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Using Pathway-Specific Comprehensive Exposure Scores in Epidemiology: Application to Oxidative Balance in a Pooled Case-Control Study of Incident, Sporadic Colorectal Adenomas

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Identifying associations of risk factors sharing the same pathway with disease risk is complicated by small individual effects and intercorrelated components; this can be addressed by creating comprehensive exposure scores. We developed and validated 3 novel weighting methods (literature review–derived, study data–based, and a Bayesian method that combines prior knowledge with study data) to incorporate components into a pathway score for oxidative balance in addition to a commonly used method that assumes all components contribute equally to the score. We illustrate our method using pooled data from 3 US case-control studies of sporadic colorectal adenoma (1991–2002). We created 4 oxidative balance scores (OBS) to reflect combined summary measures of dietary and nondietary antioxidant and prooxidant exposures. A higher score represents a predominance of antioxidant exposures over prooxidant exposures. In the pooled data, the odds ratios comparing the highest tertile of OBS with the lowest for adenoma risk ranged from 0.38 to 0.54 for the 4 measures; all were statistically significant. These findings suggest that 1) OBS are indicators of oxidative balance and may be inversely associated with colorectal adenoma risk and 2) using comprehensive exposure scores may be preferable to investigating individual component-disease associations for complex exposures, such as oxidative balance.

case-control studies; colorectal tumors; methodological study; oxidative stress; weighting

Abbreviations: CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score(s).

Published studies of diet-disease associations have usually focused on investigating 1 food or nutrient at a time. However, most foods/nutrients have small effects and are intercorrelated, either by intake or by contributing similarly to a biological pathway, which complicates attempts to analyze their individual effects (1). Advantages of combining these dietary exposures into a comprehensive variable were previously summarized (1, 2), contributing to the development and application of dietary patterns in observational epidemiology. Dietary patterns derived from a priori diet-quality scores (3–5) or the more exploratory method of principal components analysis or factor analysis (6–8) do not necessarily relate to specific biological pathways. Moreover, by definition, they do not include nondietary lifestyle factors—factors that might be correlated with dietary behaviors and act on the same pathway.

The rationale and method for combining multiple dietary and nondietary lifestyle exposures to create comprehensive scores for oxidative balance (the in vivo balance of antioxidants and prooxidants that modulate levels of potentially harmful reactive oxygen species) have been given previously (9, 10). Oxidative balance scores (OBS) have been reported to be statistically significantly associated with decreased risks of incident colorectal adenoma and prostate cancer, but the individual components of the score were weakly associated or not associated with either disease (9, 10). Other investigators, using slightly different methods to create an OBS, have mostly reported similar results for other cancers and cancer mortality (11–14).

In these studies, only 1 method for developing an OBS was used, the most common being a simple summation and equal weighting of the selected components. Because results could be unduly influenced by the weighting assumptions and because components do not contribute equally to the pathway under consideration, we present 4 different methods for constructing comprehensive exposure scores and illustrate the utility of this approach to investigate the association between oxidative balance and risk of incident, sporadic colorectal adenomas. In addition, since it is unknown whether these scores actually measure oxidative balance, we present data on the association of OBS with levels of F_2-isoprostanes, which are considered the most reliable marker of oxidative stress in vivo (15, 16).

MATERIALS AND METHODS

Study population

Data from 3 methodologically similar endoscopy-based case-control studies of incident, sporadic colorectal adenomas conducted by the same principal investigator were pooled. The first study (the Cancer Prevention Research Unit (CPRU) Study) was conducted in Minnesota from 1991 to 1994 (17); the second (the first Markers of Adenomatous Polyps (MAP) Study (MAP I)) was conducted from 1994 to 1997 in North Carolina (18); and the third (the second MAP Study (MAP II)) was conducted in 2002 in South Carolina (19). Participants in all 3 studies were recruited from patients with no history of colorectal neoplasms who were scheduled to undergo outpatient, elective endoscopy for screening or gastrointestinal symptoms in large, community-based gastroenterology practices. Participants aged 30–74 years who spoke English, had no contraindications for colonoscopy, and had no known genetic syndromes associated with colonic neoplasia or history of inflammatory bowel disease, colorectal adenoma, or cancer (except nonmelanoma skin cancer) were eligible to participate. The participation rates were similar in all 3 studies (68%–76%).

We combined data from the MAP I and MAP II studies (hereafter referred to as MAP) because the selection criteria, study protocols, and questionnaires were identical for these studies. Details of the study protocols for the CPRU (17), MAP I (18), and MAP II (19) studies were previously reported. The final sample size for the pooled data analyses was 2,289 (789 incident adenoma cases and 1,500 polyp-free controls). All participants, prior to undergoing endoscopy, completed questionnaires on demographic factors, medical and family history, lifestyle, anthropometric factors, diet (using a semiquantitative Willett food frequency questionnaire (20, 21)), and, in women, hormonal and reproductive history.

The studies were approved by the institutional review boards of the institutions at which they were conducted, and all participants provided written informed consent.

OBS components and their assessment

The 15 components included in the OBS (Table 1) were determined a priori based on their expected physiological effects on oxidative processes. The dietary components were derived from the food frequency questionnaires; nutrient values included dietary and supplemental sources. Supplemental selenium was not included in the OBS because fewer than 5% of the participants reported regular use of selenium supplements. All nutrient values were energy-adjusted according to the residual regression method, and nutrients were analyzed as continuous variables (22). Nondietary lifestyle variables included in the OBS were smoking (current, former, or never smoker), alcohol intake (<1, 1–6, or ≥7 drinks/week), obesity (body mass index (weight (kg)/height (m)^2) <30 *and* waist:hip ratio <1.0 in men or <0.8 in women; *either* body mass index ≥30 *or* waist:hip ratio ≥1.0 in men or ≥0.8 in women; or body mass index ≥30 *and* waist:hip ratio ≥1.0 in men or ≥0.8 in women), and physical activity (in metabolic equivalents).

Colorectal adenoma

Participants who had an adenoma removed during colonoscopy and verified by an index study pathologist using diagnostic criteria established in the National Polyp Study (23) were considered cases. Participants who had no adenomatous or hyperplastic polyps upon colonoscopy were considered controls. All controls in the MAP studies underwent colonoscopy, but in the CPRU Study, 518 (43%) participants were polyp-free upon sigmoidoscopic assessment and were not referred for colonoscopy.

Assessment of F_2-isoprostane levels

Plasma F_2-isoprostane levels were assessed in a validation subsample from the MAP studies (157 cases and 184 controls). Fasting peripheral venous blood samples were drawn into red-coated, prechilled Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey) and then immediately placed on ice and shielded from light. Blood fractions were aliquoted into amber-colored cryopreservation tubes, the air was displaced with argon gas, and the aliquots were then immediately placed in a −80°C freezer until analysis. Plasma F_2-isoprostane levels were measured using a method based on gas chromatography-mass spectrometry (23).

Statistical methods

We used 4 methods of weighting the 15 components (Table 1) to create the respective OBS.

OBS–equal weight (an a priori method). For OBS–equal weight, we assumed that all components are equally important and should contribute similar weights. Antioxidants and prooxidants identified a priori were assigned arbitrary weights of 1 and −1, respectively. Data for all components, including the categorical variables, were transformed to a standard normal distribution. We then multiplied the transformed variables by the respective weights (1 for antioxidants and −1 for prooxidants) and summed the weighted components to generate the OBS–equal weight.

Table 1. Components of 4 Different Oxidative Balance Scores (OBS), Rationale for Their Inclusion in the OBS, and Weights Given to Them in Different Measures of the OBS[a]

OBS Component	Rationale for Inclusion (Reference No.)	OBS Weight[b]			
		OBS–Equal Weights	OBS–Lit. Review[c]	OBS–A Posteriori	OBS–Bayesian
Dietary antioxidants					
Provitamin A carotenoids (α-carotene, β-carotene, β-cryptoxanthin)	Precursors of vitamin A, potent antioxidants (37)	+1	0.0039	−0.0230	0.0048
Lutein	Antioxidant (37)	+1	0.0325	0.0803	0.0193
Lycopene	Antioxidant (38)	+1	−0.0153	0.0149	−0.0212
Vitamin C	Prevents lipid peroxidation, helps regenerate α-tocopherol (39)	+1	0.0810	0.0541	0.0510
Vitamin E	Membrane-bound antioxidant, protects against lipid peroxidation (40)	+1	0.1368	0.1247	0.1052
ω-3 fatty acids (marine)	Induce electrophile-responsive element regulated genes responsible for transcription regulation of antioxidant enzymes (41, 42)	+1	0.0044	−0.0184	0.0309
Flavonoids	Plant polyphenols with multiple antioxidant functions: phenolic groups donate hydrogen to free radicals, prevent metal-catalyzed free-radical formation, and integrate with cell membranes to protect against lipid peroxidation (43, 44)	+1	−0.0043	0.1451	0.0060
Glucosinolates	Sulfur-containing plant compounds with antioxidant functions: induce electrophile-responsive element as ω-3 fatty acids; induce hemoxygenase-1, which catalyzes heme to biliverdin; induce glutathione peroxidase (45)	+1	0.0411	−0.0344	0.0290
Dietary prooxidants					
Dietary iron	Primarily available from red meat; preferentially catalyzes oxidative reactions through production of free radicals, resulting in lipid, protein, and DNA and other nucleic acid damage (46, 47)	−1	−0.0744	−0.0089	−0.0756
ω-6 fatty acids	Higher intakes are associated with increased oxidative stress through increased free-radical production; unlike ω-3 fatty acids, they do not induce electrophile-responsive element (42, 48, 49)	−1	0.0410	−0.1214	0.0031
Saturated fat	Oxidative DNA damage through increased production of known prooxidant bile acids in the colon (50, 51)	−1	−0.0153	−0.1024	−0.0393

Table continues

OBS–lit. review (an a priori method). Weights for the OBS–lit. review method were derived from literature reviews (Table 1). Coefficient estimates were calculated using pooled adjusted risk estimates derived from published reviews/meta-analyses of individual colorectal cancer risk factors, where available. Pooled effect estimates for ω-3 and ω-6 fatty acids, flavonoids, glucosinolates, and iron were not readily available and are based on reviews conducted by one of the authors (C.D.). For continuous components, reported effect estimates commonly compare the highest quantile of intake with the lowest. For weighting, we calculated the effect estimate for 1 standard unit increase in the continuous variable based on the highest category risk estimate (e.g., fourth quartile vs. first quartile) reported in the literature. Our calculations assumed a log-linear dose response between the OBS component and colorectal cancer risk in the published estimates. On the basis of a previously described method (24), we calculated the midpoints of the highest and lowest categories using the category boundaries of a standard normal distribution and used the following formula to calculate the coefficient estimate for a particular component (24, 25):

$$\frac{\ln(1/\text{effect estimate})}{(\text{midpoint of high category} - \text{midpoint of low category})}.$$

The inverse of the effect estimate was used so that components inversely associated with colorectal cancer had a positive weight and those with higher risk had a negative weight.

OBS–lit. review was calculated for each study participant by weighting each standardized component based on the weights derived from the literature reviews and then summing the weighted components.

OBS–a posteriori (an a posteriori method). Weights were derived from the CPRU Study and applied to the MAP data

Table 1. Continued

OBS Component	Rationale for Inclusion (Reference No.)	OBS Weight[b]			
		OBS–Equal Weights	OBS–Lit. Review[c]	OBS–A Posteriori	OBS–Bayesian
Nondietary lifestyle antioxidants					
Physical activity	Although acute bouts of exercise increase RONS production, regular exercise results in increase in adaptive response to oxidative stress by activating cellular antioxidant signaling systems and enhancing expression of antioxidant enzymes through a process termed "hormesis" (52)	+1	0.1080	0.0043	0.0976
Nondietary lifestyle prooxidants					
Smoking	Potent producer of free radicals, associated with increase in blood/tissue markers of oxidative stress (53, 54)	−1	−0.7031[d] −0.0953[e]	−0.7503[d] −0.2620[e]	−0.7764[d] −0.2426[e]
Alcohol intake	Chronic intake results in oxidative stress through oxidation of ethanol to acetaldehyde, which can lead to RONS production, nucleic acid oxidation, and decreased activity of antioxidant enzymes (55, 56)	−1	−0.2390[f] −0.0676[g]	−0.5633[f] −0.2108[g]	−0.4854[f] −0.0707[g]
Obesity	Independently associated with increased oxidative stress markers, impaired serum redox balance, and increased lipid peroxidation; source of free fatty acids, which can lead to oxidative stress through increased RONS production (57)	−1	−0.0770[h] −0.0295[i]	−0.2683[h] −0.0596[i]	−0.3507[h] −0.1766[i]

Abbreviations: CPRU, Cancer Prevention Research Unit; OBS, oxidative balance score; RONS, reactive oxygen and nitrogen species.

[a] For each participant, OBS was calculated as a weighted sum of the components listed in the table.

[b] OBS–equal weight: all OBS components received equal weights; OBS–lit. review: weights for OBS components were based on effect estimates derived from literature review; OBS–a posteriori: weights for OBS components were based on CPRU Study data; OBS–Bayesian: weights for OBS components were based on Bayesian analysis of case-control data.

[c] Weights were derived from published reviews/meta-analysis for all components except ω-3 fatty acids, ω-6 fatty acids, flavonoids, glucosinolates, and iron, where one of the authors (C.D.) conducted the meta-analyses.

[d] Current smokers.

[e] Former smokers.

[f] Heavy alcohol drinkers.

[g] Moderate alcohol drinkers.

[h] Obese persons.

[i] Overweight persons.

and pooled data. We used multivariable logistic regression to estimate the odds ratio for colorectal adenoma for each OBS component after adjusting for other components and additional covariates. The coefficient estimates for each of the components obtained from the regression model were used to calculate weights for OBS–a posteriori. Coefficients were multiplied by −1 (the natural log of the inverse of the odds ratio) so that components inversely associated with adenoma risk had a positive weight and vice versa. OBS–a posteriori was then calculated as a weighted sum of the 15 components.

OBS–Bayesian (combination of a priori and data-based methods). We conceptualized OBS–Bayesian as a combination of the weighting schemes used in OBS–lit. review and OBS–a posteriori. We employed a hierarchical modeling approach, utilizing a logistic regression model with informative priors within the Bayesian framework, to derive weights for OBS–Bayesian. The Bayesian approach is discussed in greater detail elsewhere (26–28). The priors for the OBS components were defined as normally distributed with mean and variance as determined for OBS–lit. review. The covariates (see "Statistical analysis" section below) in the model were assigned noninformative normal priors with a mean of zero and large standard deviations (10^6). The components were transformed to a standard normal distribution prior to analysis. We used the BAYES statement in PROC GENMOD in SAS, version 9.2, for the Bayesian analysis (29). Convergence of the Markov chain was determined through visual analysis of trace plots and by means of 2 diagnostic tests (Gelman-Rubin and Geweke) (30, 31). No departures from convergence were found for any of the components in the model. The first 2,000 burn-in sampling iterations were not used for determining the posterior summaries. The posterior summary estimates were multiplied by −1 and used as weights for OBS–Bayesian. Similarly to the other OBS, the result for OBS–Bayesian was then calculated as a weighted sum of the 15 components. Similarly to OBS–a posteriori, the weights for OBS–Bayesian were developed in the CPRU data and applied to the MAP and pooled data.

Nondietary lifestyle variables such as physical activity are considered stronger risk factors for colorectal neoplasia than are dietary antioxidants and prooxidants (32). To examine whether dietary factors meaningfully contribute to the

Table 2. Distributions of Selected Characteristics and OBS Components Among Cases and Controls in 3 Case-Control Studies of Incident Sporadic Colorectal Adenoma (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)[a]

	CPRU Study				MAP I Study				MAP II Study			
	Cases (n = 564)		Controls (n = 1,202)		Cases (n = 177)		Controls (n = 179)		Cases (n = 48)		Controls (n = 119)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Selected characteristics												
Age, years	58 (10)		53 (11)**		58 (8)		55 (9)**		58 (9)		53 (11)**	
Male sex		62		39**		60		37**		62		38**
College education or higher		30		28		22		31		28		29
Family history of colon or rectal cancer in first-degree relative		14		17		20		36**		15		19
Regular (≥once/week) NSAID use		9		19**		24		35*		13		22**
Regular (≥once/week) aspirin use		20		26*		35		34		24		28
Mean total estrogen exposure (in women), years	14 (19)		21 (18)**		16 (21)		24 (20)**		15 (19)		22 (19)**	
Current use of hormone therapy (in women)		22		40**		65		72		35		47**
Total energy intake, kcal/day	2,091 (775)		2,003 (718)*		2,003 (758)		1795 (677)**		2,065 (771)		1,961 (715)**	
Total calcium intake, mg/day[b]	952 (446)		990 (458)		789 (380)		859 (445)		905 (434)		964 (458)**	
Total vitamin D intake, IU/day[b]	325 (245)		350 (252)*		321 (257)		355 (306)		324 (249)		351 (263)*	
Total folate intake, μg/day[b]	398 (219)		442 (234)**		435 (230)		466 (251)		409 (222)		447 (238)**	
Dietary fiber intake, g/day	22 (7)		22 (8)		21 (8)		20 (8)		22 (7)		22 (8)	
OBS components												
Provitamin A carotenoid intake, IU/day	9,822 (9,067)		10,861 (10,330)*		5,186 (4,203)		5433 (4228)		8,501 (8,255)		9,779 (9,679)**	
Lutein intake,[c] μg/day	6.9 (6)		7.5 (6)*		3,669 (2,882)		3211 (2817)					
Lycopene intake,[c] μg/day	2.2 (2.3)		2.2 (2.5)		4,307 (3,817)		4,507 (4,075)					
Vitamin C intake, mg/day	246 (293)		299 (312)**		277 (346)		275 (303)		255 (310)		294 (310)**	
Vitamin E intake, mg-TE/day	62 (143)		83 (170)**		74 (164)		73 (147)		66 (149)		81 (166)**	
ω-3 fatty acid intake (marine), g/day	1.85 (1.48)		1.88 (1.62)		0.22 (0.20)		0.22 (0.25)		1.39 (1.45)		1.55 (1.60)*	
Flavonoid intake, mg/day	228 (194)		261 (250)**		399 (355)		388 (349)		277 (262)		286 (277)	
Glucosinolate intake, mg/day	14.9 (14.9)		15.6 (16.2)		20.5 (28.7)		17.4 (14.2)		16.5 (20.0)		16.0 (15.8)	
ω-6 fatty acid intake, g/day	11.5 (3.6)		10.8 (3.5)**		11.9 (3.8)		11.4 (4.8)		11.6 (3.7)		10.9 (3.8)**	
Saturated fat intake, g/day	11.9 (3.2)		11.4 (3.1)**		11.6 (3.1)		11.5 (3.0)		11.8 (3.2)		11.4 (3.1)**	
Dietary iron intake, mg/day	18 (14)		20 (16)*		19 (17)		22 (21)		19 (15)		21 (17)**	
Current smoker		21		13**		34		15**		25		14**
Former smoker		47		40		40		37		45		40
1–6 alcoholic drinks/week		17		18		35		36		22		21
≥7 alcoholic drinks/week		40		26**		23		14**		35		23**

Table continues

Table 2. Continued

	CPRU Study				MAP I Study				MAP II Study			
	Cases ($n = 564$)		Controls ($n = 1,202$)		Cases ($n = 177$)		Controls ($n = 179$)		Cases ($n = 48$)		Controls ($n = 119$)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Body mass index[d]	27.4 (4.7)		26.6 (4.9)**		27.9 (6.3)		27.8 (6.0)		27.6 (5.2)		26.8 (5.1)**	
Waist:hip ratio	0.93 (0.13)		0.88 (0.12)**		0.94 (0.12)		0.89 (0.14)**		0.93 (0.13)		0.88 (0.12)**	
Physical activity, MET-hours/week	37 (39)		35 (33)		27 (19)		28 (19)		34 (35)		33 (31)	

Abbreviations: CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent; NSAID, nonsteroidal antiinflammatory drug; OBS, oxidative balance score; SD, standard deviation; TE, tocopherol equivalents.

* $P < 0.05$; ** $P < 0.01$ (based on t test or χ^2 test).

[a] All nutrient data were adjusted for total energy intake.

[b] Diet plus supplements.

[c] For the CPRU Study, lutein and lycopene intake data were available as number of servings of lutein- and lycopene-rich fruits and vegetables.

[d] Weight (kg)/height $(m)^2$.

OBS–colorectal adenoma association, we created a "dietary OBS" by excluding smoking, alcohol intake, obesity, and physical activity from the OBS measures described above. We also created a "lifestyle OBS" that included only the 4 nondietary lifestyle variables.

Statistical analysis

We used multivariable logistic regression to estimate the odds ratio and corresponding 95% confidence interval for incident colorectal adenoma in relation to each OBS, adjusted for age, sex, education, family history of colorectal cancer in a first-degree relative, regular use (≥once/week) of aspirin, regular use (≥once/week) of other nonsteroidal antiinflammatory drugs, calcium, vitamin D, folate, fiber, total energy intake, cumulative estrogen exposure, excluding oral contraceptive use (in women), and use of menopausal hormone therapy (in women). These covariates were selected a priori as potential confounders based on their being established risk factors for colorectal adenoma and their potential for association with the OBS or its components. Stratified analyses were conducted to examine the association of colorectal adenoma with dietary OBS according to tertile of lifestyle OBS and vice versa. Effect-measure modification by the covariates was determined by comparing stratum-specific odds ratios and by means of the model-based log-likelihood ratio. We also examined whether the association between OBS and adenoma risk varied by tumor site (distal to the splenic flexure vs. proximal vs. rectal) or advanced adenoma status (defined as size ≥1 cm, adenoma with any villous component, or high-grade dysplasia). Prior to analyses, each OBS was categorized into tertiles based on the study-specific distribution in the controls. To test for linear trend, we created a continuous variable using the median OBS value within each tertile.

We used general linear models to evaluate the association of OBS measures with F_2-isoprostane levels, adjusted for age, race, and study. F_2-isoprostane values were log-transformed prior to analysis. Separate analyses were performed for men and women because mean F_2-isoprostane levels are reported to be higher and to have more variability in women than in men (5, 16).

All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant. All analyses were conducted in SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Selected characteristics of the study participants are shown in Table 2. Cases were more likely than controls to be older, to be male, to not be taking aspirin or nonsteroidal antiinflammatory drugs regularly, and to report lower calcium, vitamin D, and folate intakes and higher energy intake. Among women, cases were less likely to report using postmenopausal hormone therapy.

The weights for the individual OBS components differed among the 4 methods and are shown in Table 1.

The results from logistic regression modeling of the associations of the various OBS with colorectal adenoma are shown in Table 3. For both studies, participants in the

Table 3. Associations of OBS Measures With Incident, Sporadic Colorectal Adenoma in Data From 3 Case-Control Studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

OBS[a]	CPRU Study			MAP Studies			Pooled Data		
	No. of Cases	RR[b]	95% CI	No. of Cases	RR[b]	95% CI	No. of Cases	RR[b]	95% CI
OBS–equal weight									
Tertile 1	258	1.00	Referent	102	1.00	Referent	360	1.00	Referent
Tertile 2	182	0.68	0.53, 0.87	65	0.67	0.43, 1.07	247	0.67	0.54, 0.83
Tertile 3	124	0.51	0.39, 0.68	58	0.67	0.41, 1.09	182	0.54	0.43, 0.69
P_{trend}		<0.0001			0.09			<0.0001	
OBS–lit. review									
Tertile 1	301	1.00	Referent	141	1.00	Referent	442	1.00	Referent
Tertile 2	150	0.62	0.47, 0.81	36	0.32	0.19, 0.53	186	0.53	0.42, 0.67
Tertile 3	113	0.47	0.35, 0.64	48	0.44	0.27, 0.73	161	0.45	0.35, 0.58
P_{trend}		<0.0001			<0.001			<0.0001	
OBS–a posteriori									
Tertile 1	299	1.00	Referent	122	1.00	Referent	421	1.00	Referent
Tertile 2	164	0.57	0.44, 0.74	66	0.56	0.36, 0.88	230	0.57	0.46, 0.71
Tertile 3	101	0.40	0.30, 0.53	37	0.34	0.21, 0.57	138	0.38	0.29, 0.49
P_{trend}		<0.0001			<0.0001			<0.0001	
OBS–Bayesian									
Tertile 1	305	1.00	Referent	139	1.00	Referent	444	1.00	Referent
Tertile 2	150	0.57	0.43, 0.73	35	0.27	0.16, 0.46	185	0.47	0.38, 0.60
Tertile 3	109	0.45	0.34, 0.60	51	0.47	0.29, 0.76	160	0.45	0.35, 0.58
P_{trend}		<0.0001			<0.001			<0.0001	

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; RR, relative risk.

[a] OBS–equal weight: all OBS components received equal weights; OBS–lit. review: weights for OBS components were based on effect estimates derived from literature review; OBS–a posteriori: weights for OBS components were based on CPRU Study data; OBS–Bayesian: weights for OBS components were based on Bayesian analysis of case-control data. Tertiles for OBS are sex-specific, and the dietary components were adjusted for total energy intake.

[b] Adjusted for age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, regular use of nonsteroidal antiinflammatory drugs, total calcium intake, total vitamin D intake, total energy intake, total folate intake, dietary fiber intake, and hormone therapy (among women).

highest tertile of the OBS relative to the lowest tertile were, on average, 50% less likely to have colorectal adenomas. In the pooled analyses, the odds ratios were approximately 0.50 (range, 0.38–0.54) for the 4 different OBS, and all 95% confidence intervals excluded 1.0. The tests for trend for all 4 OBS were statistically significant, consistent with a dose-response association of decreasing adenoma risk with increasing OBS. Overall, the findings for OBS–lit. review, OBS–a posteriori, and OBS–Bayesian were more similar to each other than to those from OBS–equal weights.

Associations of dietary OBS with adenoma according to tertile of lifestyle OBS are presented in Table 4. For all OBS measures except OBS–equal weight, the inverse association between dietary OBS and adenoma risk was stronger (and statistically significant) among participants in the lowest tertile of lifestyle OBS (i.e., those with more prooxidant lifestyle exposures) than among those with higher lifestyle OBS. In contrast, associations of lifestyle OBS with adenoma risk were uniform across tertiles of dietary OBS (Table 5). For OBS–lit. review, there was some indication that participants with low dietary OBS scores had a greater reduction in adenoma risk associated with high lifestyle OBS than those with high dietary OBS.

The OBS, dietary OBS, and lifestyle OBS were more strongly associated with lower risk of advanced ademonas than with risk of nonadvanced adenomas (Table 6). This finding was especially true for the dietary OBS variables; the average odds ratio for adenoma risk comparing the highest tertile with the lowest was 0.88 (all 95% confidence intervals included 1.0) for nonadvanced adenoma and 0.55 (statistically significant) for advanced adenoma. The tests for trend were also statistically significant for the advanced adenoma outcome but not for the nonadvanced adenomas. Odds ratios for lifestyle OBS were stronger than those for dietary OBS for all adenomas, but the associations were more comparable between advanced and nonadvanced adenomas. Associations between the OBS and adenoma were similar for the proximal colon, distal colon, and rectal sites (data not shown).

Table 4. Associations of Dietary OBS Measures With Incident, Sporadic Colorectal Adenoma According to Lifestyle OBS in Pooled Data From 3 Case-Control Studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Dietary OBS[a]	Lifestyle OBS								
	Tertile 1			Tertile 2			Tertile 3		
	No. of Cases	RR[b]	95% CI	No. of Cases	RR[b]	95% CI	No. of Cases	RR[b]	95% CI
OBS–equal weight									
Tertile 1	160	1.00	Referent	93	1.00	Referent	67	1.00	Referent
Tertile 2	117	0.78	0.55, 1.10	69	0.92	0.61, 1.36	50	0.47	0.30, 0.76
Tertile 3	99	0.90	0.62, 1.32	86	0.91	0.62, 1.39	48	0.56	0.35, 0.91
P_{trend}		0.51			0.66			0.02	
OBS–lit. review									
Tertile 1	180	1.00	Referent	57	1.00	Referent	46	1.00	Referent
Tertile 2	156	0.69	0.50, 1.96	77	1.16	0.76, 1.77	50	1.10	0.68, 1.80
Tertile 3	108	0.51	0.35, 0.73	69	1.12	0.72, 1.72	46	0.83	0.50, 1.38
P_{trend}		<0.001			0.63			0.49	
OBS–a posteriori									
Tertile 1	188	1.00	Referent	93	1.00	Referent	52	1.00	Referent
Tertile 2	121	0.82	0.58, 1.15	72	0.81	0.54, 1.22	52	0.72	0.44, 1.17
Tertile 3	95	0.65	0.45, 0.93	74	1.01	0.66, 1.54	42	0.58	0.35, 0.98
P_{trend}		0.02			0.99			0.04	
OBS–Bayesian									
Tertile 1	197	1.00	Referent	72	1.00	Referent	50	1.00	Referent
Tertile 2	133	0.89	0.63, 1.24	57	0.70	0.45, 1.07	56	1.06	0.66, 1.70
Tertile 3	108	0.63	0.45, 0.89	76	0.96	0.63, 1.45	40	0.83	0.50, 1.39
P_{trend}		0.01			0.87			0.49	

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; RR, relative risk.

[a] OBS–equal weight: all OBS components received equal weights; OBS–lit. review: weights for OBS components were based on effect estimates derived from literature review; OBS–a posteriori: weights for OBS components were based on CPRU Study data; OBS–Bayesian: weights for OBS components were based on Bayesian analysis of case-control data. Tertiles for OBS are sex-specific, and the dietary components were adjusted for total energy intake.

[b] Adjusted for age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, regular use of nonsteroidal antiinflammatory drugs, total calcium intake, total vitamin D intake, total energy intake, total folate intake, dietary fiber intake, and hormone therapy (among women).

Associations between the OBS and F_2-isoprostane levels are presented in Table 7. F_2-isoprostane levels were lower, indicating lower systemic oxidative stress, with increasing OBS in both men and women, but the results for OBS–equal weights and OBS–a posteriori were not statistically significant among men (Table 7). Increasing tertiles of dietary OBS were also inversely associated with F_2-isoprostanes after adjustment for lifestyle OBS components. Although F_2-isoprostane levels were lower among participants in the highest tertile of lifestyle OBS than among participants in the lowest tertile after adjustment for dietary OBS, the results were not statistically significant.

DISCUSSION

We developed 3 novel weighting schemes (OBS–lit. review, OBS–a posteriori, and OBS–Bayesian) and compared them with a previously used weighting scheme (OBS–equal weights) for combining dietary and nondietary exposures associated with oxidative balance. Using data from the pooled study, we found a substantial inverse association between OBS and risk for incident, sporadic colorectal adenomas. Our approach is robust, as evidenced by the similarity of the conclusions derived from the different weighting methods, suggesting that the observed associations are unlikely to be artifacts of weighting assumptions. Our results also suggest a dose-dependent decrease in F_2-isoprostane levels with increasing levels of OBS, providing support for OBS as a valid measure of oxidative balance.

Other epidemiologic studies have found inverse associations of summary oxidative balance/stress scores with colorectal adenoma, lung cancer, esophageal cancer, prostate cancer, and total cancer mortality (9–13). However, Agalliu et al. (14) recently reported a null association between OBS and prostate cancer. These studies used only 1 method to develop the summary score variable, which raises concern

Table 5. Associations of Lifestyle OBS Measures With Incident, Sporadic Colorectal Adenoma According to Dietary OBS in Pooled Data From 3 Case-Control Studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Lifestyle OBS[a]	Dietary OBS								
	Tertile 1			Tertile 2			Tertile 3		
	No. of Cases	RR[b]	95% CI	No. of Cases	RR[b]	95% CI	No. of Cases	RR[b]	95% CI
OBS–equal weight									
Tertile 1	160	1.00	Referent	117	1.00	Referent	99	1.00	Referent
Tertile 2	93	0.63	0.44, 0.91	69	0.74	0.50, 1.11	86	0.62	0.42, 0.91
Tertile 3	67	0.60	0.40, 0.88	50	0.43	0.28, 0.66	48	0.40	0.26, 0.62
P_{trend}		0.004			<0.0001			<0.0001	
OBS–lit. review									
Tertile 1	180	1.00	Referent	156	1.00	Referent	108	1.00	Referent
Tertile 2	57	0.37	0.24, 0.58	77	0.60	0.41, 0.90	69	0.72	0.47, 1.10
Tertile 3	46	0.30	0.19, 0.47	50	0.49	0.31, 0.75	46	0.50	0.31, 0.80
P_{trend}		<0.0001			<0.001			<0.01	
OBS–a posteriori									
Tertile 1	188	1.00	Referent	121	1.00	Referent	95	1.00	Referent
Tertile 2	93	0.58	0.41, 0.82	72	0.57	0.38, 0.86	74	0.75	0.50, 1.12
Tertile 3	52	0.48	0.32, 0.71	52	0.43	0.28, 0.65	42	0.41	0.26, 0.64
P_{trend}		<0.0001			<0.0001			<0.0001	
OBS–Bayesian									
Tertile 1	197	1.00	Referent	133	1.00	Referent	108	1.00	Referent
Tertile 2	72	0.58	0.39, 0.86	57	0.40	0.26, 0.60	76	0.67	0.45, 1.01
Tertile 3	50	0.44	0.29, 0.68	56	0.46	0.30, 0.71	40	0.41	0.26, 0.66
P_{trend}		<0.0001			<0.001			<0.001	

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; RR, relative risk.

[a] OBS–equal weight: all OBS components received equal weights; OBS–lit. review: weights for OBS components were based on effect estimates derived from literature review; OBS–a posteriori: weights for OBS components were based on CPRU Study data; OBS–Bayesian: weights for OBS components were based on Bayesian analysis of case-control data. Tertiles for OBS are sex-specific, and the dietary components were adjusted for total energy intake.

[b] Adjusted for age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, regular use of nonsteroidal antiinflammatory drugs, total calcium intake, total vitamin D intake, total energy intake, total folate intake, dietary fiber intake, and hormone therapy (among women).

that the results might be sensitive to the assumptions underlying the weighting of the variables in the score. Another limitation of previous studies was the assumption that all components contribute equally to oxidative stress (10, 13). Since an equal weighting approach (OBS–equal weights) is unlikely to represent the true biological contributions of individual contributors to oxidative balance, we tested multiple approaches to weight the OBS. In addition, in contrast to previous studies, we created 3 OBS measures that are specific for colorectal neoplasms. Although each approach has certain limitations (discussed below), the conclusions from the results were generally consistent across the weighting methods. The use of multiple approaches can be viewed as sensitivity analyses for weighting OBS components.

The similarity of the conclusions obtained for the adenoma-OBS and OBS–F_2-isoprostane associations suggests that all 4 scoring methods may be valid. Although the OBS–equal weights method is the easiest to use, concerns still remain about its biological appropriateness, and it is possible that this approach might not perform as well in designing exposure scores for pathways other than oxidative stress. The weighting approaches proposed as alternatives to OBS–equal weights also have limitations. Weights for OBS–a posteriori are based on data from 1 study and might not be applicable to other studies. An obvious improvement on this weighting scheme is to derive weights from multiple studies rather than just 1. This led us to develop OBS–lit. review. However, estimates obtained from pooling prior studies may be imprecise because of the lack of uniformity in the exposure measurement and covariate selection across studies. Additionally, weighting based on epidemiologic studies considers the effect of each component on disease risk, possibly without accounting for other factors. This weighting approach may not be the most suitable given our main premise that combined effects of components are more important than their individual effects. Therefore, a priori

Table 6. Associations of OBS Measures With Incident, Sporadic Colorectal Adenoma According to Advanced Adenoma Status in Pooled Data From 3 Case-Control Studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

OBS[a]	Nonadvanced Adenoma			Advanced Adenoma[b]		
	No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI
Overall OBS						
OBS–equal weight						
Tertile 1	246	1.00	Referent	114	1.00	Referent
Tertile 2	189	0.76	0.59, 0.96	58	0.47	0.33, 0.68
Tertile 3	139	0.60	0.46, 0.79	43	0.39	0.26, 0.58
P_{trend}		<0.001			<0.0001	
OBS–lit. review						
Tertile 1	313	1.00	Referent	129	1.00	Referent
Tertile 2	141	0.56	0.43, 0.72	45	0.44	0.30, 0.65
Tertile 3	120	0.48	0.36, 0.63	41	0.41	0.27, 0.62
P_{trend}		<0.0001			<0.0001	
OBS–a posteriori						
Tertile 1	290	1.00	Referent	131	1.00	Referent
Tertile 2	177	0.65	0.51, 0.83	53	0.40	0.28, 0.58
Tertile 3	107	0.43	0.33, 0.57	31	0.27	0.17, 0.43
P_{trend}		<0.0001			<0.0001	
OBS–Bayesian						
Tertile 1	315	1.00	Referent	129	1.00	Referent
Tertile 2	140	0.51	0.39, 0.65	45	0.38	0.26, 0.56
Tertile 3	119	0.47	0.36, 0.62	41	0.41	0.27, 0.62
P_{trend}		<0.0001			<0.0001	
Dietary OBS						
OBS–equal weight						
Tertile 1	217	1.00	Referent	103	1.00	Referent
Tertile 2	180	0.86	0.67, 1.11	56	0.53	0.36, 0.77
Tertile 3	177	0.93	0.71, 1.21	56	0.57	0.39, 0.85
P_{trend}		0.57			<0.01	
OBS–lit. review						
Tertile 1	189	1.00	Referent	94	1.00	Referent
Tertile 2	219	1.08	0.84, 1.39	64	0.54	0.37, 0.79
Tertile 3	166	0.84	0.64, 1.10	57	0.53	0.36, 0.78
P_{trend}		0.22			<0.0001	
OBS–a posteriori						
Tertile 1	230	1.00	Referent	103	1.00	Referent
Tertile 2	178	0.87	0.68, 1.12	67	0.70	0.49, 1.01
Tertile 3	166	0.89	0.68, 1.16	45	0.49	0.32, 0.75
P_{trend}		0.37			<0.001	

Table continues

weighting schemes based on the association of OBS components with a panel of oxidative stress biomarkers that best represent systemic oxidative stress may need to be developed. The OBS–Bayesian approach combines elements from the "lit. review" and "a posteriori" weighting schemes and aims to strike a balance between using available study data and published information from prior studies. This approach may be preferred not only for creating an OBS but also for determining the weights for other comprehensive pathway scores.

Our results suggest that increasing dietary OBS among persons with predominantly prooxidant lifestyle exposures, such as those in the lowest tertile of lifestyle OBS (Table 4), might be a promising approach for adenoma prevention.

Table 6. Continued

OBS[a]	Nonadvanced Adenoma			Advanced Adenoma[b]		
	No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI
OBS–Bayesian						
Tertile 1	231	1.00	Referent	123	1.00	Referent
Tertile 2	169	0.85	0.66, 1.10	59	1.07	0.75, 1.54
Tertile 3	174	0.85	0.66, 1.11	33	0.59	0.39, 0.88
P_{trend}		0.23			0.01	
			Lifestyle OBS			
OBS–equal weight						
Tertile 1	266	1.00	Referent	110	1.00	Referent
Tertile 2	185	0.71	0.56, 0.90	63	0.59	0.41, 0.84
Tertile 3	123	0.51	0.39, 0.66	42	0.40	0.27, 0.60
P_{trend}		<0.0001			<0.0001	
OBS–lit. review						
Tertile 1	316	1.00	Referent	128	1.00	Referent
Tertile 2	155	0.58	0.45, 0.76	48	0.45	0.30, 0.68
Tertile 3	103	0.43	0.32, 0.58	39	0.41	0.27, 0.64
P_{trend}		<0.0001			<0.0001	
OBS–a posteriori						
Tertile 1	291	1.00	Referent	113	1.00	Referent
Tertile 2	173	0.64	0.50, 0.81	66	0.65	0.46, 0.93
Tertile 3	110	0.46	0.36, 0.61	36	0.38	0.25, 0.58
P_{trend}		<0.0001			<0.0001	
OBS–Bayesian						
Tertile 1	314	1.00	Referent	124	1.00	Referent
Tertile 2	150	0.54	0.42, 0.69	55	0.51	0.35, 0.75
Tertile 3	110	0.46	0.35, 0.61	36	0.39	0.25, 0.60
P_{trend}		<0.0001			<0.0001	

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; RR, relative risk.

[a] OBS–equal weight: all OBS components received equal weights; OBS–lit. review: weights for OBS components were based on effect estimates derived from literature review; OBS–a posteriori: weights for OBS components were based on CPRU Study data; OBS–Bayesian: weights for OBS components were based on Bayesian analysis of case-control data. Tertiles for OBS are sex-specific, and the dietary components were adjusted for total energy intake.

[b] Advanced adenoma was defined as size ≥1 cm, adenoma with any villous component, or high-grade dysplasia.

[c] Adjusted for age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, regular use of nonsteroidal antiinflammatory drugs, total calcium intake, total vitamin D intake, total energy intake, total folate intake, dietary fiber intake, and hormone therapy (among women). In addition, dietary OBS was adjusted for smoking, alcohol intake, obesity, and physical activity, and lifestyle OBS was adjusted for dietary OBS.

Overall, lifestyle OBS was more strongly associated with adenoma incidence than was dietary OBS; however, dietary OBS was more strongly associated with F_2-isoprostane levels than was lifestyle OBS (Table 7). This paradoxical observation could be due to the fact that the nondietary lifestyle components, especially compared with the dietary components, also act through other pathways in addition to oxidative stress (33).

This study had several limitations. Although the OBS components used are the most comprehensive reported to date, we might have missed potential components because of a lack of published evidence of their effects on oxidative processes. The OBS components do not include endogenous factors that modify oxidative stress, such as DNA damage-repair genes or genes responsible for cellular response against oxidative stress (34, 35). The OBS dietary components are based on self-report data from food frequency questionnaires and are subject to measurement error and biases (36), even when adjusted for total energy intake. Use of nutrient biomarkers as dietary OBS components should be evaluated in future studies. Study participants were predominantly white, and our results might not be generalizable

Table 7. Association of F_2-Isoprostane Levels with OBS Measures in a Validation Sample of Pooled Data From the MAP Case-Control Studies (MAP I Study, 1994–1997; and MAP II Study, 2002)

OBS[a]	Mean F_2-Isoprostane Level, nmol/L			
	No. of Men	Proportional Difference,[b,c,d] %	No. of Women	Proportional Difference,[b,c,d] %
		Overall OBS		
OBS–equal weights				
Tertile 1	78	Referent	122	Referent
Tertile 2	72	−7.69	89	−27.05***
Tertile 3	66	−15.38**	80	−34.43***
OBS–lit. review				
Tertile 1	76	Referent	107	Referent
Tertile 2	77	1.32	102	−4.67
Tertile 3	61	−19.74**	83	−22.43**
OBS–a posteriori				
Tertile 1	78	Referent	107	Referent
Tertile 2	70	−10.26	102	−4.67
Tertile 3	66	−15.38*	81	−24.30***
OBS–Bayesian				
Tertile 1	75	Referent	108	Referent
Tertile 2	77	2.67	96	−11.11
Tertile 3	64	−14.67*	89	−17.59**
		Dietary OBS		
OBS–equal weights				
Tertile 1	78	Referent	117	Referent
Tertile 2	73	−6.41	90	−23.08***
Tertile 3	67	−14.10**	86	−26.50***
OBS–lit. review				
Tertile 1	79	Referent	112	Referent
Tertile 2	76	−3.80	92	−17.86
Tertile 3	67	−15.19**	84	−25.00**
OBS–a posteriori				
Tertile 1	78	Referent	111	Referent
Tertile 2	72	−7.69	95	−14.41
Tertile 3	68	−12.82*	86	−22.52***
OBS–Bayesian				
Tertile 1	77	Referent	106	Referent
Tertile 2	73	−5.19	101	−4.72
Tertile 3	67	−12.99*	88	−16.98

Table continues

to nonwhite populations. In the CPRU Study, some controls did not have a colonoscopy, raising concerns about missed proximal tumors and possible outcome misclassification. However, such misclassification would be expected to attenuate the results. Most participants underwent colonoscopy for indications other than routine screening, such as gastrointestinal bleeding and other symptoms that might be related to increased oxidative stress. Although unlikely, it is also possible that participants with symptoms had recently changed their behaviors (e.g., diet) to more healthy patterns. Data on F_2-isoprostane levels were not available for the CPRU Study and were only available for a subsample from the MAP studies. Additionally, F_2-isoprostane levels are indicators of lipid peroxidation and do not represent the entire spectrum of in vivo oxidative stress biomarkers, which includes oxidation products of proteins and nucleic acids.

Strengths of our study include the use of histologically verified adenoma cases, thus reducing outcome misclassification; community-based control selection; assessment of

Table 7. Continued

OBS[a]	Mean F_2-Isoprostane Level, nmol/L			
	No. of Men	Proportional Difference,[b,c,d] %	No. of Women	Proportional Difference,[b,c,d] %
		Lifestyle OBS		
OBS–equal weights				
Tertile 1	73	Referent	105	Referent
Tertile 2	77	5.48	95	−9.52
Tertile 3	66	−9.59	86	−18.10**
OBS–lit. review				
Tertile 1	75	Referent	101	Referent
Tertile 2	69	−8.00	100	−0.99
Tertile 3	68	−9.33	88	−12.87
OBS–a posteriori				
Tertile 1	74	Referent	101	Referent
Tertile 2	75	1.35	99	−1.98
Tertile 3	68	−8.11	88	−12.87
OBS–Bayesian				
Tertile 1	74	Referent	102	Referent
Tertile 2	76	2.70	99	−2.94
Tertile 3	67	−9.46	88	−13.73

Abbreviations: CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score.

* $P < 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

[a] OBS—equal weight: all OBS components received equal weights; OBS–lit. review: weights for OBS components were based on effect estimates derived from literature review; OBS–a posteriori: weights for OBS components were based on CPRU Study data; OBS–Bayesian: weights for OBS components were based on Bayesian analysis of case-control data. Tertiles for OBS are sex-specific, and the dietary components were adjusted for total energy intake.

[b] Proportional difference in mean F_2-isoprostane levels = (tertile 2 – tertile 1)/tertile 1, expressed as a percentage for the comparison of tertile 2 with tertile 1 (referent). Similarly, the proportional difference for the comparison between tertile 3 and tertile 1 = (tertile 3 – tertile 1)/tertile 1, expressed as a percentage.

[c] Results of all analyses were adjusted for age, race, and study. Dietary OBS was additionally adjusted for smoking, alcohol, obesity, and physical activity. Lifestyle OBS was additionally adjusted for dietary OBS.

[d] *P* values were based on a *t* test of difference between the tertiles of $\log_e(F_2\text{-isoprostanes})$.

exposure and covariate information prior to endoscopy, thus reducing recall bias; and a low likelihood of unmeasured confounding because of collection of detailed information on covariates. Finally, to our knowledge, ours is the first study to have investigated the validity of OBS using biomarkers of oxidative stress.

In summary, we developed 3 novel weighting methods to create disease-specific exposure scores for oxidative balance, and we demonstrated their application to data from a large pooled case-control study of incident, sporadic colorectal adenomas. We compared the performance and validity of the different weighting schemes and concluded that all 4 methods perform equally well for OBS. However, given the potential limitations of the other methods, we recommend the use of a Bayesian approach to generate weights for multicomponent exposure scores. This method appears potentially useful for exposures, such as diet, for which small individual effects contributing to a larger pathway and the intercorrelations among the exposures limit our ability to evaluate exposure-disease associations. Finally, in contrast to the conclusions drawn from analyses that evaluated individual antioxidants/prooxidants, our approach suggests that oxidative balance may be associated with risk of incident, sporadic colorectal adenomas.

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