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Original article

Metabolically healthy obesity, vitamin D, and all-cause and cardiometabolic mortality risk in NHANES III

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SUMMARY

Background & Aims: Previous studies assessing the prognosis of metabolically healthy obesity (MHO) have been limited by a lack of a harmonized definition of MHO phenotype. Furthermore, obesity is a risk factor for vitamin D deficiency and low vitamin D status has been associated with a higher risk of mortality; however, few studies have evaluated the joint association between vitamin D, metabolic health phenotype, and mortality risk. Using a harmonized definition, we investigated whether MHO is associated with subsequent all-cause and cardiometabolic mortality, and whether serum 25-hydroxyvitamin D [25(OH)D] modifies these associations.

Methods: This study included participants aged ≥20 years from the Third National Health and Nutrition Examination Survey (NHANES III). MHO phenotype was defined as a combination of obesity (≥30 kg/m^2) and zero component of metabolic syndrome. Multivariable Cox regression was used to assess the risk of mortality across metabolic phenotypes, and the joint association between metabolic phenotype and 25(OH)D. Fine and Gray regression was performed to account for competing risk events.

Results: Among 11,333 participants, a total of 2980 deaths (937 cardiometabolic death outcomes) occurred during a median follow-up of 19.1 years. In the absence of any metabolic abnormality, obesity (MHO) was not associated with a higher risk of all-cause (hazard ratio [HR], 0.89 [95% CI, 0.52–1.51]) or cardiometabolic mortality (cause-specific HR, 1.21 [95% CI 0.33–4.46]). Similar results were obtained from competing risk analysis. No significant differences in average 25(OH)D levels were observed between MHO and non-MHO participants; however, there was a significant interaction between metabolic health phenotype and serum 25(OH)D in relation to cardiometabolic mortality such that levels of serum 25(OH)D < 50 nmol/L were associated with increased risk of cardiometabolic mortality, particularly in participants within the normal-weight and obese BMI ranges.

Conclusions: Our results support the hypothesis that MHO phenotype is a benign health condition. Vitamin D deficiency may exacerbate the risk of cardiometabolic death outcomes associated with metabolic dysfunction in normal weight and obese individuals. Further research is warranted to validate our findings.

1. Introduction

The existence of the metabolically healthy obesity (MHO) has become increasingly recognized [1]; however, the benign health condition of the MHO phenotype has been widely debated and studies have reported conflicting findings [2–16]. Moreover, the prevalence of MHO phenotype varies significantly across studies, where the prevalence has been estimated to range between 10% and 40% in the adult population [1]. Although study-specific factors such as age, ethnicity, environmental factors and genetics may explain some of these discrepant findings, the lack of a harmonized definition for risk stratification accounts for a large proportion of the reported discrepancy [17]. Most previous studies have included at least one metabolic abnormality [9–14,16], yet the type of metabolic abnormality differs across studies and this may affect the long-term risk estimates differently. Therefore, use of a harmonized definition for MHO phenotype, defined as having zero metabolic abnormality [17], is important for establishing whether obesity or

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metabolic health is a more important predictor of adverse health outcomes.

Identification of novel biomarkers is also needed to have a better understanding of the risk factors that modulate the prognosis of the MHO phenotype. Suboptimal vitamin D status has been associated with increased risk of chronic diseases and mortality [18–20]. Obesity is an established risk factor for vitamin D deficiency, where a causal link between obesity and hypovitaminosis D has been reported in a Mendelian randomization study [21], and high adiposity is consistently associated with low serum 25-hydroxyvitamin D levels [25(OH)D, the accepted measure of vitamin D status] in observational studies [22]. Vitamin D is thought to play a key role in preserving the healthy lipid and inflammatory profile of the MHO phenotype [23]; however, conflicting evidence exists in the literature [24,25].

Although previous studies have evaluated the dose-response relationship between vitamin D status and mortality risk [20,26], with some studies reporting a U-shaped or inverse J-shaped association [19,27], lack of standardized serum 25(OH)D data have impeded our understanding of the dose-response relationship between vitamin D status and non-skeletal health outcomes [28,29]. Moreover, previous studies have evaluated the individual contributions of metabolic health, obesity, and vitamin D status in relation to long-term health outcomes; however, their joint associations have been largely unexplored. Elucidating the interrelation between metabolic health, obesity, and vitamin D may aid in the development of more effective treatment strategies that may ultimately reduce the burden of obesity-related complications.

The purpose of this study was therefore to investigate whether MHO, defined as having zero metabolic abnormality, is associated with subsequent all-cause and cardiometabolic mortality, and to evaluate the joint association of metabolic health phenotype and vitamin D status in relation to mortality risk using data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994).

2. Subjects and methods

2.1. Data source

The NHANES III (1988–1994) is a representative survey of the civilian, non-institutionalized US population conducted by the National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention. The NCHS has updated mortality data for NHANES III up to December 31, 2011, and the baseline data collected in 1988–1994 was linked to mortality data using a probabilistic record matching with death certificates records obtained from the National Death Index (NDI). Follow-up time was calculated from examination date until date of death or end of study (December 31, 2011). Detailed descriptions of the survey design and mortality matching method are published elsewhere [30,31]. The NCHS institutional board approved NHANES III and all participants provided written informed consent [30].

2.2. Outcome measures

All-cause and cardiometabolic mortality status were obtained from publicly available dataset. For participants classified as “assumed deceased”, death cases were coded according to the Tenth Revision of the International Classification of Diseases (ICD-10) and with underlying cause of death further categorized into ten broad groups: Diseases of heart; malignant neoplasms; chronic lower respiratory diseases; accidents (unintentional injuries); cerebrovascular diseases; Alzheimer's disease; diabetes mellitus; influenza and pneumonia; nephritis, nephrotic syndrome and nephrosis; and all other causes (residual). For cardiometabolic death outcomes, we combined deaths classified as diseases of heart, cerebrovascular diseases and diabetes mellitus.

2.3. Exposure measures

Exposure was defined as a combination of body mass index (BMI: kg/m^2) and metabolic health. A harmonized definition of metabolic health was used [17], where ‘metabolically healthy’ individuals are defined as having zero of the metabolic syndrome (MetS) criteria (excluding waist circumference) [32]. Participants with at least one of the four metabolic risk factors were defined as ‘metabolically unhealthy’.

Systolic and diastolic blood pressure (BP) was the average of up to 6 measurements collected under standard conditions [33]. Individuals who self-reported a history of hypertension or use of BP medication were defined as having hypertension. Serum triglyceride, HDL-cholesterol, and fasting plasma glucose (FPG) concentrations were measured using standardized laboratory procedures as reported by NCHS [33]. Participants reporting a history of diabetes or current diabetes medications were considered to have dysglycemia. Similarly, participants taking lipid-modifying medications were considered to have dyslipidemia. Medication use was self-reported by questionnaire during the in-home interview.

BMI (kg/m^2) was categorized into normal weight (18.5–24.9), overweight (25–29.9), and obesity (≥30). Participants were subsequently divided into six metabolic phenotypes: metabolically healthy normal-weight (MHNW), metabolically healthy overweight (MHOW), metabolically healthy obesity (MHO), metabolically unhealthy normal-weight (non-MHNW), metabolically unhealthy overweight (non-MHOW), and metabolically unhealthy obesity (non-MHO).

2.4. Covariate data

Age, sex, ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican-American or other), smoking status, educational level, and leisure-time physical activity (LTPA) were self-reported by questionnaire during the in-home interview. Smoking status was categorized into current, former or never smokers (cigarettes only). Educational attainment was coded as less than high school, high school diploma, and more than high school. LTPA was assessed by a questionnaire that asked participants about the type and frequency of the following 9 activities: run/jog, swim, bicycle, aerobics, calisthenics, dancing, yard or garden work, weight lifting, or other physical activity). For each of these 9 activities, a validated metabolic equivalent (MET) score was assigned and using these scores, we estimated the total weekly LTPA MET. Serum creatinine was recalibrated to be traceable to an isotope-derived mass spectroscopy method using the following equation: standardized creatinine (mg/dL) = [0.960 × NHANES III serum creatinine (mg/dL)]−0.18 [34]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [35]. Serum C-reactive protein (CRP) was measured using a low sensitivity method that can detect CRP levels >0.22 mg/dL [33]. Because most individuals had values below the minimum detectable level, CRP was treated as a categorical variable using clinical cut-off points as previously described [36]: low (<0.22 mg/dL), moderate (0.22-<1.0 mg/dL), and high (≥1.0 mg/dL). We used standardized serum 25(OH)D values in this study [37]. Season of blood draw was categorized as winter (November to April) and summer (May to October).

Poverty-to-income ratio (PIR), a ratio of total family income to the official poverty threshold, was used to assess the socioeconomic status. The Healthy Eating Index (HEI) scores derived from 24-h

dietary recall was used to assess the overall diet quality of participants [38]. Alcohol consumption was assessed by questionnaire and estimated as number of drinks per month.

2.5. Analytical sample

A total of 18,825 adults aged 20 years or older were interviewed in NHANES III, and 16,573 completed the mobile examination center (MEC) and laboratory examinations. After applying the exclusion criteria, the total analytical sample included 11,333 participants aged ≥20 years with no history of CVD and cancer (excluding skin cancer) (Appendix A, Fig. 1).

2.6. Statistical analysis

Baseline characteristics were analyzed according to metabolic health phenotype using sampling weights to account for differential probability of selection [30]. Differences in continuous and categorical data were assessed using weighted Wald-F and Chi-square tests as appropriate. Survey weighted Cox proportional hazards (PH) regression models were constructed and adjusted for age, sex, ethnicity, smoking status, education level, LTPA, eGFR, serum CRP and 25(OH)D. For cardiometabolic mortality, we also performed Fine and Gray regression to estimate the cumulative incidence of cardiometabolic death while accounting for competing events (i.e., cancer and other deaths) [39]. SAS macro (%PSHREG) was used to plot the cumulative incidence curves for cardiometabolic mortality [40]. The PH assumption was tested using log-minus-log survival plots and analysis of Schoenfeld residuals, and no violations were observed.

Unweighted Cox PH models with restricted cubic splines (RCS) were used to graphically display the dose-response relations between serum 25(OH)D and all-cause and cardiometabolic mortality in the overall sample [41,42]. Knots in the RCS models were set at the 25th, 50th, and 75th percentiles of serum 25(OH)D, with 50 nmol/L set as the reference level. We examined the non-linear relation between 25(OH)D and cardiometabolic mortality non-parametrically with RCS models; tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms [42]. On the basis of previous literature, the RCS models were adjusted for age, sex, ethnicity, smoking status, education, LTPA, eGFR, serum CRP and season. The joint association between metabolic phenotype and serum 25(OH)D with mortality (all-cause and cardiometabolic death outcomes) was assessed by a formal test of interaction. Significant interaction terms were further stratified by the effect modification term.

All analyses were conducted with SAS version 9.4 (Cary, NC). P-value <0.05 was considered significant.

2.7. Sensitivity analyses

2.7.1. Adjustment for additional confounders

Due to the large number of missing data for alcohol consumption, income, and diet quality, we adjusted for these covariates in a sensitivity analysis to further account for potential residual confounding. This analysis included 9744 participants.

2.7.2. Using waist circumference to define obesity

We used waist circumference (WC) to define abdominal obesity and examine whether metabolically healthy but abdominally obese individuals are at increased risk of mortality. WC (cm) was defined as low (men, ≤94; women, ≤80), intermediate (men, >94 and ≤102; women, >80 and ≤88), and elevated (men, >102; women, >88) [43]. This analysis included 10,988 participants.

3. Results

3.1. Baseline characteristics

The total sample included 11,333 adults aged ≥20 years with no history of CVD and cancer; 2980 participants died during a median follow-up of 19.1 years, with 937 cardiometabolic death outcomes.

Table 1 shows the weighted characteristics of the study population according to metabolic phenotypes. A total of 367 participants met the MHO definition (3.2% of the total sample). The mean age was 43.6 (42.8, 44.5) years in the overall sample. Mean age was consistently higher among metabolically unhealthy participants compared to their metabolically healthy counterparts. Metabolically healthy participants had lower BMI and mean values for the four metabolic risk factors than their metabolically unhealthy counterparts. Metabolically healthy participants (irrespective of BMI status) also had lower prevalence of current smokers, better kidney function, lower CRP values and were more educated. Overall, mean serum 25(OH)D was negatively associated with BMI and was significantly higher in MHNW (67.6 nmol/L) compared to non-MHNW (63.3 nmol/L), however, no significant differences were observed between metabolically healthy and unhealthy participants within the overweight and obesity BMI ranges (overweight: 61.4 vs. 62.4 nmol/L; obesity: 53.8 vs. 55.5 nmol/L).

3.2. Metabolic health phenotype and mortality risk

Table 2 shows the hazard ratios (HRs) for all-cause mortality and cause-specific HRs for cardiometabolic and non-cardiometabolic mortality. MHNW participants were used as reference group (HR = 1.0). After adjusting for confounders, we observed a higher risk of all-cause mortality among metabolically unhealthy participants within the normal-weight and obesity BMI range. MHOW, non-MHOW, and MHO were not associated with risk of all-cause mortality. In relation to cardiometabolic mortality, being metabolically unhealthy irrespective of BMI status was associated with a significantly higher cause-specific hazard for cardiometabolic death outcomes, whereas no significant association was observed in relation to non-cardiometabolic mortality. For MHOW and MHO participants, the cause-specific HRs for cardiometabolic and non-cardiometabolic death outcomes were not significant.

Figure 1 shows the cumulative incidence curves (obtained from Fine and Gray model to adjust for competing events) for cardiometabolic mortality stratified by metabolic health phenotype. In the unadjusted cumulative incidence (Fig. 1A), the risk of cardiometabolic mortality over 23 years of follow-up remained low in metabolically healthy participants irrespective of their BMI status (<4%), whereas the risk of cardiometabolic mortality was higher in metabolically unhealthy participants, with the highest incidence observed among non-MHNW participants (12.8%). After adjusting for age, sex, ethnicity, smoking status, education, LTPA, eGFR, serum CRP and 25(OH)D (Fig. 1B), the estimated cumulative incidence of cardiometabolic mortality was lowest for MHO participants followed by MHNW and MHOW participants. Among metabolically unhealthy participants, non-MHO participants had the highest risk of cardiometabolic mortality, and non-MHNW and non-MHOW participants had comparable risk of cardiometabolic death outcomes over 23 years of follow-up.

3.3. Standardized serum 25(OH)D status and mortality risk

Figure 2 shows the dose-response relation between 25(OH)D and all-cause and cardiometabolic mortality risk in the overall sample. Serum 25(OH)D levels below 50 nmol/L were significantly and inversely associated with increased risk of all-cause and

Table 1
Baseline characteristics of participants aged 20 years and older by metabolic health status: NHANES III survey 1988 to 1994.

	Normal weight (n = 4380)		Overweight (n = 4022)		Obese (n = 2931)		P-value
	Healthy (n = 1939)	Unhealthy (n = 2441)	Healthy (n = 922)	Unhealthy (n = 3100)	Healthy (n = 367)	Unhealthy (n = 2564)	
Age, y	35.1 (34.2, 36.0)	46.3 (44.6, 47.9)	38.2 (37.0, 39.4)	48.5 (47.4, 49.6)	37.9 (36.4, 39.5)	46.9 (45.9, 47.9)	<0.0001
Fasting plasma glucose, mmol/L	4.90 (4.87, 4.92)	5.32 (5.27, 5.38)	5.02 (4.99, 5.05)	5.55 (5.49, 5.61)	4.97 (4.89, 5.05)	5.87 (5.75, 5.99)	<0.0001
Serum triglyceride, mmol/L	0.88 (0.86, 0.91)	1.47 (1.42, 1.52)	1.01 (0.98, 1.04)	1.93 (1.85, 2.01)	1.07 (1.01, 1.12)	2.10 (2.02, 2.20)	<0.0001
HDL-cholesterol, mmol/L	1.56 (1.54, 1.59)	1.30 (1.27, 1.32)	1.42 (1.39, 1.46)	1.18 (1.15, 1.20)	1.47 (1.41, 1.52)	1.13 (1.11, 1.14)	<0.0001
Systolic blood pressure, mmHg	111.1 (110.3, 111.8)	123.4 (121.9, 124.9)	113.9 (112.9, 114.9)	127.2 (125.9, 128.4)	115.1 (113.6, 116.7)	129.5 (128.5, 130.5)	<0.0001
Diastolic blood pressure, mmHg	69.2 (68.7, 69.8)	73.9 (73.1, 74.7)	71.9 (71.0, 72.8)	77.3 (76.7, 77.8)	72.9 (72.0, 73.8)	79.1 (78.5, 79.8)	<0.0001
BMI, kg/m^2	22.1 (21.9, 22.2)	22.5 (22.4, 22.6)	26.9 (26.7, 27.0)	27.2 (27.1, 27.2)	32.9 (32.5, 33.5)	34.8 (34.4, 35.2)	<0.0001
Serum 25(OH)D, nmol/L	67.6 (65.7, 69.4)	63.3 (61.7, 64.9)	61.4 (59.2, 63.5)	62.4 (60.9, 63.8)	53.8 (50.2, 57.4)	55.5 (53.7, 57.4)	<0.0001
Male, %	41.1 (39.5, 46.8)	45.3 (42.4, 48.2)	56.3 (51.3, 61.4)	60.7 (58.3, 63.0)	37.7 (27.2, 48.1)	43.2 (39.8, 46.7)	<0.0001
Ethnicity, %							<0.0001
Non-Hispanic Whites	78.7 (74.6, 82.9)	79.1 (75.8, 82.4)	73.8 (69.3, 78.3)	79.2 (76.1, 82.3)	67.2 (59.9, 74.5)	74.3 (71.1, 77.5)	
Non-Hispanic Blacks	8.99 (7.30, 10.7)	7.52 (6.34, 8.69)	12.7 (10.4, 15.1)	8.53 (7.48, 9.58)	20.5 (15.9, 25.1)	12.4 (10.5, 14.4)	
Mexican-Americans	4.28 (3.32, 5.24)	3.98 (3.12, 4.83)	6.60 (5.01, 8.20)	5.89 (4.78, 7.00)	4.61 (3.14, 6.08)	6.28 (5.08, 7.48)	
Other	7.99 (5.03, 10.9)	9.36 (6.59, 12.1)	6.83 (3.83, 9.84)	6.42 (4.07, 8.77)	7.61 (3.25, 12.0)	6.93 (4.82, 9.04)	
Current smokers, %	29.8 (26.7, 32.9)	32.8 (29.8, 35.8)	18.6 (15.3, 22.0)	28.5 (25.6, 31.3)	20.9 (13.9, 28.0)	23.9 (21.3, 26.6)	<0.0001
Education, %							<0.0001
Less than high school	15.1 (12.8, 17.4)	24.6 (21.8, 27.4)	15.7 (11.9, 19.5)	26.6 (22.9, 30.4)	17.2 (12.4, 22.0)	28.2 (25.4, 30.9)	
High school	31.2 (28.4, 34.0)	32.4 (29.9, 35.0)	33.0 (28.1, 38.0)	34.7 (31.8, 37.6)	43.9 (36.3, 51.4)	37.6 (34.1, 41.2)	
More than high school	53.7 (49.9, 57.4)	42.9 (39.4, 46.4)	51.2 (45.6, 56.9)	38.6 (34.6, 42.6)	38.9 (31.3, 46.5)	34.1 (30.1, 38.2)	
Leisure-time PA, total weekly MET	30.5 (28.0, 33.0)	27.5 (25.5, 29.6)	30.5 (26.9, 34.2)	24.6 (22.6, 26.7)	20.1 (15.9, 24.4)	21.4 (18.9, 23.9)	<0.0001
eGFR, ml/min/1.73 m^2							<0.0001
≥90	85.7 (83.1, 88.3)	69.1 (65.9, 72.4)	80.6 (76.4, 84.8)	63.3 (60.8, 65.8)	84.3 (78.2, 90.3)	64.5 (61.8, 67.2)	
60-<90	14.0 (11.4, 16.6)	26.3 (23.4, 29.3)	19.2 (15.0, 23.3)	32.3 (29.8, 34.7)	15.3 (9.20, 21.4)	30.1 (27.4, 32.7)	
<60	0.28 (0.06, 0.50)	4.50 (3.65, 5.34)	0.20 (0.00, 4.44)	4.44 (3.46, 5.42)	0.41 (0.00, 1.23)	5.45 (4.52, 6.37)	
CRP, mg/dL							<0.0001
<0.22	90.6 (89.0, 92.2)	78.5 (75.3, 81.7)	81.4 (77.6, 85.2)	71.1 (67.0, 75.2)	58.4 (48.7, 68.1)	50.0 (46.0, 54.0)	
0.22−1.0	7.76 (6.04, 9.48)	15.7 (12.7, 18.7)	15.7 (11.8, 19.6)	22.4 (19.4, 25.5)	29.7 (19.6, 39.7)	36.4 (32.8, 40.1)	
≥1.0	1.61 (0.76, 2.47)	5.75 (4.30, 7.19)	2.84 (1.22, 4.45)	6.42 (4.81, 8.03)	11.9 (7.45, 16.4)	13.5 (11.6, 15.4)	

Values are survey-weighted means or frequencies (%), and 95% CIs in parenthesis. P-values are based on Wald-F test and Chi-square tests, which test the independence of means and frequencies, respectively, across metabolic health groups.

Table 2
All-cause, cardiometabolic (CM), and non-CM mortality hazard ratios (HRs) for participants aged 20 years and older according to metabolic health status: NHANES III survey 1988 to 1994 with follow-up through 2011.

N = 11,333	Median follow-up, yr	All-cause deaths/N	All-cause mortality		CM deaths/N	CM mortality		non-CM deaths/N	Non-CM mortality	
			HR	95% CI		HR	95% CI		HR	95% CI
Healthy normal-weight (MHNW)	20.0	179/1939	1.00	–	37/1939	1.00	–	142/1939	1.00	–
Healthy overweight (MHOW)	19.7	87/922	0.85	0.59, 1.22	20/922	0.94	0.38, 2.33	67/922	0.84	0.56, 1.27
Healthy obese (MHO)	19.6	25/367	0.89	0.52, 1.51	6/367	1.21	0.33, 4.46	19/367	0.84	0.47, 1.50
Unhealthy normal-weight (non-MHNW)	18.7	891/2441	1.38*	1.12, 1.69	286/2441	2.22*	1.28, 3.82	605/2441	1.23	0.95, 1.59
Unhealthy overweight (non-MHOW)	18.7	1055/3100	1.15	0.91, 1.47	345/3100	1.94*	1.12, 3.34	710/3100	1.02	0.77, 1.33
Unhealthy obese (non-MHO)	18.7	743/2564	1.44*	1.17, 1.76	243/2564	2.51*	1.53, 4.09	500/2564	1.26	0.99, 1.61

HRs are adjusted for age, sex, ethnicity, smoking status, educational level, leisure-time physical activity, kidney function (eGFR), serum CRP and 25(OH)D. *P-value $\leq$ 0.05.

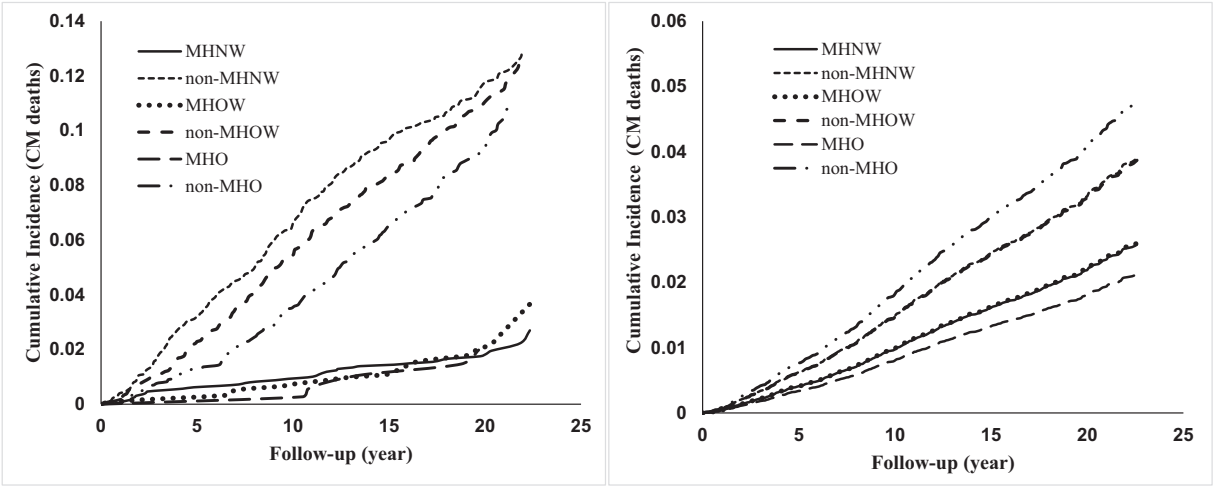

Fig. 1. Unadjusted (Fig. 1A) and adjusted (Fig. 1B) cumulative incidence curves for cardiometabolic (CM) death outcomes by metabolic health phenotypes among participants aged 20 years and older: NHANES III survey with follow-up through 2011. Cumulative incidence functions (CIFs) were obtained from Fine and Gray model (i.e., adjusting for non-cardiometabolic deaths). CIFs (Fig. 1B) were adjusted for age, sex, ethnicity, smoking status, educational level, leisure-time physical activity, kidney function (eGFR), serum CRP and 25(OH)D.

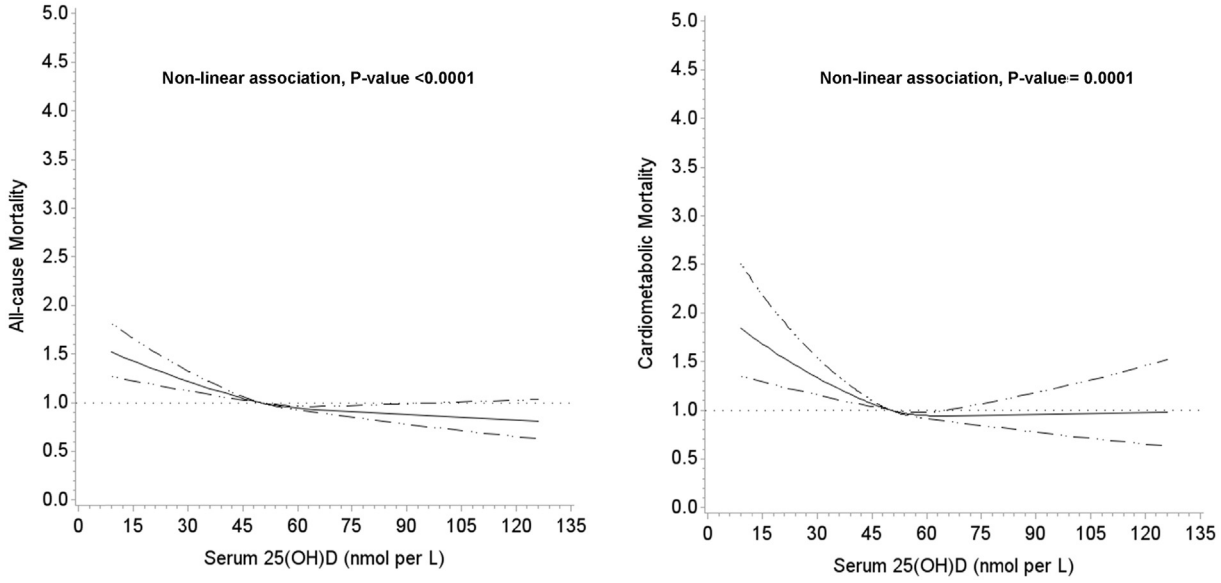

Fig. 2. Adjusted cubic spline models showing hazard ratios (HR) for all-cause and cardiometabolic mortality according to serum 25(OH)D concentration in participants aged 20 years and older: NHANES III survey. Models are adjusted for metabolic health phenotype, age, sex, ethnicity, smoking status, education level, leisure-time PA, kidney function (eGFR), serum CRP, and season of blood draw. The solid line represents HR for all-cause and cardiometabolic mortality and the dashed lines represent the 95% confidence intervals. Knots are at the 25th, 50th, and 75th percentiles for serum 25(OH)D. Reference value for serum 25(OH)D is 50 nmol/L (HR = 1.0).

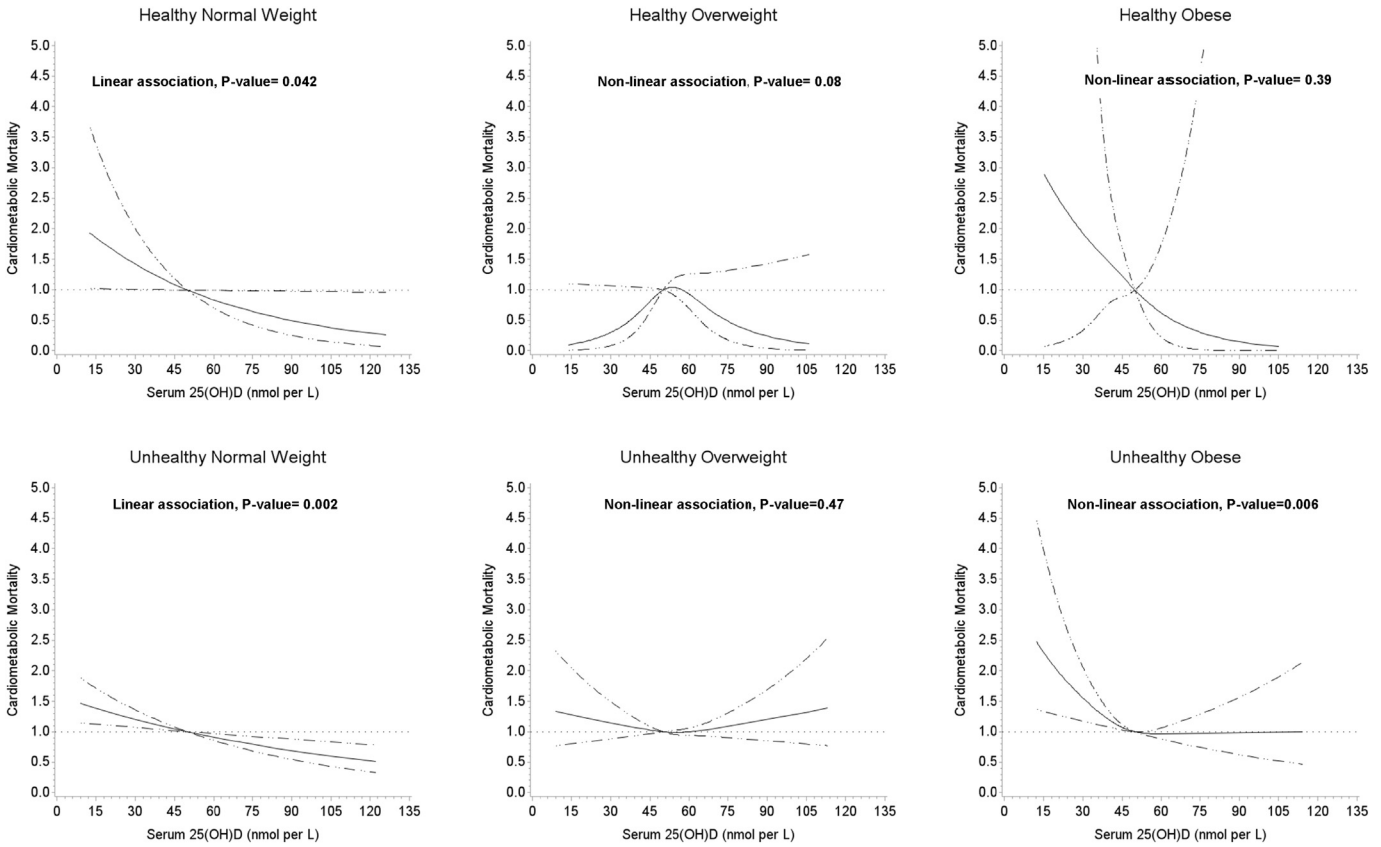

Fig. 3. Adjusted cubic spline models showing association between serum 25(OH)D levels and hazard ratios (HRs) for cardiometabolic mortality stratified by metabolic health status among participants aged 20 years and older: NHANES III survey 1988 to 1994. Models are adjusted for age, sex, ethnicity, smoking, education level, leisure-time PA, kidney function (eGFR), serum CRP, and season of blood draw. The solid line represents HR for cardiometabolic mortality and the dashed lines represent the 95% CIs. Knots are at the 25th, 50th, and 75th percentiles for serum 25(OH)D. Reference value for serum 25(OH)D is 50 nmol/L (HR = 1.0).

cardiometabolic mortality, and the minimum relative risk was observed with values near 60–75 nmol/L.

There was a significant interaction between metabolic phenotype and serum 25(OH)D in relation to cardiometabolic mortality (*P* interaction <0.0001). Figure 3 shows the dose-response relation between serum 25(OH)D and cardiometabolic mortality further stratified by metabolic health phenotype. Within the normal-weight BMI range, there was a linear inverse association between serum 25(OH)D and cardiometabolic mortality. This inverse association was stronger for non-MHNW participants where there was a clear relative risk reduction in cardiometabolic mortality with increasing serum 25(OH)D levels. For individuals within the overweight BMI range, we observed a non-significant curvilinear relation between 25(OH)D and cardiometabolic mortality. Lastly, for MHO participants, we observed a non-significant inverse association between serum 25(OH)D and cardiometabolic mortality risk. For non-MHO participants, there was a significant inverse association between low 25(OH)D (<50 nmol/L) and cardiometabolic mortality risk, however this inverse relation attenuated at the higher end of 25(OH)D concentrations (>50 nmol/L).

3.4. Sensitivity analyses

When we further adjusted our models for income, alcohol consumption, and diet quality in a subset sample of 9744 participants with complete data, HR estimates were similar to the main analysis (Appendix A, Table 1). When using WC to define obesity, a total of 630 participants were categorized as MHO (5.7% of the total sample), and results were also similar to the main analysis (Appendix A, Table 2).

4. Discussion

In a population study of 11,333 U.S. adults with a median follow-up of 19.1 years, we found that in the absence of any metabolic dysfunction, obesity (MHO) was not associated with a higher risk of all-cause and cardiometabolic mortality. We found a significant interaction between metabolic health and serum 25(OH)D in relation to cardiometabolic death outcomes. Specifically, 25(OH)D levels were inversely associated with cardiometabolic mortality in normal-weight individuals irrespective of metabolic health status (linear association) and in non-MHO individuals (non-linear association). For overweight individuals and MHO participants, we did not observe a significant inverse association between serum 25(OH)D and cardiometabolic mortality. Overall, metabolic health was a more important predictor of adverse outcomes in our study and effect modification by 25(OH)D raises the possibility that optimizing vitamin D status may improve the prognosis of cardiometabolic health outcomes, particularly in high-risk groups (i.e., individuals with metabolic dysfunction and vitamin D deficiency).

Our study findings are in agreement with studies showing MHO is not associated with increased risk of all-cause or cardiometabolic mortality [2–8], yet other studies have questioned the benign health condition of MHO [9–16]. Most recently, Lassale et al. [16] found that metabolically healthy overweight and obese individuals had higher coronary heart disease (CHD) risk than their normal-weight counterparts. However, they classified participants

as metabolically healthy if they did not meet the MetS criteria (i.e., ≤2 components) [16]. In their sensitivity analysis to assess the contribution of overweight and obesity with zero MetS component, they found that overweight and obesity was not associated with subsequent CHD risk [16]. While they appear inconsistent, their results are, in fact, in agreement with our findings. In addition, when using WC to define abdominal obesity, our results were similar to the main analysis in that metabolically healthy abdominal obese participants were not at increased risk of all-cause or cardiometabolic mortality. Our results are in agreement with a recent study by Doustmohamadian et al. in relation to all-cause mortality [44], however, Keihani et al. reported an increased risk of CVD outcomes among metabolically healthy abdominally obese individuals [45]. Studies that have questioned the benign health status of the metabolically healthy obese (using either BMI or WC to define obesity) have included a large proportion of individuals with ≤2 components of the MetS criteria [9–14,16,45]. The differences in estimated risk could be ascribed to the variation in type and severity of the MetS components across different studies, and evidence suggests that cardiometabolic risk increases with the presence of just one metabolic abnormality [46]. Therefore, we argue that use of a strict criterion to define metabolic health is more appropriate for risk stratification [17].

In relation to cardiometabolic mortality, competing risk events are common in epidemiologic research and are particularly relevant to studies with long-term follow-up [39,47]. In our study, the frequency of competing events was ~18% in the overall sample and ~5% among MHO participants. For risk prediction, it is important to account for competing events because standard survival methods overestimate the cumulative incidence of an event of interest [39,47]. Additionally, a higher hazard rate may not necessarily coincide with a higher cumulative incidence because the one-to-one correspondence between the hazard rate and the CIF is lost in the presence of competing risks [39,47]. In our study, we found the results from the cause-specific HRs for MHO participants were similar to the cumulative incidence estimates because the frequency of competing events was low among MHO participants (i.e, ~5%). To our knowledge, previous studies assessing CVD prognosis among MHO participants have not accounted for competing events, and depending on the frequency of competing events in each study cohort, an increase in hazard rate may not necessarily imply an increase in the cumulative incidence of events [47]. Studies assessing the prognosis of the MHO phenotype in relation to cause-specific events should be aware of the potential bias introduced by standard survival methods and should account for competing events to more appropriately estimate the CVD prognosis of MHO participants.

We found evidence of a nonlinear association between 25(OH)D and all-cause and cardiometabolic mortality in the overall sample, with the minimum risk observed with values near 60–75 nmol/L. In our study, 25(OH)D modified the association between metabolic phenotype and cardiometabolic mortality. Effect modification by 25(OH)D was particularly pronounced among metabolically unhealthy normal-weight individuals such that higher 25(OH)D status (>50 nmol/L) attenuated the increased risk of cardiometabolic mortality, with no evidence of a threshold effect. Higher 25(OH)D status among MHO participants had a non-significant inverse association with cardiometabolic mortality; this non-significance may be attributed to the small sample size (n = 367). For non-MHO participants, there was a significant nonlinear inverse relationship between 25(OH)D and cardiometabolic mortality, with the highest risk observed for 25(OH)D < 50 nmol/L. The nonlinear association and the wide confidence intervals for participants within the obesity BMI range may either reflect a threshold effect of vitamin D or may be a function of the insufficient data for high 25(OH)D levels (>50 nmol/L). For participants within the overweight BMI range, the non-linear association of serum 25(OH)D and cardiometabolic mortality was not significant. These results could reflect a chance finding. Moreover, the non-MHOW subgroup had the highest average age compared to other subgroups, and although we adjusted for age in our models, there may be residual confounding due to older age of non-MHOW participants, thus contributing to the non-significant association.

Vitamin D may mitigate the detrimental effects of metabolic dysfunction on cardiometabolic death outcomes (i.e., diabetes, hypertension, CVD) in several ways. Insulin resistance (IR) is the core metabolic trait associated with type-2 diabetes and several lines of evidence support a role of vitamin D in glucose homeostasis and insulin sensitivity [48]. A recent meta-analysis of randomized control trials (RCT) showed that vitamin D supplementation (with a minimum dose of 4000 IU/d) significantly improved FPG, HbA1c, and insulin sensitivity in patients with type-2 diabetes [49]. Another recent RCT showed that 2800 IU/d of vitamin D_3 in vitamin D deficient obese patients significantly reduced HbA1c by 3.52 mmol per mol of vitamin D [50]. Vitamin D supplementation has also been shown to be an effective intervention in hypertensive patients; several RCTs have shown a beneficial effect of vitamin D on central BP parameters in hypertensive patients with vitamin D deficiency [51,52]. While other RCTs have found null results in relation to BP parameter (particularly in untargeted populations), a Mendelian randomization study supported a causal role of vitamin D in hypertension [53]. Thus, the effect modification observed in our study could reflect changes in glycemic control and hypertension, particularly in metabolically unhealthy normal-weight and obese patients. While vitamin D has been shown to improve glycemic and BP parameters, no clinical trials have been performed specifically to investigate whether vitamin D supplementation can help individuals with metabolic dysfunction to transition in the metabolically healthy state. Although weight-loss through lifestyle modification is recommended for patients with obesity [54], long-term weight-loss maintenance remains challenging, and vitamin D supplementation has been proposed as an adjunct therapy in high-risk individuals [49]. Individuals with obesity have a higher risk of vitamin D deficiency [55] and may require at least 6000 IU vitamin D_3/d to maintain serum 25(OH)D > 50 nmol/L [56]. Future well-designed RCTs are needed to investigate whether vitamin D supplementation is beneficial for transition and maintenance of metabolic health in targeted populations.

The present study has several limitations. Biomarkers for metabolic health, adiposity, and serum 25(OH)D were measured only once at baseline, therefore we were not able to assess the transition from metabolically healthy to unhealthy states, as well as any changes in 25(OH)D over time. In addition, only 3% of participants were categorized as MHO and consequently there were relatively few deaths among MHO phenotype, and this lead to a relatively wide confidence intervals for the risk estimates; therefore, these estimates should be interpreted with caution. For competing risk analysis, we were unable to further adjust for NHANES survey weights using the Fine and Gray model and it is difficult to obtain a true estimate of the frequency and the distribution of competing events at the population level. Therefore, our estimate of competing events may not be transferable to other populations with a different distribution of competing events. As with any observational study, the presence of residual confounding related to measurement errors and unmeasured variables (i.e., genetic factors) cannot be eliminated in our study.

In conclusion, our study supports the hypothesis that metabolically healthy obesity is a benign health condition and our results suggest that metabolic health is a more important predictor of adverse events. MHO individuals did not have higher mean 25(OH)

D levels compared to non-MHO individuals; however, vitamin D status modified the association between metabolic phenotype and cardiometabolic mortality, particularly among metabolically unhealthy normal-weight and obesity phenotypes. Future large interventional studies are needed to help clarify the joint association between vitamin D and metabolic health.

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Statement of authorship

All authors have read and approved the final version being submitted with contributions as follows: conception (BA, SMK, CIA), data acquisition (BA), statistical analysis (BA) and interpretation of data (BA, SMK, JLK, CIA), drafting of manuscript (BA), critical review and editing (BA, SMK, JLK, CIA).

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.02.025.

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