Body Mass Index and All-Cause Mortality in a Large Prospective Cohort of White and Black U.S. Adults

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Abstract

Remaining controversies on the association between body mass index (BMI) and mortality include the effects of smoking and prevalent disease on the association, whether overweight is associated with higher mortality rates, differences in associations by race and the optimal age at which BMI predicts mortality. To assess the relative risk (RR) of mortality by BMI within Whites and Blacks, we modified the BMI-mortality relationship. Among healthy, never-smokers there was a statistically significant higher risk of mortality for BMI > 30 kg/m² (reference category was 18.5–24.9 kg/m²). Inclusion of the lowest BMI category resulted in a lower observed relative risk in the overweight group, especially when smokers and individuals with prevalent disease were included.

Introduction

Excess body weight is known to increase risk of premature mortality and various chronic diseases including cardiovascular disease, diabetes, and various types of cancer [1,2]. Both the disease etiology implications and public health impact of high body mass index (BMI) are vitally important given the extremely high rates of overweight and obesity in the U.S. and worldwide. Numerous observational studies [2–5] have reported on the relationship between obesity and mortality with quantitatively and qualitatively varied results.

Despite the large number of studies to date, four major unresolved issues in the study of obesity and mortality still exist. The first two related issues include whether overweight (BMI 23–<30 kg/m²) is beneficial or detrimental in relation to total mortality and to what extent smoking and prevalent disease, conditions that both cause weight loss and shortened survival, influence the relationship between overweight and total mortality. A large pooled analysis that included 1.46 million Caucasian men and women found that smoking and prevalent disease significantly modified the BMI-mortality relationship. Among healthy, never-smokers there was a statistically significant higher risk of mortality in underweight (BMI < 18.5 kg/m²) and in the lowest end of normal weight (18.5–19.9 kg/m²) groups as well as overweight and obese individuals compared to the upper end of normal weight (22.5–24.9 kg/m²), and optimal BMI was between 20.0 and 24.9 kg/m² [3]. Conversely, a recent meta-analysis [5] including 97 studies reported that overweight was associated with lower all-cause mortality compared to normal weight, and reported that exclusion of smokers and individuals with prevalent disease had little effect on the magnitude of risk estimates. Unlike the large pooled analysis, the meta-analysis by Flegal et al., examined associations relative to the full range of normal weight (reference category was 18.5–24.9 kg/m²). Inclusion of the lower end of the normal weight in the reference group would result in lower observed relative risk in the overweight group, especially when smokers and individuals with prevalent disease were included.

The third issue is whether the association between BMI and mortality differs by race. While recent, large pooled analyses have examined the relationship between BMI and all-cause death rates in Caucasians [3] and Asians [6], the BMI-mortality dose-response relationship has not been well-characterized in African Americans.

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Among the relatively few studies on this issue in African Americans [4,7–17], most [8,10,12–17] suggest that the association between BMI and mortality may be weaker in Blacks than Whites. However, studies of African Americans had relatively small sample sizes and/or short follow-up time. Finally, the fourth issue is that the appropriate age window of the exposure (the age at which body mass index predicts subsequent mortality) remains unclear. Results of various studies suggest that BMI measured at younger ages is more predictive of subsequent mortality long term because it is more effective in measuring adiposity and accounting for pre-existing disease than BMI measured later in life [4,8,9,18–21].

The American Cancer Society’s Cancer Prevention Study II is well-suited to the study of BMI in relation to mortality, due to its prospective design, large size of both Black and White men and women, and long follow-up period. Our initial paper examining the association between BMI and total mortality was published in 1999 when the cohort had been followed for 14 years [4]. That analysis was based on 14-years of follow-up and had a limited number deaths among Black men and women, especially among those who were obese (n = 83 deaths among men, n = 319 deaths among women). Here, we present results on the four issues described above with follow-up extended to 28 years including over 450,000 deaths.

**Methods**

**Study Population**

Subjects for this analysis were selected from the 1,184,387 participants (508,227 men and 676,160 women) in the Cancer Prevention Study II, a prospective study of mortality among men and women in the United States begun by the American Cancer Society in 1982 [22]. Participants were identified and enrolled by more than 77,000 volunteers in all 50 states, the District of Columbia, and Puerto Rico. Families were enrolled if at least one household member was 45 years of age or older, and all enrolled members were at least 30 years old. The average age of participants at enrollment was 57 years old. In 1982, participants completed a confidential questionnaire, through which they provided information on demographic characteristics, personal and family history of cancer and other diseases, environmental and occupational exposures, and factors related to lifestyle, behavior and diet. All aspects of CPS-II have been reviewed and approved by the Emory University Institutional Review Board, and all data were de-identified prior to analysis.

Participants were asked to provide their current weight, weight one year prior to enrollment, and height (without shoes). Subjects with missing values for height or current weight were excluded from the analysis (N = 29,320), as were those with extreme values (99.9th percentile) for height or weight or extreme underweight (BMI <15) (N = 6,484). In order to adequately control for smoking, we excluded subjects with missing data for the smoking questions (N = 46,900), smokers with no information on number of cigarettes per day (N = 87,342), former smokers with no information on years since quitting (N = 2,080), and smokers whose smoking status at baseline (current or former) was unknown (N = 20,068). We also excluded men who had smoked only pipes or cigars but not cigarettes (N = 40,462) because their amount of smoking was not well defined; pipe and cigar smoking was not queried in women. Finally, we excluded all races other than White or Black (N = 21,860). The remaining eligible population, after exclusions, consisted of 341,196 White men (194,388 deaths), 12,559 Black men (7,368 deaths), 550,556 White women (239,812 deaths), and 25,560 Black women (11,334 deaths).

**Classifying Body-Mass Index**

Body-mass index (BMI [kg/m²]) was classified as follows: 15.0 to 18.4, 18.5 to 19.9; 20.0 to 22.4; 22.5 to 24.9 (reference group); 25.0 to 27.4; 27.5 to 29.9; 30.0 to 34.9; 35.0 to 39.9; 40.0 and higher. Due to small numbers, the highest category examined for Black men was 35.0 and higher. This categorization scheme includes finer groupings of the World Health Organization (WHO) definitions of “underweight” as body mass index (BMI) less than 18.5 kg/m², the “normal” range 18.5 to 24.9 kg/m², “overweight” range 25.0 to 29.9 kg/m², and “obese” as greater than or equal to 30.0 kg/m² [23]. Additionally, these finer groupings were selected a priori for consistency with several previously published studies including the large pooled study of 1.46 million White participants reporting the nadir of the dose-response curve was at BMI 22.5 to 24.9 [5].

**End Points**

Deaths occurring between the months of enrollment and December 31, 2010, were ascertained through personal inquiries by volunteers in September 1984, September 1986, and September 1988, and thereafter through linkage with the National Death Index (NDI) [24]. As of December 31, 2010, 50.5 percent of the participants had died and 49.5 percent were still living: 0.3 percent were lost to follow-up on September 1, 1988 due to insufficient data for linkage with the NDI. Multiple cause-of-death codes have been obtained for 99.3 percent of all deaths.

The primary end point in this analysis was deaths from all causes. In secondary analyses, deaths from all cardiovascular disease (ICD-9 codes 390 through 459; ICD-10 codes I00 through I99), all cancer (ICD-9 codes 140 through 208; ICD-10 codes C00 through C97), and all other causes, were examined separately in relation to BMI.

**Statistical Analysis**

Age-adjusted mortality rates according to BMI in men and women, race-specific, were calculated by direct standardization to the age distribution of the CPS-II male and female populations using 5-year age categories. Multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs) were estimated in Cox proportional-hazards regression models stratifying on single year of age at enrollment, Models simultaneously adjusted for education (less than high school, high school graduate, some college/vocational training, college graduate and higher), physical activity (none, slight, moderate, or heavy exercise), alcohol use (nondrinker, <1 drink per day, 1 drink per day, >1 drink daily), marital status (married vs. single, widowed, or divorced), aspirin use (yes/no), fat consumption, vegetable consumption (sex-specific tertiles), and estrogen replacement therapy among women (yes/no). Models that included ever smokers were also adjusted for smoking status, frequency and time since quitting (current smoker with cigarettes per day [cpd] categorized as ≤10, 11–20, 21–30, 31–40, or 40 or more cpd; former smoker having quit within the last year and smoked ≤10, 11–20, 21–30, 31–40, or 40 or more cpd; former smoker having quit 1 to 9 years prior and smoked ≤10, 11–20, 21–30, 31–40, or 40 or more cpd; former smoker having quit 10–19 years prior and smoked ≤10, 11–20, 21–30, 31–40, 40 or more cpd, and former smoker having quit at least 20 years prior and smoked ≤10, 11–20, 21–30, 31–40, or 40 or more cpd) and those that included prevalent disease also adjusted for disease status (no/yes for cancer, heart disease, stroke, or emphysema; yes for chronic bronchitis or asthma).

We examined the association between BMI and all-cause mortality for each of four mutually exclusive race and gender-specific subgroups according to smoking status [never, ever] and...
### Table 1. Baseline characteristics of all CPS-II men and women by race and BMI (kg/m²).

| Characteristic | BMI (kg/m²) | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥40.0 |
|---------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| **MEN**       |             |           |           |           |           |           |           |           |           |       |
| **White Race (Total N = 341,196; Deaths = 194,588)** |             |           |           |           |           |           |           |           |           |       |
| Number of men | 2,535       | 5,115     | 36,781    | 93,990    | 115,561   | 53,776    | 29,324    | 3,744     | 370       |       |
| Number of deaths | 1,940     | 3,609     | 22,402    | 52,358    | 63,552    | 30,453    | 17,615    | 2,415     | 244       |       |
| Mean Age (yrs) | 62          | 60        | 58        | 58        | 57        | 56        | 55        | 54        | 53        |       |
| ≥High school (%) | 55.6      | 58.7      | 66.3      | 67.8      | 64.0      | 58.8      | 56.4      | 53.8      | 51.3      |       |
| Married (%) | 89.5        | 90.0      | 92.2      | 94.3      | 95.4      | 95.4      | 94.9      | 93.8      | 87.4      |       |
| Nondrinker (%) | 19.8       | 21.1      | 18.7      | 17.3      | 16.6      | 17.1      | 18.3      | 21.2      | 24.4      |       |
| Never smoker (%) | 24.0       | 26.6      | 33.0      | 34.8      | 34.1      | 33.5      | 34.2      | 34.4      | 32.4      |       |
| Prevalent diseases (%) | 50.4      | 42.4      | 33.8      | 31.7      | 32.6      | 34.9      | 37.6      | 42.5      | 41.4      |       |
| **Black Race (Total N = 12,559; Deaths = 7,368)** |             |           |           |           |           |           |           |           |           |       |
| Number of men | 119         | 250       | 1,368     | 2,799     | 3,807     | 2,289     | 1,624     | 264       | 39        |       |
| Number of deaths | 82        | 180       | 818       | 1,611     | 2,000     | 1,319     | 977       | 153       | 28        |       |
| Mean Age (yrs) | 59          | 57        | 55        | 56        | 55        | 55        | 54        | 52        | 52        |       |
| ≥High school (%) | 48.6      | 38.9      | 51.6      | 54.6      | 53.0      | 52.6      | 45.9      | 38.7      | 37.4      |       |
| Married (%) | 75.4        | 75.2      | 79.1      | 84.3      | 84.6      | 87.9      | 85.6      | 85.5      | 88.5      |       |
| Nondrinker (%) | 16.1       | 14.7      | 13.7      | 15.5      | 16.2      | 17.1      | 16.9      | 17.6      | 20.2      |       |
| Never smoker (%) | 26.6       | 17.9      | 24.4      | 31.6      | 33.7      | 38.3      | 43.9      | 44.9      | 42.4      |       |
| Prevalent diseases (%) | 44.9      | 40.9      | 32.2      | 29.2      | 31.9      | 34.2      | 40.1      | 41.6      | 48.8      |       |
| **WOMEN**     |             |           |           |           |           |           |           |           |           |       |
| **White Race (Total N = 550,556; Deaths = 239,812)** |             |           |           |           |           |           |           |           |           |       |
| Number of women | 14,076     | 41,470    | 148,270   | 144,815   | 98,373    | 46,003    | 43,610    | 10,738    | 3,201     |       |
| Number of deaths | 7,681     | 16,271    | 56,019    | 61,462    | 46,167    | 22,870    | 22,033    | 5,336     | 1,773     |       |
| Mean Age (yrs) | 58          | 55        | 55        | 57        | 58        | 58        | 57        | 54        | 53        |       |
| ≥High school (%) | 61.0      | 64.0      | 61.9      | 56.1      | 52.0      | 48.8      | 46.7      | 45.3      | 43.1      |       |
| Married (%) | 69.8        | 74.4      | 77.9      | 79.0      | 78.3      | 76.7      | 74.8      | 72.3      | 67.3      |       |
| Nondrinker (%) | 21.6       | 19.7      | 19.2      | 20.4      | 22.0      | 24.0      | 25.8      | 28.8      | 28.9      |       |
| Never smoker (%) | 45.1       | 50.0      | 53.9      | 57.8      | 61.7      | 64.2      | 66.1      | 65.0      | 64.3      |       |
| Prevalent diseases (%) | 37.2      | 30.7      | 29.7      | 32.2      | 35.2      | 38.6      | 42.1      | 47.9      | 50.6      |       |
| **Black Race (Total N = 25,560; Deaths = 11,334)** |             |           |           |           |           |           |           |           |           |       |
| Number of women | 403         | 779       | 3,324     | 5,295     | 5,757     | 3,603     | 4,513     | 1,345     | 541       |       |
| Number of deaths | 214        | 333       | 1,285     | 2,032     | 2,497     | 1,706     | 2,256     | 698       | 313       |       |
| Mean Age (yrs) | 56          | 54        | 54        | 54        | 56        | 56        | 56        | 54        | 54        |       |
| ≥High school (%) | 55.4      | 60.4      | 62.2      | 59.5      | 54.5      | 50.6      | 46.0      | 42.0      | 38.1      |       |
prevalent disease status [yes/no] defined as a history of cancer (except non-melanoma skin cancer), heart disease, stroke, respiratory diseases (chronic bronchitis, emphysema, or asthma), current illness of any kind, or weight loss of 10 or more lbs (4.5 kg) in the previous year. Effect modification by smoking and prevalent disease combined (healthy never smokers, healthy smokers, never smokers with prevalent disease, smokers with prevalent disease) and by race were evaluated in multivariate models using the likelihood ratio test and a p-value <0.05 was considered statistically significant. In Black and Whites combined, we examined the association between BMI and mortality by age at enrollment (younger than 50, 50–59, 60–69, 70 years or older) but this analysis was limited to the healthy never smokers because smoking and prevalent disease significantly modified the association between BMI and mortality. Finally, we examined the associations of BMI with cardiovascular disease and cancer mortality separately.

**Results**

The mean age at baseline was 56 years old for White men, 55 for Black men, 57 for White women and 55 for Black women. The mean BMI was 25.8, 26.8, 24.6, 27.1 kg/m² for White and Black men and women, respectively. Selected baseline characteristics for each sex-race group by BMI category are presented in Table 1. BMI was inversely related to age at baseline for all groups except Black women. A strong positive relationship was observed between BMI and the prevalence of never smokers in both men and women at the time of enrollment, regardless of race. In contrast, there was a curvilinear relationship between BMI and prevalent disease, such that individuals at both high and low extremes of BMI were more likely to report disease at baseline than persons within the WHO normal range of BMI (18.5–24.9 kg/m²). For all groups, BMI was also inversely related to educational status at BMI levels of 22.5 kg/m² or greater.

Tables 2 and 3 present the BMI-mortality relationship by race for men and women, respectively, stratified by smoking and prevalent disease status. Smoking and prevalent disease modified the association between BMI and mortality in all four groups (interaction p = 2.4 × 10^{-39} for White men, p = 0.053 for Black men, p = 1.6 × 10^{-32} for White women, and p = 0.02 for Black women). For White men and women, regardless of smoking status or prevalent disease, underweight was associated with higher risk of mortality compared to BMI 22.5–24.9 kg/m². For Black men, underweight was associated with higher risk of mortality compared to BMI 22.5–24.9 kg/m². For Black men, underweight was associated with higher risk of mortality in those with prevalent disease, regardless of smoking status, but not in Black men without prevalent disease. In Black women, underweight was associated with higher mortality in all groups, albeit a non-statistically significant elevated risk for the group defined as never smokers with prevalent disease. Among all underweight BMI categories, age-standardized death rates were highest in men and women who smoked and had prevalent disease, and rates were lowest in healthy never smokers.

Relative risks were higher for overweight and obese compared to the upper end of normal weight (BMI 22.5–24.9 kg/m²) among the healthy never smokers compared to those who smoked and/or had prevalent disease (Tables 2 and 3). In this group of never smokers without prevalent disease, among both men and women, the RR’s for overweight Blacks appear to be similar in magnitude to those for Whites whereas at the highest levels of BMI, the RR’s for Blacks appear to be marginally lower compared to those for Whites. For example, among healthy never smokers, the multivariable-adjusted RR for White women with BMI > 40 kg/m² was 2.45 (95% CI 2.25–2.67) whereas it was 1.78
Table 2. Rates and relative risks of death from any cause among men according to BMI, smoking, prevalent disease status and race, CPS-II 1982-2010.

| Group                                      | BMI          | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥40.0 |
|--------------------------------------------|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| White smoker with prevalent disease       | No. of deaths| 1,038     | 1,538     | 7,427     | 15,612    | 18,706    | 9,273     | 5,647     | 828       | 80    |
|                                            | Age-stand. rate | 8258      | 6759      | 5045      | 4048      | 3843      | 4095      | 4662      | 5357      | 6326  |
|                                            | Multivariate RR | 1.66      | 1.47      | 1.18      | 1.00      | 0.96      | 1.02      | 1.15      | 1.28      | 1.52  |
|                                            | 95% CI        | (1.15–1.76) | (1.39–1.55) | (1.15–1.22) | -         | (0.94–0.98) | (1.00–1.05) | (1.12–1.19) | (1.19–1.37) | (1.22–1.89) |
|                                            | Stand. rate difference | 4210     | 2711      | 997       | 0         | 206       | 46        | 614       | 1308      | 2278  |
| White smoker without prevalent disease    | No. of deaths | 500       | 1,217     | 8,898     | 21,389    | 26,250    | 12,248    | 6,710     | 833       | 92    |
|                                            | Age-stand. rate | 3633      | 3682      | 2977      | 2547      | 2522      | 2702      | 3125      | 3760      | 4954  |
|                                            | Multivariate RR | 1.29      | 1.34      | 1.15      | 1.00      | 0.99      | 1.06      | 1.24      | 1.50      | 2.00  |
|                                            | 95% CI        | (1.18–1.42) | (1.27–1.42) | (1.12–1.18) | -         | (0.97–1.01) | (1.04–1.08) | (1.21–1.28) | (1.40–1.60) | (1.63–2.45) |
|                                            | Stand. rate difference | 1086     | 1134      | 429       | 0         | 26        | 154       | 578       | 1213      | 2407  |
| White never smoker with prevalent disease | No. of deaths | 211       | 415       | 2,415     | 5,271     | 6,383     | 3,160     | 1,947     | 302       | 19    |
|                                            | Age-stand. rate | 4767      | 4726      | 3131      | 2657      | 2741      | 2925      | 3590      | 4323      | 3218  |
|                                            | Multivariate RR | 1.34      | 1.38      | 1.11      | 1.00      | 1.06      | 1.14      | 1.42      | 1.75      | 1.18  |
|                                            | 95% CI        | (1.16–1.54) | (1.25–1.53) | (1.05–1.16) | -         | (1.02–1.10) | (1.09–1.19) | (1.35–1.50) | (1.55–1.97) | (0.75–1.86) |
|                                            | Stand. rate difference | 2110     | 2068      | 473       | 0         | 134       | 267       | 893       | 1666      | 470   |
| White never smoker without prevalent disease | No. of deaths | 191       | 439       | 3,662     | 10,086    | 12,213    | 5,772     | 3,311     | 452       | 53    |
|                                            | Age-stand. rate | 2358      | 2015      | 1799      | 1691      | 1776      | 2038      | 2364      | 3145      | 3965  |
|                                            | Multivariate RR | 1.25      | 1.06      | 1.01      | 1.00      | 1.07      | 1.28      | 1.50      | 2.17      | 2.52  |
|                                            | 95% CI        | (1.08–1.45) | (0.96–1.17) | (0.97–1.05) | -         | (1.04–1.10) | (1.24–1.32) | (1.44–1.56) | (1.98–2.39) | (1.92–3.30) |
|                                            | Stand. rate difference | 667      | 324       | 68        | 0         | 50        | 85        | 347       | 673       | 1454  |

BMI

| Group                                      | BMI          | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥35.0 |
|--------------------------------------------|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| Black smoker with prevalent disease       | No. of deaths| 39        | 67        | 261       | 439       | 627       | 369       | 284       | 57        |       |
|                                            | Age-stand. rate | 9346      | 6692      | 5451      | 4901      | 4667      | 4715      | 4985      | 5184      |       |
|                                            | Multivariate RR | 1.35      | 1.36      | 1.10      | 1.00      | 0.97      | 0.95      | 1.06      | 1.14      |       |
|                                            | 95% CI        | (0.95–1.93) | (1.04–1.77) | (0.94–1.29) | -         | (0.86–1.11) | (0.83–1.10) | (0.90–1.23) | (0.86–1.52) |       |
|                                            | Stand. rate difference | 4445     | 1792      | 551       | 0         | -234      | -185      | 85        | 284       |       |
| Black smoker without prevalent disease    | No. of deaths | 39        | 67        | 261       | 439       | 627       | 369       | 284       | 57        |       |
|                                            | Age-stand. rate | 9346      | 6692      | 5451      | 4901      | 4667      | 4715      | 4985      | 5184      |       |
|                                            | Multivariate RR | 1.35      | 1.36      | 1.10      | 1.00      | 0.97      | 0.95      | 1.06      | 1.14      |       |
|                                            | 95% CI        | (0.95–1.93) | (1.04–1.77) | (0.94–1.29) | -         | (0.86–1.11) | (0.83–1.10) | (0.90–1.23) | (0.86–1.52) |       |
|                                            | Stand. rate difference | 4445     | 1792      | 551       | 0         | -234      | -185      | 85        | 284       |       |
| BMI       | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | ≥35.0 |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| No. of deaths | 24        | 78        | 390       | 732       | 954       | 494       | 299       | 58    |
| Age-stand. rate | 3090      | 4520      | 3652      | 3061      | 3190      | 3075      | 3386      | 3189  |
| Multivariate RR | 0.99      | 1.57      | 1.14      | 1.00      | 1.03      | 1.00      | 1.11      | 1.15  |
| 95% CI (0.66–1.50) | (1.24–2.00) | (1.00–1.29) | -         | (0.94–1.14) | (0.89–1.12) | (0.97–1.28) | (0.88–1.51) |
| Stand. rate difference | 30        | 1459      | 591       | 0         | 129       | 14        | 325       | 129   |

**Black never smoker with prevalent disease**

| No. of deaths | 15        | 18        | 65        | 158       | 201       | 166       | 159       | 24    |
|Age-stand. rate | 7523      | 7485      | 4548      | 3693      | 2989      | 3278      | 3801      | 3498  |
| Multivariate RR | 1.76      | 2.00      | 1.36      | 1.00      | 0.76      | 0.88      | 1.00      | 0.91  |
| 95% CI (0.98–3.17) | (1.17–3.45) | (0.99–1.86) | -         | (0.60–0.95) | (0.70–1.12) | (0.79–1.27) | (0.57–1.46) |
| Stand. rate difference | 3830      | 3793      | 855       | 0         | -904      | -115      | 108       | -195  |

**Black never smoker without prevalent disease**

| No. of deaths | 4         | 17        | 102       | 282       | 418       | 290       | 235       | 42    |
|Age-stand. rate | 1398      | 3448      | 2069      | 1919      | 2150      | 2307      | 2735      | 3316  |
| Multivariate RR | 0.78      | 1.60      | 1.05      | 1.00      | 1.18      | 1.24      | 1.53      | 1.97  |
| 95% CI (0.29–2.13) | (0.94–2.72) | (0.83–1.34) | -         | (1.01–1.38) | (1.05–1.47) | (1.28–1.83) | (1.41–2.76) |
| Stand. rate difference | -520      | 1529      | 151       | 0         | 232       | 388       | 817       | 1398  |

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*a* One or more of the following conditions was reported at study entry: prevalent cancer (except non-melanoma skin), heart disease, stroke, respiratory disease (chronic bronchitis, emphysema, asthma), currently sick, or weight loss of ≥10 lbs. in past year.

*b* Rate per 100,000 standardized to the age-distribution of the CPS-II men.

*c* Cox proportional hazards model, adjusted for age, race, education, physical activity, alcohol use, marital status, aspirin use, fat consumption, and vegetable consumption.

*d* None of the conditions listed in footnote(a) were reported.

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Table 3. Relative risks of death from any cause among women according to BMI, smoking, prevalent disease status and race, CPS-II 1982–2010.

| Group                                      | BMI          | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥40.0 |
|--------------------------------------------|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| White smoker with prevalent disease        | No. of deaths | 2,045     | 3,499     | 10,721    | 11,099    | 7,963     | 3,966     | 3,966     | 1,135     | 404   |
|                                            | Age-stand. rate | 4525      | 3071      | 2630      | 2565      | 2742      | 2972      | 3154      | 3496      | 4102  |
|                                            | Multivariate RR | 1.69      | 1.21      | 1.05      | 1.00      | 1.04      | 1.12      | 1.20      | 1.32      | 1.58  |
|                                            | 95% CI        | (1.61–1.77) | (1.16–1.26) | (1.03–1.08) | -         | (1.01–1.08) | (1.08–1.17) | (1.16–1.25) | (1.24–1.40) | (1.43–1.74) |
|                                            | Stand. rate difference | 1960      | 506       | 65        | 0         | 176       | 407       | 588       | 931       | 1536  |
| White smoker without prevalent disease     | No. of deaths | 2,167     | 5,161     | 16,863    | 15,393    | 9,624     | 4,126     | 3,509     | 884       | 271   |
|                                            | Age-stand. rate | 2751      | 1941      | 1735      | 1761      | 1905      | 2040      | 2259      | 2640      | 3232  |
|                                            | Multivariate RR | 1.56      | 1.14      | 1.02      | 1.00      | 1.06      | 1.13      | 1.26      | 1.53      | 1.92  |
|                                            | 95% CI        | (1.49–1.63) | (1.10–1.18) | (1.00–1.05) | -         | (1.03–1.08) | (1.09–1.17) | (1.21–1.31) | (1.43–1.64) | (1.70–2.16) |
|                                            | Stand. rate difference | 990       | 180       | -26       | 0         | 144       | 279       | 498       | 879       | 1472  |
| White never smoker with prevalent disease  | No. of deaths | 1,783     | 3,104     | 10,748    | 13,546    | 11,453    | 6,440     | 6,568     | 1,798      | 565   |
|                                            | Age-stand. rate | 3402      | 2366      | 2044      | 2047      | 2165      | 2351      | 2521      | 2901      | 3361  |
|                                            | Multivariate RR | 1.44      | 1.10      | 1.01      | 1.00      | 1.05      | 1.13      | 1.25      | 1.51      | 1.82  |
|                                            | 95% CI        | (1.37–1.52) | (1.06–1.14) | (0.98–1.03) | -         | (1.02–1.07) | (1.10–1.17) | (1.21–1.28) | (1.44–1.59) | (1.67–1.98) |
|                                            | Stand. rate difference | 1355      | 319       | -3        | 0         | 118       | 304       | 475       | 854       | 1315  |
| White never smoker without prevalent disease| No. of deaths | 1,686     | 4,507     | 17,687    | 21,424    | 17,141    | 8,341     | 7,990     | 1,719      | 533   |
|                                            | Age-stand. rate | 1765      | 1392      | 1280      | 1363      | 1514      | 1654      | 1849      | 2178      | 2798  |
|                                            | Multivariate RR | 1.20      | 1.04      | 0.97      | 1.00      | 1.09      | 1.21      | 1.39      | 1.79      | 2.45  |
|                                            | 95% CI        | (1.14–1.26) | (1.01–1.07) | (0.95–0.99) | -         | (1.07–1.11) | (1.18–1.24) | (1.35–1.43) | (1.70–1.88) | (2.25–2.67) |
|                                            | Stand. rate difference | 402       | 29        | -83       | 0         | 151       | 291       | 486       | 815       | 1486  |
| **BMI**                                    | **No. of deaths** | **60**     | **70**     | **268**    | **386**    | **445**    | **287**    | **377**    | **131**     | **73**  |
|                                            | **Age-stand. rate** | **3919**   | **3831**   | **3203**   | **2791**   | **2783**   | **3209**   | **3392**   | **3359**    | **4473** |
|                                            | **Multivariate RR** | **1.40**   | **1.52**   | **1.17**   | **1.00**   | **0.99**   | **1.10**   | **1.12**   | **1.14**    | **1.43** |
|                                            | **95% CI**     | (1.06–1.84) | (1.17–1.98) | (1.00–1.38) | -         | (0.86–1.13) | (0.94–1.29) | (0.97–1.30) | (0.93–1.40) | (1.10–1.86) |
|                                            | **Stand. rate difference** | **1128**   | **1040**   | **412**    | 0         | -8        | 417       | 601       | 568       | 1682  |

**Table 3.** Relative risks of death from any cause among women according to BMI, smoking, prevalent disease status and race, CPS-II 1982–2010.
Table 3. Cont.

| BMI       | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥40.0 |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| No. of deaths | 57       | 109       | 399       | 525       | 558       | 320       | 390       | 109       | 30    |
| Age-stand. rate<sup>b</sup> | 3328    | 2433      | 1975      | 1751      | 2026      | 2064      | 2492      | 2697      | 2630  |
| Multivariate RR<sup>c</sup> | 2.11    | 1.42      | 1.12      | 1.00      | 1.13      | 1.18      | 1.36      | 1.52      | 1.42  |
| 95% CI      | (1.59–2.80) | (1.15–1.76) | (0.98–1.28) | -       | (1.00–1.28) | (1.02–1.36) | (1.19–1.55) | (1.23–1.88) | (0.98–2.07) |
| Stand. rate difference | 1577   | 682       | 224       | 0         | 275       | 313       | 741       | 946       | 878   |

Black never smoker with prevalent disease<sup>a</sup>

| No. of deaths | 45       | 68        | 255       | 431       | 620       | 448       | 688       | 238       | 114   |
| Age-stand. rate<sup>b</sup> | 3908    | 2530      | 2554      | 2255      | 2434      | 2372      | 2510      | 3024      | 3893  |
| Multivariate RR<sup>c</sup> | 1.11    | 1.06      | 1.14      | 1.00      | 1.15      | 1.14      | 1.19      | 1.45      | 2.06  |
| 95% CI      | (0.79–1.55) | (0.81–1.38) | (0.98–1.34) | -       | (1.01–1.30) | (0.99–1.30) | (1.05–1.34) | (1.23–1.70) | (1.67–2.56) |
| Stand. rate difference | 1653   | 275       | 299       | 0         | 179       | 117       | 255       | 769       | 1638  |

Black never smoker without prevalent disease<sup>d</sup>

| No. of deaths | 52       | 86        | 363       | 690       | 874       | 651       | 801       | 220       | 96    |
| Age-stand. rate<sup>b</sup> | 2224    | 1697      | 1418      | 1479      | 1572      | 1854      | 1973      | 2298      | 2566  |
| Multivariate RR<sup>c</sup> | 1.38    | 1.04      | 0.97      | 1.00      | 1.08      | 1.27      | 1.32      | 1.64      | 1.78  |
| 95% CI      | (1.03–1.85) | (0.82–1.30) | (0.85–1.10) | -       | (0.97–1.19) | (1.14–1.42) | (1.19–1.46) | (1.40–1.91) | (1.43–2.21) |
| Stand. rate difference | 744    | 218       | 61        | 0         | 93        | 375       | 494       | 819       | 1087  |

<sup>a</sup> One or more of the following conditions was reported at study entry: prevalent cancer (except non melanoma skin), heart disease, stroke, respiratory disease (chronic bronchitis, emphysema, asthma), currently sick, or weight loss of ≥10 lbs. in past year.

<sup>b</sup> Rate per 100,000 standardized to the age-distribution of the CPS-II women.

<sup>c</sup> Cox proportional hazards model, adjusted for age, race, education, physical activity, alcohol use, marital status, aspirin use, fat consumption, vegetable consumption, and postmenopausal estrogen use.

<sup>d</sup> None of the conditions listed in footnote(a) were reported.

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Table 4. Relative risks of death from any cause according to BMI and age at enrollment among men and women who are never smokers without prevalent disease, CPS-II 1982–2010.

| Group | BMI                  | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥40.0 |
|-------|----------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
|       | MEN                  |           |           |           |           |           |           |           |           |       |
| Age <60 years |                       |           |           |           |           |           |           |           |           |       |
| No. of deaths  |                       | 46        | 91        | 1,001     | 3,093     | 4,376     | 2,506     | 1,760     | 305       | 41    |
| Age-stand. ratea |                       | 1313      | 1070      | 1044      | 1073      | 1222      | 1535      | 2005      | 2907      | 4270  |
| Multivariate RRb |                       | 1.21      | 1.00      | 0.99      | 1.00      | 1.13      | 1.39      | 1.84      | 2.63      | 3.97  |
| 95% CI |                       | (0.90–1.61)| (0.81–1.23)| (0.92–1.06)| -         | (1.08–1.18)| (1.32–1.46)| (1.73–1.95)| (2.33–2.96)| (2.91–5.41)|
| Stand. rate difference |                       | 240       | –3        | –29       | 0         | 149       | 462       | 932       | 1834      | 3198  |
| Age 60–69 years |                       |           |           |           |           |           |           |           |           |       |
| No. of deaths  |                       | 75        | 169       | 1,536     | 4,464     | 5,587     | 2,568     | 1,345     | 142       | 19    |
| Age-stand. ratea |                       | 2400      | 2083      | 1778      | 1780      | 1928      | 2278      | 2471      | 3178      | 4753  |
| Multivariate RRb |                       | 1.51      | 1.17      | 0.99      | 1.00      | 1.08      | 1.29      | 1.40      | 1.82      | 3.15  |
| 95% CI |                       | (1.20–1.89)| (1.01–1.37)| (0.94–1.05)| -         | (1.04–1.12)| (1.23–1.36)| (1.32–1.49)| (1.54–2.16)| (2.01–4.95)|
| Stand. rate difference |                       | 619       | 302       | –3        | 0         | 148       | 498       | 691       | 1398      | 2972  |
| Age ≥70 years |                       |           |           |           |           |           |           |           |           |       |
| No. of deaths  |                       | 74        | 196       | 1,227     | 2,821     | 2,668     | 988       | 441       | 40        |       |
| Age-stand. ratea |                       | 2751      | 2295      | 2349      | 2275      | 2302      | 2400      | 2334      | 2485      |       |
| Multivariate RRb |                       | 1.01      | 1.01      | 1.03      | 1.00      | 1.00      | 1.08      | 1.06      | 1.15      |       |
| 95% CI |                       | (0.80–1.28)| (0.87–1.17)| (0.96–1.10)| -         | (0.94–1.05)| (1.01–1.16)| (0.95–1.17)| (0.84–1.57)|       |
| Stand. rate difference |                       | 475       | 19        | 73        | 0         | 26        | 124       | 58        | 209       |       |
|       | WOMEN                |           |           |           |           |           |           |           |           |       |
| Age <60 years |                       |           |           |           |           |           |           |           |           |       |
| No. of deaths  |                       | 372       | 1,307     | 5,214     | 5,704     | 4,658     | 2,544     | 2,949     | 897       | 346  |
| Age-stand. ratea |                       | 966       | 768       | 740       | 802       | 978       | 1138      | 1378      | 1893      | 2556  |
| Multivariate RRb |                       | 1.18      | 0.96      | 0.93      | 1.00      | 1.19      | 1.37      | 1.66      | 2.28      | 3.31  |
| 95% CI |                       | (1.06–1.31)| (0.91–1.02)| (0.89–0.96)| -         | (1.14–1.24)| (1.31–1.44)| (1.59–1.74)| (2.12–2.44)| (2.97–3.69)|
| Stand. rate difference |                       | 164       | –34       | –63       | 0         | 175       | 336       | 576       | 1091      | 1754  |
| Age 60–69 years |                       |           |           |           |           |           |           |           |           |       |
| No. of deaths  |                       | 571       | 1,681     | 6,931     | 9,001     | 7,665     | 3,934     | 3,699     | 708       | 204  |
| Age-stand. ratea |                       | 1571      | 1416      | 1,297     | 1,353     | 1,479     | 1,659     | 1,850     | 2,090      | 2,455 |
| Multivariate RRb |                       | 1.16      | 1.08      | 0.97      | 1.00      | 1.08      | 1.23      | 1.37      | 1.59      | 1.94  |
for Black women (95% CI 1.43–2.21). However, there was no evidence of statistical interaction by race (interaction $p = 0.23$ for women and $p = 0.20$ for men).

Due to the lack of effect modification by race and the profound modifying effect of smoking and prevalent disease on the association between BMI and mortality, analyses stratified by age and groupd cause of death are presented among never smokers without prevalent disease in both races combined. The magnitude of the association between BMI and total mortality varied substantially by the age at which BMI was reported (Table 4). BMI at ages younger than 70 years was much more strongly associated with risk of death in both men and women than was BMI at older ages. For BMI at ages less than 60 years and 60–69 years, all categories of overweight and obesity were associated with higher risk of mortality. The association between BMI and mortality was greatly attenuated when BMI was reported at age 70 and above; however, in women, associations remained statistically significant for all categories of BMI $>27.4$ kg/m$^2$. Overweight and obesity were associated with all grouped causes of death, but were generally stronger for death from cardiovascular disease and other causes compared to cancer for both men and women (Table 5).

**Discussion**

In this large prospective study of approximately one million Black and White men and women, we were able to address four major unresolved issues in the study of BMI and mortality. Results showed that men and women who were underweight were at higher risk of mortality as were men and women who were overweight and obese compared to normal weight men and women, and that smoking and prevalent disease significantly modified the association between BMI and mortality, such that the strongest associations were among never smokers without prevalent disease for men and women. In healthy never smokers, mortality rates were lowest within the upper end of the normal BMI category (i.e., 22.5–24.9 kg/m$^2$) for all race-sex groups. Although the results of our study showed no statistically significant differences in associations between BMI and mortality by race, overweight and obesity were associated with subsequent mortality among smokers and/or those with prevalent disease in White men, White women and Black women but not in Black men. In addition, weight in late middle age but not older (i.e., 70 years or older) was strongly associated with future mortality.

There is growing evidence that residual confounding by smoking and/or reverse causality by prevalent disease attenuated the association between BMI and risk of mortality. Indeed, studies that included smokers (who tend to have a lower BMI) and individuals with diseases that cause weight loss generally show weaker associations with high BMI levels, and stronger associations with low BMI levels than do studies that exclude these subjects [4,8,25–28]. While controlling for smoking history can reduce its confounding effects, eliminating the residual effects of current smoking is essential for clarifying associations of BMI with mortality, and can only be achieved through exclusion of current smokers. On the other hand, prevalent disease exclusions may be more dependent on the characteristics and age of the study population. Consistent with the largest pooled analysis to date [3], in our study underweight and the lower end of the normal weight range were associated with higher risk of mortality among those who smoked or had prevalent disease.

Numerous studies have reported on the association between BMI and mortality in Caucasians [2–4,8,9,18–21,25–47]. In contrast, few studies have reported on the BMI-mortality relationship among Black men and women [4,7–17], and among
| Group                  | BMI   | 15.0–18.4 | 18.5–19.9 | 20.0–22.4 | 22.5–24.9 | 25.0–27.4 | 27.5–29.9 | 30.0–34.9 | 35.0–39.9 | ≥40.0 |
|-----------------------|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| **MEN**               |       |           |           |           |           |           |           |           |           |       |
| **Cardiovascular disease death** |       |           |           |           |           |           |           |           |           |       |
| No. of deaths         | 72    | 164       | 1,194     | 3,380     | 4,331     | 2,143     | 1,298     | 193       | 22        |       |
| Age-stand. rate       | 864   | 737       | 559       | 613       | 723       | 866       | 1,218     | 1,272     |           |       |
| Multivariate RR       | 1.23  | 1.05      | 0.95      | 1.00      | 1.15      | 1.42      | 1.74      | 2.73      | 2.89      |       |
| 95% CI                | (0.97–1.55) | (0.90–1.23) | (0.89–1.02) | -         | (1.10–1.20) | (1.34–1.50) | (1.63–1.85) | (2.36–3.16) | (1.90–4.41) |       |
| Stand. rate difference| 310   | 183       | 5         | 0         | 59        | 169       | 312       | 664       | 718       |       |
| **Cancer death**      |       |           |           |           |           |           |           |           |           |       |
| No. of deaths         | 32    | 87        | 710       | 2,082     | 2,611     | 1,171     | 696       | 80        |           |       |
| Age-stand. rate       | 390   | 397       | 341       | 348       | 373       | 392       | 454       | 431       |           |       |
| Multivariate RR       | 1.01  | 1.09      | 0.96      | 1.00      | 1.08      | 1.16      | 1.36      | 1.38      |           |       |
| 95% CI                | (0.70–1.44) | (0.88–1.35) | (0.88–1.05) | -         | (1.02–1.15) | (1.08–1.25) | (1.25–1.49) | (1.11–1.73) |           |       |
| Stand. rate difference| 42    | 49        | -6        | 0         | 25        | 44        | 106       | 83        |           |       |
| **All other causes of death** |       |           |           |           |           |           |           |           |           |       |
| No. of deaths         | 67    | 133       | 1,156     | 2,607     | 2,934     | 1,354     | 756       | 123       | 22        |       |
| Age-stand. rate       | 790   | 602       | 541       | 426       | 414       | 458       | 505       | 782       | 1,558     |       |
| Multivariate RR       | 1.57  | 1.15      | 1.21      | 1.00      | 1.00      | 1.15      | 1.29      | 2.21      | 3.66      |       |
| 95% CI                | (1.23–2.01) | (0.96–1.37) | (1.13–1.30) | -         | (0.95–1.06) | (1.08–1.23) | (1.19–1.40) | (1.84–2.65) | (2.40–5.59) |       |
| Stand. rate difference| 364   | 177       | 116       | 0         | −11       | 32        | 80        | 356       | 1,132     |       |
| **WOMEN**             |       |           |           |           |           |           |           |           |           |       |
| **Cardiovascular disease death** |       |           |           |           |           |           |           |           |           |       |
| No. of deaths         | 669   | 1,413     | 5,579     | 7,253     | 6,131     | 3,172     | 3,063     | 685       | 201       |       |
| Age-stand. rate       | 679   | 435       | 398       | 444       | 510       | 583       | 647       | 775       | 903       |       |
| Multivariate RR       | 1.26  | 0.99      | 0.95      | 1.00      | 1.11      | 1.28      | 1.46      | 2.06      | 2.39      |       |
| 95% CI                | (1.16–1.36) | (0.93–1.05) | (0.92–0.98) | -         | (1.07–1.15) | (1.23–1.34) | (1.40–1.52) | (1.90–2.22) | (2.08–2.76) |       |
| Stand. rate difference| 235   | −9        | −46       | 0         | 66        | 139       | 203       | 331       | 459       |       |
| **Cancer death**      |       |           |           |           |           |           |           |           |           |       |
| No. of deaths         | 246   | 864       | 3,316     | 4,158     | 3,321     | 1,696     | 1,690     | 365       | 130       |       |
| Age-stand. rate       | 255   | 252       | 232       | 268       | 299       | 330       | 363       | 395       | 521       |       |
### Table 5.

| BMI     | Multivariate RRb | 95% CI          | Stand. rate difference |
|---------|------------------|-----------------|------------------------|
| 15.0–18.4 | 0.93             | (0.82–1.06)     |                        |
| 18.5–19.9 | 0.97             | (0.90–1.05)     | -                      |
| 20.0–22.4 | 1.00             | (1.04–1.14)     | -                      |
| 22.5–24.9 | 1.08             | (1.23–1.41)     | -                      |
| 25.0–27.4 | 1.08             | (1.13–1.27)     | -                      |
| 27.5–29.9 | 1.13             | (1.33–1.65)     | -                      |
| 30.0–34.9 | 1.33             | (1.25–1.41)     | -                      |
| 35.0–39.9 | 1.48             | (1.25–1.41)     | -                      |

All other causes of death

| No. of deaths | Age-adjusted rate a | Multivariate RRb | 95% CI          | Stand. rate difference |
|---------------|---------------------|------------------|-----------------|------------------------|
| 520           | 1,247               | 1.42             | (1.30–1.56)     | 97 (%)                 |
| 533           | 379                 | 1.21             | (1.09–1.23)     | 89 (%)                 |
| 557           | 279                 | 1.04             | (0.96–1.07)     | 69 (%)                 |
| 627           | 252                 | 1.38             | (1.22–1.55)     | 52 (%)                 |
| 361           | 121                 | 1.69             | (1.32–1.35)     | 111 (%)                |
| 431           | 191                 | 1.69             | (1.32–1.35)     | 111 (%)                |
| 507           | 207                 | 1.69             | (1.32–1.35)     | 111 (%)                |
| 567           | 237                 | 1.86             | (1.58–2.17)     | 147 (%)                |
| 377           | 107                 | 1.86             | (1.58–2.17)     | 147 (%)                |
| 497           | 217                 | 1.86             | (1.58–2.17)     | 147 (%)                |
| 597           | 267                 | 1.86             | (1.58–2.17)     | 147 (%)                |
| 667           | 287                 | 2.03             | (1.76–2.33)     | 164 (%)                |
| 537           | 237                 | 2.03             | (1.76–2.33)     | 164 (%)                |
| 697           | 297                 | 2.03             | (1.76–2.33)     | 164 (%)                |
| 897           | 347                 | 2.03             | (1.76–2.33)     | 164 (%)                |

*Rate per 100,000 standardized to the age-distribution of the CPS-II men/women.

*aRate per 100,000 standardized to the age-distribution of the CPS-II men/women.

In summary, this large nationwide study helps to clarify four major unresolved issues in the study of BMI and mortality by demonstrating that smoking and prevalent disease significantly modify the relationship between BMI and mortality, and that among never smokers without prevalent disease, overweight and obesity are strongly associated with subsequent risk of mortality and the optimal BMI range is 20.0–24.9 kg/m². Additionally, this study demonstrated that among never smokers without prevalent disease, the BMI-mortality relationship is similar in Black and White men and women who weigh overweight (BMI 25.0–29.9 kg/m²) is associated with a modest and obesity (BMI 30.0–39.9 kg/m²) a more...
substantial increased risk of premature death. In the U.S., age-adjusted prevalence estimates of obesity are highest for African Americans (35.7%), followed by Hispanics (23.7%), and non-Hispanic Whites (23.7%) [32]. Given the high prevalence of obesity among all racial-ethnic populations, although disproportionately higher among African Americans, these findings are of considerable clinical and public health relevance.

Acknowledgments

We dedicate this manuscript in memory of Dr. Eugenia “Jeanne” Calle, an outstanding scientist and leader at the American Cancer Society whose work made seminal contributions in the public health understanding of the effects of obesity and mortality in the U.S.

Author Contributions

Conceived and designed the experiments: AVP JSH SMG. Performed the experiments: JSH AVP. Analyzed the data: JSH AVP. Contributed reagents/materials/analysis tools: JSH. Wrote the paper: AVP JSH SMG. Critical review: AVP JSH SMG.

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