A Prospective Study of Obesity, Metabolic Health and Cancer Mortality among Blacks and Whites

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Abstract

Introduction—We examined whether metabolic health status increases the risk of cancer mortality, and whether this association varied by body mass index (BMI) category.

Methods—We performed a prospective study of 22,514 participants from the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. We defined metabolic unhealthy status as having 3+ of the following: 1) elevated fasting glucose, 2) high triglycerides, 3) dyslipidemia, 4) hypertension, and 5) elevated waist circumference. We categorized participants into normal weight (BMI: 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2) and obese (BMI

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30 kg/m^2) groups. We performed Cox proportional hazards regression to estimate hazards ratios (HRs) and 95% confidence intervals (CIs) for cancer mortality during follow-up.

Results—Among participants with normal weight, those who were metabolically unhealthy had increased risk of cancer mortality (HR: 1.57; 95% CI: 1.15 – 2.16) compared with metabolically healthy participants. Overall mortality risk for participants who were metabolically unhealthy and normal-weight was stronger for obesity-related cancers (HR: 2.31, 95% CI: 1.13 – 4.73). Compared with participants with normal weight, those who were metabolically healthy overweight were at reduced risk of any cancer mortality (adjusted HR: 0.79, 95% CI: 0.63-0.98).

Conclusion—There was an increased risk of overall- and obesity-related- cancer mortality among metabolically unhealthy normal weight participants.

Keywords

INTRODUCTION

Obesity has long been understood to increase the risk of cancer mortality[1-5], and is also an established risk factor for multiple chronic diseases, including type 2 diabetes, cardiovascular disease, metabolic syndrome and cancer. The prevalence of obesity in the United States has reached epidemic proportions, with up to two-thirds of US adults currently in overweight or obese categories[6]. Concurrently, the prevalence of metabolic syndrome, a cluster of cardio-metabolic risk factors that include high fasting blood glucose, low HDL cholesterol, high blood pressure and high triglycerides, has also increased rapidly[7]. However, a recent study based on data from the US National Health and Nutrition Examination Survey showed that 32% of US adults with obesity were metabolically healthy, i.e., had none or one of the cardio-metabolic risk factors typically associated with obesity [8]. Clinical research studies suggest that this sub-group of metabolically healthy individuals with obesity display favorable insulin, inflammatory and lipid profiles and may be at lower risk for obesity-related chronic conditions compared with their metabolic unhealthy counterparts [9]. This raises the intriguing question of whether there is a universal association between metabolic health status and risk of adverse health outcomes in US adults, of if the association varies by body mass index (BMI) category [10].

Recent studies provide some evidence for differences in the biological response to obesity and the risk of cancer based on metabolic health status. For instance, a recent study observed a 200% increased risk of cancer among overweight adults with elevated blood glucose, compared with a 50% increased risk among overweight adults with normal glucose[11]. Two other recent studies examined metabolic health status and obesity in relation to cancer mortality among Korean adults; both studies observed significantly lower risk of cancer mortality among metabolically healthy adults with obesity compared with those who were metabolically unhealthy with obesity [12,13]. This is in line with prior studies showing that metabolically healthy individuals with obesity may be at lower or similar risk of cardiovascular diseases compared with adults without obesity, and thus may be protected against the cardio-metabolic complications of obesity[9]. The evidence on whether

metabolically health obesity is similarly associated with cancer mortality among US adults remains sparse. If we find consistent scientific evidence that the influence of metabolic health status on cancer outcomes varies by BMI, this information will add to the growing literature regarding the importance of metabolic risk factors in cancer prognosis. In this study, we examine the association between metabolic health and obesity (as categorized by BMI) on cancer mortality in a national US population of Blacks and Whites.

METHODS

Data Source

The REasons for Geographic And Racial Differences in Stroke (REGARDS) is one of the largest ongoing national longitudinal cohorts of community-dwelling adults in the United States [14]. Designed to identify contributors to racial and geographic differences in stroke mortality, the cohort included 30,239 participants aged 45 years at baseline; 45% were male, 41% were Black, and 69% were >60 years old. Participants were recruited between January 2003 and October 2007, and detailed information about demographics, health behaviors, chronic medical conditions, physical status, diet, and medications were collected [14]. During the course of prospective follow-up, participants are contacted by telephone every 6-months to identify any medical event or hospitalizations experienced since the prior contact. For statistical analysis, we excluded participants who were missing data on metabolic components (4846), had a prior history of cancer diagnosis at baseline (2175), were missing data on follow-up time (236), or had a BMI lower than 18.5 kg/m^2 (349), leaving a total of 22,514 participants for analysis.

Cancer Mortality Outcome

The primary outcome in this study was death due to any cancer. Cancer mortality was ascertained using death certificates, medical records, interviewed proxies, linkages with the Social Security Death Index (SSDI) as well as the National Death Index (NDI). Date of death was confirmed using death certificates, SSDI, and/or NDI, and cause of death was adjudicated by a committee of experts using all available information as recommended by national guidelines [15]. As a secondary outcome, we examined obesity-related cancer deaths defined as cancers of the breast, colorectal, kidney, pancreas, endometria, and esophagus [16]. Follow-up time for each participant was calculated from the enrollment date through date of cancer death, death, or last telephone follow-up through December 31, 2012.

Main Exposure Variables

The main variables of interest were metabolic health and BMI category. First, we defined metabolic health using the criteria for metabolic syndrome proposed by international consensus in 2009 [17]. These criteria define metabolic syndrome based on presence of three or more of the following components: 1) elevated waist circumference (WC): >102 cm for males or >88 cm for females; 2) elevated triglycerides: 150 mg/dL or reported use of medication for elevated triglycerides; 3) reduced high-density lipoprotein cholesterol (HDL-C): <40 mg/dL for males and <50 mg/dL for females, or use of lipid lowering medications; 4) elevated blood pressure: systolic blood pressure 130 mm Hg, diastolic blood pressure 80 mm Hg, or the reported use of antihypertensive agents; and 5) elevated glucose: fasting

glucose 100 mg/L or the use of insulin or oral hypoglycemic agents. For this analysis, metabolic unhealthy participants were those with at least three of the five metabolic syndrome components, while metabolic healthy participants were those with less than three. We further defined BMI category based on interviewer-measured participant height and weight during the baseline in-home examination. We classified BMI category into three categories as recommended by the Centers for Disease Control and Prevention (CDC): 1) normal weight - BMI < 25.0 kg/m^2, 2) overweight - BMI between 25.0 and 29.9 kg/m^2, and 3) obese - BMI 30 kg/m^2.[18] As a sensitivity analysis, we further classified metabolic unhealthy as those with at least two of the five metabolic syndrome components, and conducted subgroup analysis focusing only on mortality due to obesity-associated cancers.

Participant Characteristics

Baseline demographic variables used in the analysis included age, race, sex, household income, education, and geographic region. Health behaviors included tobacco, alcohol use, and physical activity. Baseline chronic medical conditions included atrial fibrillation, chronic kidney disease, deep vein thrombosis (DVT), myocardial infarction, peripheral artery disease (PAD, and stroke. Excluding components of metabolic syndrome, an individual level comorbidity score was created based on the sum of total number comorbidities at baseline for each participant (i.e., atrial fibrillation, chronic kidney disease, coronary artery disease, DVT, MI, peripheral artery disease, and stroke). We presented the distribution of comorbidity scores as means and standard deviations.

Statistical Analysis

We compared baseline characteristics by metabolic health and BMI category using Chi-square tests for categorical characteristics, Analysis of Variance (ANOVA) for normal continuous variables, and Wilcoxon test for non-normal continuous variables. We estimated any cancer and obesity-related cancer mortality rates per 1000 person-years using Poisson regression for each weight status category. To estimate the hazards of cancer mortality, we fit three series (for each BMI category group) of Cox proportional hazard models examining the association between metabolic health status and time to cancer death. We examined the effect of each metabolic syndrome component on cancer mortality, and stratified by BMI category using Cox regression. We examined the association between the total number of metabolic syndrome components and risk of cancer mortality using Cox regression. In secondary analysis, we performed additional Cox proportional hazard models to estimate the hazards of obesity-related cancer mortality by metabolic health status. To account for all-cause mortality as a competing risk, we employed the Fine and Gray method of Cox regression to calculate the sub-distribution hazard of cancer mortality and obesity related cancer mortality [19]. We adjusted all models for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, and comorbidity score. We assessed for multicollinearity among our study covariates by calculating the variance inflation factors (VIF). To obtain the VIF, we regressed each explanatory variable onto all other covariates. There was no evidence of multicollinearity between the covariates, and all VIF were less than 1.50. In sensitivity analyses, we examined the effect of BMI category on cancer mortality using Cox regression, and additionally stratified by metabolic health status. We additionally examined the main effect of obesity on obesity-related cancer mortality using

Cox regression, and additionally stratified by metabolic health status. Models examining the main effect of BMI on any/obesity-related cancer mortality were additionally adjusted for metabolic health status when not stratified by metabolic health status. We conducted sensitivity analyses excluding all cancer deaths within the first two years of entry into the REGARDS cohort, as well as excluding all participants with comorbidities at baseline. The results of all models were expressed as adjusted hazard ratios (HR) and the corresponding 95% confidence intervals (CI). Participants were censored at the time of death, loss to follow-up, or the end of cancer mortality ascertainment (December 31, 2012). SAS version 9.4 and STATA version 13 were used for all statistical analysis. Two-sided p values <0.05 were considered statistically significant.

Ethical Statement

The institutional review board of all participating universities approved the study and all participants provided written informed consent.

RESULTS

Among 30,239 REGARDS participants, 7,725 were excluded, resulting in 22,514 for analysis. Of the included participants, 5,377 (23.9%) were categorized as normal weight, 8,351 (37.1%) overweight, and 8,786 (39.0%) with obesity. In general, metabolically unhealthy participants were older, had lower education and income, and were more likely to be current tobacco users (Table 1; P values <0.01) compared with metabolically healthy participants in all weight categories. In addition, metabolically unhealthy normal weight participants had greater prevalence of atrial fibrillation, coronary artery disease, DVT, diabetes, dyslipidemia, hypertension, myocardial infarction, PAD, and stroke (P values < 0.01). Similar patterns were observed among participants with overweight and obesity, although the prevalence of diabetes was much higher among metabolically unhealthy participants with overweight and obesity.

There were 766 (3.4%) cancer deaths observed among 22,750 study participants over a mean follow up time of 6.5 years. The most common cancer types were lung (28.9%), gastro-intestinal (19.6%) and hematological (10.8%) cancers (Appendix I). Among normal weight participants, metabolically unhealthy participants were at a 65% increased risk of cancer mortality (adjusted HR: 1.65; 95% CI: 1.20 – 2.26) compared with metabolically healthy participants (Table 2), and metabolically unhealthy normal weight participants had the lowest survival probability over the follow-up period (Figure 1). Even when considering all-cause mortality as a competing risk (Table 2), the increased risk of cancer mortality among normal weight participants persisted when comparing metabolically unhealthy to metabolically healthy participants (adjusted SHR 1.67; 95% CI: 1.21 – 2.30). However, there was no statistically significant increased risk of cancer mortality for metabolically unhealthy participants with overweight (adjusted HR: 0.89, 95% CI: 0.67 – 1.17) or obesity (adjusted HR: 1.12, 95% CI: 0.84 - 1.49).

When focused on mortality due to obesity-related cancers, there were 165 total events over the observation period (Table 2). Among normal weight participants, metabolically unhealthy participants were at more than a 2-fold increased risk of an obesity-related cancer

death (adjusted HR: 2.40; 95% CI: 1.17 – 4.91) compared with metabolically healthy participants. There was no statistically significant risk of obesity-related cancer mortality for metabolically unhealthy participants with overweight (adjusted HR: 0.58; 95% CI: 0.30 – 1.12) or obesity (adjusted HR: 1.17; 95% CI: 0.68 – 2.02). Similar results were obtained in analyses unadjusted for comorbidities (data not shown). In both unadjusted (p = 0.0002) and adjusted models (p = 0.0232), the interaction terms between metabolic health status and obesity category were significant (data not shown).

In sensitivity analysis excluding participants with comorbidities at baseline (n=8,333, 49% of cancer deaths), metabolic unhealthy status was associated with a statistically non-significant 42% increased risk of any cancer mortality among normal weight participants, however the association with obesity-related cancer mortality became stronger (HR: 3.31, 95% CI: 1.38 – 7.95). In separate sensitivity analysis excluding participants who experienced a cancer death within the first 2 years of entry into the REGARDS cohort (n=111), the association between metabolic unhealthy status and any cancer mortality among normal weight participants became slightly attenuated but remained statistically significant (HR: 1.52, 95% CI: 1.07 – 2.16).

We further analyzed the association between BMI categories and any- and obesity-related cancer mortality stratified by metabolic health status (Tables 3 and 4). Participants with overweight (adjusted HR: 0.65; 95% CI: 0.54 – 0.79) or obesity (adjusted HR: 0.76; 95% CI: 0.61 – 0.94) had reduced risk of any cancer mortality after adjusting for metabolic health status (Table 3). Metabolically healthy participants with overweight, but not obesity, were at reduced risk of any cancer mortality compared with participants with normal weight (adjusted HR: 0.79, 95% CI: 0.63-0.99), while metabolically unhealthy participants with overweight (adjusted HR: 0.39; 95% CI: 0.27 – 0.55) or obesity (adjusted HR: 0.51; 95% CI: 0.36 – 0.70) were at significantly reduced risk of any cancer mortality. The associations for obesity-related cancer mortality were mostly non-significant (Table 4).

The cardio-metabolic component that was most associated with any cancer mortality was reduced HDL cholesterol (overall adjusted HR: 1.20; 95% CI: 1.03 – 1.40), with the highest risk observed among normal weight (adjusted HR: 1.89, 95% CI: 1.43 – 2.49) participants (Table 5). The cardio-metabolic component most associated with obesity-related cancer mortality were reduced HDL cholesterol (adjusted HR: 2.45, 95% CI: 1.25 – 4.79) and elevated fasting glucose (adjusted HR: 2.00, 95% CI: 1.04 – 3.85). In addition, normal weight participants with one (adjusted HR: 1.67; 95% CI: 1.08 – 2.57) and three or more (adjusted HR: 2.31; 95% CI: 1.44 – 3.72) cardio-metabolic components were at significantly increased risk of cancer mortality when compared to participants with no components. Normal weight participants with at least three metabolic unhealthy components were at nearly a 4-fold increased risk of obesity-related cancer mortality (adjusted HR: 3.78, 95% CI: 1.16 – 12.31) compared to those with none (Table 5).

DISCUSSION

In this large, prospective cohort of Black and White adults, we observed that metabolic health status was a strong predictor of cancer mortality among participants with normal

weight. Metabolically unhealthy participants experienced significantly higher risk of cancer mortality during follow-up compared with metabolically healthy participants in the normal weight category, with an observed 65% increased risk. In addition, metabolically unhealthy participants with normal weight were at a 2-fold increased risk of obesity-related cancer mortality, compared with those who were metabolically healthy. Among participants with overweight and obesity, there were no significantly increased risk of cancer mortality due to metabolic unhealthy status observed after adjusting for age, sex, income tobacco use, alcohol and physical activity at baseline. When restricted to the major obesity-related cancers (breast, colorectal, kidney, pancreatic, endometrial and esophageal cancers), there was a two-fold increased risk of mortality observed among metabolically unhealthy versus metabolically healthy participants with normal weight. Participants with normal weight and at least 3 altered cardio-metabolic components were at almost two-fold (all cancers) to over three-fold (obesity-related cancers) increased risk of cancer mortality compared with participants with none. Low HDL-cholesterol was the cardio-metabolic risk factor most consistently associated with risk of cancer mortality, while elevated fasting glucose was also important for obesity-associated cancer mortality, suggesting a likely biological mechanism linking metabolic health status and cancer mortality.

There is increasing recognition of the importance of metabolic factors in influencing health risks and mortality outcomes [9,20-22]. Metabolic dysregulation, in addition to chronic inflammation, genomic alterations and immune system dysfunction, have been shown to influence cancer etiology and mortality, and an increasing number of studies have begun to directly assess the mechanisms through which metabolic dysfunction affects cancer outcomes independent of body weight, with mixed results[12,13]. A recent study of over 22,000 adults in England and Scotland observed that metabolic healthy adults with obesity were not at increased risk of cancer mortality compared with metabolically healthy adults without obesity, while all adults (regardless of obesity status) with two or more metabolic risk factors (i.e. metabolically unhealthy) had a 59-64% increased risk of mortality[23]. Similarly, a recent study among Korean adults observed that regardless of BMI category, metabolically unhealthy participants were at significantly higher risk for cancer mortality compared with metabolically healthy adults[12]. In contrast, a recent systematic review and meta-analysis concluded that adults with obesity were at increased risk for mortality compared with normal-weight adults, even in the absence of metabolic abnormalities.[22]

We observed a significant association between reduced HDL-cholesterol and cancer mortality among participants. This suggests that the biological mechanism linking obesity, metabolic dysregulation and cancer mortality may involve dyslipidemia, and clinical strategies focused on cholesterol may provide added benefits to cancer patients, in addition to other strategies such as exercise and dietary recommendations to reduce metabolic dysfunction. Other studies have observed reduced risk of cancer with increased HDL-cholesterol[32,33], while some studies suggest that the HDL-apolipoprotein ratio may be a stronger indicator of risk of cancer mortality[32]. Future work in this area is warranted as very few studies have directly examined HDL-cholesterol levels and cancer-specific mortality prospectively. Another potential biological mechanism for this association may be through the relationship between insulin resistance and liver fat content, which may act as an independent risk factor for cancer mortality separate from the well-established association

with visceral fat mass. Several studies have observed that higher liver fat content and non-alcoholic fatty liver disease increase the risk of cardiovascular diseases [34] and type 2 diabetes [35,36], via insulin resistance, independent of visceral fat mass. This may be an important underlying mechanism for the higher risk of cancer mortality among normal weight, metabolically unhealthy individuals. Research studies focused on assessing liver fat content in addition to visceral fat among metabolically unhealthy adults may further shed light on this mechanism. Other potential mechanisms include inflammatory profile imbalance due to increased adiposity, and genetic or epigenetic changes that are important consequences of altered metabolic components such as obesity, dyslipidemia and high blood pressure, and may play an important role in the function of genes responsible for tumor angiogenesis, apoptosis or metastasis.

While still the subject of much debate, there is compelling evidence that obesity status itself may be a less informative risk or prognostic factor for many diseases, including cancer. In fact, our findings as well as others[24,29] indicate that metabolic health status may be a more important cancer prognostic factor that should be evaluated in addition to obesity. We observed consistently higher risk of cancer mortality among normal-weight, metabolically unhealthy participants with associations that were significantly higher when focused on obesity-related cancers. In addition, regardless of metabolic health status, we observed lower risk of cancer death among participants overweight and obesity. There is a large body of literature regarding the role of inflammation in cancer prognosis[30,31], and our observation that the metabolic health component most associated with mortality were reduced HDL cholesterol and elevated fasting glucose supports the hypothesis that tissue inflammation and insulin resistance, rather than obesity per se, is associated with cancer prognosis. However, considerable debate remains regarding the direct effects of obesity, versus mediating factors such as inflammation and/or metabolic dysregulation on cancer mortality. Future prospective studies of cancer will be needed to definitively identify which risk factor(s) are most strongly associated with cancer mortality and can be valuable targets of clinical interventions for cancer patients.

There are some limitations to this research. First, there are currently no established criteria for defining metabolically healthy obesity, and this analysis was based on the definition proposed in the joint harmonized criteria for metabolic syndrome. It is impossible to assess whether our definition overestimated or underestimated the prevalence of metabolic health. However, by using a strict criteria of 3 out of 5 altered metabolic components, we reduced the likelihood of overestimation, and our results did not change significantly after a sensitivity analysis using 2 out of 5 components to define metabolic health. Second, metabolically health and BMI category were assessed at baseline, and while this reduced the likelihood of reverse causality bias, it is likely that metabolic health and/or BMI category changed over the course of follow up. However, by excluding participants with a history of cancer at baseline we further reduced the likelihood of reverse causality. There are likely some participants who were classified as 'cancer-free' at baseline, but who had undiagnosed cancer, this may lead to biased estimates especially if those participants are more likely to be normal-weight. To address this possibility, we conducted sensitivity analysis excluding all cancer deaths occurring in the first 2 years after entry into the cohort, and our results remained consistent. We expect that these changes will be non-differential in relation to

baseline metabolic health or BMI status, and that our observed estimates will likely underestimate the true association between metabolic health status and cancer mortality within the REGARDS cohort. In addition, we observed stronger associations between metabolic health status and cancer mortality when focused on obesity related cancers, and this association became stronger when excluding participants with comorbidities at baseline. Third, our cohort had only up to ten years of follow-up time, limiting our availability to observe cancer-specific deaths that will occur as the cohort ages. Fourth, even though REGARDS is a large prospective cohort study with over 30,000 participants, we were limited by the number of cancer mortality events observed which inhibited our ability to conduct race- and sex- stratified analysis. The strengths of this analysis include the use of a large prospective cohort study, and cancer mortality outcomes obtained using standardized adjudication techniques that minimized the chances of outcome misclassification. Baseline measures of obesity and metabolic health components were directly measured by highly trained interviewers during in-home visits, and therefore less vulnerable to misclassification or recall bias.

In conclusion, we provide evidence that metabolic health status is an important prognostic factor for cancer among normal weight adults. Longer follow-up times in the REGARDS cohort will enable us to better characterize this association by cancer type, in different racial and sex groups, and to better evaluate the biological mechanisms underlying this association in order to inform specific strategies to reduce the risk. Meanwhile, clinical and public health strategies to reduce obesity and improve metabolic health status among metabolic unhealthy adults, especially normal-weight adults, may go a long way in improving cancer outcomes specifically, and health outcomes in general, among US patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is already known about this subject?

- Obesity has long been understood to increase the risk of cancer mortality.

- The prevalence of obesity and metabolic syndrome, a cluster of cardio-metabolic risk factors, have concurrently increased in the US over the past few decades.

What does this study add?

- Metabolic health status is an important predictor of cancer mortality among normal-weight participants.

- Among participants who were normal weight, being metabolically unhealthy increased the risk for mortality from obesity-related cancers.
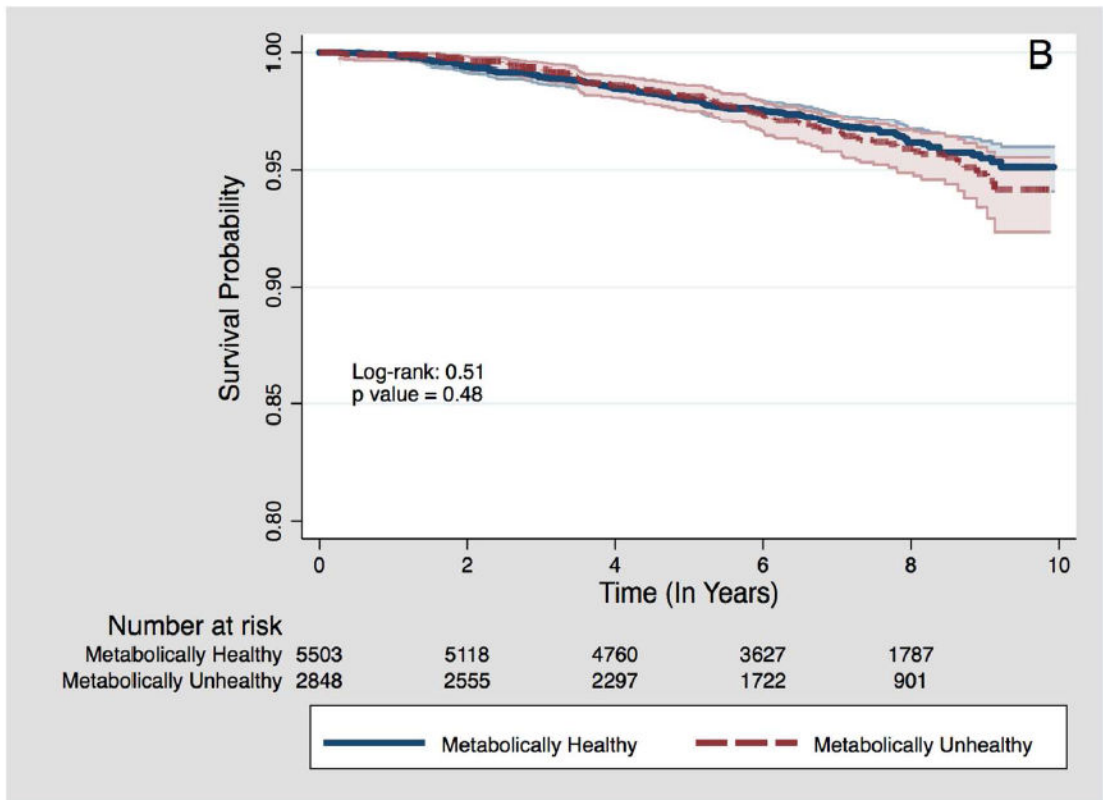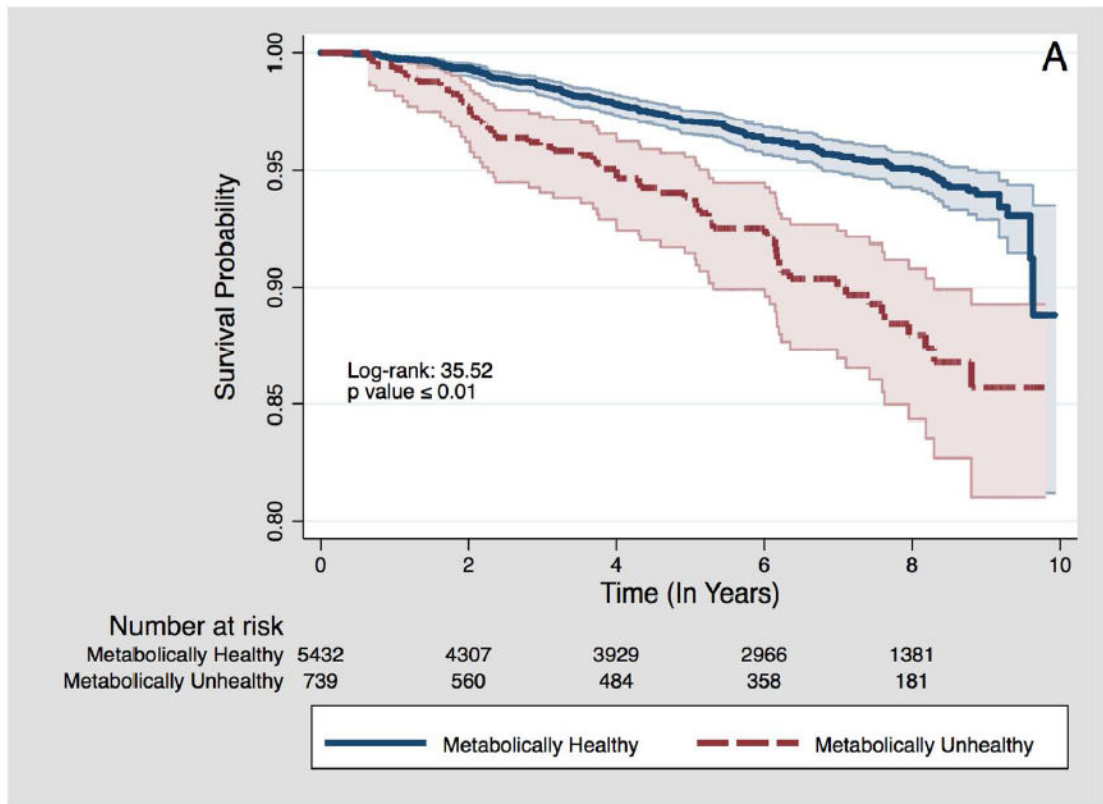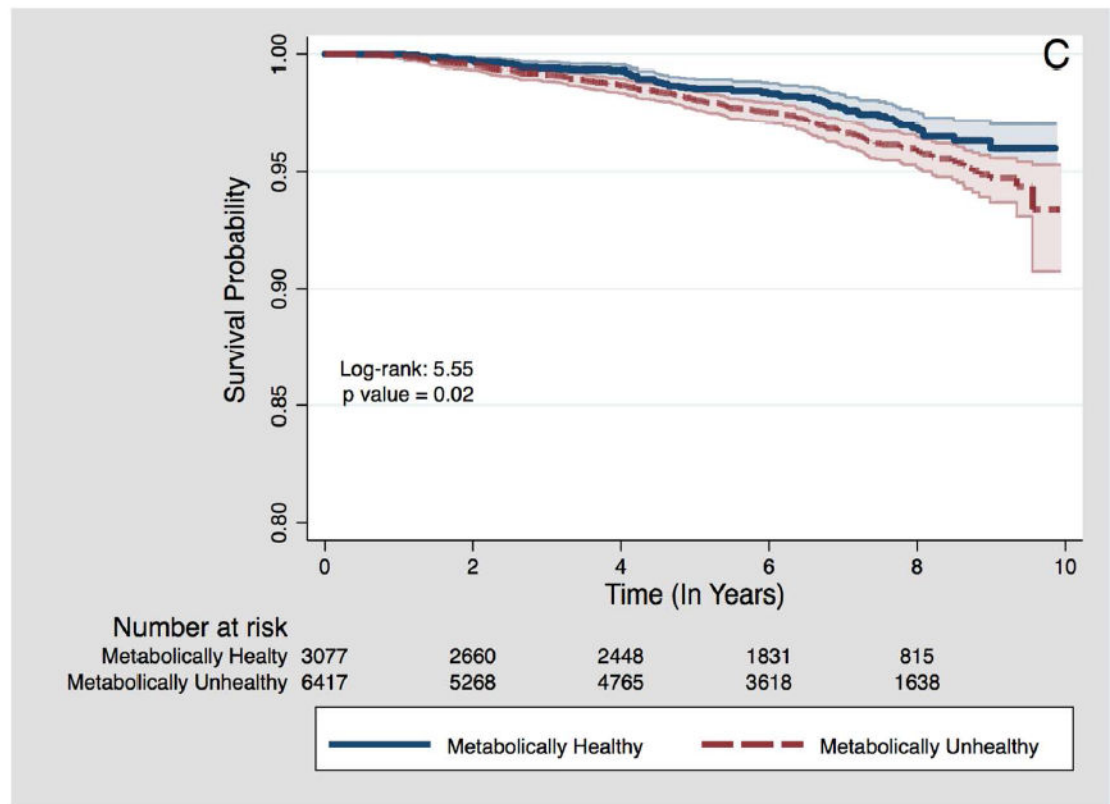
Figure 1.
Kaplan-Meier survival plots for time to cancer death by metabolic health status, stratified by BMI category.

A – Among participants with normal weight BMI category

B – Among participants with overweight BMI category

C – Among participants with obesity BMI category

Table 1

Participant characteristics by metabolic health status, stratified by BMI category. Among 22,514 REGARDS participants.

	Normal Weight BMI 18.5 – 24.9 kg/m² (N = 5377)			Overweight BMI 25.0 – 29.9 kg/m² (N = 8351)			Obese BMI 30 kg/m² (N = 8786)		
	MH (N = 4720)	MU (N = 657)	P value*	MH (N = 5503)	MU (N = 2848)	P value*	MH (N = 2872)	MU (N = 5914)	P value*
Age†	65.5 (10.2)	68.4 (9.2)	<0.01	64.2 (9.3)	66.4 (9.1)	<0.01	62.1 (8.7)	63.0 (8.5)	<0.01
Race (%)									
Black	1365 (28.9)	204 (31.0)	0.3	1963 (35.7)	1045 (36.7)	0.4	1545 (53.8)	2907 (49.2)	<0.01
White	3355 (71.1)	453 (69.0)		3540 (64.3)	1803 (63.3)		1327 (46.2)	3007 (50.8)	
Sex (%)									
Male	2020 (42.8)	285 (43.4)	0.8	2980 (54.2)	1353 (47.5)	<0.01	1029 (35.8)	2250 (38.1)	0.04
Female	2700 (57.2)	372 (56.6)		2523 (45.9)	1495 (52.5)		1843 (64.2)	3664 (61.9)	
Education High School (%)	415 (8.8)	107 (16.3)	<0.01	483 (8.8)	412 (14.5)	<0.01	319 (11.1)	888 (15.0)	<0.01
Income $20,000 (%)	683 (14.5)	162 (24.7)	<0.01	628 (11.4)	582 (20.4)	<0.01	488 (17.0)	1278 (21.6)	<0.01
Current Tobacco Use (%)	865 (18.4)	186 (28.4)	<0.01	646 (11.8)	491 (17.3)	<0.01	278 (9.7)	780 (13.2)	<0.01
Heavy Alcohol Use (%)	280 (6.0)	32 (5.0)	<0.01	258 (4.8)	104 (3.7)	<0.01	86 (3.1)	158 (2.7)	<0.01
No Physical Activity (%)	1332 (28.7)	287 (44.4)	<0.01	1427 (26.3)	1039 (37.1)	<0.01	1028 (36.2)	2406 (41.3)	<0.01
Chronic Medical Conditions (%)									
Atrial fibrillation	375 (8.1)	75 (11.7)	<0.01	369 (6.8)	273 (9.8)	<0.01	204 (7.3)	542 (9.4)	<0.01
Chronic lung disease	403 (8.6)	55 (8.4)	0.9	433 (7.9)	255 (9.0)	0.09	289 (10.1)	658 (11.1)	0.1
Coronary artery disease	689 (14.9)	157 (24.5)	<0.01	788 (14.6)	646 (23.0)	<0.01	337 (12.0)	1179 (20.3)	<0.01
Deep vein thrombosis	187 (4.0)	40 (6.2)	0.01	201 (3.7)	151 (5.3)	<0.01	157 (5.5)	394 (6.7)	0.03
Myocardial infarction	497 (10.7)	111 (17.3)	<0.01	546 (10.1)	449 (16.0)	<0.01	240 (8.5)	842 (14.5)	<0.01
Peripheral artery disease	105 (2.2)	27 (4.1)	<0.01	89 (1.6)	81 (2.9)	<0.01	27 (0.9)	139 (2.4)	<0.01
Stroke	246 (5.2)	73 (11.2)	<0.01	221 (4.0)	236 (8.3)	<0.01	101 (3.5)	385 (6.5)	<0.01
Comorbidity score†	0.52 (0.92)	0.80 (1.10)	<0.01	0.48 (0.86)	0.73 (1.05)	<0.01	0.47 (0.85)	0.69 (1.02)	<0.01
Follow-up years†	6.9 (5.5 - 8.2)	6.5 (4.6 - 8.2)	0.01	7.1 (5.6 - 8.4)	6.9 (5.4 - 8.4)	<0.01	6.8 (5.6 - 8.2)	6.8 (5.4 - 8.2)	0.12
BMI†	23.3 (1.4)	22.7 (1.6)	<0.01	27.3 (1.4)	27.8 (1.4)	<0.01	34.3 (4.4)	36.0 (5.2)	<0.01

N (%) – Presented as count and column percentages.

†Mean (Standard deviation)

†Median (Interquartile Range)

*Significance determined using ANOVA (normal continuous), Wilcoxon (non-parametric continuous), and chi-square test.

**Comorbidity score presented as means and standard deviations of the sum total of comorbidities.

MH – Metabolically healthy

MU – Metabolically unhealthy defined as the presence of three or more metabolic components including 1) elevated fasting glucose, 2) high triglycerides, 3) dyslipidemia, 4) hypertension, and 5) high waist circumference.

Table 2

Hazard Ratios (HRs)[1] and associated 95% Confidence Intervals for the association between metabolic health status and time to any cancer death, and obesity-related cancer death, stratified by BMI category.

	Any Cancer Deaths[2]	Obesity-Related Cancer Deaths[3]
Normal Weight (BMI 18.5 – 24.9 kg/m^{2})		
MH (# cancer deaths / # at risk)	**199 / 4720**	**30 / 4720**
MU (# cancer deaths / # at risk)	**57 / 657**	**12 / 657**
MH Mortality Per 1,000 Person-Years (95% CI)	**6.45 (5.62 – 7.42)**	**0.97 (0.68 – 1.39)**
MU Mortality Per 1,000 Person-Years (95% CI)	**13.94 (10.75 – 18.10)**	**2.93 (1.66 – 5.17)**
Hazard Ratio (95% CI) – Referent group MH	**1.65 (1.20 – 2.26)**	**2.40 (1.17 – 4.91)**
Subdistribution Hazard Ratio (95% CI)[4] – Referent group MH	**1.67 (1.21 – 2.30)**	**2.37 (1.13 – 4.98)**
Overweight (BMI 25.0 – 29.9 kg/m^{2})		
MH (# cancer deaths / # at risk)	167 / 5503	41 / 5503
MU (# cancer deaths / # at risk)	88 / 2848	13 / 2848
MH Mortality Per 1,000 Person-Years (95% CI)	4.50 (3.87 – 5.24)	1.11 (0.81 – 1.50)
MU Mortality Per 1,000 Person-Years (95% CI)	4.74 (3.85 – 5.85)	0.70 (0.41 – 1.21)
Hazard Ratio (95% CI) – Referent group MH	0.89 (0.67 – 1.17)	0.58 (0.30 – 1.12)
Subdistribution Hazard Ratio (95% CI)[4] – Referent group MH	0.85 (0.64 – 1.13)	0.57 (0.30 – 1.09)
Obese (BMI 30 kg/m^{2})		
MH (# cancer deaths / # at risk)	71 / 2872	20 / 2872
MU (# cancer deaths / # at risk)	184 / 5914	49 / 5914
MH Mortality Per 1,000 Person-Years (95% CI)	3.76 (2.98 – 4.75)	1.06 (0.68 – 1.64)
MU Mortality Per 1,000 Person-Years (95% CI)	4.83 (4.18 – 5.58)	1.29 (0.97 – 1.70)
Hazard Ratio (95% CI) – Referent group MH	1.12 (0.84 – 1.49)	1.17 (0.68 – 2.02)
Subdistribution Hazard Ratio (95% CI)[4] – Referent group MH	1.09 (0.81 – 1.46)	1.15 (0.67 – 1.97)

[1] Models adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, and comorbidity score.

[2] 766 total any cancer deaths.

[3] 165 total obesity-related cancer deaths. Included: breast, colorectal, kidney, pancreatic, endometrial, and esophageal cancers.

[4] Estimated using Fine & Gray method accounting for 2971 all-cause deaths as competing risk, models adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, and comorbidity score.

MH – Metabolically healthy. MU – Metabolically unhealthy defined as the presence of three or more metabolic components including 1) elevated fasting glucose, 2) high triglycerides, 3) dyslipidemia, 4) hypertension, and 5) high waist circumference.

Bold indicates statistically significant association at 0.05 alpha level.

Table 3

Hazard Ratios (HRs) and 95% Confidence Intervals for the association between obesity status and time to any cancer death, stratified by BMI category. Among 766 total cancer deaths, and 2971 competing all-cause deaths.

			Any Cancer Deaths			
Overall	**(# Deaths /# At risk)**	**Mortality Rate[1] (95% CI)**	**Model 1[2] HR (95% CI)**	**Model 1 Subdistribution HR (95% CI)[4]**	**Model 2[3] HR (95% CI)**	**Model 2 Subdistribution HR (95% CI)[4]**
Normal Weight (Referent)	256 / 5377	7.33 (6.49 – 8.29)	-	-	-	-
Overweight	255 / 8351	4.58 (4.05 – 5.18)	**0.67 (0.55 – 0.81)**	**0.69 (0.57 – 0.83)**	**0.65 (0.54 – 0.79)**	**0.67 (0.55 – 0.82)**
Obese	255 / 8786	4.48 (3.96 – 5.06)	**0.81 (0.67 – 0.98)**	**0.82 (0.68 – 0.99)**	**0.76 (0.61 – 0.94)**	**0.78 (0.62 – 0.97)**
Metabolically Healthy						
Normal Weight (Referent)	199 / 4720	6.45 (5.62 – 7.42)	-	-		
Overweight	167 / 5503	4.50 (3.87 – 5.24)	**0.79 (0.63 – 0.99)**	0.83 (0.66 – 1.03)	-	-
Obese	71 / 2872	3.76 (2.98 – 4.75)	0.89 (0.66 – 1.20)	0.91 (0.68 – 1.22)	-	-
Metabolically Unhealthy						
Normal Weight (Referent)	57 / 657	13.94 (10.75 – 18.07)	-	-	-	
Overweight	88 / 2848	4.74 (3.85 – 5.85)	**0.39 (0.27 – 0.55)**	**0.39 (0.28 – 0.56)**	-	-
Obese	184 / 5914	4.83 (4.18 – 5.58)	**0.51 (0.36 – 0.70)**	**0.51 (0.36 – 0.71)**	-	-

[1] Rate per 1,000 Person-Years

[2] Adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, and comorbidity score.

[3] Adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, comorbidity score, and metabolic health status.

[4] Estimated using Fine & Gray method accounting for all-cause mortality as competing risk, models adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, and comorbidity score.

Metabolically unhealthy defined as the presence of three or more metabolic components including 1) elevated fasting glucose, 2) high triglycerides, 3) dyslipidemia, 4) hypertension, and 5) high waist circumference. Normal weight: BMI 18.5 – 24.9 kg/m^2; Overweight: BMI 25.0 – 29.9 kg/m^2; Obese: BMI = 30 kg/m^2

Bold indicates statistically significant association at 0.05 alpha level.

Table 4

Hazard Ratios (HRs) and 95% Confidence Intervals for the association between obesity status and time to obesity-related cancer death, stratified by BMI category. Among 165 total obesity-related cancer deaths, and 3,572 competing all-cause deaths.

	(# Deaths / # At risk)	Mortality Rate[1] (95% CI)	Model 1[2] HR (95% CI)	Model 1 Subdistribution HR (95% CI)[4]	Model 2[3] HR (95% CI)	Model 2 Subdistribution HR (95% CI)[4]
Obesity-Related Cancer Deaths						
Overall						
Normal Weight (Referent)	42 / 5377	1.20 (0.19 – 1.63)	-	-	-	-
Overweight	54 / 8351	0.97 (0.74 – 1.27)	0.86 (0.57 – 1.31)	0.89 (0.58 – 1.35)	0.85 (0.56 – 1.31)	0.88 (0.56 – 1.37)
Obese	69 / 8786	1.21 (0.96 – 1.53)	1.32 (0.87 – 2.01)	1.32 (0.87 – 2.01)	1.29 (0.82 – 2.05)	1.29 (0.79 – 2.09)
Metabolically Healthy						
Normal Weight (Referent)	30 / 4720	0.97 (0.68 – 1.39)	-	-	-	-
Overweight	41 / 5503	1.11 (0.81 – 1.50)	1.29 (0.79 – 2.12)	1.33 (0.82 – 2.17)	-	-
Obese	20 / 2872	1.06 (0.68 – 1.64)	1.50 (0.82 – 2.77)	1.52 (0.83 – 2.80)	-	-
Metabolically Unhealthy						
Normal Weight (Referent)	12 / 657	2.93 (1.67 – 5.17)	-	-	-	-
Overweight	13 / 2848	0.70 (0.41 – 1.21)	**0.27 (0.12 – 0.63)**	**0.27 (0.12 – 0.64)**	-	-
Obese	49 / 5914	1.29 (0.97 – 1.70)	0.65 (0.33 – 1.31)	0.61 (0.30 – 1.25)	-	-

[1] Rate per 1,000 Person-Years

[2] Adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, and comorbidity score.

[3] Adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, comorbidity score, metabolic health status.

[4] Estimated using Fine & Gray method accounting for all-cause mortality as competing risk, models adjusted for age, race, sex, education, income, tobacco use, alcohol use, physical inactivity, LDL cholesterol, and comorbidity score.

Metabolically unhealthy defined as the presence of three or more metabolic components including 1) elevated fasting glucose, 2) high triglycerides, 3) dyslipidemia, 4) hypertension, and 5) high waist circumference.

Normal weight: BMI 18.5 – 24.9 kg/m^2; Overweight: BMI 25.0 – 29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

Bold indicates statistically significant association at 0.05 alpha level.

Table 5

Hazard Ratios[a] (HRs) and 95% confidence intervals for the association between components of metabolic health status and time to cancer death and time to obesity-related[c] cancer death stratified by BMI category.

| | Obesity Status | | | |
	All	Normal Weight (BMI 18.5 – 24.9 kg/m²)	Overweight (BMI 25.0 – 29.9 kg/m²)	Obese (BMI 30 kg/m²)
Cancer Mortality				
Components[b]				
High WC	1.00 (0.86 – 1.17)	1.21 (0.74 – 1.97)	1.05 (0.79 – 1.39)	1.37 (0.86 – 2.18)
Elevated Triglycerides	0.95 (0.80 – 1.13)	1.10 (0.80 – 1.52)	1.17 (0.88 – 1.56)	0.75 (0.55 – 1.01)
Reduced HDL Cholesterol	**1.20 (1.03 – 1.40)**	**1.89 (1.43 – 2.49)**	0.84 (0.64 – 1.11)	1.26 (0.97 – 1.65)
Elevated blood pressure	1.14 (0.95 – 1.38)	1.21 (0.90 – 1.62)	1.03 (0.76 – 1.41)	1.35 (0.89 – 2.05)
Elevated fasting glucose	1.01 (0.87 – 1.18)	1.01 (0.75 – 1.36)	0.99 (0.76 – 1.30)	1.14 (0.88 – 1.49)
Overall[a]		Ref	**0.67 (0.55 – 0.80)**	**0.82 (0.68 – 0.99)**
Obesity-Related Cancer Mortality[c]				
Components[b]				
High WC	1.29 (0.92 – 1.79)	0.71 (0.17 – 3.06)	0.86 (0.45 – 1.61)3	**4.22 (1.02 – 17.40)**
Elevated Triglycerides	0.87 (0.60 – 1.28)	1.34 (0.62 – 2.88)	0.89 (0.46 – 1.73)3	0.61 (0.33 – 1.10)
Reduced HDL Cholesterol	1.21 (0.87 – 1.68)	**2.45 (1.25 – 4.79)**	0.70 (0.38 – 1.31)3	1.15 (0.70 – 1.90)
Elevated blood pressure	1.32 (0.88 – 1.98)	1.17 (0.57 – 2.37)	1.28 (0.64 – 2.55)3	1.36 (0.64 – 2.89)
Elevated fasting glucose	1.20 (0.87 – 1.66)	**2.00 (1.04 – 3.85)**	1.04 (0.59 – 1.83)	0.94 (0.58 – 1.54)
Overall[a]		Ref	0.86 (0.57 – 1.31)	1.32 (0.87 – 2.01)
Cancer Mortality				
# Metabolic Unhealthy Components				
0 (Referent)	-	-	-	-
1	1.31 (0.94 – 1.82)	**1.67 (1.08 – 2.57)**	1.07 (0.62 – 1.84)	0.78 (0.17 – 3.56)
2	1.28 (0.92 – 1.77)	1.48 (0.93 – 2.36)	1.13 (0.67 – 1.93)	1.13 (0.27 – 4.65)
3+	1.29 (0.95 – 1.77)	**2.31 (1.44 – 3.72)**	0.95 (0.56 – 1.62)	1.18 (0.29 – 4.77)
p value for trend	0.41	**<0.01**	0.74	0.65
Obesity-Related Cancer Mortality[c]				
# Metabolic Unhealthy Components				
0 (Referent)	-	-	-	-
1	2.25 (0.94 – 5.40)	1.74 (0.56 – 5.40)	2.85 (0.66 – 12.36)	Undefined
2	**2.72 (1.15 – 6.39)**	1.92 (0.59 – 6.28)	2.68 (0.62 – 11.62)	Undefined
3+	**2.65 (1.14 – 6.15)**	**3.78 (1.16 – 12.31)**	1.41 (0.31 – 6.45)	Undefined
p value for trend	0.12	**0.10**	0.15	0.46

766 cancer deaths

[a]Models adjusted for age, sex, race, education, income, tobacco use, alcohol use, physical inactivity, and comorbidity score.

[b]Referent groups for each hazard ratio is the absence of metabolic component.

[c]165 obesity-related cancer deaths included: breast, colorectal, kidney, pancreatic, endometrial, and esophageal cancers.

Bold indicates statistically significant association at 0.05 alpha level.