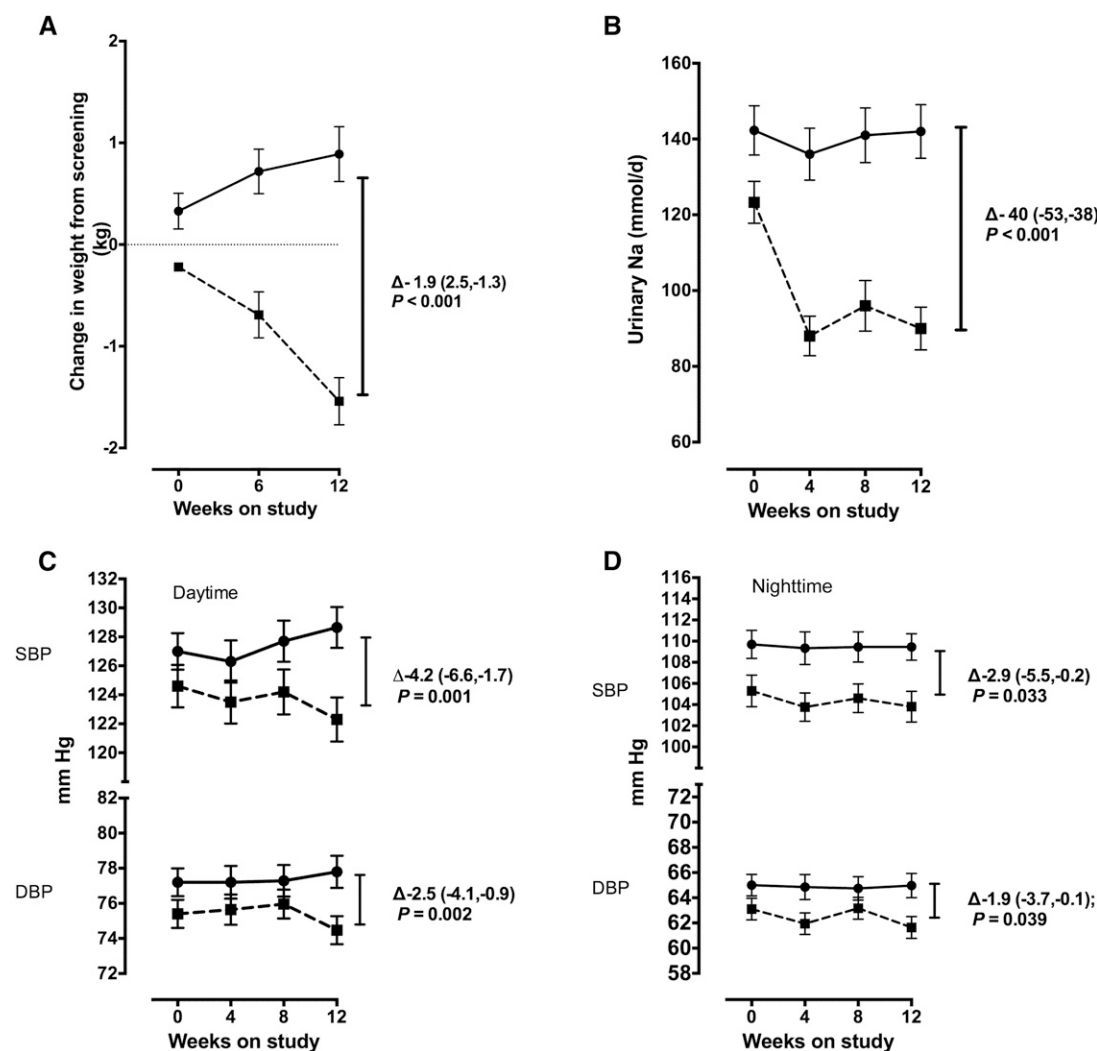


FIGURE 1 Mean ($\pm$ SEM) changes in body weight from screening value during study (A), 24-h urinary sodium excretion (B), and daytime (C) and nighttime (D) ambulatory SBP and DBP in participants allocated to the dietary guideline (dashed line, $n = 80$) or control diet (solid line, $n = 82$). Data were analyzed by regression models adjusted for the baseline value, sex, and categories of age, BMI, and ethnic group. The treatment effect shown at 12 wk is adjusted for differences in baseline values with 95% CIs. DBP, diastolic blood pressure; SBP, systolic blood pressure.

from the food-frequency questionnaire fell mean from a mean of 20 ± 20 g/d at baseline to 10 ± 12 g/d in the DG group but remained unchanged at 21 ± 20 g/d in the control group. The 4-d food records indicated a lower intake of nonmilk extrinsic sugars, consisting mainly of added sucrose, in the DG group. The lower urinary sucrose and fructose excretion in the DG compared with the control group is consistent with a reduced intake of added sugar. However, total sugar intake remained unchanged owing to the increase in sugar intake from fruit. Compliance with the lower sodium intake was corroborated by a 40-mmol Na/d difference in urinary excretion, with 66% of the DG group meeting the target of <100 mmol/d for sodium. Completeness of urinary collection was checked by using PABA excretion: the mean (95% CI) recovery of PABA was 86% (95% CI: 83, 89) in both treatment groups, and sodium excretion was stable in each group throughout the study (Figure 1B). At baseline, the self-reported intakes of fruit and vegetables were a median of 6 servings/d according to the food-frequency questionnaire but slightly less than 5 servings/d in the 4-d food records compared with 4 servings/d in the National Diet and

Nutritional Survey. Urinary potassium excretion was generally high but 9 mmol/d greater in the DG group, indicating that the participants were indeed consuming plenty of fruit and vegetables. Dietary fiber intakes were slightly greater than those in the National Diet and Nutritional Survey (24 g/d compared with 20 g/d) at baseline. Whole-grain intake increased to 81 g/d in the DG group compared with 32 g/d in control group and was derived mainly from wheat, oats, and rice. Dietary fiber intake was consequently 7 g/d higher, reflecting increased cereal fiber from whole grains and corroborated by higher plasma alkylresorcinol concentrations, which reflect intakes of whole grains mainly from wheat, barley, and rye but not rice or oats. Oily fish intake increased to 1.8 servings/wk, which was corroborated by an increase in the erythrocyte n-3 index.

With regard to micronutrients (**Supplemental Table 1**), intakes of biotin, magnesium, and vitamins B-12, C, D, and E were higher and those of vitamin A, thiamin, riboflavin, vitamin B-6, folate, and iron were lower in men, and vitamin D and magnesium were higher in women in the DG compared with the control group. Serum vitamin D concentrations increased by

TABLE 3

Comparison of dietary intakes in the participants at baseline compared with a nationally representative sample of United Kingdom adults and after intervention in the control group and the DG groups and biomarkers of intake compared with targets¹

	Average United Kingdom ²	Baseline ³ (n = 162)	Control (n = 82)	DG (n = 80)	Target	Meeting target in DG, ⁴ %
Total fat, % of energy	34.7 ± 6.4 ⁵	35.4 ± 6.1	37.1 ± 5.3	33.8 ± 5.4	≤35	57
SFA, % of energy	12.7 ± 3.4	12.0 ± 3.3	14.8 ± 2.8	7.7 ± 1.7 ⁶	<11	96
NMESs, % of energy	11.6 ± 6.2	9.8 ± 4.5	9.5 ± 4.3	7.1 ± 3.9 ⁶	<11	85
Urinary sucrose + fructose, ⁷ μmol/24 h		43 (35, 52)	62 (49, 77)	28 (21, 37) ⁶	<60	76
Sodium intake, mmol/d		139 ± 53	147 ± 58	84 ± 31 ⁶	<100	75
Sodium excretion, ⁸ mmol/d	132 ⁹	132 ± 48	142 ± 58	93 ± 5.4 ⁶	<100	66
Fruit and vegetables, servings/d	4	5 ± 3	5 ± 3	7 ± 3 ⁶	≥5	80
Potassium excretion, ⁸ mmol/d		87 ± 26	94 ± 31	83 ± 21 ⁶	≥90	83
Whole grains, servings/d	~1	1.4 ± 1.1	1.0 ± 1	2.7 ± 1.3 ⁶	>2	82
Plasma alkylresorcinols, nmol/L		69 (71, 78)	57 (47, 69)	85 (73, 98) ⁶	>70	66
Oily fish, servings/wk	<1	1.0 ± 1.0	0.2 ± 0.3	1.7 ± 1.5 ⁶	≥1	71
n-3 index, %		7.1 ± 2.2	6.6 ± 1.8	8.2 ± 2.5 ⁶	>8.0	85

¹80 g fruit or vegetable = 1 serving; 140 g oily fish = 1 serving; n-3 index is the sum of eicosapentaenoic acid and docosahexaenoic acid in erythrocyte phosphoglycerides; 30 g whole grains = 1 serving. DG, dietary guideline; NMES, nonmilk extrinsic sugar.

²Data from the National Diet and Nutrition Survey (29, 30).

³No differences between groups at baseline.

⁴Percentage meeting target in DG group. Dietary intakes are from 4-d food records.

⁵Mean ± SD (all such values).

⁶ $P < 0.01$ for comparisons with the control group based on ANCOVA with value on treatment regressed against the baseline value, age group, sex, ethnicity, and BMI category.

⁷Data for urinary sucrose + fructose and plasma alkylresorcinols were log_e transformed, and values are shown as geometric means; 95% CIs in parentheses.

⁸Adjusted for completeness of collection by using para-amino benzoic acid recovery.

⁹Intake adjusted for similar proportion of men and women as in the study.

9 nmol/L (95% CI: 4, 14; $P < 0.001$) and serum folate was 16% (95% CI 7, 25; $P = 0.001$) lower in the DG than in the control group; these differences could be attributed to the higher intake of oily fish and avoidance of folic acid-fortified breakfast cereals, respectively, in the DG group. However, there were no differences between groups in serum ferritin concentrations (−5%; 95% CI: −17, 7; $P = 0.43$) or homocysteine concentration (−3.5%; 95% CI: −8.8, 1.9; $P = 0.206$), which are indexes of iron and folate status, respectively.

Outcomes

Figure 1 shows significant falls in ambulatory SBP/diastolic BP (DBP) of 4.2/2.5 mm Hg for daytime and 2.9/1.9 mm Hg for nighttime in the DG compared with the control group, adjusting for baseline values. The treatment effect for 24-h SBP/DBP (not shown in tables or figure) included reductions (95% CIs) in mm Hg of 3.5 (1.2, 5.7; $P = 0.003$)/2.2 (0.8, 3.2; $P = 0.002$). Clinic supine central SBP/DBP and heart rate were 3.5 (95% CI: 1.6, 5.4; $P < 0.001$)/2.4 (1.1, 3.8; $P < 0.001$) mm Hg and 1.8 beats/min (95% CI: 0.3, 3.3; $P = 0.022$) lower, respectively (Table 4). Regression analysis adjusting for the 32% fall in sodium excretion indicated that sodium reduction explained a fall in SBP of 2.4 mm Hg (95% CI: 1.0, 3.9), and the 0.7 decrease in BMI suggested an explanation for a further fall of 1.1 mm Hg (95% CI: −0.05, 2.4). PWV_{c-f} was 0.29 m/s (95% CI: 0.07, 0.52; $P = 0.011$) lower, and after adjusting for central mean arterial pressure, a difference of 0.19 m/s (95% CI: 0.10, 0.28; $P < 0.001$) remained. Post hoc measurements of plasma endothelin 1 found no differences (data not shown). At baseline, 36% of participants had FMD values <4%, which in our laboratory is taken to indicate impaired endothelial function. There was no

significant treatment effect on FMD, and the difference between treatments was small (−0.62%). There were no changes in endothelium-independent vasodilation (glycerol trinitrate). Serum hsCRP values were generally, low but the treatment effect was 36% ($P = 0.017$) lower. TC, LDL cholesterol, apolipoprotein B, HDL cholesterol, apolipoprotein A, and triglycerides were 0.46 mmol/L (8%, $P < 0.001$), 0.30 mmol/L (10%, $P < 0.001$), 0.065 g/L (7%, $P = 0.0002$), 0.10 mmol/L (6%, $P = 0.005$), 0.043 g/L (3%, $P = 0.035$), and 0.12 mmol/L (9%, $P = 0.027$) lower, respectively. The treatment effect for the TC:HDL cholesterol ratio was 0.13 (4%, $P = 0.044$) lower, paralleled by a 0.021 (3%, $P = 0.035$) lower apolipoprotein B:apolipoprotein A1 ratio. Waist circumference was 1.7 cm lower (95% CI: 0.7, 2.8; $P = 0.002$), but there were no significant treatment effects on indexes of insulin sensitivity (Revised Quantitative Insulin Sensitivity Check Index, adiponectin) or secretion (C-peptide).

DISCUSSION

The novelty of this work is that it is a randomized controlled trial with sufficient power to evaluate the combined impact on CVD risk of dietary guidelines compared with a typical diet in middle-aged and older adults at average risk. Indeed, the statistically significant changes in CVD risk were in a favorable direction with only 2 exceptions (HDL cholesterol, apolipoprotein A1). The control diet was nutritionally balanced, besides the slightly higher intake of saturated fat (8 g/d), but otherwise differed little from the participants' usual diet and generally was not inferior in terms of micronutrient content. Consequently, the treatment effects were almost entirely attributable to the changes resulting from the DG diet.



TABLE 4Changes in indexes of vascular function and lipids and indexes of insulin secretion and sensitivity after randomization to DG and control diets¹

	Baseline		Follow-up		Main comparison between groups ²	P value ³
	DG (n = 82)	Control (n = 83)	DG (n = 80)	Control (n = 82)		
Vascular function						
FMD, ⁴ %	5.61 ± 3.00 ⁵	5.33 ± 3.24	4.94 ± 2.54	5.44 ± 3.30	−0.62 (−1.48, 0.24)	0.16
GTN, ⁶ %	11.27 ± 4.83	10.63 ± 4.94	11.78 ± 5.63	10.98 ± 4.24	0.17 (−1.20, 1.53)	0.80
Supine central SBP, mm Hg	109.1 ± 13.8	109.9 ± 12.4	105.0 ± 11.6	109.4 ± 12.4	−3.5 (−5.4, −1.6)	<0.001
Supine central DBP, mm Hg	75.1 ± 8.1	75.7 ± 8.5	72.2 ± 7.6	75.5 ± 8.8	−2.4 (−3.8, −1.1)	0.001
Supine heart rate, beats/min	57.5 ± 7.4	57.1 ± 8.3	55.2 ± 7.7	57.8 ± 9.2	−1.8 (−3.3, −0.3)	0.022
PWV _{c-f} , m/s	7.65 ± 1.31	7.39 ± 1.09	7.43 ± 1.22	7.61 ± 1.14	−0.29 (−0.52, −0.07)	0.011
hsCRP, ⁷ mg/dL	0.7 (0.3, 1.9)	1.0 (0.3, 2.1)	0.5 (0.2, 1.7)	1.3 (0.6, 2.4)	−36% (−48, −7)	0.017
Serum lipids						
Total cholesterol, mmol/L	5.33 ± 1.11	5.35 ± 0.86	5.06 ± 0.93	5.49 ± 0.89	−0.46 (−0.64, −0.28)	<0.0001
LDL cholesterol, mmol/L	3.18 ± 0.89	3.18 ± 0.77	3.00 ± 0.75	3.29 ± 0.78	−0.30 (−0.43, −0.17)	<0.0001
Apo B, g/L	0.96 ± 0.25	0.99 ± 0.22	0.92 ± 0.21	1.00 ± 0.22	0.065 (−0.098, −0.032)	0.0002
HDL cholesterol, mmol/L	1.61 ± 0.40	1.56 ± 0.42	1.58 ± 0.38	1.62 ± 0.44	−0.10 (−0.17, −0.03)	0.005
Apo A-I, g/L	1.57 ± 0.31	1.55 ± 0.30	1.55 ± 0.33	1.57 ± 0.30	−0.043 (−0.090, −0)	0.035
Triglycerides, mmol/L	1.24 ± 0.59	1.33 ± 0.58	1.06 ± 0.45	1.23 ± 0.55	−0.12 (−0.23, −0.01)	0.027
Total cholesterol:HDL cholesterol ratio	3.46 ± 0.91	3.63 ± 0.98	3.31 ± 0.87	3.59 ± 0.96	−0.13 (−0.26, −0.00)	0.044
Apo B:apoA-I ratio	0.626 ± 0.171	0.649 ± 0.155	0.609 ± 0.163	0.651 ± 0.158	−0.021 (−0.041, −0.001)	0.035
Indexes of insulin sensitivity						
Waist, cm	91.3 ± 12.2	94.1 ± 11.3	90.6 ± 11.9	95.2 ± 11.7	−1.7 (−2.8, −0.7)	0.002
Fasting insulin, mU/L	6.6 ± 4.2	8.5 ± 6.3	7.2 ± 4.8	8.0 ± 5.6	9.6% (−21.6, 21.5)	0.120
Urinary C-peptide, nmol/mmol creatinine	1.97 ± 1.13	2.10 ± 1.17	2.12 ± 1.19	2.05 ± 1.04	−3.5% (−11.3, 4.3)	0.379
Plasma glucose, mmol/L	5.33 ± 0.51	5.21 ± 0.44	5.31 ± 0.20	5.20 ± 0.44	−1% (−3, 1)	0.397
Plasma NEFAs, mmol/L	0.46 ± 0.18	0.45 ± 0.18	0.49 ± 0.18	0.49 ± 0.18	−1% (−12, 10)	0.757
RQUICKI	0.432 ± 0.069	0.419 ± 0.064	0.419 ± 0.056	0.415 ± 0.062	2% (−2, 5)	0.286
Serum adiponectin, mg/L	13.5 ± 7.2	12.6 ± 7.7	13.7 ± 6.7	12.3 ± 7.0	−4% (−11, 13)	0.514

¹apo, apolipoprotein; DBP, diastolic blood pressure; DG, dietary guideline; FMD, flow-mediated endothelium-dependent dilation; GTN, glycerol trinitrate-mediated endothelium-independent dilation; hsCRP, high-sensitivity C-reactive protein; NEFA, nonesterified fatty acid; PWV_{c-f}, carotid-to-femoral pulse wave velocity; RQUICKI, Revised Quantitative Insulin Sensitivity Check Index; SBP, systolic blood pressure.

²Values are means; 95% CIs in parentheses.

³Probability based on analysis of covariance with value on treatment regressed against the baseline value, age group, sex, ethnicity, and BMI category. Where the treatment effect is shown as percent change, the data were log_e transformed before analysis.

⁴DG (n = 73), control (n = 76).

⁵Mean ± SD (all such values).

⁶DG (n = 72), control (n = 76).

⁷Median (IQR), DG (n = 69), control (n = 69); values >5 mg/L were excluded.

Most remarkable was the 4.2-mm Hg fall in daytime SBP in healthy adults achieved by following the dietary guidelines, accompanied by falls in DBP and nighttime BP. This extends findings in higher-risk subjects (11–13, 31) to those at average risk of CVD. Causal mediated effects analyses indicate that a 2.4-mm Hg change in daytime SBP could be attributed to the reduction in sodium intake, consistent with a recent meta-analysis (32), with a 0.7 difference in BMI possibly accounting for a further ~1 mm Hg. The falls in BP were further corroborated by reductions in clinic central BP and an associated fall in PWV_{c-f} by ~0.3 m/s. However, we found no evidence for any change in FMD, consistent with another report (33) by our group but in contrast to an earlier report in 29 participants that suggested a 1.5% improvement in FMD on a low- compared with high-sodium diet (34). This would argue against a high-sodium intake having its effects on BP by decreasing nitric oxide bioavailability. Risk estimates from a meta-analysis of prospective cohort studies (25) suggest that a 4.2-mm Hg lower daytime ambulatory SBP would decrease the risk of fatal stroke and ischemic heart disease by 54% and 39%, respectively, depending on age.

The 0.46-mmol/L (8%) reduction in serum TC and the 10%, 7%, 6%, and 3% lower LDL cholesterol, apolipoprotein B, HDL cholesterol, and apolipoprotein A1 concentrations, respectively, agree with predictions from metabolic feeding studies of dietary fat modification (35). However, the 0.30-mmol/L reduction in LDL cholesterol is greater than that achieved in most community-based studies of dietary advice (36) in which the mean reduction is 0.16 mmol/L. Our advice was probably effective because it targeted the main source of variability in fat intake (fatty meat, butter fat, culinary oils, cakes, and cookies), achieved by advising against consuming fatty meat products and advocating consumption of lean meat, fish, and poultry; reducing fat dairy products; and replacing cakes and cookies with fruit and nuts. We also supplied culinary oils and spreads high in monounsaturated fat. The 9% lower fasting triglyceride concentration is likely to have resulted from reduced triglyceride synthesis in the liver brought about by the higher intake of long-chain n-3 PUFAs from oily fish, which inhibit triglyceride synthesis in the liver, as well as the lower intake of sucrose and fructose, which promote hepatic triglyceride synthesis.



The 0.13 (4%) reduction in the TC:HDL cholesterol ratio and the corresponding reduction in the apolipoprotein B:apolipoprotein A1 ratio agree with the 0.12 reduction in TC/HDL cholesterol observed in the 24-wk Reading Imperial Surrey King's study, which examined the replacement of SFAs with MUFAs in participants with features of the metabolic syndrome (37). The change in the TC:HDL cholesterol ratio is modest compared with drugs such as statins. The higher SFA intake slightly increased HDL cholesterol and apolipoprotein A1 in addition to increasing LDL cholesterol and apolipoprotein B. There is, however, some debate as to whether the TC:HDL cholesterol ratio should be the touchstone for estimating lipid-related CVD risk, because changes in HDL cholesterol do not seem to affect risk (38), or whether LDL cholesterol should be the primary risk indicator. However, risk estimates for the lipid changes from prospective cohort studies using either the TC:HDL cholesterol ratio (24) or LDL cholesterol (39) indicate similar risk reductions of fatal and nonfatal CHD of 3% and 6%, respectively. Mean SFA intakes in the United States (10) and United Kingdom (29) have fallen markedly over the past few decades to a range of 11–13% of energy, owing in part to the replacement of animal fats and partially hydrogenated vegetable oils with unhydrogenated vegetable oils in the food supply. Meeting the target of <11% of energy is likely to have a more modest effect on TC:HDL cholesterol or LDL cholesterol than reported here.

Despite the fall in added sugar intake, total sugar intake was unaffected because the added sugars were replaced by sugar supplied by fruit. In this study, we were unable to show any effects on insulin secretion as measured by 24-h urinary C-peptide excretion or on indexes of insulin sensitivity. A low intake of sugar-sweetened beverages and a high intake of whole grains are associated with a lower BMI (10) and lower hsCRP concentrations (40). Two recent trials of whole grains found no effect on C-reactive protein (41, 42), but a recent Finnish study (43) showed a fall in C-reactive protein after advice to consume whole grains, fish, and berries. We noted a treatment effect on hsCRP, and this is consistent with reports of reduced hsCRP after advice to consume fish (44) but not with long-chain n-3 PUFAs (23). Although body weight was relatively stable over the intervention period, we were able to detect a small but statistically significant favorable effect on body weight and waist circumference in the DG diet compared with the control diet, which may reflect the greater satiating capacity of a diet rich in whole grains and fruit and vegetables or a reduced digestibility of energy-providing nutrients.

Strengths and weakness

The strengths of the study are as follows: it investigated the impact of changing the whole diet rather than individual components; it was conducted in middle-aged and older nonsmoking men and women who were not receiving medication for BP or hyperlipidemia, which is a strength because evidence is lacking for prevention in populations without overt CVD or who are not already at high risk of CVD; the participants were free living, and the duration of intervention was longer than most previous studies; the diet was affordable and acceptable; and there was strong evidence of compliance with the dietary intervention and the use of ambulatory BP monitoring. A limitation is that there

was a small change in body weight, but this may be an unavoidable consequence of conforming to the dietary guidelines. The main limitation is that risk was estimated by using surrogate markers. However, randomized controlled trials with clinical endpoints in healthy participants are unlikely to be conducted because of the large numbers of participants required and the practicalities of sustaining differences in dietary intake over several years (7). Although this diet was well received by participants, it may be a greater challenge to bring about change in groups who are less health conscious.

Conclusion

Selecting a diet consistent with current dietary guidelines compared with a traditional United Kingdom dietary pattern would be predicted on the basis of the changes in BP and lipids, to reduce the risk of fatal and nonfatal CVD (24) by 15% and 30%, respectively, in the general population.

We thank the other members of the CRESSIDA study investigators (Sarah Berry, Louise Goff, Zoe Maniou, Benju Jiang, and Roy Sherwood) for their support; Karen McNeil, Robert Gray, Virginia Govoni, and Tracy Dew for technical support; and Laura O'Sullivan for administrative support.

The authors' responsibilities were as follows—TABS (principal investigator and guarantor of the study), WLH, PTS, and PJC: devised the study; DPR and JD: recruited subjects into the study and supported the dietary intervention; PTS: undertook the statistical analysis; and TABS: wrote the manuscript, which was approved by all authors. TABS is a trustee and governor of the British Nutrition Foundation and reported a financial interest in respect of payment for attendance at scientific advisory panels for Heinz PLC, Global Dairy Platform, Malaysian Palm Oil Board and the Natural Hydration Council, and GlaxoSmithKline and lecture fees from Lilly. PJC reported a financial interest in Centron Diagnostics. DPR, JD, WLH, and PTS reported no conflicts of interest.

REFERENCES

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, et al. A comparative risk assessment of burden of disease and injury attributable, 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380:2224–60.
2. Strom BL, Anderson CM, Ix JH. Sodium reduction in populations: insights from the Institute of Medicine committee. *JAMA* 2013;310:31–2.
3. DiNicolantonio JJ. The cardiometabolic consequences of replacing saturated fats with carbohydrates or Ω -6 polyunsaturated fats: do the dietary guidelines have it wrong? *Open Heart* 2014;8:e000032.
4. Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, Willett WC, Hu FB. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation* 2014 28;130:1568–78.
5. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Balter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* 2009;89:1425–32.
6. Jakobsen MU, Dethlefsen C, Joensen AM, Stegger J, Tjønneland A, Schmidt EB, Overvad K. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. *Am J Clin Nutr* 2010;91:1764–8.
7. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014;160:398–406.
8. Astrup A, Dyerberg J, Elwood P, Hermansen K, Hu FB, Jakobsen MU, Kok FJ, Krauss RM, Lecerf JM, LeGrand P, et al. The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? *Am J Clin Nutr* 2011;93:684–8.



9. Department of Health. Nutritional aspects of cardiovascular disease: report on health and social subjects no. 46. London: HMSO; 1994.
10. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation* 2011;123:2870–91.
11. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;336:1117–24.
12. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001;344:3–10.
13. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, et al. Effects of protein, monounsaturated fat and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* 2005;294:2455–64.
14. Collins GS, Altman DG. Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2. *BMJ* 2012;344:e4181.
15. Scientific Advisory Committee on Nutrition. The nutritional wellbeing of the British population [Internet]. London: Scientific Advisory Committee on Nutrition. 2008 [cited 2014 Aug 6]. Available from: http://www.sacn.gov.uk/pdfs/nutritional_health_of_the_population_final_oct_08.pdf.
16. Bingham SA, Welch AA, McTaggart A, Mulligan AA, Runswick SA, Luben R, Oakes S, Khaw KT, Wareham N, Day NE. Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. *Public Health Nutr* 2001;4:847–58.
17. Ekelund U, Sepp H, Brage S, Becker W, Jakes R, Hennings M, Wareham NJ. Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. *Public Health Nutr* 2006;9:258–65.
18. Berry SE, Mulla UZ, Chowiecnyk PJ, Sanders TA. Increased potassium intake from fruit and vegetables or supplements does not lower blood pressure or improve vascular function in UK men and women with early hypertension: a randomised controlled trial. *Br J Nutr* 2010;104:1839–47.
19. Kuhnle GG, Joosen AM, Wood TR, Runswick SA, Griffin JL, Bingham SA. Detection and quantification of sucrose as dietary biomarker using gas chromatography and liquid chromatography with mass spectrometry. *Rapid Commun Mass Spectrom* 2008;22:279–82.
20. Sanders TA, Lewis F, Slaughter S, Griffin BA, Griffin M, Davies I, Millward DJ, Cooper JA, Miller GJ. Effect of varying the ratio of n–6, n–3 fatty acids by increasing the dietary intake of alpha-linolenic acid, eicosapentaenoic and docosahexaenoic acid, or both on fibrinogen and clotting factors VII and XII in persons aged 45–70 y: the OPTILIP study. *Am J Clin Nutr* 2006;84:513–22.
21. Landberg R, Aman P, Friberg LE, Vessby B, Adlercreutz H, Kamal-Eldin A. Dose response of whole-grain biomarkers: alkylresorcinols in human plasma and their metabolites in urine in relation, intake. *Am J Clin Nutr* 2009;89:290–6.
22. Bingham S, Cummings JH. The use of 4-aminobenzoic acid as a marker to validate the completeness of 24 h urine collections in man. *Clin Sci (Lond)* 1983;64:629–35.
23. Sanders TA, Hall WL, Maniou Z, Lewis F, Seed PT, Chowiecnyk PJ. Effect of low doses of long-chain n–3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. *Am J Clin Nutr* 2011;94:973–80.
24. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. *Lancet* 2007;370:1829–39.
25. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.
26. Frison L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Stat Med* 1992;11:1685–704.
27. Perseghin G, Caumo A, Caloni M, Testolin G, Luzi L. Incorporation of the fasting plasma FFA concentration into QUICKI improves its association with insulin sensitivity in nonobese individuals. *J Clin Endocrinol Metab* 2001;86:4776–81.
28. Imai K, Keele L, Yamamoto T. Identification, inference and sensitivity analysis for causal mediation effects. *Stat Sci* 2010;25:51–71.
29. Public Health England and the Food Standards Agency. National Diet and Nutrition Survey: results from years 1 to 4 (combined) of the rolling programme for 2008 and 2009 to 2011 and 2012. London: Public Health England. 2014 [cited 2014 Aug 6]. Available from: <https://www.gov.uk/government/publications/national-diet-and-nutrition-survey-results-from-years-1-to-4-combined-of-the-rolling-programme-for-2008-and-2009-to-2011-and-2012>.
30. Sadler K, Nicholson S, Steer T, Gill V, Bates B, Tipping S, Cox L, Lennox A, Prentice A. National Diet and Nutrition Survey—assessment of dietary sodium in adults (aged 19, 64 years) in England, 2011. London: Department of Health; 2012.
31. Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, Stevens VJ, Vollmer WM, Lin PH, Svetkey LP, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 2003;289:2083–93.
32. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev* 2013;4:CD004937.
33. Sanders TAB, Lewis FJ, Goff L, Chowiecnyk PJ. SFAs do not impair endothelial function and arterial stiffness. *Am J Clin Nutr* 2013;98:1–3.
34. Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. *Am J Clin Nutr* 2009;89:485–90.
35. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total, HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;77:1146–55.
36. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. *Cochrane Database Syst Rev* 2013;12:CD002128.
37. Jebb SA, Lovegrove JA, Griffin BA, Frost GS, Moore CS, Chatfield MD, Bluck LJ, Williams CM, Sanders TA; RISCK Study Group. Effect of changing the amount and type of fat and carbohydrate on insulin sensitivity and cardiovascular risk: the RISCK (Reading, Imperial, Surrey, Cambridge, and Kings) trial. *Am J Clin Nutr* 2010;92:748–58.
38. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117 411 patients. *BMJ* 2014;349:g4379.
39. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81.
40. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr* 2005;82:163–73.
41. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr* 2010;104:125–34.
42. Tighe P, Duthie G, Vaughan N, Britten J, Simpson WG, Duthie S, Mutch W, Wahle K, Horgan G, Thies F. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial. *Am J Clin Nutr* 2010;92:733–40.
43. de Mello VD, Schwab U, Kolehmainen M, Koenig W, Siloaho M, Poutanen K, Mykkanen H, Uusitupa M. A diet high in fatty fish, bilberries and wholegrain products improves markers of endothelial function and inflammation in individuals with impaired glucose metabolism in a randomised controlled trial: the Sysdimet study. *Diabetologia* 2011;54:2755–67.
44. Pot GK, Geelen A, Majsak-Newman G, Harvey LJ, Nagengast FM, Witteman BJ, van de Meeberg PC, Hart AR, Schaafsma G, Lund EK, et al. Increased consumption of fatty and lean fish reduces serum C-reactive protein concentrations but not inflammation markers in feces and in colonic biopsies. *J Nutr* 2010;140:371–6.