HHS Public Access

Author manuscript

Ann Epidemiol. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Ann Epidemiol. 2015 April ; 25(4): 256–262.e1. doi:10.1016/j.annepidem.2015.01.004.

Oxidative Balance Score as Predictor of All-Cause, Cancer, and Non-cancer Mortality in a Biracial US Cohort

So Yeon Kong, PhD, MPH[a,*], **Michael Goodman, MD, MPH**[a,b], **Suzanne Judd, PhD, MPH**[c], **Roberd M. Bostick, MD, MPH**[a,b], **W. Dana Flanders, MD, DSc**[a], and **William McClellan, MD, MPH**[a]

[a]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

[b]Winship Cancer Institute, Emory University, Atlanta, GA

[c]Department of Biostatistics, University of Alabama at Birmingham, AL

Abstract

Purpose—We previously proposed an oxidative balance score (OBS) that combines pro- and anti-oxidant exposures to represent the overall oxidative balance status of an individual. In this study, we investigated associations of the OBS with all-cause and cause-specific mortality, and explored alternative OBS weighting methods in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study cohort.

Methods—The OBS was calculated by combining information from 14 *a priori* selected pro- and anti-oxidant factors, and then divided into quartiles with the lowest quartile (predominance of pro-oxidants) as reference. Cox proportional hazard models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for each OBS category compared to the reference.

Results—Over a median 5.8 years of follow-up, 2,079 of the 21,031 participants died. The multivariable adjusted HRs (95% CI) for all-cause, cancer, and non-cancer mortality for those in the highest vs. the lowest equal-weighting OBS quartile were: 0.70 (0.61, 0.81), 0.50 (0.37, 0.67), and 0.77 (0.66, 0.89), respectively (P-trend < 0.01 for all). Similar results were observed with all weighting methods.

Conclusion—These results suggest that individuals with a greater balance of anti-oxidant to pro-oxidant lifestyle exposures may have lower mortality.

Keywords

Oxidative Balance Score; Oxidative Stress; Mortality

[*]Correspondence to: So Yeon Kong, PhD, MPH. Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, GA 30322., Phone number: +1 (404) 727-2734, Fax: +1 (404) 727-8737, soyeon.kong@gmail.com.

Introduction

Oxidative stress, defined as the disruption of the balance between pro- and antioxidants, has been implicated in the etiology and pathophysiology of many chronic diseases, which in turn act as leading contributors to mortality [1]. There is increasing evidence that high intakes of certain nutrients, including vitamin C [2], vitamin E [3], and carotenoids (e.g., lycopene, β-carotene, and lutein) [4, 5], may protect against oxidative stress while pro-oxidant factors, including smoking [6] and iron intake [7], increase reactive oxygen and nitrogen species production and accelerate oxidative stress-related cellular damage. However, despite the substantial body of evidence from basic science and animal studies, observational and clinical studies that evaluated the effects of individual antioxidant or pro-oxidant factors have produced inconsistent results [8–12].

One potential explanation for this discrepancy is the complex and multi-factorial mechanisms by which oxidative stress may affect health. The independent effects of individual exposures may not offer complete insights into their roles in maintaining an overall oxidative balance because of the likely inter-correlations and biological interactions involving the multiple pro- and anti-oxidant factors [13]. The concept of an integrated antioxidant network has been proposed, given that antioxidants of different solubility reside next to each other in cellular structures and tissues, integrating and regenerating each other [14].

Recently, we [15–17] and others [18, 19] proposed an oxidative balance score (OBS) as a measure of combined pro- and anti-oxidant exposure status, and used various versions of it in studies of various chronic diseases. Only one of those studies [19] examined an association of an OBS with mortality and the score in that study was limited by a relatively few components which included only iron, vitamin C, and beta-carotene. In addition most previous studies used a simple summation and equal weighting of the selected components, with an assumption that the contributions of all pro- and anti-oxidants were roughly equal. It is important to point out, however, that equal weighting approach is difficult to justify [20, 21]. Some previous studies assigned OBS weights based on the reported associations between individual OBS components and outcomes of interest such as colorectal tumors [22] and prostate cancer [23]; however no previous study used weighting based on biochemical measures of oxidative stress.

In this study, we used data from a large national prospective cohort study to investigate an association of an OBS comprised of 14 *a priori* selected oxidative stress related exposures with all-cause and cause-specific mortality while exploring alternative methods of weighting the OBS components. We hypothesized that a higher OBS, which reflects a predominance of antioxidant exposures, is associated with lower mortality.

Materials and Methods

Study population and data collection

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study is a national, population-based prospective cohort study to examine reasons for variation in

stroke incidence and mortality in the United States. Details on recruitment and data collection were reported previously [24]. Briefly, between January 2003 and October 2007, 30,239 black and white individuals aged 45 years or older were randomly selected and recruited through mail and telephone contacts from across the US with oversampling of blacks and persons from the "stroke belt" region of the United States. The "stroke belt" describes the southeastern region of the United States (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas) with high stroke incidence and mortality [25]. Exclusion criteria were race other than black or white, active treatment for cancer, impairment of global cognitive function, which include recall and temporal orientation as judged by the telephone interviewer, medical conditions preventing long-term participation, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. The REGARDS study was approved by the institutional review boards of all participating institutions.

After obtaining verbal and written informed consent, information on demographics, medical history, and other risk factors was obtained by computer-assisted telephone interviewing (CATI). Variables included age, race, sex, education, income, use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), cigarette smoking, and alcohol intake. Following the telephone interview, an in-home visit was completed to collect blood and urine samples and information on risk factors, such as blood pressure, height, and weight. Additional information was collected through self-administered questionnaires, including the Block 98 food-frequency questionnaire (FFQ). At six-month intervals, participants were followed via telephone interviews to ascertain the development of stroke and other outcomes.

Of the 30,239 participants enrolled in the REGARDS Study, 8,603 who did not complete the modified Block 98 FFQ were excluded from the current analysis. In addition, we excluded 456 participants with missing data on at least one OBS component, and 149 participants with missing data on key covariates. After these exclusions, data for 21,031 participants were available for the final analyses.

Oxidative balance score (Main exposure variable)

The oxidative balance score (OBS) was calculated by combining information from a total of 14 *a priori* selected pro- and anti-oxidant factors, including dietary intakes of polyunsaturated fatty acids, iron, vitamin C, lycopene, α-carotene, β-carotene, lutein, β-crypoxanthin, α-tocopherol, selenium, and alcohol; smoking status; and regular use of aspirin and other NSAIDs (Table 1). The continuous variables reflecting pro-oxidant (unsaturated fat and iron) and antioxidant (vitamin C, lycopene, α-carotene, β-carotene, lutein, β-cryptoxanthin, α-tocopherol, and selenium) exposures were divided into low, medium, and high categories based on each exposure's sex-specific tertile values. For antioxidants, the first through third tertiles were assigned 0 through 2 points, respectively, whereas the corresponding point assignment for pro-oxidants was the reverse (0 points for the highest tertile and 2 points for the lowest tertile). A similar scoring approach was used for pro- and antioxidant categorical variables. Smoking status was categorized as never (2 points), former (1 point), and current (0 points). For aspirin and NSAID use, 0 points were

assigned to participants with no regular use, 1 point to those with unknown or missing data, and 2 points to those with regular use. For alcohol consumption, non-drinkers, moderate drinkers (1–7 drinks/week for women and 1–14 drinks/week for men), and heavy drinker (>7 drinks/week for women and >14 drinks/week for men) received 2, 1 and 0 points, respectively. The overall OBS was then calculated by adding up the points assigned to each participant with a higher OBS score representing predominance of anti-oxidants over pro-oxidant exposures.

OBS weighting

Each OBS component was included in the overall score using four weighting methods: 1) equal weights; 2) literature-based weights; 3) weights based on the magnitude of the associations between each component and plasma/serum fluorescent oxidation products (FOP) levels; and 4) weights based on the magnitude of the associations between each component and plasma/serum F_2-isoprostanes (FIP) levels.

The equal weights approach assumes that all OBS component contribute equally to oxidative balance. By contrast, for the other three methods, weights were assigned based on the presumed magnitude of their contributions to oxidative balance.

For the literature-based method each OBS component was weighted according to the results of the most recent systematic reviews/meta-analysis that evaluated an association between the component and mortality. In the absence of a recent systematic review/meta-analysis for an OBS component, a *de novo* meta-analysis was conducted. For each OBS component, weights were calculated based on the pooled (i.e., meta-) risk estimates (meta-RR). For each pro-oxidant the weights were equal to the meta-RR, while for antioxidants the corresponding weights were calculated as 1/meta-RR. For the two-biomarker (FOP and FIP)-based weighting methods, we used pooled data from two previously completed case-control studies of colorectal adenoma that employed virtually identical protocols. The first study, Markers of Adenomatous Polyps I (MAP I), recruited cases and controls from gastroenterology practices in Winston-Salem and Charlotte, North Carolina. The second study, Markers of Adenomatous Polyps II (MAP II), was conducted at Consultants in Gastroenterology, PA, a large, private practice in Columbia, South Carolina. The detailed study methods for MAP I [26, 27] and MAP II [28, 29] were previously published. Both studies collected information that allowed calculating an OBS, and both studies involved analyses of FOP and FIP.

For both FIP- and FOP-based weighting, we used multivariable logistic regression models to quantify the associations between each OBS component and each of the two markersof oxidative stress. Each model adjusted for the other OBS components and confounding factors, including age, race, sex, total energy and fiber intakes, body mass index (BMI), plasma cholesterol, hormone replacement therapy (among women), physical activity, fiber, and study. The adjusted odds ratio estimates from these logistic models were used to assign weights. Weights for each methods were summarized in Supplemental Table 1.

Outcome measurements

The primary outcome in this study was all-cause mortality. In the REGARDS cohort, participants' deaths were ascertained via telephone or Web-based restricted-access database searches (e.g., Lexis-Nexis), and later confirmed through death certificates. In addition, interviews with next-of-kin or proxies of deceased participants were conducted to confirm the death and date of death. Information on the cause of death was also obtained from death certificates. Two adjudicators reviewed death/death causes independently, and disagreements were resolved by committee. Adjudicators used baseline participant clinical characteristics, proxy interviews, death certificates, and if available, medical records from hospitalizations occurring within 30 days of the participant's death to determine the cause of death.

Statistical analysis

Each OBS version (unweighted, and weighted using literature-, FOP- and FIP-based methods) was divided into quartiles, with the lowest quartile (predominance of pro-oxidants) used as reference. The total follow-up time for each individual was calculated as the time between the first visit interview and the date of death, the date of the last study contact, the date of withdrawal or loss to follow-up, or March 1, 2012, whichever came first. The adjusted associations between the OBS and both all-cause and cause-specific mortality were examined using Cox proportional hazard models, controlling for age, sex, race, socioeconomic status (SES), region, BMI, total daily energy intake, and physical activity. The results of the multivariable survival analyses were expressed as adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI). Tests for linear trend were performed using a score variable with values from 1 to 4, consistent with the quartile grouping. Since tobacco smoking is a powerful pro-oxidant and strong risk factor for mortality, we conducted a separate set of analyses in which smoking was removed from the OBS but controlled for in the model. Proportional hazards assumptions were tested by inspecting –ln(ln) survival curves for each variable in the model. Collinearity was tested and a condition index of ≥ 30, coupled with a variance decomposition proportion of ≥ 0.5 was considered as evidence of collinearity. We tested all statistical models for the presence of two-way interactions by adding the product terms involving OBS and study covariates; each interaction term was accompanied by a likelihood ratio test. We also conducted a sensitivity analysis by excluding participants who died within the first year of follow-up. A two-sided *P* value of < 0.05 was considered to be statistically significant. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC) statistical software package.

Results

Compared with blacks (58%), whites (81%) were more likely to return the baseline FFQ (P < 0·001) and college graduates (77 %) were also more likely than non-graduates (55 %) to return the FFQ (P < 0·001). Participants who did not return the FFQ had a slightly higher BMI (30.0, versus. 29.1, kg/m^2, P < 0·001), while age was not associated with the likelihood of returning the FFQ.

The baseline characteristics of the study cohort by OBS category are summarized in Table 2. Compared to those in the lowest OBS quartile, participants in the highest quartile were, on average, three years older (66 vs. 63), and were modestly more likely to be white (69.3% vs. 64.9%) and female (58.0% vs. 54.3%). Persons in the highest OBS quartile were also more likely to have more education, a higher income, and reside in non-stroke belt states. Evaluations of individual OBS components according to OBS quartiles are presented in Table 3. Contrary to expectation, intakes of polyunsaturated fatty acids (PUFA) and iron were higher in the upper OBS quartile groups. As expected, intakes of antioxidants (vitamin C, lycopene, α-carotene, β-carotene, lutein, β-cryptoxanthin, and vitamin E) were higher among cohort members with higher OBS values. Participants in the higher OBS quartiles were also more likely to be never smokers and non-drinkers, take a selenium supplement, and regularly take an NSAID and/or aspirin.

Over an average follow-up period of 5.8 years (range 0 – 9.1 years), 2,079 of the 21,031 participants died. A higher equal-weight OBS was associated with statistically significant lower all-cause, cancer, and non-cancer mortality in the multivariable analyses (Table 4). After adjusting for the potential confounders, participants in the highest OBS quartile (quartile 4) relative to the lowest had a statistically significant 30% lower risk of all-cause mortality (HR 0.70 [95% CI: 0.61, 0.81]; *P*-trend < 0.001). Excluding smoking from the OBS slightly attenuated the hazard ratios, but the associations remained significant and with an inverse linear trend (*P*-trend = 0.01). After exclusion of participants who died during the first year of followup, similar results were obtained.

Among the 1,566 deaths of known cause, about 30% were attributable to cancer. A higher equal-weights OBS was associated with 50% (HR 0.50 [95% CI: 0.37, 0.67]) and 23% (HR 0.77 [95% CI: 0.66, 0.89]) lower risk of death due to cancer and non-cancer causes, respectively. After smoking was excluded from the OBS, the significant association between the OBS and cancer mortality remained, but the association between the OBS and non-cancer mortality was no longer observed. The significant linear trend between the OBS and chronic lung disease mortality (*P*-trend = 0.02) was also attenuated after removing smoking from the score (*P*-trend = 0.26).

Table 5 shows the associations between the OBS and all-cause, cancer, and non-cancer mortality based on different weighting methods. Very similar results were observed across all weighting methods. When comparing the equal weights approach (Table 4) to the three weighted approaches (Table 5), it can be seen that all estimates were within 15% of each other and only three differed by more than 10%.

Table 6 presents the sensitivity analyses in which the observed results for the original 14-component OBS (treated as a continuous variable) were compared to the corresponding results after each OBS component was removed from the score one at a time and included in the model as a covariate. Removing any single OBS component, except smoking, did not produce meaningful changes in the risk estimates (no resulting HR differed from the original estimate by more than 2%). When smoking was removed from the OBS, the association was no longer significant for all-cause and non-cancer mortality (as in Table 4), but was still statistically significant for cancer mortality. After testing potential effect modification, none

of the covariates modified the association between OBS and mortality ($p_{interaction} > 0.05$ for all).

Discussion

In this large, population-based prospective cohort study, we found a higher OBS, which indicates a predominance of antioxidant exposures, to be associated with substantially lower risk for all-cause mortality and mortality due to cancer and non-cancer causes, after controlling for multiple confounders. The associations for all-cause and cancer mortality were only modestly attenuated when smoking was excluded from the OBS, suggesting that smoking did not drive the associations. The association between the OBS and mortality did not differ substantially when different weighting methods were used. Although approximately 28% of the sample did not return the FFQ, it is important to keep in mind that in a prospective cohort study such as REGARDS losses at baseline are less likely to lead to considerable selection bias unless there is evidence that non-participation was associated with both OBS and mortality. While the idea of combining individual pro- and anti-oxidants into a single score is not new, to our knowledge, the present study is one of the first to evaluate whether a comprehensive OBS is associated with all-cause mortality in the US population. Overall, our results are consistent with those from other similar studies. Knoops *et al.* [30] investigated an association of a lifestyle score (combined individual scores for the Mediterranean dietary pattern, alcohol use, smoking status, and physical activity) with all-cause mortality in 11 European countries. Persons in the low categories for all four score components were found to have a 65% lower rate of all-cause mortality. In another cohort study, conducted among male smokers in Belgium, Van Hoydonck *et al.* combined intakes of two dietary antioxidants (vitamin C and β-carotene) and one pro-oxidant (iron) to develop their oxidative balance score [19]. Men in the highest OBS category, which unlike ours was constructed to reflect a presumably harmful effect, had a statistically significant 44% higher all-cause mortality and an even greater (62%) increase in cancer mortality compared with men in the lowest OBS group. As in our study, van Hoydonck *et al.* also found no association between their OBS and cardiovascular disease mortality.

In the current study, we used different weighting schemes for combining pro- and antioxidant exposures into a single score. Previous studies used equal weighting of the OBS components [16, 17, 19, 31], which raised a concern that the resulting score does not represent the true biological contributions of the individual pro- or anti-oxidant exposures. However, in the present analyses, the associations between the OBS and mortality estimated by the different OBS weighting methods were very similar to one another.

Advantages of this study include its prospective design, large sample size, diverse population, and inclusion of multiple pro- and anti-oxidant components in the OBS. We used 14 pro- and anti-oxidant factors that were selected *a priori* based on previous research [32–42], as well as data-based, *a priori* tertile cut-points for continuous variables to minimize subjective categorization, which is a general problem with scores for attempting to describe complex processes. In this study, mortality and cause of death were adjudicated by expert clinicians using death certificates, medical records from recent hospitalizations, and

interviews with proxies, a methodological feature that helped decrease outcome misclassification.

This study had several potential limitations. We used self-reported intakes to assess pro- and anti-oxidant exposures. It has long been acknowledged that dietary questionnaires may not capture all the possible sources of each nutrient, do not account for bioavailability, and are subject to recall bias [43]. The validity and reliability of the FFQ used in our study has been extensively evaluated [44–46], and any misclassification would be expected it to be non-differential. Also, we had no data on specific cancers in this study. Another study limitation was that the OBS score in our study was limited to dietary / lifestyle exposures and did not include any endogenous factors that influence cellular anti-oxidant defense, DNA damage and repair, cell growth, and cell death, which all contribute to the survival of individuals [47]. Furthermore, covariate information was available only at baseline. Although this may be viewed as a limitation, many of these covariates are demographic factors such as sex, race, SES, and region, which are not likely to change over time.

In conclusion, the results from this large prospective study suggest that a higher OBS, reflecting a greater balance of anti-oxidant to pro-oxidant lifestyle exposures, may reduce risk for premature all-cause and cancer morality. The observed inverse association between OBS and non-cancer mortality was driven primarily by smoking. These findings confirm results from previous studies and suggest that the OBS might be a useful tool for evaluating the roles of oxidative stress-related lifestyle factors, including diet, as determinants of morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services.

Abbreviations used

OBS	oxidative balance score
REGARDS	Reasons for Geographic and Racial Differences in Stroke
HR	hazards risk
CI	confidence interval
RONS	reactive oxygen and nitrogen species
NSAIDs	non-steroidal anti-inflammatory drugs
FFQ	food-frequency questionnaire
PUFA	polyunsaturated fatty acid
FOP	fluorescent oxidation products

FIP	F_2-isoprostanes
MAP	Markers of Adenomatous Polyps
BMI	body mass index
SES	socioeconomic status

References

1. Stanner SA, Hughes J, Kelly CN, Buttriss J. A review of the epidemiological evidence for the 'antioxidant hypothesis'. Public Health Nutr. 2004; 7:407–422. [PubMed: 15153272]
2. Arrigoni O, De Tullio MC. Ascorbic acid: much more than just an antioxidant. Biochim Biophys Acta. 2002; 1569:1–9. [PubMed: 11853951]
3. Burton GW, Traber MG. Vitamin E: antioxidant activity, biokinetics, and bioavailability. Annu Rev Nutr. 1990; 10:357–382. [PubMed: 2200468]
4. Chaudiere J, Ferrari-Iliou R. Intracellular antioxidants: from chemical to biochemical mechanisms. Food Chem Toxicol. 1999; 37:949–962. [PubMed: 10541450]
5. Mortensen A, Skibsted LH, Truscott TG. The interaction of dietary carotenoids with radical species. Arch Biochem Biophys. 2001; 385:13–19. [PubMed: 11361009]
6. Barreiro E, Peinado VI, Galdiz JB, et al. Cigarette smoke-induced oxidative stress: A role in chronic obstructive pulmonary disease skeletal muscle dysfunction. Am J Respir Crit Care Med. 2010; 182:477–488. [PubMed: 20413628]
7. Puntarulo S. Iron, oxidative stress and human health. Mol Aspects Med. 2005; 26:299–312. [PubMed: 16102805]
8. The effect of vitamin E beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med. 1994; 330:1029–1035. [PubMed: 8127329]
9. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA. 1996; 276:1957–1963. [PubMed: 8971064]
10. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996; 334:1145–1149. [PubMed: 8602179]
11. Lee IM, Cook NR, Manson JE, Buring JE. Randomised beta-carotene supplementation and incidence of cancer and cardiovascular disease in women: is the association modified by baseline plasma level? Br J Cancer. 2002; 86:698–701. [PubMed: 11875728]
12. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996; 334:1150–1155. [PubMed: 8602180]
13. Wright ME, Mayne ST, Stolzenberg-Solomon RZ, et al. Development of a comprehensive dietary antioxidant index and application to lung cancer risk in a cohort of male smokers. Am J Epidemiol. 2004; 160:68–76. [PubMed: 15229119]
14. Eastwood MA. Interaction of dietary antioxidants in vivo: how fruit and vegetables prevent disease? QJM. 1999; 92:527–530. [PubMed: 10627873]
15. Goodman M, Bostick RM, Dash C, et al. Hypothesis: oxidative stress score as a combined measure of pro-oxidant and antioxidant exposures. Ann Epidemiol. 2007; 17:394–399. [PubMed: 17462547]
16. Goodman M, Bostick RM, Dash C, et al. A summary measure of pro- and anti-oxidant exposures and risk of incident, sporadic, colorectal adenomas. Cancer Causes Control. 2008; 19:1051–1064. [PubMed: 18543072]

17. Goodman M, Bostick RM, Gross M, et al. Combined measure of pro- and anti-oxidant exposures in relation to prostate cancer and colorectal adenoma risk: an update. Ann Epidemiol. 2010; 20:955–957. [PubMed: 21074110]
18. Slattery ML, Lundgreen A, Welbourn B, et al. Oxidative balance and colon and rectal cancer: Interaction of lifestyle factors and genes. Mutat Res. 2012; 734:30–40. [PubMed: 22531693]
19. Van Hoydonck PG, Temme EH, Schouten EG. A dietary oxidative balance score of vitamin C, beta-carotene and iron intakes and mortality risk in male smoking Belgians. J Nutr. 2002; 132:756–761. [PubMed: 11925473]
20. Thomas SR, Neuzil J, Mohr D, Stocker R. Coantioxidants make alpha-tocopherol an efficient antioxidant for low-density lipoprotein. Am J Clin Nutr. 1995; 62:1357S–1364S. [PubMed: 7495231]
21. Geybels MS, Verhage BA, van Schooten FJ, van den Brandt PA. Measures of combined antioxidant and pro-oxidant exposures and risk of overall and advanced stage prostate cancer. Ann Epidemiol. 2012
22. Dash C, Goodman M, Flanders WD, et al. Using pathway-specific comprehensive exposure scores in epidemiology: application to oxidative balance in a pooled case-control study of incident, sporadic colorectal adenomas. Am J Epidemiol. 2013; 178:610–624. [PubMed: 23639935]
23. Lakkur S, Goodman M, Bostick RM, et al. Oxidative balance score and risk for incident prostate cancer in a prospective U.S. cohort study. Ann Epidemiol. 2014; 24:475–478 e474. [PubMed: 24731700]
24. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005; 25:135–143. [PubMed: 15990444]
25. Alberts MJ. The Stroke Belt Consortium. J Stroke Cerebrovasc Dis. 1996; 6:54–58. [PubMed: 17894966]
26. Boyapati SM, Bostick RM, McGlynn KA, et al. Calcium, vitamin D, and risk for colorectal adenoma: dependency on vitamin D receptor BsmI polymorphism and nonsteroidal anti-inflammatory drug use? Cancer Epidemiol Biomarkers Prev. 2003; 12:631–637. [PubMed: 12869402]
27. Gong YL, Xie DW, Deng ZL, et al. Vitamin D receptor gene Tru9I polymorphism and risk for incidental sporadic colorectal adenomas. World J Gastroenterol. 2005; 11:4794–4799. [PubMed: 16097046]
28. Daniel CR, Bostick RM, Flanders WD, et al. TGF-alpha expression as a potential biomarker of risk within the normal-appearing colorectal mucosa of patients with and without incident sporadic adenoma. Cancer Epidemiol Biomarkers Prev. 2009; 18:65–73. [PubMed: 19124482]
29. Sidelnikov E, Bostick RM, Flanders WD, et al. MutL-homolog 1 expression and risk of incident, sporadic colorectal adenoma: search for prospective biomarkers of risk for colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2009; 18:1599–1609. [PubMed: 19423536]
30. Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA. 2004; 292:1433–1439. [PubMed: 15383513]
31. Agalliu I, Kirsh VA, Kreiger N, et al. Oxidative balance score and risk of prostate cancer: results from a case-cohort study. Cancer Epidemiol. 2011; 35:353–361. [PubMed: 21145797]
32. Dagenais GR, Marchioli R, Yusuf S, Tognoni G. Beta-carotene, vitamin C, and vitamin E and cardiovascular diseases. Curr Cardiol Rep. 2000; 2:293–299. [PubMed: 10953262]
33. Galli C, Marangoni F. Recent advances in the biology of n-6 fatty acids. Nutrition. 1997; 13:978–985. [PubMed: 9433715]
34. Heber D, Lu QY. Overview of mechanisms of action of lycopene. Exp Biol Med (Maywood). 2002; 227:920–923. [PubMed: 12424335]
35. Hercberg S, Galan P, Preziosi P, et al. The potential role of antioxidant vitamins in preventing cardiovascular diseases and cancers. Nutrition. 1998; 14:513–520. [PubMed: 9646292]
36. Lee IM. Antioxidant vitamins in the prevention of cancer. Proc Assoc Am Physicians. 1999; 111:10–15. [PubMed: 9893152]

37. Li GX, Lee MJ, Liu AB, et al. delta-tocopherol is more active than alpha – or gamma -tocopherol in inhibiting lung tumorigenesis in vivo. Cancer Prev Res (Phila). 2011; 4:404–413. [PubMed: 21372040]

38. Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. Free Radic Biol Med. 1999; 26:746–761. [PubMed: 10218665]

39. Pandey DK, Shekelle R, Selwyn BJ, et al. Dietary vitamin C and beta-carotene and risk of death in middle-aged men. The Western Electric Study. Am J Epidemiol. 1995; 142:1269–1278. [PubMed: 7503047]

40. Swain JH, Alekel DL, Dent SB, et al. Iron indexes and total antioxidant status in response to soy protein intake in perimenopausal women. Am J Clin Nutr. 2002; 76:165–171. [PubMed: 12081830]

41. van der Vaart H, Postma DS, Timens W, ten Hacken NH. Acute effects of cigarette smoke on inflammation and oxidative stress: a review. Thorax. 2004; 59:713–721. [PubMed: 15282395]

42. Velthuis-te Wierik EJ, van den Berg H, Weststrate JA, et al. Consumption of reduced-fat products: effects on parameters of anti-oxidative capacity. Eur J Clin Nutr. 1996; 50:214–219. [PubMed: 8730607]

43. Schatzkin A, Kipnis V. Could exposure assessment problems give us wrong answers to nutrition and cancer questions? J Natl Cancer Inst. 2004; 96:1564–1565. [PubMed: 15523078]

44. Boucher B, Cotterchio M, Kreiger N, et al. Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. Public Health Nutr. 2006; 9:84–93. [PubMed: 16480538]

45. Caan BJ, Slattery ML, Potter J, et al. Comparison of the Block and the Willett self-administered semiquantitative food frequency questionnaires with an interviewer-administered dietary history. Am J Epidemiol. 1998; 148:1137–1147. [PubMed: 9867257]

46. Subar AF, Thompson FE, Kipnis V, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. Am J Epidemiol. 2001; 154:1089–1099. [PubMed: 11744511]

47. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. Annu Rev Pharmacol Toxicol. 2004; 44:239–267. [PubMed: 14744246]

Table 1

Oxidative Balance Score (OBS) Assignment Scheme

OBS Components	Assignment Scheme†
1. PUFA intake [P]	0 = High (3rd tertile), 1 = Intermediate (2nd tertile), 2 = Low (1st tertile)
2. Total* iron intake [P]	0 = High (3rd tertile), 1 = Intermediate (2nd tertile), 2 = Low (1st tertile)
3. Total vitamin C intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
4. Total lycopene intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
5. Total α-carotene intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
6. Total β-carotene intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
7. Total lutein intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
8. Total β-cryptoxanthin intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
9. Total α-tocopherol intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
10. Selenium intake [A]	0 = Low (1st tertile), 1 = Intermediate (2nd tertile), 2 = High (3rd tertile)
11. Smoking history [P]	0 = Current smoker, 1 = Former smoker, 2 = Never smoker
12. Regular‡ aspirin use [A]	0 = No regular use, 1 = Unknown (missing data), 2 = Regular Use
13. Regular‡ NSAID use [A]	0 = No regular use, 1 = Unknown (missing data), 2 = Regular Use
14. Alcohol consumption [P]	0 = Heavy, 1 = Moderate, 2 = None

Abbreviations: OBS = oxidative balance score; PUFA = polyunsaturated fatty acid; NSAID = non-steroidal anti-inflammatory drug; A = anti-oxidant; P = pro-oxidant

† Low, intermediate, and high categories correspond to baseline sex-specific tertile values among participants in the REGARDS cohort.

* Total intake = dietary intake + supplemental intake (when available)

‡ Regular use defined as daily use

Table 2

Selected Baseline Characteristics of the REGARDS Cohort, by OBS Quartile

Characteristic (Units)†	Quartile 1 (n = 5,668)	Quartile 2 (n = 5,593)	Quartile 3 (n = 5,523)	Quartile 4 (n = 4,247)
Age, years	63.5 (9.3)	64.7 (9.4)	65.5 (9.1)	66.0 (9.1)
Race				
White	3,680 (64.9%)	3,654 (65.3%)	3,745 (67.8%)	2,944 (69.3%)
Black	1,988 (35.1%)	1,939 (34.7%)	1,778 (32.2%)	1,303 (30.7%)
Sex				
Male	2,589 (45.7%)	2,455 (43.9%)	2,424 (43.9%)	1,785 (42.0%)
Female	3,079 (54.3%)	3,138 (56.1%)	3,099 (56.1%)	2,462 (58.0%)
BMI* (kg/m^2)	28.8 (6.0)	29.1 (6.2)	29.1 (6.0)	29.3 (6.1)
Total energy intake (kcal/day)	1,474.6 (604.5)	1,641.6 (669.5)	1,809.9 (726.8)	1972.3 (758.5)
Education				
Less than high school	681 (12.0%)	567 (10.1%)	478 (8.6%)	290 (6.8%)
High school graduate	1,700 (30.0%)	1,469 (26.3%)	1,286 (23.3%)	9190 (21.6%)
Some college	1,590 (28.0%)	1,559 (27.9%)	1,469 (26.6%)	1,140 (26.9%)
College graduate and above	1,697 (30.0%)	1,998 (35.7%)	2,290 (41.5%)	1,898 (44.7%)
Income				
< $20k	1,001 (17.7%)	878 (15.7%)	850 (15.4%)	576 (13.5%)
$20k – $34k	1,458 (25.7%)	1,370 (24.5%)	1,253 (22.7%)	1,002 (23.6%)
$35k – $74k	1,680(29.6%)	1,718 (30.7%)	1,806 (32.7%)	1,379 (32.5%)
≥ $75k	891 (15.7%)	745 (16.9%)	973 (17.6%)	806 (19.0%)
Refused	638 (11.3%)	682 (12.2%)	641 (11.6%)	484 (11.4%)
Region				
Stroke belt	2,058 (36.3%)	1,969 (35.2%)	1,821 (33.0%)	1,378 (32.4%)
Stroke buckle	1,306 (23.0%)	1,234 (22.1%)	1,190 (21.5%)	888 (21.0%)
Non-belt	2,304 (40.7%)	2,390 (42.7%)	2,512 (45.5%)	1,981 (46.6%)
Follow-up time, years	5.7 (2.0)	5.8 (2.0)	5.9 (1.9)	5.9 (1.9)

† Values for age, BMI, energy, and follow-up years are mean (SD), and those for race, sex, education, income, and region are number (percent)

* BMI = body mass index

Table 3

Individual Components of the Score by OBS Quartile

Characteristic (Units)†	Mean (by OBS Quartile) Quartile 1 (n = 5,668)	Quartile 2 (n = 5,593)	Quartile 3 (n = 5,523)	Quartile 4 (n = 4,247)
PUFA intake (g/day)				
Men (n = 9,253)	18.1 (9.7)	19.7 (10.7)	21.1 (11.0)	21.7 (11.1)
Women (n = 11,778)	15.7 (9.1)	16.9 (9.8)	18.2 (10.1)	19.2 (10.4)
Total* iron intake (mg/d)				
Men	17.7 (13.6)	23.6 (16.0)	27.5 (17.3)	30.9 (19.3)
Women	18.1 (16.5)	23.1 (18.9)	26.7 (19.0)	30.4 (21.2)
Total vitamin C intake (mg/d)				
Men	121.1 (177.9)	280.9 (356.2)	421.9 (467.2)	644.8(563.2)
Women	148.8 (231.2)	284.7 (349.9)	433.2 (439.2)	621.5 (520.7)
Total lycopene intake (μg/d)				
Men	2,918.5 (3,155.0)	4,263.4 (4,646.0)	5,364.0 (5,002.0)	7,431.1 (7,083.0)
Women	2,292.8 (2,493.0)	3,348.4 (3,752.0)	4,313.1 (4,626.0)	5,849.7 (5,785.0)
Total α-carotene intake (μg/d)				
Men	327.0 (287.8)	530.8 (494.2)	843.5 (759.9)	1,258.5 (1,120.0)
Women	295.6 (239.3)	517.4 (556.4)	852.8 (901.0)	1,261.0 (1,124.0)
Total β-carotene intake (μg/d)				
Men	2,161.6 (1,883.0)	3,806.6 (3,639.0)	9,096.7 (5,701.0)	9,110.9 (7,596.0)
Women	2,250.2 (1,563.0)	4,075.5 (3,982.0)	6,395.9 (5,496.0)	9,384.6 (7,433.0)
Total lutein intake (μg/d)				
Men	829.2 (602.7)	1,327.1 (1,041.0)	1,958.5 (1,624.0)	2,837.8 (2,452.0)
Women	964.0 (821.3)	1,527.3 (1,304.0)	2,380.4 (2,201.0)	3,358.1 (2,796.0)
Total β-cryptoxanthin intake (μg/d)				
Men	63.1 (82.6)	113.9 (120.4)	157.9 (142.7)	209.7 (159.2)
Women	53.6 (71.7)	102.2 (111.0)	142.9 (140.6)	193.1 (157.9)
Total vitamin E intake (α-TE/d)				
Men	34.2 (87.9)	85.0 (151.1)	130.9 (183.5)	193.5 (193.6)
Women	39.7 (93.5)	87.0 (155.6)	126.4 (171.5)	189.3 (193.9)
Daily selenium intake (mcg/d)				
Men	79.4 (35.6)	98.4 (48.6)	117.7 (61.1)	141.5 (75.0)
Women	66.3 (31.7)	81.6 (42.7)	97.4 (50.3)	118.2 (62.6)
Smoking				
Never	1,775 (31.3%)	2,410 (43.1%)	2,726 (49.4%)	2,615 (61.6%)
Former	2,429 (42.9%)	2,449 (43.8%)	2,320 (42.0%)	1,445 (34.0%)
Current	1,464 (25.8%)	734 (13.1%)	477 (8.6%)	187 (4.4%)
Alcohol consumption°				
None	3,030 (53.5%)	3,355 (60.0%)	3,311 (60.0%)	2,858 (67.3%)
Moderate	2,198 (38.8%)	2,015 (36.0%)	2,028 (36.7%)	1,310 (30.8%)

Characteristic (Units)†	Mean (by OBS Quartile)			
	Quartile 1 (n = 5,668)	Quartile 2 (n = 5,593)	Quartile 3 (n = 5,523)	Quartile 4 (n = 4,247)
Heavy	440 (7.7%)	223 (4.0%)	184 (3.3%)	79 (1.9%)
Regular‡ NSAID Use	451 (8.0%)	698 (12.5%)	885 (16.1%)	1,114 (26.3%)
Regular‡ aspirin Use	1,545 (27.3%)	2,327 (41.6%)	2,646 (47.9%)	2,749 (64.8%)
Total OBS	9.2 (1.6)	13.0 (0.8)	16.0 (0.8)	19.4 (1.4)

Abbreviations: PUFA = polyunsaturated fatty acid; NSAID = non-steroidal anti-inflammatory drug; OBS = oxidative balance score; SD = standard deviation

†Values are presented as mean (SD) or number (%)

*Total intake = dietary intake + supplemental intake (when available)

°Moderate = 1 – 7 drinks/week for women and 1 – 14 drinks/week for men; heavy = > 7 drinks/week for women and > 14 drinks/week for men

‡Regular use defined as daily use

Table 4

Associations of the OBS with All-cause and Cause-specific Mortality in the REGARDS Cohort: Equal Weighing

Endpoints / OBS Quartiles (OBS Range: 3 – 26)	Alive (n = 18,952)	Died (n = 2,079)	With Smoking°	Without Smoking+
			HR (95% CI)†	HR (95% CI)‡
All cause-mortality				
Continuous			0.96 (0.95,0.98)	0.99 (0.98, 1.00)
Q 1	5,025	643	1.0	1.0
Q 2	5,047	546	0.81 (0.72, 0.91)	0.89 (0.79, 1.00)
Q 3	4,999	524	0.77 (0.68, 0.87)	0.94 (0.82, 1.07)
Q 4	3,881	366	0.70 (0.61, 0.81)	0.87 (0.77, 0.99)
P-trend*			< 0.001	0.01
Cancer mortality				
Continuous			0.93 (0.90, 0.95)	0.97 (0.94, 0.99)
Q 1	5,025	163	1.0	1.0
Q 2	5,047	112	0.64 (0.50, 0.82)	0.84 (0.66, 1.06)
Q 3	4,999	106	0.60 (0.47, 0.78)	0.79 (0.59, 1.05)
Q 4	3,881	69	0.50 (0.37, 0.67)	0.68 (0.52, 0.90)
P-trend*			< 0.001	0.01
All non-cancer mortality				
Continuous			0.97 (0.96, 0.99)	0.99 (0.98, 1.01)
Q 1	5,02	480	1.0	1.0
Q 2	5,047	434	0.86 (0.75, 0.98)	0.91 (0.79, 1.03)
Q 3	4,999	418	0.83 (0.72, 0.95)	0.99 (0.85, 1.15)
Q 4	3,881	297	0.77 (0.66, 0.89)	0.93 (0.80, 1.07)
P-trend*			0.001	0.66
Cardiac mortality				
Continuous			0.96 (0.92, 1.01)	0.98 (0.94, 1.03)
Q 1	5,025	26	1.0	1.0
Q 2	5,047	23	0.69 (0.45, 1.08)	0.65 (0.42, 1.02)
Q 3	4,999	27	0.66 (0.41, 1.04)	0.78 (0.47, 1.28)
Q 4	3,881	21	0.68 (0.41, 1.13)	0.77 (0.49, 1.23)
P-trend*			0.10	0.37
Heart failure mortality				
Continuous			0.93 (0.83, 1.05)	1.01 (0.96,1.08)
Q 1	5,025	74	1.0	1.0
Q 2	5,047	59	0.81 (0.45, 1.45)	0.83 (0.47, 1.46)
Q 3	4,999	61	1.08 (0.62, 1.89)	1.19 (0.65, 2.18)
Q 4	3,881	48	1.12 (0.60, 2.07)	1.14 (0.64, 2.02)
P-trend*			0.53	0.39

Endpoints / OBS Quartiles (OBS Range: 3 – 26)	Alive (n = 18,952)	Died (n = 2,079)	With Smoking°	Without Smoking+
			HR (95% CI)†	HR (95% CI)‡
Chronic lung disease mortality				
Continuous			0.93 (0.88, 0.99)	0.98 (0.92, 1.05)
Q 1	5,025	24	1.0	1.0
Q 2	5,047	32	1.28 (0.75, 2.19)	1.52 (0.88, 2.61)
Q 3	4,999	17	0.66 (0.35, 1.25)	0.95 (0.47, 1.91)
Q 4	3,881	11	0.48 (0.22, 1.05	0.74 (0.37, 1.49)
P-trend*			0.02	0.26

Abbreviations: OBS = oxidative balance score; HR = hazards ratio; CI = confidence interval; Q = quartile

†Adjusted for age, sex, race, body mass index, total daily energy, education, exercise, and region of residence

‡Adjusted for the same variables as above plus smoking

*P-trend assessed by X^2 test for linear trend

°Smoking was included in the OBS

+Smoking was removed from the OBS but controlled for in the model

Table 5

Associations between the OBS and All-cause, Cancer, and Non-cancer Mortality in the REGARDS Cohort: Different Weighting Approaches

OBS Weighting	All-cause Mortality		Cancer Mortality		Non-cancer Mortality	
	OBS With Smoking HR (95% CI)†	OBS Without Smoking HR (95% CI)‡	OBS With Smoking HR (95% CI)†	OBS Without Smoking HR (95% CI)‡	OBS With Smoking HR (95% CI)†	OBS Without Smoking HR (95% CI)‡
FIP weights						
Q 1	1.0	1.0	1.0	1.0	1.0	1.0
Q 2	0.84 (0.74, 0.94)	0.91 (0.80, 1.03)	0.71 (0.56, 0.92)	0.84 (0.65, 1.09)	0.88 (0.77, 1.01)	0.94 (0.82, 1.08)
Q 3	0.79 (0.70, 0.90)	0.93 (0.82, 1.06)	0.62 (0.48, 0.81)	0.82 (0.63, 1.07)	0.85 (0.74, 0.98)	0.98 (0.85, 1.13)
Q 4	0.67 (0.59, 0.77)	0.84 (0.73, 0.96)	0.48 (0.36, 0.64)	0.66 (0.49, 0.88)	0.73 (0.63, 0.85)	0.89 (0.76, 1.04)
P-trend*	< 0.001	0.08	< 0.001	0.01	< 0.001	0.34
FOP weights						
Q 1	1.0	1.0	1.0	1.0	1.0	1.0
Q 2	0.83 (0.73, 0.92)	0.92 (0.78, 1.07)	0.69 (0.54, 0.87)	0.80 (0.62, 1.04)	0.88 (0.76, 1.00)	0.97 (0.84, 1.11)
Q 3	0.76 (0.66, 0.84)	1.09 (0.93, 1.27)	0.52 (0.40, 0.68)	0.82 (0.63, 1.07)	0.82 (0.72, 0.95)	1.04 (0.90, 1.20)
Q 4	0.66 (0.58, 0.75)	0.90 (0.76, 1.06)	0.45 (0.34, 0.59)	0.67 (0.51, 0.89)	0.73 (0.63, 0.85)	0.98 (0.84, 1.13)
P-trend*	< 0.001	0.89	< 0.001	0.01	< 0.001	0.68
Lit. review weights						
Q 1	1.0	1.0	1.0	1.0	1.0	1.0
Q 2	0.82 (0.73, 0.92)	0.94 (0.83, 1.06)	0.66 (0.52, 0.85)	0.81 (0.63, 1.05)	0.88 (0.76, 1.00)	0.98 (0.85, 1.13)
Q 3	0.73 (0.65, 0.83)	0.96 (0.85, 1.09)	0.56 (0.43, 0.73)	0.86 (0.66, 1.11)	0.79 (0.69, 0.91)	0.99 (0.86, 1.14)
Q 4	0.65 (0.57, 0.74)	0.88 (0.77, 1.01)	0.43 (0.32, 0.57)	0.66 (0.49, 0.88)	0.71 (0.61, 0.82)	0.95 (0.82, 1.10)
P-trend*	< 0.001	0.15	< 0.001	0.02	< 0.001	0.69

Abbreviations: OBS = oxidative balance score; HR = hazards ratio; CI =confidence interval; FIP = F_2-isoprostanes; FOP = fluorescent oxidation products; Lit. = literature; Q = quartile

†Adjusted for age, sex, race, body mass index, total daily energy intake, education, exercise, and region of residence

‡Adjusted for the same variables as above plus smoking

*P-trend assessed by X^2 test for linear trend

Table 6

Sensitivity Analyses to Evaluate the Impact of Individual OBS Components on Study Results

Model	All-cause Mortality	Cancer Mortality	Non-Cancer Mortality
	HR (95% CI)†	HR (95% CI)†	HR (95% CI)†
Original model (reference)	0.96 (0.95, 0.98)	0.93 (0.90, 0.95)	0.97 (0.96, 0.99)
OBS excluding PUFA, controlled for PUFA	0.96 (0.95, 0.97)	0.93 (0.90, 0.95)	0.97 (0.96, 0.98)
OBS excluding iron, controlled for iron	0.96 (0.95, 0.98)	0.93 (0.91, 0.96)	0.97 (0.96, 0.98)
OBS excluding vitamin C, controlled for vitamin C	0.96 (0.95, 0.98)	0.93 (0.90, 0.96)	0.97 (0.96, 0.99)
OBS excluding lycopene, controlled for lycopene	0.96 (0.95, 0.97)	0.92 (0.90, 0.95)	0.97 (0.95, 0.98)
OBS excluding α-carotene, controlled for α-carotene	0.96 (0.95, 0.97)	0.93 (0.90, 0.96)	0.97 (0.95, 0.98)
OBS excluding β-carotene, controlled for β-carotene	0.95 (0.94, 0.97)	0.92 (0.89, 0.96)	0.96 (0.94, 0.98)
OBS excluding lutein, controlled for lutein	0.97 (0.96, 0.98)	0.92 (0.90, 0.95)	0.98 (0.97, 1.00)
OBS excluding β-cryptoxanthin, controlled for β-cryptoxanthin	0.96 (0.95, 0.98)	0.92 (0.89, 0.94)	0.98 (0.96, 0.99)
OBS excluding α-tocopherol, controlled for α-tocopherol	0.97 (0.95, 0.98)	0.92 (0.90, 0.95)	0.98 (0.96, 0.99)
OBS excluding selenium, controlled for selenium	0.96 (0.95, 0.98)	0.93 (0.90, 0.95)	0.97 (0.96, 0.99)
OBS excluding smoking, controlled for smoking	0.99 (0.98, 1.00)	0.97 (0.94, 0.99)	0.99 (0.98, 1.01)
OBS excluding aspirin, controlled for aspirin	0.96 (0.94, 0.97)	0.93 (0.90, 0.95)	0.96 (0.95, 0.98)
OBS excluding NSAID, controlled for NSAID	0.96 (0.95, 0.98)	0.93 (0.90, 0.95)	0.97 (0.96, 0.99)
OBS excluding alcohol, controlled for alcohol	0.96 (0.95, 0.97)	0.93 (0.91, 0.96)	0.97 (0.95, 0.98)

Abbreviations: OBS = oxidative balance score; HR = hazards ratio; CI = confidence interval; PUFA = polyunsaturated fatty acid; NSAID = non-steroidal anti-inflammatory drug

†HR represents change in hazards for each additional OBS point; all results adjusted for age, sex, race, body mass index, total daily energy intake, education, exercise, and region of residence