Comparison of 4 established DASH diet indexes: examining associations of index scores and colorectal cancer^{1–3}

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ABSTRACT

Background: Multiple diet indexes have been developed to capture the Dietary Approaches to Stop Hypertension (DASH) dietary pattern and examine relations with health outcomes but have not been compared within the same study population to our knowledge.

Objective: We compared 4 established DASH indexes and examined associations with colorectal cancer.

Design: Scores were generated from a food-frequency questionnaire in the NIH-AARP Diet and Health Study (n = 491,841). Separate indexes defined by Dixon (7 food groups, saturated fat, and alcohol), Mellen (9 nutrients), Fung (7 food groups and sodium), and Günther (8 food groups) were used. HRs and 95% CIs for colorectal cancer were generated by using Cox proportional hazard models.

Results: From 1995 through 2006, 6752 incident colorectal cancer cases were ascertained. In men, higher scores were associated with reduced colorectal cancer incidence by comparing highest to lowest quintiles for all indexes as follows: Dixon (HR: 0.77; 95% CI: 0.69, 0.87), Mellen (HR: 0.78; 95% CI: 0.71, 0.86), Fung (HR: 0.75; 95% CI: 0.68, 0.83), and Günther (HR: 0.81; 95% CI: 0.74, 0.90). Higher scores in women were inversely associated with colorectal cancer incidence by using methods defined by Mellen (HR: 0.79; 95% CI: 0.68, 0.91), Fung (HR: 0.84; 95% CI: 0.73, 0.96), and Günther (HR: 0.84; 95% CI: 0.73.0.97) but not Dixon (HR: 1.01; 95% CI: 0.80, 1.28).

Conclusion: The consistency in findings, particularly in men, suggests that all indexes capture an underlying construct inherent in the DASH dietary pattern, although the specific index used can affect results. *Am J Clin Nutr* 2013;98:794–803.

INTRODUCTION

Epidemiologic studies have traditionally assessed effects of single nutrients, foods, and other individual dietary constituents on cancer risk. Research that has used this approach is valuable for understanding potential biological mechanisms that underlie observed associations, but it has been limited by the multi-collinearity of dietary intake variables and the inability to detect small effects of single dietary components (1). The investigation of dietary patterns or overall diet quality is a promising complementary approach to help overcome some of these limitations (1–4) and provide useful information for developing guidelines and public health recommendations. National and international cancer organizations have recommend a largely plant-based dietary pattern that is rich in fruits, vegetables, whole grains, and legumes and low in red and processed meat, refined grains,

added sugar, and energy density for cancer prevention (5). The 2010 Dietary Guidelines for Americans also provided similar recommendations based on dietary patterns, with the addition of low-fat dairy products, to promote health and reduce risk of chronic disease, including cancer. This guidance has suggested 2 eating patterns, the USDA Food Patterns and the Dietary Approaches to Stop Hypertension (DASH)⁴ Eating Plan, the latter of which aligns with the DASH diet that was examined in 2 multicenter, randomized controlled feeding trials (6, 7).

The first DASH trial showed that a diet rich in fruit, vegetables, and low-fat dairy products and reduced in saturated and total fat (labeled the DASH diet) significantly reduced blood pressure (6). A follow-up trial, entitled the DASH-Sodium Trial, showed that a reduction of sodium intake in conjunction with the original DASH diet further reduced blood pressure (7). This sodiumreduced DASH diet represents an overall dietary pattern because it aims to encompass the whole diet, including combinations of foods and nutrients consumed together. Although this dietary pattern was originally designed to reduce hypertension and cardiovascular disease risk, it may have relevance to colorectal cancer prevention, particularly because several of its characteristics, such as high fruit and vegetable intake and reduced intake of meat, have been implicated in the cause of this malignancy. Associations between an adherence to a DASH dietary pattern, assessed by scores on DASH diet indexes, and different endpoints, such as diabetes (8), coronary heart disease (9), colorectal adenoma (10), and colorectal cancer (11), have been evaluated previously. However, these earlier studies have operationalized

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⁴ Abbreviations used: DASH, Dietary Approaches to Stop Hypertension; FFQ, food-frequency questionnaire; MPED, MyPyramid Equivalents Database.

the DASH dietary pattern into indexes by using considerably different approaches. Therefore, the purpose of the current study was to compare scores of 4 established DASH diet indexes that were identified from the literature (9, 10, 12, 13) and examine associations with colorectal cancer incidence.

SUBJECTS AND METHODS

Study population

Details of the NIH-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study have been described previously (14). In brief, 3.5 million self-administered questionnaires were sent to AARP members, who were aged 50-71 y and resided in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI) in 1995-1996. Of the 566,399 AARP members who successfully completed the baseline questionnaire and consented to be in the study, respondents were excluded if they were proxies for intended respondents (n = 15,760), had prevalent cancer except nonmelanoma skin cancer (n = 51,223), had end-stage renal disease at baseline (n = 997), or had a cancer cause of death record but no cancer registry data (n = 2143). In addition, 4435 participants were excluded because of extreme energy intakes, which were defined as 2 times the interquartile range of sexspecific Box-Cox log-transformed intake of total energy. The final analytic cohort consisted of 293,248 men and 198,593 women. The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and informed consent was obtained from all participants.

Cohort follow-up and cancer ascertainment

Cohort members were followed from enrollment in 1995-1996 through the end of 2006. Changes of address were identified through linkage to the US Postal Service's National Change of Address database (a commercial address-change database; https://ribbs.usps.gov/index.cfm?page=ncoalink), the processing of undeliverable mail, other address-change services, or direct communication from the participants. Incident colorectal cancer cases were identified through probabilistic linkage with cancer registries in the states and metropolitan areas from which the cohort was recruited. The cancer-ascertainment area was expanded by adding the cancer registries of Arizona, Nevada, and Texas, which were 3 states where participants tended to move during follow-up. An earlier validation study in the NIH-AARP Diet and Health Study reported that >90% of all cancers were ascertained (15). Annual linkage of the cohort to the US Social Security Administration Death Master File, follow-up searches of the National Death Index, cancer registry linkage, questionnaire responses, and responses to other mailings were used to obtain vital status.

Colorectal cancer endpoints were defined by anatomic site and histologic code of the International Classification of Diseases for Oncology (16), including codes C180–C189, C199, C209, and C260. For subsite-specific analyses, colorectal cancers were classified as colon (C180–187) and rectum (C199 and C209) cancers. Only first primary invasive colorectal cancer diagnoses were included. For this analysis, there were 4552 colorectal cancer cases in men and 2200 colorectal cancer cases in women.

Exposure assessment

At baseline, study participants completed a self-administered questionnaire, with questions about demographic characteristics, current body height and weight, medical history, family history of cancer, and lifestyle factors, including the frequency of vigorous physical activity that lasted ≥ 20 min, menopausal hormone therapy use, and current and past smoking.

Dietary intakes were assessed at baseline by using a self-administered 124-item semiquantitative food-frequency questionnaire (FFQ), which was an early version of the Diet History Questionnaire, a validated FFQ developed at the National Cancer Institute (17, 18). Respondents were queried about their usual frequency of intake and portion size over the past 12 mo and asked to select from 10 frequency categories that ranged from never to ≥ 2 times/d for each solid food and 9 frequency categories that ranged from never to ≥ 6 times/d for each beverage. Three foodand beverage-specific portion sizes were available for each question. The food items, portion sizes, and nutrient database for this FFQ were constructed by using the USDA 1994-1995 Continuing Survey of Food Intakes by Individuals (19). FFQ data were merged with both the USDA's Pyramid Servings Database (20) and MyPyramid Equivalents Database (MPED) (21) to be consistent with previously used methods from earlier studies that created DASH diet indexes (9, 10, 12, 13). Food mixtures were disaggregated into their component ingredients, which were assigned to their respective individual food groups and composite food groups as defined by the Pyramid Servings Database and MPED. DASH index scores were generated on the basis of predefined algorithms for each of the 4 previously described indexes. Although nutrient intakes from dietary supplements were captured by the FFQ, only nutrient intakes from food were used to generate index scores to be consistent with the methods used in the established indexes. Scoring standards and points for use in these algorithms are shown in Table 1. An additional index (22) was developed and used in a study of women and did not contain criteria and standards for men; therefore, the index was excluded from our current analysis.

Dixon's DASH diet index

The DASH index created by Dixon et al (10) assesses adherence to the DASH Eating Plan shown in the 2005 Dietary Guidelines for Americans (23). This index is comprised of 8 food group components and one nutrient component, each of which is worth 1 point. To generate intake estimates for different food groups, we used the Pyramid Servings Database (20) because this database was used by Dixon et al (10) to create the first DASH diet index. The index rewards 1 point for meeting, and 0 points for not meeting, the minimum recommended number of servings for fruit, which includes fruit juice (≥ 4 servings/d for men and women), vegetables, which includes potatoes (≥ 4 servings/d for men and \geq 3 servings/d for women), whole grains [\geq 4.7 servings/d for men and ≥ 4 servings/d for women on the basis of Dietary Guidelines recommendation for most grain servings to be whole, which Dixon et al (10) defined as 67%], total dairy (≥ 2 servings/d for men and women), and nuts, seeds, and legumes (\geq 4 servings/wk for men and ≥ 3 servings/wk for women). Remaining components

TABLE 1

Standards for maximum scores on each DASH diet index¹

	Standards for maximum score						
	Dixon's DASH index ²	Mellen's DASH index ³	Fung's DASH index ⁴	Günther's DASH index ^{5,6}			
Individual components	Sex-specific (men/women)	Same standards for men and women	Sex-specific	Standards based on sex, age, and activity level			
Dietary components for which greater							
intakes receive higher scores							
Total fruit	\geq 4 servings/d ⁷	—	Fifth quintile	\geq 4 servings/d ⁷			
Total vegetables	$\geq 4/\geq 3$ servings/d ^{7,8}	—	—	\geq 4 servings/d ⁷			
Vegetables without potatoes	—	—	Fifth quintile				
Total grains		_	_	$\geq 6 \text{ servings/d}^7$			
Whole grains	\geq 4.7/ \geq 4 servings/d ^{7,8}	_	Fifth quintile	_			
High-fiber grains	—	—	—	≥50% of total grain servings/d ^{7,9}			
Total dairy products	$\geq 2 \text{ servings/d}^7$	_	_	$\geq 2 \text{ servings/d}^7$			
Low-fat dairy products	_	—	Fifth quintile	\geq 75% of total dairy servings/d ^{7,9}			
Nuts, seeds, legumes	$\geq 4/\geq 3$ servings/d ⁷	_	Fifth quintile	$\geq 4 \text{ servings/wk}^7$			
Protein		$\geq 18\%$ of total daily kcal		_			
Fiber	_	\geq 14.8 g/1000 kcal per day	_	_			
Magnesium	_	\geq 238 mg/1000 kcal per day	_	_			
Calcium	_	\geq 590 mg/1000 kcal per day	_	_			
Potassium	_	\geq 2238 mg/1000 kcal per day	_	_			
Dietary components for which lower		8					
intakes receive higher scores							
Meat/meat equivalents	$<6 \text{ oz } (170 \text{ g})/\text{d}^7$	_	_	_			
Meat, poultry, fish, eggs	_	_	_	$\leq 2 \text{ servings/d}^7$			
Red and processed meat	_	_	First quintile	_			
Sugar-sweetened beverages	_	_	First quintile	_			
Sweets	_	_		\leq 5 servings/wk ⁷			
Fats, oils	_	_	_	$\leq 3 \text{ servings/d}^7$			
Added sugar	$\leq 3\%$ of total daily kcal	_	_	_			
Alcoholic beverages	$\leq 2/\leq 1$ drink/d ⁷	_	_	_			
Total fat	_	$\leq 27\%$ of total daily kcal	_	_			
Saturated fat	\leq 5% of total daily kcal	$\leq 6\%$ of total daily kcal	_	_			
Cholesterol		\leq 71.4 mg/1000 kcal per day	_	_			
Sodium	_	\leq 1143 mg/1000 kcal per day	1st quintile	_			
Total score (points)	0–9	0–9	8-40	0-80			

¹DASH, Dietary Approaches to Stop Hypertension.

²Participants receive 1 point for meeting and zero points for not meeting the recommendation; standards were sex-specific.

³ Participants receive 1 point for meeting a target, 0.5 points for meeting an intermediate target, and 0 points for meeting neither target; standards were the same for men and women.

⁴ For recommended components, the highest quintile receives 5 points, and the lowest quintile receives 1 point; for components for which lower intakes are desirable, the lowest quintile of intake receives 5 points and the highest quintile of intake receives 1 point. Quintiles were sex-specific.

⁵ Standards shown are based on recommendations for a 2000-kcal diet; different standards are available for 3 other energy intakes (1600, 2300, and 3100 kcal) on the basis of age, sex, and physical activity level.

⁶Components are scored from 0 to 10, with the exception of whole grains, high-fiber grains, total dairy, and low-fat dairy, which are scored from 0 to 5.

⁷Values are based on the Pyramid Servings database (20).

⁸ A total of 4.7 servings for men and 4 servings for women were based on the Dietary Guidelines recommendation for most grains to be whole, which Dixon et al (10) defined as 67%.

⁹ If servings of total grains or total dairy were zero, components of high-fiber grains or low-fat dairy products, respectively, would receive a score of 0 points.

are reverse coded, in that men and women receive 1 point if their meat and meat equivalent intake is ≤ 6 oz (170 g)/d, added sugar intake is $\leq 3\%$ of total energy intake, and saturated fat intake is $\leq 5\%$ of total energy intake. Men and women receive 1 point if their intake of alcoholic beverages is ≤ 2 drinks/d or ≤ 1 drink/d, respectively. Recommendations for cutoff values are based on sex-specific energy intakes of 2000 kcal/d for men and 1600 kcal/d for women. The total score is a summation of the 9 components, with a minimum total score of 0 points and a maximum total score of 9 points.

Mellen's DASH diet index

Mellen et al (13) developed an entirely nutrient-based DASH diet index on the basis of target nutrient values from the DASH

diet used in 2 clinical trials (6, 7). The 9 nutrients are those expected to be higher (ie, protein, fiber, magnesium, calcium, and potassium) or lower (ie, total fat, saturated fat, sodium, and cholesterol) with greater adherence to the DASH diet. This method uses absolute targets on the basis of a 2100-cal diet for both men and women. Individuals who meet the goal for each component receive 1 point, those who meet an intermediate goal [defined as the midpoint between the DASH diet goal and the nutrient content of the DASH control diet (6] receive one-half of a point, and those who meet neither goal receive 0 points. Micronutrient targets are indexed to total energy (per 1000 kcal) as follows: ≥ 14.8 g for fiber, ≥ 238 mg for magnesium, ≥ 590 mg for calcium, \geq 2238 mg for potassium, \leq 71.4 mg for cholesterol, and ≤1143 mg for sodium. Goals for macronutrient intakes are as a percentage of total energy intakes as follows: $\geq 18\%$ for protein, $\leq 27\%$ for total fat, and $\leq 6\%$ for saturated fat. The total score is generated by summing all nutrient components for a minimum of 0 and a maximum of 9 points.

Fung's DASH diet index

The DASH diet index developed by Fung et al (9) is comprised of 8 components (7 food groups and one nutrient) on the basis of foods and nutrients emphasized or minimized in the DASH diet according to the eating guide developed by the National Heart, Lung and Blood Institute (24). The scoring system is based on quintile rankings; for intakes of fruit (includes fruit juice), vegetables (excludes potatoes), low-fat dairy products, whole grains, and nuts, seeds, and legumes, individuals receive a score from 1 (lowest quintile) to 5 (highest quintile). In contrast, individuals receive a score from 1 (highest quintile) to 5 (lowest quintile) for intakes of sodium, sugar-sweetened beverages, and red and processed meat. Because Fung et al (9) created a DASH diet index in the Nurses' Health Study, they used the foodcomposition database linked with the Nurses' Health Study to generate food group intake estimates in servings per day and sodium in milligrams per day. Comparable food-group intakes were generated by using the MPED (21), which was linked to our FFQ, with the exception of red and processed meat, because the MPED provides lean meat equivalents but not total red and processed meat, and sugar-sweetened beverages. The red and processed meat variable was created by summing gram intakes of all types of beef, pork, and lamb, including bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, and steak; the variable also included gram intakes of meats added to complex food mixtures (eg, chili, lasagna, pizza, and stew). In the method of Fung et al (9), sugar-sweetened beverages include sugar-sweetened fruit drinks and sodas; therefore, gram intakes of these beverages were summed to create the sugar-sweetened beverage component. Men and women are classified into quintiles separately. Component scores are summed to a total DASH score that ranges from a minimum of 8 to a maximum of 40 points.

Günther's DASH diet index

Günther et al (12) designed a food-based DASH diet index with 10 components that assess adherence to the DASH Eating Plan in the 2005 Dietary Guidelines for Americans (23). Target intakes for each component are based on recommendations for 4 different energy intake (1600, 2000, 2300, and 3100 kcal/d) that

account for age, sex, and activity level defined by Dietary Reference Intakes (25). Six components are on a 10-point scale [fruit (includes fruit juice); vegetables (includes potatoes); meat, poultry, fish, and eggs; nuts, seeds, and legumes; fats and oils; and sweets] and 4 components are on a 5-point scale (total grains, high-fiber grains, total dairy products, and low-fat dairy products). For components in which higher intakes are desirable in the DASH Eating Plan (ie, fruit; vegetables; nuts, seeds, and legumes; total grains, high-fiber grains; total dairy; and low-fat dairy), individuals receive the maximum score if their intakes meet the recommendation. Lower intakes are scored proportionally, with a minimum score of 0 for no servings/d (or 0 servings/wk of nuts, seeds, and legumes). Individuals also receive the minimum score of 0 for high-fiber grains and low-fat dairy products if their intakes account for none of their intakes of total grains or total dairy products, respectively. If servings of total grains or total dairy were zero, the components of highfiber grains or low-fat dairy products, respectively, would receive a score of 0 points. Remaining components are reverse coded; individuals receive a maximum score of 10 if their intakes of sweets, fats and oils, and meat, poultry, fish, and eggs are at or below the target for each energy intake and a minimum score of zero if intakes are $\geq 200\%$ of the upper recommended amount for each energy intake. Intakes between minimum and maximum amounts are scored proportionally. Although Günther et al (12) used the Nutrition Data System for Research (database 3, version 4.05/33, 2002; University of Minnesota) for foodgroup intakes, we generated comparable food groups by using the Pyramid Serving Database (http://www.ars.usda.gov/Services/ docs.htm?docid=8634), the MPED, and gram intakes of select food items (ie, low-fat dairy and total dairy). Component scores are summed to a total DASH score that ranges from a minimum of 0o to a maximum of 80 points.

Statistical analysis

Cox proportional hazards regression models, with personyears as the underlying time metric, were used to determine HRs and 95% CIs for colorectal cancer for each of the 4 indexes stratified by sex. For these analyses, DASH scores for Mellen's, Fung's, and Günther's indexes were categorized into distribution-based quintiles, with the lowest quintile serving as the referent category. Score categories ≤ 1 (referent category), 2, 3, and ≥ 4 were selected for Dixon's DASH index because the index was on a 9-point scale with only whole numbers and a limited range of values. Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of a cancer diagnosis, death, move out of the registry areas (only 5% of the cohort, which preserved a high level of retention within the cohort), or end of follow-up (31 December 2006), whichever came first. The proportional hazard assumption was verified by modeling an interaction term of time with total DASH scores for each index. Additional models were used to examine subsite-specific associations for colon and rectal cancers. Heterogeneity across subsites (colon compared with rectum) was evaluated by calculating the weighted average of the 2 β coefficients from the Cox proportional hazards model, with weights proportional to the inverse of the variances and performing Wald's test.

Additional analyses were conducted to examine independent associations between individual components of each DASH index and colorectal cancer risk. Separate Cox proportional hazards regression models were performed for each component (component *i*), with adjustment for a modified DASH score that did not include the respective component as follows:

Modified DASH score = total DASH score – component
$$i$$
 (1)

All multivariable models were adjusted for the following a priori-determined covariates: age at entry (y), alcohol intake (g/d), BMI (in kg/m²), education (less than high school, high school, some college, or college graduate), ethnicity (non-Hispanic white; non-Hispanic black; Hispanic; Asian, Pacific Islander, American Indian, or Alaskan Native; or unknown), physical activity (≥ 20 min of moderate to vigorous physical activity reported rarely or never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, or ≥ 5 times/wk) (26), smoking (never, former, or current smoker), total energy intake (kcal/d), and, in the case of women, menopausal hormone therapy (never, former, or current). Missing values were included in the model as dummy variables. In addition, Spearman's correlation coefficients were calculated to compare total scores on the 4 indexes. All statistical tests were 2 sided and considered statistically significant at P < 0.05; analyses were conducted with SAS software (version 9.1.3; SAS Institute).

RESULTS

Baseline characteristics across categories of total DASH scores for each of the 4 indexes are shown in **Table 2**. In men, participants in the top category of scores across all indexes were more likely to be physically active, be a college graduate or postgraduate, never have smoked, be slightly leaner, and have lower intakes of alcohol. Women in the top category of total DASH scores across all indexes were more likely to be physically active, never have smoked, and have lower intakes of

TABLE 2

Baseline characteristics by category or quintiles of DASH diet index scores for men and women in the NIH-AARP Diet and Health Study¹

	Dixon's DASH index		Mellen's DASH index		Fung's DASH index		Günther's DASH index	
	<1 point	\geq 4 points	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5
Men $(n = 293, 248)$								
Median score	1	4	1	5.5	19	30	21.4	43.0
Colorectal cancer cases	569	726	900	876	971	778	987	793
Person-years	8.9 ± 0.02^2	9.0 ± 0.01	8.9 ± 0.01	9.0 ± 0.01	8.9 ± 0.01	9.0 ± 0.01	8.9 ± 0.01	9.0 ± 0.01
Age at entry (y)	61.5 ± 0.03	62.5 ± 0.02	61.7 ± 0.02	62.6 ± 0.02	61.1 ± 0.02	62.8 ± 0.02	61.3 ± 0.02	62.8 ± 0.02
BMI (kg/m ²)	27.5 ± 0.03	27.0 ± 0.02	27.7 ± 0.02	26.6 ± 0.02	$27.4~\pm~0.02$	26.8 ± 0.02	27.4 ± 0.02	26.6 ± 0.02
Total energy (kcal/d)	2267 ± 4.3	2357 ± 3.8	2334 ± 4.1	1747 ± 2.8	1947 ± 3.7	2161 ± 3.4	1884 ± 3.0	2061 ± 3.6
Physical activity, ≥ 5 times/wk (%)	17.2	30.1	15.9	30.2	13.4	31.8	13.5	32.3
Education, college graduate or postgraduate (%)	43.6	47.3	36.7	51.9	34.1	52.5	36.3	52.4
Non-Hispanic white (%)	94.4	91.0	92.6	92.3	91.0	93.2	92.3	92.3
Smoking (%)								
Never smoker	20.8	35.0	26.7	33.0	23.4	34.7	24.0	34.0
Former smoker	55.8	53.6	49.7	57.5	50.1	56.1	50.8	56.3
Current smoker	19.7	7.2	19.7	5.5	22.3	5.4	21.2	5.8
Unknown	3.7	4.1	3.9	4.1	4.1	3.8	4.0	3.9
Alcohol (g/d)	42.4 ± 0.26	11.5 ± 0.16	14.6 ± 0.11	10.9 ± 0.11	22.8 ± 0.23	11.7 ± 0.11	20.6 ± 0.20	13.2 ± 0.12
Women $(n = 198,593)$								
Median score	1	4	1.5	6.5	19	30	21.3	41.0
Colorectal cancer cases	97	510	496	343	563	453	491	430
Person-years	9.3 ± 0.03	9.4 ± 0.01	9.3 ± 0.01	9.4 ± 0.01	9.3 ± 0.01	9.4 ± 0.01	9.3 ± 0.01	9.4 ± 0.01
Age at entry (y)	61.5 ± 0.06	62.1 ± 0.02	61.4 ± 0.03	62.4 ± 0.03	61.1 ± 0.03	62.4 ± 0.03	61.4 ± 0.03	62.3 ± 0.03
BMI (kg/m ²)	25.7 ± 0.06	26.7 ± 0.03	27.7 ± 0.03	25.8 ± 0.03	27.2 ± 0.03	26.2 ± 0.03	27.4 ± 0.03	25.9 ± 0.03
Total energy (kcal/d)	1563 ± 6.4	1931 ± 3.2	1792 ± 3.8	1389 ± 3.0	1422 ± 2.9	1777 ± 3.2	1304 ± 2.3	1799 ± 4.1
Physical activity, ≥ 5 times/wk (%)	13.5	22.3	10.1	25.3	9.5	24.7	8.6	24.8
Education, college graduate or postgraduate (%)	33.0	31.9	23.1	37.2	22.1	36.5	23.9	36.0
Non-Hispanic white (%) Smoking (%)	93.0	86.5	88.7	90.3	87.3	89.8	89.4	88.4
Never smoker	26.7	49.8	41.1	45.8	38.9	48.2	37.7	48.7
Former smoker	42.1	35.3	31.3	41.3	31.0	39.5	33.2	37.9
Current smoker	27.7	11.0	24.2	9.2	26.5	8.8	25.5	9.7
Unknown	3.4	3.9	3.4	3.9	3.7	3.6	3.6	3.7
Alcohol (g/d)	25.5 ± 0.25	3.4 ± 0.07	6.1 ± 0.07	3.4 ± 0.04	7.4 ± 0.10	4.2 ± 0.05	7.7 ± 0.11	4.4 ± 0.06
Menopausal hormone users (%)	8.8	9.2	8.8	8.9	8.7	9.4	8.7	9.3

^{*I*} Dixon's DASH index scores were grouped into 4 categories [≤ 1 (n = 30,511), 2 (n = 122,048), 3 (n = 71,067), and ≥ 4 (n = 48,008) points] because of a limited range of values. DASH, Dietary Approaches to Stop Hypertension.

²Mean \pm SE (all such values).

Spearman's correlation coefficients in summary scores for the 4 DASH diet indexes in men and women¹

	Dixon's DASH index		Mellen's DASH index		Fung's DASH index		Günther's DASH index	
	Men	Women	Men	Women	Men	Women	Men	Women
Dixon's DASH index	_	_	0.42	0.37	0.56	0.55	0.51	0.53
Mellen's DASH index	—	—	—	—	0.60	0.61	0.51	0.47
Fung's DASH index	—	_	—	—	—	_	0.75	0.71
Günther's DASH index	—	—	—	—	—	—	_	—

¹ All P < 0.0001. DASH, Dietary Approaches to Stop Hypertension.

alcohol. Women with higher scores on Mellen's, Fung's, and Günther's DASH indexes, but not Dixon's DASH index, tended to be leaner and to be a college graduate or postgraduate. As expected, energy intake was greater in men and women with higher scores on all indexes, with the exception of Mellen's DASH index because it is energy adjusted.

Correlations between total scores for each DASH index are shown in **Table 3**. Correlation coefficients ranged from 0.42 to 0.75 in men and from 0.37 to 0.71 in women (P < 0.0001 for all. Strongest correlations were between Fung's and Günther's indexes (r = 0.75 for men and r = 0.71 for women), whereas weakest correlations were between Dixon's and Mellen's DASH indexes (r = 0.42 for men and r = 0.37 for women).

Results of the Cox proportional hazards regression analyses for total DASH scores and colorectal cancer incidence are shown in **Table 4**. Higher scores were associated with a reduction of colorectal cancer risk of similar magnitude highest to lowest categories or quintiles for all indexes in men were compared [Dixon's HR: 0.77 (95% CI: 0.69, 0.87); Mellen's HR: 0.78 (95% CI: 0.71, 0.86); Fung's HR: 0.75 (95% CI: 0.68, 0.83); and Günther's HR: 0.81 (95% CI: 0.74, 0.90)]. On additional investigation by subsite, risks remained significantly reduced for both colon and rectal cancer for all indexes, with no statistical evidence of heterogeneity between subsites (*P*-heterogeneity > 0.05 for all comparisons). In women, higher scores on Mellen's (HR: 0.79; 95% CI: 0.68, 0.91), Fung's (HR: 0.84; 95% CI:

TABLE 4

Multivariable-adjusted HRs (95% CIs) for colorectal cancer in men and women by category or quintiles of DASH diet index scores¹

	Category 1	Category 2	Category 3	Category 4	
	or quintile 1	or quintile 2	or quintile 3	or quintile 4	Quintile 5
Men					
Colorectal cancer					
Dixon's DASH index	1.00 (referent)	0.90 (0.82, 0.99)	0.84 (0.76, 0.92)	0.77 (0.69, 0.87)	_
Mellen's DASH index	1.00 (referent)	0.89 (0.81, 0.98)	0.87 (0.79, 0.95)	0.79 (0.71, 0.87)	0.78 (0.71, 0.86)
Fung's DASH index	1.00 (referent)	0.88 (0.81, 0.96)	0.85 (0.77, 0.93)	0.79 (0.72, 0.87)	0.75 (0.68, 0.83)
Günther's DASH index	1.00 (referent)	0.94 (0.86, 1.03)	0.96 (0.88, 1.05)	0.88 (0.80, 0.97)	0.81 (0.74, 0.90)
Colon cancer					
Dixon's DASH index	1.00 (referent)	0.92 (0.82, 1.04)	0.88 (0.78, 0.99)	0.84 (0.73, 0.96)	_
Mellen's DASH index	1.00 (referent)	0.91 (0.82, 1.02)	0.87 (0.78, 0.97)	0.85 (0.76, 0.96)	0.83 (0.74, 0.94)
Fung's DASH index	1.00 (referent)	0.90 (0.81, 1.00)	0.88 (0.78, 0.98)	0.82 (0.74, 0.92)	0.78 (0.69, 0.88)
Günther's DASH index	1.00 (referent)	0.89 (0.80, 0.99)	0.96 (0.86, 1.07)	0.85 (0.76, 0.95)	0.81 (0.72, 0.91)
Rectal cancer					
Dixon's DASH index	1.00 (referent)	0.83 (0.70, 0.99)	0.73 (0.61, 0.88)	0.63 (0.51, 0.78)	_
Mellen's DASH index	1.00 (referent)	0.84 (0.71, 1.00)	0.85 (0.72, 1.00)	0.64 (0.53, 0.77)	0.66 (0.54, 0.79)
Fung's DASH index	1.00 (referent)	0.84 (0.71, 0.99)	0.78 (0.65, 0.94)	0.72 (0.61, 0.86)	0.68 (0.56, 0.82)
Günther's DASH index	1.00 (referent)	1.08 (0.91, 1.28)	0.97 (0.81, 1.16)	0.97 (0.81, 1.15)	0.82 (0.68, 0.99)
Women					
Colorectal cancer					
Dixon's DASH index	1.00 (referent)	1.14 (0.92, 1.42)	1.09 (0.87, 1.36)	1.01 (0.80, 1.28)	_
Mellen's DASH index	1.00 (referent)	0.84 (0.73, 0.96)	0.84 (0.73, 0.96)	0.78 (0.69, 0.89)	0.79 (0.68, 0.91)
Fung's DASH index	1.00 (referent)	0.94 (0.82, 1.08)	0.82 (0.73, 0.93)	0.81 (0.70, 0.93)	0.84 (0.73, 0.96)
Günther's DASH index	1.00 (referent)	0.86 (0.75, 0.98)	0.79 (0.69, 0.91)	0.91 (0.80, 1.05)	0.84 (0.73, 0.97)
Colon cancer					
Dixon's DASH index	1.00 (referent)	1.14 (0.89, 1.48)	1.08 (0.84, 1.40)	1.00 (0.77, 1.31)	_
Mellen's DASH index	1.00 (referent)	0.85 (0.73, 0.99)	0.83 (0.72, 0.97)	0.77 (0.66, 0.89)	0.81 (0.69, 0.96)
Fung's DASH index	1.00 (referent)	0.93 (0.79, 1.09)	0.83 (0.72, 0.95)	0.77 (0.65, 0.91)	0.84 (0.72, 0.98)
Günther's DASH index	1.00 (referent)	0.87 (0.75, 1.02)	0.80 (0.68, 0.94)	0.96 (0.82, 1.12)	0.88 (0.74, 1.03)
Rectal cancer					
Dixon's DASH index	1.00 (referent)	1.13 (0.73, 1.76)	1.10 (0.71, 1.72)	1.04 (0.65, 1.66)	_
Mellen's DASH index	1.00 (referent)	0.79 (0.60, 1.05)	0.85 (0.65, 1.12)	0.83 (0.64, 1.08)	0.69 (0.50, 0.94)
Fung's DASH index	1.00 (referent)	0.97 (0.73, 1.29)	0.82 (0.63, 1.06)	0.94 (0.70, 1.26)	0.91 (0.61, 1.08)
Günther's DASH index	1.00 (referent)	0.80 (0.61, 1.05)	0.76 (0.57, 1.00)	0.78 (0.59, 1.04)	0.74 (0.55, 1.00)

¹ Dixon's DASH index scores were grouped into 4 categories ($\leq 1, 2, 3, \text{ and } \geq 4$ points) because of a limited range of values (total score range is 0–9). Cox proportional hazard models were adjusted for age, education, BMI, alcohol intake, smoking, total energy intake, ethnicity, physical activity, and, in the case of women, use of hormone-replacement therapy. DASH, Dietary Approaches to Stop Hypertension.

0.73, 0.96), and Günther's (HR: 0.84; 95% CI: 0.73, 0.97) DASH indexes, but not Dixon's index (HR: 1.01; 95% CI: 0.80, 1.28), were associated with reduced colorectal cancer incidence. In the subsite-specific analyses in women, risk estimates were significantly reduced for colon cancer with higher scores on Mellen's (HR: 0.81; 95% CI: 0.69, 0.96) and Fung's (HR: 0.84; 95% CI: 0.72, 0.98) indexes and for rectal cancer with higher scores on Mellen's index (HR: 0.69; 95% CI: 0.50, 0.94). No other subsite-specific associations in women were significant, and there was no statistical evidence of heterogeneity between subsites (*P*-heterogeneity > 0.05 for all comparisons).

Results in men from the by-component analyses are shown in **Table 5**, whereby each individual component was investigated separately, with the total index score minus the respective component controlled for. Of components in which greater intakes received higher scores, the following components were significantly associated with reduced risk of colorectal cancer: total dairy products with Dixon's DASH index, calcium with

Mellen's DASH index, total fruit, whole grains, and low-fat dairy products with Fung's DASH index, and total fruit, total grains, high-fiber grains, and low-fat dairy products with the Günther's DASH index. Meeting the recommendation for al-coholic beverages (≤ 2 drinks/d), a component only present in Dixon's index, was also significantly inversely associated with colorectal cancer incidence. For components that were reverse-coded, in that lower intakes resulted in higher scores, significant inverse associations were observed for red and processed meat with Fung's method and meat, poultry, fish, and eggs with Günther's method. Unexpectedly, higher scores (reflecting lower intakes) on total fat and sodium components with Mellen's DASH index were significantly associated with modestly increased colorectal cancer incidence [HRs (95% CIs): 1.13 (1.04, 1.23) and 1.21 (1.06, 1.38), respectively].

Results from the by-component analyses in women are presented in **Table 6**. Significant decreased risk of colorectal cancer was observed with higher scores for total dairy products in

TABLE 5

Multivariable-adjusted HRs (95% CIs) for colorectal cancer for highest compared with lowest categories or quintiles of DASH individual component scores for each index in men^{1}

	Dixon's DASH index ²	Mellen's DASH index ²	Fung's DASH index ³	Günther's DASH index ⁴
Dietary components for which greater				
intakes receive higher scores				
Total fruit	0.95 (0.88, 1.03)		0.89 (0.80, 0.99)	$0.88 (0.82, 0.95)^5$
Total vegetables	0.97 (0.91, 1.04)		· _ ·	$0.96 (0.88, 1.05)^5$
Vegetables without potatoes			0.92 (0.83, 1.02)	
Total grains			· _ ·	$0.82 (0.72, 0.94)^3$
Whole grains	0.87 (0.65, 1.17)		0.82 (0.74, 0.91)	
High-fiber grains				$0.79 (0.71, 0.88)^3$
Total dairy products	0.85 (0.78, 0.92)		—	$1.04 (0.94, 1.15)^3$
Low-fat dairy products			0.76 (0.69, 0.84)	$0.73 (0.66, 0.80)^3$
Nuts, seeds, legumes	1.08 (0.71, 1.63)		1.11 (1.00, 1.23)	$0.90 (0.81, 1.00)^3$
Protein		0.96 (0.89, 1.04)	· _ ·	
Fiber		1.03 (0.92, 1.16)		
Magnesium		0.90 (0.77, 1.04)	—	
Calcium		0.88 (0.79, 0.97)		
Potassium		0.96 (0.85, 1.08)	—	
Dietary components for which lower				
intakes receive higher scores				
Meat/meat equivalents	0.96 (0.88, 1.04)		—	
Meat, poultry, fish, eggs			—	$0.88 (0.81, 0.96)^5$
Red and processed meat			0.82 (0.74, 0.93)	
Sugar-sweetened beverages			0.94 (0.85, 1.03)	
Sweets			· _ ·	$0.99 (0.92, 1.06)^5$
Added sugar	1.10 (0.98, 1.23)			
Fats, oils			—	$1.05 (0.95, 1.16)^6$
Total fat		1.13 (1.04, 1.23)		
Saturated fat	0.93 (0.80, 1.07)	0.93 (0.82, 1.06)	—	
Cholesterol		0.91 (0.83, 1.00)		
Sodium		1.21 (1.06, 1.38)	1.12 (0.95, 1.31)	
Alcoholic beverages	0.81 (0.73, 0.89)	·	·	

¹Cox proportional hazard models were conducted for each component with adjustment for the total DASH score without the respective component in addition to age, education, BMI, alcohol intake (g/d), smoking, total energy intake, ethnicity, and physical activity. DASH, Dietary Approaches to Stop Hypertension.

 2 Meeting the recommendation (1 point) compared with not meeting the recommendation (0 points).

³Quintile 5 compared with quintile 1.

⁴ Top quartile consists of the highest intakes for recommended components and the lowest intakes for components for which moderate or lower intakes are recommended.

⁵Components were categorized into tertiles because of a limited range of values.

⁶Components were categorized into 2 groups (0 or >0 points) because of a majority of 0 values.

DASH DIET INDEXES AND COLORECTAL CANCER

TABLE 6

Multivariable-adjusted HRs (95% CIs) for colorectal cancer for highest compared with lowest categories or quintiles of DASH individual component scores for each index in women^l

	Dixon's DASH index ²	Mellen's DASH index ²	Fung's DASH index ³	Günther's DASH index ⁴
Dietary components for which greater				
intakes receive higher scores				
Total fruit	1.04 (0.93, 1.16)		0.99 (0.85, 1.16)	$1.05 (0.82, 1.34)^5$
Total vegetables	0.99 (0.90, 1.10)			$1.02 (0.91, 1.14)^5$
Vegetables without potatoes			1.09 (0.93, 1.27)	
Total grains				$0.95 (0.80, 1.13)^3$
Whole grains	1.04 (0.67, 1.60)		0.81 (0.70, 0.94)	
High-fiber grains	· _ ·			$0.86 (0.74, 1.00)^3$
Total dairy products	0.81 (0.72, 0.92)			$1.10(0.95, 1.26)^3$
Low-fat dairy products			0.69 (0.59, 0.80)	$0.64 (0.56, 0.74)^3$
Nuts, seeds, legumes	0.90 (0.60, 1.36)		1.25 (1.07, 1.46)	$0.90 (0.77, 1.04)^3$
Protein		0.99 (0.89,1.11)		
Fiber		1.19 (1.03, 1.38)		
Magnesium		1.03 (0.85, 1.24)		
Calcium		0.80 (0.70, 0.91)		
Potassium		1.19 (1.02, 1.39)		
Dietary components for which lower				
intakes receive higher score				
Meat/meat equivalents	0.82 (0.70, 0.97)			
Meat, poultry, fish, eggs				$1.13 (0.88, 1.45)^5$
Red and processed meat			0.82 (0.70, 0.96)	
Sugar-sweetened beverages			1.09 (0.93, 1.26)	
Sweets				$1.09 (0.96, 1.23)^5$
Added sugar	1.07 (0.87, 1.33)		—	
Fats, oils				$0.99 (0.87, 1.11)^6$
Total fat		1.01 (0.84,1.21)	—	
Saturated fat	1.07 (0.88, 1.30)	0.93 (0.82, 1.05)		
Cholesterol		0.96 (0.85, 1.09)		
Sodium		1.20 (0.98, 1.46)	0.90 (0.71, 1.14)	—
Alcoholic beverages	1.11 (0.95, 1.31)		·_· /	

¹Cox proportional hazard models were conducted for each component with adjustment for the total DASH score without the respective component in addition to age, education, BMI, alcohol intake (g/d), smoking, total energy intake, ethnicity, physical activity, and hormone-replacement therapy. DASH, Dietary Approaches to Stop Hypertension.

²Meeting the recommendation (1 point) compared with not meeting the recommendation (0 points).

³ Quintile 5 compared with quintile 1.

⁴Top quartile consists of the highest intakes for recommended components and lowest intakes for components for which moderate or lower intakes are recommended.

⁵Components were categorized into tertiles because of a limited range of values.

⁶Components were categorized into 2 groups (0 or >0 points) because of a majority of 0 values.

Dixon's DASH index, calcium in Mellen's DASH index, whole grains and low-fat dairy products in the Fung's DASH index, and low-fat dairy products in Günther's DASH index. Scores for 2 components that were reverse-coded (ie, meat and meat equivalents in Dixon's DASH index and red and processed meat in the Fung's DASH index) were inversely associated with co-lorectal cancer, which meant lower intakes of those meats were protective. There were 2 unexpected findings in women such that higher scores (which reflected greater intakes) on the fiber component with Mellen's DASH index and the nuts, seeds, and legumes component with the Fung's DASH were significantly associated with increased colorectal cancer incidence [HRs (95% CIs): 1.19 (1.03, 1.38) and 1.25 (1.07, 1.46), respectively].

DISCUSSION

In this large prospective examination of 4 established DASH diet indexes and colorectal cancer, men with the highest scores on all 4 of the indexes and women with the highest scores on 3 of the

indexes had significant reduced risk of colorectal cancer. Risk estimates were of similar magnitude for all indexes in men and 3 of the indexes in women (Mellen's, Fung's, and Günther's indexes). These findings suggested that the key underlying construct of the DASH dietary pattern is captured in each index, and greater compliance with this dietary pattern is protective against colorectal cancer. The findings also showed that differences in how the DASH dietary pattern is operationalized affects the ability of the DASH indexes to predict colorectal cancer risk, as evidenced in the results in women.

The lack of an association between Dixon's DASH scores and colorectal cancer in women in the current study was in contrast to the consistently inverse associations observed by using the other 3 DASH indexes. This finding highlighted how differences in the composition of the indexes and scoring algorithms can affect results. Some indexes are designed to reflect specific food choices, whereas other indexes focus on the resulting nutrient intakes. In addition, there are differences in the use of absolute compared with relative standards. Mellen's index uses a density-based approach (ie, intakes relative to total calories), whereas the other indexes use either absolute cutoffs (Dixon and Günther) or rankings of intakes (Fung). The methods developed by Dixon and Mellen directly assess the adherence to the saturated fat recommendation in the DASH diet; both Fung's and Günther's DASH indexes evaluate saturated fat intake indirectly through components composed of saturated fat–rich foods. Each index captures various aspects of DASH adherence and addresses a slightly different research question. For example, the method developed by Dixon examines whether meeting DASH recommendations is associated with disease risk, whereas Mellen's index addresses whether the meeting of goals for the nutrients that are expected to be higher or lower with greater adherence to the DASH diet is associated with disease risk.

A key difference between Dixon's index and the other 2 primarily food-based indexes (Fung's and Günther's indexes) is the scoring system. Dixon's index has 2 possible values for each component (0 or 1 for not meeting or meeting, respectively, the recommendation); partial adherence is not rewarded. Fung's index assigns scores 1 through 5 according to quintile rankings, and Günther's index allows for a score from 0 to 5 or 10. Therefore, components in Fung's and Günther's indexes allow for a wider range of possible scores. Although components in the Fung's method are identified beforehand, the scoring is based on the distribution of the sample at hand. These differences were explored in a by-component analysis in which each individual component was included in a model that controlled for all other components in each respective index. One component for which the scoring method had a considerable effect was whole grains (or high-fiber grains in Günther's index); higher scores on this component were significantly inversely associated with colorectal cancer in Fung's and Günther's indexes but not Dixon's index, which did not capture partial adherence.

Differing compositions of the indexes also can affect results. Dixon's index has a component for total dairy products, and although this component was inversely associated with colorectal cancer risk in the by-component analysis in women, the magnitude of this protective effect was greater when we examined scores on low-fat dairy components in Fung's and Günther's indexes. These findings with dairy and calcium as protective dietary factors were consistent with the Continuous Update Project report on colorectal cancer issued by the World Cancer Research Fund and the American Institute on Cancer Research (27). Fung's index captured red and processed meat intake, whereas Dixon's and Günther's indexes captured meat and meat equivalents and meat, poultry, fish, and eggs, respectively. The red and processed meat component, in which lower intakes result in higher scores, was the only component consistently associated with reduced risk in both men and women, which was a finding that was consistent with a previously published analysis from this same cohort (28).

Another difference between indexes is the treatment of sodium; only Mellen's and Fung's indexes include a sodium component. Sodium intake was targeted in the DASH-Sodium Trial (7), which showed that a reduction of sodium intake in conjunction with the original DASH diet (6) further reduced blood pressure. To our knowledge, sodium has not been independently associated with colorectal cancer risk, although lower scores (reflecting higher intakes) of sodium on Mellen's index, but not Fung's index, were inversely associated with colorectal cancer in our study. Although these inconsistent findings across the 2 indexes could have been a result of a spurious relation, it also may have been related to differences in how the components are constructed and scored. Fung's index scores the sodium component according to quintile rankings, whereas Mellen's index is scored on the basis of meeting the recommendation of 1143 mg/1000 kcal (1 point), an intermediate target (0.5 points), or not meeting either of the 2 targets (zero points). Because <9% of men and <8% of women met the sodium recommendation used in Mellen's index, this component was likely limited in its ability to discriminate between high and low intakes.

To our knowledge, our study was the first to calculate and compare 4 established DASH diet indexes within the same study for the same outcome. This approach allowed for the confirmation of diet-disease associations. The large sample size and prospective design of our study were both notable strengths. There were also several limitations, including the possibility of measurement error associated with FFQs, which may have contributed to a nondifferential misclassification of respondents into dietary exposure categories, which would have attenuated risk estimates (29). In general, FFOs collect less-detailed information on the food consumed, cooking and food-preparation methods, and portion size compared with other self-reported methods, such a 24-h dietary recalls (30). Findings from the bycomponent analysis should be interpreted with caution because significant findings could have been a result of chance because of the multiple comparisons performed. Higher DASH scores may have been a marker of higher socioeconomic status or an overall healthy lifestyle, as evidenced by higher education levels and lower BMI, alcohol intake and current smoking in the highest compared with lowest categories of scores across all indexes in men and all but Dixon's index in women. Although we examined and included potential lifestyle-related and socioeconomic confounders in our multivariable models, residual or unknown confounding was possible.

In conclusion, the overall consistency in findings suggests that the main underlying construct of the DASH dietary pattern is captured by each index and greater compliance with this dietary pattern can reduce colorectal cancer risk. Nevertheless, nuances with each method can affect results and, therefore, should be considered in future research efforts. The objective of this research was not to determine a superior DASH diet index, but rather to elucidate the methodologic differences in indexes and examine their influence on observed associations. This research provides a foundation for future efforts aimed at developing a standardized index to assess the DASH dietary pattern.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the Cancer Surveillance Section, California Department of Health Services. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, state of Michigan. Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center, in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania.

The authors' responsibilities were as follows—PEM and JR: conceptualized the study and designed the analysis plan; PEM: performed the analyses, interpreted results, and drafted the manuscript with substantial support from JR; AFS and AH: contributed to acquisition of data; AJC, AFS, SMK-S, YP, TP-W, AH, and JR: contributed to the interpretation of study findings and critical revision of the manuscript for intellectual content; and all authors: approved the final version of the manuscript. None of the authors had a conflict of interest.

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