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ORIGINAL CONTRIBUTION

Associations of dietary and lifestyle oxidative balance scores with mortality risk among older women: the Iowa Women's Health Study

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Abstract

Purpose Substantial basic science evidence suggests that oxidative stress may play a role in aging-related health outcomes, including cardiovascular diseases (CVD) and cancer, and oxidative stress markers were linked with all-cause and cause-specific mortality in epidemiologic studies. However, the associations of many individual dietary and lifestyle anti-/pro-oxidant exposures with mortality are inconsistent. Oxidative balance scores (OBS) that incorporated multiple dietary and lifestyle factors were previously developed and reported to reflect the collective oxidative effects of multiple exposures.

Methods We investigated associations of 11-component dietary and 4-component (physical activity, adiposity, alcohol, and smoking) lifestyle OBS (higher scores were considered more anti-oxidative) with all-cause and cause-specific mortality among women 55–69 years of age at baseline in the prospective Iowa Women's Health Study (1986–2012). We assessed OBS-mortality associations using multivariable Cox proportional hazards regression.

Results Of the 34,137 cancer-free women included in the analytic cohort, 18,058 died (4521 from cancer, and 6825 from CVD) during a mean/median 22.0/26.1 person-years of follow-up. Among participants in the highest relative to the lowest lifestyle OBS quintiles, the adjusted hazards ratios and their 95% confidence intervals for all-cause, all-cancer, and all-CVD mortality were 0.50 (0.48, 0.53), 0.47 (0.43, 0.52), and 0.54 (0.50, 0.58) (all $P_{trend} < 0.001$), respectively. The associations of the dietary OBS with mortality were close to null.

Conclusion Our findings, combined with results from previous studies, suggest that a predominance of antioxidant over pro-oxidant lifestyle exposures may be associated with lower all-cause, all-CVD, and all-cancer mortality risk.

Keywords Diet · Lifestyle · Mortality · Oxidative stress · Cohort studies

Introduction

Chronic diseases, including cancer and cardiovascular diseases (CVD), are the leading causes of death worldwide [1]. Multiple dietary and lifestyle factors, such as smoking and obesity, have been linked to the incidence of and mortality from several chronic diseases, especially cancer and CVD. Oxidative stress has also been implicated in the etiology of multiple chronic diseases [2–4]. Oxidative stress was defined as an imbalance of pro-oxidants to antioxidants [5, 6]. A predominance of pro-oxidant exposures leads to excess reactive oxygen and nitrogen species (RONS) production, leading to cellular and DNA damage [5, 6]. Substantial basic science evidence suggested that oxidative stress may play a role in accelerating the aging of cells, and was associated with risk for chronic diseases, including CVD and multiple types of cancer [2–4].

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Although oxidative stress has also been linked to all-cause and cause-specific mortality in epidemiologic studies [4, 7–10] through investigations of oxidative stress markers and mortality, the results in the epidemiologic literature regarding the associations of many specific dietary and lifestyle anti-/pro-oxidant exposures with mortality are inconsistent [11]. On the other hand, there are some suggestions that the anti-/pro-oxidative effects of individual dietary and lifestyle exposures on risk and mortality may be small, but collectively may be substantial [12]. To address this, oxidative balance scores (OBS) were developed and reported [12–15] to reflect the collective oxidative effects of multiple dietary and lifestyle exposures. The rationale for creating a comprehensive score incorporating multiple dietary and lifestyle exposures to reflect oxidative balance was previously described [14, 15], and the associations of OBS with various outcomes reviewed [16]. OBS were reported to be associated with multiple health outcomes, such as colorectal neoplasms [12–15] and cancers of the esophagus [17], lung [18], breast [19], and prostate [14]. However, reported investigations of OBS-mortality risk associations were limited to only two epidemiologic studies [20, 21]; one [21] included only dietary exposures in the score, and neither study reported separate dietary and lifestyle OBS.

Therefore, to clarify associations of the OBS with all-cause and cause-specific mortality, we investigated separate and joint associations of the dietary and lifestyle OBS with all-cause, all-cancer, and all-CVD mortality risk in the prospective Iowa Women's Health Study (IWHS). We hypothesized that more anti-oxidant relative to pro-oxidant dietary and lifestyle exposures would be associated with lower all-cause and cause-specific mortality risk. To our knowledge, this is the largest prospective cohort study so far to investigate OBS-mortality associations.

Methods

Study population

Details of the IWHS were previously reported [22]. Briefly, the IWHS is a prospective cohort study initiated in 1986, with follow-up for the present analysis through 2012. A total of 41,836 Iowa women aged 55–69 years completed mailed questionnaires to self-report information on demographics, diet, lifestyle, anthropometrics, and medical and reproductive history at baseline. Follow-up questionnaires were mailed in 1987, 1989, 1992, 1997, and 2004. The study was approved by the Minnesota Institutional Review Board (IRB), the current analysis was approved by the Emory University IRB, and all participants provided informed consent prior to inclusion in the study.

Collection of exposure and outcome information

A Willett 127-item food frequency questionnaire (FFQ) was used to measure dietary, supplement, and alcohol intakes over the previous 12 months; the validity and reliability in the study population were previously reported [23]. Total nutrient and energy intakes were calculated by adding energy and nutrients from all food and supplement sources using Willett's dietary database [23]. Physical activity was assessed via two questions regarding participants' usual frequencies of moderate and vigorous activity, and then categorized into three levels: high (vigorous activity twice a week or moderate activity > 4 times/week), medium (vigorous activity once a week plus moderate activity once a week, or moderate activity 2–4 times/week), and low [24]. Anthropometrics were self-measured; the reliability and validity of self-measurement in the study population were previously reported [23]. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist and hip circumferences were used to calculate a waist: hip ratio (WHR). Information on diet and physical activity were not comprehensively reassessed until 2004, at which time only 68.3% of participants remained alive. Therefore, for our primary analyses, we used only baseline (1986) exposure information, but included 2004 exposure information in one of two sensitivity analyses (described further below) that supported the validity of this choice.

Information on deaths was collected from the State Health Registry of Iowa and the National Death Index. Cause of death was assigned and coded by state vital registries according to the International Classification of Diseases (ICD). Cancer mortality was defined according to ICD-9 codes 140–239 and ICD-10 codes C00–D48; CVD mortality was defined according to ICD-9 codes 390–459 and ICD-10 codes I00–I99. Follow-up time was calculated as the time between the date of baseline questionnaire completion and the date of death or the end of the last follow-up (December 31, 2012), whichever was first.

OBS components and calculations

Details of the creation of the questionnaire-based, multicomponent OBS were previously published [12, 13] and are summarized below. The OBS was previously validated via its association with circulating F_2-isoprostanes concentrations—the most reliably measured, valid in vivo biomarker of systemic oxidative stress currently used in epidemiologic studies [25–28]. In previous studies, associations of OBS with health outcomes were comparable regardless of the different weighting methods used for

OBS creation (equal-weight, literature review-derived, study data-based, and Bayesian method) [12, 13]. In the present study, we used the more straightforward equal-weight OBS, which incorporates 11 dietary and 4 lifestyle OBS components. The 15 OBS components were determined a priori based on their literature-supported physiological effects on oxidative processes as previously reported in detail [12, 13] (also see a referenced summary in Supplemental Table 1). The dietary OBS components included carotene (α and β), flavonoids, lutein/zeaxanthin, lycopene, selenium, omega-3 fatty acids, vitamin C, and vitamin E as antioxidants; and iron, omega-6 fatty acids, and saturated fats as pro-oxidants. The lifestyle OBS components included physical activity as having indirect antioxidant effects; and adiposity, alcohol intake, and smoking as having pro-oxidant effects.

All dietary OBS components were continuous variables derived from the FFQ. For all nutrients except selenium, we used total (i.e., from foods plus supplements) nutrient values; we used only supplement values for selenium since selenium intake from foods depends on the soils in which selenium's plant sources are grown. Prior to inclusion in the score, macronutrients were energy-adjusted as a percentage of total energy contributed by the macronutrient, and micronutrients were energy-adjusted using the density method (i.e., mg of vitamin C/1000 kcal of total energy intake). Lifestyle OBS components were obtained from the lifestyle questionnaire. All were initially 3-level categorical variables as follows: adiposity (low: BMI < 30 and WHR < 0.8; moderate: either BMI ≥ 30 or WHR ≥ 0.8; or high: BMI ≥ 30 and WHR ≥ 0.8), alcohol intake (< 1 drinks/week, 1 – 7 drinks/week, or ≥ 7 drinks/week), smoking status (non-smoker, former smoker, or current smoker), and physical activity (low, medium, or high; described in the data collection sub-section above). We then assigned the lifestyle OBS categories initial values of 0, 1, or 2 for each category from the lowest to the highest level.

Next, we standardized all components' values to a mean of zero and standard deviation of one by subtracting a participant's value from the study population mean, and dividing it by the population standard deviation. The assumption for the equal-weight OBS is that all components are equally important and should contribute similar weights to the score, so we then multiplied these values by + 1 or − 1 for antioxidants or pro-oxidants, respectively. We then summed the resulting values for each of the dietary and lifestyle OBS to constitute an individual's dietary and lifestyle OBS. A higher score would be considered more anti-oxidative. We also calculated a total OBS by summing all the components of the dietary and lifestyle OBS. For subsequent analyses, we categorized all three OBS according to quintiles of their distributions in the analytic population at baseline.

Statistical analyses

Exclusion criteria

Prior to the scores' calculations and statistical analyses, we excluded participants who had a history of cancer (other than non-melanoma skin cancer) at baseline ($n = 3830$), left > 10% of the FFQ items blank ($n = 2499$), self-reported implausible energy intakes (< 600 or > 5000 kcal/day; $n = 286$), had an invalid contributed person-time ($n = 2$), or were missing data on any lifestyle OBS component ($n = 1082$), leaving an analytic cohort of 34,137.

Main analyses

We categorized participants' dietary and lifestyle OBS according to quintiles of their distributions in the entire analytic population at baseline, and summarized selected participant characteristics by lifestyle and dietary OBS quintiles, using descriptive statistics. To investigate associations of the dietary, lifestyle, and total OBS with all-cause, all-cancer, and all-CVD mortality risk, we used multivariable Cox proportional hazards regression models to calculate adjusted hazards ratios (HR) and their corresponding 95% confidence intervals (CI). We included the median values of lifestyle, dietary, and total OBS quintiles as continuous variables in models to test for trend. We chose the covariates in the models a priori based on biological plausibility and previous literature. We included only baseline age (years) and total energy intake (kcal/day) as covariates in minimally adjusted models. Fully adjusted models for all three OBS included baseline age (years), total energy intake (kcal/day), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (HRT) (yes/no), marital status (yes/no), and comorbidity status (defined as having one or more chronic diseases [diabetes, heart disease, and cirrhosis]) (yes/no). The lifestyle OBS models additionally included the dietary OBS, and the dietary OBS models additionally included physical activity, alcohol intake, smoking status, and our above-described adiposity variable. We tested the proportional hazards assumptions using Schoenfeld residuals for each exposure and covariate.

We assessed correlation between the lifestyle and dietary OBS via a Spearman correlation coefficient. We also estimated the cumulative incidence of mortality due to all causes, CVD, and cancer using methods for competing risks analysis in all models [29], and reported it within quintiles of the dietary, lifestyle, and total OBS.

Joint/combined (cross-classification) analyses

To examine potential interaction between the lifestyle and dietary OBS in relation to all-cause, all-cancer, and all-CVD mortality risk, we conducted joint/combined analyses, considering the lowest joint quintile of the two scores as the reference category. We calculated $P_{interaction}$ using the Wald test by including a lifestyle times dietary OBS interaction term in the multivariable Cox proportional hazards regression model.

Stratified analyses

We conducted stratified analyses to assess whether the associations differed by categories of selected participants' baseline characteristics. We stratified on age (≤/> median age of 61 years), current HRT use (yes/no), and comorbidity (yes/no). We categorized all three OBS according to tertiles for the stratified analyses due to sample size constraints. We calculated $P_{interaction}$ by including an interaction term of the stratification factor times the OBS in the multivariable Cox proportional hazards regression models.

Sensitivity analyses

We also conducted several sensitivity analyses to assess the robustness of our a priori planned analyses to alternative considerations. Since our primary analyses were based on baseline data for the OBS calculations, and some participants could have changed their exposures during follow-up, we conducted two sensitivity analyses. First, we assessed OBS-mortality risk associations considering study end dates of 5, 10, 15, 20, and 25 years after baseline. Second, we assessed the associations after incorporating exposure data from the 2004 follow-up questionnaire two ways: among those who were not censored prior to 2004, we used (i) the average of their baseline (1986) and 2004 follow-up OBS, and (ii) their 2004 OBS only. Other sensitivity analyses included, first, censoring participants when they reached 75 years of age (to assess a potential attenuating effect of chance due to aging). Second, we excluded participants who died within the first two years of follow-up (to rule out reverse causality within early follow-up affecting the estimated associations). Third, some evidence suggested a *U*-shaped alcohol-mortality association [30], so we repeated our primary analysis using the following alternative alcohol intake scoring: < 1 drinks/week was assigned value of 2; alcohol intake 1–7 drinks/week was assigned value of 0, and alcohol intake ≥ 7 drinks/week was assigned value of 2. Fourth, to assess whether the lifestyle OBS-mortality risk associations were driven by any particularly influential component, we removed individual components from the lifestyle OBS, with replacement, one at a time, and then examined the associations of the remaining 3-component lifestyle OBS with mortality risk separately, adjusted for the removed component as a covariate.

We conducted all analyses using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). All *P*-values were two-sided. We considered *P* values ≤ 0.05 or 95% CIs that excluded 1.0 statistically significant.

Results

Of the 34,137 cancer-free women included in the analytic cohort, over a mean/median 22.0/26.1 person-years of follow-up, 18,058 died (4521 from cancer, and 6825 from CVD). The Spearman correlation between the dietary and lifestyle OBS was $r = 0.10$.

Participant characteristics

Selected baseline characteristics of the participants according to dietary and lifestyle OBS quintiles are summarized in Table 1. Study participants were 61 years of age, on average, and > 99% were white. Participants in the upper relative to the lower quintiles of both the dietary and lifestyle scores were slightly more likely to take HRT, and had higher mean total vegetables and fruit and total calcium intakes, and lower mean red and processed meat intakes. Women in the higher dietary OBS quintiles, aside from dietary OBS components, also were slightly less likely to be a current smoker, and more likely to have a high physical activity level. Exclusive of lifestyle OBS components, those in the upper lifestyle OBS quintiles had, on average, higher total vitamin A, vitamin C, and vitamin E intakes.

OBS and mortality risk

Associations of the lifestyle, dietary, and total OBS with all-cause and cause-specific mortality are presented in Table 2. For the lifestyle and total OBS, the estimated associations from the minimally and fully adjusted models differed minimally; for the dietary OBS, full adjustment attenuated all estimated associations. In the fully-adjusted analyses, OBS-mortality associations tended to statistically significantly decrease with higher lifestyle and total OBS. Among women in the highest relative to the lowest lifestyle OBS quintiles, all-cause, all-cancer, and all-CVD mortality risks were statistically significantly 50%, 53%, and 46% lower, respectively; among those in the highest relative to the lowest total OBS quintiles, all-cause, all-cancer, and all-CVD mortality risks were statistically significantly 34%, 39%, and 29% lower, respectively. For the dietary OBS, all fully adjusted associations with mortality risks were close to null.

Table 1 Selected baseline participant characteristics[a] according to dietary and lifestyle oxidative balance score quintiles; the Iowa Women's Health Study (n = 34,137), 1986–2012

Characteristics	Dietary oxidative balance score quintiles[b]			Lifestyle oxidative balance score quintiles[b]		
	1 (n = 6827)	3 (n = 6827)	5 (n = 6827)	1 (n = 6923)	3 (n = 7019)	5 (n = 7683)
	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %
Age, years	61.0 ± 4.1	61.6 ± 4.2	61.7 ± 4.2	61.1 ± 4.1	61.7 ± 4.2	61.7 ± 4.2
High school graduate or higher, %	79.0	83.6	83.1	80.1	81.4	83.8
Currently use hormone therapy, %	9.7	11.7	13.3	10.1	11.1	12.3
Currently married, %	78.3	77.3	75.3	73.0	77.3	79.9
Have a comorbidity[c] %	13.2	14.2	17.0	15.8	15.8	11.2
Dietary intakes						
Total energy, kcal/day	1911 ± 665	1837 ± 587	1743 ± 553	1825 ± 625	1794 ± 603	1800 ± 583
Total vegetables and fruit, servings/week	32.4 ± 15.2	44.2 ± 18.2	54.7 ± 28.2	40.7 ± 20.8	42.8 ± 20.8	47.2 ± 21.9
Red and processed meats, servings/week	10.8 ± 6.5	7.8 ± 4.3	5.2 ± 3.7	8.3 ± 5.3	8.1 ± 5.4	7.3 ± 4.9
Total calcium[d] mg/(10^3 kcal·day)	379 ± 264	400 ± 289	791 ± 410	585 ± 322	621 ± 325	683 ± 344
Total vitamin A[d] IU/(10^3 kcal·day)	4594 ± 2422	7336 ± 2809	14,459 ± 8197	7373 ± 4823	7999 ± 5539	8967 ± 6063
Total vitamin C[d] mg/(10^3 kcal·day)	88 ± 93	143 ± 122	352 ± 314	164 ± 190	169 ± 189	186 ± 206
Total vitamin E[d] mg/(10^3 kcal·day)	22 ± 45	31 ± 60	119 ± 165	43 ± 90	46 ± 93	54 ± 106
Take multivitamin, %	26.3	32.2	45.8	30.2	31.5	36.3
Lifestyle characteristics						
High physical activity[e] %	16.4	24.7	35.3	7.9	5.1	56.5
Current smoker, %	19.6	14.3	13.1	51.3	5.7	0.0
> 7 alcoholic drinks/week, %	6.4	8.3	7.8	32.4	0.0	0.0
High adiposity[f] %	20.8	20.3	18.3	34.2	15.4	0.0

Abbreviations: *IU* international units, *SD* standard deviation

[a]Continuous variables presented as means (standard deviation); categorical variables presented as percentages

[b]Oxidative balance scores (OBS) composed of the dietary or lifestyle exposures listed in Supplemental Table 1; see the text for construction of the 'equal-weight' scores; a higher score represents a higher balance of antioxidant relative to pro-oxidant exposures

[c]Self-reported history of diabetes mellitus, heart disease, and/or cirrhosis

[d]Total = diet plus supplements

[e]Physical activity level derived from two questions regarding the frequency of moderate and vigorous physical activity, and categorized as high (vigorous activity twice a week or moderate activity > 4 times/week), medium (vigorous activity once a week plus moderate activity once a week, or moderate activity 2–4 times/week), and low

[f]Adiposity defined as high if body mass index (BMI; weight [kg]/height [m^2]) ≥ 30 and waist:hip ratio (WHR) ≥ 0.8; medium if either BMI ≥ 30 or WHR ≥ 0.8; and low if BMI < 30 and WHR < 0.8

The cumulative incidences of all-cause and cause-specific mortality by OBS quintiles, summarized in Supplemental Figs. 1, 2, 3 and Supplemental Table 2, were consistent with the estimated HRs in Table 2. Throughout the study follow-up period, participants in the highest relative to the lowest lifestyle and total OBS quintiles appeared to have a lower cumulative incidence of all mortality types; for the dietary OBS, there were no differences in the cumulative incidences of any of the three mortality types across dietary OBS quintiles. The 25-year cumulative mortality incidence was lower among participants in the highest relative to the lowest lifestyle OBS quintiles (all-cause mortality [57.8% vs. 36.8%], all-cancer mortality [21.2% vs. 10.8%], and all-CVD mortality risks [25.9% vs. 16.1%], respectively) and the total OBS (all-cause mortality [46.7% vs. 43.2%], all-cancer mortality [18.3% vs. 12.3%], and all-CVD mortality risk [23.6% vs. 19.8%], respectively).

Joint/combined (cross-classification) analyses

The joint/combined (cross-classification) associations of the dietary and lifestyle OBS with all-cause and cause-specific mortality risk are shown in Table 3. There were patterns of decreasing risk with an increasing lifestyle OBS among women in the lowest dietary OBS quintile for all mortality types. On the other hand, there were no definitive patterns of decreasing risk with an increasing dietary OBS among women in the lowest lifestyle OBS quintile. However, those

Table 2 Associations[a] of the oxidative balance scores with all-cause, all-cancer, and all-cardiovascular disease mortality risk in the Iowa Women's Health Study (n = 34,137), 1986–2012

Mortality type/ OBS variable forms	Oxidative balance score[b]											
	Dietary				Lifestyle				Total			
	Minimally-adjusted model[c]		Fully-adjusted model[d]		Minimally-adjusted model[c]		Fully-adjusted model[e]		Minimally-adjusted model[c]		Fully-adjusted model[f]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-causes												
Continuous	1.00	0.99, 1.00	1.00	1.00, 1.01	0.88	0.87, 0.89	0.88	0.88, 0.89	0.97	0.97, 0.97	0.97	0.97, 0.98
Quintiles												
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.89	0.85, 0.93	0.93	0.89, 0.98	0.76	0.73, 0.79	0.76	0.73, 0.80	0.80	0.76, 0.83	0.80	0.77, 0.83
3	0.88	0.84, 0.93	0.95	0.91, 1.00	0.62	0.59, 0.65	0.61	0.59, 0.64	0.71	0.67, 0.74	0.73	0.70, 0.77
4	0.89	0.85, 0.93	0.96	0.91, 1.01	0.58	0.56, 0.61	0.59	0.56, 0.61	0.67	0.64, 0.71	0.70	0.66, 0.73
5	0.90	0.86, 0.95	0.99	0.94, 1.04	0.49	0.46, 0.51	0.50	0.48, 0.53	0.65	0.62, 0.68	0.66	0.63, 0.69
P_{trend}	*0.002*		*0.81*		*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Cancer												
Continuous	0.99	0.98, 1.00	1.00	0.99, 1.01	0.87	0.86, 0.88	0.87	0.86, 0.88	0.97	0.96, 0.97	0.97	0.96, 0.97
Quintiles												
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.94	0.85, 1.03	0.98	0.89, 1.07	0.70	0.65, 0.77	0.71	0.65, 0.77	0.77	0.71, 0.85	0.77	0.71, 0.84
3	0.91	0.83, 0.99	0.96	0.88, 1.06	0.55	0.51, 0.60	0.55	0.51, 0.60	0.71	0.65, 0.77	0.72	0.66, 0.79
4	0.94	0.86, 1.03	1.00	0.91, 1.10	0.53	0.48, 0.58	0.53	0.49, 0.59	0.66	0.60, 0.72	0.67	0.61, 0.73
5	0.89	0.80, 0.98	0.96	0.87, 1.06	0.46	0.42, 0.50	0.47	0.43, 0.52	0.60	0.55, 0.66	0.61	0.55, 0.67
P_{trend}	*0.03*		*0.60*		*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
CVD												
Continuous	1.00	0.99, 1.01	1.01	1.00, 1.01	0.89	0.88, 0.90	0.90	0.89, 0.91	0.98	0.97, 0.98	0.98	0.97, 0.98
Quintiles												
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.88	0.82, 0.95	0.92	0.85, 0.99	0.80	0.75, 0.86	0.80	0.75, 0.86	0.83	0.77, 0.89	0.84	0.78, 0.91
3	0.89	0.83, 0.96	0.96	0.89, 1.04	0.67	0.62, 0.72	0.66	0.62, 0.71	0.73	0.67, 0.78	0.76	0.70, 0.82
4	0.90	0.83, 0.97	0.97	0.89, 1.04	0.66	0.62, 0.72	0.67	0.62, 0.72	0.73	0.68, 0.79	0.77	0.70, 0.83
5	0.94	0.87, 1.02	1.02	0.94, 1.11	0.52	0.48, 0.56	0.54	0.50, 0.58	0.69	0.64, 0.75	0.71	0.66, 0.77
P_{trend}	*0.49*		*0.18*		*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	

Abbreviations: *CI* confidence interval, *CVD* cardiovascular disease, *HR* hazard ratio, *OBS* oxidative balance score

[a]HRs and 95% CIs from Cox proportional hazards models

[b]Oxidative balance scores (OBS) composed of the dietary or lifestyle exposures listed in Supplemental Table 1; see the text for construction of the 'equal-weight' scores; a higher score represents a higher balance of antioxidant relative to pro-oxidant exposures

[c]Minimally-adjusted models: adjusted for age (years; continuous) and total energy intake (kcal/day; continuous)

[d]Model for dietary OBS adjusted for age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (yes/no), marital status (yes/no), comorbidity (yes/no), physical activity (low/medium/high; see text and Table 1 footnote 'e' for definitions), smoking status (current/former/non-smoker), alcohol consumption (drinks/week; continuous), and adiposity (low/medium/high; see text and Table 1 footnote 'f' for definitions)

[e]Model for lifestyle OBS adjusted for age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (yes/no), marital status (yes/no), comorbidity (yes/no; see text for definition), and the equal-weight dietary OBS

[f]Model for total OBS adjusted for age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (yes/no), marital status (yes/no), and comorbidity (yes/no; see text for definition)

Table 3 Multivariable-adjusted joint/combined associations[a] of the dietary and lifestyle oxidative balance scores[b] with all-cause, all-cancer, and all-cardiovascular disease mortality risk; the Iowa Women's Health Study ($n = 34,137$), 1986–2012

Mortality type/lifestyle OBS quintiles	Dietary OBS quintiles														
	1			2			3			4			5		
	n	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI
All causes[c]															
1	1604	1.00	Referent	1440	0.90	0.82, 0.98	1371	0.91	0.83, 1.00	1328	0.83	0.75, 0.91	1180	0.93	0.84, 1.03
2	1470	0.72	0.66, 0.79	1400	0.66	0.60, 0.73	1301	0.67	0.60,0.73	1289	0.72	0.65, 0.80	1283	0.73	0.65, 0.80
3	1485	0.55	0.50, 0.61	1502	0.55	0.50, 0.60	1459	0.56	0.51, 0.62	1353	0.58	0.53, 0.65	1220	0.59	0.53, 0.65
4	929	0.58	0.52, 0.65	1100	0.52	0.47, 0.58	1154	0.49	0.44, 0.55	1246	0.53	0.48, 0.59	1340	0.56	0.50, 0.62
5	1339	0.50	0.45, 0.55	1386	0.45	0.40, 0.50	1542	0.48	0.43, 0.53	1612	0.45	0.40, 0.50	1804	0.44	0.39, 0.49
Cancer[d]															
1	1604	1.00	Referent	1440	0.93	0.79, 1.10	1440	0.96	0.81, 1.15	1328	0.94	0.79, 1.13	1180	0.90	0.73, 1.09
2	1470	0.73	0.61, 0.86	1400	0.66	0.55, 0.79	1400	0.65	0.54, 0.79	1289	0.70	0.58, 0.85	1283	0.64	0.52, 0.78
3	1485	0.44	0.36, 0.54	1502	0.55	0.46, 0.67	1502	0.52	0.42, 0.63	1353	0.58	0.47, 0.70	1220	0.53	0.42, 0.65
4	929	0.58	0.47, 0.72	1100	0.54	0.44, 0.67	1100	0.41	0.32, 0.51	1246	0.52	0.42, 0.64	1340	0.51	0.41, 0.64
5	1339	0.44	0.36, 0.54	1386	0.41	0.34, 0.51	1386	0.50	0.41, 0.60	1612	0.44	0.35, 0.53	1804	0.46	0.38, 0.57
CVD[e]															
1	1604	1.00	Referent	1440	0.85	0.72, 0.99	1440	0.94	0.81, 1.11	1328	0.82	0.69, 0.96	1180	1.04	0.87, 1.24
2	1470	0.77	0.66, 0.90	1400	0.72	0.62, 0.85	1400	0.71	0.60, 0.84	1289	0.76	0.64, 0.89	1283	0.79	0.66, 0.94
3	1485	0.62	0.53, 0.73	1502	0.58	0.50, 0.69	1502	0.59	0.50, 0.70	1353	0.67	0.57, 0.80	1220	0.66	0.55, 0.79
4	929	0.66	0.55, 0.79	1100	0.61	0.51, 0.72	1100	0.60	0.51, 0.72	1246	0.62	0.52, 0.74	1340	0.63	0.53, 0.75
5	1339	0.57	0.48, 0.67	1386	0.49	0.41, 0.58	1386	0.51	0.43, 0.61	1612	0.46	0.39, 0.55	1804	0.47	0.39, 0.56

Abbreviations: *CI* confidence interval, *CVD* cardiovascular disease, *HR* hazards ratio, *OBS* oxidative balance scores

[a]HRs and 95% CIs from Cox proportional hazards models; covariates included age (years; continuous), education (</≥high school), current hormone replacement therapy use (yes/no), marital status (yes/no), comorbidity (includes sum of yes/no for diabetes, heart disease, or cirrhosis), and total energy intake (kcal/day; continuous)

[b]For construction of the "equal-weight" scores, see text and Supplemental Table 1; a higher score represent a higher balance of antioxidant over pro-oxidant exposures

[c]$P_{\text{interaction}} = 0.52$; from Wald test

[d]$P_{\text{interaction}} = 0.17$; from Wald test

[e]$P_{\text{interaction}} = 0.29$; from Wald test

in the highest relative to the lowest joint lifestyle/dietary OBS quintile were at the lowest all-cause mortality risk; risk was statistically significantly 56%, 54%, and 53% lower for all-cause, all-cancer, and all-CVD mortality, respectively ($P_{\text{interaction}} = 0.52$, 0.17, and 0.29, respectively).

Stratified analyses

The multivariable-adjusted associations of the OBS with all-cause and cause-specific mortality risk according to selected participant characteristics are summarized in Table 4. The lifestyle OBS-CVD mortality risk association was more strongly inverse among those who were younger (< 61 years): for those in the highest relative to the lowest lifestyle OBS quintiles, the HRs (95% CIs) among those who were younger and older were 0.43 (0.37, 0.49) and 0.64 (0.59, 0.71), respectively ($P_{\text{interaction}} < 0.001$). These findings were reflected, to a lesser degree, in the total OBS-CVD mortality and the lifestyle- and total OBS-all-cause mortality risk associations. The lifestyle OBS-cancer mortality risk association was more strongly inverse among those who did not take HRT and among those with a co-morbidity at baseline (both $P_{\text{interaction}} = 0.04$); for those in the highest relative to the lowest lifestyle OBS quintile, the HRs—all statistically significant—among those who did/did not take HRT and those with/without a comorbidity were, respectively, 0.45/0.64 and 0.37/0.49. Although the $P_{\text{interaction}}$ for differences in the total OBS-all-cause mortality risk association according to co-morbidity status was statistically significant, the magnitude of the difference appeared modest and driven by the lifestyle OBS-all-cancer mortality risk association. The estimated dietary OBS-mortality associations were close to null within all strata and none of the point estimates was statistically significant, although the $P_{\text{interaction}}$ for the dietary OBS and comorbidity in relation to all-cause mortality was 0.02.

Table 4 Adjusted associations[a] of the oxidative balance scores[b] with all-cause, all-cancer and all-CVD mortality risk, according to categories of selected participant characteristics; the Iowa Women's Health Study (n = 34,137), 1986–2012

Stratification variables, OBS quintiles	Causes of death								
	All-causes			Cancer			CVD		
	Dietary[c]	Lifestyle[d]	Total[e]	Dietary[c]	Lifestyle[d]	Total[e]	Dietary[c]	Lifestyle[d]	Total[e]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age, years									
≤61 (n = 17,764)									
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	0.97 (0.91, 1.05)	0.72 (0.68, 0.77)	0.76 (0.71, 0.82)	0.98 (0.86, 1.12)	0.68 (0.60, 0.76)	0.79 (0.70, 0.89)	0.91 (0.80, 1.04)	0.76 (0.68, 0.86)	0.82 (0.72, 0.92)
3	0.99 (0.90, 1.07)	0.58 (0.54, 0.62)	0.70 (0.65, 0.75)	1.02 (0.89, 1.16)	0.52 (0.46, 0.59)	0.72 (0.64, 0.82)	0.99 (0.87, 1.13)	0.65 (0.57, 0.73)	0.70 (0.62, 0.80)
4	0.98 (0.91, 1.06)	0.54 (0.50, 0.58)	0.67 (0.63, 0.72)	0.99 (0.86, 1.13)	0.51 (0.45, 0.59)	0.65 (0.57, 0.74)	0.95 (0.83, 1.09)	0.60 (0.53, 0.69)	0.74 (0.65, 0.84)
5	1.03 (0.95, 1.11)	0.43 (0.40, 0.47)	0.62 (0.58,0.67)	0.99 (0.86, 1.14)	0.45 (0.40, 0.51)	0.60 (0.52, 0.69)	1.04 (0.91, 1.19)	0.43 (0.37, 0.49)	0.64 (0.56, 0.73)
P_{trend}	*0.41*	*< 0.001*	*< 0.001*	*0.94*	*< 0.001*	*< 0.001*	*0.4*	*< 0.001*	*< 0.001*
> 61 (n = 16,374)									
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	0.94 (0.88, 0.99)	0.83 (0.78, 0.88)	0.85 (0.80, 0.90)	0.98 (0.87, 1.02)	0.77 (0.68, 0.86)	0.76 (0.67, 0.87)	0.96 (0.88, 1.06)	0.87 (0.79, 0.96)	0.89 (0.81, 0.98)
3	0.96 (0.90, 1.02)	0.68 (0.65, 0.73)	0.79 (0.74, 0.83)	0.93 (0.81, 1.06)	0.60 (0.53, 0.68)	0.73 (0.64, 0.83)	0.98 (0.89, 1.08)	0.73 (0.67, 0.80)	0.83 (0.76, 0.91)
4	0.97 (0.92, 1.04)	0.67 (0.63, 0.71)	0.75 (0.71, 0.80)	1.03 (0.90, 1.17)	0.58 (0.51, 0.66)	0.70 (0.62, 0.80)	1.01 (0.92, 1.11)	0.76 (0.69, 0.84)	0.84 (0.77, 0.92)
5	0.99 (0.93, 1.05)	0.58 (0.55, 0.62)	0.72 (0.68, 0.86)	0.94 (0.82, 1.08)	0.51 (0.45, 0.58)	0.63 (0.55, 0.72)	1.04 (0.95, 1.15)	0.64 (0.59, 0.71)	0.79 (0.72, 0.87)
P_{trend}	*0.63*	*< 0.001*	*< 0.001*	*0.56*	*< 0.001*	*< 0.001*	*0.17*	*< 0.001*	*< 0.001*
$P_{interaction}$[f]	*0.97*	*< 0.001*	*0.002*	*0.74*	*0.12*	*0.35*	*0.64*	*< 0.001*	*< 0.001*
Current HRT use									
No (n = 30,225)									
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	0.93 (0.89, 0.98)	0.76 (0.73, 0.80)	0.79 (0.75, 0.82)	0.99 (0.90, 1.09)	0.69 (0.63, 0.76)	0.76 (0.70, 0.84)	0.91 (0.84, 0.99)	0.82 (0.76, 0.89)	0.84 (0.77, 0.90)
3	0.95 (0.90, 0.99)	0.61 (0.58, 0.64)	0.72 (0.69, 0.76)	0.98 (0.88, 1.08)	0.55 (0.50, 0.60)	0.72 (0.65, 0.79)	0.93 (0.86, 1.01)	0.67 (0.62, 0.72)	0.74 (0.69, 0.80)
4	0.96 (0.91, 1.01)	0.58 (0.56, 0.61)	0.69 (0.66, 0.73)	1.03 (0.93, 1.14)	0.53 (0.48, 0.58)	0.68 (0.61, 0.74)	0.95 (0.88, 1.03)	0.68 (0.63, 0.74)	0.76 (0.70, 0.82)
5	1.00 (0.95, 1.05)	0.50 (0.48, 0.53)	0.66 (0.63, 0.69)	0.98 (0.88, 1.09)	0.45 (0.41, 0.50)	0.61 (0.55, 0.67)	1.00 (0.92, 1.09)	0.55 (0.51, 0.60)	0.71 (0.65, 0.77)
P_{trend}	*0.49*	*< 0.001*	*< 0.001*	*0.88*	*< 0.001*	*< 0.001*	*0.40*	*< 0.001*	*< 0.001*
Yes (n = 3913)									
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	0.92 (0.79, 1.08)	0.74 (0.64, 0.85)	0.93 (0.80, 1.09)	0.87 (0.65, 1.15)	0.90 (0.69, 1.18)	0.86 (0.65, 1.13)	1.00 (0.75, 1.32)	0.63 (0.49, 0.81)	0.96 (0.73, 1.26)
3	1.02 (0.87, 1.18)	0.65 (0.57, 0.76)	0.84 (0.73, 0.98)	0.86 (065, 1.14)	0.58 (0.44, 0.78)	0.74 (0.57, 0.97)	1.26 (0.96, 1.65)	0.60 (0.47, 0.76)	0.98 (0.76, 1.27)
4	0.99 (0.84, 1.16)	0.60 (0.52, 0.70)	0.72 (0.62, 0.84)	0.82 (0.61, 1.10)	0.60 (0.45, 0.80)	0.63 (0.48, 0.83)	1.14 (0.86, 1.51)	0.55 (0.43, 0.71)	0.84 (0.64, 1.10)

Table 4 (continued)

Stratification variables, OBS quintiles	Causes of death								
	All-causes			Cancer			CVD		
	Dietary[c]	Lifestyle[d]	Total[e]	Dietary[c]	Lifestyle[d]	Total[e]	Dietary[c]	Lifestyle[d]	Total[e]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
5	0.96 (0.82, 1.12)	0.52 (0.45, 0.60)	0.68 (0.58, 0.79)	0.83 (0.63, 1.11)	0.64 (0.49, 0.83)	0.60 (0.46, 0.80)	1.25 (0.95, 1.64)	0.43 (0.33, 0.54)	0.80 (0.62, 1.04)
P_{trend}	*0.82*	*< 0.001*	*< 0.001*	*0.26*	*< 0.001*	*< 0.001*	*0.08*	*< 0.001*	*< 0.001*
$P_{interaction}$[f]	*0.50*	*0.22*	*0.80*	*0.18*	*0.04*	*0.55*	*0.27*	*0.24*	*0.51*
Comorbidity									
No ($n = 29{,}091$)									
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	0.93 (0.88, 0.89)	0.76 (0.72, 0.79)	0.78 (0.74, 0.82)	0.95 (0.86, 1.04)	0.73 (0.67, 0.89)	0.76 (0.69, 0.83)	0.92 (0.85, 1.01)	0.78 (0.72, 0.85)	0.83 (0.76, 0.90)
3	0.94 (0.89, 0.99)	0.60 (0.57, 0.63)	0.70 (0.66, 0.73)	0.95 (0.86, 1.06)	0.56 (0.51, 0.62)	0.70 (0.63, 0.77)	0.95 (0.87, 1.03)	0.66 (0.61, 0.72)	0.72 (0.66, 0.78)
4	0.94 (0.89, 0.99)	0.57 (0.54, 0.61)	0.66 (0.63, 0.69)	0.96 (0.86, 1.06)	0.55 (0.49, 0.61)	0.65 (0.59, 0.72)	0.95 (0.87, 1.04)	0.64 (0.59, 0.70)	0.72 (0.66, 0.79)
5	0.97 (0.92, 1.03)	0.50 (0.48, 0.53)	0.64 (0.61, 0.67)	0.93 (0.84, 1.04)	0.49 (0.45, 0.54)	0.59 (0.53, 0.66)	1.01 (0.92, 1.11)	0.54 (0.50, 0.59)	0.70 (0.64, 0.76)
P_{trend}	*0.70*	*< 0.001*	*< 0.001*	*0.28*	*< 0.001*	*< 0.001*	*0.43*	*< 0.001*	*< 0.001*
Yes ($n = 5046$)									
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	0.95 (0.85, 1.05)	0.78 (0.71, 0.86)	0.86 (0.78, 0.95)	1.22 (0.94, 1.57)	0.61 (0.49, 0.76)	0.88 (0.70, 1.11)	0.91 (0.78, 1.07)	0.86 (0.75, 0.99)	0.87 (0.75, 1.02)
3	1.02 (0.92, 1.14)	0.66 (0.60, 0.73)	0.87 (0.79, 0.97)	1.05 (0.80, 1.37)	0.50 (0.40, 0.62)	0.88 (0.69, 1.12)	0.99 (0.85, 1.17)	0.67 (0.58, 0.78)	0.89 (0.77, 1.04)
4	1.06 (0.96, 1.18)	0.63 (0.57, 0.70)	0.84 (0.76, 0.93)	1.34 (1.04, 1.73)	0.47 (0.37, 0.60)	0.79 (0.62, 1.01)	1.00 (0.86, 1.17)	0.75 (0.64, 0.87)	0.90 (0.78, 1.05)
5	1.06 (0.95, 1.18)	0.51 (0.46, 0.57)	0.74 (0.67, 0.83)	1.17 (0.89, 1.52)	0.37 (0.29, 0.48)	0.69 (0.54, 0.88)	1.05 (0.89, 1.23)	0.53 (0.45, 0.63)	0.75 (0.64, 0.88)
P_{trend}	*0.07*	*< 0.001*	*< 0.001*	*0.28*	*< 0.001*	*0.002*	*0.25*	*< 0.001*	*0.001*
$P_{interaction}$[f]	*0.02*	*0.73*	*0.005*	*0.11*	*0.04*	*0.30*	*0.41*	*0.34*	*0.27*

Abbreviations *CI* confidence interval, *CVD* cardiovascular disease, *HR* hazard ratio; *HRT* hormone replacement therapy, *OBS* oxidative balance score

[a]HRs and 95% CIs from Cox proportional hazards models

[b]Oxidative balance scores (OBS) composed of the dietary or lifestyle exposures listed in Supplemental Table 1; see the text for construction of the 'equal-weight' scores; a higher score represents a higher balance of antioxidant relative to pro-oxidant exposures

[c]Model for dietary OBS adjusted for age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (yes/no), marital status (yes/no), comorbidity (yes/no), physical activity (low/medium/high; see text and Table 1 footnote 'e' for definitions), smoking status (current/former/non-smoker), alcohol consumption (drinks/week; continuous), and adiposity (low/medium/high; see text and Table 1 footnote 'f' for definitions)

[d]Model for lifestyle OBS adjusted for age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (yes/no), marital status (yes/no), comorbidity (yes/no; see text for definition), and the equal-weight dietary OBS

[e]Model for total OBS adjusted for age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), current use of hormone replacement therapy (yes/no), marital status (yes/no), and comorbidity (yes/no; see text for definition)

[f]$P_{interaction}$ from stratified risk factor*score interaction term in Cox proportional hazards model

Sensitivity analyses

In the sensitivity analyses, the estimated OBS-mortality risk associations after 5, 10, 15, 20, and 25 years of follow-up (Supplemental Table 3) were similar to those from the primary analyses. In addition, when we incorporated 2004 exposure data from those who completed the 2004 follow-up questionnaire, the OBS-mortality risk associations estimated using the average of the baseline and 2004 exposures were similar to those from our primary analyses; however, using 2004 exposure only attenuated the lifestyle- and total OBS-mortality risk associations modestly (Supplemental Table 4). In other sensitivity analyses, the estimated associations of the OBS with all-cause and cause-specific mortality risk were modestly stronger after censoring participants when they reached the age of 75 years (Supplemental Table 5). Exclusion of participants who died within the first two years after baseline (1986) (Supplemental Table 6) had minimal effects on our results. Using alternative alcohol intake scoring (Supplemental Table 7) tended to yield slightly stronger inverse associations of the lifestyle and total OBS with all-cause and all-CVD mortality risk. Finally, removal of any one component from the lifestyle OBS (Supplemental Table 8) tended to result in a slightly weaker inverse lifestyle OBS-mortality risk association. Removal of smoking status from the lifestyle OBS tended to attenuate the association the most: e.g., among those in the highest relative to the lowest lifestyle OBS quintiles, the HRs (which were all statistically significant) before/after removing smoking status were 0.50/0.76, 0.47/0.76, and 0.54/0.71, for all-cause, all-cancer, and all-CVD mortality, respectively.

Discussion

Our findings suggest that a predominance of antioxidant over pro-oxidant lifestyle exposures may be associated with lower all-cause, all-cancer, and all-CVD mortality risks. The associations of the dietary OBS with mortality in this study population of older, white, Iowa women were null, and the total OBS-mortality associations appeared largely driven by the lifestyle exposures; however, our joint/combined analysis findings suggested that those who jointly had high dietary and lifestyle OBS may have been at particularly low all-cause mortality risk.

A substantial literature supports the biological plausibility of multiple dietary and lifestyle exposures contributing to oxidative stress. Increasing evidence supports that higher intakes of certain nutrients, including carotenoids (e.g., lycopene, β-carotene, and lutein) [31, 32], vitamin C [33], vitamin E [34], selenium [35], omega-3 fatty acids [36, 37], and flavonoids [38–41], and regular physical activity [42], may protect against oxidative stress. Pro-oxidative factors, including iron [43], omega-6 fatty acids [37, 44, 45], and saturated fats [46, 47] intakes, obesity [48], smoking [49, 50], and alcohol intake [51, 52], increase RONS production and accelerate cellular damage caused by oxidative stress. The rationale for inclusion of each of the components of the dietary and lifestyle OBS was reported previously [12, 13] and is summarized in Supplemental Table 1.

Dietary and lifestyle exposures that were mechanistically linked or associated with oxidative stress were also associated with risk for several chronic diseases and mortality. Antioxidant-related micronutrients, including vitamin C, vitamin E, the carotenoids (e.g., β-carotene, lycopene and lutein), selenium, and the flavonoids, were suggested to protect against chronic diseases and mortality by reducing oxidative damage [18]. A substantial previous literature also supported associations of lifestyle factors (e.g., physical activity, smoking, alcohol intake, and adiposity) with all-cause and cause-specific mortality risk [53–57]. In epidemiologic studies, multiple oxidative stress markers were also strongly linked to mortality risk, especially all-cause and all-CVD mortality risk. Urinary oxidative stress markers, such as 8-isoprostane and oxidized guanine/guanosine, were reported to be associated with all-cause [7, 8, 10] and CVD mortality [8, 10]. A nested case–control study found the oxidative stress biomarker plasma F_2-isoprostanes to be associated with all-cause mortality risk [9].

As reviewed elsewhere [16], associations of OBS, comprising multiple anti- and pro-oxidative exposures, with various outcomes have been reported [16], but only two such studies [20, 21] focused on mortality. A prospective cohort study [21] of male smokers ($n = 2814$) reported statistically significant associations of a dietary OBS (comprising vitamin C, β-carotene, and iron; scored in the reverse direction from ours, such that a higher OBS was more pro-oxidant) with all-cause and all-cancer mortality risk. Men in the highest (most pro-oxidant) relative to the lowest (most antioxidant) dietary OBS group had higher relative risks (RR) for all-cause (RR = 1.44; 95% CI 1.13–1.82) and total cancer mortality (RR = 1.62; 95% CI 1.07–2.45). A population-based cohort of male and female, black and white US adults [20] ($n = 21{,}301$) reported associations of an OBS similar to ours with mortality risk. Among participants in the highest relative to the lowest OBS quartile, risk was statistically significantly 30%, 50%, and 23% lower for all-cause, all-cancer, and non-cancer mortality, respectively; the authors did not report findings by sex. These findings are consistent with those for our total OBS. Although the previous study did not report separate dietary or lifestyle OBS, it did report that removing smoking from the score attenuated the results, which might suggest that lifestyle exposures may have contributed more to the overall OBS-mortality associations than did the dietary exposures.

Other studies reported investigations of other dietary and lifestyle scores that were similar to our OBS with mortality. Of the lifestyle scores, despite the heterogeneity in score components and construction, most had some common elements with our lifestyle OBS, such as physical activity, alcohol consumption, smoking, and adiposity; however, all included some dietary component. Overall, previous studies on lifestyle scores support our findings of inverse associations of a lifestyle or total OBS with all-cause and cause-specific mortality risk [53–56, 58–61]. Of the three studies [54, 59, 61] that reported sex-specific results, two [59, 61] supported slightly stronger inverse associations of the lifestyle scores with all-cause mortality risk among women, while another [54] reported stronger associations of the lifestyle score with all-cause and all-CVD mortality risk among men.

Other studies also investigated associations of other dietary scores that were similar to our dietary OBS (e.g., the dietary inflammation score [DIS] and the dietary inflammatory index [DII]) with mortality risk [62–65]. The DIS and DII were developed based on associations of their component food groups/nutrients with circulating inflammation biomarker concentrations [66, 67]. Inconsistent with our results, most studies [62–65] reported statistically significant associations of the dietary scores with all-cause and cause-specific mortality. A meta-analysis of 12 prospective studies [63] found 23% higher all-cause mortality risk among those in the highest relative to lowest DII (a higher score is more pro-inflammatory) category. Another meta-analysis of 14 studies (including 11 prospective studies) [62] found that individuals in the highest relative to the lowest DII category had 36% higher risk of CVD incidence and mortality (RR = 1.36; 95% CI 1.19–1.57). The consistency of the findings across these studies might be due less to the differences between the scores and our dietary OBS than to the relative lack of heterogeneity of diets among IWHS participants. We note that in other study populations, dietary scores, such as the Mediterranean diet score [58, 68–71] and the evolutionary concordance diet score [68], were inversely associated with mortality risk, but were not in the IWHS [72]. An analysis to compare dietary heterogeneity within the IWHS with that within the REasons for Geographic and Racial Differences in Stroke cohort of black and white men and women from the 48 contiguous US states [73], revealed that the diets across the IWHS participants were relatively homogeneous, thus possibly explaining the null associations of the various diet pattern scores with mortality risk in the IWHS.

We are the first to report associations of dietary and lifestyle OBS with mortality risk separately, as well as in a joint/combined (cross-classification) analysis to assess potential interaction between dietary and lifestyle OBS in relation to mortality risk. Our results suggested that dietary factors that may contribute to oxidative balance, collectively, were not associated with mortality risk in our study population. However, our joint/combined analyses of the dietary and lifestyle OBS suggested that those in the highest joint dietary/lifestyle OBS quintile may have been at the lowest all-cause mortality risk. Our results also suggest that the total OBS, which includes (i) multiple dietary factors modestly associated with risk and (ii) a few lifestyle factors strongly associated with risk, may represent the average of the separate dietary and lifestyle OBS, rather than reflecting synergistic effects of lifestyle and diet that is suggested from the joint/combined analysis.

We also found that the associations of the lifestyle and total OBS with all-cause and all-CVD mortality risk tended to be stronger among those who were younger. The reason(s) is unclear. Participants who were older may have been less genetically susceptible to the effects of environmental exposures; specific antioxidant enzyme, DNA repair enzyme, and other longevity-relevant genes could dominate over environmental effects in lifespan determination in some people [74]. This could also explain why our inverse OBS-mortality associations became modestly stronger after censoring participants when they reached 75 years of age. Further, our estimated associations of the lifestyle and total OBS with all-cause and all-CVD mortality risk became modestly weaker with longer follow-up; this may also have reflected higher genetic-related resistance to oxidative stress or damage, but could also have been due to increasing exposure misclassification during follow-up. Our findings also suggest that OBS-mortality risk associations were modestly attenuated when we used exposure data only from 2004 from participants on whom they were available. This suggests that earlier lifestyle exposures may be more important than later ones in relation to mortality risk in an older population. However, given the multiple comparisons involved in the stratified and other sensitivity analyses, we cannot rule out that some of these results may have been due to chance. Overall, it would appear that our secondary and sensitivity analyses support our main findings, which if anything could have been under estimated.

Major strengths of this study include the prospective study design, large sample size and long follow-up, and comprehensive collection and assessment of multiple potential confounding/effect modifying risk factors. We also conducted a joint/combined (cross-classification) analysis to assess potential interaction between the dietary and lifestyle OBS in relation to mortality risk. Finally, to our knowledge, our study is the largest prospective cohort study to report OBS-mortality risk associations.

Our study also had several limitations. First, for our primary analyses, all OBS components were derived from information collected at baseline (1986). Some participants' diet and lifestyle exposures could have changed somewhat during follow-up. However, it is expected that in

a prospective cohort study, changes occur before a participant has their outcome, thus resulting in non-differential error that would be expected to attenuate associations. Consistent with expectations, in our sensitivity analyses, we found that the estimated OBS-mortality risk associations were similar (i) at follow-up intervals of 5, 10, 15, 20, and 25 years, and (ii) when the 2004 follow-up exposure data were incorporated two ways. Taken together, it would appear that changes in diet or lifestyle during follow-up likely would have affected our estimates only minimally. Second, food frequency questionnaires have known limitations (e.g., limited food choices and recall error); however, in a prospective study, these types of error are also considered non-differential. Third, physical activity assessment in the IWHS was based on only two questions; however, physical activity alone was previously reported to be statistically significantly inversely associated with mortality risk [24] and other outcomes in the IWHS [75, 76]. Finally, all participants in our study were older white Iowa women, which might limit the generalizability of our findings.

In conclusion, the results from this prospective study, combined with those from previous studies, suggest that a predominance of antioxidant over pro-oxidant lifestyle exposures may be associated with lower all-cause, all-CVD, and all-cancer mortality risk. Although the associations of our dietary OBS with mortality in our study population of older, white, Iowa women were null, our findings suggested that those who jointly had high dietary and lifestyle OBS may have been at particularly low risk for all-cause mortality, a finding that needs to be investigated in other study populations. Other needed future research includes (i) the development of OBS comprising components weighted by their strengths of association with a panel of valid, reliably measured biomarkers of oxidative stress in a population with strong diversity of exposures, and (ii) more investigations of associations of OBS with mortality and various chronic disease outcomes in other populations.

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Author contributions All authors contributed to the study conception and design, data interpretation, and manuscript writing. R.M.B. and Z.M. were primarily responsible for the project conception and design. D.L. and A.E.P. collected the data. Z.M. and R.M.B. were primarily responsible for analyzing and interpreting the data and writing the manuscript. R.M.B. supervised the analysis project and manuscript writing. All authors read and approved the final manuscript.

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Availability of data and material Data from this study are available upon application to DeAnn Lazovich, PhD, MPH, Division of Epidemiology and Community Health, University of Minnesota, 1300 S 2nd St., Room 300 West Bank Office Building, Minneapolis, MN 55,454.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics approval The study was approved by the Minnesota Institutional Review Board (IRB), and the current analysis was approved by the Emory University IRB.

Consent to participate All participants provided written informed consent.

Code availability The code supporting this current study is available from the corresponding author upon request.

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