MORTALITY RISK IN PERSONS WITH OBESITY: THE ROLE OF CARDIOVASCULAR AND METABOLIC MEDICATION USE

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A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

GRADUTE PROGRAM IN KINESOLOGY AND HEALTH SCIENCE

YORK UNIVERSITY
TORONTO, ONTARIO

July 2024

Abstract

Persons with obesity (PwO) are at an elevated risk of both cardiovascular and metabolic diseases as well as increased mortality risk. The effects of medication use on this relationship has not been investigated and is the focus of the current investigation. This study utilized data from 1999-2018 pooled cycles of the US NHANES. In general, death rates were higher in those taking medications. PwO aged 65 years and older who were taking cardiovascular or metabolic medications had a lower risk of mortality than those of a normal weight over 65 years of age and older without each respective medication. Conversely, PwO aged 30 to 64 years old showed a higher mortality risk than those of a normal weight, with greater risk of mortality observed in those using medication than those without.

Acknowledgements

I would like to give a special thanks to my supervisor Dr. Ardern for the opportunity to join the lab and conduct research under his guidance. I would also like to thank Dr. Kuk for her support throughout this project. Lastly, I would like to express my gratitude to my lab members, friends, and family for their support.

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1.0 BACKGROUND

1.1 Obesity

Obesity is a complex chronic disease that is defined as abnormal or excessive fat accumulation that presents a risk to overall health (1). While only recently classified as a disease, obesity is persistent and often relapsing. Similar to other chronic diseases such as type 2 diabetes or cardiovascular disease, obesity can last one year or longer, limit daily living, and require ongoing medical attention (2).The primary mechanism of action causing obesity is excess energy that the body is unable to use and subsequently stores as fat (3). The resulting accumulation of additional fat mass can have systemic consequences, including stress on anatomical structures, dysfunctional metabolic and physiological processes, and impairments of psychological well-being (4). These consequences often manifest as increased likelihood of other chronic disease – including type 2 diabetes, cardiovascular diseases, cancers, poor mental health, and more which subsequently increases risk of all-cause death (5).

1.2 Prevalence of Obesity

Over the past four decades the prevalence of obesity has increased substantially, to the point where the World Health Organization now reports that 1 in 8 people in the world (~890 million) are living with obesity, and a further 1.61 billion are overweight (6). Worldwide, 43% of the population is currently living with overweight or obesity as compared to 25% in 1990. Similarly, in 1999-2000, 30.5% U.S adults were persons living with obesity, and as of 2017-2020 that number has increased to 41.9% (7). This increase has been particularly pronounced in the segment of the population with Class III obesity (>40.0 BMI), with increases from 4.7% to 9.2%

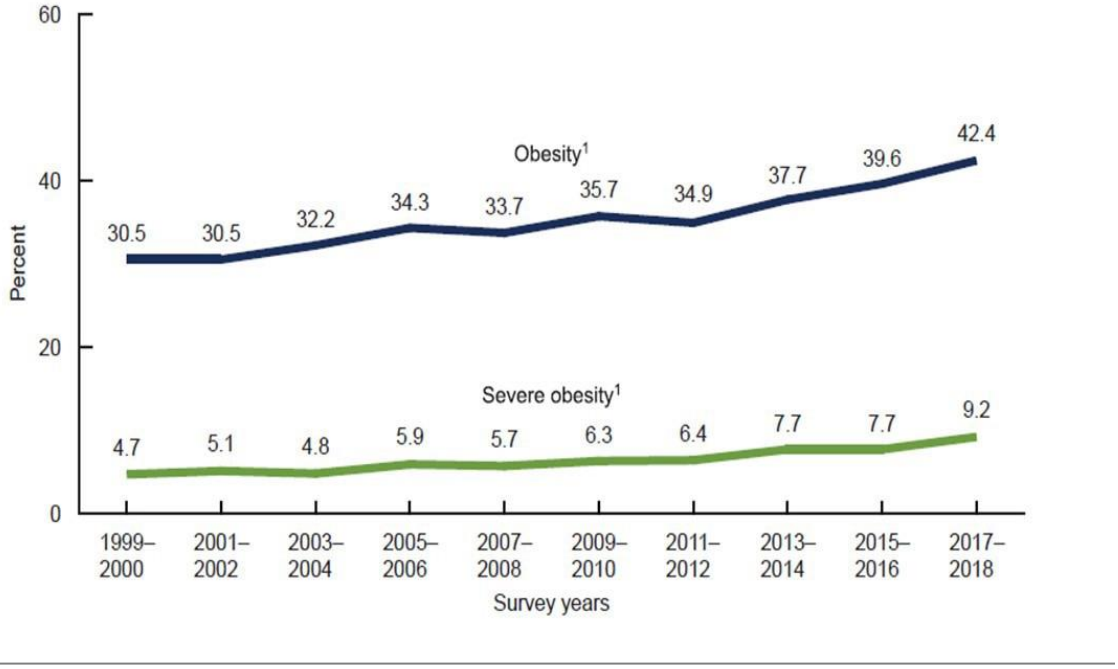

Figure 1. Prevalence of obesity and severe (>40.0 BMI) obesity in the United States from 1999-2000 to 2017-2018 (8).

in the same time frame (7) (**Figure 1**). Zachary et al.(9) predicts the prevalence will only increase, projecting that by the year 2030 nearly half of U.S. adults will have obesity and nearly 1 in 4 adults will be living with severe obesity.

1.3 Predictors of Obesity

PwO are often the source of bias, stigma, and discrimination (10), and this can be attributed in part due to an over-simplification in thinking that obesity is primarily caused by a lack of physical activity and poor diet (11). With the classification of obesity as a disease, it is now understood that other health conditions, genetics, socioeconomic status, medications, and environmental factors, to name a few, are also involved (12). Mahmoud et al. (13) not only identified a number of the genetic differences that can contribute to a person's weight, but also highlighted a number of syndromes in which a person is more susceptible to weight gain. Kaur et al. (14) has identified 27 syndromes that have been mapped to a chromosomal region, and 19 which have been fully genetically elucidated. Further expanding on genetic influence, Wardle et al. (15) examined 5 092 preadolescent twin pairs, and found that BMI was highly heritable (77%). Moreover, socioeconomic status can also play a role in obesity risk. Previous literature assessing the effects of neighbourhood differences on central adiposity found that people living in neighborhoods with higher levels of poverty and unfair treatment were at an increased risk of central adiposity (16). Furthermore, Ogden et al. (17) found distinct sex differences in how income affects obesity prevalence: as woman's income decreased, their obesity rates increased, a pattern not seen in men (**Figure 2**). The complexity of obesity is further highlighted in a recent systematic review (18), aimed at understanding the intersection of socioeconomic status and ethnicity/race with obesity. While many studies have hypothesized that racial differences in obesity are a result of socioeconomic differences, results of the meta-analysis found that these differences were largely explained by variation in body image and physical environments (18). Collectively, these studies highlight that obesity is not simply a result of eating too much and

moving too little, but rather a complex network of interacting factors that can contribute to life-long changes in weight status and health.

1.4 Obesity Measurement

In population-based studies, the most common measure of obesity is the Body Mass Index (BMI), which is a measure of a person's weight in kilograms divided by their height in meters squared. Common classifications of BMI include categories of "Underweight", "Normal weight", "Overweight", and "Obesity", the latter of which can be further divided into different classes (Class I: 30.0-34.9kg/m^2; Class II: 35.0-39.9kg/m^2; Class III: ≥40.0kg/m^2) (19) as seen in **Table 1**. Those who fall into the class of normal weight are thought to be in a healthy weight range, while those in the underweight, overweight, or obesity class are thought to be in an unhealthy weight range. In general terms, a high BMI can indicate a high level of body fat, while a low BMI can indicate a low level of body fat; however, BMI fails to differentiate "types" of mass, and is unable to capture variation by age, sex, and ethnicity (20). Despite these flaws, BMI can provide useful population-level information as it is inexpensive and easy to use, but should not be used as a diagnostic tool by itself (21). Ideally, obesity should be diagnosed using a number of comprehensive measures that include BMI, waist circumference, physical examinations, laboratory measures, as well as diagnostic imaging when necessary (22).

Table 1. BMI categories (19).

Weight Status	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5 -24.9
Overweight	25.0-29.9
Obesity Class I	30.0-34.9
Obesity Class II	35.0-39.9
Obesity Class III	≥40.0

BMI: Body Mass Index.

1.5 Obesity-Related Comorbidities

A number of chronic conditions can arise as a result of obesity (23). These conditions include cardiovascular disease, hypertension, type 2 diabetes, stroke, certain cancers, and gall bladder disease to name a few (24). These conditions are often co-occurring with obesity, where the Centre for Disease Control has found that nearly 90% of people with type 2 diabetes have overweight or obesity, and an estimated 65-78% of individuals with hypertension also suffer from obesity (25,26). Similarly, for individuals of an average height, every one unit increase in BMI (approximately 7 pounds) increases the risk for ischemic stroke by 5% (27–29). These findings suggest that obesity is often seen in a comorbid state, where individuals with obesity often also suffer from other comorbidities, which necessitates more complex clinical management (30,31).

Compared to those of normal weight, the risk of cardiovascular disease among PwO is higher, and increases in a positive gradient with BMI (32). Whereas the relationship with heart failure and obesity is very strong (32), to a lesser extent, there are a range of diseases of the heart and blood vessels that can also be impacted by obesity (**Table 2**). Excess body weight has been heavily linked to the onset of these disorders, both directly and indirectly. For example, Koliaki et al. (33) found that a 10 kg increase in weight is associated with a 12% increased risk of coronary artery disease. Likewise, it has been observed that PwO develop heart failure approximately 10 years earlier than individuals with a normal body weight (34), and 75% of individuals with heart failure before the age of 40 were persons with obesity (35). Being overweight is one of the top 10 risk factors for developing a stroke, as displayed by a 22% increased risk of cerebrovascular events in persons with overweight, and a 64% increased risk in PwO (36).

Cardiovascular disease is the leading cause of death globally, and in 2019, it accounted for 32% of global deaths (37). Of these, 85% of cardiovascular deaths were attributable to heart attacks and stroke (37). While there isn't one mechanisms of action that causes cardiovascular disease, atherosclerosis-characterized as a build-up of plaque in the arteries is a major risk factor (38), and contributes to a narrowing of blood vessels and more pulsative flow (38). Key risk factors for atherosclerosis include high blood pressure, diabetes, and high cholesterol (39), all of which co-occur with, and are exacerbated by obesity. While the co-occurrence of risk factors (obesity in addition to another risk factor) has been shown to cause even greater risk for cardiovascular disease (40,41) this association may be mediated by the other comorbidities that arise from obesity acting as an endocrine disorder, and not obesity itself (42,43). Indeed, Bogers et al. (44) conducted a meta-analysis and found that 45% of the increased risk of coronary heart disease from overweight was a result of high blood pressure and cholesterol levels. Moreover, Ndumele et al. (45) found that traditional mediators (blood pressure, diabetes, triglycerides, and more) were able to explain the association between higher BMI with coronary heart disease and stroke, but not heart failure. Conversely, Hubert et al. (40) found that after 26 years of follow-up, participants in the Framingham Heart Study who had overweight and obesity were not at an increased risk of coronary disease or congestive heart failure solely as a result of co-existing risk factors. Regardless of the mechanism of action, obesity has shown to play a significant role in the development of cardiovascular disease.

In addition to cardiovascular disease, obesity has also been linked to other metabolic conditions. These conditions include type 2 diabetes, high cholesterol, and high blood pressure, and are described in **Table 3**. In 1980, there were 108 million global chases of type 2 diabetes, and by 2014, this number had risen to 422 million (46). Klein et al. (47) posited that the

worldwide increase in prevalence of type 2 diabetes is likely a direct result of the increase in prevalence of obesity. Similarly, the global cases of high blood pressure has risen from 594 million in 1975 to 1.13 billion in 2015 (48). In the U.S, approximately 1 in 10 adults have type 2 diabetes (9%) (49,50), 1 in 3 have high cholesterol (35%) (51), and 50% have undiagnosed high blood pressure (52). Each of these conditions can lead to the onset of other health conditions: type 2 diabetes can lead to the onset of cardiovascular disease, diabetic kidney disease, high blood pressure, and high cholesterol (50,53); high cholesterol is major cause of disease burden as a risk factor for ischemic heart and stroke (54), and; uncontrolled high blood pressure is a major cause of both large (stroke, heart failure, ischemic heart disease, and kidney disease/failure) and small vessel diseases, including vision loss (55). While each of these conditions can occur independent of obesity, it is far more likely they arise as a result of it. Obesity is a known risk factor for poor cholesterol health; it increases LDL (bad cholesterol), which contributes to plaque build-up, decreases HDL (good cholesterol), which carries away LDL from arteries preventing plaque build-up, and increases triglycerides the most commonly found type of fat in the body which, when combined with high LDL levels further contributes to plaque buildup (56,57). The negative impacts obesity has on cholesterol levels can be further understood through the impacts of weight loss (58). Research has shown a dose-response relationship between *weight loss* and levels of LDL, HDL, and triglycerides. For example, a weight loss of 10kg has shown to reduce cholesterol levels by 5% (60). Weight loss in the range of 5-8kg has shown even greater results lowering LDL by 5mg/dl and increasing HDL by 2-3mg/dl (59,61–63). These improvements in cholesterol profile highlight the determinantal effect that excess weight can have on cholesterol levels. Further highlighting the risk of excess fat, Vasan et al. (64) found that an increase of weight by only 5% resulted in a 20-30% increase in hypertension.

The primary treatment option for all of the above conditions includes a combinations of lifestyle modification and progressive pharmacotherapy, as defined within the Clinical Practice Guidelines for each condition (65–68). For example, those with hypertension are recommended to start anti-hypertension medication, while those with high cholesterol are recommended to take lipid lowering medications (statins) (66,67). While each of these comorbidities have separate pharmacotherapy options, they hold the same underlying principles of treating comorbidities that may have caused or worsened the impact of the disease; therefore, each of these guidelines also acknowledge the need for obesity treatment and management as a key element of further chronic disease management (65–68). Of note, the Clinical Practice Guidelines for Type 2 Diabetes recommends a targeted weight loss of 5-10% for PwO through the use of lifestyle modification and medication use (68).

1.6 Mortality

Globally an estimated 2.8 million deaths each year occur as a result of obesity (69), in large part because of the elevated risk of death among individuals with metabolic and cardiovascular conditions as described above. For example, high BMI accounted for 4 million deaths worldwide in 2015, with more than two-thirds of these deaths attributed to cardiovascular disease (70). Moreover, the *Global BMI Mortality Collaboration* (71) confirmed that that those with overweight and obesity were at a higher risk of all-cause mortality compared to those of a normal weight. While this may be intuitive, some evidence suggests that PwO may accrue survival benefits from their additional weight - particularly better survival outcomes after cardiovascular events - a phenomenon known as the “obesity paradox” (72). This protective effect on survival has been observed for both all-cause and cardiovascular mortality among PwO with

comorbidities. While multiple theories have been proposed to explain this finding (73–76), Tan et al. (77) suggest one of primary interest -- that obesity had protective effects against percutaneous coronary intervention (PCI) as a result of medication use. Similarly, Lancefield et al. (78) have also reported that PwO had a higher rate of guideline-based medication use in patients with PCI. An alternate, but supporting explanation is that PwO may be diagnosed earlier with diabetes, leading to earlier initiation of treatment (using medication); in turn, this earlier and more aggressive treatment would cause fewer diabetic and cardiovascular events, resulting in improved survival probability (79). Despite these theories, few studies have assessed the impact of medication use for comorbidities on the relationship between obesity and mortality.

1.7 Rationale

This study will explore the association between comorbidity specific medication usage and mortality across a range of BMI. Metabolic and cardiovascular conditions are common amongst PwO, and a primary form of treatment of these comorbidities is the use of medication. It is understood that these comorbidities increase the risk of mortality, and that medication treating these comorbidities are effective. Therefore, using NHANES 1999-2018, this study will examine the impact of metabolic and cardiovascular medication usage on mortality.

1.8 Objectives

This study aims to assess the impacts of cardiovascular and metabolic medication usage on mortality across the spectrum of weight status on U.S. adults.

Aim 1: To assess if medication use amongst PwO is positively related to survival compared to

those not on medication.

Aim 2: To assess the impact of medication usage on mortality amongst persons with obesity compared to those who are normal weight.

1.8 Tables and Figures

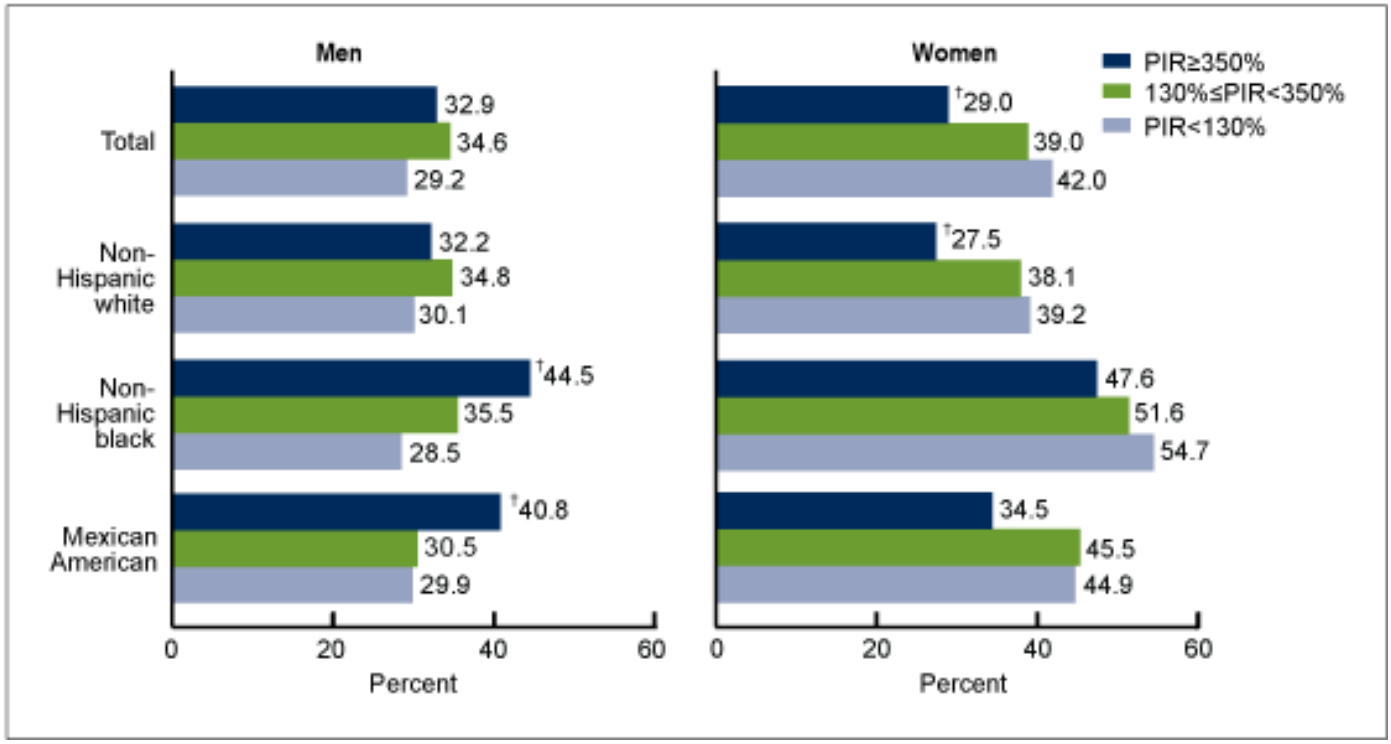

Figure 2. Prevalence of obesity by poverty income ratio, sex, and race and ethnicity in the United States from 2005-2008 (17).

Table 2. Definitions of cardiovascular disease and related conditions.

Disease/Health Condition	Definition
Cardiovascular Disease	General term for a group of disorders affecting the heart or blood vessels.(37)
Coronary Heart Disease	Arteries surrounding the heart are impeded in their ability to deliver oxygen rich blood.(80)
Congestive Heart Failure	Any functional or structural impairment of ventricular filling and or ejection of blood to the rest of the body.(81)
Stroke	Characterized by a change in blood flow through the brain.(82) • Ischemic Stroke: Result of a blood clot or narrowing of blood vessels resulting in reduced blood flow to the brain. • Hemorrhagic Stroke: Result of a burst blood vessel causing blood to leak into or around the brain.
Angina	Characterized as pain or discomfort as a result of reduced oxygen rich blood supply to the heart.(83)
Myocardial Infraction (Heart Attack)	When damage or death of parts of the heart occurs as a result of ischemia.(84) • Ischemia: A condition where certain part of the body is receiving reduced or restricted blood flow and therefore reduced oxygen rich blood.
Congenital Heart Defect	A birth defect affecting the heart and or its surrounding vessels.(85)

Table 3. Definitions of metabolic conditions.

Disease/Health Condition	Definition
Type II Diabetes	A chronic disease where insulin resistance takes place resulting in high blood sugar (glucose) levels.(49)
Hyperlipidemia (High Cholesterol)	Elevated levels of total cholesterol (equal to or greater than 200 mg/dl)(86) • Elevated low density lipoprotein (LDL) cholesterol >130mg/dl (67,87)
Hypertension (High Blood Pressure)	Characterized by the force in which blood pushes against the walls of blood vessels (88). A blood pressure of 120mmHg/80mmHg is defined as hypertensive.(89)

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2.0 MANUSCRIPT

2.1 Abstract

Introduction

Persons with obesity (PwO) are at an elevated risk of both cardiovascular and metabolic diseases as well as increased mortality risk. To date, the effects of medication use on this relationship has not been investigated, and is the focus of the current investigation.

Methods

This study utilized data from 1999-2018 pooled cycles of the US NHANES (analytic sample; n=37,837, 20y+). Measured weight and height (calculated BMI; normal weight, overweight, obesity), and medication use were captured at baseline, with follow-up until Dec. 31st, 2019 for all-cause mortality.

Results

There were 6,741 deaths over an average 9 years of follow-up. In general, death rates were higher in those taking medications. In adjusted models, PwO aged 65 years who were taking cardiovascular (HR = 0.78; 95% CI: 0.71-0.86) or metabolic (HR = 0.83; 95% CI: 0.72-0.97) medications had a lower risk of mortality than those of a normal weight over 65 years of age without each respective medication. Conversely, PwO aged 30 to 64 years old showed a higher mortality risk than those of a normal weight, with greater risk of mortality observed in those using medication than those without.

Discussion

Consistent with previous literature, PwO ages 65 y+ are at similar or lower mortality risk than individuals with normal weight, regardless of medication status. Future research should explore these relationships with a focus on medication adherence and weight status in longitudinal analyses.

2.2 Introduction

Obesity is a complex chronic and persistent disease that, as of 2018, affected nearly 2 in 5 U.S. adults (1). Among the many health effects of excess weight, comorbidities such as cardiovascular disease, hypertension, and diabetes are among the most common (2). Irrespective of other health risk factors, the risk of type 2 diabetes increases linearly with an increase in body mass index (BMI) (3,4), and persons with obesity (PwO) are at a 28% increased risk of heart disease compared to those who are normal weight (5). Comorbidities, such as cardiovascular disease, are in turn a leading cause of death globally and the combined presences of obesity and obesity-related comorbidities are associated with an increase in mortality risk observed across populations (6).

Current guidelines for the treatment and management of obesity advocate for the use of medication in conjunction with lifestyle modification, for weight loss (7). While effective for some, interventions focused on physical activity and diet may not be sufficient, particularly for class II or III obesity, where interventions such as bariatric surgery are recommended (8,9)**.** Nonetheless, medication has been shown to be effective in the treatment of obesity through weight loss; however, due to side effects, early generation medications are not a viable long-term option; this lack of longer-term adherence to medication in turn results in weight regain over time (10). With the rapidly changing landscape of GLP-1 drugs and longer-term studies, the addition of new medications to the market may contribute to weight loss with reduced side effects, resulting in long term use and sustained weight loss (11).

While a range of obesity treatments have the potential to improve the health of people with obesity-related comorbidities, the optimal treatment will be individual, and may involve the use of medications specifically targeting each medical condition, rather than weight loss alone

(12,13). Indeed, the primary action of diabetes medications is to lower blood sugar (13), whereas medications for cardiovascular disease may target a reduction in blood clot formation, lower blood pressure, or slow heart rate. This method of treatment yields beneficial results, as demonstrated by Parikh et al. (14) who observed an increased effectiveness of angiotensin receptor blocker use in PwO versus those with normal weight in order to lower blood pressure. Despite the increased effectiveness of medication use, few if any studies have evaluated how the use of these medications may influence mortality in PwO. Therefore, the aim of this study is to assess the joint effect of BMI with cardiovascular and metabolic medication use on mortality risk in the U.S. population.

2.3 Methods

2.3.1 Study population

This study was conducted using data from 1999-2018 pooled cycles of the National Health and Nutrition Examination Survey (NHANES; n=55,081 age 20y+). NHANES is a nationally-representative cross-sectional survey of the U.S. population which provides data from both interviews and physical examination. The interview portion involves the collection of demographic, behavioral, and medical information, whereas the examination component involves the collection of physiological data through standardized tests by trained personnel. Individuals with missing data and those under the age of 30 were excluded, as shown in **Figure 1**. The analytical sample for this study was comprised of 37,837 United States adults aged 30 years and older.

2.3.2 Outcome

The main study outcome was all-cause mortality, which included both known and unknown causes of death. Information on all-cause death was collected via data linkage of several National Center for Health Statistics (NCHS) population surveys with death certificate records obtained through the National Death Index (15). Restricted linked mortality files were then probability matched by the NCHS Research Data Center to maintain confidentiality (15), made accessible for linkage with the NHANES public use datasets [available at: https://www.cdc.gov/nchs/nhanes/index.htm (16)]. Follow-up for mortality was available until Dec. 31st, 2019

2.3.3 Exposures

The primary exposure of this study was the use of cardiovascular or metabolic medications (yes/no), which is assessed in NHANES via questionnaire. To ascertain medication usage, participants were asked if they have taken medications *in the past 30 days* which required a prescription. If "yes", participants were prompted to show the medication container to the interviewer for all products they use. Interviewers subsequently recorded the medication names

of all medications except prescription dietary supplements. Medication names were then converted to a standard generic drug name, which are associated with a unique drug code from Multum's Lexicon Drug Database (17). Via Multum, drug ingredients were captured, and organized according to therapeutic category ID. All therapeutic category IDs corresponding with "CARDIOVASCULAR AGENTS" were categorized as "Cardiovascular medications", and "METABOLIC AGENTS" were categorized as "Metabolic medications". Individuals who did not meet our classification of cardiovascular medications were categorized as "no cardiovascular medication", while those who did not meet our classification of metabolic medications were classified as "no metabolic medication".

The second exposure in this study was measured Body Mass Index (BMI: kg/m^2). This study used objectively measured BMI; participants had their height and weight collected at the NHANES Mobile Examination Center by a trained health technician. BMI was categorized as: "normal weight" (18.5-24.9 kg/m^2), "overweight" (25.0-29.9 kg/m^2), and "obesity" (30.0 kg/m^2 and above). BMI and medication groups were then cross-classified into six separate categories ["Normal weight / no medication"; "normal weight / medication"; "overweight / no medication"; "overweight / medication"; "obesity / no medication", and; "obesity / medication"] for analysis of their joint effects.

2.3.4 Comorbidity

In this study, cardiovascular (cardiovascular disease, stroke, angina, myocardial infraction, congenital heart disease), or metabolic (diabetes, high cholesterol, high blood pressure) comorbidity status of participants was determined by doctor diagnosis via the question *"Have you (the participant) ever been told by a doctor or health professional that you have...(comorbidity)?"*.

2.3.5 Covariates

Covariate were assessed via questionnaires and included: sex, age, ethnicity, education, health insurance, smoking status, and family income. Sex was self-reported as male or female. Age was self-reported at time of screening and dichotomized into younger (30-64 y) and older (65 y+) groups, as individuals aged 65 years and older are at a greater mortality risk, but also display increased medication usage (18). Ethnicity was classified by asking participants to identify their reported race and Hispanic origin information; closed option categories for ethnicity included: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race Including Multi-Racial. Educational attainment was assessed by the question: *"What is the highest grade or level of school you have completed, or the highest degree received?"*. Education was then dichotomized as high school or less and post-secondary experience or higher. Health insurance status (yes/no) was captured by asking participants *"Are you covered by health insurance or some other kind of health care plan?"* and categorized as those with vs without health insurance. For smoking, participants were classified as a current / former smoker if they responded "yes" to either of the following two questions: i) *"Do you now smoke cigarettes?"*, or; ii) *"Have you smoked at least 100 cigarettes in your life?"*. Epidemiology studies largely capture smoking status as those who have smoke 100 or more cigarettes. Given recent literature questioning the accuracy of this cutoff, this study used "currently smoking" to bolster the accuracy of the smoking status group (19). Finally, family income was assessed via family poverty-to-income ratio (PIR). This ratio is calculated in NHANES through the division of family income by the poverty guidelines specific to every survey year and geographic location. Family PIR was dichotomized as "low" (<1.3) or "adequate" (1.3 or above), consistent with the eligibility criterion for the federal Supplemental Nutrition Assistance Program (20).

2.3.6 Exclusion

Adults aged 20-29y were excluded from this study due to the higher relative health and low

prevalence of chronic conditions, as the comorbidities assessed in this study typically arise around the age of 45 years and older (13,21,22). Individuals 30-39 years of age remained in the study to account for those who may have early onset of respective comorbidities, but further inclusion of those aged 20-29 would unnecessarily skew the data in the less than 64 years of age cohort. Individuals who were underweight were also excluded as the focus of our study was to understand the risk that arose from elevated weight status (overweight and obesity).

2.3.7 Statistical Analysis

Characteristics of the sample were reported as frequencies and percent (sex, age, ethnicity, education, family income, smoking status, health insurance) and compared across mortality and medication-by-BMI categories by chi-squared analysis. Kaplan Meier curves were used to assess survival probability across medication-by-BMI strata. Unadjusted and adjusted (sex, age, ethnicity, education, health insurance, smoking status, and family income) Cox proportional hazard regressions were then used to assess mortality risk in the cross-classified BMI and medication groups. Adjusted analyses, stratified by i) age (30-64 y, 65y+); ii) age and sex (30-64y M/F, 65y+ M/F), and; iii) age and comorbidity status, were then performed to assess their associations with mortality risk across the cross-classified BMI and medication usage groups separately for the cardiovascular and metabolic disease cohorts. Results for males and females were combined for the comorbidity stratified analysis, as sample size did not permit further stratification by sex when examining the effect of age. To address the weaknesses that arise with the use of BMI as an anthropometric measure, a sensitivity analysis was conducted where the above analyses were repeated using waist circumference as a substitute for BMI, using the waist circumference cutoffs of "normal weight" (M: ≥90cm, F: ≥80cm), "overweight" (M: ≥100cm, F:≥90cm), and "obesity" (M: ≥110cm, F: ≥105cm) (23). Like results were obtained when using waist circumference as a substitute for BMI. Statistical analysis was conducted using statistical

analysis system (SAS v .9.4, Cary, NC). All analyses were weighted using SAS survey procedures to ensure national representativeness of the data. Statistical significance was set an alpha of 0.05.

2.4 Results

Tables 1 and 2 display characteristics of the sample by BMI groups and cardiovascular and metabolic medication status, respectively. Overall, the majority of the sample report no cardiovascular or metabolic medication use, are below the age of 65 years, are non-Hispanic white, and have health insurance. Aside from being older, both the cardiovascular and metabolic medication groups largely exhibit the same demographic distributions as their "no medication" counterparts. As expected, a greater prevalence of mortality was seen in both cardiovascular and metabolic medication (compared to "no medication") groups.

Figure 2 displays the survival probability of the cardiovascular (Panel A) and metabolic (Panel B) cohorts in each BMI-by-medication group. Log-rank tests revealed differences across strata in both cardiovascular (log rank=585.23, P<0.001) and metabolic cohorts (619.07, <0.001), where similar survival probability profiles were observed. Individuals coded by BMI as normal weight, overweight, or obesity and on medication displayed a lower survival probability than those who were normal weight and not on medication (reference, p<0.01).

Risk of mortality (hazard ratio (HR), 95% CI) by BMI and medication usage group are presented in **Table 3**. In unadjusted analyses of both cardiovascular and metabolic cohorts, those who reported cardiovascular or metabolic medication use had a similar increase in risk of all-cause death across all BMI categories. When adjusted for covariates, these results largely persisted for the metabolic, but not cardiovascular cohort, wherein the overweight BMI group had a *lower* risk of mortality compared to the normal weight / no medication group.

Figure 3 displays the all-cause mortality risk across BMI and cardiovascular (A) or metabolic (B) medication usage, stratified by age. Regardless of medication status or disease, older adults (65y+) with overweight (No Med HR=0.78-0.79; Med 0.73-0.77) and obesity (No

med= 0.78; Med = 0.75-0.83) had a lower mortality risk compared to those of the same age, a normal weight status, and no medication use. By contrast, younger adults (30-64y) taking either metabolic or cardiovascular medication were at an elevated risk of mortality across all BMI groups (NW: Med=2.21-2.34, No Med=1.59-3.08; OV: 1.59-1.82, 1.35-2.47; OB: 1.98-3.09, 1.50-2.63), relative of those with normal weight not on respective medications.

2.5 Discussion

This study contributes new insights to the existing literature by assessing the association between medication usage with mortality in PwO. Overall, those using cardiovascular or metabolic medication usage did not have a lower mortality risk for persons with overweight, while higher mortality risk was seen in persons with normal weight taking medications in both cohorts, and in PwO taking metabolic medications. Age stratified analyses revealed that regardless of medication status, adults 65 years and older with overweight or obesity were at a reduced mortality risk compared to normal weight, whereas adults aged 30 to 64 years old on cardiovascular or metabolic medication displayed elevated mortality across all BMI categories.

The link between obesity and mortality has been widely studied in individuals with cardiovascular disease or metabolic conditions, with mixed results; some studies indicate reduced mortality risk in PwO (24–27), while others report increased mortality risk (28–31). The current study builds on previous work by assessing medication usage and stratifying results by age (to account for its role as an effect modifier). Although mortality risk was higher in PwO aged 30 to 64 years old, mortality risk was lower in PwO aged 65 years and older. These findings suggest that mortality risk in PwO is heavily influenced by age. Similarly, Kuk and Ardern (32) found age to have a strong influence on the relationship between obesity and mortality. Although their study did not assess medication usage, they found the adverse effects of obesity on mortality risk to be apparent only in adults younger than 65 years old. The reasons for these findings remain unclear, considering these results account for factors such as smoking, insurance, and medication use. Previous works have also shown increased mortality in older individuals who are underweight (33–35), further highlighting the protective effects of weight in older individuals. Susceptibility to comorbid conditions become more apparent with age, and

having additional weight may be beneficial, as this additional mass may prevent or delay older adults from reaching a state of frailty, an independent risk factor for all-cause death (36,37). However, the protective effects of obesity in older adults are largely limited to class I obesity, as studies have found that those with class III obesity have a higher risk of mortality relative to those of a normal weight and other classes of obesity (38–42).

Dorner and Rieder (43) have also assessed this paradox and raised concerns that many existing studies have failed to compare unhealthy individuals with healthy individuals of the same age. Our study directly addresses this issue by assigning referent groups to consist of individuals within the normal weight group and the same age strata who did not report use of cardiovascular or metabolic medication. Findings from the current study provide further evidence that the use of existing BMI categories may not be a useful tool for the assessment of higher mortality risk in older adults.

This work highlights the importance of treating obesity as a disease, rather than merely focusing on its comorbidities. Clinical practice guidelines have long supported the use of anti-obesity medications as a way to treat not only obesity but help manage the comorbidities that arise from it (44,45). Notable trials, such as SUSTAIN 6 (46) or LOOK AHEAD (47) have demonstrated that obesity treatment, specifically weight loss, not only lowers the risk factors associated with obesity, but also decreases mortality risk in adults (48–50). As shown in this study, obesity is a significant risk factor for mortality, as PwO aged 30 to 64 years old were at a higher risk of mortality, even with medication usage. This is surprising, however, as medications such as low-intensity statins lower LDL levels by <30%, and blood pressure medications reduce systolic and diastolic pressure by an average of 9/5 mmHg (51,52). This finding further highlights that the use of medications in the management of cardiometabolic conditions may not

be sufficient to mitigate the increased mortality risk from obesity and its related comorbidities. Indeed, this work provides evidence both in support of, and varying from, existing clinical recommendations. Of note, this study found that persons with overweight and obesity had lower mortality risk regardless of medication status in persons aged 65 years and older. These findings may suggest that for some older individuals, managing comorbidities with medication might be sufficient, and that additional obesity treatment may not provide significant benefits for mortality risk in this particular group. While these finding do need to be interpreted conservatively as a result of their cross-sectional nature, they also highlight a gap within the literature. Specifically, weight loss can improve health (53), yet lifestyle modifications and anti-obesity medications yielding this loss in weight are often short term, conveying little effect on mortality (54–56). With the advancement of obesity management – including the approval of multiple GLP-1 agonist drugs by the U.S. Food and Drug Administration (57) - it is important to identify which groups will benefit most from these treatments and those for whom the weight loss may not be necessary, so that treatment plans for obesity can be enacted to improve longer-term health outcomes.

2.5.1 Strength and Limitations

This study is distinguished by several key strengths. Through the use of NHANES data this study leverages a large nationally representative cohort of the U.S population spanning from 1999-2018. This dataset also allowed for the examination of mortality follow-up over 20-years, which provides a time frame for this specific type of study that to the best of our knowledge has yet to be examined. Building on previous studies, we accounted for key social and behavioral confounders, including health insurance, income, and smoking status. Lastly, this study uses objectively assessed weight and height measures for BMI, which greatly helps reduce information bias and self-report bias. Aside from these strengths, several limitations also warrant

mention. First, due to the cross-sectional nature of the NHANES data, the *incidence* of disease, or changes in baseline behaviors, relative to the incidence of obesity, cannot be assessed. This is of great importance as Carnethon et al. (36) have reported a *decreased* risk of mortality in PwO when obesity precedes diabetes onset. This finding further highlights the importance of capturing the incidence of disease relative to one another. Second, weight change and duration of obesity cannot be tracked over time. Consistent with other literature (58), we can not exclude the possibility of a survival bias in this study, as the older NHANES cohort may not be representative of those in the younger cohort when they were of at the same age. Lastly, medication adherence could not be assessed in the current study. Even though our analyses adjust for factors such as education, health insurance, and income, which are known to be associated with adherence levels (59), we cannot exclude the possibility of residual confounding. This presents the largest limitation in the study, as previous literature has shown that medication adherence can improve with age (60,61), and may directly influence the results observed in this study.

2.6 Conclusion

Findings from this study show that medication use for the treatment of cardiovascular and metabolic comorbidities in PwO was not associated with a lower mortality risk in those aged 30-64 years old. These findings reinforce the independent effect of obesity treatment, beyond medical management of comorbid (cardiometabolic) conditions in younger and middle-aged adults, while for older adults these independent effects of obesity treatment are not reinforced. Further research is necessary to confirm these findings in longitudinal studies by focusing on temporal incidence of comorbidities, longitudinal medication adherence, and changes in BMI.

2.7 Tables and Figures

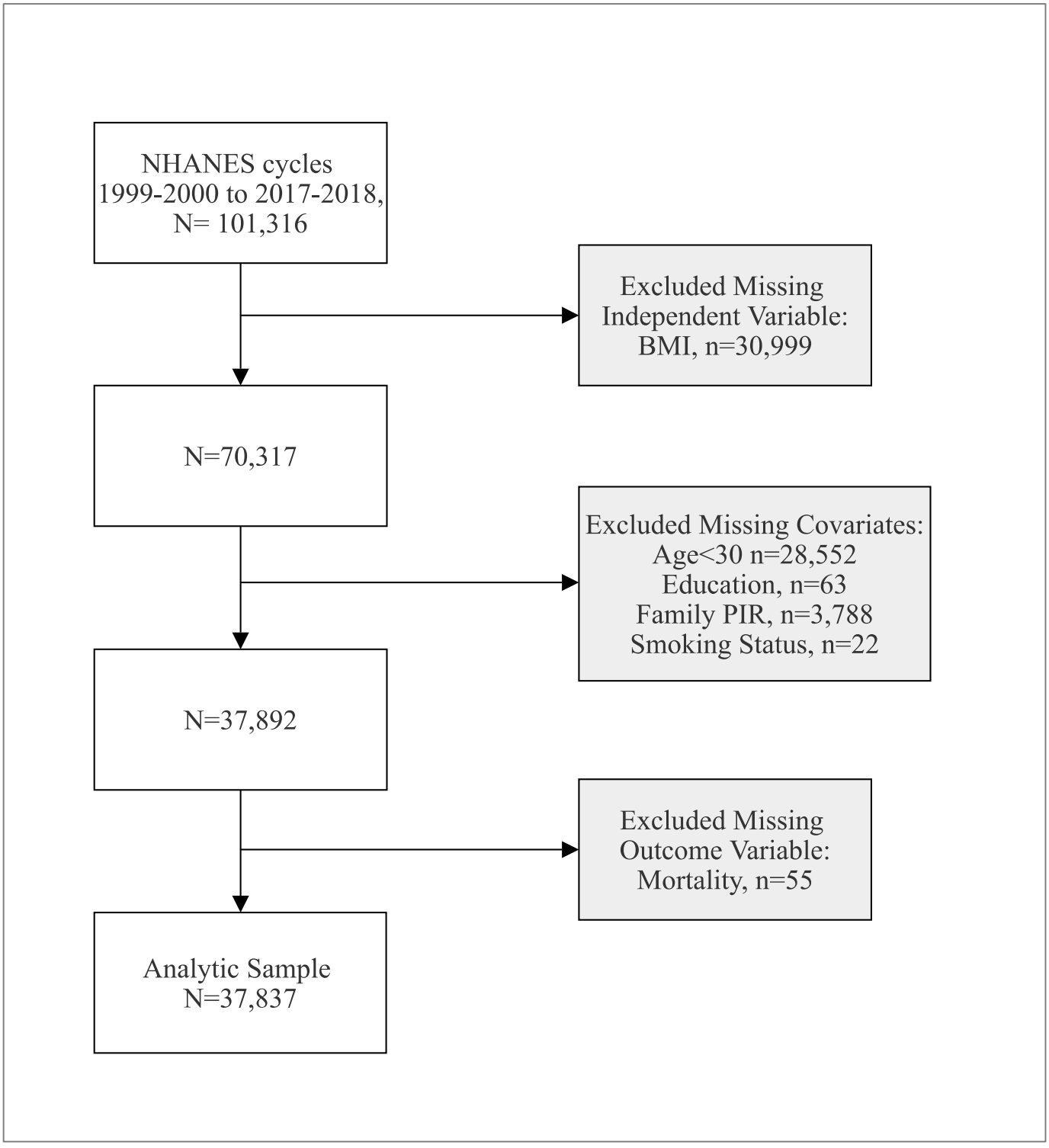

Figure 1. Flow chart displaying the processes in which the final analytic sample was reached.

Table 1 displays the demographic and mortality make-up of the sample across cardiovascular medication status and respective BMI categories.

	No Cardiovascular Medication *n=32 945(89.1%)*			Cardiovascular Medication *n=4 892 (10.9%)*		
	Normal Weight *n=8901*	Overweight *n=11678*	Obesity *n=12366*	Normal Weight *n=964*	Overweight *n=1721*	Obesity *n=2207*
	Weighted % ± SE			Weighted % ± SE		
Age, years						
30 to 64	81.6 ± 0.5	79.3 ± 0.6	82.1 ± 0.5	46.9 ± 2.2	56.2 ± 1.8	68.6 ± 1.2
Sex						
Male	40.2 ± 0.6	55.8 ± 0.6	45.5 ± 0.5	43.9 ± 2.3	58.6 ± 1.4	49.0 ± 1.5
Ethnicity						
Mexican American	4.4 ± 0.3	8.2 ± 0.6	8.7 ± 0.6	2.5 ± 0.4	3.7 ± 0.5	4.9 ± 0.5
Other Hispanic	4.1 ± 0.4	6.1 ± 0.6	5.0 ± 0.4	3.0 ± 0.7	4.2 ± 0.6	4.6 ± 0.6
Non-Hispanic White	73.9 ± 0.9	70.9 ± 1.2	69.2 ± 1.2	73.7 ± 1.9	73.5 ± 1.5	68.3 ± 1.5
Non-Hispanic Black	7.6 ± 0.4	8.7 ± 0.5	12.7 ± 0.7	12.0 ± 1.1	13.3 ± 1.0	19.2 ± 1.2
Other Race/Multiracial	10.0 ± 0.5	6.2 ± 0.4	4.5 ± 0.3	8.8 ± 1.1	5.3 ± 0.7	3.0 ± 0.4
Education						
Low	36.5 ± 1.0	40.7 ± 0.9	42.9 ± 0.7	47.1 ± 2.4^{NS}	43.8 ± 1.8^{NS}	44.2 ± 1.3^{NS}
Health Insurance						
No	15.9 ± 0.7	15.3 ± 0.5	14.3 ± 0.5	6.6 ± 1.1	7.0 ± 0.8	8.6 ± 0.8
Smoking						
Yes	22.7 ± 0.8	16.3 ± 0.5	15.4 ± 0.5	16.0 ± 1.8	11.3 ± 1.1	8.2 ± 0.7
Family PIR						
Low	17.4 ± 0.7	18.5 ± 0.6	21.4 ± 0.7	20.7 ± 1.7^{NS}	15.3 ± 1.0^{NS}	16.2 ± 0.9 ^{NS}
Mortality Status						
Deceased	12.7 ± 0.5	11.7 ± 0.4	11.6 ± 0.4	30.2 ± 1.9	22.6 ± 1.3	17.5 ± 1.0

Weighted prevalence's are reported for variable columns followed by SE. BMI categories were defined as follows 20-25 kg/m^2 Normal weight, 25-30kg/m^2 Overweight, and ≥30 kg/m^2 Obesity. Significance set at $p<0.05$ was seen in all variables, aside from those denoted with NS signifying no statistical significance. SE: standard error.

Low Education: High School graduate or below; **Low Family PIR**: <1.3 PIR

Table 2 displays the demographic and mortality make-up of the sample across metabolic medication status and respective BMI categories.

	No Metabolic Medication *n=31 869 (86.25%)*			Metabolic Medication *n=5 968 (13.75%)*		
	Normal Weight *n=8754*	Overweight *n=11278*	Obesity *n=11837*	Normal Weight *n=1111*	Overweight *n=2121*	Obesity *n=2736*
	Weighted % ± SE			Weighted % ± SE		
Age, years						
30 to 64	82.2 ± 0.5	80.7 ± 0.6	83.2 ± 0.5	47.8 ± 2.1	51.8 ± 1.6	66.4 ± 1.2
Sex						
Male	40.5 ± 0.7	55.5 ± 0.6	44.9 ± 0.6	40.8 ± 1.9	59.9 ± 1.6	51.2 ± 1.1
Ethnicity						
Mexican American	4.4 ± 0.3	8.0 ± 0.6	8.5 ± 0.6	3.6 ± 0.5	6.1 ± 0.7	6.6 ± 0.7
Other Hispanic	4.0 ± 0.4	5.9 ± 0.5	5.1 ± 0.4	3.3 ± 0.5	5.3 ± 0.7	4.0 ± 0.5
Non-Hispanic White	74.2 ± 0.9	70.9 ± 1.2	68.4 ± 1.2	70.8 ± 2.0	72.9 ± 1.5	72.7 ± 1.4
Non-Hispanic Black	8.0 ± 0.4	9.4 ± 0.5	13.8 ± 0.8	6.9 ± 0.7	8.2 ± 0.7	12.4 ± 0.9
Other Race/Multi Racial	9.4 ± 0.5	5.9 ± 0.4	4.3 ± 0.3	15.3 ± 1.6	7.5 ± 0.9	4.3 ± 0.6
Education						
Low	36.6 ± 1.0	40.9 ± 0.9	42.1 ± 0.7	44.8 ± 2.2^{NS}	41.4 ± 1.8^{NS}	48.1 ± 1.4^{NS}
Health Insurance						
No	16.2 ± 0.7	15.8 ± 0.5	14.9 ± 0.5	5.6 ± 0.9^{NS}	5.2 ± 0.5^{NS}	7.0 ± 0.7^{NS}
Smoking						
Yes	23.0 ± 0.8	16.4 ± 0.5	14.7 ± 0.5	13.9 ± 1.4^{NS}	11.3 ± 1.1^{NS}	13.0 ± 0.8^{NS}
Family PIR						
Low	17.8 ± 0.7	18.5 ± 0.6	21.1 ± 0.6	16.2 ± 1.3	15.7 ± 1.1	18.8 ± 0.9
Mortality Status						
Deceased	12.8 ± 0.5	11.7 ± 0.4	11.0 ± 0.4	26.2 ± 1.7	20.7 ± 1.2	19.1 ± 0.8

Weighted prevalence's are reported for variable columns followed by SE. BMI categories were defined as follows 20-25 kg/m^2 Normal weight, 25-30kg/m^2 Overweight, and ≥30 kg/m^2 Obesity. Significance set at $p<0.05$ was seen in all variables, aside from those denoted with NS signifying no statistical significances. SE: standard error.

Low Education: High School graduate or below; **Low Family PIR**: <1.3 PIR.

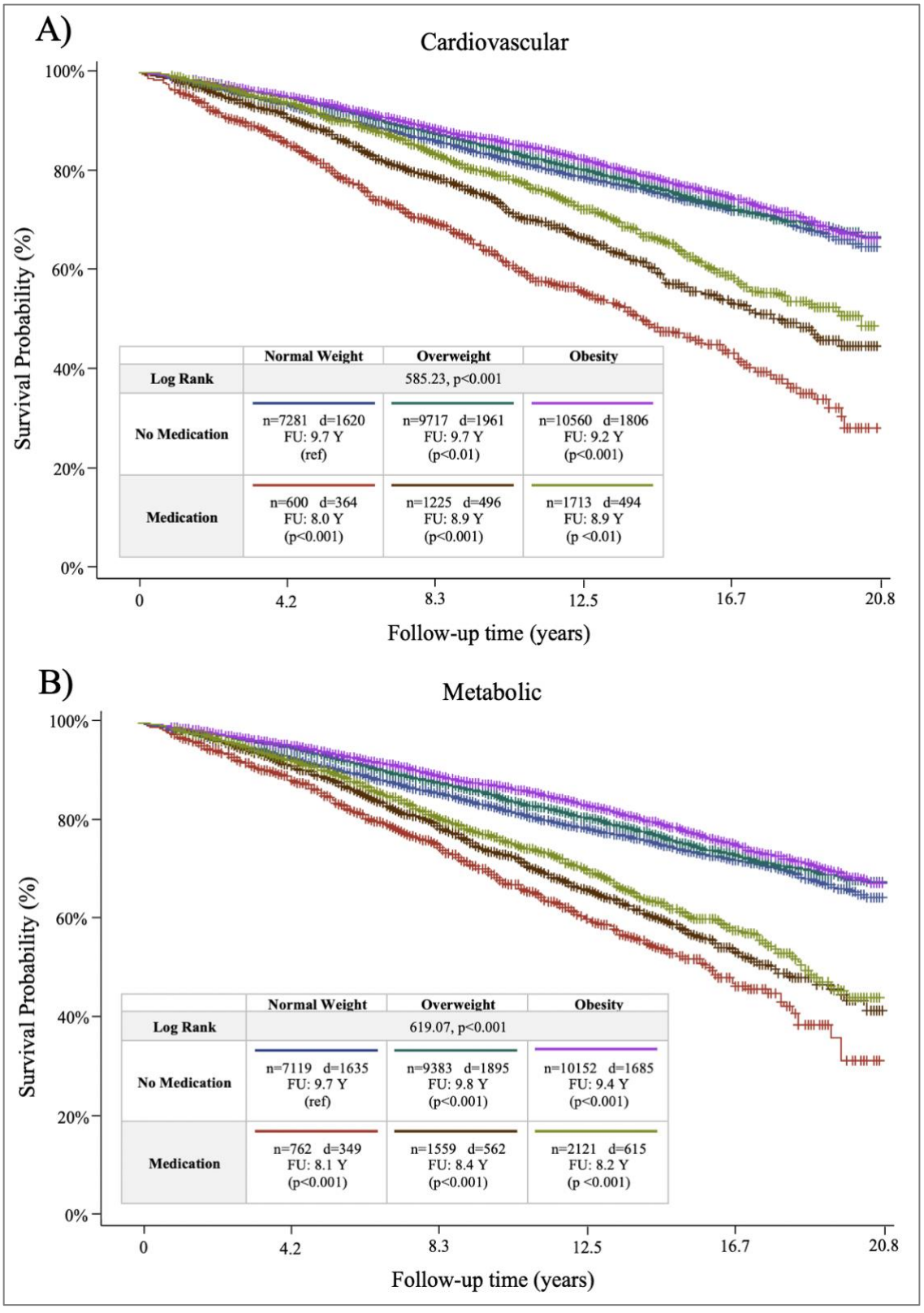

Figure 2. Kaplan-Meier curves illustrating survival probability across BMI categories and medication status. Panel A displays cardiovascular medication status and panel B displays metabolic medication status. Log rank displays the statistical significance (significance set at $p<0.05$) across all groups.

n=unweighted sample size
d=unweighted number of deaths
FU=average follow up time in years.

Table 3: All-cause mortality risk across medication status and BMI categories.

	BMI Category	No Medication		Medication	
		HR	***95% CI***	***HR***	***95% CI***
Cardiovascular	**Unadjusted**				
	Normal weight	*1.00*	*Referent*	3.00*	2.53-3.55
	Overweight	0.97	0.88-1.06	2.03*	1.78-2.33
	Obesity	1.04	0.96-1.13	1.67*	1.44-1.92
	Adjusted				
	Normal weight	*1.00*	*referent*	1.26*	1.08-1.47
	Overweight	0.87*	0.80-0.94	0.97	0.85-1.11
	Obesity	1.01	0.93-1.10	1.12	0.98-1.28
Metabolic:	**Unadjusted**				
	Normal Weight	*1.00*	*referent*	2.54*	2.18-2.96
	Overweight	0.95	0.87-1.04	2.05*	1.78-2.36
	Obesity	0.96	0.88-1.05	2.00*	1.78-2.25
	Adjusted				
	Normal Weight	*1.00*	*referent*	1.18*	1.02-1.35
	Overweight	0.85*	0.78-0.93	0.97	0.85-1.11
	Obesity	0.96	0.88-1.05	1.26*	1.12-1.41

HR= Hazard Ratio
95% CI= 95% Confidence Interval
*denotes significance set at $p<0.05$
Adjusted model accounted for age, sex, ethnicity, education, health insurance status, smoking status, and family poverty income ratio.

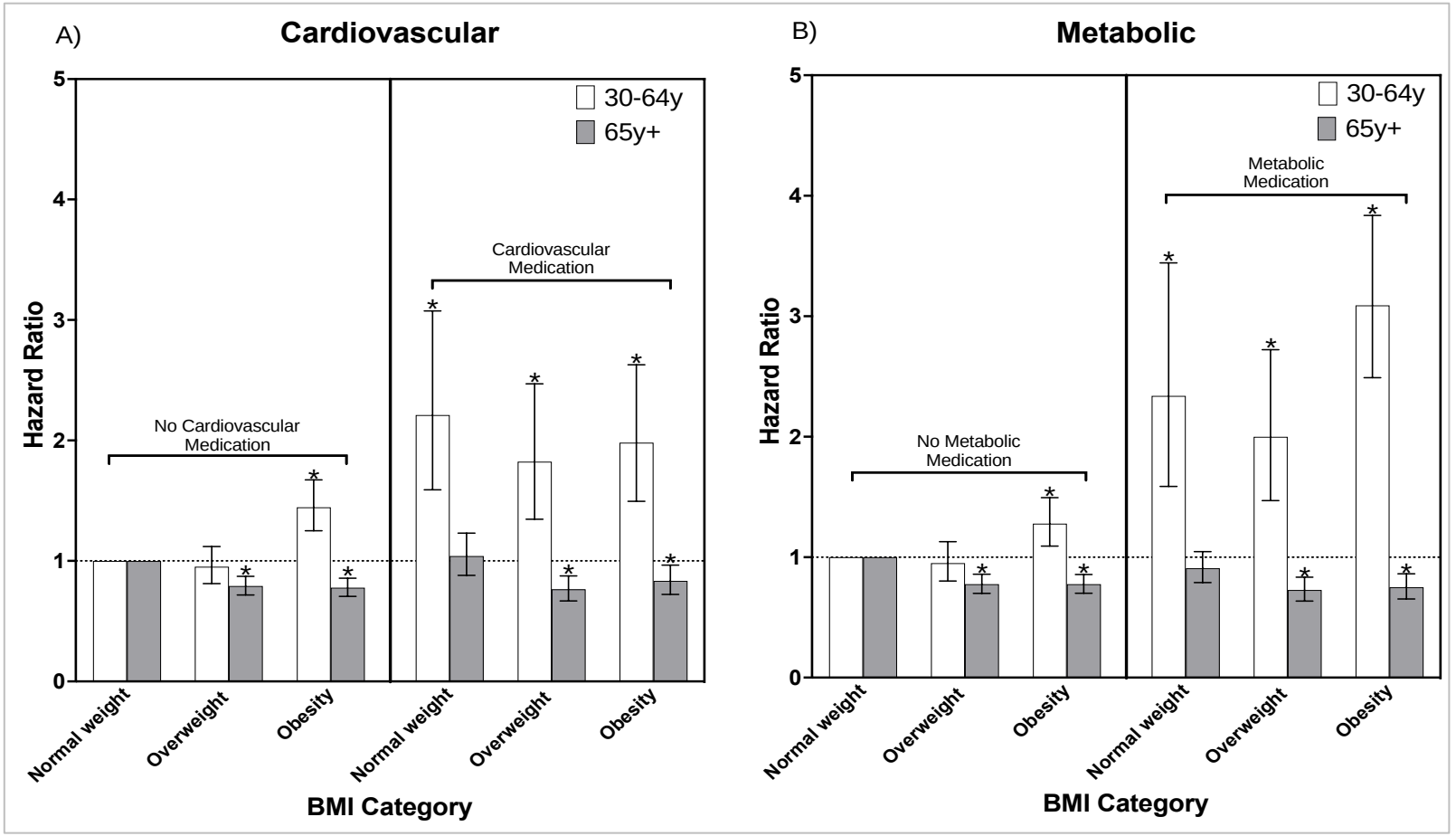

Figure 3. Adjusted cox proportional hazard ratios for all-cause mortality risk by cardiovascular (A) and metabolic (B) medication status, BMI category and age.

White bars denote individuals aged 30-64 years old and grey bars denote individuals aged 65 years and older.
Model adjusted for sex, ethnicity, education, health insurance, smoking status, and family poverty income ratio.
Normal weight no medication bars = referent group.
*statistical significance difference set at $p<0.05$.
Error bars represent 95% confidence intervals of hazard ratio.

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2.8 Appendix A: Stratified Sex and Comorbidity Analysis

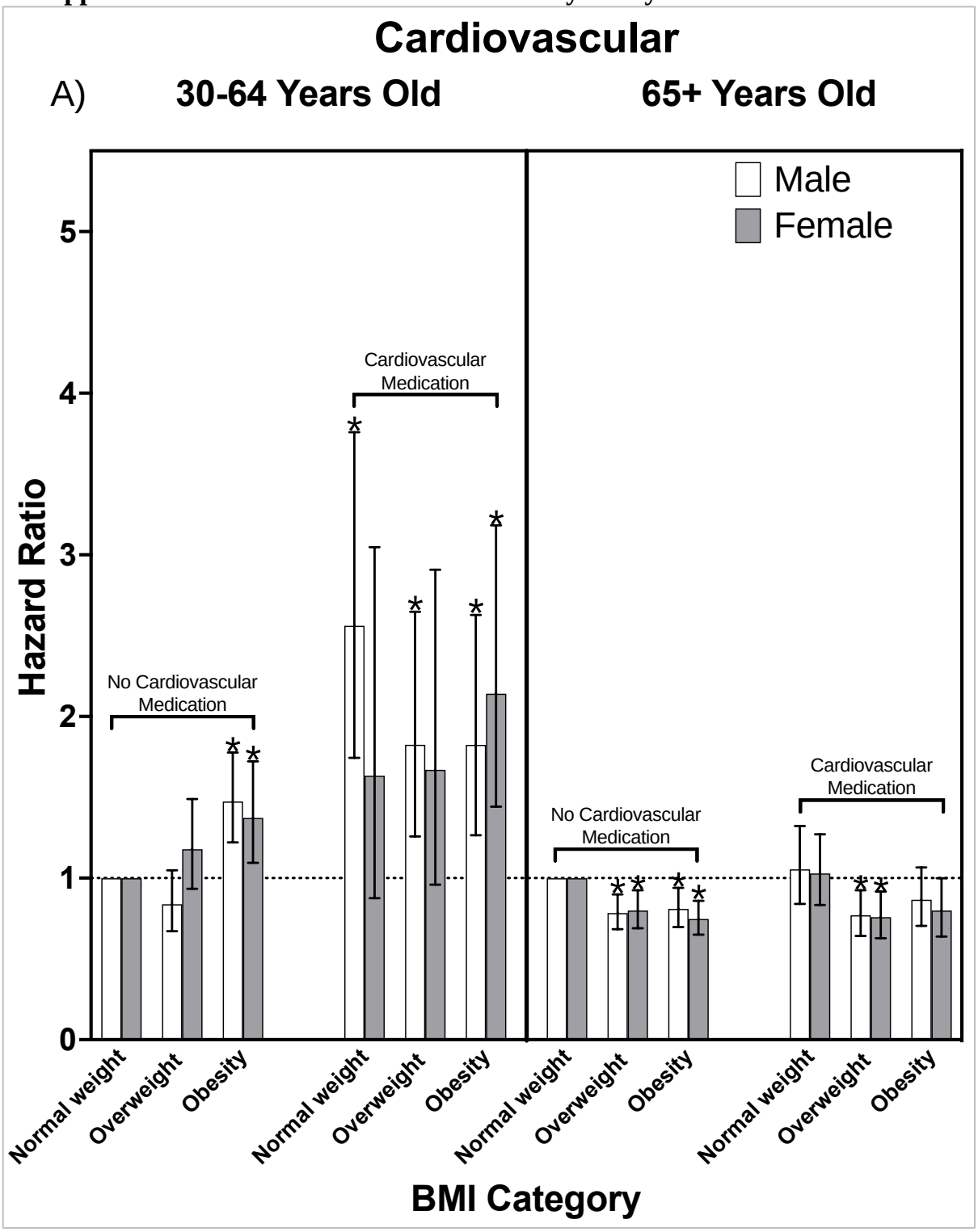

Figure 4A. Displays fully adjusted cox proportional hazard regression assessing mortality risk by cardiovascular medication, with younger (left: 30-64y) and older (right: 65y+) individuals. White bars denote males and grey bars denote females.

Model adjusted for sex, ethnicity, education, health insurance, smoking status, and family poverty income ratio.

Normal weight no medication bars= referent group.

*statistical significance difference set at $p<0.05$.

Error bars represent 95% confidence intervals of hazard ratio.

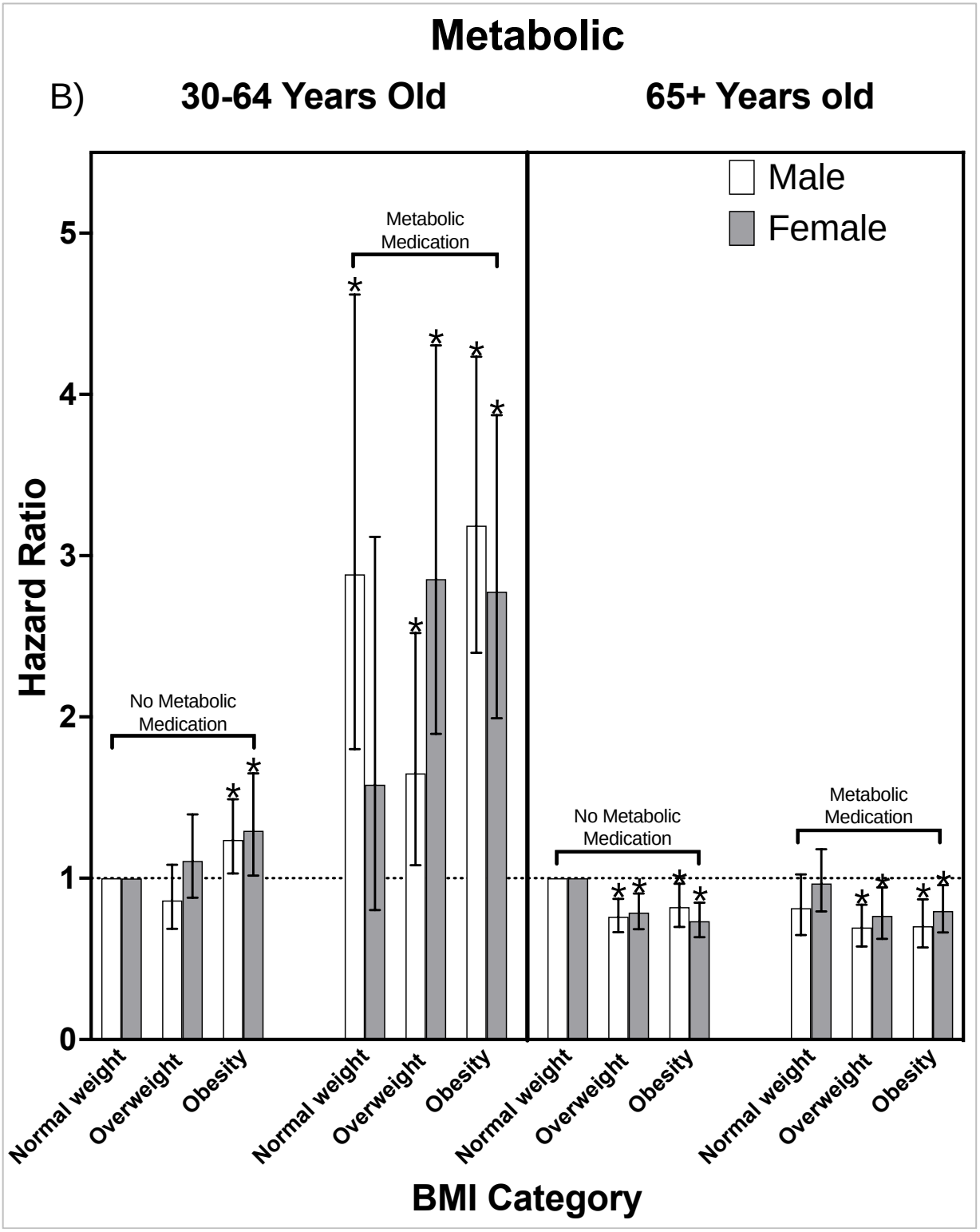

Figure 4B. Displays fully adjusted cox proportional hazard regression assessing mortality risk by metabolic medication status with younger (left: 30-64y) and older (right: 65y+) individuals. White bars denote males and grey bars denote females.

Model adjusted for sex, ethnicity, education, health insurance, smoking status, and family poverty income ratio.

Normal weight no medication bars= referent group.

*statistical significance difference set at $p<0.05$.

Error bars represent 95% confidence intervals of hazard ratio.

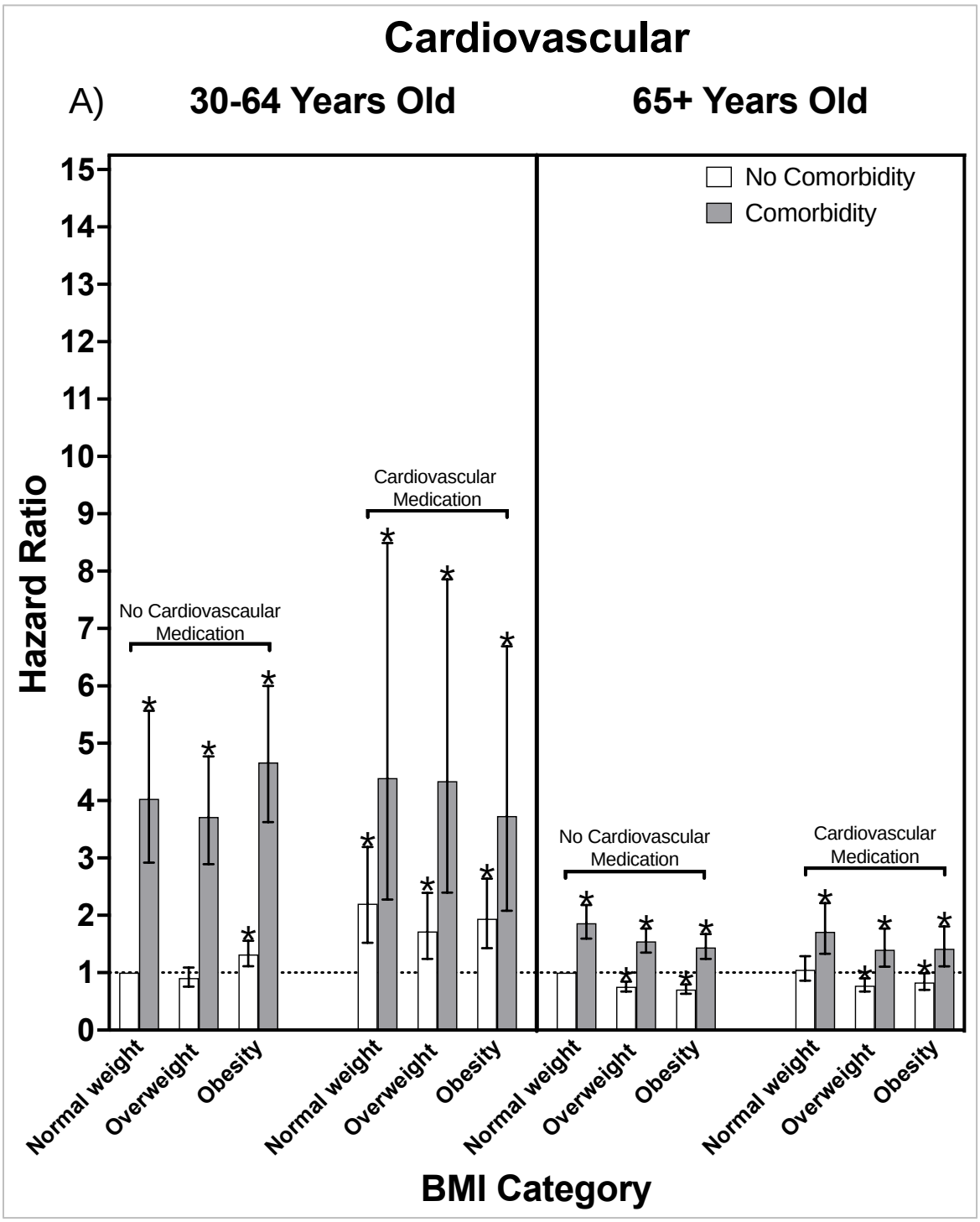

Figure 5A. Fully adjusted cox proportional hazard regression assessing mortality risk by cardiovascular medication status in young (aged 30-64) and older (65 years and older) individuals. White bars denote those without comorbidities and grey bars denote those with comorbidities.

Model adjusted for sex, ethnicity, education, health insurance, smoking status, and family poverty income ratio.
Normal weight no medication bars= referent group.
* statistical significance difference set at $p<0.05$.
Error bars represent 95% confidence intervals of hazard ratio.

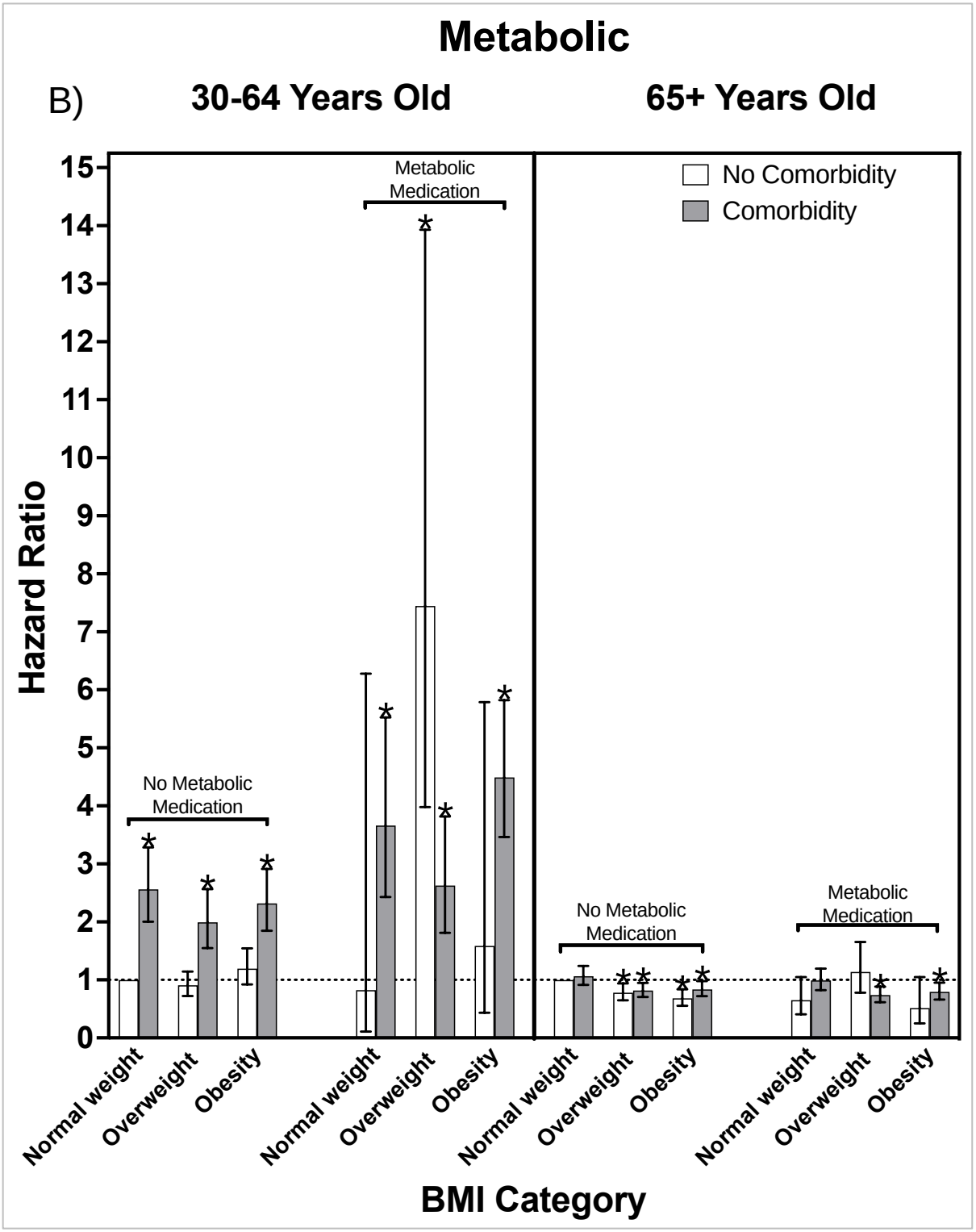

Figure 5B. Fully adjusted cox proportional hazard regression assessing mortality risk by metabolic medication status in young (aged 30-64) and older (65 years and older) individuals. White bars denote those without comorbidities and grey bars denote those with comorbidities.
Model adjusted for sex, ethnicity, education, health insurance, smoking status, and family poverty income ratio.
Normal weight no medication bars= referent group.
* statistical significance difference set at $p<0.05$.
Error bars represent 95% confidence intervals of hazard ratio.

3.0 EXTENDED DISCUSSION

3.1 General Conclusion

This study aimed to ascertain the impact of cardiovascular and metabolic medication use on mortality across different weight strata. Results from this study revealed that regardless of medication usage, persons with overweight and obesity above the age of 65 were at a lower risk of mortality. Moreover, persons aged 30-64 years old on respective medications displayed higher risk of mortality compared to their same age, normal weight counterparts who did not use medication.

A key strength in this study is the multitude of covariates that were accounted for - including health insurance, ethnicity, and education – which are known to be associated with obesity and mortality. However, a number of study limitations are also worth mentioning, most notably, the lack of adjustment for physical activity. Indeed, physical activity is recommended for the prevention and management of obesity-related health risk in Canadian and U.S. clinical practice guidelines (1,2). Despite this, physical activity was not accounted for in this study. In the NHANES dataset, physical activity is captured through two methods: questionnaire and accelerometery, each of which has flaws. Questionnaire data is subject to recall and information bias, whereas the use of accelerometry would introduce cut-point bias and healthy responder bias (3-5). In an effort to preserve sample size, it was ultimately decided to exclude "any" measure of physical activity, due to the expected reduction in sample size within the analytic sample, and the differential response patterns for physical activity that have been observed with age (6–8). Future works should aim to account for objectively assessed physical activity, but also sedentary time. Ideally this would be done in two ways: i) using physical activity guideline recommendations, and; ii) using clinical practice recommended guidelines for weight loss.

Second, our adjustment for cigarette smoking also warrants comment, in light of its relationship to both obesity and mortality risk. Of note, regular smokers have a lower prevalence of obesity than the general population (9), but a higher risk of mortality (9). There are also methodological considerations in that the categorization of smoking in NHANES involved two approaches: i) categorizing individuals as current smoker's vs non-current smokers, and; ii) individuals that have smoked over 100 cigarettes in their life vs those

who have not. Based on this method of classification it is possible that a lifelong smoker that recently quit would classify themselves as a non-smoker, while someone could go on to smoke more than 100 cigarettes, but either responded incorrectly or did not yet achieve this level. Although smoking was adjusted for, accumulating literature suggests that approach is not sufficient (10,11), as smokers are often leaner than nonsmokers and the intensity of smoking is often directly related to BMI and mortality (9). To best address this issue, groups were cross-classified with smoking status captured as "yes" if they had smoked 100 or more cigarettes OR currently reported smoking, whereas smoking status was captured as "no" if the respondent had never smoked more than 100 cigarettes AND currently did not report smoking. Although biomarkers of smoking are available – such as serum cotinine levels in NHANES – their use would have led to further restriction of our sample, and were not justifiable in the current study. As it stands, more "smokers" are likely to under-report their cigarette consumption, leading to *mis*representation of smoking status and a higher proportion of non-smokers, an effect that would bias towards the null (12). Future research should aim to better assess the impact of smoking by stratification of non-smoker and smokers among persons with obesity who are taking medications. Lastly, the use of BMI as an anthropometric measure presents additional limitations. BMI does not account for different types of mass, meaning that it is impossible to ascertain if an elevated BMI is a result of high fat mass or high lean mass. Despite this concern, Romero-Corral et al. (13) found a strong correlation between BMI and body fat percentage. Subsequent studies should aim to use other longitudinally collected anthropometric measures such as body fat percentage in order to assess the impact of medication usage on mortality in PwO.

To conclude, this study offers new insights into the relationship between medication use for comorbidities, obesity, and mortality risk. It also gives rise to additional considerations, including whether weight loss should be prioritized for individuals over the age of 65, or whether it should it be only prioritized for younger cohorts. Future works should aim to address these limitations through longitudinal study of participants with multiple measures of obesity and health status, inclusive of objective measures of physical activity and smoking status to deepen our understanding of these issues.

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