Effect of a tomato-rich diet on markers of cardiovascular disease risk in moderately overweight, disease-free, middle-aged adults: a randomized controlled trial[1–4]

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ABSTRACT

Background: Cardiovascular disease (CVD) is a major cause of mortality in the United Kingdom. Epidemiologic studies suggest that consumption of tomato-based foods may lower CVD risk. Such potential benefits have been ascribed in part to high concentrations of lycopene in the tomatoes. However, these findings have not yet been validated by comprehensive intervention trials.

Objective: The aim of this study was to conduct a single-blind, randomized controlled intervention trial with healthy middle-aged volunteers to assess whether the consumption of tomato-based foods affects recognized biomarkers of CVD risk.

Design: After a 4-wk run-in period with a low-tomato diet, 225 volunteers (94 men and 131 women) aged 40–65 y were randomly assigned into 1 of 3 dietary intervention groups and asked to consume a control diet (low in tomato-based foods), a high-tomato-based diet, or a control diet supplemented with lycopene capsules (10 mg/d) for 12 wk. Blood samples were collected at baseline, at 6 wk, and after the intervention and were analyzed for carotenoid and lipid profiles and inflammatory markers. Blood pressure, weight, and arterial stiffness were also measured. Dietary intake was also determined during the intervention.

Results: None of the systemic markers (inflammatory markers, markers of insulin resistance and sensitivity) changed significantly after the dietary intervention. Moreover, lipid concentrations and arterial stiffness were also unaffected by the interventions.

Conclusion: These data indicate that a relatively high daily consumption of tomato-based products (equivalent to 32–50 mg lycopene/d) or lycopene supplements (10 mg/d) is ineffective at reducing conventional CVD risk markers in moderately overweight, healthy, middle-aged individuals. This trial was registered at isrctn.org as ISRCTN34203810. *Am J Clin Nutr* 2012;95:1013–22.

INTRODUCTION

Epidemiologic evidence indicates that high consumption of fruit and vegetables reduces the risk of chronic disease such as cardiovascular disease (CVD)[5] (1). The consumption of ≥7 servings/wk of tomato-based products has been associated with a 30% reduction in the relative risk of CVD (2).

Such potential benefits to vascular health from a tomato-rich diet are often ascribed to high concentrations of lycopene, as tomato products can account for >80% of the intake of this carotenoid (3). The relation between lycopene intake and CVD risk has recently been reviewed (4) and shows that a small majority of studies (57%) found an inverse relation between CVD risk markers and/or CVD incidence. High lycopene concentrations in blood and adipose tissue correlate with a reduction in CVD incidence (5–8), and low concentrations are associated with early atherosclerosis (9) and elevated C-reactive protein concentrations (12, 13). Low arterial intimal wall thickness associated with higher adipose tissue lycopene concentrations suggests a decreased risk of arterial occlusion (7, 10, 11). Serum carotenoids, including lycopene, are inversely correlated with markers of inflammation and vascular endothelial dysfunction (14). Corroborative evidence includes an inverse association between neopterin (a marker for cellular immune activation) and serum lycopene concentrations (15), which suggests that lower serum lycopene concentrations may relate to a higher grade of chronic immune activation—a common feature in cardiovascular disorders.

Trial-based evidence related to the beneficial effects of lycopene and/or a tomato-rich diet is also ambiguous. Of the 65 intervention studies with lycopene supplements or tomato-based products recently reviewed, only 55% showed positive effects (4). Most of these studies considered potential but not recognized established markers for CVD risk, such as antioxidant capacity or ex vivo measurement of LDL oxidizability (16–18). However, others described beneficial effects of tomato-rich products or lycopene supplements on recognized CVD risk markers, such as plasma cholesterol concentrations (19–21), or blood pressure in

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[5] Abbreviations used: CVD, cardiovascular disease; hsCRP, highly sensitive C-reactive protein; sICAM-1, soluble intercellular adhesion molecule 1.

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type 2 patients with diabetes (22) and hypertensive patients (23), which suggests that lycopene could be beneficial for reducing CVD risk in these patient groups. In addition, lycopene may modulate the expression of adhesion molecules in human vascular endothelial cells and increase the expression of LDL receptors involved in the regulation of cholesterol metabolism (24).

Most trials carried out to date involved a small number of subjects, were not controlled, were of short duration, and did not comprehensively investigate many relevant CVD risk markers. Consequently we conducted a well-controlled, large-scale, and comprehensive human intervention study to identify whether consumption of tomato-based foods moderates markers of CVD. To establish the degree to which any observed changes could be ascribed to lycopene, one set of volunteers consumed a tomato-poor diet with a lycopene supplement aimed at providing a similar amount of lycopene as the tomato-rich diet.

SUBJECTS AND METHODS

Participants

Between September 2007 and August 2010, a single-blind, randomized controlled dietary intervention study was carried out in men and women aged 40–65 y and with a BMI (in kg/m^2) between 18.5 and 35. Participants were recruited from the surrounding community of Aberdeen, Scotland, and the study was approved by the North of Scotland Research Ethics Committee (07/S0801/32). Individuals were included if they were sedentary or moderately active (<2 aerobic sessions/wk). Individuals presenting signs of the metabolic syndrome or moderate hypercholesterolemia were also eligible, but these criteria were not compulsory. Exclusion criteria included diagnosed CVD or diabetes or a fasting blood glucose concentration >7.0 mmol/L, asthma, systolic blood pressure >160 mm Hg and diastolic blood pressure >99 mm Hg, or a thyroid condition. Subjects with eating disorders, with high habitual intake of tomatoes and tomato-based products, or taking regular medication or supplements known to affect any dependent variable measured were also excluded.

Study design

We conducted a 16-wk single-blind, randomized controlled dietary intervention study involving 3 treatment groups: a control diet low in tomato-based foods, a control diet supplemented with 70 mg lycopene/wk, and a diet high in tomato-based foods (corresponding to an estimated minimum of 70 mg lycopene/wk). The supplement was purchased from Holland and Barret (one capsule per day, each containing 10 mg lycopene, 0.8 mg β-carotene, 0.1 mg γ-tocopherol, and 1.3 mg α-tocopherol). After a 4-wk run-in period on the control diet, volunteers were randomized (stratified by sex, age, and BMI) to the above treatment groups. The dietary interventions were designed to be practical and realistic for free-living individuals to achieve, with minor alteration of their usual lifestyle. A dietary interview was conducted before the run-in period to screen for high tomato-based food consumers.

Participants in the high tomato-based food group were provided with tomato-based products (tomato sauces, juice, ketchup, soup, puree, and canned tomatoes) widely available from the main United Kingdom food retailers. Aside from these products, the volunteers selected their own foods to eat. The lycopene content of these products was estimated based on the best available information at the time, including the USDA-NCC carotenoid database for US foods (1998), websites for Heinz (http://www.heinz.co.uk) and Campbells soup (http://www.campbellsoup.com), and http://www.leffingwell.com/lycopene.htm (all accessed December 2006). Guidance was provided on the estimated number of portions needed to reach the required lycopene intake by using a points-based system. The lycopene content of the actual products provided were later determined by reversed-phase HPLC as previously described (25).

Intake of tomato-based foods in the control group was restricted. Volunteers were not allowed to consume any of the forbidden foods listed below but were able to consume up to one portion of tomato soup, tomato juice, or tomato sauce per week and either *1*) ≤4 raw tomatoes or 24 cherry tomatoes/wk or *2*) ≤1 portion of tomato ketchup/wk. The forbidden foods were passata, canned tomatoes, cooked tomatoes (eg, fried, grilled), tomato paste, tomato puree, pizza, salsa, chutney, canned beans, spaghetti, ravioli in tomato sauce, barbeque sauce, brown sauce, pink grapefruit, guava, watermelon, and apricots.

During each visit, fasting blood samples were collected and weight, waist circumference, and blood pressure were measured. Furthermore, in vivo measurements of arterial stiffness were conducted, and the volunteers were asked to complete health and physical activity questionnaires. Compliance was assessed by measuring serum lycopene concentrations and by analyzing a weekly checklist of tomato-based foods consumed.

Dietary assessment

Dietary intake was assessed by using 7-d food diaries before and during the run-in period as well as during the intervention. Diaries were analyzed by using WISP software (version 3.0; Tinuviel Software). Lycopene intake was estimated from a weekly checklist of tomato-based foods, which all participants were asked to complete.

Blood pressure and anthropometric measurements

Blood pressure was measured with an OMRON705CP sphygmomanometer according to guidelines from the British Hypertension Society, with additional consecutive measurements (6 on average), until the last 3 measurements varied by <8%. Arterial stiffness was then assessed by pulse contour analysis (Pulse Trace PCA; Micromedical Ltd). Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest.

Biochemistry

During each visit, 12-h fasting blood samples were collected from the antecubital fossa vein. Plasma and serum were isolated from the blood and stored at −80 C until analyzed. All routine lipid analyses were conducted at the Department of Clinical Biochemistry at Aberdeen Royal Infirmary, Aberdeen, United Kingdom, by using standardized automated procedures: total and HDL cholesterol and triglycerides were measured by using Siemens automated systems, LDL cholesterol was calculated by using the Friedewald equation, and apolipoproteins B-100 and A-I were analyzed by using the Behring nephelometry system.

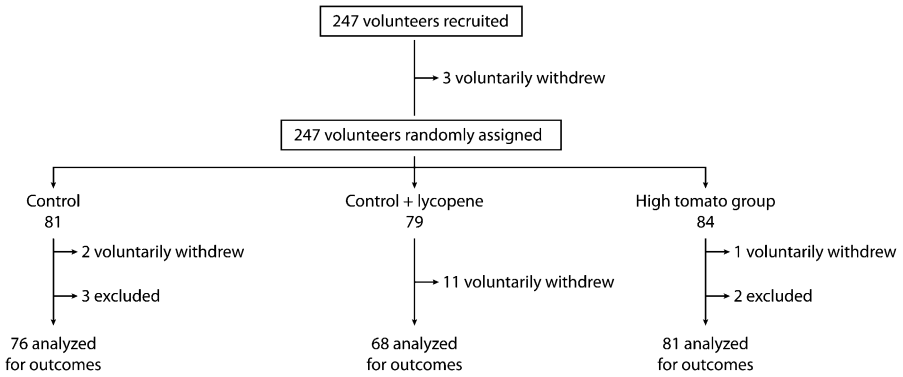

FIGURE 1. Trial profile.

Oxidized LDL, soluble intercellular adhesion molecule 1 (sICAM-1), and IL-6 were determined by enzyme-linked immunosorbent assay (Mercodia and R&D Systems, respectively). Concentrations of plasma lycopene and other carotenoid (α- and β-carotene, β-cryptoxanthin, lutein/zeaxanthin), retinol, α-tocopherol, and γ-tocopherol concentrations were measured by reversed-phase HPLC (25). Mathematical combinations of fasting insulin and glucose measures (HOMA-IR and the Quantitative Insulin Sensitivity Check Index) were used to estimate insulin resistance and sensitivity. All samples were analyzed in a single batch to reduce variability.

Statistical analysis

The sample size was based on the primary outcomes of total and LDL-cholesterol as well as sICAM-1 concentrations in serum. Because the variability of cholesterol concentrations between individuals was shown by other authors (26, 27) to be 10–20%, we assumed that the baseline adjustment should reduce the variability to 5–10%, which indicated that 60 subjects per group would give a sufficient experimental power (90%) to detect intervention effects of 5–7% for a significance level <0.05. The variability of sICAM-1 concentrations between individuals was shown by other authors (26–30) to be 13–30%. We also assumed that the baseline adjustment should reduce the variability to 10–20%, which indicated that 60 subjects per group would give a sufficient experimental power (90%) to detect intervention effects of 10–15%. To allow a dropout of 20% over the trial period, we aimed to recruit 230 participants in total. All volunteers who fulfilled the inclusion/exclusion criteria and completed the intervention, compliant or not, were included in the analysis.

Most statistical analyses were performed with Genstat v12 (VSN International). Analysis of the weekly checklists was carried out by using Stata/SE (version 11.1; StataCorp LP). Data were analyzed by subtracting the baseline measurements and by using 2-factor ANOVA, with dietary group and sex as factors, and adjustment for age and BMI by including these as covariates. At baseline, characteristics of participants in the 3 groups were

TABLE 1
Participant characteristics at baseline, by intervention group

	High tomato (n = 81)	Lycopene (n = 68)	Control (n = 76)	P[1]
Age (y)	51.0 ± 0.7[2]	51.1 ± 0.9	51.1 ± 0.7	0.889
Sex (n)				0.878[3]
Male	35	28	30	
Female	46	40	46	
Current smokers (n)	5	6	1	—
BMI (kg/m^2)	26.4 ± 0.5	26.7 ± 0.5	26.8 ± 0.5	0.831
Waist circumference (cm)	88.1 ± 1.2	89.0 ± 1.4	88.2 ± 1.3	0.907
Systolic BP[4] (mm Hg)	129.4 ± 1.8	130.8 ± 2.1	130.8 ± 1.7	0.953
Diastolic BP (mm Hg)	78.8 ± 1.4	79.6 ± 1.3	79.0 ± 1.1	0.380
Pulse wave velocity (m/s)	8.20 ± 0.25	8.34 ± 0.29	8.32 ± 0.19	0.605
Stiffness index (m/s)[5]	8.2 ± 0.3	7.7 ± 0.3	7.6 ± 0.2	0.272
Metabolic syndrome (n)[6]	1	3	2	—
Alcohol (g/d)	12.0 ± 1.2	11.1 ± 1.2	13.0 ± 1.4	0.479

[1] Differences between groups were assessed by using 2-factor ANOVA ($P < 0.05$ indicates significance).
[2] Mean ± SEM (all such values).
[3] Pearson's chi-square test.
[4] BP, blood pressure.
[5] Calculated by using pulse contour analysis.
[6] Defined according to the International Diabetes Federation as subjects with central obesity (waist circumference >102 cm for men, >88 cm for women) plus 2 of the following conditions: fasting plasma glucose >6.1 mmol/L, triacylglycerol >1.7 mmol/L, low HDL cholesterol (<1.04 mmol/L for men, <1.29 mmol/L for women), and hypertension (>130/85 mm Hg).

compared by using 2-factor ANOVA for continuous data or Pearson's chi-square test for categorical data. Relations between variables at baseline were examined by using Pearson's or Spearman's correlation coefficient for normally distributed or skewed data respectively. *P* values for individual comparisons between diets were adjusted by using the Bonferroni method.

RESULTS

Recruitment

We recruited 247 volunteers. Of these, 17 withdrew (14 for personal reasons, 1 for clinical reasons, and 2 were lost to follow-up). Of the 11 volunteers who withdrew from the lycopene group, 5 left immediately after randomization because they were unhappy with their group allocation. High blood pressure and/or hypercholesterolemia requiring pharmacologic treatment during the intervention were diagnosed in 5 volunteers, who were excluded; 225 participants completed the intervention (**Figure 1**).

Baseline characteristics

After the run-in period, the baseline characteristics of the participants (**Table 1**) were similar between the groups. More women than men were recruited; however, the proportion of women was similar in all 3 groups. The number of volunteers in each group was slightly unbalanced. This did not occur because of the randomization, because the randomization program used minimization where allocation to treatment ensured balance in respect of key prognostic variables (sex, age, and BMI). However, 5 volunteers, seemingly unhappy with the randomization results, withdrew immediately after their allocation into the lycopene-supplemented group, which led to a higher dropout rate in this group. Baseline energy and nutrient intakes were also similar for all of the groups (**Table 2**). The plasma lycopene concentration at baseline (all groups combined: 0.39 ± 0.23 μg/mL; high-tomato group: 0.42 ± 0.21 μg/mL; lycopene-supplemented group: 0.39 ± 0.26 μg/mL; low-tomato group: 0.34 ± 0.20 μg/mL) was inversely associated with sICAM-1 (Spearman's correlation = −0.203, $P = 0.02$) and was positively associated with total cholesterol (Pearson's correlation = 0.340,

TABLE 2
Daily nutrient intakes, by intervention group[1]

	High tomato ($n = 75$)	Lycopene ($n = 59$)	Control ($n = 71$)	P^2	P^3
Energy (kcal)					
Baseline	2112 ± 46	2116 ± 63	2094 ± 49	0.972	
12 wk[4]	2030 ± 47[a]	2104 ± 68[a,b]	2077 ± 58[b]		0.029
Protein (g)					
Baseline	82.6 ± 2.0	81.8 ± 2.4	81.2 ± 2.0	0.734	
12 wk	81.0 ± 2.0	85.2 ± 2.3	82.0 ± 2.8		0.064
Carbohydrate (g)					
Baseline	248 ± 6	244 ± 8	241 ± 7	0.847	
12 wk	238 ± 7	238 ± 9	237 ± 8		0.096
Total fat (g)					
Baseline	85.2 ± 2.6	88.5 ± 3.2	85.9 ± 2.4	0.602	
12 wk	82.2 ± 2.7	89.0 ± 3.8	86.1 ± 2.9		0.080
SFA (g)					
Baseline	29.5 ± 1.1	31.8 ± 1.4	30.8 ± 1.0	0.391	
12 wk	28.0 ± 1.1	32.1 ± 1.7	30.9 ± 1.4		0.100
PUFA (g)					
Baseline	14.7 ± 0.6	15.0 ± 0.7	14.8 ± 0.6	0.629	
12 wk	14.4 ± 0.6	15.2 ± 0.8	15.4 ± 0.6		0.191
MUFA (g)					
Baseline	27.3 ± 0.9	27.7 ± 1.0	27.4 ± 0.8	0.853	
12 wk	27.7 ± 0.9	28.3 ± 1.2	27.4 ± 1.0		0.398
NSP[4] (g)					
Baseline	15.7 ± 0.5	13.9 ± 0.6	14.4 ± 0.4	0.526	
12 wk	15.8 ± 0.6	13.7 ± 0.6	13.6 ± 0.7		0.932
Calcium (mg)					
Baseline	911 ± 27	940 ± 37	922 ± 33	0.820	
12 wk	857 ± 31[a]	947 ± 35[a,b]	966 ± 44[b]		0.017
Vitamin E (mg)					
Baseline	9.3 ± 0.4	9.3 ± 0.56	9.0 ± 0.4	0.841	
12 wk	12.0 ± 0.5[a]	9.2 ± 0.5[b]	9.4 ± 0.4[b]		0.001

[1] All values are means ± SEMs. Values with different superscript letters indicate that the changes from baseline differ significantly, $P < 0.05$ (Bonferroni post hoc test).
[2] Differences between groups at baseline were assessed by using 2-factor ANOVA.
[3] Differences in intake change from baseline between the dietary intervention groups were assessed by using 2-factor ANOVA.
[4] NSP, nonstarch polysaccharide.

$P < 0.001$), LDL-cholesterol (Pearson's correlation = 0.240, $P < 0.001$), HDL-cholesterol (Pearson's correlation = 0.161, $P = 0.016$), and triacylglycerol (Pearson's correlation = 0.191, $P = 0.004$) concentrations.

The weight and BMI of the volunteers did not differ significantly between the groups for all the time points considered and remained unchanged during the course of the dietary intervention (data not shown). For all the groups, no significant differences in age, BMI, energy intake, systolic and diastolic blood pressures, and lipid concentrations were observed at baseline between those participants who completed the intervention and those who withdrew (data not shown). Whereas smoking could be a confounder for some of the CVD markers measured, excluding the smokers in the statistical analysis had no effect on any of the study outcomes.

Effect of intervention on dietary intake

Only the results from the volunteers who returned food diaries at both baseline and 12 wk were included in the analysis. Energy intake decreased slightly in the 3 groups during the intervention, attaining significance when the high-tomato group was compared with the control group (Table 2). However, none of the interventions changed the macronutrient intake significantly. Micronutrient intake remained unchanged by the dietary interventions (data not shown), except for calcium and vitamin E. Calcium intake was significantly lower in the tomato group than in the control group, whereas vitamin E intake was significantly higher (by 30%) in the high-tomato group than in the control group (Table 2). However, plasma vitamin E concentrations remained unchanged after the intervention (**Table 3**).

Lycopene intake and compliance with the dietary interventions

Analyzed lycopene concentrations in the tomato-based foods were higher than the estimated content based on values supplied by some food manufacturers and the carotenoid database for US foods (**Table 4**). As a result, median lycopene intakes for each of the 12 wk were above the minimum target of 70 mg/wk (between 226 and 351 mg/wk) in the high-tomato group, whereas median dietary lycopene intakes of the lycopene-supplemented and control groups were only between 0 and 2 mg/wk (**Figure 2**). The main contributors to lycopene intake in the high-tomato group were tomato soup and pasta sauce (results not shown).

Plasma lycopene concentrations tended to decrease in all the groups after the 4-wk run-in period on a control diet (**Figure 3**). Maximum lycopene enrichment in plasma was already observed after 6 wk of a high-tomato diet and represented a 267% increase in the high-tomato group after 12 wk of intervention. In the control group, plasma lycopene remained low and unchanged throughout. Levels of compliance based on plasma lycopene enrichment were 93%, 90%, and 96% for the high-tomato, lycopene, and control groups, respectively. Plasma concentrations of α- and γ-tocopherol, retinol, β-cryptoxanthin, lutein/zeaxanthin, and α- and β-carotene were similar before run-in and at baseline between the groups.

TABLE 3
Plasma concentrations of tocopherols, retinol, and other carotenoids, by intervention group[1]

	High tomato ($n = 81$)	Lycopene ($n = 68$)	Control ($n = 76$)	P^2	P^3
	μg/mL	*μg/mL*	*μg/mL*		
Retinol					
Baseline	0.60 ± 0.02	0.58 ± 0.03	0.56 ± 0.02	0.976	
12 wk	0.61 ± 0.02	0.59 ± 0.02	0.55 ± 0.02		0.420
α-Tocopherol					
Baseline	14.21 ± 0.59	13.70 ± 0.55	13.39 ± 0.47	0.967	
12 wk	15.66 ± 1.33	13.91 ± 0.56	13.44 ± 0.51		0.318
γ-Tocopherol					
Baseline	0.74 ± 0.05	0.76 ± 0.04	0.73 ± 0.04	0.683	
12 wk	0.65 ± 0.04	0.74 ± 0.04	0.70 ± 0.03		0.140
Lutein/zeaxanthin					
Baseline	0.22 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.495	
12 wk	0.22 ± 0.01	0.19 ± 0.01	0.19 ± 0.01		0.078
β-Cryptoxanthin					
Baseline	0.22 ± 0.03	0.18 ± 0.03	0.15 ± 0.03	0.596	
12 wk	0.23 ± 0.03	0.19 ± 0.03	0.12 ± 0.01		0.683
α-Carotene					
Baseline	0.14 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.711	
12 wk	0.11 ± 0.01[a]	0.13 ± 0.02[b]	0.12 ± 0.01[a,b]		0.001
β-Carotene					
Baseline	0.47 ± 0.05	0.40 ± 0.04	0.42 ± 0.04	0.652	
12 wk	0.55 ± 0.05[a]	0.43 ± 0.05[a,b]	0.38 ± 0.03[b]		0.018

[1] All values are means ± SEMs. Values with different superscript letters indicate that the changes from baseline differ significantly, $P < 0.05$ (Bonferroni post hoc test).
[2] Differences between groups at baseline were assessed by using 2-factor ANOVA.
[3] Differences in concentration change from baseline between the dietary intervention groups were assessed by using 2-factor ANOVA.

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TABLE 4
Comparison between estimated and analyzed lycopene content

Food	Portion size	Estimated						Analyzed[1]		Difference (analyzed – estimated)		
		Source 1[2]	Source 2[3]	Source 3[4]	Source 4[5]	Average	Per portion					
	g	*mg/100 g*	*mg/100 g*	*mg/100 g*	*mg/100 g*	*mg/100 g*	*mg*	*mg/100 g*	*mg/portion*	*mg/100 g*	*mg/portion*	%
Juice	120	9.3	8	7.83	8.8	8.5	10.2	9.1 ± 0.1[6]	10.9	0.6	0.7	7
Puree	30	16.67	—[7]	—	—	16.7	5.0	51.4 ± 10.1	15.4	34.7	10.4	208
Ketchup	30	17.0	15	16.6	—	16.2	4.9	20.6 ± 0.3	6.2	4.4	1.3	27
Pasta sauce	160	15.92	22	17.5	—	18.5	29.6	26.9 ± 6.7	43.0	8.4	13.4	45
Soup	300	—	4		—	4	12	7.7 ± 4.0	23.1	3.7	11.1	93
Canned tomatoes	150	9.708	—	—	—	9.7	14.6	19.5 ± 3.1	29.3	9.8	14.7	101

[1] Lycopene content determined for food items provided to the volunteers (n = 3).
[2] USDA-NCC carotenoid database for US foods–1998 (cited December 2006).
[3] http://www.heinz.co.uk (cited December 2006).
[4] http://www.leffingwell.com/lycopene.htm (cited December 2006).
[5] http://www.campbellsoup.com (cited December 2006).
[6] Mean ± SD (all such values).
[7] Not available.

FIGURE 2. Estimated lycopene intake in the high-tomato, lycopene-supplemented, and control groups. The box represents the 25th, 50th (median), and 75th percentiles; the ends of the whiskers represent the 5th and 95th percentiles.

None of the interventions significantly affected plasma concentrations of these compounds, except for α- and β-carotene, which decreased and increased slightly, respectively, but significantly in the high-tomato group compared with the control group (Table 3).

Plasma lipids, blood pressure, and arterial stiffness

Serum lipid concentrations, systolic blood pressure, diastolic blood pressure, and arterial stiffness—as measured by pulse wave velocity—were similar between the different groups at baseline and remained unchanged after the intervention (**Table 5**).

Oxidized LDL, inflammatory markers, and insulin sensitivity

Serum oxidized LDL, insulin, glucose, and inflammatory marker concentrations and insulin sensitivity were similar between groups at baseline. None of the treatments significantly affected highly sensitive C-reactive protein (hsCRP), IL-6, ICAM-1, or oxidized LDL. Glucose and insulin concentrations and markers of insulin resistance (HOMA-IR) and sensitivity (Quantitative Insulin-Sensitivity Check Index) also remained unchanged by the dietary interventions (**Table 6**).

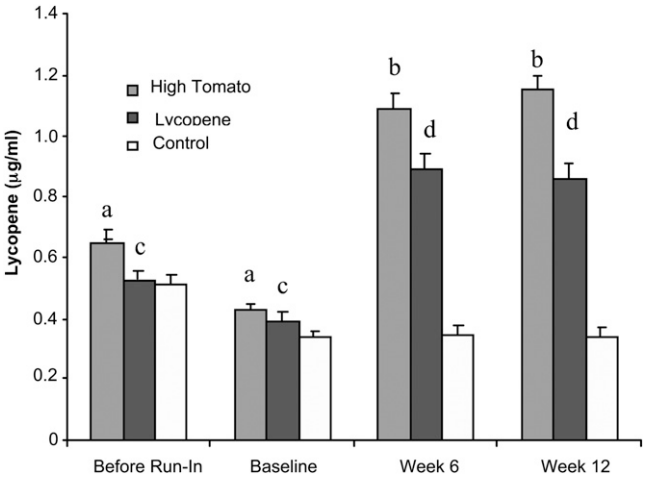

FIGURE 3. Effect of the dietary interventions on plasma lycopene concentrations. Data are means ± SEMs; $n = 81$, 68, and 76 for the high-tomato, lycopene-supplemented, and control groups, respectively. Differences between the dietary intervention groups before the run-in period, at baseline, and at 6 and 12 wk were assessed by using 2-factor ANOVA ($P < 0.05$). For within-group comparisons, values with different letters are significantly different, $P < 0.001$ (Bonferroni post hoc test).

DISCUSSION

None of the interventions affected any of the markers for CVD risk, which suggested that a nutritionally relevant daily intake of tomato-based foods does not decrease CVD risk in a middle-aged population. The lack of any observed effect did not result from poor compliance, which ranged from 88–95% to 75–92%, based on the weekly checklists, for each of the 12 wk in the high-tomato and control groups, respectively (data not shown). Good compliance was also confirmed by plasma lycopene concentrations, which increased by >2-fold as a result of the interventions. The plasma lycopene concentrations at the end of the intervention period in the high-tomato group are similar to concentrations observed in populations with a high lycopene intake (31). Two factors contributed to this finding: *1*) lycopene intakes in the high-tomato group tended to be above the minimum target of 70 mg/wk (median intakes between 80 and 113 mg/wk, based on the estimated lycopene content of foods obtained from manufacturers and composition databases), and *2*) the actual analysis of the tomato products indicated a greater lycopene content of tomato puree, tomato sauce, and soups than originally estimated from the limited data available from manufacturers and composition databases. Consequently, the high-tomato group actually consumed between 226 and 351 mg lycopene/wk: 3–5 times more than originally estimated. Unfortunately, logistical constraints precluded analysis of the lycopene content of the food items before the start of the trial. Plasma lycopene concentrations in the current trial are similar to those described in other studies in which volunteers consumed 210–280 mg lycopene/wk from tomato-based products (20, 32).

None of the interventions dramatically modified nutrient intake. However, the decrease in energy intake from baseline was

TABLE 5
Serum lipids, blood pressure, and arterial stiffness values, by intervention group[1]

	High tomato ($n = 81$)	Lycopene ($n = 68$)	Control ($n = 76$)	P^2	P^3
Cholesterol (mmol/L)					
Baseline	5.54 ± 0.10	5.57 ± 0.13	5.56 ± 0.11	0.981	
12 wk	5.47 ± 0.10	5.50 ± 0.13	5.63 ± 0.17		0.350
Triacylglycerol (mmol/L)					
Baseline	1.12 ± 0.06	1.12 ± 0.06	1.07 ± 0.07	0.820	
12 wk	1.17 ± 0.06	1.14 ± 0.06	1.13 ± 0.07		0.955
HDL cholesterol (mmol/L)					
Baseline	1.73 ± 0.06	1.67 ± 0.05	1.68 ± 0.05	0.679	
12 wk	1.69 ± 0.06	1.68 ± 0.06	1.70 ± 0.04		0.443
LDL cholesterol (mmol/L)					
Baseline	3.31 ± 0.09	3.39 ± 0.11	3.40 ± 0.10	0.782	
12 wk	3.25 ± 0.09	3.32 ± 0.11	3.43 ± 0.10		0.600
Apolipoprotein A-I (g/L)					
Baseline	1.71 ± 0.04	1.67 ± 0.04	1.67 ± 0.03	0.624	
12 wk	1.71 ± 0.03	1.70 ± 0.04	1.70 ± 0.03		0.595
Apolipoprotein B-100 (g/L)					
Baseline	0.98 ± 0.02	0.99 ± 0.03	0.98 ± 0.03	0.942	
12 wk	0.96 ± 0.02	0.97 ± 0.03	1.00 ± 0.03		0.554
SBP (mm Hg)					
Baseline	126.6 ± 1.6	127.9 ± 2.0	127.4 ± 1.9	0.516	
12 wk	127.3 ± 1.6	124.7 ± 3.0	127.1 ± 1.9		0.286
DBP (mm Hg)					
Baseline	76.6 ± 1.0	78.0 ± 1.2	77.0 ± 1.1	0.933	
12 wk	77.4 ± 0.9	77.0 ± 1.2	76.3 ± 1.1		0.227
Pulse wave velocity (m/s)					
Baseline	8.63 ± 0.20	8.43 ± 0.26	8.21 ± 0.26	0.817	
12 wk	9.11 ± 0.52	8.65 ± 0.25	8.18 ± 0.25		0.203

[1] All values are means ± SEMs. DBP, diastolic blood pressure; SBP, systolic blood pressure.
[2] Differences between groups at baseline were assessed by using 2-factor ANOVA.
[3] Differences in concentration changes from baseline between groups were assessed by using 2-factor ANOVA.

TABLE 6
Serum glucose and insulin concentrations, insulin sensitivity, hsCRP, IL-6, and oxidized LDL at baseline and after dietary intervention, by intervention group[1]

	High tomato (n = 81)	Lycopene (n = 68)	Control (n = 76)	P^2	P^3
Insulin (mU/L)					
Baseline	5.27 ± 0.49	5.78 ± 0.56	6.21 ± 0.59	0.467	
12 wk	4.84 ± 0.48	6.99 ± 0.99	5.88 ± 0.54		0.065
Glucose (mmol/L)					
Baseline	5.28 ± 0.06	5.28 ± 0.06	5.30 ± 0.07	0.961	
12 wk	5.25 ± 0.06	5.30 ± 0.07	5.27 ± 0.08		0.675
HOMA-IR					
Baseline	1.28 ± 0.13	1.39 ± 0.14	1.52 ± 0.16	0.490	
12 wk			1.41 ± 0.14		0.094
QUICKI					
Baseline	0.88 ± 0.04	0.82 ± 0.04	0.82 ± 0.04	0.354	
12 wk	0.92 ± 0.04	0.84 ± 0.04	0.84 ± 0.04		0.190
hsCRP (mg/L)					
Baseline	1.51 ± 0.24	2.27 ± 0.45	3.18 ± 0.70	0.056	
12 wk	1.37 ± 0.29	2.16 ± 0.40	2.08 ± 0.29		0.523
IL-6 (pg/L)					
Baseline	1.21 ± 0.09	1.44 ± 0.18	1.37 ± 0.12	0.452	
12 wk	1.15 ± 0.08	1.31 ± 0.16	1.38 ± 0.13		0.981
ICAM-1 (pg/L)					
Baseline	189.4 ± 6.7	203.3 ± 7.8	199.3 ± 6.2	0.337	
12 wk	200.1 ± 8.2	211.5 ± 6.9	207.9 ± 4.1		0.335
Ox-LDL (mmol/L)					
Baseline	72.3 ± 3.6	75.5 ± 3.6	71.0 ± 3.7	0.647	
12 wk	70.7 ± 3.5	75.3 ± 3.4	69.9 ± 3.6		0.923

[1] All values are means ± SEMs. hsCRP, highly sensitive C-reactive protein; ICAM-1, intercellular adhesion molecule 1; Ox, oxidized; QUICKI, Quantitative Insulin-Sensitivity Check Index.
[2] Differences at baseline were assessed by using 2-factor ANOVA. For insulin, hsCRP, and IL-6, 1-factor ANOVA was performed on log-transformed values.
[3] Differences in concentration changes at week 12 from baseline between the dietary intervention groups were assessed by using 2-factor ANOVA.

slightly greater in the high-tomato group than in the control group. Tomato soup was the most popular tomato-based food item eaten; however, it is not particularly energy dense (~59 kcal/100 g). Therefore, replacement of more energy-dense foods by tomato soup may have contributed to the observed decline in energy intake. However, this was not associated with weight loss, possibly reflecting a lack of precision of the dietary assessment method.

Calcium intake decreased significantly in the high-tomato group compared with the control group, which may be due to slight differences between groups in the intake of dairy products. Vitamin E intake increased significantly in the high-tomato group compared with both the lycopene-supplemented and control groups, which may reflect the presence of tocopherol-containing vegetable oils in some tomato-based products. The increase in vitamin E intake was not reflected by increases in plasma α-tocopherol concentrations, although this is not unexpected as plasma vitamin E concentrations do not change markedly over a range of dietary intakes (33).

The primary endpoints of the trial were serum total and LDL-cholesterol and sICAM-1 concentrations. Previous trials with tomato-based foods and/or lycopene supplements tended to be short and smaller than our trial. Serum lipid responses in such trials were conflicting. For example, daily consumption of tomato soup and canned tomatoes with olive oil (46 mg lycopene/d) for 7 d in 6 healthy adults resulted in a decrease in plasma triglycerides (34). Two other short-term studies also found reductions in plasma cholesterol; a high-tomato diet (27 mg lycopene/d) for 3 wk reduced total and LDL cholesterol by 5.9% and 12.9%, respectively (19), whereas daily consumption of 250 mL tomato juice (41.8 mg lycopene/d) for 2 wk in 24 young healthy adults reduced plasma cholesterol by 3% (21). However, these studies lacked control groups, which confounded the interpretation. In the current study, circulating lipid concentrations remained unchanged in both the high-tomato and lycopene-supplemented groups compared with the control group. These null findings agree with previous shorter-term studies that used similar or higher levels of lycopene (17, 35–38). In contrast, a study in 32 diabetic patients reported that consumption of 200 g fresh tomatoes/d for 8 wk significantly decreased systolic and diastolic blood pressures and increased serum apolipoprotein A-I concentrations (23). However, serum cholesterol and apolipoprotein B concentrations were unaffected, and the study lacked a control group.

Oxidized LDL concentrations remained unchanged after intervention. In 2 trials with Mediterranean diets, plasma oxidized LDL concentrations decreased after the intervention (39, 40), whereas lutein, and not lycopene, was suggested to be responsible for this effect (40). Plasma lutein concentrations remained unchanged after intervention in our study, which may explain the lack of effects.

Markers of endothelial dysfunction, such as arterial stiffness (measured by pulse wave velocity) and von Willebrand factor concentrations, were also unaffected by the interventions. This corroborates findings from a small intervention with tomato products on flow-mediated dilation, which remained unchanged by the treatments (41).

At baseline, the plasma lycopene concentration was inversely correlated with the sICAM-1 concentration, which supports findings from other studies (14, 42). Other tomato-based interventions focused on alternative markers of CVD risk, such as circulating concentrations of adhesion molecules and hsCRP. A study involving 103 overweight middle-aged adults indicated that consumption of 300 g tomatoes/d for 1 mo had no effect on E-selectin, sICAM-1, and hsCRP concentrations (43).

An independent inverse relation between serum lycopene concentration and arterial stiffness and C-reactive protein has been described (44); however, serum sICAM-1, hsCRP, and IL-6 concentrations remained unchanged in our study. Our results support the findings of a study involving 8 obese patients with abnormally high markers of inflammation, in which supplementation for 4 wk with 30 mg lycopene/d did not decrease plasma IL-6, hsCRP, and TNF-α concentrations (32). In contrast, one study reported a decrease of plasma hsCRP concentrations in 24 healthy young adults after 2 wk of intervention with 250 mL tomato juice/d (41.8 mg lycopene/d), although this study did not include a control group (35).

Observational studies have shown no association between intake of lycopene or lycopene-containing foods and the risk of type 2 diabetes (45) or glycated hemoglobin concentrations (46). Similarly, none of the interventions in the current trial influenced markers of insulin resistance.

Overall, our findings do not support potential health claims that increased lycopene and tomato intakes provide cardiovascular protection and do not justify, at least for the level of intake considered in this study, recommendations to increase tomato-based food intake as part of nutritional policies to combat CVD. However, other nondetermined markers, such as platelet activation, could have been modified by our interventions (47). Furthermore, the volunteers enrolled in this trial were perhaps too "healthy" to allow detection of significant changes in CVD risk markers. For example, the mean BMIs in men and women aged 45–54 and 55–64 y in Scotland in 2008 were 28.1 and 29.0, respectively, which is higher than the mean BMI in any of the intervention groups in this study (48). Enrolling volunteers with established elevated risk markers for CVD and/or with a higher BMI may have increased the probability of detecting changes. As discussed, only some, but not all, previous intervention studies carried out in obese individuals and/or patients with diabetes with lycopene/tomato-based products showed some beneficial effects. However, the benefit of lycopene in individuals at high risk of CVD remains to be proven in a well-designed, comprehensive intervention trial with lycopene/tomato-rich diets.

The authors' responsibilities were as follows—FT and GD: conceived and designed the study; AR and CT: recruited the volunteers, assigned the volunteers to treatment groups, obtained and collated the volunteers' dietary and clinical data, and administered the intervention under the supervision of FT; AR: performed the dietary data analysis, supervised by LFM; NV and AR: performed the biochemical analyses, supervised by FT, GD, JB, WGS, and SD; GWH, FT, and LFM: performed the statistical analyses; and FT: drafted the report. None of the authors had any conflicts of interest to report. CT, AR, and NV were employed on a grant from the Food Standards Agency.

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