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Associations of Evolutionary-concordance Diet, Mediterranean Diet, and Evolutionary-concordance Lifestyle Pattern Scores with All-cause and Cause-specific Mortality

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Abstract

Various individual diet and lifestyle factors are associated with mortality. Investigating these factors collectively may help clarify whether dietary and lifestyle patterns contribute to life expectancy. We investigated associations of previously-described evolutionary-concordance and Mediterranean diet pattern scores and a novel evolutionary-concordance lifestyle pattern score with all-cause and cause-specific mortality in the prospective Iowa Women's Health Study (1986 – 2012). We created the diet pattern scores from Willett food frequency questionnaire responses, and the lifestyle pattern score from self-reported physical activity, body mass index, and smoking status, and assessed their associations with mortality using multivariable Cox proportional hazards regression. Of the 35,221 55–69-year-old cancer-free women at baseline, 18,687 died during follow-up. The adjusted hazard ratios (HR) and 95% confidence intervals (CI) for all-cause, all-cardiovascular disease, and all-cancer mortality among participants in the highest relative to the lowest quintile of the evolutionary-concordance lifestyle score were, respectively, 0.52 (0.50, 0.55), 0.53 (0.49, 0.57), and 0.51 (0.46, 0.57). The corresponding findings for the Mediterranean diet score were HRs (95% CIs) 0.85 (0.82, 0.90), 0.83 (0.76, 0.90), and 0.93 (0.84, 1.03), and for the evolutionary-concordance diet score they were close to null and not statistically significant. The lowest estimated risk was among those in the highest joint quintile of either diet score and the lifestyle score (both $P_{interaction} < 0.01$). Our findings suggest that 1) a more Mediterranean-like diet pattern and 2) a more evolutionary-concordant lifestyle pattern, alone and in interaction with a

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more evolutionary-concordant or Mediterranean diet pattern, may be inversely associated with mortality.

Keywords

Mortality; Lifestyle; Paleolithic Diet; Mediterranean Diet; Cohort Studies

Introduction

Cancer and cardiovascular disease (CVD) are the two leading causes of death worldwide⁽¹⁾. Diet and lifestyle are associated with these and other diseases^(2, 3, 4, 5). Increased attention is being placed on dietary patterns rather than individual food components in epidemiologic investigations of associations of diet with mortality⁽⁶⁾. Various diet patterns, which contain multiple constituents, acting and interacting along the same and different pathways, have been inversely associated with chronic disease risk and mortality^(7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17), supporting further research into dietary patterns in chronic disease prevention⁽¹⁸⁾. Physical activity, excess adiposity, smoking, and other modifiable lifestyle factors have been associated with higher mortality^(3, 19, 20, 21, 22, 23, 24, 25). Lifestyle factors coexist and may interact, and underlying causes of death may be multi-causal⁽⁵⁾, suggesting that investigating associations of various lifestyle factors, in combination, with mortality may help with developing public health recommendations^(3, 4, 5, 8, 26, 27, 28, 29). Recently, we developed a “Paleolithic diet” pattern score and a modified Mediterranean diet pattern score, and found both diet pattern scores to be strongly inversely associated with biomarkers of oxidative stress and inflammation⁽³⁰⁾, colorectal adenoma⁽³¹⁾, and all-cause, all-CVD, and all-cancer mortality⁽³²⁾.

The Paleolithic diet pattern was developed to address the increase in “diseases of civilization” (cancer, CVD, etc.) as being the possible consequence of evolutionary discordance between the general diets and lifestyles of *Homo sapiens* living in the range of environments of evolutionary adaptedness before the agricultural revolution and those during the modern era⁽³³⁾. The Paleolithic diet pattern, which was estimated from anthropological studies of fossils and extant hunter-gather societies, is characterized as rich in a marked diversity of fruits and vegetables, lean meats, eggs, and nuts; excluding grains, dairy products, and refined fats and sugar; and very low in salt⁽³⁴⁾. Furthermore, lifestyle patterns that are more “Paleolithic-like” include high levels of physical activity, energy balances resulting in lean body masses, and no tobacco use^(34, 35). Given the constraints in investigating Paleolithic diet and lifestyle patterns in the modern context (e.g., limited wild foods intakes, food preparation methods, types of physical activity), herein, we use the alternative terms evolutionary-concordance diet and lifestyle patterns rather than “Paleolithic” (our re-termed evolutionary-concordance diet pattern score is identical to our previously-reported Paleolithic diet score).

The Mediterranean diet has been consistently reported to be beneficial for health and longevity^(36, 37), and is characterized by high intakes of fruits, cereals, nuts, vegetables, legumes, and olive oil; moderate intakes of fish and poultry; low intakes of eggs, dairy

products, red and processed meats, and sweets; and moderate consumption of alcohol with meals^(38, 39). Prospective cohort studies and recent meta-analyses found adherence to the Mediterranean diet pattern to be inversely associated with all-CVD and all-cause mortality^(8, 9, 10, 11, 13, 15, 17, 40), and inconsistently inversely associated with all-cancer mortality^(8, 10, 11, 14, 16, 40). Thus, the Mediterranean diet pattern can serve as a reference for comparisons of associations of a more evolutionary-concordant diet with mortality.

We previously reported similar inverse associations of evolutionary-concordance and Mediterranean diet pattern scores with all-cause, all-CVD, and all-cancer mortality in a prospective cohort of white and black adults⁽³²⁾. However, there are no reported studies of associations of an evolutionary-concordance lifestyle pattern score, alone or combined with an evolutionary-concordance or a Mediterranean diet pattern score, with mortality.

Therefore, we addressed this in the prospective Iowa Women's Health Study (IWHs).

Methods

Study population and data collection

As described previously⁽⁴¹⁾, the IWHs, established in 1986, is a prospective cohort study of 41,836 55–69-year-old Iowa women. In addition to the original survey, follow-up surveys were mailed in 1987, 1989, 1992, 1997, and 2004. The University of Minnesota Institutional Review Board (IRB) approved the study, and the Emory University IRB also approved the present analysis.

At baseline, detailed information on demographics, self-measured anthropometrics, lifestyle, medical and family history, diet, and other factors were collected. Dietary intakes and vitamin and mineral supplement use were collected at baseline using a 127-item semi-quantitative Willett food frequency questionnaire (FFQ), for which the validity and reliability in the study population was previously reported⁽⁴²⁾. Total energy and nutrient intakes were calculated by adding energy and nutrients from all food sources using the dietary database developed by Willett, et al⁽⁴³⁾. Physical activity was assessed via two questions regarding the frequency of partaking in moderate and vigorous physical activities⁽⁴⁴⁾, and categorized as low, medium, and high (see Table 2 footnote §). Diet and physical activity were only comprehensively reassessed in 2004 when only 68.3% of the participants remained alive (therefore, only baseline exposure information was used in the present analyses).

Deaths were identified through the State Health Registry of Iowa and the National Death Index for those who did not respond to the follow-up questionnaires or had emigrated from Iowa. Underlying cause of death was assigned and coded by state vital registries according to the International Classification of Diseases (ICD). Cardiovascular disease mortality was defined using ICD-9 codes 390–459 and ICD-10 codes I00–I99, and cancer mortality was defined using ICD-9 codes 140–239 and ICD-10 codes C00–D48. Follow-up time was calculated as the time from the date of completing the baseline questionnaire to the date of death, the last follow-up contact, or the end of follow up (December 31, 2012), whichever was first⁽⁴⁵⁾.

Scores

The evolutionary-concordance and Mediterranean diet pattern scores were constructed in a similar manner as described previously^(30, 31, 32). Based on the distribution of all study participants' baseline intakes, each participant was assigned a quintile rank (a corresponding score from 1 to 5) of intake for each food category. Higher scores were given for higher intakes of foods considered characteristic of the diet pattern, and lower scores were given for lower-to-no consumption of foods considered not characteristic of the diet pattern (Table 1). For the evolutionary-concordance diet score, two unique variables were created. The first, a fruit and vegetable diversity score, was created by summing the total number of different fruits and vegetables that participants reported consuming >1–3 servings/month. Second, since the Paleolithic diet had little dairy food but high amounts of calcium (from wild plant foods)⁽³⁴⁾, to consider dietary calcium separately from dairy products we used the residuals of a linear regression of total calcium intake on total dairy consumption. A modified Mediterranean diet score, the alternative Mediterranean diet score, originally developed as an adaptation to FFQs in the United States⁽⁴⁶⁾, was calculated according to previous literature^(46, 47). However, instead of basing it on dichotomizing the component dietary intake categories (high vs. low, based on median intake) as is most common, we used quintiles of intakes to facilitate a more direct comparison of the two diet scores. The components of the dietary scores were not weighted because 1) in our previously reported studies of dietary scores, weighting made no difference^(48, 49, 50), and 2) the components of Mediterranean diet scores traditionally are not weighted. The points for each of the food groups comprising diet scores were summed. Therefore, the final, possible score ranges were 14–70 for the 14-component evolutionary-concordance diet score, and 9–45 for the 9-component Mediterranean diet score, with higher scores indicating higher concordance with a dietary pattern.

For our novel, weighted, evolutionary-concordance lifestyle score, we combined physical activity, body mass index (BMI; weight [kg]/height [m]²), and smoking status (Table 2). First, because there were only three categories for each lifestyle variable (rather than five categories as for the dietary variables), to put the lifestyle variables on the same initial scale as the dietary variables, each component was assigned a preliminary score of 1, 3, or 5, for, respectively, low/medium/high physical activity, BMI 30/25–<30/<25 kg/m², and current/former/never smoking. Then, because the individual lifestyle factors are more strongly associated with all-cause, CVD, and cancer mortality than are the individual dietary factors, the preliminary scores were weighted by dividing the two “most exposed” category scores by summary relative risks from meta-analyses of associations of physical activity^(21, 22, 25), BMI⁽²³⁾, and smoking status^(19, 20, 24) with all-cause, CVD, and cancer mortality. The summary relative risk values from these meta-analyses that were used for weighting the lifestyle score components are shown in Table 2. The final 3-component lifestyle scores for all-cause, all-CVD, and all-cancer mortality could range from 2.26–15.81, 2.10–17.69, and 2.34–17.25, respectively, with higher scores indicating a more evolutionary-concordant lifestyle.

Statistical analysis

For our analyses, we excluded participants with a history of cancer (other than non-melanoma skin cancer) at baseline (n=3,830), and those who left >10% of the FFQ questions blank (n=2,499) or had implausible total energy intakes (<600 or >5,000 kcal/day; n=286), leaving an analytic cohort of 35,221.

Participants' characteristics, by score quintiles, were summarized and compared using the χ^2 test for categorical variables and analysis of variance for continuous variables. Cox proportional hazards regression was used to calculate hazards ratios (HR) and 95% confidence intervals (CI) to estimate associations of the various scores with cause-specific and all-cause mortality. The scores were analyzed as continuous and categorical variables (quintiles) based on the distributions of all participants' scores at baseline. The median value of each diet score quintile was used for conducting all trend tests. Correlations between scores were assessed using Pearson correlation coefficients.

Based on previous literature and biological plausibility, the following variables were considered as potential confounders for the diet score models: age (years; continuous), smoking status (current, past, never smoker), education (< high school, high school, > high school), BMI (continuous), physical activity (low, medium, high), total energy intake (kcal/day; continuous), hormone replacement therapy (HRT) use (current, past, never), marital status (married, never married, widowed, divorced/separated), and chronic disease (yes/no). Participants with chronic disease were defined as those who had a self-reported history of diabetes, heart disease, or cirrhosis. For the lifestyle score model, the evolutionary-concordance diet score was also considered as a covariate. Criteria for inclusion in the final models were biological plausibility and/or whether inclusion/exclusion of the variable from the model changed the adjusted HR for the primary exposure variable by 10%. The covariates for the final adjusted models are noted in the Tables' footnotes.

To assess potential interaction of the two diet scores with the lifestyle score, we conducted joint/combined (cross-classification) analyses. In these analyses, the reference group was participants who were in the first quintile of both the lifestyle score and the diet score of interest.

To assess whether associations differed by categories of other risk factors not included in the scores, we conducted separate analyses within each category of: age (< /> median age of 61 years), education (< high school/>high school), chronic disease (yes/no), total energy intake (< /> median of 1,717.4 kcal/day), and HRT use (current or past/never).

To assess the sensitivity of the associations to various considerations, we repeated the analyses with the following variations: 1) excluded participants who died within one or two years of follow up, 2) used a lifestyle score composed of unweighted components, and 3) used a Mediterranean diet score based on dichotomized components. Finally, we investigated whether removing and replacing each component of each score one at a time materially affected the observed associations.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All *P*-values were 2-sided. A *P*-value ≤ 0.05 or a 95% CI that excluded 1.0 was considered statistically significant.

Results

Of the 18,687 participants who died during 310,762 person-years of follow up over 26 years (interquartile range: 11.6 – 22.6 years), 7,064 died of CVD and 4,665 of cancer. The baseline characteristics of the study participants according to quintiles of the evolutionary-concordance and Mediterranean diet scores and the evolutionary-concordance lifestyle score are presented in Table 3. Participants in the highest relative to the lowest quintile of each diet score were more likely to be more educated, use HRT, be more physically active, and have higher mean total calcium and dietary fiber intakes. Participants in the highest quintile of the evolutionary-concordance diet score had lower mean total energy, alcohol, protein, and carbohydrate intakes, and were more likely to have a chronic disease, while those in the highest quintile of the Mediterranean diet score had higher mean total energy, alcohol, protein, carbohydrate, and total fat intakes. Exclusive of variables included in the evolutionary-concordance lifestyle score, participants in the highest quintiles of the score were more likely to be more educated, less likely to have a chronic disease, and had higher mean total energy, total calcium, total fat, dietary fiber, protein, and carbohydrate intakes and lower alcohol intakes.

The evolutionary-concordance and Mediterranean diet scores ranged from 19–68 and 9–45, respectively. The correlation between the two diet scores was $r=0.54$ ($P<0.01$). The lifestyle score for all-cause mortality ranged from 2.34–17.25. The correlations between the lifestyle score and the evolutionary-concordance and Mediterranean diet scores were $r=0.17$ and 0.19 , respectively (both $P<0.01$).

Multivariable-adjusted associations of the scores with all-cause and cause-specific mortality are presented in Table 4. For each score, the findings for all-CVD and all-cancer mortality were similar to those for all-cause mortality, and the lifestyle score was more strongly inversely associated with mortality than was either diet pattern score. When the lifestyle score was treated as a continuous variable, each point increase was associated with statistically significant 7%, 6%, and 8% lower risk of all-cause, all-CVD, and all-cancer mortality, respectively; when the score was categorized as quintiles, the corresponding estimates for those in the highest relative to the lowest quintiles were for 48%, 47%, and 49% lower risk, respectively (all point estimates and tests for trend were statistically significant). The evolutionary-concordance diet score, whether treated as a continuous or categorical variable, was minimally inversely, but not statistically significantly, associated with all-cancer and all-cause mortality. For those in the upper relative to the lowest quintile of the Mediterranean diet score, risk for all-cause, all-CVD, and all-cancer mortality was estimated to be 15%, 17%, and 7% lower, respectively (point estimates for all-cause and CVD mortality were statistically significant).

As shown in Table 5, being in the highest quintile of the lifestyle score jointly with being in either the highest quintile of the evolutionary-concordance diet score or the Mediterranean

diet score, was associated with modestly lower risk for all-cause mortality (HR, 0.46 [95% CI, 0.42, 0.50] and HR, 0.45 [95% CI, 0.41, 0.49]; respectively) than was being in the highest quintile of only one or the other of the scores (both $P_{\text{interaction}} < 0.01$).

There were no consistent, clear patterns of differences in associations of any of the scores with all-cause mortality according to age, education, total energy intake, or HRT use (Supplemental Table 1). However, whereas the associations of the diet scores with all-cause mortality were null among those with a history of a chronic disease at baseline, there was a statistically significant trend for decreasing risk with an increasing score among those with no such history, and for those in the upper relative to the lowest quintile of the evolutionary-concordance and the Mediterranean diet scores, the HRs were 0.92 (95% CI, 0.87, 0.97) and 0.80 (95% CI, 0.76, 0.84) ($P_{\text{interaction}} < 0.01$ and $P_{\text{interaction}} = 0.05$, respectively) (Supplemental Table 1).

Removal of physical activity and BMI from the lifestyle score did not substantially change the association of the score with all-cause mortality (Supplemental Table 2). However, removal of smoking status from the score attenuated the association: for those in the upper relative to the lowest quintile, the HR changed from 0.52 (95% CI, 0.50, 0.55) to 0.76 (95% CI, 0.72, 0.80). Also, 1) exclusion of participants who died within one or two years of follow up, 2) using an unweighted lifestyle score, and 3) using a Mediterranean diet score based on dichotomized components did not materially alter the results (Supplemental Tables 3 – 5). In the sensitivity analyses, removal/replacement of each individual dietary score component one at a time did not materially change the results.

Discussion

Our findings suggest that 1) a more Mediterranean-like diet pattern and 2) a more evolutionary-concordant lifestyle pattern, alone and in interaction with a more evolutionary-concordant or Mediterranean-like diet pattern, may be inversely associated with all-cause, all-CVD, and all-cancer mortality. Although our findings for a more evolutionary-concordant diet were close to the null, its association with all-cause mortality was more inverse and statistically significant among those without a history of a chronic disease at baseline, suggesting that the diet pattern may possibly more strongly influence preventing than ameliorating chronic diseases that lead to premature mortality.

More evolutionary-concordant and Mediterranean-like diet patterns and more evolutionary-concordant lifestyle patterns may reduce risk of chronic diseases that lead to premature mortality by several plausible mechanisms. Both diet patterns include high intakes of fruits, vegetables, and nuts, which are rich sources of a variety of nutrients that may reduce risk via modulating detoxification enzymes, stimulating the immune system, reducing platelet aggregation, modulating cholesterol synthesis and hormone metabolism, reducing blood pressure, and antioxidant, antibacterial, and antiviral effects^(51, 52). Both diet patterns also include low intakes of red, processed, and fatty meats, which are high in high-calorie total and saturated fats, which contribute to a positive energy balance, oxidative stress, inflammation, and mutagenic/mitogenic bile acids in the gut^(53, 54, 55), and have been linked to hypercholesterolemia, endothelial dysfunction, atherosclerosis, insulin resistance,

hypertension, CVD, type 2 diabetes, and colorectal cancer^(55, 56, 57, 58). Physical inactivity, obesity, and smoking individually have been consistently reported in epidemiologic studies and systematic reviews with meta-analyses to be associated with higher risk of all-cause and cause-specific mortality^(19, 20, 21, 22, 23, 24, 25). Being more physically active was found to reduce obesity and risk of falling and associated injuries, and to improve glucose metabolism, bone health, independent living, and physical well-being, all of which may help reduce mortality risk⁽⁵⁹⁾. Obesity increases insulin resistance, inflammation, and oxidative stress, and contributes to risk of death from some cancers, CVD, and all causes combined^(60, 61, 62). Smoking delivers known toxicants and carcinogens, which cause DNA damage leading to mutations and thus to multiple types of cancer; cell damage—especially in small airways—leading to chronic airway diseases; and endothelial dysfunction, dyslipidemia, and platelet activation—leading to vascular occlusion, thereby contributing to premature death^(63, 64).

Several reported studies investigated possible health benefits of following a more evolutionary- concordant diet pattern. In four small, uncontrolled trials, four short-term randomized trials, and one two-year randomized trial, participants on an evolutionary-concordance diet pattern intervention, either short-term or long-term, had reductions in weight and waist circumference^(65, 66, 67, 68, 69); improved glucose control, lipid profiles, and insulin sensitivity^(66, 67, 69, 70, 71, 72, 73, 74); and decreases in blood pressure^(68, 71, 72, 73). An evolutionary-concordance diet pattern was inversely associated with inflammation and oxidative stress biomarkers in a cross-sectional study (n=646)⁽³⁰⁾; with incident, sporadic colorectal adenoma in a case-control study (n=2,301)⁽³¹⁾; and with all-cause, all-CVD, and all-cancer mortality in the REasons for Geographic and Racial Differences in Stroke (REGARDS) prospective cohort study (n=21,423; 2,513 deaths during follow-up)⁽³²⁾. In REGARDS, for participants in the highest relative to the lowest evolutionary-concordance (“Paleolithic”) diet pattern score quintile, the HRs for all-cause, all-CVD, and all-cancer mortality were 0.77 (95% CI, 0.67, 0.89), 0.78 (95% CI, 0.61, 1.00), and 0.72 (95% CI, 0.55, 0.95), respectively; the associations did not substantially differ by sex. Our minimally inverse, non-statistically significant results may be explained by the relative homogeneity of the dietary exposures in the IWHs population. Example first and fifth quintile median intakes in the IWHs vs. the REGARDS cohorts are: total vegetables, 11.5 and 43 vs. 6.5 and 52.6 servings/week; sugar-sweetened beverages, 0 and 4 vs. 0 and 11.8 servings/week; and alcohol, 0 and 12.1 vs. 0 and 23.1 g/day (Supplemental Table 6).

Our findings of inverse associations of a Mediterranean diet pattern with all-cause, all-CVD, and all-cancer mortality are consistent with those reported in previous prospective studies. Of 10 reported prospective cohort studies^(8, 9, 10, 11, 12, 13, 14, 16, 17, 28), all found inverse associations with all-cause mortality, of which nine were statistically significant^(8, 9, 10, 11, 12, 13, 14, 17, 28); the estimated associations were generally stronger among men^(10, 11, 12, 14, 16). Of eight reported prospective cohort studies^(8, 10, 11, 12, 13, 14, 15, 16), all reported inverse associations with all-CVD mortality, of which seven were statistically significant^(8, 10, 11, 12, 13, 14, 15); five reported associations by sex, of which two reported stronger, statistically significant, associations among women^(11, 14). Of six reported prospective cohort studies of associations of Mediterranean diet pattern scores with all-cancer mortality^(8, 10, 11, 12, 14, 16), all reported inverse

associations, of which three were statistically significant^(8, 10, U); five reported associations by sex, of which one reported stronger, statistically significant, associations among women⁽¹¹⁾.

Eight prospective cohort studies reported associations of lifestyle scores (some studies considered diet as part of lifestyle) with all-cause and cause-specific mortality. Common score components included alcohol, dietary behavior (primarily framed as adherence to existing dietary recommendations; for example, Mediterranean diet, Danish Dietary Recommendations, Dietary Guidelines to Australians, etc.), physical activity, sedentary behavior, smoking, BMI, and waist circumference^(3, 4, 5, 8, 26, 27, 28, 29). Although these studies created different lifestyle scores, their results are consistent with ours in relation to all-cause^(3, 4, 5, 8, 26, 27, 28, 29), all-CVD^(5, 8, 26), and all-cancer^(5, 8, 26, 29) mortality. Of eight studies that investigated associations of lifestyle scores with all-cause mortality, all reported statistically significant, inverse associations^(3, 4, 5, 8, 26, 27, 28, 29). Of three studies of all-CVD mortality, all reported inverse, statistically significant associations^(5, 8, 26). Of four studies of all-cancer mortality, all reported statistically significant inverse associations^(5, 8, 26, 29). Of the three studies that reported results by sex, all found stronger inverse associations with all-cause and all-CVD mortality, but not with all-cancer mortality, among women^(3, 5, 29).

In line with previous studies^(3, 4, 5, 8, 26, 27, 28, 29), our findings of statistically significant, albeit modest, estimated interactions between a more evolutionary-concordant or Mediterranean-like diet and lifestyle score suggest that multiple lifestyle factors and diet may interact to influence mortality. Since the effects of adverse factors may accumulate throughout life, it is particularly essential for elderly people to adhere to healthy diets and lifestyles that minimize their risk of death⁽⁷⁵⁾.

Our study strengths include that this is the first study of associations of a weighted evolutionary- concordance lifestyle score with all-cause and cause-specific mortality, the long-term prospective study design, and the large sample size and number of deaths. However, the study has certain limitations. The FFQ has known limitations (e.g., recall error, limited number of food items, complex task of estimating and calculating intake frequencies, etc.). There was also limited reassessment of diet and other key exposures during follow up. Although we adjusted for many potential confounders, residual and unmeasured confounding cannot be ruled out. Our study population was limited to older, white Iowa women, limiting the generalizability of our findings. Furthermore, as noted above, there was more homogeneity of diet and other exposures in our study population than found in other cohorts. However, our findings are generally consistent with those of other investigators.

In conclusion, our findings, taken together with previous literature, suggest that 1) a more Mediterranean-like diet pattern, and 2) a more evolutionary-concordant lifestyle pattern, alone and in interaction with a more evolutionary- or Mediterranean-concordant diet pattern, may be inversely associated with all-cause, all-CVD, and all-cancer mortality. Also, our findings for a more evolutionary-concordant diet alone, considering a) its statistically significant, albeit modest, estimated interaction with the lifestyle score; b) that it was inversely associated with mortality among those without a history of a chronic disease at baseline (which may suggest possible stronger influence on preventing than on ameliorating

chronic diseases that lead to premature mortality); and c) previous findings that it was inversely associated with mortality in a population with more heterogeneous diets, suggest that a more evolutionary-concordant diet pattern may contribute to lower mortality risk. Given that this is the first study of associations of an evolutionary-concordance lifestyle score—alone or jointly with evolutionary concordance and Mediterranean diet pattern scores—with mortality, further study in other populations is indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Constituents and construction of evolutionary-concordance and Mediterranean diet pattern scores in the prospective Iowa Women’s Health Study (n = 35,221), 1986 – 2012 *

Diet pattern score	Highest intake “best”	Lowest intake “best”	Other
Evolutionary-concordance diet scored †	Vegetables	Red and processed meats	/
	Fruits	Sodium	
	Lean meats §	Dairy foods	
	Fish	Grains and starches	
	Nuts	Baked goods †	
	Fruit & vegetable diversity/	Sugar-sweetened beverages	
Mediterranean diet score ‡	Calcium ¶	Alcohol	/
	Vegetables (excluding potatoes)	Red and processed meats	
	Whole grains		
	Fruits		
	Legumes		
	Fish		
	Nuts		
	Monounsaturated: saturated fat ratio		

* All constituents measured in servings/week unless otherwise indicated. Highest intake “best”: Number of points assigned to each quintile = quintile rank (e.g., highest and lowest quintiles scored +5 and +1 points, respectively); Lowest intake “best”: Number of points assigned to each quintile = reverse quintile rank (e.g., highest and lowest quintiles scored +1 and +5 points, respectively). Other: Alcohol intake 5–15 g/day scored +5 points, outside of the range scored +1 point.

† The evolutionary-concordance diet pattern score had 14 components; range of possible scores, 14 – 70.

‡ The Mediterranean diet pattern score had 9 components; range of possible scores, 9 – 45.

§ Lean meats included skinless chicken or turkey and lean beef.

/ Fruit & vegetable diversity calculated by summing the total number of different fruits and vegetables items in the food frequency questionnaire the participants indicated that they ate more than 1 – 3 times per month.

¶ Intake of calcium independent of non-calcium components of dairy foods; calculated as residuals from the linear regression of total calcium intake (mg/day) on dairy-food intake.

† Consumption of nitrate-processed meats and non-lean red meat combined.

Baked goods included items such as cake, pie, and other pastry-type foods.

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Constituents and construction of the evolutionary-concordance lifestyle pattern score in the prospective Iowa Women's Health Study (n = 35,221), 1986 – 2012

Table 2.

Constituents	Evolutionary-concordance lifestyle score categories and initial points			Weights [‡]		
	+1 [*]	+3	+5 [†]	All causes	Cardiovascular	Cancer
Physical activity [§]	Low	Medium	High	0.69 (High)	0.76 (Medium)	0.86 (High & Medium)
Smoking status	Current smoker	Former smoker	Never smoker	1.80 (Current), 1.34 (Former)	2.22 (Current), 1.40 (Former)	2.86 (Current), 1.80 (Former)
Body mass index , kg/m ²	30	25 – <30	< 25	0.97 (25 – <30 kg/m ²), 1.28 (< 30 kg/m ²)	1.03 (25 – <30 kg/m ²), 1.53 (< 30 kg/m ²)	0.99 (25 – <30 kg/m ²), 1.10 (< 30 kg/m ²)

^{*} Least evolutionary concordant category.

[†] Most evolutionary concordant category.

[‡] Weights based on summary relative risks from reported meta-analyses of observational epidemiologic studies of associations of physical activity (21; 22; 25), smoking status (19; 20; 24), and body mass index (23) with all-cause, cardiovascular and cancer mortality; the initial points in the two most evolutionary concordant categories of physical activity (hypothesized to be inversely associated with risk) and the two least evolutionary concordant categories of smoking and body mass index (hypothesized to be directly associated with risk) were divided by these values to yield the weighted values to be summed for the lifestyle score (e.g., for high physical activity and all-cause mortality: 5/0.69 = 7.25; for current smoker: 1/1.80 = 0.56).

[§] Physical activity level derived from two questions regarding the frequency of moderate and vigorous physical activity (39), and categorized as high (vigorous activity twice a week or moderate activity >4 times/week), medium (vigorous activity once a week plus moderate activity 2–4 times/week), and low.

^{||} Categories are for obese, overweight, and normal/underweight, respectively, according to WHO guidelines.

Table 3.

Selected characteristics of participants according to quintiles of the evolutionary-concordance and Mediterranean diet and evolutionary-concordance lifestyle pattern scores at baseline in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

Characteristics*	Evolutionary-concordance diet score quintiles			Mediterranean diet score quintiles			Evolutionary-concordance lifestyle score quintiles		
	1 (n = 7,846)	5 (n = 6,260)	P [†]	1 (n = 8,475)	5 (n = 6,641)	P [†]	1 (n = 8,309)	5 (n = 5,760)	P [†]
Age, years	61.3 (4.2)	61.6 (4.2)	<0.01	61.7 (4.2)	61.7 (4.2)	<0.01	61.2 (4.2)	61.7 (4.2)	<0.01
White race, %	99.4	99.0	<0.01	99.2	99.2	0.72	98.8	99.5	<0.01
> High school education, %	31.2	49.6	<0.01	30.4	50.6	0.07	33.6	48.6	<0.01
Currently married, %	78.2	77.4	0.11	76.1	78.5	0.01	73.4	81.0	<0.01
First-degree relative with cancer, %	38.6	37.5	0.23	38.1	37.2	0.13	39.1	37.1	0.09
Current or past HRT use, %	35.2	43.8	<0.01	35.7	42.7	<0.01	36.8	39.8	<0.01
Current or past smoker, %	36.8	33.7	<0.01	37.8	33.5	<0.01	63.0	0	<0.01
High physical activity [‡] , %	15.9	38.9	<0.01	16.6	35.6	<0.01	0	100	<0.01
Body mass index, kg/m ²	26.6 (5.0)	27.0 (5.0)	<0.01	27.0 (5.2)	26.5 (4.8)	<0.01	30.4 (6.2)	24.4 (2.7)	<0.01
Chronic disease [§] , %	11.6	18.3	<0.01	13.9	15.3	0.09	19.0	11.5	<0.01
Total energy intake, kcal/day	2,021 (605)	1,590 (481)	<0.01	1,552 (530)	2,110 (635)	<0.01	1,787 (631)	1,810 (590)	<0.01
Total calcium intake, mg/day	983 (493)	1,259 (580)	<0.01	923 (516)	1,312 (558)	<0.01	996 (541)	1,229 (569)	<0.01
Total fat intake, g/day	82.7 (28.7)	54.2 (20.0)	<0.01	63.7 (26.3)	74.8 (28.9)	<0.01	70.3 (29.3)	65.9 (26.3)	<0.01
Saturated fat intake, g/day	30.0 (11.2)	18.1 (7.0)	<0.01	23.7 (10.6)	24.5 (10.4)	<0.01	24.8 (11.0)	23.0 (10.0)	<0.01
Dietary fiber intake, g/day	17.9 (6.8)	22.2 (8.3)	<0.01	13.6 (5.0)	27.4 (8.5)	<0.01	17.9 (7.6)	21.9 (8.6)	<0.01
Alcohol intake, g/day	4.8 (10.1)	2.9 (7.7)	<0.01	3.5 (10.3)	4.4 (7.4)	<0.01	4.8 (11.3)	3.4 (7.5)	<0.01
Protein intake, g/day	84.9 (29.2)	78.6 (27.3)	<0.01	69.4 (26.6)	96.0 (31.3)	<0.01	79.9 (31.1)	82.6 (29.3)	<0.01
Carbohydrates intake, g/day	235 (81)	203 (70)	<0.01	176 (65)	270 (86)	<0.01	209 (81)	227 (81)	<0.01

Abbreviations: HRT, hormone replacement therapy.

* Continuous variables presented as mean ± standard deviation, and categorical variables as percentage.

[†] P-values calculated using the χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

[‡] Physical activity level derived from two questions regarding the frequency of moderate and vigorous physical activity⁽⁴⁴⁾, 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.

[§] History of diabetes, heart disease, or cirrhosis.

supplements + diet = Total

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Multivariable-adjusted associations of evolutionary-concordance and Mediterranean diet and evolutionary-concordance lifestyle pattern scores with total and cause-specific mortality in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

Table 4.

Cause of death	Evolutionary-concordance				Mediterranean diet score*			
	Diet*		Lifestyle†					
	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
All causes	18,687		18,687		18,687			
Continuous		1.00 (0.99, 1.00)		0.93 (0.93, 0.94)		0.99 (0.99, 0.99)		
Quintiles								
1	4,243	1.00	5,362	1.00	4,774	1.00		
2	3,874	0.98 (0.94, 1.03)	2,896	0.67 (0.64, 0.71)	3,753	0.95 (0.91, 0.99)		
3	4,062	0.97 (0.92, 1.01)	3,790	0.69 (0.66, 0.72)	3,785	0.93 (0.89, 0.98)		
4	3,316	0.96 (0.91, 1.01)	3,572	0.61 (0.58, 0.63)	3,113	0.91 (0.87, 0.96)		
5	3,192	0.95 (0.91, 1.00)	2,510	0.52 (0.50, 0.55)	3,262	0.85 (0.82, 0.90)		
<i>P for trend</i>		0.04		<0.01		<0.01		
Cardiovascular	7,064		7,064		7,064			
Continuous		1.00 (1.00, 1.00)		0.94 (0.94, 0.95)		0.99 (0.98, 0.99)		
Quintiles								
1	1,543	1.00	1,984	1.00	1,774	1.00		
2	1,436	0.98 (0.90, 1.04)	1,083	0.67 (0.62, 0.72)	1,384	0.92 (0.86, 0.99)		
3	1,528	0.96 (0.90, 1.04)	1,392	0.69 (0.64, 0.74)	1,452	0.94 (0.83, 1.01)		
4	1,279	0.97 (0.97, 1.05)	1,442	0.65 (0.61, 0.70)	1,257	0.96 (0.83, 1.04)		
5	1,278	1.00 (0.92, 1.08)	956	0.53 (0.49, 0.57)	1,197	0.83 (0.76, 0.90)		
<i>P for trend</i>		0.85		<0.01		0.08		
Cancer [‡]	4,665		4,665		4,665			
Continuous		1.00 (0.99, 1.00)		0.92 (0.91, 0.93)		0.99 (0.99, 1.00)		
Quintiles								
1	1,089	1.00	1,390	1.00	1,207	1.00		
2	968	0.99 (0.90, 1.08)	698	0.65 (0.60, 0.71)	911	0.94 (0.86, 1.03)		
3	1,032	1.00 (0.91, 1.09)	954	0.62 (0.57, 0.68)	957	0.97 (0.89, 1.06)		
4	824	0.99 (0.90, 1.09)	865	0.59 (0.54, 0.64)	738	0.91 (0.82, 1.00)		

Evolutionary-concordance				Mediterranean diet score*		
Cause of death	Diet*		Lifestyle†			
	n	HR (95% CI)		n	HR (95% CI)	n
5	752	0.93 (0.84, 1.02)	625	0.51 (0.46, 0.57)	852	0.93 (0.84, 1.03)
P for trend	0.20		<0.01		0.06	

Abbreviations: HR, hazards ratio; CI, confidence interval.

* For score construction, see text and Table 1. HRs from Cox proportional hazards models; covariates included age (years; continuous), smoking status (current, past, never smoker), education (< high school, high school, > high school), body mass index (weight [kg]/height [m]²; continuous), physical activity (low, medium, high), total energy intake (kcal/day; continuous), hormone replacement therapy use (current, past, never), marital status (married, never married, widowed, divorced/separated), and chronic disease (yes/no).

† Includes smoking, physical activity, and body mass index; for score construction, see text. HRs from Cox proportional hazards models; covariates included age (years; continuous), education (< high school, high school, > high school), total energy intake (kcal/day; continuous), hormone replacement therapy use (current, past, never), marital status (married, never married, widowed, divorced/separated), chronic disease (yes/no), and evolutionary-concordant diet score (quintiles).

‡ For all-cancer mortality, family history of cancer in a first-degree relative (yes/no) was added to Cox proportional hazards models.

Table 5.

Multivariable-adjusted joint/combined associations* of the evolutionary-concordance lifestyle score, and evolutionary-concordance and Mediterranean diet pattern scores with all-cause mortality in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

	Evolutionary-concordance lifestyle score quintiles				
	1	2	3	4	5
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Evolutionary-concordance diet score quintiles	1	1.00 (Ref)	0.64 (0.59, 0.71)	0.67 (0.62, 0.73)	0.61 (0.56, 0.67)
	2	0.97 (0.90, 1.05)	0.68 (0.62, 0.75)	0.65 (0.60, 0.71)	0.59 (0.54, 0.65)
	3	0.93 (0.86, 1.01)	0.66 (0.60, 0.72)	0.65 (0.60, 0.71)	0.54 (0.49, 0.59)
	4	0.94 (0.87, 1.03)	0.60 (0.54, 0.66)	0.64 (0.58, 0.70)	0.56 (0.51, 0.62)
	5	0.92 (0.84, 1.01)	0.63 (0.56, 0.71)	0.68 (0.62, 0.75)	0.59 (0.54, 0.64)
Mediterranean diet score quintiles	1	1.00 (Ref)	0.67 (0.61, 0.72)	0.70 (0.64, 0.75)	0.61 (0.56, 0.67)
	2	0.98 (0.91, 1.05)	0.65 (0.59, 0.71)	0.62 (0.57, 0.67)	0.57 (0.52, 0.63)
	3	0.91 (0.84, 0.99)	0.63 (0.57, 0.69)	0.65 (0.60, 0.71)	0.53 (0.48, 0.57)
	4	0.85 (0.78, 0.93)	0.60 (0.54, 0.66)	0.60 (0.55, 0.66)	0.55 (0.51, 0.61)
	5	0.77 (0.70, 0.85)	0.53 (0.48, 0.59)	0.59 (0.54, 0.64)	0.52 (0.48, 0.57)

Abbreviations: HR, hazards ratio; CI, confidence interval.

* HRs from Cox proportional hazards models; covariates included age (years; continuous), education (< high school, high school, > high school), total energy intake (kcal/day; continuous), hormone replacement therapy use (current, past, never), marital status (married, never married, widowed, divorced/separated), and chronic disease (yes/no).

[†] $P_{Interaction} < 0.01$; from lifestyle score*diet score interaction term in the Cox proportional hazards model.