# Association between obesity and biomarkers of inflammation and metabolism with cancer mortality in a prospective cohort study

**Daniel T. Dibaba**[1,2], **Suzanne E. Judd**[3], **Susan C. Gilchrist**[4], **Mary Cushman**[5], **Maria Pisu**[6], **Monika Safford**[7], **Tomi Akinyemiju**[1,2]

[1]Department of Epidemiology, University of Kentucky, Lexington, KY

[2]Markey Cancer Center, University of Kentucky, Lexington, KY

[3]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, Alabama

[4]Department of Clinical Cancer Prevention and Cardiology, University of Texas MD, Anderson Cancer Center, Houston, TX

[5]Department of Medicine and University of Vermont Cancer Center, Larner College of Medicine at the University of Vermont, Burlington VT

[6]Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham AL

[7]Department of Medicine, Weill Cornell Medical College, New York, NY

## Abstract

**Objective:** To investigate the association between biomarkers of inflammation and metabolic dysregulation and cancer mortality by obesity status.

**Methods:** Data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort was used to examine the associations between baseline biomarkers of inflammation (IL-6, IL-8, IL-10, and CRP) and metabolism (adiponectin, resisting and lipoprotein (a)) with cancer mortality among 1,822 participants cancer-free at baseline. Weighted Cox proportional hazard regression with the robust sandwich method was used to estimate the hazard ratios and 95% confidence intervals (CIs) adjusting for baseline covariates and stratified by BMI (normal, overweight/obese) given the significant interaction between biomarkers and BMI (*P*<0.1).

**Correspondence to:** Dr. Tomi Akinyemiju, Department of Epidemiology, University of Kentucky, 111 Washington Ave, Lexington, KY, 40508, USA, Phone: 859-323-1147, tomiakin@uky.edu.

Conflict of Interest
The authors declare no conflict of interest.

**Results:** During a mean follow-up of 8 years, there were statistically significant associations between cancer mortality and being in the highest vs. lowest tertile of IL-6 (HR: 5.3; 95% CI: 1.6, 17.8), CRP (HR: 3.4; 95% CI: 1.0, 11.2) and resistin (HR: 3.7; 95% CI: 1.2, 11.2) among participants with normal BMI. IL-6 was also associated with a 3-fold (HR: 3.5; 95% CI: 1.5, 8.1) increased risk of cancer mortality among participants with overweight/obesity; however, neither CRP nor resistin was significantly associated with cancer mortality in this group.

**Conclusions:** Higher baseline inflammatory and metabolic biomarkers were associated with significantly increased risk of cancer mortality after adjusting for baseline risk factors and the associations varied by BMI. Cancer patients may benefit from interventions that modulate inflammatory and metabolic biomarkers.

**Keywords**

inflammatory cytokines; metabolic biomarkers; cancer mortality; obesity

## 1. Introduction

The established risk factors for cancer mortality include obesity, physical inactivity, smoking, and alcohol use [1–4]. These risk factors are associated with chronic inflammation and metabolic dysregulation, and growing evidence links these mechanisms with development, progression and mortality of cancer [5–7]. Obesity, specifically, has long been associated with increased risk of cancer mortality [8], and studies indicate every 5 kg/m$^2$ increase in BMI increases the risk of cancer mortality by about 10% [9]. Furthermore, obesity is associated with adipose tissue dysfunction and chronic low-grade inflammation that leads to worse prognosis in cancer patients. However, there is also evidence of adipose tissue inflammation and protumorigenic consequences in some lean individuals[10]. Metabolism-related biomarkers [11–13] such as adiponectin, resistin, and lipoprotein (a) (Lp(a)), and inflammation-related cytokines [5, 6] such as interleukin (IL)-6, IL-8, IL-10 and C-reactive protein (CRP) have been shown to reflect a fertile, pro-tumorigenic inflammatory microenvironment that promotes tumor initiation, angiogenesis, and metastasis [14].

Recent studies, including by our group, suggests that metabolic health status may be a more clinically and epidemiologically important risk factor for cancer risk and mortality than obesity alone [15, 16]. Increased risk of cancer mortality has been observed in normal BMI individuals with metabolic dysregulation, an association not consistently observed among obese individuals who are metabolically healthy- a phenomenon termed 'metabolic healthy obesity' [15]. While the prevalence of obesity has increased significantly among US adults[17], it is important to better delineate the role of obesity, metabolic dysregulation and chronic inflammation in cancer risk. This helps to improve risk prediction and stratification, target appropriate clinical and interventions strategies based on precise biomarkers, and reduce the reliance on the crude measure of BMI as a predictor of cancer mortality risk. The aim of the present study was to investigate the role of pre-diagnostic metabolic and inflammatory biomarkers in the risk of cancer mortality by obesity status and to assess whether racial disparities exist in this association given the higher risk of cancer mortality and higher prevalence of obesity and associated conditions among Blacks.

## 2.    Material and Methods

### 2.1   Study participants

Data for this study was obtained from the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study. The REGARDS study is a prospective cohort study of Black and White participants recruited nationally in the United States between 2003 and 2007, with oversampling of Blacks and residents of the Stroke Belt (South Carolina, North Carolina, Tennessee, Georgia, Louisiana, Arkansas, Mississippi, and Alabama). Detailed data on demographics, health behaviors, and history of comorbid conditions were collected at baseline using a computer-assisted telephone interview. Blood sample collection after 10–12 hours overnight fasting, echocardiography, and physical measurements including height and weight were conducted during initial in-home visits by trained staff following informed consent. Overall, 30,239 participants aged   45 years at baseline, 55% female, 42% Black, and 50% from the Stroke Belt region were recruited. The REGARDS study is ongoing and it is described in detail elsewhere [18, 19]. In the present analysis, 1,822 individuals who were cancer-free at baseline and selected into a sub-cohort with available inflammatory and metabolic biomarker data were included. The sub-cohort was randomly selected from the stratified random sample defined by equal distribution by race (Black/White), sex, and age (20% from each 10-year interval from 45 to 64, 25% from each 10-year interval from 65 to 84, and 10% from those over 84 years old) and region (50% from Stroke Belt) using study weights created based on the inverse probability of being selected. REGARDS participants were followed-up every 6 months for hospitalizations and for any medical event, and medical events or deaths were ascertained using death certificates, medical records, and/or interviewed proxies to determine the causes of the death. All participating institutional review boards approved the REGARDS study.

### 2.2   Exposure variables

The main exposure variables of interest in this study were inflammatory biomarkers- IL-6, IL-8, IL-10, and CRP, and metabolic biomarkers- adiponectin, resistin, and Lp(a). Biomarkers were analyzed from blood samples that were collected during the baseline in-home visit, centrifuged, separated and shipped overnight on gel ice packs to the central laboratory (Laboratory for Clinical Biochemistry Research at the University of Vermont). Ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay, R&D Systems, Minneapolis, MN) was used to measure IL-6 (minimum detectable dose /sensitivity=0.031 pg/ml and inter-assay coefficient of variation=6.3%) and no significant cross-reactivity was observed. The Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc., St. Charles, MO) was used to measure IL-8 (sensitivity=0.20 pg/ml, intra-assay coefficient of variation ranged from 1.4% to 7.9%, and inter-assay-coefficient of variation was <21%) and no significant cross-reactivity was observed. Milliplex MAP Human Cardiovascular Disease Panel 3 (Millipore Corporation, Billerica, MA) run as a singleplex assay was used to measure IL-10 (sensitivity=0.30 pg/ml and the average analytical coefficient of variation =8.09%) and no significant cross-reactivity was observed. CRP was measured in special plasma in batches during enrollment utilizing a validated high-sensitivity particle-enhanced immunonephelometric assay on the BN II nephelometer (N High Sensitivity CRP, Dade Behring Inc., Deerfield, IL), (sensitivity=0.16 μg/ml, intra-assay-coefficient of variation

ranged from 2.3% to 4.4%, and inter-assay coefficient of variation=2.1% to 5.7%) and no significant cross-reactivity was observed. Adiponectin and resistin were measured using the Human Serum Adipokine Panel A LINCOplex Kit (Linco Research, Inc., St. Charles, MO) (for adiponectin: sensitivity=80.3 pg/ml, inter-assay coefficient of variation ranged from 5.68 to 8.20%, and for resistin: sensitivity=4.5 pg/ml and inter-assay coefficient of variation ranged from 8.04% to 9.42%) and no significant cross-reactivity was observed. Lp(a) was measured with the BN II nephelometer utilizing a particle-enhanced immunonephelometric assay (N Latex Lipoprotein-a, Siemens Healthcare Diagnostics, Deerfield, IL) (sensitivity=0.002 g/L, inter-assay coefficient of variation ranged from 6.10% to 10.28%). For LP(a), no cross-reactivity with apolipoprotein B (<1%) and plasminogen (<5%) was observed.

### 2.3   Covariates

The study covariates included baseline demographic variables such as age (continuous), gender (male/female), education (college graduate, some college, high school graduate or less than high school), race (Black/White), and income ( $75K, $35K-$74K, $20K-$34K, < $20K or refused). Additionally, analyses included baseline data on exercise ( 4 times/week, 1–3 times/week or none), BMI (kg/m$^2$), smoking (current, past, or never smoker), alcohol intake (heavy, moderate, or none), comorbidity score (number of comorbidities-score ranging from 0 to 7), regular aspirin use (yes/no), and statin use (yes/no).

### 2.4   Cancer Mortality

Cancer mortality was identified through semi-annual telephone follow-up, death information from participants' proxies, linkages with the Social Security Death Index (SSDI) and the National Death Index (NDI). Date of death was confirmed using death certificates, SSDI and/or NDI. A committee of experts adjudicated the cause of death using all available information as recommended by national guidelines [20]. Follow-up data for this analysis was available through December 31, 2015.

### 2.5   Statistical Analysis

Chi-squared test was used to compare baseline categorical participants' characteristics by BMI category i.e. obese/overweight (BMI  25 kg/m$^2$) and normal BMI (BMI=18.5–24.9 kg/m$^2$), and t-test was used to compare continuous variables by BMI category. Weighted Cox proportional hazard regression analysis was used to compare the risk of cancer mortality by the levels of metabolic and inflammatory biomarkers stratified by BMI category in models sequentially adjusted for potential confounding variables. Robust sandwich estimation method was used to estimate the confidence intervals around the hazard ratio. The crude model included each of the main exposure variable (IL-6, IL-8, IL-10, CRP, adiponectin, leptin, resistin or Lp(a)) and age. Model 1 further adjusted for sex, BMI, education, income, and race. Model 2 (the main analytical model) further adjusted for exercise. Model 3 additionally adjusted for alcohol, smoking, aspirin and statin use, and comorbidity score. Since the continuous exposure variables were not normally distributed, they were log-transformed. Statistical interactions between log-transformed biomarker levels and BMI were tested using the likelihood ratio test and the interaction *p-values*  0.1 were considered statistically significant. In addition, participants were ranked into tertiles

according to the levels of biomarkers and the highest tertiles were compared to the lowest for the risk of cancer mortality. The associations between the exposure variables and mortality were considered statistically significant if the 95% confidence intervals (95% CIs) do not include the null value (1.0) or if the p-values are 0.05, and for interaction terms, if the *p*-values are 0.1. The interactions between BMI and each biomarker in the non-stratified crude models were statistically significant at α=0.1, therefore results from BMI stratified models were presented. Participants were censored at the date of death, loss to follow-up or December 31, 2015, whichever happened first. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.)

## 3. Results

At baseline, compared with participants with normal BMI, those with overweight or obesity were younger, more likely to be male and Blacks, have less than high school education, and a higher average comorbidity score (all p-values <0.05, Table 1). Participants with normal BMI tended to have higher IL-8 and adiponectin levels, while those with overweight or obesity tended to have higher CRP, IL-6, and Lp(a) (p-value<0.05). The distribution of IL-10 and resistin were not significantly different between BMI categories, Table 2. A higher proportion of participants with normal BMI tended to be in the highest tertile of IL-6 and CRP than the participants with overweight/obesity, Figure 1. A higher proportion of the participants with normal BMI also tended to be in the highest tertile of adiponectin than those with overweight/obesity while those with overweight/obesity tended to be in the highest tertile of leptin than those with normal BMI, Figure 1.

The average follow-up time in the REGARDS sub-cohort was 8 years (SD=3.3). Figures 2 and 3 present the survival probabilities by tertiles of IL-6 and resistin, respectively. Among participants with normal BMI, participants in the highest vs. lowest tertile of IL-6 had a 5-fold (HR: 5.3, 95% CI: 1.6–17.8) increased risk of cancer mortality. Similar results were observed for log-transformed values of IL-6. In addition, those in the highest tertile of CRP had over a 3-fold (HR: 3.4; 95% CI: 1.0, 11.2) increased risk of cancer mortality (Table 3), while those in the highest tertile of resistin had a nearly 4-fold increased risk of cancer mortality (HR: 3.7; 95% CI: 1.2, 11.2), (Table 4). The interactions between the exposure variables and BMI were statistically significant, *p*-values were <0.05, Table 3 and 4. Among participants with overweight/obesity, the highest tertile of IL-6 was associated with more than a 3-fold increased risk of cancer mortality (HR: 3.5; 95% CI: 1.5, 8.1), (Table 3). However, CRP and resistin were not significantly associated with cancer mortality in this group (Table 4).

In race-stratified analyses (Table 5), IL-6 was significantly associated with higher risk of cancer mortality among Black participants with normal BMI (HR: 4.7; 95% CI: 1.3, 16.9) and overweight/obesity (HR: 3.3; 95% CI: 1.6, 7.0), and among White participants with overweight/obesity (HR: 3.1; 95% CI: 1.3, 7.5). Furthermore, CRP was significantly associated with an increased risk of cancer mortality, but only among White participants with normal BMI (HR: 1.9; 95% CI: 1.0, 3.4). The interactions between BMI and the exposure variables remained among Black participants (p-values<0.05) but disappeared among White participants (p-values>0.1), Table 5. In a sensitivity analysis excluding those

who died of cancer within 6 months from baseline, the associations remained consistent for all biomarkers evaluated (data not shown).

## 4. Discussion

In prospective REGARDS cohort, after adjusting for study covariates, higher baseline IL-6, CRP, and resistin were significantly associated with increased risk of cancer mortality among participants with normal BMI, while higher IL-6 was also associated with increased risk of cancer mortality among participants with overweight/obesity. When stratified by race, IL-6 remained significantly associated with higher risk of cancer mortality among Blacks regardless of BMI, but only among Whites with overweight/obesity. To our knowledge, this is the first study to simultaneously evaluate the independent associations of inflammatory and metabolic biomarkers with cancer mortality across levels of obesity.

Obesity has been well studied in relation to the risk of cancer mortality; however, estimates of the risk associated with higher BMI have been inconsistent due to the limitations in the validity of BMI as a measure of adiposity, and due to differences in the type and pattern of adiposity. This has led to a renewed interest in identifying biomarkers that may be less vulnerable to measurement error and can more reliably predict cancer risk. Recent studies have also shown that independent of obesity, metabolic health status is a key risk factor for cancer. Significant associations have been observed between high blood pressure [21], dyslipidemia, and type 2 diabetes [22–25] with cancer risk and mortality. Furthermore, obesity is associated with low-grade chronic inflammation, which is independently associated with cancer risk [26, 27]. Therefore, it is likely that obesity induces measurable changes in metabolism and inflammatory biomarkers associated with risk of cancer. It is also likely that non-obese individuals with higher levels of certain risk-associated biomarkers may be at higher risk of cancer. However, studies evaluating the impact of obesity in modifying the association between biomarkers of inflammation and metabolic dysregulation are limited. In particular, given that obesity has been evaluated well as a risk factor for cancer incidence and mortality, the emphasis to date has been on identifying biomarkers of this association in obese individuals. Our finding suggests that chronic inflammation and metabolic dysregulation in normal BMI individuals may substantially increase their risk of cancer mortality.

We observed a robust association between IL-6 and cancer mortality in both obese and non-obese participants after adjusting for socio-demographics, physical activity, and comorbidities. The association became attenuated and non-significant, although still a 2-fold increased risk, among normal BMI but not obese individuals when adjusted for behavioral risk factors (smoking, alcohol) and statin use. In contrast, estimates for overweight/obese participants became stronger after adjusting for the behavioral risk factors and statin use. We also observed significantly increased cancer mortality risk with higher CRP levels in normal BMI participants in the fully adjusted models. These findings suggest that regardless of BMI, certain markers of inflammation may influence the risk of cancer mortality. In addition, the results suggest that while behavioral factors may explain the increased risk associated with IL-6 in individuals with normal BMI but not overweight/obese, the association between CRP and cancer mortality risk in normal BMI individuals regardless of

behavioral risk factors highlights a potentially important role for chronic inflammation. Past studies have also observed independent and significant associations of high levels of IL-6 [28–30], CRP [31–34], and obesity [35–37] with cancer mortality. Our study adds to this body of work by showing that the association between inflammatory biomarkers and cancer mortality varies by BMI. Mechanistically, it has been suggested that a chronic inflammatory microenvironment promotes tumor cell motility, invasion, epithelial to mesenchymal transition and metastasis which in turn lead to poor prognosis [38]. IL-6 promotes tumorigenesis, angiogenesis, invasiveness, and metastasis, and inhibits apoptosis [29, 39]. IL-6 also protects cancer cells from therapy-induced DNA damage and oxidative stress by facilitating the repair and induction of counter-signaling pathways, thus increasing cancer mortality [39].

We found a consistent association between higher baseline resistin, a metabolism biomarker, and increased risk of cancer mortality, but only among participants with normal BMI. This association remained statistically significant after adjusting for behavioral risk factors. Of note, mean resistin was not significantly different by BMI categories. Thus, the differences in the association between resistin and cancer mortality by BMI may be attributable to the interaction between resistin and BMI and may not be due to resistin alone. Resistin has been studied as a potential missing link between obesity, chronic inflammation, and cancer [40] due to its association with increased low-density lipoprotein production and inflammatory response. A previous study has found a direct association between resistin and cancer mortality [41], and studies have documented that resistin promotes insulin resistance [42], chronic low-grade inflammation [43], and tumor cells adhesion to endothelium-a critical step for metastasis [44, 45]. The differences by BMI in the risk of cancer mortality associated with resistin may be at least partially explained in that resistin may not increase the risk any further in the obese individuals who already may have chronic inflammation. However, in individuals with normal BMI who might otherwise be without chronic inflammation, having high resistin may lead to chronic inflammation and thus worsen the prognosis of cancer. Lp(a), another metabolism-related biomarker, is involved in cholesterol transport, wound healing and tissue repair-pathways that are co-opted by cancer cells to enhance invasion and metastasis. We did not observe a significantly increased risk of cancer mortality associated with Lp(a) or adiponectin in the current study, although there was a suggestion of increased risk for adiponectin. Studies with larger sample sizes may be needed to definitively evaluate the role of adiponectin and Lp(a) in cancer mortality among obese and non-obese individuals; it is possible that these associations are easier to detect in lean individuals.

The association between baseline biomarkers and risk of cancer mortality also varied by race. For instance, IL-6 was associated with an increased risk of cancer mortality among normal BMI and overweight/obese Blacks, but only among overweight/obese Whites. CRP was associated with increased risk of cancer mortality among normal BMI Whites, but not among Blacks despite those with overweight/obesity having significantly higher mean CRP levels. This difference might be partially explained by the fact that obese/overweight participants might already have other risk factors that cumulatively increase the risk of cancer mortality and inflammation due to CRP may not significantly increase the risk while in those with normal BMI there may be fewer factors to mask the role of chronic

inflammation. In addition, a higher proportion of those with normal BMI died of cancer than the proportion of overweight/obese participants that died of cancer. In a previous study, IL-6 was associated with increased cancer mortality in both Blacks and White participants [46]. Our analysis was likely underpowered given the limited sample sizes to detect racial differences in cancer mortality risk. None of the interaction terms between inflammatory and metabolic biomarkers on cancer mortality risk were statistically significant, likely due to the small sample size and the limited number of events. Future studies with larger, racially diverse prospective cohorts, or including a larger subset of this cohort, are needed to definitively evaluate racial differences in the independent and synergistic associations of inflammatory and metabolic biomarkers in cancer mortality risk. The finding from this study improves our understanding of the role of metabolic health status and obesity in cancer outcomes and informs race-specific cancer prevention interventions.

The strengths of the study include the consistent results in the sensitivity analysis that excluded those who died of cancer within six months from baseline and the use of a large biracial prospective cohort with detailed baseline measures of the biomarkers of interest and covariates. REGARDS participants were recruited nationally across the US, although residents of the stroke belt were over-sampled, thus improving the generalizability of the study results. This study also has some limitations relevant to the interpretation of the results. First, the mean follow-up period was 8 years. This also resulted in a limited number of events especially in stratified analysis, leading to reduced power to detect significant associations especially in the race-stratified and interaction analyses. Second, since REGARDS was originally designed to evaluate stroke outcomes, there is currently no data on cancer incidence. While cost-effective and convenient, the methods used to determine the assay levels in this study such as the BN II nephelometer, Milliplex MAP Human Cardiovascular Disease Panel 3, and Human Serum Adipokine Panel B LINCOplex Kit may have low sensitivities, especially for LP(a); however, in this study, they had satisfactory sensitivities with MDD well below the 1% for each biomarker except for LP(a), and the methods have been used previously and had similar coefficients of variations as in our study [47, 48]. Larger cohorts of racially diverse participants using different assay measurement methods are needed to confirm these findings and potentially identify other relevant biomarkers that may vary by BMI and race.

In conclusion, biomarkers of inflammation (IL-6 and CRP) and metabolism (resistin) were significantly associated with increased risk of cancer mortality independent of obesity, suggesting that both pathways may play a synergistic role in creating a favorable microenvironment for tumorigenesis and prognosis. This supports the need for improved risk stratification based on metabolic health and/or inflammatory biomarkers regardless of BMI or obesity status in predicting cancer outcomes. Interventions targeting the inflammatory and metabolic biomarkers may improve cancer survival.

## Funding

## Abbreviations:

| | |
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| **BMI** | Body Mass Index |
| **IL-6** | : Interleukin-6 |
| **IL-8** | Interleukin-8 |
| **IL-10** | Interleukin-10 |
| **CRP** | C-Reactive Protein |
| **Lp(a)** | Lipoprotein (a) |
| **REGARDS** | Reasons for Geographic and Racial Disparities in Stroke |
| **SSDI** | Social Security Death Index |
| **NDI** | National Death Index |
| **HR** | Hazard Ratio |
| **CI** | Confidence Interval |

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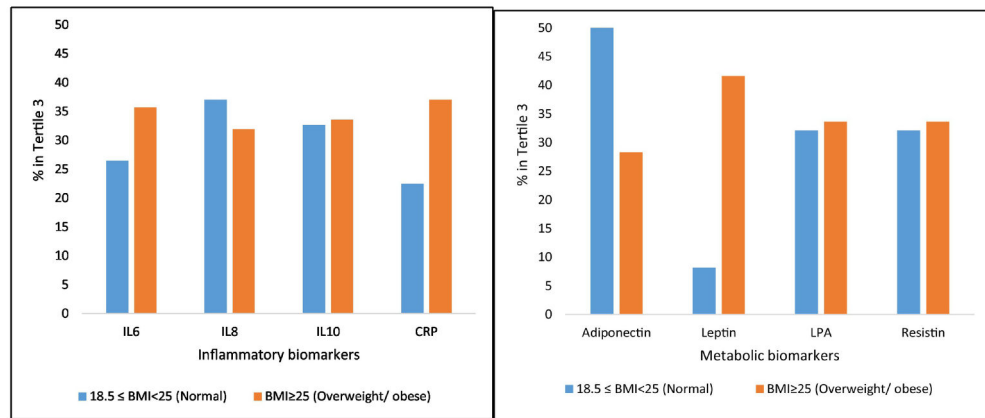
**Figure 1:**
Distribution of inflammatory (A) and metabolic (B) biomarkers by BMI in REGARDS BMI in kg/m$^2$.
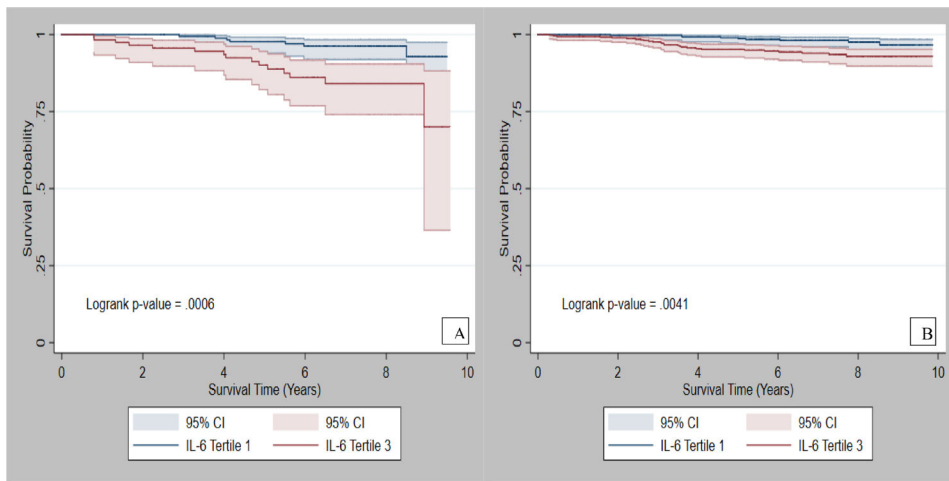
**Figure 2:**
Survival probability of cancer patients with A) normal BMI, and B) overweight/obesity by tertiles of IL-6.
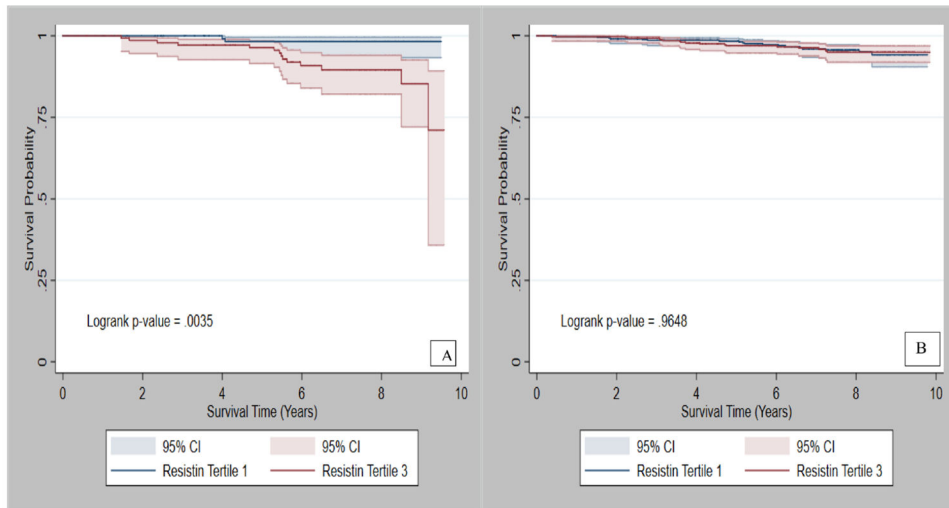
**Figure 3:**
Survival probability of cancer patients with A) normal BMI and B) overweight/obese by tertiles of resistin.

**Table 1.**

Baseline characteristics of REGARDS participants by BMI category

| | BMI Categories | | |
|---|---|---|---|
| | Normal (18.5–24.9 kg/m$^2$) | Overweight or Obese ( 25kg/m$^2$) | *P*-value |
| *Participants n* | *454* | *1368* | |
| *Weighted Participants n* | *6402* | *19904* | |
| Age at baseline, mean (SE)$^\S$ | 70.3 (12.0) | 66.4 (10.2) | <0.0001 |
| Race (Blacks)% $^\Psi$ | 28.4 | 45.7 | <0.0001 |
| Male Gender, % | 42.4 | 46.9 | 0.0001 |
| Education < High School, % | 10.0 | 12.9 | 0.003 |
| Income <$20,000, % | 14.7 | 16.7 | 0.501 |
| No Exercise Activity, % | 34.0 | 32.5 | 0.740 |
| BMI (kg/m$^2$), Median (IQR)$^\gamma$ | 23.2 (2.3) | 30 (6.4) | |
| Current Smoking Status, % | 18.0 | 12.7 | 0.353 |
| Heavy Alcohol Consumption, % | 6.0 | 3.3 | 0.558 |
| Medication Use, % | | | |
| NSAIDs - Aspirin | 43.9 | 45.1 | 0.836 |
| Statins | 28.6 | 35.9 | 0.243 |
| Comorbid Conditions, % | | | |
| Atrial fibrillation | 12.2 | 8.0 | 0.030 |
| Chronic lung disease | 6.7 | 9.0 | 0.516 |
| Coronary artery disease | 16.5 | 16.6 | 0.551 |
| Deep vein thrombosis | 4.5 | 6.6 | <0.0001 |
| Diabetes | 9.9 | 27.5 | <0.0001 |
| Dyslipidemia | 50.6 | 63.6 | <0.0001 |
| Hypertension | 44.7 | 63.8 | <0.0001 |
| Myocardial infarction | 13.2 | 12.8 | 0.685 |
| Peripheral artery disease | 1.1 | 1.4 | 0.827 |
| Stroke | 7.6 | 4.6 | 0.081 |
| Comorbidity Score, mean (SE) | 1.9 (1.4) | 2.3 (1.4) | <0.0001 |

$^\S$Results are mean and standard deviation (SD)

$^\Psi$Results are percent

$^\gamma$Results are median and interquartile ranges

**Table 2.**

Distribution of inflammatory and metabolic biomarkers among study participants

| | BMI Category | | |
| | Normal (18.5–24.9 kg/m$^2$) | Overweight or Obese ( 25 kg/m$^2$) | *P*-value |
|---|---|---|---|
| **Inflammatory Biomarkers (n=1822)** | | | |
| IL-6 (pg/ml) [*] | 2.2 (1.9) | 3.1 (2.4) | <0.0001 |
| IL-8 (pg/ml) [*] | 2.7 (1.8) | 2.5 (1.8) | 0.013 |
| IL-10 (pg/ml) [*] | 9.5 (7.1) | 9.1 (7.1) | 0.58 |
| CRP (mg/L) [§] | 3.5 (6.5) | 4.8 (7.1) | <0.0005 |
| **Metabolic Biomarkers (n=1733)** | | | |
| Adiponectin (ng/ml) [*] | 14568 (20982.2) | 10072 (20904.2) | <0.0001 |
| Resistin (pg/ml) [*] | 23.1 (20) | 24.3 (12.1) | 0.69 |
| Lp(a) (mg/dl) [*] | 0.13 (0.3) | 0.20 (0.40) | 0.045 |

Abbreviation: CRP, C-reactive protein; IQR, inter quartile range; IL, interleukine; Lp(a), lipoprotein (a); SD, standard deviation

[*] Median (IQR)

[§] Results are mean and SD

**Table 3.**

Hazard ratios (HR) and 95% confidence intervals (CI) for cancer mortality by baseline inflammatory biomarkers

| | BMI categories | | | | |
| --- | --- | --- | --- | --- | --- |
| | Normal (18.5 ≤ BMI<25 kg/m²) | | Overweight or Obese (BMI ≥ 25 kg/m²) | | $P_{int \; with \; BMI}$ |
| | Log Transformed | T3 [§] | Log Transformed | T3 | |
| **IL-6 (pg/ml)**, *N* (Cases) | *454 (29)* | *120 (15)* | *1368 (54)* | *488 (27)* | |
| Weighted *N* (Cases) | *6402 (371)* | *1136 (195)* | *19904 (937)* | *6310 (492)* | |
| Crude | **3.3 (1.5, 6.7)** [**] | **5.5 (1.8, 16.4)** [**] | **2.8 (1.6, 4.7)** [**] | **3.2 (1.5, 6.7)** [*] | <0.0001 |
| Model 1 | **3.0 (1.4, 6.3)** [**] | **4.2 (1.5, 11.9)** [**] | **2.8 (1.6, 5.0)** [**] | **3.4 (1.4, 7.0)** [**] | 0.007 |
| Model 2 | **3.2 (1.5, 7.0)** [**] | **5.3 (1.6, 17.8)** [**] | **3.0 (1.7, 5.4)** [**] | **3.5 (1.5, 8.1)** [**] | 0.007 |
| Model 3 | 2.1 (0.8, 5.4) | 2.4 (0.6, 9.0) | **2.6 (1.4, 4.9)** [**] | **2.9 (1.2, 6.6)** [*] | 0.716 |
| **IL-8 (pg/ml)**, *N* (Cases) | *454 (29)* | *168 (12)* | *1368 (54)* | *436 (25)* | |
| Weighted *N* (Cases) | *6402 (371)* | *2101 (187)* | *19904 (937)* | *6228 (552)* | |
| Crude | 1.1 (0.7, 1.8) | 1.8 (0.6, 5.2) | **1.4 (1.0, 2.2)** [**] | **1.5 (0.8, 3.1)** [*] | 0.047 |
| Model 1 | 0.9 (0.5, 1.7) | 1.5 (0.5, 4.2) | 1.4 (0.9, 2.3) | 1.4 (0.7, 2.8) | 0.049 |
| Model 2 | 0.9 (0.5, 1.7) | 1.5 (0.5, 4.1) | 1.4 (0.9, 2.3) | 1.4 (0.7, 2.9) | 0.043 |
| Model 3 | 0.9 (0.4, 1.9) | 1.1 (0.3, 4.4) | 1.2 (0.7, 2.2) | 1.3 (0.6, 2.8) | 0.710 |
| **IL-10 (pg/ml)**, *N* (Cases) | *454 (29)* | *148 (9)* | *1368 (54)* | *459 (22)* | |
| Weighted *N* (Cases) | *6402 (371)* | *2307 (148)* | *19904 (937)* | *6230 (367)* | |
| Crude | 0.7 (0.5, 1.1) | 0.7 (0.3, 1.7) | 1.0 (0.6,1.5) | 1.2 (0.6, 2.2) | 0.006 |
| Model 1 | 0.8 (0.5,1.2) | 0.7 (0.3, 1.9) | 0.9 (0.6, 1.6) | 1.0 (0.5, 2.0) | 0.021 |
| Model 2 | 0.7 (0.5, 1.2) | 0.7 (0.2, 2.1) | 0.9 (0.6, 1.5) | 1.0 (0.5, 2.0) | 0.016 |
| Model 3 | 0.6 (0.4, 1.1) | 0.6 (0.2, 2.6) | 0.9 (0.5, 1.6) | 0.8 (0.4, 1.7) | 0.636 |
| **CRP (mg/L)**, *N* (Cases) | *678 (31)* | *102 (8)* | *1368 (54)* | *506 (20)* | |
| Weighted *N* (Cases) | *6402 (371)* | *1217 (92)* | *19904 (937)* | *6987 (364)* | |
| Crude | **1.7 (1.2, 2.4)** [**] | **3.6 (1.2, 10.4)** [**] | 1.1 (0.8, 1.4) | 1.1 (0.6, 2.2) | 0.0003 |
| Model 1 | **1.6 (1.1, 2.2)** [**] | **3.5(1.1, 11.4)** [*] | 1.1 (0.8, 1.4) | 1.2 (0.6, 2.4) | 0.009 |
| Model 2 | **1.6 (1.1, 2.2)** [**] | **3.4 (1.0, 11.2)** [*] | 1.1 (0.8, 1.5) | 1.3 (0.6, 2.8) | 0.008 |
| Model 3 | **1.6 (1.1, 2.2)** [*] | **4.2 (1.1,16.4)** [*] | 1.2 (0.9, 1.6) | 1.6 (0.7, 3.5) | 0.412 |

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Crude model included the exposure and age.

Model 1: Adjusted for age, gender, education, race, and income.

Model 2: Additionally adjusted for exercise

Model 3: Additionally adjusted for smoking status, alcohol use, aspirin use, statin, and comorbidity score

$^{g}$T1: 1st tertile, was the reference category; T3: 3rd tertile

**Bold** indicates significance at 0.05 alpha level.

\*\*
p-values were  0.01;

\*
p-values were  0.05 while the rest of p-values were >0.05.

$p$int, p for the interaction of the log form with BMI. The p-values are from type 3 tests. $P$ for the interaction is considered significant at alpha=0.1.

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**Table 4.**

Hazard ratios (HR) and 95% confidence intervals (CI) for cancer mortality by baseline metabolic biomarkers

| | Normal (18.5 BMI <25 kg/m²) | | Overweight or Obese (BMI 25 kg/m²) | | p_int with BMI |
|---|---|---|---|---|---|
| | Log-Transformed | T3§ | Log Transformed | T3 | |
| **Weighted N (case)** | | | | | |
| **Adiponectin (pg/ml),** N (Cases) | 418 (31) | 207 (19) | 1315 (55) | 178 (214) | |
| **Weighted** N (Cases) | 5664 (322) | 2713 (191) | 18694 (938) | 2563 (102) | |
| Crude | 1.0 (0.7, 1.5) | 0.9 (0.4, 2.3) | 0.9 (0.6, 1.3) | 0.9 (0.5, 1.6) | 0.029 |
| Model 1 | 1.2 (0.8, 1.8) | 1.7 (0.6, 4.9) | 1.1 (0.8, 1.7) | 1.3 (0.6, 2.6) | 0.025 |
| Model 2 | 1.3 (0.9, 1.9) | 2.1 (0.7, 6.0) | 1.1 (0.7, 1.6) | 1.3 (0.6, 2.7) | 0.014 |
| Model 3 | 1.4 (0.9, 2.2) | 2.3 (0.5, 9.4) | 1.1 (0.7, 1.7) | 1.3 (0.6, 2.9) | 0.141 |
| **Lipoprotein a (mg/dl),** N (Cases) | 418 (31) | 134 (10) | 1315 (55) | 220 (9) | |
| **Weighted** N (Cases) | 5664 (322) | 1467 (99) | 18694 (938) | 3339 (170) | |
| Crude | 0.8 (0.5, 1.3) | 1.2 (0.5, 2.8) | 0.9 (0.7, 1.2) | 0.8 (0.5, 1.7) | 0.008 |
| Model 1 | 0.7 (0.4, 1.1) | 0.8 (0.3, 2.2) | 0.9 (0.6, 1.2) | 0.8 (0.4, 1.7) | 0.082 |
| Model 2 | 0.7 (0.4, 1.2) | 0.9 (0.3, 2.6) | 0.9 (0.6, 1.2) | 0.8 (0.4, 1.8) | 0.066 |
| Model 3 | 1.0 (0.5, 1.9) | 1.7 (0.5, 6.3) | 0.9 (0.7, 1.3) | 1.0 (0.4, 2.3) | 0.712 |
| **Resistin (pg/ml),** N (Cases) | 418 (31) | 134 (15) | 1315 (55) | 224 (8) | |
| **Weighted** N (Cases) | 5664 (322) | 1528 (112) | 18694 (938) | 3025 (148) | |
| Crude | **2.5 (1.1, 5.7)** * | **3.7 (1.3, 11.0)** * | 0.8 (0.5, 1.5) | 0.7 (0.4, 1.5) | 0.001 |
| Model 1 | **2.4 (1.1, 5.3)** * | **4.0 (1.3, 11.7)** * | 1.0 (0.5, 1.8) | 0.8 (0.4, 1.6) | 0.012 |
| Model 2 | **2.3 (1.0, 5.0)** * | **3.7 (1.2, 11.2)** * | 1.0 (0.5, 1.8) | 0.7 (0.3, 1.5) | 0.008 |
| Model 3 | 2.5 (0.9, 7.0) | **8.7 (1.9, 39.9)** ** | 1.0 (0.5, 2.0) | 0.9 (0.4, 1.8) | 0.001 |

Crude model included the exposure and age.

Model 1 adjusted for age, gender, education, race, and income.

Model 2 additionally adjusted for exercise.

Model 3 additionally adjusted for smoking status, alcohol use, aspirin use, statin, and comorbidity score

§T1: 1st tertile was the reference category; T3: 3rd tertile

**Bold** indicates significance at 0.05 alpha level.

\*\*
p-values were 0.01;

\*
p-values were 0.05 while the rest of p-values were >0.05.

$p$int, p for the interaction of the log form with BMI. The p-values are from type 3 tests. $P$ for the interaction is considered significant at alpha=0.1.

**Table 5.**

Hazard ratios (HR) and 95% confidence intervals (CI) for cancer mortality by inflammatory and metabolic biomarkers by race

| | BMI categories | | |
|---|---|---|---|
| | Normal BMI (18.5 ≤ BMI <25 kg/m$^2$) | Ove rweight or Obese (BMI ≥ 25 kg/m$^2$) | $p_{int\ with\ BMI}$ |
| | Log-Transformed$^\S$ | Log Transformed$^\S$ | |
| **Black Participants (N=798, cancer death=40)** | | | |
| **IL-6** | | | |
| Model 1 | **3.6(1.2, 10.6)** * | **3.4 (1.6, 7.0)** ** | 0.008 |
| Model 2 | **4.7 (1.3, 16.9)** * | **3.3 (1.6, 7.0)** * | 0.021 |
| Model 3 | **5.9 (1.5, 23.1)** * | **3.0 (1.3, 6.9)** * | 0.156 |
| **CRP** | | | |
| Model 1 | 1.4 (0.9, 2.0) | 1.3 (0.9, 2.0) | 0.039 |
| Model 2 | 1.4 (0.9, 1.9) | 1.3 (0.9, 2.0) | 0.043 |
| Model 3 | 1.3 (0.7, 2.2) | 1.3 (0.9, 2.0) | 0.396 |
| **Resistin** | | | |
| Model 1 | 4.4 (0.6, 31.4) | 1.3 (0.7, 2.3) | 0.007 |
| Model 2 | 4.2 (0.7, 26.9) | 1.3 (0.7, 2.3) | 0.013 |
| Model 3 | **8.5 (2.0, 35.8)** ** | 1.3 (0.7, 2.5) | 0.008 |
| **White Participants (N=1024, cancer death=46)** | | | |
| **IL-6** | | | |
| Model 1 | 2.6 (0.8, 9.1) | **2.4 (1.0, 5.7)** * | 0.269 |
| Model 2 | 3.0 (0.8, 12.0) | **3.1 (1.3, 7.5)** * | 0.278 |
| Model 3 | 1.0 (0.20, 4.6) | **2.7 (1.1, 6.4)** * | 0.649 |
| **CRP** | | | |
| Model 1 | **1.8(1.1, 3.1)** * | 0.9 (0.6, 1.3) | 0.115 |
| Model 2 | **1.9 (1.0, 3.4)** * | 0.9 (0.6, 1.4) | 0.131 |
| Model 3 | **1.7 (1.2, 2.5)** ** | 1.0 (0.6, 1.5) | 0.571 |
| **Resistin** | | | |
| Model 1 | 1.3 (0.3, 5.5) | 0.4 (0.1, 1.6) | 0.625 |
| Model 2 | 1.3 (0.3, 6.0) | 0.4 (0.1, 1.8) | 0.454 |
| Model 3 | 3.6 (0.5, 24.2) | 0.4 (0.1, 2.5) | <0.0001 |

Crude model included the exposure and age.

Model 1 adjusted for age, gender, education, and income

Model 2 additionally adjusted for exercise

Model 3 further adjusted for comorbidity scores, smoking, alcohol, aspirin, and statin use

$^\S$Biomarkers (except CRP) were log-transformed due to non-normal distributions

Bold indicates significance at 0.05 alpha level.

**
p-values were ≤ 0.01;

*
p-values were 0.05 while the rest of p-values were >0.05.

$p$int, p for the interaction of the log form with BMI. The p-values are from type 3 tests. $P$ for the interaction is considered significant at alpha=0.1