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**ORIGINAL ARTICLE**

# Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes

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**BACKGROUND:** The Mediterranean diet has been consistently associated with reduced mortality risk. Few prospective studies have examined whether the benefits from a Mediterranean diet are equally shared by obese individuals with varying metabolic health.
**OBJECTIVE:** The objective of this study was to investigate the association between Mediterranean diet, metabolic phenotypes and mortality risk in a representative obese US population.
**METHODS:** Data from 1739 adults aged 20–88 years were analyzed from participants of the National Health and Nutrition Examination Survey III, 1988–1994 followed up for deaths until 31 December 2011 in a prospective cohort analysis. Mediterranean Diet Scores (MDS) were created to assess the adherence to Mediterranean diet. Participants were classified as metabolically healthy obese (MHO) phenotype (0 or 1 metabolic abnormality) or metabolically unhealthy obese (MUO) phenotype (two or more metabolic abnormalities), based on high glucose, insulin resistance, blood pressure, triglycerides, C-reactive protein and low high-density lipoprotein cholesterol.
**RESULTS:** The MHO phenotype ($n = 598$) was observed in 34.8% (s.e., 1.7%) of those who were obese (mean body mass index was 33.4 and 34.8 in MHO and MUO phenotypes, respectively). During a median follow-up of 18.5 years, there were 77 (12.9%) and 309 (27.1%) deaths in MHO and MUO individuals, respectively. In MHO individuals, the multivariable-adjusted hazard ratio (HR) of all-cause mortality in the highest tertile compared with the first tertile of MDS was 0.44 (95% confidence interval (CI), 0.26–0.75; $P$ for trend $< 0.001$), after adjustment for potential confounders. A five-point (1 s.d.) increment in the adherence to MDS was associated with a 41% reduction in the risk of all-cause mortality (HR, 0.59; 95% CI, 0.37–0.94). Similar findings were obtained when we restricted our analyses to those with
or without prevalent diabetes mellitus and hypertension. We did not observe mortality risk reduction in either individuals with MUO phenotype or all obese participants combined.
**CONCLUSIONS:** Adherence to a Mediterranean dietary pattern appears to reduce mortality in the MHO phenotype, but not among the MUO phenotype in an obese population.

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## INTRODUCTION

The Mediterranean diet is characterized by high intake of olive oil and polyunsaturated fats, legumes, grains, fish, fruits and vegetables; moderate intake of milk, dairy products and alcohol; and low intake of meat and meat products.[1] Multiple epidemiological studies have demonstrated that adherence to the Mediterranean diet is associated with lower risk of cardiometabolic disease in addition to lower risk of all-cause mortality, cardiovascular disease (CVD) and cancer mortality.[2–4]

The risk of developing obesity-related metabolic complications corresponds to the degree of obesity.[5,6] However, the existence of these obesity-related metabolic abnormalities varies extensively in obese individuals.[7] Despite being outwardly obese, a subset of obese individuals appears to be protected or more resistant to the development of cardiometabolic abnormalities associated with obesity. These individuals with a metabolically healthy obese (MHO) phenotype, namely benign or uncomplicated obesity, demonstrate favorable metabolic characteristics such as normal insulin sensitivity, relatively low visceral fat, lower liver enzyme profiles, no sign of dyslipidemia or hypertension[8–10] and lower risk of CVD,[11] compared with their metabolically unhealthy obese (MUO) counterparts.

As healthy dietary behaviors are crucial to reduce obesity-related morbidity and mortality,[12] it is important to understand how the beneficial effects of established healthy dietary patterns such as Mediterranean diet differ according to MHO and MUO phenotypes. A few previous studies examined the potential differential association of dietary factors between MHO and MUO phenotypes; however, many of these studies were cross-sectional,[13–16] without consideration of dietary pattern,[15] had small sample size[17,18] or with a short follow-up.[17–20] In addition, it is unclear how dietary patterns may influence the natural history of these phenotypes differentially.

Therefore, we tested the hypotheses that Mediterranean diet would have differential benefits in relation to mortality in MHO individuals and MUO individuals, in a nationally representative obese US population.

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## METHODS

### Study population

Data from 1739 adults aged 20–88 years were analyzed from participants of the National Health and Nutrition Examination Survey (NHANES) III, 1988–1994, followed up for deaths until 31 December 2011 in a prospective cohort analysis. In NHANES III, a complex multi-stage stratified clustered probability sampling scheme was applied to achieve a nationally representative sample of the civilian, non-institutionalized US population.

We included 2535 obese (body mass index (BMI) $\geqslant$ 30 kg m$^{-2}$ based on measured height and weight) adults aged 20 years and older who were eligible for mortality follow-up and had complete data on food frequency questionnaire (FFQ) and 24-h dietary recall, those with complete data on cardiometabolic parameters including fasting glucose, insulin, blood pressure (BP), triglycerides, high-density lipoprotein cholesterol (HDL-C) and high-sensitivity C-reactive protein (hs-CRP). We excluded those who reported a history of myocardial infarction, stroke, congestive heart failure or cancer (other than skin cancer) ($n$ = 299). To minimize misclassification, we excluded the participants who reported changing their dietary patterns during the previous 12 months because of pre-existing obesity, high BP, high blood cholesterol, diabetes mellitus or general health ($n$ = 415). In addition, we excluded those who reported implausible extreme energy intakes ($<$ 1st and $>$ 99th percentiles of energy intake per day in adults), those with hs-CRP $>$ 10 mg l$^{-1}$, BMI $>$ 60 kg m$^{-2}$, or pregnant or lactating women ($n$ = 82). Finally, a total of 1739 individuals were analyzed.

### Assessment of Mediterranean diet

Dietary intake was assessed using the FFQ and the 24-h dietary recall data that were validated by the Nutrition Methodology Working Group.[21] Adherence to the Mediterranean diet was assessed using the scoring methodology developed by Panagiotakos *et al*.[22,23] In this methodology, scores 0–5 or 5–0 were assigned for the weekly consumption of food items assumed to be contributing to or against the Mediterranean dietary pattern, respectively (Supplementary Table S1). This Mediterranean Diet Score (MDS) has been shown to be highly associated with prevalent cardiometabolic diseases, 10-year CVD risk, and inflammation and coagulation markers, in addition to capturing inherent characteristics of Mediterranean dietary pattern.[22–24] It also has been reported that the MDS used in the present study was correlated with widely used indexes of adherence to the Mediterranean diet such as MDS developed by Trichopoulou *et al*.[1] (r = 0.64) and MDS used in the PREDIMED study[2] (r = 0.53).[25]

The NHANES III FFQ was used to collect information on usual diet during the previous month, but did not include information on portion sizes. We calculated the MDS, assuming that the number of servings per week were equivalent to the number of times that a food item was consumed per week. Potatoes were excluded from our MDS assessment because preparation methods for potatoes in US are quite different from European countries.[26] Light to moderate alcohol consumption, one of the Mediterranean diet components, is associated with a reduced risk of cardiovascular morbidity and mortality.[27] As the benefit from alcohol consumption mainly comes from alcohol rather than the components of each type of drink,[28] we used the summary measure to estimate the amount of alcohol consumed daily using the following assumption: 12.8 g for 12- oz beer, 11 g for 4-oz glass of wine and 14 g for an ounce of liquor based on the questionnaire provided. In addition, assessment of alcohol consumption was modified using gender-specific cutoffs.[29] Olive oil consumption was not measured in the NHANES III FFQ. Thus, we approximated olive oil consumption by calculating the ratio of total monounsaturated fatty acids (MUFA) to total saturated fatty acids (SFA)[30] using the 24-h dietary recall data, then dividing it into the six even intervals. The possible overall MDS ranged from 0 to 50, with higher values indicating greater adherence to the Mediterranean diet.

### Assessment of metabolic health

Metabolic health was assessed using the metabolic parameters that were measured under quality control standards of Centers for Disease Control and Prevention. BMI was calculated as kg m$^{-2}$; height was measured to the nearest 0.1cm and weight to the nearest 0.01 kg. BP was averaged over five separate measurements. Serum glucose was measured using a modified hexokinase enzymatic method. Serum insulin was measured using radioimmnuoassay (Pharmacia Diagnostics, Kalamazoo, MI, USA). HDL-C and triglycerides were measured using a Hitachi 704 analyzer (Boehringer-Mannheim Diagnostics, Indianapolis, IN, USA). Serum hs-CRP concentrations were measured by latex-enhanced nephlometry (Department of Laboratory Medicine, Immunology Division, University of Washington, Seattle, WA, USA). As NHANES III participants did not comply with fasting instruction strictly, 6-h fasting data were used to increase the sample size.[31]

Metabolic health was defined when the individual had fewer than two cardiometabolic abnormalities (systolic/diastolic BP $\geqslant$ 130/85 mm Hg or antihypertensive medication use, triglycerides $\geqslant$ 150 mg l$^{-1}$ or on cholesterol-lowering medication, fasting glucose $\geqslant$ 100 mg dl$^{-1}$ or anti-diabetic medication use, homeostasis model assessment of insulin resistance (HOMA-IR = fasting glucose (mg dl$^{-1}$) $\times$ fasting insulin (IU ml$^{-1}$)/405) $>$ the 90th percentile, hs-CRP $>$ the 90th percentile, and HDL-C $<$ 40 mg dl$^{-1}$ in men or $<$ 50 mg dl$^{-1}$ in women or on cholesterol-lowering medication).[32]

### Assessment of mortality

To identify mortality and cause of death, the National Center for Health Statistics linked information from all participants aged 20 years and older to the National Death Index to 31 December 2011. Therefore, for each participant, follow-up extended from the date of the examination to the date of death or 31 December 2011. The underlying cause listed on the death certificate was applied to determine cause of death that was identified using the underlying Cause of Death-113 groups (international classification of disease (ICD), 10th revision). Total mortality was defined as deaths with any underlying cause of death; CVD and cancer mortality had underlying cause of death codes of ICD-10 I00-I69 and C00-C97, respectively (http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhanes3_linkage.htm).

### Assessment of covariates

Demographic variables included age, gender, race or ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American or others), educational attainment ($<$ 12 years, 12 years or $>$ 12 years of education), living with spouse, level of income based on poverty income ratio (PIR), which is the ratio of household income to the appropriate poverty threshold (low (PIR $\leqslant$ 1.3), middle (1.3 $<$ PIR $\leqslant$ 3.5) and high (PIR $>$ 3.5)). The potential risk factors for CVD included smoking status (never, former and current) and the presence of family history of CVD. Physical activity was classified based on the recommended levels of physical activity.[33] A group with recommended physical activity was defined as those who had self-reported leisure time moderate activity (3 $\leqslant$ metabolic equivalents $<$ 6) of five or more times per week or leisure time vigorous activity (metabolic equivalents $\geqslant$ 6) three or more times per week; physically inactive group as those with no reported leisure time physical activity; a group with insufficient physical activity as those who did not meet the criteria for recommended levels of physical activity but not inactive.

### Statistical analysis

The statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA), using the appropriate survey procedures to account for the complex sampling design and weights. For the subgroup analysis, domain option was applied in survey procedure to preserve appropriate subsample in the complex sampling design, and it utilized the entire samples to estimate the variance of subpopulations. Continuous variables were presented by mean (s.e.: standard error) and compared using linear regression analyses. Categorical variables were expressed by percentage with s.e. and were compared using Rao-Scott $\chi$2 tests. $P$ value of less than 0.05 was considered statistically significant.

We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, CVD and cancer mortality. The proportional hazards assumption of the Cox proportional hazards models was evaluated with log of negative log survival curves based on Kaplan–Meier estimates for MDS tertile group as well as categorical age, gender and race/ethnicity. In addition to crude HRs, we estimated age-, gender- and race/ethnicity-adjusted HRs as well as the multivariable-adjusted HRs including age, BMI and total energy intake as continuous covariates; gender, race/ethnicity, educational attainment, income, living with spouse, smoking status, level of physical activity, family history of CHD as categorical covariates, all of which were identified using the prior literature. Missing values in the covariates were added as a dummy variable in the multivariable models. To assess potential differential association of MDS by age ($<$ 65 vs $\geqslant$ 65 years), sex, race/ethnicity, smoking (ever vs never smoked), conformity to recommended

**Table 1.** Comparison of general characteristics according to the tertile categories of Mediterranean Diet Score between metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes at baseline

| *Characteristics* | *MHO phenotype* | | | | |
|---|---|---|---|---|---|
| | *Overall* (n = *598*) | *MDS tertile 1* (n = *181*) | *MDS tertile 2* (n = *240*) | *MDS tertile 3* (n = *177*) | P |
| Age, years | 40.7 ± 0.6 | 40.8 ± 0.9 | 40.5 ± 0.8 | 40.8 ± 1.3 | 0.76 |
| Men, % | 33.2 ± 3.4 | 36.5 ± 5.4 | 23.8 ± 4.9 | 41.7 ± 7.0 | 0.07 |
| *Race/ethnicity, %* | | | | | |
| Non-Hispanic white | 68.7 ± 3.4 | 68.7 ± 5.6 | 68.8 ± 5.4 | 68.5 ± 3.8 | 0.43 |
| Non-Hispanic black | 19.5 ± 2.4 | 21.5 ± 3.8 | 21.6 ± 3.8 | 14.9 ± 2.5 | |
| Mexican-American | 4.5 ± 0.7 | 2.3 ± 0.7 | 4.7 ± 1.0 | 6.4 ± 1.1 | |
| Other | 7.3 ± 1.7 | 7.5 ± 4.2 | 4.9 ± 2.8 | 10.3 ± 2.7 | |
| *Educational attainment, %* | | | | | |
| < 12 years | 24.3 ± 2.2 | 29.1 ± 4.9 | 24.8 ± 4.3 | 19.0 ± 4.5 | 0.39 |
| 12 years | 40.0 ± 3.0 | 39.8 ± 5.4 | 43.6 ± 5.7 | 35.6 ± 7.6 | |
| > = 13 years | 35.8 ± 3.3 | 31.1 ± 6.0 | 31.7 ± 5.1 | 45.4 ± 5.3 | |
| *Income, %* | | | | | |
| PIR = < 1.3 | 21.2 ± 2.9 | 21.1 ± 4.5 | 25.5 ± 5.3 | 16.0 ± 3.7 | 0.001 |
| PIR = < 3.5 | 42.2 ± 3.2 | 60.7 ± 6.0 | 37.0 ± 5.6 | 30.5 ± 5.7 | |
| PIR > 3.5 | 36.5 ± 3.5 | 18.2 ± 5.7 | 37.5 ± 6.6 | 53.5 ± 6.1 | |
| Living with spouse, % | 69.0, 2.9 | 68.8, 5.6 | 67.8, 4.5 | 70.7, 5.5 | 0.92 |
| *Smoking status, %* | | | | | |
| Never | 55.1 ± 3.4 | 50.6 ± 5.2 | 60.5 ± 5.9 | 52.8 ± 6.1 | 0.58 |
| Former | 21.8 ± 2.9 | 27.7 ± 5.0 | 16.7 ± 3.7 | 22.6 ± 5.1 | |
| Current | 23.1 ± 3.2 | 21.8 ± 4.7 | 22.8 ± 5.5 | 24.6 ± 6.4 | |
| *Physical activity, %* | | | | | |
| Inactive | 14.7 ± 2.1 | 23.5 ± 5.2 | 12.0 ± 2.6 | 9.6 ± 2.9 | 0.07 |
| Insufficient activity | 59.5 ± 3.4 | 54.1 ± 4.5 | 63.5 ± 6.0 | 59.8 ± 5.0 | |
| Recommended activity | 25.8 ± 3.4 | 22.4 ± 4.7 | 24.4 ± 5.3 | 30.6 ± 5.3 | |
| CHD family history, % | 16.9 ± 2.9 | 18.5 ± 4.5 | 15.4 ± 5.3 | 17.2 ± 4.8 | 0.89 |
| Diabetes mellitus, % | 3.8 ± 1.1 | 4.5 ± 1.7 | 4.4 ± 1.6 | 2.5 ± 2.2 | 0.73 |
| Hypertension, % | 23.6 ± 3.6 | 19.5 ± 3.2 | 26.0 ± 6.2 | 24.5 ± 5.5 | 0.58 |
| BMI, kg $m^{-2}$ | 33.4 ± 0.1 | 34.0 ± 0.2 | 33.0 ± 0.2 | 33.2 ± 0.3 | 0.07 |
| Waist circumference, cm | 104.0 ± 0.7 | 106.3 ± 0.8 | 101.8 ± 1.1 | 104.4 ± 1.2 | 0.16 |
| Fasting glucose, mg $dl^{-1}$ | 91 ± 0.4 | 91.0 ± 0.6 | 90.7 ± 0.8 | 90.9 ± 0.7 | 0.61 |
| HOMA-IR | 2.4 ± 0.0 | 2.5 ± 0.1 | 2.4 ± 0.1 | 2.3 ± 0.1 | < 0.001 |
| SBP, mmHg | 120 ± 0.6 | 120 ± 0.8 | 119 ± 0.9 | 122 ± 1.6 | 0.24 |
| DBP, mmHg | 74 ± 0.5 | 73 ± 0.7 | 74 ± 0.7 | 77 ± 1.0 | 0.002 |
| hs-CRP, mg $dl^{-1}$ | 0.4 ± 0.02 | 0.4 ± 0.03 | 0.4 ± 0.03 | 0.4 ± 0.03 | 0.56 |
| Triglycerides, mg $dl^{-1}$ | 107 ± 5.0 | 111 ± 5.3 | 96 ± 3.4 | 117 ± 14.1 | 0.62 |
| HDL-C, mg $dl^{-1}$ | 52 ± 0.8 | 49 ± 0.9 | 54 ± 1.3 | 51 ± 1.6 | 0.06 |

| *Characteristics* | *MUO phenotype* | | | | | |
|---|---|---|---|---|---|---|
| | *Overall* (n = *1141*) | *MDS tertile 1* (n = *340*) | *MDS tertile 2* (n = *465*) | *MDS tertile 3* (n = *336*) | P | *P (MHO* vs *MUO)* |
| Age, years | 47.2 ± 0.7 | 45.9 ± 1.1 | 46.8 ± 1.0 | 49.7 ± 0.8 | 0.05 | < 0.001 |
| Men, % | 49.9 ± 2.7 | 45.6 ± 3.9 | 53.5 ± 4.3 | 49.5 ± 3.9 | 0.29 | < 0.001 |
| *Race/ethnicity, %* | | | | | | |
| Non-Hispanic white | 75.0 ± 2.6 | 81.9 ± 2.4 | 73.9 ± 3.5 | 67.6 ± 4.0 | < 0.001 | < 0.001 |
| Non-Hispanic black | 11.2 ± 1.4 | 10.0 ± 1.7 | 11.9 ± 1.9 | 11.5 ± 1.7 | | |
| Mexican-American | 7.1 ± 1.2 | 3.8 ± 0.9 | 6.3 ± 1.1 | 13.0 ± 2.5 | | |
| Other | 6.7 ± 1.6 | 4.4 ± 1.7 | 7.9 ± 2.3 | 7.9 ± 3.0 | | |
| *Educational attainment, %* | | | | | | |
| < 12 years | 27.1 ± 2.4 | 30.6 ± 3.8 | 24.3 ± 2.8 | 27.3 ± 4.3 | 0.02 | 0.55 |
| 12 years | 37.0 ± 2.5 | 42.0 ± 3.2 | 37.6 ± 4.1 | 29.4 ± 3.1 | | |
| ⩾13 years | 35.9 ± 3.3 | 27.5 ± 3.9 | 38.1 ± 4.5 | 43.3 ± 5.1 | | |

**Table 1.** (Continued)

| *Characteristics* | *MUO phenotype* | | | | | |
|---|---|---|---|---|---|---|
| | *Overall* (n = *1141*) | *MDS tertile 1* (n = *340*) | *MDS tertile 2* (n = *465*) | *MDS tertile 3* (n = *336*) | P | *P (MHO vs MUO)* |
| *Income, %* | | | | | | |
| PIR = < 1.3 | 17.4 ± 1.9 | 25.4 ± 3.6 | 13.5 ± 2.4 | 13.3 ± 2.2 | < 0.001 | 0.28 |
| PIR = < 3.5 | 48.0 ± 2.5 | 52.8 ± 3.7 | 49.4 ± 4.0 | 38.6 ± 5.0 | | |
| PIR > 3.5 | 34.6 ± 3.1 | 21.8 ± 3.0 | 37.2 ± 4.9 | 48.1 ± 4.9 | | |
| Living with spouse, % | 30.5, 1.8 | 65.6, 3.5 | 72.2, 3.4 | 70.1, 3.8 | 0.41 | 0.88 |
| *Smoking status, %* | | | | | | |
| Never | 42.4 ± 2.1 | 40.9 ± 3.1 | 44.0 ± 3.2 | 41.7 ± 5.5 | 0.004 | 0.003 |
| Former | 33.7 ± 2.1 | 25.0 ± 3.7 | 35.7 ± 2.7 | 41.9 ± 5.5 | | |
| Current | 23.9 ± 1.7 | 34.1 ± 3.7 | 20.3 ± 3.2 | 16.3 ± 2.6 | | |
| *Physical activity, %* | | | | | | |
| Inactive | 16.2 ± 1.7 | 22.6 ± 2.9 | 13.3 ± 2.3 | 12.9 ± 2.6 | 0.04 | 0.60 |
| Insufficient activity | 55.8 ± 2.3 | 56.2 ± 4.5 | 56.1 ± 3.6 | 54.6 ± 4.2 | | |
| Recommended activity | 28.0 ± 2.1 | 21.2 ± 4.1 | 30.6 ± 3.3 | 32.5 ± 3.8 | | |
| CHD family history, % | 21.6 ± 2.2 | 27.8 ± 3.8 | 18.8 ± 3.4 | 18.3 ± 3.7 | 0.13 | 0.28 |
| Diabetes mellitus, % | 18.2 ± 1.5 | 16.9 ± 2.9 | 16.3 ± 2.4 | 23.5 ± 3.0 | 0.19 | < 0.001 |
| Hypertension, % | 49.4 ± 2.6 | 46.9 ± 3.9 | 47.7 ± 3.9 | 56.0 ± 4.6 | 0.27 | < 0.001 |
| BMI, kg $m^{-2}$ | 34.8 ± 0.2 | 35.8 ± 0.3 | 34.3 ± 0.2 | 34.3 ± 0.4 | 0.001 | < 0.001 |
| Waist circumference, cm | 110.9 ± 0.4 | 113.3 ± 0.7 | 110.2 ± 0.7 | 108.9 ± 0.8 | < 0.001 | < 0.001 |
| Fasting glucose, mg $dl^{-1}$ | 107 ± 0.9 | 107.5 ± 2.5 | 107.5 ± 1.5 | 106.8 ± 1.6 | 0.31 | < 0.001 |
| HOMA-IR | 5.0 ± 0.2 | 5.3 ± 0.2 | 5.1 ± 0.3 | 4.4 ± 0.2 | < 0.001 | < 0.001 |
| SBP, mmHg | 131 ± 0.6 | 129 ± 0.8 | 130 ± 0.8 | 134 ± 1.1 | < 0.001 | < 0.001 |
| DBP, mmHg | 80 ± 0.5 | 80 ± 0.4 | 80 ± 0.5 | 81 ± 1.2 | 0.21 | < 0.001 |
| hs-CRP, mg $dl^{-1}$ | 0.6 ± 0.02 | 0.6 ± 0.02 | 0.6 ± 0.03 | 0.6 ± 0.04 | 0.19 | < 0.001 |
| Triglycerides, mg $dl^{-1}$ | 195 ± 4.0 | 208 ± 6.0 | 187 ± 5.8 | 190 ± 9.0 | 0.02 | < 0.001 |
| HDL-C, mg $dl^{-1}$ | 42 ± 0.4 | 40 ± 0.7 | 41 ± 0.8 | 45 ± 1.3 | 0.003 | < 0.001 |

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MDS, Mediterranean Diet Score; PIR, poverty income ratio. Data are presented as mean ± s.e. or proportion (%) ± s.e. *P* values for continuous variables represent *P* for trend.

physical activity (yes vs no), BMI (< 35 vs ⩾35) and the presence or absence of chronic disease including diabetes mellitus and hypertension, we also stratified our analysis and performed interaction tests using all-cause mortality as the outcome by including the cross-product interaction terms in the Cox proportional hazards models based on Satterthwaite adjusted F test. In addition, we performed sensitivity analyses with an alternative common definition of metabolic health as metabolic syndrome (defined when the individual had fewer than three cardiometabolic abnormalities (systolic/diastolic BP ⩾ 130/85 mm Hg or antihypertensive medication use, triglycerides ⩾ 150 mg $l^{-1}$ or on cholesterol-lowering medication, fasting plasma glucose ⩾ 100 mg $dl^{-1}$ or antidiabetic medication use, HDL-C < 40 mg $dl^{-1}$ in men or < 50 mg $dl^{-1}$ in women or on cholesterol-lowering medication, and waist circumference ⩾ 102 cm in men or ⩾ 88 cm in women),[34] and after exclusion of subjects who died during the first 5 years of follow-up.

## RESULTS

The MHO phenotype ($n = 598$) was observed in 34.8% (s.e., 1.7%) of those who were obese. MHO individuals with the highest MDS tertile were more likely to have a higher income, lower insulin resistance and higher diastolic BP (Table 1). MUO individuals with the highest MDS tertile tended to be older and not non-Hispanic white; were more likely to have a higher education, higher income, lower proportion of current smokers and recommended physical activity, lower BMI and waist circumference, lower insulin resistance, higher systolic BP, lower triglycerides and higher HDL-C than MUO individuals with other tertiles. Comparing MHO and MUO individuals, MHO individuals tended to be younger, female, not non-Hispanic white and non-smokers, and have a more favorable metabolic status (Table 1).

In both phenotypes, consumption of grains, legumes, fruit, vegetable, fish, ratio of MUFA to SFA tended to increase with increasing tertile of MDS (Table 2). In addition, consumption of red meats and dairy products tended to decrease with increasing tertile of MDS. However, consumption of poultry and alcohol was higher with increasing tertile of MDS only in MUO individuals. Overall, MHO individuals showed higher ratio of MUFA to SFA ($P = 0.03$), and consumed less red meats and dairy products ($P = 0.001$ and 0.02, respectively), resulting in higher MDS for those components, compared with MUO individuals (Table 2). No significant difference in the ratio of polyunsaturated fatty acids to SFA was observed between MHO and MUO individuals (data not shown).

During a median follow-up of 18.5 years, there were 77 and 309 deaths in 598 MHO and 1141 MUO individuals, respectively. Overall, higher mortality risk was observed in MUO compared with MHO individuals after adjusting for potential confounders (HRs were 1.50 (95% CI, 1.12–2.00) for all-cause mortality, 2.50 (95% CI, 1.20–5.21) for CVD mortality and 1.27 (95% CI, 0.81–1.98) for cancer mortality). In the total obese participants, we did not observe a significant association between MDS and risk of all-cause, CVD and cancer mortality (Supplementary Table S2).

HRs of all-cause, CVD and cancer mortality by tertile categories and a five-point (1 s.d.) increment in the MDS in MHO and MUO individuals were shown in Table 3. In MHO individuals, compared with the lowest tertile, HRs in the second and the highest tertiles, respectively, were 0.35 (95% CI, 0.19–0.64) and 0.44 (0.26–0.75) (*P* for trend < 0.001) for all-cause mortality, and 0.13 (0.06–0.26) and 0.23 (0.02–2.10) (*P* for trend = 0.03) for cancer mortality, after

**Table 2.** Comparison of consumption frequency for each component of the Mediterranean diet in metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes at baseline

| | *MHO phenotype* | | | | |
|---|---|---|---|---|---|
| | *Overall* (n = *598*) | *MDS tertile 1* (n = *181*) | *MDS tertile 2* (n = *240*) | *MDS tertile 3* (n = *177*) | P *for trend* |
| Score range | (13–39) | (13–23) | (24–28) | (29–39) | |
| MDS | 26.0 ± 0.2 | 20.8 ± 0.2 | 25.9 ± 0.1 | 31.1 ± 0.2 | < 0.001 |
| Grains (times per wk) | 4.7 ± 0.4 | 3.8 ± 0.7 | 4.2 ± 0.4 | 6.3 ± 0.6 | < 0.001 |
| Legumes (times per wk) | 2.6 ± 0.1 | 1.5 ± 0.1 | 3.0 ± 0.2 | 3.2 ± 0.3 | < 0.001 |
| Fruit (times per wk) | 5.9 ± 0.4 | 4.9 ± 0.4 | 4.6 ± 0.3 | 8.4 ± 1.0 | 0.002 |
| Vegetable (times per wk) | 13.1 ± 0.3 | 11.2 ± 0.6 | 12.3 ± 0.5 | 16.0 ± 0.9 | < 0.001 |
| Fish (times per wk) | 1.4 ± 0.1 | 1.0 ± 0.1 | 1.1 ± 0.1 | 2.3 ± 0.3 | < 0.001 |
| MUFA:SFA | 1.23 ± 0.03 | 1.02 ± 0.02 | 1.26 ± 0.02 | 1.41 ± 0.10 | < 0.001 |
| Red meats (times per wk) | 5.2 ± 0.3 | 6.2 ± 0.3 | 5.3 ± 0.5 | 4.0 ± 0.2 | < 0.001 |
| Poultry (times per wk) | 2.3 ± 0.1 | 2.1 ± 0.2 | 2.3 ± 0.2 | 2.3 ± 0.3 | 0.47 |
| Dairy products (times per wk) | 10.3 ± 0.4 | 12.3 ± 0.6 | 10.2 ± 0.6 | 8.3 ± 0.5 | < 0.001 |
| Alcohol (g per day) | 2.7 ± 0.3 | 2.4 ± 1.0 | 2.3 ± 0.3 | 3.5 ± 0.4 | 0.15 |
| Total energy intake, kcal | 2032 ± 47 | 2121 ± 72 | 2016 ± 61 | 1966 ± 128 | 0.66 |

| | *MUO phenotype* | | | | | |
|---|---|---|---|---|---|---|
| | *Overall* (n = *1141*) | *MDS tertile 1* (n = *340*) | *MDS tertile 2* (n = *465*) | *MDS tertile 3* (n = *336*) | P *for trend* | P *(MHO VS MUO)* |
| Score range | (12–40) | (12–23) | (24–28) | (29–40) | | |
| MDS | 25.5 ± 0.2 | 20.5 ± 0.1 | 26.0 ± 0.1 | 31.2 ± 0.1 | < 0.001 | 0.04 |
| Grains (times per wk) | 5.0 ± 0.3 | 3.2 ± 0.3 | 5.3 ± 0.5 | 6.6 ± 0.4 | < 0.001 | 0.49 |
| Legumes (times per wk) | 2.4 ± 0.1 | 1.6 ± 0.1 | 2.7 ± 0.2 | 3.2 ± 0.2 | < 0.001 | 0.14 |
| Fruit (times per wk) | 6.1 ± 0.3 | 4.0 ± 0.2 | 5.5 ± 0.3 | 9.9 ± 0.5 | < 0.001 | 0.59 |
| Vegetable (times per wk) | 13.5 ± 0.4 | 10.1 ± 0.4 | 13.8 ± 0.5 | 17.7 ± 0.7 | < 0.001 | 0.53 |
| Fish (times per wk) | 1.4 ± 0.1 | 1.2 ± 0.3 | 1.2 ± 0.1 | 2.0 ± 0.1 | 0.005 | 0.50 |
| MUFA:SFA | 1.19 ± 0.02 | 1.06 ± 0.02 | 1.20 ± 0.02 | 1.35 ± 0.05 | < 0.001 | 0.03 |
| Red meats (times per wk) | 5.6 ± 0.2 | 6.7 ± 0.3 | 5.5 ± 0.3 | 4.1 ± 0.2 | < 0.001 | 0.01 |
| Poultry (times per wk) | 2.1 ± 0.1 | 2.0 ± 0.1 | 2.1 ± 0.1 | 2.2 ± 0.1 | 0.010 | 0.12 |
| Dairy products (times per wk) | 11.6 ± 0.4 | 14.2 ± 0.8 | 10.9 ± 0.5 | 9.2 ± 0.3 | < 0.001 | 0.03 |
| Alcohol (g per day) | 2.7 ± 0.2 | 2.2 ± 0.7 | 2.3 ± 0.3 | 4.0 ± 0.3 | 0.01 | 0.96 |
| Total energy intake, kcal | 2222 ± 47 | 2221 ± 65 | 2235 ± 69 | 2200 ± 69 | 0.89 | < 0.001 |

Abbreviations: MDS, Mediterranean Diet Score; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; wk, week. Data are presented as mean ± s.e.

multivariable adjustment. A five-point increment in the adherence to MDS was inversely associated with risk of all-cause mortality (HR, 0.59; 0.37–0.94). However, no mortality risk reduction was observed in MUO phenotypes with increasing MDS, and there was no association between MDS and CVD mortality in either group.

In stratified analyses for all-cause mortality with a five-point increase in MDS score, stronger inverse associations were observed in men and those meeting physical activity recommendations (*P* for interaction = 0.002 and 0.008, respectively) (Table 4). In addition, the inverse association between MDS and all-cause mortality in MHO individuals was consistent among individuals with and without prevalent chronic disease including diabetes mellitus and hypertension. In MUO individuals, higher MDS tended to increase mortality risk for those who met physical activity recommendations and decrease mortality risk for those who did not meet physical activity recommendations (*P* for interaction = 0.003).

When we excluded subjects who died in the first 5 years of follow-up, the overall results did not materially change (Supplementary Table S3). In addition, using an alternative definition of metabolic health as metabolic syndrome shows similar results in terms of the reduction of all-cause mortality only in MHO individuals (Supplementary Table S4).

## DISCUSSION

In this prospective analysis of a nationally representative sample of obese US adults, higher adherence to Mediterranean diet was associated with a lower risk of all-cause mortality in the MHO phenotype, after adjustment for potential confounders. We observed a 41% reduction in all-cause mortality with each five-point increment in the MDS among MHO individuals. This association persisted when we restricted our analyses to those with or without diabetes mellitus and hypertension. However, the inverse association between the MDS and mortality was not observed in MUO phenotype. To our knowledge, the present study is the first to evaluate a differential beneficial association of Mediterranean diet on mortality risk reduction in MHO and MUO phenotype.

Several epidemiologic studies have explored the association between Mediterranean diet and the risk of mortality in the obese population in subgroup analyses, showing inconsistent results. Trichopoulou *et al.*[1] showed inverse association of MDS with all-cause mortality in Greek adults who had a BMI ⩾ 28.06. In contrast, George *et al.*[35] showed that there was a weak association of MDS with all-cause mortality and no association with CVD and cancer mortality in US postmenopausal women with BMI ⩾ 30. Mitrou *et al.*[36] also showed that the associations with all-cause mortality

**Table 3.** Adjusted HR and 95% CI of all-cause, cardiovascular and cancer mortality according to the tertile categories and a five-point (1 s.d.) increment in the Mediterranean Diet Score in metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes

| | *MHO phenotype* | | | | | *MUO phenotype* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Tertile 1* | *Tertile 2* | *Tertile 3* | P *trend* | *HR for a five-point increase in MDS* | *Tertile 1* | *Tertile 2* | *Tertile 3* | P *trend* | *HR for a five-point increase in MDS* |
| No. of participants | 181 | 240 | 177 | | | 340 | 465 | 336 | | |
| No. of person years | 3191 | 4394 | 3284 | | | 5639 | 8006 | 5625 | | |
| Deaths from all causes, *n* | 35 | 26 | 16 | | | 105 | 116 | 88 | | |
| Model 1 | 1.00 (ref.) | 0.47 (0.26–0.84) | 0.36 (0.23–0.57) | < 0.001 | 0.67 (0.56–0.81) | 1.00 (ref.) | 0.75 (0.56–1.01) | 0.98 (0.56–1.74) | 0.84 | 1.01 (0.83–1.22) |
| Model 2 | 1.00 (ref.) | 0.40 (0.24–0.66) | 0.35 (0.20–0.59) | < 0.001 | 0.59 (0.48–0.73) | 1.00 (ref.) | 0.69 (0.54–0.88) | 0.77 (0.45–1.31) | 0.28 | 0.91 (0.75–1.10) |
| Model 3 | 1.00 (ref.) | 0.35 (0.19–0.64) | 0.44 (0.26–0.75) | < 0.001 | 0.59 (0.37–0.94) | 1.00 (ref.) | 0.74 (0.58–0.95) | 0.92 (0.48–1.76) | 0.66 | 0.96 (0.78–1.17) |
| CVD deaths, n | 6 | 5 | 5 | | | 26 | 33 | 27 | | |
| Model 1 | 1.00 (ref.) | 0.64 (0.18–2.29) | 1.15 (0.12–11.0) | 0.89 | 0.92 (0.38–2.24) | 1.00 (ref.) | 1.57 (0.84–2.93) | 1.76 (0.94–3.29) | 0.07 | 1.08 (0.89–1.31) |
| Model 2 | 1.00 (ref.) | 0.43 (0.12–1.49) | 1.15 (0.12–10.7) | 0.88 | 0.87 (0.28–2.67) | 1.00 (ref.) | 1.46 (0.75–2.83) | 1.41 (0.79–2.50) | 0.22 | 1.12 (0.93–1.35) |
| Model 3 | 1.00 (ref.) | 0.18 (0.05–0.58) | 1.25 (0.41–3.83) | 0.65 | 1.01 (0.29–3.51) | 1.00 (ref.) | 1.28 (0.61–2.67) | 1.61 (0.56–4.62) | 0.34 | 1.15 (0.87–1.54) |
| [a]Cancer deaths, *n* | 11 | 6 | 3 | | | 25 | 25 | 24 | | |
| Model 1 | 1.00 (ref.) | 0.12 (0.07–0.22) | 0.19 (0.04–0.95) | 0.03 | 0.45 (0.21–0.97) | 1.00 (ref.) | 0.58 (0.19–1.72) | 1.07 (0.41–2.80) | 0.99 | 1.13 (0.73–1.77) |
| Model 2 | 1.00 (ref.) | 0.11 (0.06–0.20) | 0.16 (0.04–0.76) | 0.01 | 0.36 (0.15–0.86) | 1.00 (ref.) | 0.54 (0.20–1.50) | 0.90 (0.34–2.40) | 0.78 | 1.07 (0.67–1.71) |
| Model 3 | 1.00 (ref.) | 0.13 (0.06–0.26) | 0.23 (0.02–2.10) | 0.03 | 0.28 (0.04–1.79) | 1.00 (ref.) | 0.61 (0.34–1.09) | 1.17 (0.41–3.33) | 0.90 | 1.27 (0.77–2.10) |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MDS, Mediterranean Diet Score. Data are presented as hazard ratio (95% confidence interval). Model 1 represents a crude model. Model 2 adjusted for age, gender and race/ethnicity. Model 3 further adjusted for educational attainment, income, living with spouse, smoking status, level of physical activity, family history of coronary heart disease, body mass index and total calorie intakes. Owing to small sample sizes, cautious interpretation of finding is needed for CVD and cancer deaths in MHO individuals. [a]Those who had a history of skin cancer were also excluded.

were only observed in ever-smoker in middle to older aged US adults with BMI ⩾ 30. On the basis of the findings from these previous studies, the Mediterranean diet might not be a useful indicator in reducing the risk of mortality in obese population owing to the possibility of underreporting of food intake[37] and physiological impact of obesity itself on mortality risk.[38]

However, these studies assumed that all obese individuals were at the same metabolic health and same risk of mortality. Previous studies have demonstrated that MHO individuals are not at increased risk of mortality and CVD compared with their MUO counterparts.[39] The mechanisms explaining favorable cardiometabolic, hormonal and inflammatory profiles in MHO individuals remain largely unknown. However, several potential pathophysiologic mechanisms include differences in degree of gene marker expression reflecting adipose cell differentiation,[40] the role of key genes in insulin-signaling pathways[41] and amino acid homeostasis[42] between MHO and MUO individuals.

Our results show that inverse associations of Mediterranean diet on risk of mortality were observed only in MHO individuals, which persisted in our sensitivity analyses. Underlying mechanisms for health benefits of Mediterranean diet are complex, but can be explained by the improvement of cardiometabolic profiles including insulin sensitivity, lipid profiles, BP, endothelial dysfunction, reactive oxidation and inflammatory markers.[43] It has been reported that MHO individuals are at increased risk of unfavorable long-term outcomes compared with metabolically healthy normal weight individuals, even with few metabolic abnormalities.[44] In addition, one-third of MHO phenotype can be converted to MUO phenotype within a decade because of unhealthy lifestyle.[45] Thus, our results suggest that there could be a synergistic physiological mechanism to prevent adverse health outcomes, along with improving the favorable cardiometabolic profiles linking MHO phenotype and the adherence to Mediterranean diet. Furthermore, those who reported meeting physical activity recommendations had more benefits in mortality reduction from Mediterranean diet, representing the possible synergistic effects of healthy lifestyles.[46–48]

On the basis of our findings, MUO individuals might not be as responsive to diet because they are already metabolically overburdened.[49] Cardiometabolic comorbidities might explain the lack of association between Mediterranean diet and the risk of mortality in MUO individuals. However, a stratified analysis with and without diabetes mellitus and hypertension showed similar results. Interestingly, MUO individuals meeting physical activity recommendations tended to have a higher risk of all-cause mortality, although the effect estimate was imprecise. Although we cannot completely rule out the possibility of reverse causality in this association, these results suggest that healthy lifestyle alone might not be adequate to reverse the deleterious prognosis of MUO individuals. Thus, the MUO individuals may need to be prioritized for intensive weight loss program along with healthy dietary habits to reduce obesity-related comorbidities.[50] Furthermore, appropriate therapeutic approaches may be warranted to reduce the mortality risk of MUO individuals. [51]

Several dietary intervention studies have explored whether MHO and MUO individuals had the same benefits from CVD risk reduction.[18,19,52] However, their hypotheses were focused on the short-term effects of energy-restricted diet on change of cardiometabolic parameters in MHO and MUO phenotypes with inconsistent findings. Thus, the interpretation of these results might not be applicable to the present long-term prospective cohort study using a Mediterranean dietary pattern as an exposure. Therefore, more evidence would be necessary based on long-term follow-up studies evaluating the effects of healthy dietary pattern on mortality reduction, considering MHO and MUO phenotypes. [51]

Strengths of our study include its prospective study design with nearly 18 years of follow-up for mortality based on the

**Table 4.** Subgroup analyses of the association between a five-point (1 s.d.) increment in the Mediterranean Diet Score and the risk of all-cause mortality in metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes

| | *MHO phenotype* | | | *MUO phenotype* | | |
|---|---|---|---|---|---|---|
| | *No. of participants (deaths)* | *HR for a five-point increase in MDS* | P *interaction* | *No. of participants (deaths)* | *HR for a five-point increase in MDS* | P *interaction* |
| Age, years | | | 0.55 | | | 0.79 |
| $<65$ | 535 (43) | 0.59 (0.32–1.06) | | 908 (152) | 0.97 (0.68–1.37) | |
| $\geqslant 65$ | 63 (34) | 0.41 (0.23–0.75) | | 233 (157) | 1.13 (0.95–1.34) | |
| Gender | | | 0.002 | | | 0.68 |
| Men | 163 (22) | 0.02 (0.01–0.67) | | 495 (146) | 0.96 (0.76–1.21) | |
| Women | 435 (55) | 0.83 (0.50–1.38) | | 646 (163) | 0.98 (0.70–1.38) | |
| Race/ethnicity | | | 0.29 | | | 0.52 |
| Non-Hispanic white | 175 (31) | 0.39 (0.17–0.87) | | 432 (158) | 1.02 (0.82–1.27) | |
| Others | 423 (46) | 0.76 (0.44–1.31) | | 709 (151) | 0.84 (0.58–1.21) | |
| Body mass index, kg $m^{-2}$ | | | 0.46 | | | 0.36 |
| $<35$ | 429 (55) | 0.43 (0.26–0.71) | | 720 (208) | 1.01 (0.80–1.29) | |
| $\geqslant 35$ | 162 (22) | 0.64 (0.31–1.36) | | 421 (101) | 0.95 (0.70–1.30) | |
| Smoking status | | | 0.07 | | | 0.96 |
| Non-smoker | 378 (40) | 0.54 (0.25–1.18) | | 589 (136) | 1.08 (0.76–1.52) | |
| Ever-smoker | 220 (37) | 0.20 (0.10–0.43) | | 552 (173) | 0.96 (0.75–1.22) | |
| Recommended physical activity | | | 0.008 | | | 0.003 |
| Yes | 148 (24) | 0.30 (0.11–0.80) | | 278 (85) | 1.29 (0.89–1.87) | |
| No | 450 (53) | 0.67 (0.45–1.00) | | 863 (224) | 0.95 (0.75–1.20) | |
| Chronic disease | | | 0.13 | | | 0.57 |
| Absence | 457 (35) | 0.56 (0.29–0.95) | | 480 (61) | 1.09 (0.60–1.95) | |
| Presence | 141 (42) | 0.50 (0.29–0.86) | | 661 (248) | 0.92 (0.71–1.18) | |

Models are adjusted as model 3 in Table 3, except for the stratifying factor. A group with recommended physical activity was defined as those who had self-reported leisure time moderate activity ($3 \leqslant$ metabolic equivalents (METs) $< 6$) of five or more times per week or leisure time vigorous activity (METs $\geqslant 6$) three or more times per week. Presence of chronic disease indicates having diabetes mellitus and hypertension.

representative US population. In addition, data were collected based on extensive laboratory and physical examinations using standardized protocols to minimize the influence of measurement errors. Furthermore, we were able to replicate the findings using sensitivity analyses. However, our study has limitations. First, we used 'times per week' in assessing the consumption frequency instead of 'servings per week' in MDS calculation. This approach may cause exposure misclassification, but the direction would be non-differential. In addition, the MDS-scoring methodology used in the present study has not been validated in this population. Second, a ratio of total MUFA to total SFA may not be equal to olive oil consumption as one of MDS components, because the main sources of MUFA are different between the United States and Mediterranean countries. It has been reported that olive oil consumption contributed less than 10% of all monounsaturated fat intake from the Nurses' Health Study conducted during the similar period as our study.[30] In addition, our MDS scoring based on the US data may differ from that of Mediterranean countries owing to difference of dietary patterns and eating behaviors,[30] which might contribute to inconsistent results when applied to Mediterranean countries. A previous meta-analysis also showed that the effect of Mediterranean diet on metabolic syndrome was more outstanding in Mediterranean countries than others.[3] Third, because of a single measure of diet collected at baseline, we could not account for any changes in dietary intake over time. Also, it is possible that FFQ could not assess accurately individual usual intake, and that single 24-h dietary recalls might be subject to misclassification in a categorical approach to MDS tertiles, all of which may lead to bias in MDS measurements. Despite the limitations of reporting errors, however, it has been known that FFQ data are reproducible and adequately able to rank individuals with regard to food and nutrient intake.[53,54] Finally, there may be residual confounding due to measurement error of self-reported covariates.

In conclusion, our results suggest that higher adherence to Mediterranean diet was associated with a lower risk of all-cause mortality exclusively in the MHO phenotype, based on a nationally representative US adult population. The lack of a beneficial association between adherence to Mediterranean diet with the mortality reduction in MUO individuals may warrant the need of alternative strategies to reduce mortality risk in MUO individuals.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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