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Paleolithic and Mediterranean Diet Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Balance in Adults[1–3]

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Abstract

Background: Chronic inflammation and oxidative balance are associated with poor diet quality and risk of cancer and other chronic diseases. A diet–inflammation/oxidative balance association may relate to evolutionary discordance.

Objective: We investigated associations between 2 diet pattern scores, the Paleolithic and the Mediterranean, and circulating concentrations of 2 related biomarkers, high-sensitivity C-reactive protein (hsCRP), an acute inflammatory protein, and F_2-isoprostane, a reliable marker of in vivo lipid peroxidation.

Methods: In a pooled cross-sectional study of 30- to 74-y-old men and women in an elective outpatient colonoscopy population (n = 646), we created diet scores from responses on Willett food-frequency questionnaires and measured plasma hsCRP and F_2-isoprostane concentrations by ELISA and gas chromatography–mass spectrometry, respectively. Both diet scores were calculated and categorized into quintiles, and their associations with biomarker concentrations were estimated with the use of general linear models to calculate and compare adjusted geometric means, and via unconditional ordinal logistic regression.

Results: There were statistically significant trends for decreasing geometric mean plasma hsCRP and F_2-isoprostane concentrations with increasing quintiles of the Paleolithic and Mediterranean diet scores. The multivariable-adjusted ORs comparing those in the highest with those in the lowest quintiles of the Paleolithic and Mediterranean diet scores were 0.61 (95% CI: 0.36, 1.05; P-trend = 0.06) and 0.71 (95% CI: 0.42, 1.20; P-trend = 0.01), respectively, for a higher hsCRP concentration, and 0.51 (95% CI: 0.27, 0.95; P-trend 0.01) and 0.39 (95% CI: 0.21, 0.73; P-trend = 0.01), respectively, for a higher F_2-isoprostane concentration.

Conclusion: These findings suggest that diets that are more Paleolithic- or Mediterranean-like may be associated with lower levels of systemic inflammation and oxidative stress in humans. *J Nutr* 2016;146:1217–26.

Keywords: inflammation, C-reactive protein, oxidative balance, F_2-isoprostanes, Paleolithic diet, Mediterranean diet, diet patterns, cross-sectional study

Introduction

Chronic inflammation is associated with many chronic diseases that have become increasingly common in the Western world (1). Reactive oxygen species can cause lipid peroxidation (2), a major result and indicator of oxidative stress (3), and oxidative stress can increase inflammation and vice versa (4). Both chronic inflammation and oxidative stress have been associated with cardiovascular disease (5, 6), cancer (7–10), and other chronic diseases (11). Several dietary factors influence a person's chronic inflammation level (12, 13). For example, a higher ratio of ω-6 to ω-3 FAs, a high intake of saturated fat or foods with a high glycemic load, and lower dietary fiber intake are associated with higher inflammation levels (12). Investigations into which foods alter systemic inflammation and oxidative balance led to several large clinical trials of nutritional supplementation to prevent

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[3] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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cardiovascular disease (14) and cancer (15, 16), most finding limited effects and even harm in some instances (17–20). Although there are many reasons why these trials might not have found the expected benefits, it may be that, at least in part, the nutritional supplements used in the trials cannot sufficiently address the relevant complex and likely interacting components of diet (21–23).

To better capture the potential synergistic effects of food constituents in a complex diet, nutrition researchers have used dietary patterns. Dietary patterns can be entirely data driven, decided entirely a priori, or a combination thereof, and they can be used to quantify a person's entire diet, rather than its individual components. One such pattern that is of increasing interest is a Paleolithic diet pattern. The Paleolithic diet of preagricultural hunter-gatherer humans was estimated from anthropologic evidence from fossils and extant hunter-gatherer groups (24). The diet pattern is characterized as a predominantly plant-food–based diet, with a wide diversity of fruits, nuts, and vegetables, and very little to no grains, dairy products, or sugar. It is also high in calcium and other minerals, which are found in relatively high amounts in various wild plant foods (24). The consequences of the discrepancies between the diets and lifestyles of *Homo sapiens* before the agricultural revolution and those during the modern, postindustrial revolution era are referred to as evolutionary discordance, and they have been proposed to account for some of the dramatic increase in chronic disease in the past century (25). To our knowledge, there has been very limited study of this diet reported in the scientific literature, with some indications that it may improve cardiovascular and metabolic biomarkers (26–32), perhaps similar to or even more so than a Mediterranean diet (28, 33). The Mediterranean diet is considered to be one of the healthiest diets for preventing many chronic diseases (34–36), and it is associated with lower concentrations of biomarkers of inflammation and oxidative stress (37–39). The Mediterranean diet is similar to the Paleolithic diet in that it emphasizes a high consumption of fruits, vegetables, and lean meats, with little added sugars; but, unlike a Paleolithic diet, it is characterized by a moderate intake of dairy, grains, and alcohol (40).

We previously reported an inverse association of Paleolithic and Mediterranean diet scores with incident sporadic colorectal adenoma (33). In this paper we present a cross-sectional analysis of data from another pooled elective, outpatient colonoscopy population, to *1*) investigate the association of a Paleolithic diet score with circulating markers of inflammation [high-sensitivity C-reactive protein (hsCRP)[9]] and oxidative stress (F_2-isoprostanes), and *2*) compare these findings with those from a parallel analysis of associations of a Mediterranean diet score with the same markers.

Methods

Study population and data collection. Data from 2 methodically similar studies, both cross-sectional studies of elective outpatient colonoscopy populations conducted by the same principal investigator (RMB), were pooled. The first study, Markers of Adenomatous Polyps I (MAPI), was conducted from 1994–1997 in Winston-Salem and Charlotte, North Carolina, and the second, Markers of Adenomatous Polyps II (MAPII), was conducted in 2002 in Columbia, South Carolina. Participants in the 2 studies were recruited from patients with no prior history of colorectal neoplasms who were scheduled for an elective outpatient colonoscopy for colorectal cancer screening or gastrointestinal symptoms in several large community-based gastroenterology practices. Initial eligibility for participation in both studies required that patients be 30–74 y old; English speaking; free of known genetic syndromes associated with a predisposition to colonic neoplasia; and with no individual history of inflammatory bowel disease, adenomatous polyps, or cancers except for nonmelanoma skin cancer.

In MAPI, 669 (30%) of the 2246 colonoscopy patients identified met these eligibility criteria; 617 (92%) were contacted, and 472 (76%) consented to participate. In MAPII, 305 (87%) of the 351 colonoscopy patients identified were eligible and 203 (67%) agreed to participate. We combined the 2 studies, because their selection criteria, study protocols, and questionnaires were nearly identical. Details of the study protocols for MAPI and MAPII were previously reported (41–46). An additional 33 participants were excluded from the present analyses because of implausibly low or high estimated total energy intake (<500 or >5000 kcal/d). The study protocols for both studies were approved by the respective institutional review boards of the corresponding institutions, and all participants provided informed consent.

Mailed questionnaires were completed at home and collected at the colonoscopy visit. Study participants provided detailed information on demographic characteristics, personal medical history, smoking history, usual physical activity (via a modified Paffenbarger questionnaire), anthropometric characteristics, reproductive history and hormone use (women only), and family history of cancer. Frequency of aspirin and other nonsteroidal anti-inflammatory drug (NSAID) use were assessed as the number of pills taken per week. A 153-item (MAPI) or 85-item (MAPII) self-administered semiquantitative Willett FFQ was completed before colonoscopy to assess food and nutritional supplement intake over the previous 12 mo. A standard portion size and 9 possible frequency-of-consumption responses, ranging from "never, or less than once per month" to "6 or more times per day" were given for each item. Total daily energy and nutrient intake was calculated by summing energy and nutrients from all food sources with the use of the dietary database developed by Willett (47, 48).

On the day of the colonoscopy, fasting peripheral venous blood samples were drawn into red-coated, prechilled tubes and then immediately placed on ice and shielded from light to prevent sample degradation. Blood fractions were portioned into amber-colored cryopreservation tubes, air was displaced with an inert gas (nitrogen in MAPI and argon in MAPII), and then the aliquots were placed immediately in a −80°C freezer until analysis. The present study was conducted after most of the stored plasma samples were exhausted from prior studies; samples for hsCRP were available on 87% (n = 558) of the eligible participants, and samples for F_2-isoprostanes were available on 67.6% (n = 434) of eligible participants; the analyses reported herein are based on these sample sizes (**Figure 1**).

hsCRP was measured via latex-enhanced immunonephelometry on a Behring nephelometer II analyzer (interassay CV: 4%; Behering Diagnostics). F_2-isoprostanes were measured via a highly specific and quantitative gas chromatography–mass spectrometry method (49) by the Molecular Epidemiology and Biomarker Research Laboratory at the University of Minnesota. This method, considered to be the gold standard for measuring F_2-isoprostanes, measures a well-defined set of F_2-isoprostane isomers. These were extracted from participants' samples with the use of deuterium-labeled (4) 8-iso-prostaglandin $F_2\alpha$ as an internal standard. Quality control procedures included the analysis of 2 control pools that had varying concentration ranges of F_2-isoprostanes (CV: 9.5% and 11%, respectively).

Dietary scores. The Paleolithic and Mediterranean diet pattern scores were constructed as described previously (33). Briefly, for each score, each study participant was assigned a quintile rank (and score from 1–5) of intake for each score component (Paleolithic diet score—14 components; Mediterranean diet score—11 components), based on the sex-specific distributions in each original study population. For the most part, higher points were given for a higher intake of foods considered to be characteristic of a given score or for low to no consumption of foods considered to be uncharacteristic of that dietary pattern (**Table 1**). For

[9] Abbreviations used: hsCRP, high-sensitivity C-reactive protein; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; NSAID, nonsteroidal anti-inflammatory drug.

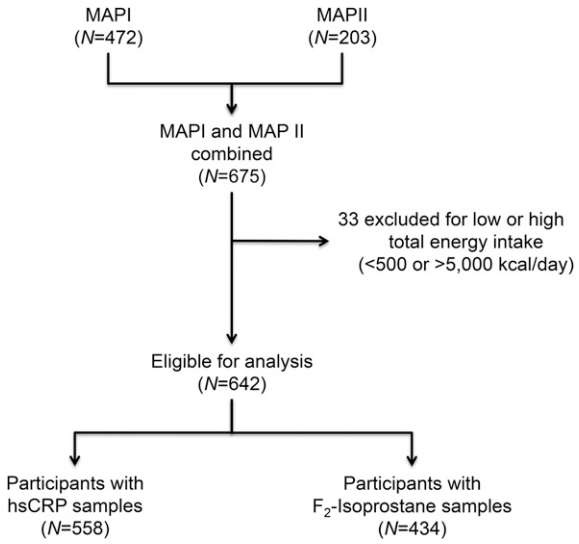

FIGURE 1 Inclusion criteria and sample availability, pooled MAPI and MAPII studies. hsCRP, high-senstivity C-reactive protein; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II.

the Mediterranean diet, this scheme was modified in relation to dairy, grains and starches, and alcohol intake, as noted in Table 1. For the Paleolithic diet score, 2 unique variables were created. The first, a fruit and vegetable diversity score, was created by summing the total number of responses on the fruit and vegetable sections of the FFQ that indicated that the participant had eaten >1–3 servings of a given food item/mo. More diversity was considered desirable. Second, because the Paleolithic diet had little dairy but high amounts of calcium (from wild plant foods) (24), to consider dietary calcium separately from dairy products, we used the residuals of a linear regression of total (i.e., dietary plus supplemental) calcium on total dairy intake to represent calcium intake independent of dairy consumption. The points for each food component were then summed to create the final diet pattern score. The final scores could range from 14–70 for the 14-component Paleolithic diet score and 11–55 for the 11-component Mediterranean diet score.

Statistical analysis. The characteristics of the study population, by quintile of each diet pattern score, were summarized and compared by using chi-square tests for categorical variables and for continuous variables following a normal distribution, or the Kruskal-Wallis nonparametric test for continuous variables that did not follow a normal distribution. Because the distributions of hsCRP and F_2-isoprostanes were right skewed, their values were transformed by ln, and then the adjusted geometric means ± SEs by quintile of each dietary pattern were computed by using a general linear model (implemented with the use of the SAS GLM procedure), controlling for potential confounding by other factors. Correlations between the 2 scores were assessed with the use of a Spearman correlation coefficient. To facilitate interpretation and comparisons between the relative strengths of the diet pattern–biomarker associations, ordinal logistic regression analysis also was used, in which hsCRP and F_2-isoprostane concentrations were categorized into quintiles based on the sex-specific concentrations in the pooled study population. The multivariable unconditional ordinal logistic regression models were used to calculate ORs and 95% CIs for associations of each dietary score with each sex-specific quintile

TABLE 1 Paleolithic and Mediterranean diet score constituents and point assignments[1]

Intake category	Scoring	Paleolithic diet score[2]	Mediterranean diet score[3]
Higher intake best	Points assigned = quintile rank	Vegetables	Vegetables
		Fruits	Fruits
		Lean meats[4]	Lean meats[4]
		Fish	Fish
		Nuts	Nuts
		Fruit and vegetable diversity[5]	Monounsaturated:saturated fat ratio
		Calcium[6]	
Lower intake best	Points assigned = reverse quintile rank	Red and processed meats[7]	Red and processed meats[7]
		Sodium (milligrams)	Sodium (milligrams)
		Dairy	
		Grain and starches[8]	
		Baked goods[9]	
		Sugar-sweetened beverages	
		Alcohol	
Moderate intake best	Quintile 3 scored +5		Dairy
	Quintiles 2 and 4 scored +3		Grains and starches[8]
	Quintiles 1 and 5 scored +1 points		
Other			Alcohol:
			Women: 5–15 g/d (+5 points)
			Men: 10–25 g/d (+5 points)
			Otherwise (+1 point)

[1] All constituents measured in servings per week unless otherwise indicated.
[2] Fourteen components; range of possible scores 14–70.
[3] Eleven components; range of possible scores 11–55.
[4] Includes skinless chicken or turkey, lean beef.
[5] Total number of types of fruits and vegetables someone ate >1–3 times/mo.
[6] Intake from sources other than dairy; calculated as residuals from linear regression of total (i.e., dietary plus supplemental) calcium intake (milligrams per day) on dairy food intake.
[7] Nitrate-processed meats and nonlean red meat (including pork) consumption together.
[8] Includes items such as breads, rice, and white potatoes.
[9] Includes items such as cake, pie, and other pastry-type food.

increase in each biomarker. The median of each diet score quintile was used for calculating all tests for trend.

Based on previous literature and biological plausibility, potential confounding variables considered included the study (MAPI or MAPII), regular NSAID or aspirin use (≥4 times/wk), age, total energy intake, hormone replacement use (in women), sex, current smoking status, BMI, education, physical activity, regular multivitamin use, season of the year the questionnaire was filled out, race, and family history of colon cancer in a first-degree relative. Inclusion in the final models required ≥1 of the following criteria: biological plausibility, statistical significance, and/or whether inclusion/exclusion of the variable from the model changed the adjusted OR for the primary exposure variable by ≥10%. The final adjusted models controlled for study (MAPI or MAPII), regular NSAID or aspirin use (≥4 times/wk), age, total energy intake (kilocalories; continuous), regular hormone replacement use (in women), sex, smoking (current or former/never), BMI (in kg/m^2; categorized by WHO criteria into normal/underweight, overweight, and obese), education (no college education or some college education), physical activity (high or low based on the study population median weekly metabolic equivalent task–hour per week expenditure from moderate and vigorous activities), regular multivitamin use (≥3 times/wk), and the season of the year the questionnaire was filled out.

To assess potential effect measure modification, separate analyses were conducted within dichotomous categories (as defined above) of smoking (current or former/never), BMI (underweight/normal or overweight/obese), sex, NSAID and aspirin use (regular or nonregular users), multivitamin use (regular or nonregular users), physical activity (higher or lower than the pooled study population's median of 195.5 metabolic equivalent task–h/wk), age (younger or older than the pooled study population's median age of 56.9 y), and education (any college or no college).

To assess the sensitivity of the observed associations to how we defined the scores, each food component was removed from each a priori score one at a time to determine whether any one component substantially influenced the diet score–biomarker associations. Diet scores also were constructed with the use of medians rather than quintiles for the food groups, and an alternative calculation of the fat ratio variable (mono- plus polyunsaturated fat:saturated fat) was used for the Mediterranean diet score. The presence of colon or rectal adenomas in this study population was also assessed as a potential confounder and an effect measure modifier. All analyses were conducted with the use of SAS statistical software, version 9.3). Two-sided tests were considered to be statistically significant at $P \leq 0.05$.

TABLE 2 Selected characteristics of participants, pooled MAPI and MAPII studies, Paleolithic diet score[1]

	Paleolithic diet score						
	Quintile 1		Quintile 3		Quintile 5		
Characteristics	Mean ± SD	*n* (%)	Mean ± SD	*n* (%)	Mean ± SD	*n* (%)	*P*[2]
Plasma hsCRP,[3,4] μg/mL	6.0 ± 6.5		5.3 ± 6.3		4.7 ± 6.2		0.72
Plasma F_2-isoprostanes,[3,4] ng/L	90.0 ± 34.0		89.3 ± 40.8		74.8 ± 28.8		0.01
Prevalent colorectal adenoma[4]		47 (21.0)		40 (17.9)		43 (19.2)	0.70
Age,[3] y	54.5 ± 9.4		56.1 ± 8.9		60.4 ± 7.9		<0.01
Male		76 (24.0)		63 (19.9)		62 (19.6)	0.15
White		121 (21.1)		116 (20.2)		118 (20.6)	0.11
Current smoker[4]		47 (30.1)		29 (18.6)		18 (11.5)	<0.01
Physical activity,[3] MET-h/wk	340 ± 638		537 ± 923		672 ± 1030		0.08
BMI,[4] kg/m^2							
Normal and underweight (<25)		44 (20.5)		43 (20.0)		45 (20.9)	
Overweight (25–29.9)		43 (19.0)		43 (19.0)		54 (23.9)	
Obese (≥30)		44 (22.9)		40 (20.8)		30 (15.6)	0.49
Current ethanol intake,[4] g/d							
<14		110 (19.2)		113 (19.7)		119 (20.8)	
14–28		14 (33.3)		8 (19.1)		8 (19.1)	
>28		6 (23.1)		7 (26.9)		2 (7.7)	0.41
Taking NSAID or aspirin, ≥4 times/wk		56 (20.2)		51 (18.4)		64 (23.1)	0.55
Bachelor's degree or higher[4]		21 (12.8)		35 (21.3)		45 (27.4)	0.01
Hormone replacement therapy (women)		24 (14.3)		32 (19.1)		44 (26.2)	0.08
Total energy intake, kcal/d	2074 ± 709		1800 ± 782		1808 ± 619		0.01
Total calcium intake,[5] mg/d	776 ± 415		763 ± 415		940 ± 483		<0.01
Dietary fiber, g/d	18.0 ± 7.6		19.5 ± 9.5		26.2 ± 11.1		<0.01
Total fat intake, g/d	80.0 ± 33.1		66.4 ± 32.3		55.5 ± 21.2		<0.01
ω-3:ω-6 FA ratio	0.1 ± 0.1		0.1 ± 0.1		0.3 ± 0.2		<0.01
Total red and processed meat intake, servings/d	1.0 ± 0.9		0.7 ± 0.8		0.5 ± 0.5		<0.01
Total vegetable intake, servings/d	1.8 ± 1.6		2.6 ± 2.8		4.3 ± 3.0		<0.01
Carbohydrates, en%	50.1 ± 8.5		49.4 ± 9.6		53.7 ± 9.0		<0.01
Protein, en%	14.7 ± 2.8		16.8 ± 3.4		19.1 ± 2.2		<0.01
Fat, en%	35.2 ± 7.5		33.9 ± 8.1		27.2 ± 7.8		<0.01

[1] *n* = 646. en%, percentage of energy; hsCRP, high-sensitivity C-reactive protein; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; MET-h, metabolic equivalent task-hours; NSAID, nonsteroidal anti-inflammatory drug.
[2] Calculated by using chi-square tests for categorical variables and ANOVA for continuous variables, unless otherwise noted.
[3] *P* values calculated by using Kruskal-Wallis nonparametric test.
[4] Missing data: plasma hsCRP (*n* = 84), plasma F_2-isoprostane (*n* = 209), prevalent colorectal adenoma (*n* = 48), age (*n* = 57), smoking status (*n* = 15), BMI (*n* = 9), current ethanol intake (*n* = 1), and education level (*n* = 4).
[5] Dietary plus supplemental.

Results

Selected characteristics of the participants by diet score quintile are summarized in **Table 2** (Paleolithic diet score) and **Table 3** (Mediterranean diet score). Compared with those in the lowest quintile of the Paleolithic diet score, those in the highest quintile on average were older; were less likely to smoke; were more likely to have a bachelor's degree or higher; and consumed less total energy, more calcium (mainly via supplements), more dietary fiber and vegetables, more ω-3 FAs per gram of ω-6 FAs, and less fat and red and processed meat. The descriptive comparisons for the Mediterranean diet score were similar to those for the Paleolithic diet score. The Paleolithic diet score ranged from 25 to 62, whereas the Mediterranean diet score ranged from 14 to 48; the mean score for each diet pattern did not differ appreciably between the 2 original study populations. Also, the score ranges did not differ appreciably by sex, and the correlation between the scores was linear ($\rho = 0.72$, $P = 0.01$). For each quintile of the Paleolithic diet score, the percentages of participants who were in the same or different quintiles of the Mediterranean diet score are shown in **Table 4**. Among those in the lowest and highest quintiles of the Paleolithic diet score, 62.6% and 55.8%, respectively, were in the corresponding quintile of the Mediterranean diet score.

The multivariable-adjusted geometric means of serum hsCRP and F_2-isoprostanes for each quintile of each dietary pattern score are presented in **Table 5**. For each diet pattern, there was a pattern of decreasing hsCRP and F_2-isoprostane concentrations with increasing diet score quintile. For those in the highest compared with the lowest quintile of the Paleolithic and Mediterranean diet scores, the geometric mean hsCRP concentrations were proportionately 31% and 19% lower, respectively, and the geometric mean F_2-isoprostane concentrations were proportionately 11% and 16% lower, respectively. The *P*-trend was statistically significant for each biomarker for each diet pattern.

For additional perspective, the overall associations of the diet scores with each serum biomarker from the ordinal logistic regression analyses are presented in Table 5. In the multivariable-adjusted analyses, all tests for trend, except for the

TABLE 3 Selected characteristics of participants, pooled MAPI and MAPII studies, Mediterranean diet score[1]

	Mediterranean diet score						
	Quintile 1		Quintile 3		Quintile 5		
Characteristics	Mean ± SD	*n* (%)	Mean ± SD	*n* (%)	Mean ± SD	*n* (%)	*P*[2]
Plasma hsCRP,[3,4] μg/mL	5.4 ± 5.4		5.3 ± 5.9		4.8 ± 6.1		0.37
Plasma F_2-isoprostanes,[3,4] ng/L	101.1 ± 43.7		88.6 ± 65.7		79.6 ± 44.6		<0.01
Prevalent colorectal adenoma[4]		58 (25.9)		54 (24.1)		41 (18.3)	0.65
Age,[3] y	55.2 ± 9.4		56.5 ± 8.7		57.9 ± 8.1		0.10
Male		81 (25.6)		69 (21.2)		66 (20.3)	0.68
White		138 (24.1)		119 (20.8)		109 (19.0)	0.26
Current smoker[4]		50 (32.1)		30 (19.2)		21 (13.5)	0.15
Physical activity,[3] MET-h/wk	424 ± 753		573 ± 951		505 ± 891		0.48
BMI,[4] kg/m^2							
Normal/underweight (<25)		48 (22.3)		47 (21.9)		40 (18.6)	
Overweight (25–29.9)		47 (20.8)		52 (23.0)		45 (19.9)	
Obese (≥30)		58 (30.2)		40 (20.8)		31 (16.2)	0.65
Current ethanol intake,[4] g/d							
<14		144 (25.1)		122 (21.3)		105 (18.3)	
14–28		7 (16.7)		10 (23.8)		9 (21.4)	
>28		4 (15.4)		8 (30.8)		4 (15.4)	0.86
Taking NSAID or aspirin ≥4 times/wk		66 (23.8)		56 (20.2)		47 (17.0)	0.02
Bachelor's degree or higher[4]		22 (13.4)		37 (22.6)		46 (28.1)	<0.01
Hormone replacement therapy (women)		36 (21.4)		33 (19.6)		40 (23.8)	0.34
Total energy intake, kcal/d	1794 ± 717		2003 ± 780		1986 ± 596		0.04
Total calcium intake,[5] mg/d	781 ± 440		786 ± 396		923 ± 441		0.03
Dietary fiber, g/d	16.5 ± 8.1		21.3 ± 9.2		27.1 ± 10.8		<0.01
Total fat intake, g/d	69.7 ± 32.4		71.3 ± 34.9		63.0 ± 24.8		0.20
ω-3:ω-6 FA ratio	0.1 ± 0.1		0.2 ± 0.1		0.2 ± 0.2		<0.01
Total red and processed meat intake, servings/d	0.9 ± 0.9		0.9 ± 0.9		0.5 ± 0.5		<0.01
Total vegetable intake, servings/d	2.0 ± 1.8		2.9 ± 2.7		4.0 ± 3.2		<0.01
Carbohydrates, en%	49.5 ± 9.6		50.6 ± 8.9		53.6 ± 8.6		<0.01
Protein, en%	14.7 ± 2.8		16.8 ± 3.4		19.1 ± 2.2		<0.01
Fat, en%	35.0 ± 8.2		32.3 ± 7.9		28.4 ± 8.2		<0.01

[1] *n* = 646. en%, percentage of energy; hsCRP, high-sensitivity C-reactive protein; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; MET-h, metabolic equivalent task-hours; NSAID, nonsteroidal anti-inflammatory drug.
[2] Calculated by using chi-square tests for categorical variables and ANOVA for continuous variables unless otherwise noted.
[3] *P* values calculated by using Kruskal-Wallis nonparametric test.
[4] Missing data: plasma hsCRP (*n* = 84), plasma F_2-isoprostane (*n* = 209), prevalent colorectal adenoma (*n* = 48), age (*n* = 57), smoking status (*n* = 15), BMI (*n* = 9), current ethanol intake (*n* = 1), education level (*n* = 4).
[5] Dietary plus supplemental.

TABLE 4 Study participants who were in the same and different quintiles of the Mediterranean diet score for each quintile of the Paleolithic diet score; pooled MAPI and MAPII studies[1]

	Paleolithic diet score quintile				
	1	2	3	4	5
Mediterranean diet score quintile					
1	82 (62.6)	41 (29.5)	23 (18.0)	7 (6.1)	2 (1.6)
2	29 (22.1)	41 (29.5)	22 (17.2)	14 (12.2)	4 (3.1)
3	17 (13.0)	42 (30.2)	40 (31.3)	31 (27.0)	11 (8.5)
4	3 (2.3)	13 (9.4)	25 (19.5)	37 (32.2)	40 (31.0)
5	0 (0.0)	2 (1.4)	18 (14.1)	26 (22.6)	72 (55.8)
Total	131 (100)	139 (100)	128 (100)	115 (100)	129 (100)

[1] Values are *n* (%) of participants in each quintile of the Paleolithic diet score, by quintile of the Mediterranean diet score. MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II.

association of the Paleolithic diet score hsCRP, were statistically significant. For those in the upper compared with those in the lowest quintile of the Paleolithic and Mediterranean diet scores, there was an estimated 37% and 29% lower odds, respectively, of having a higher plasma hsCRP concentration and an estimated 49% and 61% lower odds, respectively, of having a higher plasma F_2-isoprostane concentration.

The results of analyses of the diet–biomarker associations stratified by age, sex, education, current smoking status, current NSAID/aspirin use, and physical activity are summarized in **Figures 2** and **3** (see **Supplemental Table 1** for all exact geometric means). The inverse associations of the Paleolithic diet score with hsCRP concentrations tended to be stronger in participants who were current smokers, overweight/obese, or less physically active, or who did not attend college. For the Mediterranean diet score and hsCRP, the inverse association was stronger in those who did not attend college (*P*-interaction = 0.02). The inverse associations of the Paleolithic diet with F_2-isoprostane concentrations tended to be stronger in those who were female, younger (*P*-interaction = 0.04), or current smokers, or those with some college education (*P*-interaction = 0.03); whereas for the Mediterranean diet score, the inverse association was stronger in those who were female or younger, or had low physical activity levels or some college education (no statistically significant tests for multiplicative interaction).

In the sensitivity analyses in which each component of each dietary score was removed individually to determine its influence on the observed associations, no single component substantially altered the associations between the diet scores and concentrations of either biomarker. Yet, removing some components that most clearly define the differences between the 2 scores (e.g., grain, dairy, fruit, and vegetable diversity) did lessen the differences between the associations of the 2 scores with F_2-isoprostanes (data not shown). Combining all red meats, separating all red meats from processed meats, and awarding points for more consumption of all red meats and for less consumption of processed meats did not alter the observed associations materially. There were also no appreciable differences in diet–biomarker associations between those found to have colorectal adenomas at their colonoscopy and those who did not, and including adenomas as a covariate in the models did not appreciably alter the estimated associations.

TABLE 5 Associations of Paleolithic and Mediterranean diet scores with plasma concentrations of hsCRP and F_2-isoprostanes; pooled MAPI and MAPII studies[1]

	Paleolithic diet score					Mediterranean diet score				
	n	Adjusted geometric mean[2] (95% CI)	*P*-trend[3]	Adjusted OR[4] (95% CI)	*P*-trend[3]	*n*	Adjusted geometric mean[2] (95% CI)	*P*-trend[3]	Adjusted OR[4] (95% CI)	*P*-trend[3]
hsCRP, μg/mL										
Quintiles of diet score										
1	110	3.9 (3.2, 4.7)		1.00		122	3.6 (3.0, 4.3)		1.00	
2	102	3.3 (2.7, 4.0)		0.97 (0.59, 1.60)		85	3.5 (2.8, 4.3)		0.86 (0.52, 1.43)	
3	96	3.4 (2.8, 4.2)		0.96 (0.58, 1.61)		112	3.5 (2.9, 4.3)		1.01 (0.62, 1.63)	
4	92	3.0 (2.4, 3.7)		0.79 (0.47, 1.34)		84	2.7 (2.1, 3.3)		0.61 (0.36, 1.02)	
5	94	2.7 (2.2, 3.3)	0.05	0.61 (0.36, 1.05)	0.06	91	2.9 (2.3, 3.5)	0.02	0.71 (0.42, 1.20)	0.01
F_2-isoprostanes, ng/L										
Quintiles of diet score										
1	83	88.3 (81.5, 95.7)		1.00		87	92.6 (85.7, 100.1)		1.00	
2	85	90.5 (83.8, 97.7)		1.09 (0.62, 1.91)		64	81.1 (74.2, 88.5)		0.53 (0.29, 0.96)	
3	67	85.7 (78.7, 93.4)		0.87 (0.48, 1.59)		94	85.7 (79.6, 92.2)		0.65 (0.37, 1.14)	
4	73	79.8 (73.6, 86.5)		0.53 (0.29, 0.95)		64	85.1 (77.9, 92.9)		0.63 (0.34, 1.15)	
5	72	78.5 (72.0, 85.5)	<0.01	0.51 (0.27, 0.95)	0.01	71	77.5 (71.1, 84.4)	<0.01	0.39 (0.21, 0.73)	0.01

[1] There were unequal sample sizes in quintiles because of ranking ties. Differences in the numbers of participants having the 2 biomarker assays were related to serum sample availability. hsCRP, high-sensitivity C-reactive protein; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; NSAID, nonsteroidal anti-inflammatory drug.

[2] From general linear model; covariates included study (MAPI or MAPII), regular NSAID or aspirin use (≥4 times/wk), age, total energy intake (kilocalories), current hormone replacement use (in women), sex, smoking (current or former and never), BMI (in kg/m^2; categorized by WHO criteria into underweight, normal, overweight, and obese), education level (no college education or some college education), physical activity level (high or low based on the median weekly metabolic equivalent task–h/wk expenditure in the pooled population), regular multivitamin use (≥3 times/wk), and season of the year the FFQ was completed.

[3] Calculated by assigning the median of each diet score quintile to each quintile, and treating this quintile exposure as continuous.

[4] From unconditional ordinal logistic regression model; covariates adjusted for were the same as in footnote 2. hsCRP and F_2-isoprostanes are categorized into sex-specific quintiles from the pooled study population. For each diet score quintile, e^{β} is the odds that the biomarker concentration is greater than the quintile cutoff if the diet score is in the nonreferent category compared with the odds if it is in the referent category.

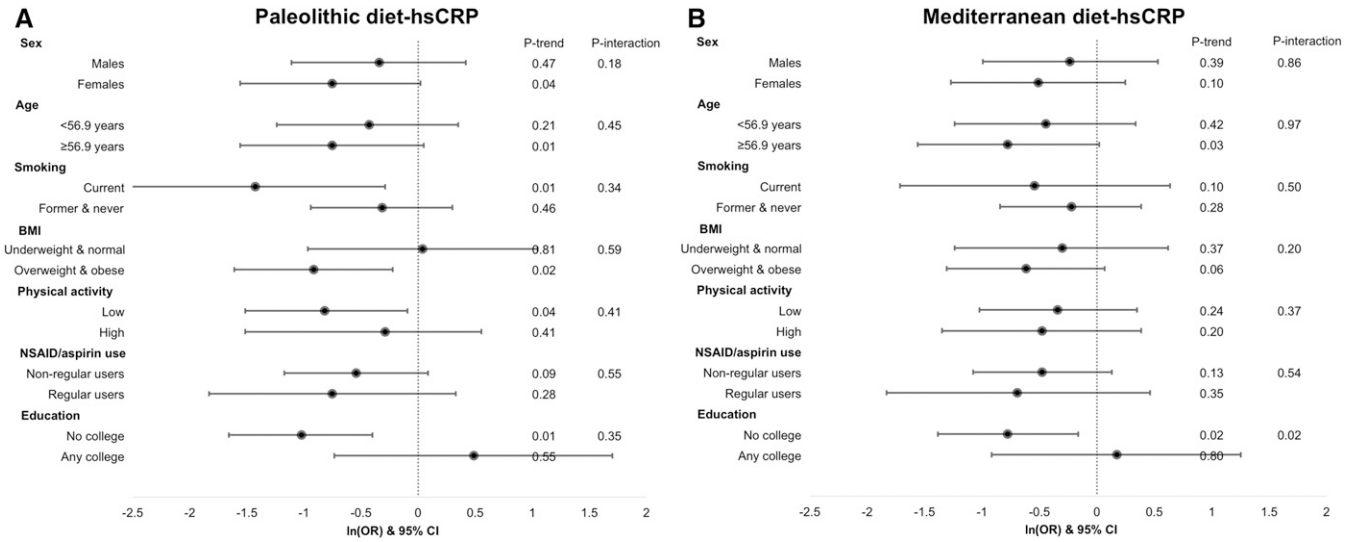

FIGURE 2 Associations of the Paleolithic (A) and Mediterranean (B) diet scores with plasma hsCRP concentrations, according to selected participant characteristics; pooled MAPI and MAPII studies. From an unconditional ordinal logistic regression model; only the comparison of quintile 5 relative to quintile 1 of each diet score with the sex-specific quintiles of the biomarkers is shown. Model covariates included study (MAPI or MAPII), regular NSAID or aspirin use (≥4 times/wk), age, total energy intake (kilocalories), current hormone replacement use (in women), sex, smoking (current or former and never), BMI (in kg/m^2; categorized by WHO criteria into underweight, normal, overweight, and obese), education level (no college education or some college education), physical activity level (high or low based on the median weekly metabolic equivalent task–h/wk expenditure in the pooled population), regular multivitamin use (≥3 times/wk), and season of the year the FFQ was completed. hsCRP is categorized into sex-specific quintiles from the pooled study population. *P*-trend was calculated by assigning the median of each diet score quintile to each quintile, and treating this quintile exposure as continuous. For each quintile of each diet score, e^{β} is the odds that the biomarker concentration is greater than the quintile cutoff if the diet score is in the nonreferent category compared with the odds if it is in the referent category. hsCRP, high-sensitivity C-reactive protein; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; NSAID, nonsteroidal anti-inflammatory drug.

Discussion

Our results suggest that diets that are more Paleolithic- or Mediterranean-like may be associated with lower levels of systemic inflammation and oxidative stress. Although the 2 diet patterns are similar in some but not all respects, and the overlap in how persons in this study were categorized was only moderate, the associations of the 2 diet patterns with the markers of inflammation and oxidative stress were quite similar. Our results also suggest that the Paleolithic diet–biomarker associations may be stronger in those who smoke, and that for either diet score, the association with F_2-isoprostanes may be stronger in those who are younger. Although there were other differences across subgroups, they were not consistent across diets or biomarkers.

Both the Paleolithic and Mediterranean diet patterns have elements that may reduce chronic inflammation or improve oxidative balance. Both are high in fruits, vegetables, fish, and nuts; have more antioxidant and fewer pro-oxidant nutrients, a more favorable ω-6:ω-3 FA ratio, and a lower glycemic load; and are less energy dense than a Western diet [likely leading to an improved energy balance (12, 13)], all of which are thought to improve systemic inflammation and oxidative balance. Research into other dietary patterns would tend to support these mechanisms. Diets that are meat-based or Western-like tend to be associated directly with inflammation biomarker concentrations, whereas produce-based, or "healthy" diet patterns are usually inversely associated with them (13, 37, 50, 51). Studies of other diets that are similar to the produce-based diets also found inverse associations with systemic inflammation biomarker concentrations; other such diets included those with a low glycemic load (52) or high fiber (53), those that replaced SFAs with PUFAs (54), and low-carbohydrate diets (55, 56). More comprehensive diet patterns, such as a healthy Nordic diet (57) and the Dietary Approaches to Stop Hypertension diet, were also associated with lower concentrations of inflammation biomarkers and improved oxidative balance (58–63), and may share underlying mechanisms with the 2 dietary patterns examined in this paper.

To our knowledge, there are few reported studies of a Paleolithic diet pattern in relation to biomarkers of disease risk. Six small pilot trials that examined the effects of a Paleolithic diet on cardiovascular disease risk and glycemic control biomarkers, such as glycated hemoglobin, plasma insulin, blood pressure, and serum TGs and cholesterol (26–31), generally observed improvements in these markers, although only 3 of these pilot trials had a control group (27–29). A slightly larger study (n = 70) of the effects of a Paleolithic diet on long-term weight loss found statistically significant greater weight loss at 6 mo in the Paleolithic diet group than in the control group, although the difference mostly dissipated after 24 mo (32). Maintenance of a more normal body weight may be one way a Paleolithic diet may maintain lower levels of inflammation and oxidative stress. However, because we controlled for BMI in our models, our findings suggest that a Paleolithic diet may also reduce inflammation and oxidative stress via other mechanisms. In further, although indirect, support of the inverse associations found in the present study of the 2 diet pattern scores with inflammation and oxidative stress levels, in part because colorectal neoplasms are thought to be associated with inflammation and oxidative stress (45, 46, 64–66), we previously investigated associations of the 2 diet pattern scores with incident, sporadic colorectal adenoma in a case-control study in a different population from that reported herein (33). In that

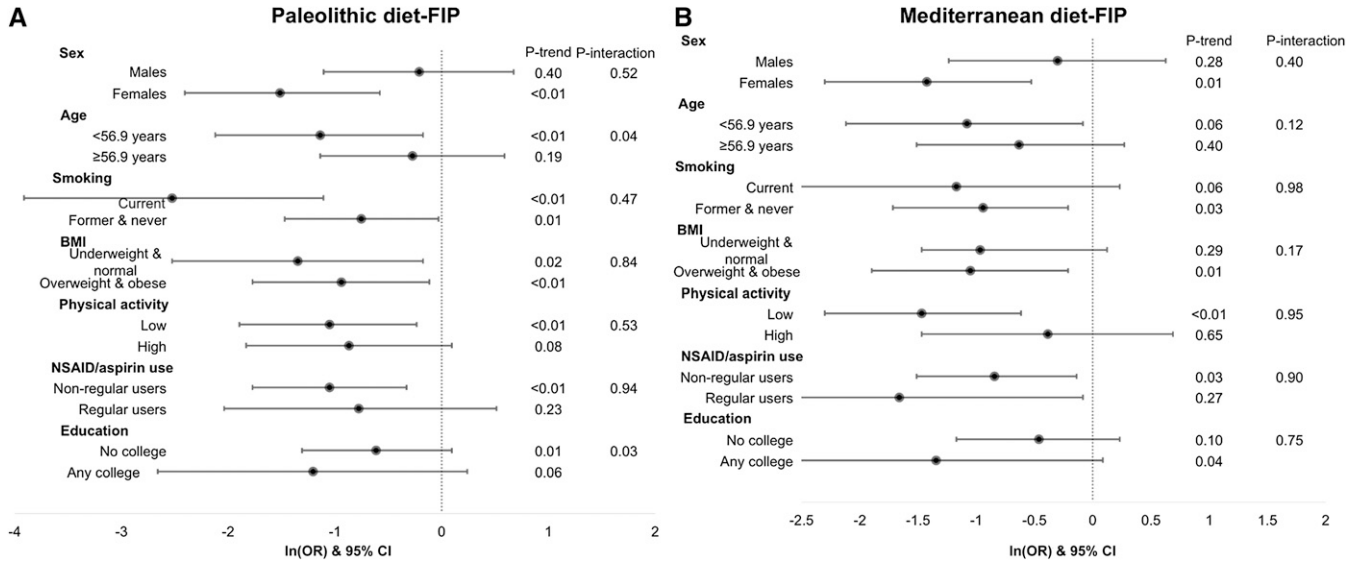

FIGURE 3 Associations of the Paleolithic (A) and Mediterranean (B) diet scores with FIP concentrations, according to selected participant characteristics; pooled MAPI and MAPII studies. From an unconditional ordinal logistic regression model; only the comparison of quintile 5 relative to quintile 1 of each diet score with the sex-specific quintiles of the biomarkers is shown. Model covariates included study (MAPI or MAPII), regular NSAID or aspirin use (≥4 times/wk), age, total energy intake (kilocalories), current hormone replacement use (in women), sex, smoking (current or former and never), BMI (in kg/m^2; categorized by WHO criteria into underweight, normal, overweight, and obese), education level (no college education or some college education), physical activity level (high or low based on the median weekly metabolic task equivalent–h/wk expenditure in the pooled population), regular multivitamin use (≥3 times/wk), and season of the year the FFQ was completed. FIPs are categorized into sex-specific quintiles from the pooled study population. *P*-trend was calculated by assigning the median of each diet score quintile to each quintile, and treating this quintile exposure as continuous. For each quintile of each diet score, e^{β} is the odds that the biomarker concentration is greater than the quintile cutoff if the diet score is in the nonreferent category compared with the odds if it is in the referent category. FIP, F_2-isoprostane; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; NSAID, nonsteroidal anti-inflammatory drug.

study we found that both diets were similarly inversely associated with adenoma (33).

The Mediterranean diet was associated with lower circulating concentrations of biomarkers of inflammation and oxidative stress in several prior studies. This diet generally has been more strongly inversely associated with hsCRP than have other healthy diet patterns reported in the literature (37), and greater adherence to a Mediterranean diet pattern also has been associated with lower F_2-isoprostane concentrations, as well as with other biomarkers of lipid peroxidation (38). In the Prevención con Dieta Mediterránea substudy (n = 110) of participants with metabolic syndrome, those randomly assigned to a Mediterranean diet supplemented with either olive oil or nuts were estimated to have an almost 50% greater reduction in mean F_2-isoprostane concentrations (P = 0.06) than did those in the comparison diet arm after 1 y (39). The results of the current study support these previously published findings.

Unlike most diet patterns, for which stronger inverse associations for a wide range of outcomes are usually observed for men but not women (22), we found the Paleolithic and Mediterranean diet patterns to be more strongly inversely associated with the biomarkers—especially F_2-isoprostanes—in women. However, the tests for interaction mostly were not statistically significant, and our sex-specific findings may be due to the sex-specific diet scoring procedure we used, which allowed for different consumption patterns across the sexes.

This study has several strengths and limitations. Strengths include that, to our knowledge, it is the first investigation of associations of a Paleolithic diet pattern with biomarkers of inflammation or oxidative stress. The Paleolithic and the Mediterranean diet patterns were constructed with the use of similar methods, so differences in the findings for the 2 diets would be attributable to the differences in the dietary patterns, rather than to the mechanics of how the scores were constructed. Limitations include the fact that participants' diets were not perfectly consistent with the ideal of either pattern; however, this likely yielded more modest inverse associations with hsCRP and F_2-isoprostanes than would be expected with stronger adherence, and it suggests that even moderate adherence to one of the diet patterns may be associated with lower levels of inflammation and oxidative balance. Other limitations include the study's cross-sectional design, the known limitations of assessing diet with self-reported semiquantitative FFQs (47, 67), and the limited number of biomarkers to characterize inflammation and oxidative balance. The 2 original studies that were pooled for the present analysis used different versions of the Willett FFQ; however, within each study, the diet pattern components and scores were similarly highly correlated. Last, individuals undergoing elective outpatient colonoscopy may not be representative of the general US population.

In conclusion, our findings, taken together with those from previous studies, suggest that diets that are more Paleolithic- or Mediterranean-like may be associated with lower levels of systemic inflammation and oxidative stress in humans.

Acknowledgments

KAW, MLM, WDF, TJH, SJ, and RMB designed the research; KAW analyzed the data; KAW and RMB wrote the paper; and KAW and RMB had primary responsibility for the final content. All authors read and approved the final manuscript.

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