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Determining the Potential Joint Effect of Obesity and Diabetes on Clinical Outcomes following Ischemic Stroke and Issues Related to the Measures of Obesity

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Abstract

COLLEEN BAUZA. Determining the Potential Joint Effect of Obesity and Diabetes on Clinical Outcomes following an Ischemic Stroke & Issues Related to the Measures of Obesity. (Under the direction of MARVELLA E. FORD)

Since 1980, the prevalence of obesity and diabetes mellitus (or diabetes) in the US has each increased over 200%. Furthermore, obesity and diabetes are each a risk factor for the incidence of an ischemic stroke and are each independently associated with clinical outcomes following an ischemic stroke (*e.g.,* functional disability, all-cause mortality, and cardiovascular-related mortality).

To date, no study has investigated the presence of a joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke. Further, no study has illustrated the extent to which misclassification and measurement error are present in exposure assessment of obesity within a cohort of ischemic stroke survivors. Based on recent research that has supported the heterogeneity of the metabolic profile among obese individuals coupled with prior scientific evidence of the presence of a joint effect, or interaction effect, of obesity and diabetes on the risk of stroke, it is hypothesized that the effect of obesity on clinical outcomes following an ischemic stroke may differ according to diabetes status. The overarching goals of this dissertation were to determine if a joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke exists and to illustrate issues related to measures of obesity. The dissertation addressed five specific aims.

A post-hoc analysis using data from the Interventional Management of Stroke (IMS) III clinical trial and the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) clinical trial were used in this dissertation. The IMS III clinical trial informed Specific Aims 1-2. Additionally, data from the PRoFESS clinical trial were used to examine Specific Aims 3-4. Specific Aim 5 illustrates the extent to which misclassification and measurement error were present in exposure assessment of obesity using data from the PRoFESS clinical trial.

In the post-hoc analysis of the IMS III data, there was not sufficient evidence to declare that the effect of obesity on functional disability as well as on all-cause mortality differed by diabetes status on the multiplicative or additive scales. Using data from the PRoFESS trial, there was insufficient evidence to conclude that the effect of obesity on all-cause mortality differed by diabetes status on either the multiplicative or additive scale. In contrast, there was evidence that the effect of obesity on cardiovascular-related mortality differed by diabetes status on the multiplicative scale and the attributable proportion due to interaction of the additive scale. However, there was insufficient evidence of an additive interaction for the relative excess risk due to interaction for this outcome. Furthermore, this dissertation also sought to illustrate the extent to which misclassification and measurement error were present in exposure assessment of obesity based on the anthropometric measures of body mass index (BMI), waist circumference, and waist circumference-to-height ratio within a cohort of ischemic stroke survivors using data from the PRoFESS clinical trial. Of the three anthropometric measures, BMI was the best at discriminating the patient-relevant clinical outcome of all-cause mortality following an ischemic stroke. However, all of the anthropometric measures were barely

able to discriminate between subjects with and without the outcome slightly better than chance (area under the curve ≤ 0.60). Error in measurement may impact outcomes of obesity and, therefore, will not reflect the true magnitude of the problem.

Overall, this dissertation was the first to investigate the joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke. The results of this dissertation support recent research of the heterogeneity of the metabolic profile among obese individuals. This work also highlights the need for future research to improve calibration of the available measures of obesity and/or to develop alternative methods for determining body adiposity.

1 Introduction and Significance

1.1 **Overview and Specific Aims**

Since 1980, the prevalence of both obesity and diabetes mellitus (or diabetes) in the US has each increased tremendously.[1–4] Specifically, the prevalence of obesity rose dramatically from 15% in 1980 to 34% in 2010,[1,2] while the prevalence of diabetes more than doubled, from 3.5% in 1980 to 9.3% in 2010.[3,4] Furthermore, obesity and diabetes are risk factors for the incidence of an ischemic stroke[5–7] and are each related to clinical outcomes following an ischemic stroke (*i.e.*, functional disability, all-cause mortality, and cardiovascular-related mortality).[8–30] Although the prevalence of obesity and diabetes varies by region and country, it is estimated that between 18% and 44% of individuals who previously had an ischemic stroke are obese, and between 25% and 45% of individuals who previously had an ischemic stroke have diabetes.[31] By reducing the prevalence of obesity and diabetes, it may be possible to also minimize the risk of incident stroke as well as negative health events following a stroke. [1–7]

To date, Olofindayo *et al.*[32] was the first to examine the joint effect, or interactive effect, of obesity and diabetes on the risk of incident stroke. However, no study has determined the presence of a joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke. The pathogenesis of stroke is a heterogeneous process that involves molecular, cellular, neuronal, individual, and environmental factors.[33] Because diabetes is related to obesity,[34,35] diabetes may potentially modify the inflammatory effects of body mass on risk of clinical outcomes following an ischemic stroke. If so,

elucidation of the joint effect of obesity and diabetes may help to identify high risk subgroups and provide new insights into underlying mechanisms. As a result, the goal of this dissertation is to determine whether the effect of obesity on clinical outcomes following an ischemic stroke differs by diabetes status. An additional goal of this dissertation is to illustrate issues related to the measures of obesity.

A post-hoc analysis was conducted using data from the Interventional Management of Stroke (IMS) III clinical trial and the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) clinical trial. The IMS III clinical trial includes data obtained from 656 participants who underwent randomization between August 2006 and April 2012 into a multi-center, open-label, randomized Phase III clinical trial after onset of an ischemic stroke.[36] These data informed Specific Aims 1-2. Additionally, the PRoFESS clinical trial includes information from a sample of 20,332 participants who suffered an ischemic stroke within 90 days prior to recruitment and underwent randomization between September 2003 and June 2006 into the multi-center, double-blind, double-dummy, active and placebo-controlled Phase IV clinical trial.[37] This information was examined in Specific Aims 3-4. Anthropometric measures from the PRoFESS clinical trial informed Specific Aim 5.

1.2 **Specific Aims**

1.2.1 IMS III Clinical Trial Related Specific Aims

1. To explore the presence of the joint effect of obesity and diabetes on functional disability at 3-months following an ischemic stroke.

2. To explore the presence of the joint effect of obesity and diabetes on all-cause mortality at 1-year following an ischemic stroke.

1.2.2 PRoFESS Clinical Trial Related Specific Aims

3. To evaluate the presence of the joint effect of obesity and diabetes on all-cause mortality following ischemic stroke onset.
4. To evaluate the presence of the joint effect of obesity and diabetes on cardiovascular-related mortality following ischemic stroke onset.

1.2.3 Issues Related to Measures of Obesity Specific Aim

5. To illustrate the extent to which misclassification and measurement error are present in exposure assessment of obesity using data from the PRoFESS clinical trial.

2 Background and Significance

2.1 **Introduction**

Obesity and diabetes mellitus (or diabetes) research are crucial areas of scientific investigation. Since 1980, the prevalence rates of obesity and diabetes have each increased more than 200%.[1–4] These factors also impose a significant economic burden on the world. Specifically, the global economic impact of obesity in 2014 and diabetes in 2015 was estimated to total over US $2 trillion and over US $1.3 trillion, respectively.[38,39]

As part of an effort to improve the lives of Americans, the US Department of Health and Human Services published a 10-year national health agenda in 2010 titled Healthy People 2020.[40] The goal of Healthy People 2020 is to promote health and prevent disease for all Americans.[40] In addition, Healthy People 2020 includes specific sub-goals targeted toward reducing the proportion of Americans who are obese and/or have diabetes.[41,42] Healthy People 2020 also aims to lessen the economic burden associated with obesity and diabetes as well as to improve the quality of life of the individuals with these comorbid risk factors.[41] Thus, obesity and diabetes are national public health concerns.

Obesity and diabetes are also considered risk factors for the incidence of an ischemic stroke[5–7] and are related to clinical outcomes following an ischemic stroke (*i.e.*, functional disability, all-cause mortality, and cardiovascular-related mortality).[8–30] Although the prevalence of obesity and diabetes vary by region and country, it is

estimated that between 18% and 44% of individuals who previously had an ischemic stroke are obese, and between 25% and 45% of individuals who previously had an ischemic stroke have diabetes.[31] By reducing the prevalence of obesity and diabetes, it may be possible to also minimize the risk of incident stroke as well as poor health outcomes following a stroke.

Based on prior scientific evidence, the joint effect of central obesity and diabetes on the risk of incident stroke exists, meaning that the effect of central obesity on the risk of incident stroke differs by diabetes status.[32] Further the pathogenesis of stroke is a heterogeneous process that involves molecular, cellular, neuronal, individual, and environmental factors.[33] Because diabetes is related to obesity,[34,35] diabetes may potentially modify the inflammatory effects of body mass (*e.g.*, obesity) on clinical outcomes following an ischemic stroke. If so, elucidation of the joint effect of obesity and diabetes may help identify high risk subgroups and provide new insights into underlying mechanisms. As a result, this dissertation includes a scientific question that has yet to be addressed: Does a joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke exist? Further, data presented in this dissertation also illustrates the extent to which misclassification and measurement error are present in exposure assessment of obesity using data from a clinical trial.

2.2 **Epidemiology of Ischemic Stroke**

Each year approximately 795,000 individuals experience a stroke.[43] Between 2009 and 2012, over 6.6 million (2.6%) Americans age 20 or older had a stroke.[43] Furthermore, 66% of Americans who had a stroke in 2009 were at least 65 years old.[44]

Stroke is also a leading cause of long-term disability and death.[43] In 2011, the estimated direct stroke-related cost of stroke were $17.5 billion.[43] The direct stroke-related cost are expected to triple between 2012 and 2030 from $71.6 billion to $184.1 billion due to the increase in the aging population.[43]

Ischemic strokes, due to thrombosis or an embolism, account for 87% of all strokes and occur when there is a lack of blood flow to perfuse cerebral tissue due to blocked arteries to or within the brain.[6,43] Thrombosis-related ischemic strokes occur when a blood clot forms within an artery supplying blood to the brain, whereas embolic-related ischemic strokes occur when a blood clot forms somewhere in the body, typically the heart, and travels to the brain, blocking the blood flow in narrower blood vessels.[45] Commonly, the literature related to stroke does not distinguish between the type of stroke (*e.g.*, ischemic or hemorrhagic). However, since 87% of all strokes are ischemic, it may be assumed that the reported results are indicative of ischemic stroke, the focus of this research.

Risk Factors for Ischemic Stroke

Stroke risk factors are typically grouped into two categories: non-modifiable and potentially modifiable risk factors.[5–7,46] Non-modifiable risk factors for ischemic stroke include age, gender, racial/ethnic group, and a family history of stroke.[5,6,46] Age is considered one of the most important risk factors for ischemic stroke;[7] specifically, the incidence of ischemic stroke doubles for each decade after age 55.[7,46] Furthermore, the risk of ischemic stroke varies by gender. According to Sacco *et al.*[7] men are 1.25 times more likely to experience an ischemic stroke compared with women overall. However,

Allen and Bayraktutan[6] note that males only have higher incident ischemic stroke rates at middle to old age whereas females have higher incident ischemic stroke rates at young and elderly ages. Rates of ischemic stroke also vary by racial/ethnic group[6,7,46,47] with non-Hispanic Blacks having the highest ischemic stroke incidence rates followed by Hispanics and non-Hispanic Whites.[6,46,47] Finally, a family history of stroke is considered a risk factor for ischemic stroke because families are thought to share a common exposure either to the environment or to lifestyle risks.[5,7]

Potentially modifiable risk factors for ischemic stroke include hypertension, atrial fibrillation, coronary heart disease, obesity, and diabetes.[5–7] Hypertension, a systolic blood pressure of greater than 140 mmHg and/or a diastolic blood pressure of more than 90 mmHg, is the most important risk factor for ischemic stroke.[5–7,46] Allen and Bayraktutan[6] observed that the risk of ischemic stroke doubles with each 7.5 mmHg increase in diastolic blood pressure for industrialized countries. Another risk factor for ischemic stroke is atrial fibrillation, or an irregular heartbeat.[7] With increasing age, the incidence and prevalence of atrial fibrillation likewise increase.[7] A third risk factor for ischemic stroke is coronary heart disease, resulting from plaque accumulation inside the coronary arteries.[5–7,46] When plaques accumulate in the coronary arteries, blood flow is constricted to the brain, increasing the risk of ischemic stroke.[6,7] Individuals with severe plaque, specifically within the heart, are at a 2.4 times higher risk of ischemic stroke as compared with individuals without plaque.[6] Two additional potentially modifiable risk factors for ischemic stroke are obesity and diabetes.[5–7,46] The epidemiology of obesity

and diabetes in relation to ischemic stroke will be discussed separately in the next sections.

2.3 **Epidemiology of Obesity in Relation to Ischemic Stroke**

Obesity is considered an important area of scientific inquiry due to its prevalence in the US, variable rates between racial/ethnic groups, economic burden, and effect on other diseases. Obesity is the result of a combination of individual factors, including behavior and genetics.[48] Based on an individual's BMI, the World Health Organization (WHO) suggests that individuals be classified into one of the following BMI categories: *underweight* (< 18.5 kg/m^2), *normal-weight* (18.5-24.9 kg/m^2), *overweight* (25-29.9 kg/m^2), *and obese* (≥ 30 kg/m^2).[49] Obesity has been further categorized into *grade 1* (BMI 30-34 kg/m^2), *grade 2* (BMI 35-39 kg/m^2), and *grade 3* (BMI ≥ 40 kg/m^2) as points for public health action.[49] Although the WHO BMI categorizations are intended for international use to reflect the risk of type 2 diabetes, hypertension, and cardiovascular disease, there was growing debate on whether different BMI cut points were necessary for different racial/ethnic groups.[50] As a result, the WHO expert consultation on BMI in Asian-Pacific populations convened based on the following factors: the growing prevalence of type 2 diabetes and other cardiovascular risk factors in parts of Asia and the Pacific where the average BMI was below the overweight classification cut point of 25 kg/m^2; mounting evidence of the differences between BMI, body fat distribution, and percentage of body fat across populations; and the two prior attempts to discuss the WHO BMI cut points in Asian-Pacific populations.[50] Despite the growing evidence to have racial/ethnic specific cut points classify overweight and obesity, the WHO expert

consultation decided to retain the standard WHO BMI cut points.[50] However, the WHO expert consultation did identify additional public health action points along the BMI continuum.[50] Despite the WHO expert consultation, some studies which include subjects from Asian-Pacific populations have adopted alternative cut points for various BMI categories (*i.e.*, BMI $\geq$ 23 kg/m^2 for overweight and BMI $\geq$ 27.5 kg/m^2 for obesity).[50]

Prevalence of Obesity in the US and Racial/Ethnic Differences in Prevalence

The prevalence of obesity has continued to increase since 1980.[1] Specifically, the prevalence of obesity dramatically rose from 15% in 1980 to 34% in 2010.[1] Additionally, the prevalence of obesity differs across racial/ethnic groups, with non-Hispanic Black and Hispanic adults having higher rates of obesity than non-Hispanic White adults.[1] Based on data from the National Health and Nutrition Examination Survey 2011-2014, 48.1% of non-Hispanic Blacks and 42.5% of Hispanics were obese whereas 34.5% of non-Hispanic Whites were obese.[1] While obesity rates vary by racial/ethnic group, these rates are a significant public health concern for all racial/ethnic groups in the US.[1]

The Cost of Treating Obesity in the World

Obesity places a significant economic burden on the world. The global economic impact of obesity in 2014 was estimated to total over US $2 trillion.[38] Specifically in the US, the Harvard School of Public Health estimated that the US spent over $190 billion on obesity-related health care expenses in 2005.[51] Reducing the prevalence of obesity has the potential to curb the economic cost of treating obesity and associated conditions.

Obesity as a Potentially Modifiable Risk Factor for Ischemic Stroke

Obesity is a potentially modifiable risk factor for ischemic stroke.[2,5,7,52–57] While the prevalence of obesity among individuals who have had an ischemic stroke has not been extensively explored, it is estimated that between 18% and 44% of individuals who experience a stroke are obese.[31] In general, obese individuals have approximately a two-fold increase in risk of ischemic stroke compared with normal-weight individuals independent of other contributing risk factors of stroke.[5,54–57] The Women's Health Study, a prospective study of more than 39,000 women, showed a significant trend in ischemic stroke risk across BMI categories.[54] Specifically, the risk of ischemic stroke significantly increased beginning with BMI values of at least 27 kg/m^2, considered overweight, and continued to steadily rise as BMI increased.[54] Additionally, the Nurses' Health Study, a prospective cohort study of more than 116,000 registered nurses in the US, found that women with a BMI of 32 kg/m^2 or greater had more than a two-fold increase in risk of ischemic stroke compared with women with a BMI of less than 21 kg/m^2.[55] The Physician's Health Study, a prospective cohort study of approximately 21,000 male physicians in the US, found that men with an elevated BMI of 30 kg/m^2 or greater had approximately a two-fold risk of an ischemic stroke as compared with men with a BMI of less than 23 kg/m^2.[56] Similar to results of the Physician's Health Study, a Swedish prospective study of 7,000 middle-aged men also determined that men with a BMI of greater than 30 kg/m^2 had a two-fold increased risk of ischemic stroke as compared with men who had a BMI of less than 23 kg/m^2.[57] Thus, obesity is a significant risk factor for ischemic stroke.

Relationship between Obesity and Chronic Conditions Other than Ischemic Stroke

Obesity is a major risk factor not only for ischemic stroke but also for other chronic conditions such as diabetes, heart disease, endometrial cancer, breast cancer, and colon cancer.[2,52] Many of these obesity-related conditions are considered leading causes of death in the US.[48,58] In order to reduce the rates of obesity-related conditions, Healthy People 2020 aims to decrease the proportion of US adults who are obese.[41] Additionally, reducing the prevalence of obesity could lead to a reduction in the prevalence of the obesity-related leading causes of death in the US (*e.g.*, heart disease, and some cancers).[48,49,52,58]

2.4 **Epidemiology of Diabetes in Relation to Ischemic Stroke**

Distinction between Type 1 and Type 2 Diabetes

Diabetes mellitus, or diabetes, is a heterogeneous group of diseases marked by high levels of blood glucose.[4] Type 1 diabetes, a chronic condition in which the pancreas produces little or no insulin, contributes to approximately 5% of all diagnosed diabetes cases in the US.[4,59] The age of diagnosis for type 1 diabetes is typically in the mid-teens.[4,59] In comparison, type 2 diabetes is a chronic condition that affects the way the body metabolizes glucose and accounts for nearly 95% of all diagnosed cases of diabetes in the US.[4,59] While it is possible to treat and manage both types of diabetes, type 2 diabetes is considered preventable by managing weight, exercising regularly, eating a healthy and balanced diet, and not smoking.[4] The majority of published trend data related to diabetes do not distinguish between type 1 and type 2 diabetes. Therefore, because

95% of all diagnosed cases are type 2 diabetes, it may be assumed that reported trends are primarily indicative of type 2 diabetes, the focus of this dissertation.

Prevalence of Diabetes in the US and Racial/Ethnic Differences in Prevalence

Diabetes is a national epidemic that is expected to increase.[4,59] In fact, between 1980 and 2012, the prevalence of diabetes more than doubled from 3.5% to 9.3% in the US.[4] Similar to obesity, the prevalence of diabetes differs among racial/ethnic groups in the US.[4] Specifically, non-Hispanic Blacks (13.2%) and Hispanics (12.8%) experience rates of diabetes that are nearly double those of non-Hispanic whites (7.6%).[4] The alarming increase in prevalence of diabetes coupled with disparities in the prevalence among different racial/ethnic groups is a cause for public health concern.

The Cost of Treating Diabetes in the World

Diabetes places a significant economic burden on the world. The global economic impact of diabetes in 2015 was estimated to total over US $1.3 trillion.[39] Specifically in the US, more than $176 billion on direct medical costs and more than $69 billion on indirect costs (*e.g.,* disability, work loss, and/or premature death) for individuals with diagnosed diabetes in 2012.[4] In addition, health care expenditures for individuals with diabetes was approximately 2.3 times higher than for individuals without diabetes.[4] Thus, reducing the prevalence of diabetes is essential in order to reduce the economic cost related to diabetes.

Diabetes as a Modifiable Risk Factor for Ischemic Stroke

Diabetes is an established risk factor for ischemic stroke;[7,60–64] however, unlike obesity, diabetes is considered a key factor of the Framingham stroke risk prediction

score.[63,64] The Framingham stroke risk prediction score was developed to allow physicians to quantify an individual's risk for stroke. Risk factors for stroke were identified based on a 36-year follow-up population cohort study in Framingham, Massachusetts. Age, systolic blood pressure, use of antihypertensive therapy, cigarette smoking, prior cardiovascular disease (*i.e.*, coronary heart disease, cardiac failure), atrial fibrillation, and left ventricular hypertrophy in addition to diabetes were identified as risk factors for stroke based on the Framingham cohort study.[64] While obesity is not included in the Framingham stroke risk prediction score, it is considered a risk factor for many of the components of the Framingham stroke risk prediction score.

With the increasing prevalence of obesity, the prevalence of diabetes is also expected to increase.[4,65] On behalf of the American Heart Association and American Stroke Association, Kernan *et al.*[31] estimated that between 25% and 45% of individuals who previously had an ischemic stroke have diabetes. The incidence of stroke in the US is expected to rise concurrently with the expected increase in the prevalence of diabetes.[60,66] Similar to the findings of obesity and risk of ischemic stroke, individuals with type 2 diabetes have a two-fold higher risk of having an ischemic stroke compared with individuals without type 2 diabetes.[61,62,66,67] For example, Janghorbani *et al.*[62] examined the association between type 2 diabetes and risk of ischemic stroke using data from the Nurses' Health Study and determined that the risk of ischemic stroke was 2.3 times higher for women with type 2 diabetes than women without diabetes. These results corroborate the findings of the Asia Pacific Cohort Studies, which consisted of 24 cohort studies from Asia, Australia, and New Zealand with over 160,000 individuals.[67] Of the

161,214 subjects, only 3.0% (4,873) had baseline diabetes information.[67] Despite the significant amount of missing information on baseline diabetes and inability to differentiate between individuals with type 1 and type 2 diabetes, the risk of ischemic stroke for individuals with diabetes was 2.6 times higher when compared with individuals without diabetes.[67] Hence, there is a consensus that diabetes is a significant risk factor for ischemic stroke.

Relationship between Diabetes and Chronic Conditions Other than Ischemic Stroke

Diabetes is associated with several other chronic conditions, including hypertension, hypoglycemia, heart disease, cancer, and kidney failure.[3,4,59] Diabetes is also linked to disability and potential amputation.[3,4,59] In 2010, diabetes was the seventh leading cause of death in the US.[3,4]

As part of the effort to address this public health concern, Healthy People 2020 has an overall goal to decrease the prevalence and economic burden of diabetes in the US.[42] Additionally, Healthy People 2020 has dedicated numerous sub-goals to attain this goal including improving glycemic control, reducing the proportion of prevalent cases of diabetes, and decreasing the rate of death due to diabetes.[42] If the national campaign succeeds in reducing the prevalence of diabetes, the burden of diabetes and diabetes-related health complications will likely lessen.

2.5 **Heterogeneity of Obesity**

Obesity is a strong predictor of diabetes.[34,48,68,69] In fact, Eckel *et al.*[69] attribute the increase in the incidence and prevalence of diabetes, specifically type 2 diabetes, to obesity. For each additional unit of BMI over 22 kg/m^2, the relative risk of diabetes

increases by approximately 25%.[70] Despite the increased risk of diabetes for obese individuals, not all obese individuals will develop diabetes. Research has supported the heterogeneity of the metabolic profile among obese individuals.[71–75] It has been recognized that not all obese individuals have the same cardiometabolic risk.[71,72,74,75] Evidence shows that there is a subgroup of obese individuals that has less metabolic complications (*i.e.*, insulin resistance, hypertension, dyslipidemia) than expected; this group has been classified as having a metabolically healthy obese phenotype.[73–76] Most observational studies include insulin resistance, blood pressure, or fasting plasma glucose to define metabolic health, whereas other studies include inflammatory markers, the absence of abdominal obesity measured by waist circumference (WC), or cardiovascular fitness.[75,76] Unfortunately, no standard definition of metabolic health or consistent cutoffs for the components of metabolic health exist.[75,76]

There are multiple methods in which to measure obesity, which may be related to the heterogeneity of obesity. For example, obesity can be quantified and defined using BMI, waist circumference (WC), WC-to-height ratio (WHR), WC-to-hip circumference ratio, skinfold thickness, dual x-ray absorptiometry (DEXA), underwater weighing, or air displacement.[77,78] Of these methods, DEXA, underwater weighing, and air displacement offer more precise measures of body adiposity.[77,78] However, these methods are not viable options to be applied at the population or clinical level due to cost and convenience.[77–80] BMI, instead, is the most utilized diagnostic criteria to measure obesity in epidemiologic studies as well as in clinical practice.[77,81,82] Numerous expert panels such as the US Preventive Services Task Force and the American Heart

Association/American Stroke Association recommend using BMI to screen for obesity utilizing the BMI $\geq$ 30 kg/m^2 cut point.[5,43,82,83] Although BMI is the recommended diagnostic measure for obesity, there are limitations to using BMI as a proxy measure to identify or represent obesity. BMI cannot differentiate between excess adipose tissue, the distribution of adipose tissue, or high muscle mass.[77–80] Further, BMI does not account for differences in gender, age, or bone structure.[77–80] While BMI has relatively high specificity (between 92-95% in men and 93-99% in women), it has poor sensitivity (between 36-41% for men and 32-49% for women) to detect obesity.[79,84] Although BMI is the recommended measure of obesity, it should be recognized as an imperfect reference standard because it misclassifies a large number of individuals who are obese based on a more precise measure of obesity. Further, the number of measures of obesity is concerning. Each measure provides a different piece of the obesity construct, yet there is not a measure of obesity that adequately estimates excess adiposity and predicts cardiometabolic risk. As a result, a consistent definition and accurate measure of both metabolic health and obesity are needed to accurately classify individuals in order to predict health outcomes. This dissertation aims to illustrate the extent to which misclassification and measurement error are present in exposure assessment of obesity measured by several anthropometric measures.

It has been suggested that obesity and diabetes, and their interactions, should be considered when investigating clinical outcomes in order to assess the differential effect of obesity and metabolic health.[76] The exact mechanisms by which the effect of obesity differs by metabolic health are not clear, although several hypotheses exist. One

hypothesis to explain the differences in cardiometabolic risk is based on the distribution of regional fat.[69,74] Whereas some studies have shown that visceral abdominal fat is linked with insulin resistance due to greater inflammation,[69,74,76,85] other studies demonstrated that liver fat was more strongly associated with the development of insulin resistance.[76,85] Related to the distribution of fat, another hypothesis posits that the differential risk may be due to the method in which adipocytes differentiate and fat storage potential.[69,74] As adipose tissue expands, adipocytes either become hypertrophic or hyperplasmic.[74] It is suggested that the increased risk of insulin resistance is linked to the differentiation and storage of adipocytes,[69,74] although, additional research is needed. Inflammation is another hypothesized mechanism responsible for linking obesity to insulin resistance.[69,74,76] Evidence demonstrates that both overweight and obese individuals tend to have low-grade chronic inflammation, originating from adipose tissue.[86] As adipose tissue expands due to oversaturation of nutrients and lack of physical activity, the metabolic process becomes damaged thereby causing the adipocytes to signal immune system response cells (*e.g.*, leukocytes, cytokines, and macrophages) to aid in restoring homeostasis.[69,74] However, homeostasis is not achieved due to the constant signaling of the positive feedback loop caused by the overabundance of nutrients in the body;[69] this low-grade inflammation has been noted to predict insulin resistance.[69,74,76,86] Overall, the mechanism responsible for the differential insulin resistance response is unknown and additional research is needed.

Evidence of a Differential Effect of Obesity and Diabetes on Risk of Stroke

Olofindayo *et al.*[32] appear to be the first researchers to determine whether the effect of central obesity, measured by WC, on stroke incidence differed between individuals with and without diabetes. They hypothesized that individuals with both central obesity and diabetes would have a greater risk for stroke than individuals who did not have either of these risk factors. To answer this question, Olofindayo *et al.*[32] assessed whether the joint effect, or interaction effect, of central obesity and diabetes on the risk of stroke was present on the additive and/or multiplicative scales. To evaluate the interaction effect between central obesity and diabetes on the additive scale, the researchers calculated Rothman's relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and Rothman's synergy index (SI).[87] To test for the presence of a multiplicative interaction, they included a cross-product interaction term of central obesity and diabetes in the multivariable models.[32]

Overall, Olofindayo *et al.*[32] discovered that there was evidence of an interaction effect of central obesity and diabetes on stroke risk in their inner Mongolian study population. Despite the relatively small proportion of incident strokes (n=121) in a cohort of 2,561 subjects, they found that the effect of central obesity on risk of stroke differed by diabetes on the multiplicative scale ($P_{interaction}$=0.024). Additionally, Olofindayo *et al.*[32] determined that 57.1% (95% CI: 1.7-112.5%) of stroke risk could be attributed to the interaction effect of central obesity and diabetes; this result also provides evidence of a potential biological interaction between central obesity and diabetes.[32] Although these results need to be verified in other diverse populations, the results lead to a subsequent

question of whether there is a joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke, such as functional disability and mortality-related events (*e.g.*, all-cause mortality and cardiovascular-related mortality). To date, no study has explored whether the effect of obesity on clinical outcomes following an ischemic stroke differs by diabetes status. Thus, this dissertation focuses on addressing this gap in knowledge.

2.6 Independent Effects of Obesity and Diabetes on Clinical Outcomes following an Ischemic Stroke

There is a lack of scientific evidence on the joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke (*e.g.*, functional disability, all-cause mortality, and cardiovascular-related mortality). However, summarizing the literature on the independent effects of obesity and diabetes on these outcomes is essential. Therefore, the following sections describe the independent effects of obesity and diabetes on clinical outcomes following a stroke.

2.6.1 Functional Disability

Stroke is one of the leading causes of long-term disability, or functional disability, in the US.[43] The WHO defines functional disability as "any long term limitation in activity resulting from a condition or health problem."[88] As a result, assessing functional disability for subjects following an ischemic stroke is often a primary outcome for many acute stroke trials. Several instruments exist to measure functional disability, or independence, of a stroke subject following a stroke. The Agency for Health Care Policy and Research Post-Stroke Rehabilitation Panel suggests using the Barthel Index (BI) or

the Functional Independence Measures (FIM) to quantify measures of disability and the modified Rankin Scale (mRS) to assess global disability.[89] Further, the mRS and the BI are the most widely utilized instruments of functional disability within the acute stroke literature.[90] In general, all of these instruments are ordinal measurement scales; lower scores on the BI and higher scores on the FIM and the mRS indicate a subject is more functionally disabled. For this dissertation, the mRS will be used to analyze functional disability at 3-months following onset of an ischemic stroke because 1) the goal of the specific aim is to assess global functional disability and 2) the American Heart Association and American Stroke Association guidelines recommend the mRS over the other instruments.[91]

2.6.1.1 Effect of Obesity

Four studies have investigated the effect of obesity on functional disability following a stroke.[11,20,21,92] Whereas obesity is a modifiable risk factor for ischemic stroke,[6,7] three of these studies have reported that obesity is associated with less functional disability following onset of ischemic stroke.[11,20,21] This apparent discrepancy is referred to as the obesity paradox, a phenomena where being overweight or obese is a protective factor compared with normal body weight for outcomes following the onset of a stroke.[8] Based on the research on the effect of obesity on all-cause mortality following a stroke,[8] it is hypothesized that being overweight or obese is a protective factor for functional disability following the onset of a stroke compared with normal body weight.[11,20,21]

Doehner *et al.*[11] investigated the association between obesity and the composite outcome of functional dependency or death at 30-months following a stroke using data from the Telemedical Project for Integrative Stroke Care trial. They used the following BMI categories of *underweight* (< 18.5 kg/m^2), *normal-weight* (18.5-24.9 kg/m^2), *overweight* (25-29.9 kg/m^2), *mild obesity* (30-34.9 kg/m^2), and *advanced obesity* (> 34.9 kg/m^2) to classify subjects.[49] Severe functional dependency was defined as a mRS greater than 3 or a BI of less than 60 at 30-months following onset of a stroke. They found that overweight subjects had 0.74 (95% CI: 0.50-1.00) lower odds of functional dependency or death at 30-months following a stroke compared with normal-weight subjects. No justification was provided for 30-months as the time point of interest. Further, mildly obese subjects had a protective OR 0.60 (95% CI: 0.39-0.91) of functional dependency or death at 30-months following a stroke compared with normal-weight subjects. These results were adjusted for age, gender, living with a partner prior to the event, severity of the event, stroke type, diabetes, hypolipoproteinemia, atrial fibrillation, previous stroke, and other previous vascular disease. However, Doehner *et al.*[11]did not adjust for smoking history, an important prognostic indicator of functional disability following a stroke.

Zhao *et al.*[20] examined the impact of obesity on poor functional recovery at 3-months, defined as a mRS score greater than 2, following an ischemic stroke using the China National Stroke Registry. They used the WHO's Asian recommendations to categorize subjects as *underweight* (< 18.5 kg/m^2), *normal-weight* (18.5-22.9 kg/m^2), *overweight* (23-27.4 kg/m^2), *obese* (27.5-32.4 kg/m^2), and *severely obese* (>32.4 kg/m^2). After adjusting for potential confounders (*i.e.*, age, gender, neurological severity, pre-

stroke mRS, ischemic stroke subtype, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, smoking history, and history of stroke), Zhao *et al.*[20] found that overweight subjects had 0.81 (95% CI: 0.72-0.89) lower odds of a poor functional recovery at 3-months following an ischemic stroke compared with normal-weight subjects. While not statistically different from normal-weight subjects, obese subjects had 0.87 (95% CI: 0.75-1.01) lower odds of a poor functional recovery at 3-months following an ischemic stroke.

Finally, Jang *et al.*[21] investigated the impact of obesity on functional status at 6-months following an ischemic stroke onset for the 2,057 subjects in the Korean Stroke Cohort for Functioning and Rehabilitation. They classified the Korean ischemic stroke subjects into five groups based on their BMI using the WHO's Asian recommendations: *underweight* (< 18.5 kg/m^2), *normal-weight* (18.5-22.9 kg/m^2), *overweight* (23-24.9 kg/m^2), *obese* (25-29.9 kg/m^2), and *extremely obese* (> 29.9 kg/m^2). Rather than using the mRS or the Barthel index to measure functional disability, the investigators used the FIM.[93] Further, Jang *et al.*[21] stratified the analyses by age group (*i.e.*, < 65 years old, ≥ 65 years old). Using the FIM as a continuous measure, they found that extremely obese, older (*i.e.*, older than 65 years old) subjects had a significantly increased mean FIM (7.95, 95% CI: 1.4-14.4) at 6-months following an ischemic stroke compared with normal-weight, older subjects after adjusting for fasting blood sugar, chronic kidney disease, diastolic blood pressure, systolic blood pressure, diabetes, estimated glomerular filtration rate, high density lipoprotein, low density lipoprotein, neurological severity,

total cholesterol, and triglyceride.[76] Similar to Doehner *et al.*,[11] Jang *et al.*[21] did not adjust for subjects' smoking history.

Despite the limited studies investigating the relationship between obesity and functional disability following an ischemic stroke, the majority of the available literature suggests that obesity, indicated by a higher BMI, is associated with lower odds of functional disability following onset of an ischemic stroke. Although the literature includes study populations with the same type of stroke (*i.e.,* ischemic stroke), the studies lack consistency in the instrument used to measure functional disability, the time point at which functional disability is collected, the definition of a poor functional outcome, and the definition of obesity. Specifically concerning the definition of obesity, various cut points of BMI were utilized to classify subjects as obese. Of the four studies that investigated the effect of obesity on functional disability following a stroke, none utilized the same cut point for obesity, three included subgroups of obesity (*e.g.,* grade 1, grade 2, *etc.*), [11,20,21] and three based their cut points on racial/ethnic differences.[20,21,92]

2.6.1.2 Effect of Diabetes

Similar to obesity, three epidemiological studies have investigated the effect of diabetes on functional disability following an ischemic stroke. Of these studies, the majority demonstrate that individuals with diabetes have higher rates of functional disability following an ischemic stroke compared with individuals without diabetes.[22–24]

Tziomalos *et al.*[23] are among the contemporary researchers who have investigated this topic. They prospectively followed 482 hospitalized subjects with acute ischemic stroke to determine if subjects with type 2 diabetes experienced higher rates of functional

disability compared with subjects without type 2 diabetes following onset of an ischemic stroke. Based on self-reported information of a prior diagnosis of type 2 diabetes or prior use of antidiabetic treatment, subjects were designated as having type 2 diabetes. Functional disability, or an adverse outcome, at the time of hospital discharge was defined as a mRS score of 2 or greater. After adjusting for potential confounders (*i.e.*, weight, consumption of alcohol, and prevalence of: congestive heart failure, hypertension, and coronary heart disease), Tziomalos *et al.*[23] determined that subjects with type 2 diabetes had 2.39 (95% CI: 1.21-4.72) times higher odds of being functionally disabled at the time of hospital discharge following an ischemic stroke than subjects without type 2 diabetes. However, they did not adjust for smoking history. They hypothesized that glycemic control for subjects with diabetes during the acute phase following the onset of an ischemic stroke may lead to decreased rates of functional disability.[23]

Intensive glucose control following an ischemic stroke is hypothesized to minimize the number of recurrent vascular events as well as to improve functional disability rates.[94] According to Bruno *et al.*,[94] ischemic stroke subjects with a history of diabetes generally have persistent hyperglycemia unless treated with insulin. To address this hypothesis, the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is currently evaluating the effect of intensively controlling hyperglycemia during the acute phase following an ischemic stroke in order to reduce poor outcomes, such as functional disability.[94,95]

Since the SHINE clinical trial started enrolling subjects, Bellolio *et al.*[96] conducted a systematic review of 11 randomized clinical trials that included 1,583 subjects (791 in the intervention group and 792 in the control group) on behalf of the Cochrane Collaboration. The goal of the review was to determine if functional disability differed between hyperglycemic and normoglycemic subjects after an ischemic stroke. Bellolio *et al.*[96] concluded that the administration of insulin to maintain normoglycemia in hyperglycemic subjects during the acute phase after an ischemic stroke onset did not improve functional disability rates following an ischemic stroke. They also discovered that acute intensive glycemic control after an ischemic stroke resulted in no difference in rates of functional disability following an ischemic stroke for subjects with and without diabetes.[96]

The literature on the relationship between diabetes and functional disability post-ischemic stroke is unclear. Findings from clinical trials and observational studies do not agree with one another. Observational studies, for example, have found a clear association between diabetes and higher rates of functional disability following onset of an ischemic stroke,[22–24] whereas the results of clinical trials have not shown whether intensive glycemic control during the acute phase will have an impact on functional disability rates following onset of an ischemic stroke.

2.6.2 *All-Cause Mortality*

2.6.2.1 Effect of Obesity

Although obesity is a modifiable risk factor for stroke,[6,7,43] the reported effects of obesity on all-cause mortality following a stroke have been conflicting. Several

epidemiological studies have demonstrated a variety of relationships–including linear, inversely linear, U-shaped, or no relationship–between obesity, defined by an elevated BMI, and the likelihood of all-cause mortality following a stroke.[8–12,14,20,25–27,92,97,98] One study found a linear association between BMI and all-cause mortality.[27] This relationship was only significant when diabetes and blood pressure were not included in the model; however, when these important covariates were included in the analysis, the association was greatly attenuated.[27] In contrast, several other studies determined an inversely linear relationship between BMI and all-cause mortality.[8–11,25,26] Of the six studies that claimed evidence of the obesity paradox, only one study did not adjust for the important confounder of smoking history. Skolarus *et al.*[12] found a U-shaped relationship between obesity and post-stroke all-cause mortality. Specifically, subjects who were either underweight or severely obese were more likely to die following a stroke compared with subjects who were normal-weight.[12] Finally, four studies determined that there was no difference in rates of all-cause mortality following a stroke between overweight and obese subjects when compared with normal-weight subjects.[20,92,98,99]

Whereas observational studies of the general population have found that increasing body mass concurrently increases the risk of all-cause mortality,[100,101] a number of observational stroke studies have reported that obesity is associated with a decreased risk of all-cause mortality following a stroke,[8–12,25,26] or the obesity paradox. Despite evidence supporting the obesity paradox in the stroke literature as well as in the literature of other chronic diseases such as myocardial infarction, heart failure, and renal disease,[92,102,103] several investigators have questioned the validity of studies supporting

the obesity paradox, citing methodological issues (*e.g.*, the measurement of obesity, treatment and/or selection bias due to the study population) or residual confounding as potential explanations.[92,102–105] Olsen *et al.*[8] were the first to document the obesity paradox.

Given the inconsistency of the definitions used, the measurement of obesity is a potential explanation of the obesity paradox. Although the epidemiological studies that have investigated the relationship between obesity and all-cause mortality following a stroke utilized BMI to classify subjects as obese, various cut points to designate obesity were used. For example, six studies used one category to denote obesity.[9,10,26,92,97,98] Specifically, five[9,10,26,92,98] used the WHO standard cut point (*i.e.*, BMI $\geq$ 30 kg/m^2) for obesity whereas one[97] utilized the WHO BMI cut point (*i.e.*, BMI $\geq$ 27.5 kg/m^2) for obesity specific to Asian-Pacific populations. Of these studies, half[9,10,26] cited evidence of the obesity paradox. In contrast, the other three studies[92,97,98] determined there was no difference in rates of all-cause mortality following a stroke between obese and normal-weight subjects.

Of the twelve studies that investigated the effect of obesity on all-cause mortality following a stroke, six[8,11,12,14,20,25] subdivided obesity into at least two categories. Of these studies, four[8,11,12,25] partitioned obesity according to the standard WHO public health action points and two[14,20] subdivided obesity based on the WHO public health action points specific to Asian-Pacific populations. Of the six studies that utilized at least two categories to denote obesity, three[8,11,25] cited evidence of the obesity paradox. Overall,

there is not only a lack of consensus about the relationship between obesity and all-cause mortality following a stroke but also a lack of a consistent definition of obesity.

2.6.2.2 Effect of Diabetes

Of the six epidemiological studies that have investigated the association between diabetes and all-cause mortality following a stroke, the majority reported higher all-cause mortality rates following a stroke for subjects with diabetes compared with those without diabetes.[16–19,29,30] Using data from the Minnesota Heart Study, Sprafka *et al.*[29] were among the first researchers to determine the effect of diabetes on 5-year survival rate following a stroke in subjects who survived at least to 1-year following an ischemic stroke. They determined that subjects with diabetes who survived to 1-year following an ischemic stroke were 2.00 (95% CI: 1.30-3.20) times more likely to die at 5-years post-ischemic stroke compared with subjects without diabetes after adjusting for age, gender, and level of consciousness at the time of the stroke. However, they did not adjust for smoking history. In a US Veterans' ischemic stroke population of at least 30-day survivors, Kamalesh *et al.*[17] similarly determined that subjects with diabetes were 1.15 (95% CI: 1.11-1.19) times more likely to die from all causes at 1-year after discharge than subjects without diabetes after adjusting for age, gender, ethnicity (*i.e.*, white and non-white), hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, atrial fibrillation, and region of US. However, they also did not adjust for smoking history. Further, Winell *et al.*[18] used the Finnish National Hospital Discharge Register to determine that first-time ischemic stroke survivors with diabetes who survived to 28-days were between 1.20-2.20 times more likely to die from all-causes at 1-

year following a ischemic stroke compared with their non-diabetic counterparts while adjusting for age and hospital district. They also determined that the odds of all-cause mortality differed by gender. Specifically, men with diabetes were 1.43 (95% CI: 1.15-1.77) times more likely to die at 1-year post-ischemic stroke compared with men without diabetes; women with diabetes were 2.17 (95% CI: 1.71-2.74) times more likely to die at 1-year following an ischemic stroke compared with women without diabetes.[18] Eriksson *et al.*[19] found that first-time stroke subjects with diabetes from the Northern Sweden MONICA Stroke Registry were at 1.67 (95% CI: 1.58-1.76) times higher risk of death from all-causes than subjects without diabetes when adjusting for age, sex, stroke type, smoking use, history of myocardial infarction, atrial fibrillation, use of antihypertensive medication, and use of antithrombotic medication. They also determined that the risk of all-cause mortality between subjects with and without diabetes varied by gender and age.[19]

While the majority of these studies did not account for obesity or neurological severity at the time of stroke, the investigators found that diabetes is a risk factor for an increased risk of all-cause mortality following a stroke. Based on the available literature, evidence exists that subjects with diabetes have a higher risk of all-cause mortality following an ischemic stroke compared with subjects without diabetes.

2.6.3 Cardiovascular-Related Mortality

Cardiovascular-related mortality, or vascular death, following an ischemic stroke is not often an outcome of primary interest for acute stroke trials or observational studies. However, cardiovascular-related mortality is sometimes considered part of a composite,

or secondary outcome.[9,15] Few studies have examined the independent effects of obesity or diabetes on cardiovascular-related mortality following an ischemic stroke.

2.6.3.1 Effect of Obesity

To date, three studies have investigated the relationship between obesity and cardiovascular-related mortality following an ischemic stroke. Each of these studies found that overweight and obese subjects have a lower risk of cardiovascular-related mortality following an ischemic stroke compared with their normal-weight counterpart.[9,14,15]

Ovbiagele *et al.*[15] examined the effect of obesity on the first major vascular event after an ischemic stroke as a secondary outcome using data from PRoFESS. The composite outcome was defined as the time to the first recurrent stroke, myocardial infarction, or vascular death. PRoFESS subjects were categorized into three BMI groups: *lean* (< 25 kg/m^2), *overweight* (25-29.9 kg/m^2), and *class I obesity* (≥ 30 kg/m^2) in which the lean group was the reference group. Ovbiagele *et al.*[15] found that the risk of the first major vascular event following an ischemic stroke was lower in overweight (HR: 0.84, 95% CI: 0.77-0.92) subjects and in obese (HR: 0.86, 95% CI: 0.77-0.96) subjects compared with lean subjects after adjusting for age, sex, previous stroke, diabetes, previous myocardial infarction, baseline systolic blood pressure, hypertension, ischemic stroke subtype, hyperlipidemia, coronary artery disease, smoking status, use of antihypertensive medication at baseline, NIHSS at baseline, previous transient ischemic attack, and ethnicity.

Other studies also investigated the relationship between obesity and cardiovascular-related mortality following an ischemic stroke. Vemmos *et al.*[9] investigated the differences in the cause of death by BMI group in a cohort of 2,870 Greek, first-time ischemic stroke subjects. Subjects were categorized into three groups based on their BMI: *normal-weight* (< 25 kg/m^2), *overweight* (25-29.9 kg/m^2), and *obese* ($\geq$ 30 kg/m^2). Cause of death was ascertained using death certificates up to 10 years following the incident stroke; cause of death categories included: neurological damage, infection, cardiovascular, recurrent stroke, malignancy, other known cause, and unknown cause. Using a Chi-square test, this study determined that obese first-time ischemic stroke subjects (3.2%, 16/504) died less frequently due to neurological damage compared with overweight (7.5%, 86/1,143) and normal-weight (8.9%, 101/1,138) subjects. Similar to death due to neurological damage, the same trend was seen for recurrent stroke mortality. Specifically, obese subjects (3.0%, 15/504) died less frequently compared with overweight (5.7%, 65/1,143) and normal-weight (5.9%, 67/1,138) subjects. In contrast, no statistically significant differences between the three groups for cardiovascular-related causes of death were found. Namely, 11.5% (131/1,138) of normal-weight first-time ischemic stroke subjects died due to cardiovascular-related causes compared with 9.1% (104/1,143) of overweight and 10.9% (55/504) of obese subjects. It is important to note that these findings are a result of using crude measures of association that are subject to confounding bias and should be interpreted with caution.

Finally, Kim *et al.*[14] evaluated the association between obesity and risk of mortality stratified by causes of death in a cohort of 34,132 ischemic stroke subjects from

30 Korean stroke centers. Cause of death was ascertained from death certificates up to 7.5 years following the qualifying ischemic stroke and was categorized into one of three groups: cancer, vascular, or other. Subjects' obesity status was determined by their BMI and was subsequently divided into the following eight categories based on the WHO's consultation: < 18.5 kg/m^2, 18.5-19.9 kg/m^2, 20.0-22.9 kg/m^2, 23.0-24.9 kg/m^2, 25.0-27.4 kg/m^2, 27.5-29.9 kg/m^2, 30.0-32.4 kg/m^2, and ≥ 32.5 kg/m^2. The BMI category 20.0-22.9 kg/m^2 was used as the reference category. Kim *et al.*[14] found an inverse association between obesity status and vascular mortality following an ischemic stroke adjusted for gender, age, ischemic stroke mechanism/subtype, prior stroke history, hypertension, diabetes, smoking history, in-facility ischemic stroke treatment, mRS score at discharge and the following confounders measured at admission: NIHSS, systolic blood pressure, white blood cell count, hemoglobin, fasting blood glucose, HbA1c, and total cholesterol. Specifically, ischemic stroke subjects with a BMI range of between 30.0 and 32.5 kg/m^2 had a 23% lower risk of vascular mortality than ischemic stroke subjects with a BMI range of between 20.0 and 22.9 kg/m^2.

Similar to the literature on the effect of obesity on functional disability and all-cause mortality following a stroke, the definition of obesity used in the topic area of cardiovascular-related mortality also varied. Ovbiagele *et al.*[15] and Vemmos *et al.*[9] utilized the WHO standard cut point (*i.e.*, BMI ≥ 30 kg/m^2) to define obesity whereas Kim *et al.*[14] subdivided obesity into multiple categories based on public health action points specific to Asian-Pacific populations. Although all studies determined there was evidence of an obesity paradox, a limited number of studies have investigated the

relationship between obesity and cardiovascular-related, or vascular, mortality. Further, Kim *et al.*[14] were among the only investigators, to date, to examine this association specifically by cause of death in which cardiovascular-related mortality was not part of a composite outcome. Thus, additional research is needed to determine the relationship between obesity and cardiovascular-related mortality.

2.6.3.2 Effect of Diabetes

Just as the research on the association between diabetes and all-cause mortality is limited, information on the relationship between diabetes and cardiovascular-related, or vascular, mortality is even more sparse. To date, only one study that investigated this relationship has been identified.[18]

Winell *et al.*[18] sought to determine whether survival after a first-ischemic stroke differed between subjects with and without type 2 diabetes using the Finnish National Hospital Discharge Register and Causes of Death Register. The presence of diabetes was determined based on the date of diagnosis of type 2 diabetes in the National Hospital Discharge Register or the date of first reimbursement for hypoglycemic medication. Cardiovascular-related mortality at 28-days following the first ischemic stroke was determined using the Causes of Death Register. Additionally, cardiovascular-related mortality at 1-year after the first ischemic stroke for the subjects who survived at least to 28-days was also included as an outcome of interest. Analyses were stratified by gender and further adjusted for university hospital district and 5-year age groups.

Winell *et al.*[18] demonstrated that subjects with type 2 diabetes have a consistently higher risk of cardiovascular-related mortality compared with subjects without type 2

diabetes. Specifically, for 28-day cardiovascular-related mortality, men with type 2 diabetes had 1.32 (95% CI: 1.14-1.52) times the risk of cardiovascular-related mortality compared with men without type 2 diabetes; women with type 2 diabetes were found to have 1.23 (95% CI: 1.05-1.44) times the risk of cardiovascular-related mortality compared with women without type 2 diabetes. Additionally, of those subjects who survived at least 28-days following stroke, men with type 2 diabetes had 1.43 (95% CI: 1.15-1.77) times the risk of cardiovascular-related mortality compared with men without type 2 diabetes; women with type 2 diabetes had 2.17 (95% CI: 1.71-2.74) times the risk of cardiovascular-related causes compared with women without type 2 diabetes.

2.7 **Significance**

The prevalence of obesity has increased drastically over the last 30 years from 15% in 1980 to 34% in 2010, or a 226% increase.[1] Concurrent with the increase in obesity, the prevalence of diabetes has grown substantially from 3.5% in 1980 to 9.3% in 2010, or a 265% increase.[4] Furthermore, obesity and diabetes are risk factors for an ischemic stroke.[2,5,7,52–57,60–64] Of individuals who previously had an ischemic stroke, it is estimated that between 18% and 44% of individuals are obese, and between 15% and 27% of all individuals have diabetes.[31] In addition to the incidence of ischemic stroke, obesity and diabetes are also independently related to clinical outcomes following an ischemic stroke (*e.g.*, functional disability, all-cause mortality, and cardiovascular-related mortality).[8–30] Reducing the burden of obesity and diabetes has the potential to minimize the risk of incident stroke as well as clinical outcomes following an ischemic stroke.

This dissertation is important and novel because it addresses a scientific question that has yet to be addressed: Does a joint effect between obesity and diabetes on clinical outcomes following an ischemic stroke exist? Previous research has determined that obesity and diabetes are independently associated clinical outcomes following an ischemic stroke. However, no study has investigated the presence of a joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke. Based on recent research that has supported the heterogeneity of the metabolic profile among obese individuals,[71,72] coupled with prior scientific evidence of the presence of an interaction effect of central obesity and diabetes on the risk of stroke,[32] it is suggested that the effect of obesity on clinical outcomes following an ischemic stroke may differ according to diabetes status.

Secondly, the proposed research will answer the scientific question using data from two completed clinical trials. Compared with prior studies, the study populations from these clinical trials are more diverse and have more complete information. Studying this topic area allows this research to assess whether certain subgroups of individuals are at higher (or lower) risk for outcomes following an ischemic stroke. Thus, these results will aid in targeting subgroups for which a future intervention will be most effective.

As previously indicated, the definition of obesity is heterogeneous within the literature of the relationship of obesity on clinical outcomes following a stroke. Although BMI is the recommended measure of obesity,[77,81,82] it has several limitations that may result in the misclassification, or misdiagnosis, of obesity.[77–80] Hence, BMI may not be the best measure to quantify or define obesity. Given the increasing prevalence of obesity

in the general population[1] as well as in the ischemic stroke population[31] coupled with the fact that obesity is a leading cause of morbidity and mortality,[106] it is critical for the construct of obesity to be accurately quantified and defined. Acknowledging that BMI is an imperfect reference measure of obesity, the reported effects of obesity on clinical outcomes following a stroke may be biased.[107–110] Thus, this dissertation illustrates the extent to which misclassification and measurement error are present in exposure assessment of obesity measured by several anthropometric measures using data from the PRoFESS clinical trial. Results may signify the need for increased efforts aimed towards determining an accurate measure of obesity that can be easily used in clinical practice and research.

3 Original Manuscript 1

Title: Determining the joint effect of obesity and diabetes on functional disability at 3-months and on all-cause mortality at 1-year following an ischemic stroke

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3.1 **Abstract**

Background – Obesity and diabetes mellitus, or diabetes, are independently associated with post-ischemic stroke outcomes (*e.g.*, functional disability and all-cause mortality). Although obesity and diabetes are also associated with post-ischemic stroke outcomes, the joint effect of obesity and diabetes on these post-ischemic stroke outcomes has not been explored previously. The current study explored the joint effect of obesity and diabetes on post-ischemic stroke outcomes in acute ischemic stroke subjects with at least a moderate stroke severity.

Methods– Data from the Interventional Management of Stroke (IMS) III clinical trial was analyzed for this post-hoc analysis. A total of 656 subjects were enrolled in IMS III and were followed for one year. The joint effects of obesity and diabetes on functional disability at 3-months and all-cause mortality at 1-year were examined.

Results – Of 645 subjects with complete obesity and diabetes information, few were obese (25.74%) or had diabetes (22.64%). Obese subjects with diabetes and non-obese subjects without diabetes had similar odds of functional disability at 3-months following an ischemic stroke (adjusted common odds ratio, 1.04, 95% CI: 0.63, 1.71). For all-cause mortality at 1-year following an ischemic stroke, obese subjects with diabetes had a similar hazard compared with non-obese subjects without diabetes (adjusted hazard ratio, 1.00, 95% CI: 0.56, 1.81). There was insufficient evidence to declare a joint effect between obesity and diabetes on either the multiplicative scale or the additive scale for both outcomes.

Conclusions – In this post-hoc analysis of data from the IMS III clinical trial of acute ischemic stroke patients with at least a moderate stroke severity, there was not sufficient evidence to determine that the effect of obesity differed by diabetes status on post-ischemic stroke outcomes.

3.2 **Introduction**

Obesity and diabetes mellitus, or diabetes, are not only highly prevalent in both the general US and international populations,[1–4] but these factors are also prevalent among individuals who have been diagnosed with an ischemic stroke.[31] It is estimated that between 18% and 44% of individuals who previously had an ischemic stroke are obese, and between 25% and 45% of individuals who previously had an ischemic stroke have diabetes.[31]

Stroke is a leading cause of long-term disability and death.[43] As a result, it is important to target modifiable factors in order to reduce the burden of these post stroke outcomes. Obesity and diabetes are independently associated with functional disability[11,20–24] and all-cause mortality[8–12,14,16–19,25,26,29,30] following an ischemic stroke. Although obesity is a modifiable risk factor for ischemic stroke,[6,7] the reported effects of obesity on post-stroke outcomes of functional disability and of all-cause mortality have been conflicting. Whereas studies of the general population have found that increasing body mass concurrently increases the risk of functional disability[111] and of all-cause mortality,[100,101] a number of observational studies in a stroke population have reported that obesity is associated with a decreased risk of functional disability[11,20,21] and all-cause mortality;[8–12,14,25,26] this apparent discrepancy is referred to as the obesity paradox. As a result of these findings, the American Heart Association and American Stroke Association recommend all individuals who are diagnosed with an ischemic stroke be screened for obesity.[31] However, these agencies do not recommend weight reduction for overweight or obese individuals due to the null results of the Look Action for Health in

Diabetes trial, a clinical trial that randomized overweight and obese individuals with type 2 diabetes to intensive behavioral intervention or usual care to compare the risk of vascular events (*e.g.*, stroke, myocardial infarction, or vascular death).[5,31] Despite evidence supporting the obesity paradox in the stroke literature as well as in the literature of other chronic diseases such as myocardial infarction, heart failure, and renal disease,[102,103] several investigators have questioned the validity of studies supporting the 'obesity paradox,' citing methodological issues (*e.g.,* the measurement of obesity, duration of obesity, treatment and/or selection bias due to the study population) or residual confounding as potential explanations.[102,103,105,112] In contrast to the conflicting reported effects of obesity on functional disability and all-cause mortality following a stroke, prior studies have established that diabetes is consistently associated with higher rates of functional disability[22–24] and higher risk of all-cause mortality[16–19,29,30] following a stroke.

Although obesity is a strong predictor of diabetes,[34,35] it is unknown whether diabetes modifies the inflammatory effects of obesity on functional disability or on all-cause mortality after an ischemic stroke. Research has recently supported the heterogeneity of the metabolic profile among obese individuals[71,72], which suggests that the effect of obesity on functional disability and all-cause mortality following an ischemic stroke may differ according to diabetes status. The primary objective of this study was to explore the presence of a joint effect of obesity and diabetes on functional disability and on all-cause mortality following an ischemic stroke.

3.3 **Materials and Methods**

Study population

This present study used data from the Interventional Management of Stroke (IMS) III clinical trial (IMS III, ClinicalTrials.gov number NCT00359424).[113] Details of the scientific rationale, eligibility requirements, and baseline characteristics of the IMS III subjects have been published elsewhere.[36,113] Briefly, the objective of the IMS III trial was to determine if subjects treated with a combined approach of intravenous recombinant tissue plasminogen activator (IV rt-PA) and endovascular therapy were more likely to have a better functional outcome than subjects treated with standard IV rt-PA alone.[36,113] Eligibility was restricted to subjects between 18 and 80 years old, initiated with IV rt-PA within three hours of ischemic stroke onset, and with a moderate-to-severe ischemic stroke, defined by a baseline National Institutes of Health Stroke Scale (NIHSS) score of at least 8.[36,113] Subjects were followed for one year after onset of the ischemic stroke.[113] The Data and Safety Monitoring Board recommended the trial to stop in April 2012, after 656 subjects were randomized, due to crossing the pre-specified boundary for futility.[36] Specifically, the trial failed to show a benefit in functional outcome for the combined approach of IV rt-PA and endovascular therapy compared with standard IV rt-PA alone.[36]

Exposures of interest

Obesity and diabetes are the exposures of interest for this study. Based on source documentation and the IMS III Case Report Form Guidelines, obesity (yes, no) and diabetes (yes, no) were collected at the baseline visit. No further information was

included in the Case Report Form Guidelines regarding the source for identifying this information (*i.e.* medical record documentation, patient reported history of disease, medically documented history of disease, lab test).

Outcomes

The outcomes of interest for this study include functional disability at 3-months and all-cause mortality at 1-year following an ischemic stroke. Functional disability was measured using the modified Rankin scale (mRS), a 7-point ordinal scale that measures a subject's degree of functional disability in daily activities after suffering from a stroke.[114] The mRS ranges from 0 to 6, with higher scores indicating greater functional disability.[114] For the current study, the full scale of the mRS was analyzed in order to incorporate response information from all categories. The mRS categories of 5 and 6 were collapsed into a single category based on the opinions of stroke subjects who indicated that being severely disabled (*i.e.*, category 5) is just as bad as or worse than death (*i.e.*, category 6).[115] All-cause mortality at 1-year was defined as death due to any cause.

Baseline data

A number of potential confounders were considered in the modeling approach on the basis of prognostic value or consistency within the literature.[8–12,16–26,29,30] Multivariable models for each outcome were fit including pre-specified variables that were forced into the final model in addition to potential confounders, which are shown in **Table 1**.

Statistical analysis

All subjects were followed from the date of enrollment until the date of death, loss to follow-up, or the end of their 1-year follow-up, whichever occurred first. The relationship between functional disability at 3-months following an ischemic stroke and exposures of obesity and diabetes was modeled via proportional odds regression. A cross-product interaction term was used to derive adjusted common odds ratios (OR) and 95% confidence intervals (CI). The proportional odds assumption was assessed for all exposure variables and potential confounders using the Score test. The relationship between all-cause mortality at 1-year following an ischemic stroke and exposures of obesity and diabetes was modeled via Cox proportional hazards regression. A cross-product interaction term was used to derive adjusted hazard ratios (HR) and 95% CIs. The proportional hazards assumption was verified for all exposure variables and potential confounders using Schoenfeld residuals and time-dependent covariates.[116] For both models, multicollinearity between covariates was assessed by calculating individual variance inflation factors for each of the exposure variables and the potential confounders.

The joint effect of obesity and diabetes was examined on both the multiplicative and additive scales. The likelihood ratio test of the cross-product interaction term was used to determine the significance of the joint effect on the multiplicative scale. The joint effect on the additive scale, or the biologic interaction, was evaluated by two indices: the relative excess risk because of the interaction (RERI); and the attributable proportion because of the interaction (AP).[87] RERI is an estimate of the excess risk attributable to

the joint effect of obesity and diabetes and AP is defined as the proportion of risk attributable to the joint effect of obesity and diabetes.[87] These indices, along with their 95% CIs, were constructed using the approach of Li and Chambless.[117] A value of 0 indicates that there is no biologic interaction present.[117,118]

All statistical tests were two-sided and used an alpha-level of 0.05 with the exception of the joint effect on the multiplicative scale. For the joint effect on the multiplicative scale, statistical significance was defined at an alpha-level of 0.10, rather than 0.05, because clinical trials are not designed to detect a joint effect, only a main effect.[119] Statistical analyses were conducted using SAS software package version 9.4 (SAS Institute, Cary, NC). Institutional Review Board approval for this analysis was obtained from the Medical University of South Carolina (Pro00063231).

3.4 **Results**

Baseline characteristics of the IMS III study sample

Of the 656 IMS III subjects who were enrolled and randomized, obesity or diabetes information was not available for 11 (1.68%) subjects. Baseline characteristics according to obesity and diabetes information are shown in Table 2. Among these 645 subjects with complete obesity and diabetes information, few subjects were obese (25.74%) or had diabetes (22.64%). The majority of subjects was older than 65 years (58.45%), male (51.78%), white (84.50%), had a history of hypertension (74.73%), and were former/never smokers (75.19%). Among subjects without diabetes, obese subjects were more likely to have the following characteristics: be younger than 65 years, female, have a history of hypertension, have a baseline systolic blood pressure of at least 140

mmHg, and have a higher baseline median glucose. Among subjects with diabetes, obese subjects were also more likely to be younger than 65 years and have a higher baseline median glucose but were more likely to be male, white, and have a baseline systolic blood pressure of at least 140 mmHg.

Joint effect of obesity and diabetes on functional disability at 3-months

The adjusted joint effect of obesity and diabetes on functional disability at 3-months following an ischemic stroke is shown in **Table 3**. Obese subjects with diabetes had similar odds of functional disability at 3-months compared with the reference group (common OR: 1.04, 95% CI: 0.63, 1.71). Similarly, there was not sufficient evidence to declare a joint effect between obesity and diabetes on either the multiplicative scale ($P_{\text{interaction}}$, 0.6746) or the additive scale (RERI: 0.078, 95% CI: -0.260, 0.416; AP:0.075, 95% CI: -0.169, 0.319). To further illustrate the distribution of functional disability at 3-months following an ischemic stroke, the mRS scores according to obesity and diabetes are displayed using Grotta bars in **Figure 1**.

Main effects of obesity and diabetes on functional disability at 3-months

There was insufficient evidence to demonstrate that obesity was associated with increased odds of functional disability at 3-months following an ischemic stroke (**Table 4**, common OR: 0.74, 95% CI: 0.52, 1.04), after adjusting for diabetes and other factors. Similarly, there was also not sufficient evidence to determine that diabetes was not associated with increased odds of functional disability at 3-months following an ischemic stroke (common OR: 1.34, 95% CI: 0.92, 1.94), after adjusting for obesity and other factors.

Joint effect of obesity and diabetes on all-cause mortality at 1-year

The adjusted joint effects of obesity and diabetes on all-cause mortality at 1-year following an ischemic stroke are shown in **Table 5**. Obese subjects with diabetes had a similar hazard of all-cause mortality at 1-year following an ischemic stroke compared with the reference group (HR: 1.01, 95% CI: 0.56, 1.81). Furthermore, there was not sufficient evidence to declare a joint effect between obesity and diabetes on either the multiplicative scale ($P_{\text{interaction}}$, 0.5311) or the additive scale (RERI: -0.257, 95% CI: -0.842, 0.327; AP:-0.256, 95% CI: -0.557, 0.045).

Main effects of obesity and diabetes on all-cause mortality at 1-year

There was insufficient evidence to demonstrate that obesity was associated with an increased hazard of all-cause mortality at 1-year following an ischemic stroke (**Table 4**, HR: 1.09, 95% CI: 0.74, 1.60), after adjusting for diabetes and other factors. Similarly, there was also not sufficient evidence to determine that diabetes was not associated with an increased hazard of all-cause mortality at 1-year following an ischemic stroke (HR: 0.98, 95% CI: 0.64, 1.51), after adjusting for obesity and other factors.

3.5 **Discussion**

The purpose of this post-hoc analysis of data from the IMS III clinical trial of acute ischemic stroke patients with at least a moderate stroke severity was to explore the presence of a joint effect of obesity and diabetes on functional disability and on all-cause mortality following an ischemic stroke. Overall, there was not sufficient evidence to determine that the effect of obesity differed by diabetes status on functional disability at 3-months, or on all-cause mortality at 1-year, following an ischemic stroke on either the

multiplicative scale or the additive scale. In addition, although obesity[8–11,25–27,120] and diabetes[16–19,29,30] have been previously shown to be independently associated with all-cause mortality following a stroke, there was not sufficient evidence to determine that each factor was independently associated with all-cause mortality after adjusting for potential confounders in this cohort of acute ischemic stroke patients with at least a moderate stroke severity. In contrast, the point estimates for the independent associations between each factor and functional disability at 3-months following an ischemic stroke were consistent with the findings from the literature.[11,20–24]

In comparison to some of the studies that cite the obesity paradox on post-stroke outcomes, there are several potential reasons for the discrepant results in the present study. First, the population only consisted of acute ischemic stroke subjects.[92,102,105] Some of the results from this study are consistent with several other studies that included only ischemic stroke subjects whereas the majority of the studies that support the obesity paradox included different patient populations (*i.e.*, only hemorrhagic,[28] only ischemic,[8,9,12,20,21,23,24,92,97] stroke or TIA,[11,25] or both ischemic and hemorrhagic strokes[10,22,26,27]). It is important to point out these differences in the study population because the pathogenesis of ischemic stroke is markedly different from that of hemorrhagic stroke, thus the effect of obesity on post-stroke outcomes may not be the same.[121] However, results of this study were similar to several other studies that only included recent ischemic stroke subjects.[20,21,97] Second, the outcomes of interest in studies that support the association between obesity and a decreased risk of all-cause mortality post-stroke were assessed at widely varying periods ranging from a week to 10

years.[92,102,105] However, the studies that had time points similar to the time points of acute stroke trials (IMS III, for example) determined that there was no functional or survival benefit for obese subjects.[14,20,92] Third, the inclusion of important prognostic factors, such as stroke severity and smoking use, as potential confounders differed across studies.[92,102,105] It is critical to account for these important confounders to reduce residual confounding, however many of the studies that assessed these associations did not account for these confounding variables. Lastly, the measure of obesity is nearly always body mass index (BMI). Although BMI is the most commonly used diagnostic tool for obesity in clinical practice,[31,78] BMI is unable to differentiate between body fat percentage and lean mass which leads to misclassification[122] nor does it tell the distribution of body fat in the body. Rather than using BMI to measure obesity, it is critical to determine alternative diagnostic tools capable of differentiating risk of poor clinical outcomes following an ischemic stroke such as waist circumference or waist-to-hip ratio.[79,102]

The present study has a number of limitations that could influence the interpretation of the study results. First, due to the restrictive criteria of the IMS III clinical trial, the results of the present study may not be generalizable to all ischemic stroke patients. For example, patients were excluded if they had mild stroke severity (NIHSS < 8). As a result, the generalizability of the results of this study is limited to ischemic stroke patients with at least a moderate stroke severity and who met all of the study eligibility criteria. Second, results of this study were limited in the interpretability of the results partially due to how obesity and diabetes information was captured (*i.e.*,

binary summary measures). Further, there may be measurement error based on the how obesity and diabetes information was ascertained. Specifically, no further definition of these variables was provided in the IMS III Case Report Form Guidelines. Therefore, we were not able to accurately define obesity or diabetes based on their BMI or fasting blood glucose levels, respectively. Future studies should capture multiple measures of obesity, specifically raw BMI, and waist circumference and/or waist-to-hip ratio, rather than a summary measure for obesity, which would allow for greater interpretability. Third, IMS III was not designed to answer the research questions of the present study. Examining joint effects, or interactions, is challenging because tests for interactions are typically underpowered.[123] Despite these limitations and the confines of statistical power, this study was able to demonstrate the joint effect of obesity and diabetes on functional disability and on all-cause mortality following an ischemic stroke is insignificant. Although other analytical strategies were applied to offset these problems, it is imperative to strive for sufficient power to examine the potential joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke. Thus, it is critical to utilize a national or international ischemic stroke registry that would provide sufficient resources and power for future studies to address these research questions.

Despite some limitations, the present study includes several notable strengths. First, this is the first study to explore the potential multiplicative and additive joint effects of obesity and diabetes on functional disability and all-cause mortality following an ischemic stroke. Results of this research provide evidence for generating hypotheses for future studies investigating how obesity and diabetes could potentially interact with one

another to affect the clinical outcomes following an ischemic stroke. Second, the rigorous data collection of the IMS III trial reduced information bias. Rather than relying on subjects self-reporting their medical history, the use of source documentation to verify sociodemographic characteristics, clinical characteristics, and risk factors and comorbidities prevented bias that may have resulted from self-reporting. Third, IMS III investigators followed strict study procedures, which minimized the potential bias from incorrect documentation of the trial's outcomes.

3.6 **Conclusions**

Overall, it is important to continue to study joint effects of these common modifiable factors to identify susceptible subgroups of individuals that would potentially benefit from effective interventions targeted at reducing the burden of functional disability and all-cause mortality.[123] This topic is of high public health priority. Obesity and diabetes are not only highly prevalent in both the general US and international populations,[1,3,4,124] but they are also prevalent among individuals who have been diagnosed with a stroke.[31] It is estimated that between 18% and 44% of individuals who previously had an ischemic stroke are obese, and between 25% and 45% of individuals who previously had an ischemic stroke have diabetes.[31] Recent research has supported the heterogeneity of the metabolic profile among obese individuals.[71,72] Overall, the underlying mechanisms by which obesity and diabetes may interact to affect functional disability or all-cause mortality following an ischemic stroke remain unclear. Thus, future studies should differentiate between metabolically healthy and metabolically unhealthy patients within BMI categories (or other diagnostic tools for obesity) to determine if the

effect of obesity on post-stroke outcomes differs by diabetes (or some other metabolic health measure).

3.7 **Tables and Figures**

Table 1. Variables and Definitions of Pre-Specified Variables and Potential Confounders for Analysis.

Variables	Definition
Pre-Specified Variables	
Age [a,b]	≤ 65 years, > 65 years
Gender [a,b]	Male, Female
Race/ethnicity [a,b]	White, Black/Other
Treatment assignment [a,b]	IV rt-PA + Endovascular therapy, IV rt-PA
Baseline stroke severity [a,b]	NIHSS < 20, NIHSS ≥ 20
Ischemic stroke sub-type [a,b]	Large-artery atherosclerosis, Cardioembolic, Small-artery occlusion/Other/Unknown
Potential Confounders	
Baseline systolic blood pressure [a,b]	< 140 mmHg, ≥ 140 mmHg
Baseline diastolic blood pressure [a,b]	in mmHg
Baseline glucose [a,b]	in mmol/L
History of previous stroke [a,b]	Yes, No
History of atrial fibrillation [a,b]	Yes, No
History of coronary artery disease [a,b]	Yes, No
History of hypertension [a,b]	Yes, No
Smoking status [a,b]	Current smoker, Former/Never smoker
Alcohol use [a,b]	Current drinker, Former/Never drinker

[a] Potential confounder for functional disability; [b] Potential confounder for all-cause mortality

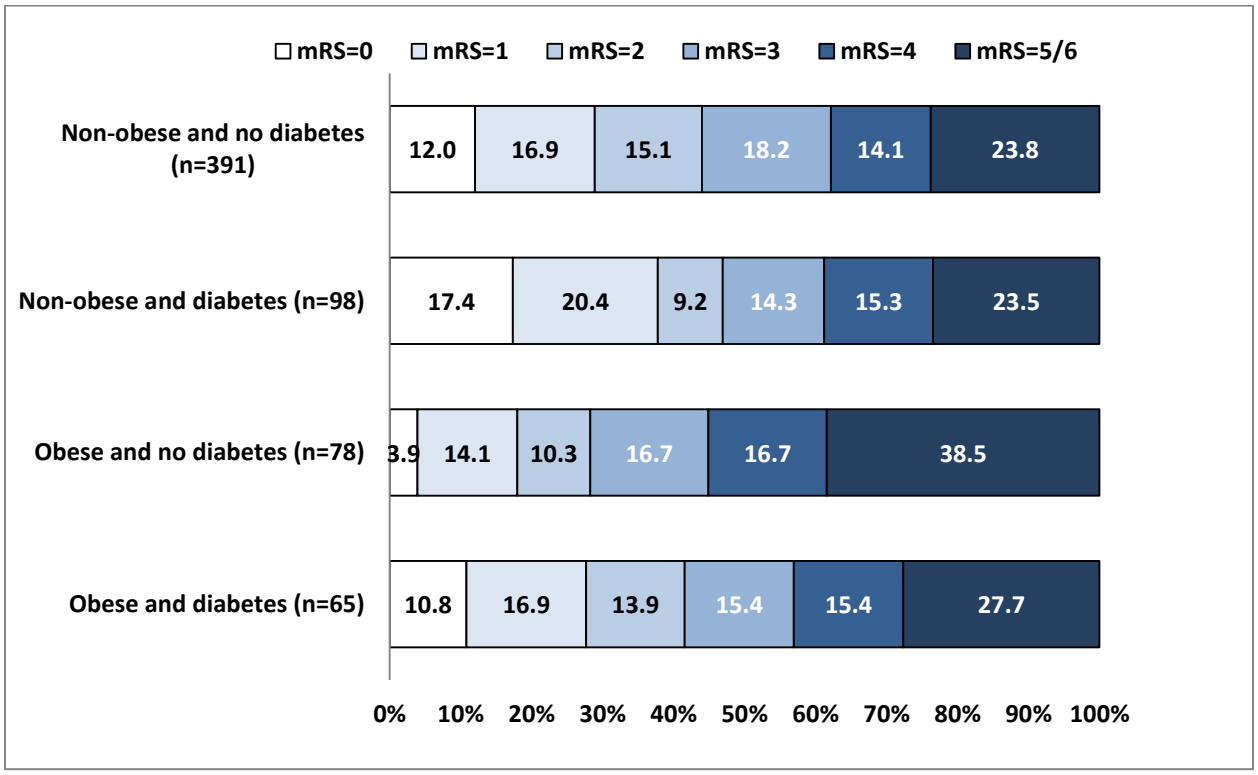
Table 2. Baseline Characteristics of IMS III Subjects and by Obesity Categories and Diabetes Status.

Characteristic	All subjects	No Diabetes		Diabetes	
		Non-Obese	Obese	Non-Obese	Obese
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
No. of subjects [a]	645	398	101	81	65
Obese					
Yes	166 (25.74)				
No	479 (74.26)				
Diabetes					
Yes	146 (22.64)				
No	499 (77.36)				
Sociodemographic Characteristics					
Age					
> 65 years	377 (58.45)	230 (57.79)	48 (47.52)	64 (79.01)	35 (53.85)
Gender					
Male	334 (51.78)	222 (55.78)	37 (36.63)	37 (45.68)	38 (58.46)
Race/ethnicity					
White	545 (84.50)	339 (85.18)	87 (86.14)	61 (75.31)	58 (89.23)
Black/Other	100 (15.50)	59 (14.82)	14 (13.86)	20 (24.69)	7 (10.77)
Clinical Characteristics					
Qualifying stroke subtype					
Large vessel atherosclerosis	127 (19.69)	70 (17.59)	24 (23.76)	18 (22.22)	15 (23.08)
Cardioembolic	299 (46.36)	185 (46.48)	46 (45.54)	37 (45.68)	31 (47.69)
Small vessel disease/Other/Unknown	219 (33.95)	143 (35.93)	31 (30.69)	26 (32.10)	19 (29.23)
Baseline stroke severity					
Severe (NIHSS ≥ 20)	198 (30.99)	6.3 (5.6-7.5)	6.7 (5.9-7.4)	8.2 (6.2-10.0)	8.8 (6.9-12.5)
Baseline glucose (median, IQR)	6.7 (5.7-8.1)	6.3 (5.6-7.4)	6.7 (5.9-7.4)	8.2 (6.1-10.0)	8.8 (6.9-12.3)
Baseline systolic blood pressure					
≥ 140 mmHg	386 (60.60)	219 (55.73)	67 (67.68)	62 (77.50)	38 (58.46)
Baseline diastolic blood pressure (median, IQR)	81 (71-94)	80 (70-93)	85 (70.5-98)	85 (73-96)	80 (71-91)
Treatment assignment					
IV rt-PA+ Endovascular therapy	429 (66.51)	274 (68.84)	61 (60.40)	50 (61.73)	44 (67.69)
IV rt-PA	216 (33.49)	124 (31.16)	40 (39.60)	31 (38.27)	21 (32.31)
Risk Factors and Comorbidities					
Smoking status					
Current smoker	160 (24.81)	106 (26.63)	30 (29.70)	14 (17.28)	10 (15.38)
Alcohol use					
Current drinker	251 (38.91)	165 (41.46)	43 (42.57)	21 (25.93)	22 (33.85)
History of a previous stroke					
Yes	86 (13.33)	46 (11.56)	9 (8.91)	21 (25.93)	10 (15.38)
History of hypertension					
Yes	482 (74.73)	269 (67.59)	79 (78.22)	72 (88.89)	62 (95.38)
History of coronary artery disease					
Yes	170 (26.36)	90 (22.61)	22 (21.78)	37 (45.68)	21 (32.31)
History of atrial fibrillation					
Yes	192 (29.77)	120 (30.15)	30 (29.70)	22 (27.16)	20 (30.77)

[a] 11 subjects were excluded due to missing obesity or diabetes information

IMS III – Interventional Management of Stroke III; NIHSS – National Institutes of Health Stroke Scale; IV rt-PA – intravenous recombinant tissue plasminogen activator; IQR – interquartile range

Figure 1. Distribution of modified Rankin Scale scores at 3-months following an ischemic stroke.



Distribution of scores on the modified Rankin Scale at 3-months following an ischemic stroke according to obesity and diabetes in 632 IMS III subjects.
mRS – modified Rankin Scale; IMS III – Interventional Management of Stroke III

Table 3. Adjusted Common ORs for Functional Disability at 3-months in Relation to Obesity and Diabetes.

Functional Disability at 3-months following the ischemic stroke	**Obesity Categories**	
	Non-obese	Obese
	OR (95% CI)	OR (95% CI)
Diabetes		
No	1.00	0.70 (0.466, 1.063)
Yes	1.26 (0.78, 2.02)	1.04 (0.63, 1.71)
Joint effect (additive): RERI (95% CI)		0.078 (-0.260, 0.416)
AP (95% CI)		0.075 (-0.169, 0.319)
Joint effect on the multiplicative scale: p-value		*P*=0.6746

ORs are adjusted for age, gender, race/ethnicity, ischemic stroke sub-type, baseline stroke severity, baseline glucose, treatment assignment, smoking status, alcohol use, history of previous stroke, history of hypertension, and history of coronary artery disease.

RERI – relative excess risk due to interaction; AP – attributable proportion due to interaction

Table 4. Adjusted Effect Measures for Associations between Obesity, Diabetes and Outcomes of Interest.

Outcome	
3-month functional disability[a]	**OR (95% CI)**
Obesity	0.74 (0.52, 1.04)
Diabetes	1.34 (0.92, 1.94)
All-cause mortality[b]	**HR (95% CI)**
Obesity	1.09 (0.74, 1.60)
Diabetes	0.98 (0.64, 1.51)

[a] ORs are adjusted for age, gender, race/ethnicity, ischemic stroke sub-type, baseline stroke severity, baseline glucose, treatment assignment, smoking status, alcohol use, history of previous stroke, history of hypertension, and history of coronary artery disease.

[b] HRs are adjusted for age, gender, race/ethnicity, ischemic stroke sub-type, baseline stroke severity, baseline glucose, baseline diastolic blood pressure, treatment assignment, smoking status, alcohol use, history of hypertension, and history of previous stroke.

Table 5. Adjusted HRs for All-Cause Mortality at 1-year in Relation to Obesity and Diabetes.

All-Cause Mortality at 1-year	Obesity Categories			
	Non-obese		Obese	
	Deaths/ total	HR (95% CI)	Deaths/ total	HR (95% CI)
Diabetes				
No	85/398	1.00	24/101	1.198 (0.74, 1.93)
Yes	27/81	1.06 (0.64, 1.76)	17/65	1.01 (0.56, 1.81)
Joint effect (additive): RERI (95% CI)			-0.257 (-0.842, 0.327)	
AP (95% CI)			-0.256 (-0.557, 0.045)	
Joint effect on the multiplicative scale: p-value			*P*=0.5311	

HRs are adjusted for age, gender, race/ethnicity, ischemic stroke sub-type, baseline stroke severity, baseline glucose, baseline diastolic blood pressure, treatment assignment, smoking status, alcohol use, history of hypertension, and history of previous stroke.

RERI – relative excess risk due to interaction; AP – attributable proportion due to interaction

4 Original Manuscript 2

Title: Determining the joint effect of obesity and diabetes on all-cause mortality and cardiovascular-related mortality following an ischemic stroke

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obesity; diabetes; joint effect; all-cause mortality; cardiovascular-related mortality; ischemic stroke

4.1 **Abstract**

Although obesity and diabetes mellitus, or diabetes, are independently associated with mortality-related events (*e.g.*, all-cause mortality and cardiovascular-related mortality) following an ischemic stroke, little is known about the joint effect of obesity and diabetes on mortality-related events following an ischemic stroke. The aim of this study is to evaluate the joint effect of obesity and diabetes on mortality-related events in subjects with a recent ischemic stroke. Data from the multicenter Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial was analyzed for this study. The joint effect of obesity and diabetes on mortality-related events was estimated via Cox proportional hazards regression models. No difference in the hazard of all-cause mortality following an ischemic stroke was observed between obese subjects with diabetes and underweight/normal-weight subjects without diabetes. In contrast, obese subjects with diabetes had an increased hazard of cardiovascular-related mortality following an ischemic compared with underweight/normal-weight subjects without diabetes. Additionally, there was evidence of an attributable proportion due to interaction as well as evidence of a highly statistically significant interaction on the multiplicative scale for cardiovascular-related mortality. In this clinical trial cohort of ischemic stroke survivors, obesity and diabetes synergistically interacted to increase the hazard of cardiovascular-related mortality.

4.2 **Introduction**

Although obesity and diabetes are established independent risk factors for ischemic stroke,[5] their joint effect on stroke risk is not well explored. In the only published study of the joint effect of obesity and diabetes on stroke risk, Olofindayo *et al.*[32] determined that the effect of central obesity, measured by waist circumference, on the risk of a stroke differed by diabetes status (*e.g.*, having or not having a prior diagnosis of diabetes). Specifically, they found that individuals with both central obesity and diabetes had an increased risk for stroke greater than the sum (and product) of the risk of individuals with either central obesity or diabetes.[32]

To date, there is no known study on the joint effect, or interactive effects, of these factors on mortality-related events (*e.g.*, all-cause mortality and cardiovascular-related mortality) following an ischemic stroke. It is known, however, that obesity and diabetes are independently associated with mortality-related events following an ischemic stroke. The reported effects of obesity on mortality-related events following an ischemic stroke have been conflicting. Whereas studies of the general population have found that increasing weight increases the risk of mortality,[100,101] a number of observational studies have reported that obesity is associated with a decreased risk of both all-cause[8–13] and cardiovascular-related[9,14,15] mortality following a stroke; this apparent discrepancy is referred to as the obesity paradox.[8–15] Several investigators have questioned the validity of the obesity paradox, citing methodological issues (*e.g.*, the measurement of obesity, treatment and/or selection bias due to the study population) or residual confounding as potential explanations.[102–104] In contrast to the conflicting reported effects on obesity and

mortality-related events following a stroke, prior studies have established that diabetes is associated with higher risk of all-cause mortality[16–19] and cardiovascular-related mortality[18] following a stroke.

The current study assumed that the conflicting findings in the obesity and diabetes literature may be due to a joint effect of obesity and diabetes that is previously unexamined. The pathogenesis of stroke is a heterogeneous process that involves molecular, cellular, neuronal, individual, and environmental factors.[33] Because diabetes is related to obesity,[34,35] diabetes may potentially modify the inflammatory effects of body mass on risk of mortality-related events after an ischemic stroke. If so, elucidation of the joint effect of obesity and diabetes may help identify high risk subgroups and provide new insights into underlying mechanisms.

Although previous studies have shown evidence that obesity and diabetes are independently associated with mortality-related events in a stroke population, there is a lack of research on the joint effect of obesity and diabetes on mortality-related events following an ischemic stroke. The current research has tremendous public health relevance given the increasing prevalence of obesity and the expected increase in prevalence of diabetes in the US and internationally. The objective of this study was to determine the joint effect of obesity and diabetes on the risk of mortality-related events following an ischemic stroke in a cohort of ischemic stroke survivors.

4.3 **Materials and Methods**

Study population

The data source for the current study is the PRoFESS trial, a double-blind 2-by-2

factorial trial (ClinicalTrials.gov number NCT00153062).[125] The objective of the PRoFESS trial was to determine if extended-release dipyridamole and aspirin were superior to clopidogrel, and if telmisartan was superior to placebo, in preventing a recurrent stroke in subjects who were recently diagnosed with an ischemic stroke.[125] Details of the scientific rationale, eligibility requirements, and baseline characteristics of the PRoFESS subjects have been published elsewhere. [37,125–127] Briefly, 20,332 subjects were enrolled in PRoFESS between September 2003 and July 2006 at 695 study centers in 35 countries and were followed for a median time of 2.4 years (range 1.5-4.4 years) from randomization.[37,126,127] To be eligible, subjects had to be at least 55 years and were randomized within 90 days of experiencing an ischemic stroke, or had to be between 50 and 54 years, have at least two additional risk factors, and were randomized between 90 and 120 days after experiencing an ischemic stroke.[125]

Exposures

BMI and diabetes are the exposures of interest for the current study and were defined based on information identified at the baseline visit. Typically, BMI is defined as weight in kilograms per the square of height in meters (kg/m^2).[52] Subjects were categorized into underweight/normal-weight (BMI < 25.0 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2) based on the published guidelines of the World Health Organization.[52] Prior diagnosis of diabetes (yes, no) was measured as a summary variable. Diagnosis of diabetes was ascertained using source documentation (*i.e.,* the subject's medical record).

Outcomes

All-cause mortality, defined as death due to any cause, and cardiovascular-related mortality, defined as death due to stroke (*i.e.*, ischemic, hemorrhagic, or uncertain cause), myocardial infarction, hemorrhage excluding intracranial bleeding, and other vascular causes,[127] were the primary outcomes for this research. At the completion of the PRoFESS trial, 1,495 subjects had died from all causes, and 894 subjects had died due to cardiovascular-related causes. These dependent variables were confirmed by the PRoFESS trial's Adjudication and Assessment Committee.[125]

Statistical analysis

Subjects with missing obesity and diabetes information were excluded from the analysis. All subjects were followed from the date of enrollment until the date of death, lost to follow-up, or the end of the clinical trial, whichever occurred first. Baseline characteristics were presented as a median and interquartile range for continuous variables and as a number and proportion for categorical variables.

Cox proportional hazards (CPH) regression models were utilized to model the relationship between all-cause and cardiovascular-related mortality and exposures of BMI and diabetes as defined above; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were constructed according to a common reference category of underweight/normal-weight subjects without diabetes. A multivariable CPH regression model for each mortality-related event was fit including pre-specified variables that were forced into the final model in addition to potential confounders, which are shown in **Table 1**. Due to their known prognostic value, age, gender, race/ethnicity, baseline stroke

severity, ischemic stroke sub-type, and treatment assignment were forced into the final models for both mortality-related events. A variable was considered a potential confounder if it was significant univariately at the $\alpha = 0.25$ level or its presence resulted in at least a 10% difference in the effect measure between the crude and adjusted estimates. Backward selection using the likelihood ratio test was used to obtain the final models that included the significant confounders. The proportional hazards assumption was assessed using Schoenfeld residuals and time-dependent covariates.[116] For continuous variables, linearity in the log hazard was evaluated by assessing the cumulative martingale residuals. Additionally, multicollinearity between covariates was assessed by calculating individual variance inflation factors for each of the exposure variables and the potential confounders.

The joint effect of BMI and diabetes was examined on both the multiplicative and additive scales in relation to the hazard of all-cause mortality (and cardiovascular-related mortality) following an ischemic stroke. The likelihood ratio test was used to determine the significance of the cross-product interaction term between BMI and diabetes. Additionally, the joint effect on the additive scale, or the biologic interaction, was evaluated by two indices: the relative excess risk because of the interaction (RERI); and the attributable proportion because of the interaction (AP).[87] RERI is an estimate of the excess risk attributable to the joint effect of obesity and diabetes and AP is defined as the proportion of risk attributable to the joint effect of obesity and diabetes.[87] These indices, along with their 95% CIs, were constructed using the approach of Li and Chambless.[117] A value of 0 indicates that there is no biologic interaction present.[117,118]

All statistical tests were two-sided and used an alpha-level of 0.05 with the exception of the joint effect on the multiplicative scale. For the joint effect on the multiplicative scale, statistical significance was defined at an alpha-level of 0.10, rather than 0.05, because clinical trials are not designed to detect a joint effect, only a main effect.[119] Statistical analyses were conducted using SAS software package version 9.4 (SAS Institute, Cary, NC). Institutional Review Board approval for this analysis was obtained from the Medical University of South Carolina.

4.4 **Results**

Baseline characteristics of the PRoFESS study sample

Of the 20,332 subjects enrolled in the PRoFESS trial, BMI or diabetes information was not available for 86 subjects (0.42%). As a result, data from 20,246 subjects were analyzed in the current study. Baseline characteristics and the number of deaths due to all causes and due to cardiovascular-related causes observed according to BMI category and diabetes status are shown in **Table 2.** Among these 20,246 subjects with complete BMI and diabetes information, few subjects were obese (20.96%), and had a prior diagnosis of diabetes (28.22%). The majority of subjects were male (64.09%), older than 65 years (54.86%), white (57.30%), had a history of hypertension (74.03%), had no prior stroke or TIA (75.42%), were current smokers (57.34%), and had mild neurological severity for their qualifying stroke defined as a NIHSS < 8 (93.35%). Among subjects without diabetes, compared with underweight/normal-weight subjects, obese subjects were more likely to have the following characteristics: female, White, have a history of hypertension, have a history of coronary artery disease, have a history

of congestive heart failure, have a history of myocardial infarction, have a history of hyperlipidemia, and be sedentary. Similarly, among subjects with diabetes, compared with underweight/normal-weight subjects, obese subjects were also more likely to be female, White, have a history of hypertension, have a history of coronary artery disease, have a history of congestive heart failure, have a history of myocardial infarction, have a history of hyperlipidemia, and be sedentary. In contrast, among subjects with diabetes, obese subjects were more likely to have a mild neurological severity for their qualifying stroke.

All-cause mortality following an ischemic stroke

The adjusted joint effects of BMI categories and diabetes status on all-cause mortality are shown in **Table 3.** Obese subjects with diabetes had a similar hazard of all-cause mortality following an ischemic stroke compared with the reference group, or subjects who were underweight/normal-weight without diabetes (HR: 0.97,; 95% CI: 0.79, 1.19). There was insufficient evidence to declare an interaction between obesity and diabetes on either the multiplicative ($P_{\text{interaction}}$=0.1487) or the additive scale (RERI: -0.0206, 95% CI: -0.317, 0.276; AP: -0.0213, 95% CI: -0.113, 0.0708).

Cardiovascular-related mortality following an ischemic stroke

The adjusted joint effects of BMI categories and diabetes status on cardiovascular-related mortality are shown in **Table 4.** Obese subjects with diabetes had an increased hazard of cardiovascular-related mortality following an ischemic stroke compared with underweight/normal-weight subjects without diabetes (HR: 1.43; 95% CI: 1.12, 1.84). On the multiplicative scale, there was a significant joint effect of obesity and

diabetes ($P_{interaction}$= 0.0048). In addition, a significant additive interactive effect between obesity and diabetes on cardiovascular-related mortality was indicated by the significant AP estimate and its confidence interval (AP: 0.260, 95% CI: 0.157, 0.362). In contrast, there was insufficient evidence of an additive interaction for the RERI (0.372, 95% CI: -0.061, 0.806).

4.5 **Discussion**

Although obesity[8–15] and diabetes[16–19] are independently associated with mortality-related events following an ischemic stroke, this was the first study to explore the potential joint effect of obesity and diabetes on mortality-related events following an ischemic stroke on the additive and multiplicative scales. Studying joint effects can identify susceptible subgroups of individuals that would potentially benefit from effective interventions.[128] Joint effects on the additive scale are important public health indices[128,129] because they have been suggestive of a biological interaction, or an underlying causal mechanism.[128,129]

In the current study, there was insufficient evidence to determine a joint effect of obesity and diabetes on all-cause mortality on either the multiplicative scales. However, compared with underweight/normal-weight subjects without diabetes, obese subjects with diabetes were approximately 43% (HR: 1.43, 95% CI: 1.12, 1.84) more likely to die from cardiovascular-related causes following an ischemic stroke. Although the combined effect of obesity and diabetes did not exceed the sum of the separate effects of obesity and diabetes (RERI: 0.372, 95% CI: -0.061, 0.806), approximately 26.0% of the cardiovascular-related deaths following an ischemic stroke in this cohort of ischemic

stroke survivors could be attributed to the joint effect of obesity and diabetes (AP: 0.260, 95% CI: 0.157, 0.362).

The World Health Organization (WHO) expert consultation recently advocated for different BMI cut-off limits for individuals of Asian race/ethnicity. [50] As a result, subgroup analyses were performed to investigate the consistency in results among Asians using the WHO standard BMI and the Asia Pacific Guidelines from the WHO. Conclusions were not substantively altered in the subgroup of Asian race/ethnicity when the Asia Pacific Guidelines for BMI categories were applied.

The exact mechanisms by which obesity and diabetes increase the hazard of cardiovascular-related mortality following an ischemic stroke cannot be determined from the present study. Given that obesity and diabetes are major risk factors for cardiovascular morbidity and mortality and are additionally associated with hypertension, dyslipidemia, and elevated levels of fibrinogen and C-reactive protein, other risk factors for cardiovascular morbidity and mortality,[34,35,130] future studies can focus on understanding the mechanisms for this finding. Hence, it is hypothesized that these mechanisms are multifactorial and involve molecular, cellular, neuronal, individual, and environmental factors.[33]

Limitations and strengths

The present study included several limitations, one of which was survivorship bias related to study sample selection. This study's sample consisted of a cohort of individuals who survived a period of time (median time=15 days) following onset of a qualifying stroke and who met specific inclusion criteria of the PRoFESS trial. Hence,

there was the potential for selection bias because individuals with a more severe neurologic deficit at the time of the qualifying stroke may have not been included in the PRoFESS trial.

Other limitations identified were associated with the exposure variables of obesity and diabetes. The data available for the study measured weight only at randomization, and thus the potential impact of weight change over the course of the follow-up period could not be assessed. Although weight loss after a stroke is relatively common, Jönsson *et al.*[131] noted that the median weight loss four months following a stroke was only 0.6 kg (or 1.32 lbs) in a cohort of first-time stroke patients. Hence, in the present study, it was assumed that the median amount of weight that subjects may have lost between ischemic stroke onset and baseline BMI assessment would result in subjects maintaining a relatively consistent BMI or BMI category between these two time periods. In addition, the PRoFESS trial data did not differentiate between type 1 and type 2 diabetes. However, as type 2 diabetes accounts for approximately 95% of all diagnosed cases of diabetes in the US,[4,59] it may be assumed that the majority of diabetes cases in the PRoFESS trial were type 2 diabetes.

Due to the restrictive inclusion criteria of the PRoFESS trial, the results of the present study may not be generalizable to all ischemic stroke survivors. For example, individuals were excluded if they had a severe disability after the qualifying stroke.[125] Furthermore, the PRoFESS trial was not designed to answer the research questions of the present study. Examining joint effects, or interactions, is challenging because tests for interactions are typically underpowered.[123] Hence, it is critical to utilize a national or

international ischemic stroke registry that would provide sufficient resources and power for future studies to address these research questions.

Despite some limitations, the present study includes several notable strengths. First, this study utilized data from a large clinical trial with prospective ascertainment of the dependent variables of interest. Further, the rigorous data collection of the PRoFESS trial reduced information bias. Rather than relying on subjects self-reporting their medical history, the PRoFESS trial utilized source documents to verify subjects' medical history. Additionally, the use of clinical trial data ensured that strict study procedures were followed, which minimized the potential bias from incorrect documentation of the trial's outcomes.

This study was the first to examine the joint effects, or the interactive effects, of BMI and diabetes on mortality-related events following an ischemic stroke on the additive and multiplicative scales. Additionally, the results of this study provide evidence for generating hypotheses for future studies investigating how BMI and diabetes could potentially interact with one another to affect the risk of mortality-related events following an ischemic stroke. These results could also be used by future investigators to develop interventions focused on reducing the burden of all-cause, and cardiovascular-related mortality, following onset of an ischemic stroke.

Clinical relevance

The American Heart Association and the American Stroke Association recommend using BMI to diagnose obesity.[31] However, BMI may not be the best diagnostic tool to measure obesity because this diagnostic tool is unable to differentiate

between body fat and lean mass.[79] It has recently been hypothesized that there are different phenotypes of obesity, namely obese metabolically healthy and obese metabolically unhealthy.[71] Thus, it is critical to determine new diagnostic tools capable of differentiating risk of poor outcomes following an ischemic stroke based on BMI (or waist circumference or waist-to-hip ratio) [79,102] and metabolic health.

Public health relevance

Obesity and diabetes are highly prevalent in both the general US and international populations[1–4] as well as among individuals who have been diagnosed with a stroke.[31] Although the prevalence of obesity and diabetes vary by region and country, it is estimated that between 18% and 44% of individuals who previously had an ischemic stroke are obese, and between 25% and 45% of individuals who previously had an ischemic stroke have diabetes.[31] Despite the high prevalence of these risk factors among stroke survivors, the current guidelines from the American Heart Association and American Stroke Association only recommend that all individuals who are diagnosed with an ischemic stroke be screened for diabetes and obesity.[31] The guidelines no longer recommend weight reduction for individuals with a BMI over 25 kg/m^2 due to the unexpected relationship between obesity and prognosis after stroke and the null results of a weight loss intervention.[31] Thus, it is important to focus research on understanding the mechanism by which diabetes modifies the relationship between BMI and mortality-related events following an ischemic stroke in order to develop more focused guidelines and interventions to reduce mortality rates for individuals with these risk factors.

Future directions

The current study included a post-hoc analysis of data from the PRoFESS trial. Results from this study add valuable information to the literature regarding post-ischemic stroke outcomes. Specifically, the findings suggest that obese individuals with diabetes have an increased hazard of cardiovascular-related mortality following an ischemic stroke compared with underweight/normal-weight individuals without diabetes. Thus, results from the current study suggest that future interventions should focus resources on obese individuals with diabetes in order to reduce the excess burden of cardiovascular-related mortality in this group. Additionally, future population-based cohort studies are needed to examine whether the effect of obesity, measured by BMI or another diagnostic tool, on mortality-related events following an ischemic stroke differs by diabetes status.

Disclosure Statement/Data Availability

This work was facilitated by the Boehringer Ingelheim Policy of Transparency and Publication of Clinical Study Data, under which researchers may access and analyse clinical trial data with appropriate analytical tools. BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

4.6 **Tables and Figures**

Table 1. Variables and Definitions of Pre-Specified Variables and Potential Confounders for Analysis.

Variables	Definition
Pre-Specified Variables	
Age *†	< 65 years, ≥ 65 years
Gender *†	Male, Female
Race/ethnicity *†	non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other
Treatment assignment *†	Aspirin + extended release dipyridamole/ telmisartan, Clopidogrel /telmisartan, Aspirin + extended release dipyridamole/placebo, Clopidogrel/ placebo
Qualifying stroke neurological severity *†	Mild (NIHSS < 8), Moderate/Severe (NIHSS ≥ 8)
Ischemic stroke sub-type *†	Large-artery atherosclerosis, Cardioembolism, Small-artery occlusion, Other, Undetermined
Potential Confounders	
Baseline systolic blood pressure *†	in mmHg
History of previous stroke or TIA *†	Yes, No
History of previous myocardial infarction *†	Yes, No
History of atrial fibrillation *	Yes, No
History of congestive heart failure *	Yes, No
History of coronary artery disease *†	Yes, No
History of hypertension *†	Yes, No
History of hyperlipidemia †	Yes, No
Smoking status *†	Current smoker, Former/Never smoker
Regular alcohol consumption *	At least 1 drink/week, No alcohol consumption
Average physical activity prior to qualifying stroke *†	Sedentary: walking <1 mile/day, Some physical activity: 20-30 minutes, 3 times/week, Intense physical activity: > 30 minutes, > 3 times/week

* Potential confounder for all-cause mortality; † Potential confounder for cardiovascular-related mortality

Table 2. Baseline Characteristics of 20,246 Ischemic Stroke Survivors and by BMI Categories and Diabetes, the PRoFESS trial.

Characteristic	All participants	No diabetes		
		Underweight/ normal-weight	Overweight	Obese
	No. (%)	No. (%)	No. (%)	No. (%)
No. of participants [a]	20246	5958	5881	2693
No. of participants who died from all causes	1485	495	337	126
No. of participants who died from cardiovascular-related causes	887	288	190	67
Diabetes				
No	14532 (71.78)			
Yes	5714 (28.22)			
BMI categories				
Underweight/normal-weight	7864 (38.84)			
Overweight	8138 (40.20)			
Obese	4244 (20.96)			
BMI (kg/m^2) (median, IQR)	26.1 (23.6-29.3)	22.9 (21.3-24.1)	27.1 (26.0-28.3)	32.5 (31.1-35.2)
Sociodemographic Characteristics				
Age				
≥ 65 years	11107 (54.86)	3558 (59.72)	3288 (55.91)	1364 (50.65)
Gender				
Male	12976 (64.09)	3843 (64.50)	4025 (68.44)	1450 (53.84)
Race/ethnicity				
White	11600 (57.3)	2834 (47.57)	3972 (67.54)	2118 (78.65)
Black	804 (3.97)	146 (2.45)	177 (3.01)	149 (5.53)
Asian	6645 (32.82)	2712 (45.52)	1416 (24.08)	236 (8.76)
Hispanic	987 (4.88)	223 (3.74)	271 (4.61)	148 (5.50)
Other	210 (1.04)	43 (0.72)	45 (0.77)	42 (1.56)
Clinical Characteristics				
Qualifying stroke neurological severity				
Mild	18896 (93.35)	5512 (92.53)	5571 (94.76)	2555 (94.88)
Moderate/Severe	1347 (6.65)	445 (7.47)	308 (5.24)	138 (5.11)
Qualifying stroke subtype				
Large vessel atherosclerosis	5789 (28.61)	1851 (31.09)	1594 (27.12)	639 (23.75)
Cardioembolic	369 (1.82)	111 (1.86)	126 (2.14)	64 (2.38)
Small vessel disease	10530 (52.04)	2999 (50.38)	2986 (50.80)	1399 (52.01)
Other	411 (2.03)	109 (1.83)	133 (2.26)	66 (2.45)
Unknown	3135 (15.49)	883 (14.83)	1039 (17.68)	522 (19.41)
Baseline systolic blood pressure (median, IQR)	142 (130-156)	141 (130-155)	142 (131-156)	143 (131-157)
Treatment group				
A †	5024 (25.01)	1499 (25.36)	1464 (25.07)	672 (25.17)
B ‡	5004 (24.91)	1442 (24.39)	1472 (25.21)	680 (25.47)
C §	5041 (25.09)	1462 (24.73)	1461 (25.02)	636 (23.82)
D | |	5019 (24.99)	1509 (25.52)	1442 (24.70)	682 (25.54)
Risk Factors and Comorbidities				
History of previous stroke or TIA				
Yes	4975 (24.58)	1482 (24.89)	1337 (22.74)	602 (22.37)
History of previous myocardial infarction				
Yes	1362 (6.73)	292 (4.90)	382 (6.50)	199 (7.39)
History of atrial fibrillation				
Yes	538 (2.66)	165 (2.77)	183 (3.11)	89 (3.30)
History of congestive heart failure				
Yes	532 (2.63)	113 (1.90)	143 (2.43)	121 (4.49)
History of coronary artery disease				
Yes	3296 (16.28)	729 (12.24)	994 (16.90)	534 (19.83)
History of hypertension				
Yes	14987 (74.03)	3788 (65.58)	4264 (72.52)	2152 (79.91)
History of hyperlipidemia				
Yes	9453 (46.76)	2245 (37.73)	2730 (46.48)	1366 (50.89)
Smoking status				
Current smoker	11606 (57.34)	3563 (59.81)	3481 (59.21)	1443 (53.62)
Regular alcohol consumption				
≥ 1 drink/week	7206 (35.45)	2217 (37.22)	2434 (41.39)	959 (35.64)
Average physical activity prior to qualifying stroke				
Sedentary	7209 (35.83)	1824 (30.76)	1865 (31.95)	1175 (44.01)
Some physical activity	6446 (32.04)	1979 (33.37)	1937 (33.18)	786 (29.44)
Intense physical activity	6465 (32.13)	2127 (35.87)	2036 (34.87)	709 (26.55)

Table continues

Table 2. Continued

Characteristic	Diabetes		
	Underweight/ normal-weight No. (%)	Overweight No. (%)	Obese No. (%)
No. of participants*	1906	2257	1551
No. of participants who died from all causes	219	180	128
No. of participants who died from cardiovascular-related causes	136	111	95
Diabetes			
No			
Yes			
BMI categories			
Underweight/normal-weight			
Overweight			
Obese			
BMI (kg/m^2) (median, IQR)	23.0 (21.5-24.0)	27.2 (26.0-28.4)	33.1 (31.3-36.3)
Sociodemographic Characteristics			
Age			
≥ 65 years	1000 (52.47)	1178 (52.19)	719 (46.36)
Gender			
Male	1271 (66.68)	1530 (67.79)	857 (55.25)
Race/ethnicity			
White	482 (25.29)	1106 (49.00)	1088 (70.15)
Black	51 (2.68)	118 (5.23)	163 (10.51)
Asian	1277 (67.00)	847 (37.53)	157 (10.12)
Hispanic	82 (4.30)	159 (7.04)	104 (6.71)
Other	14 (0.73)	27 (1.20)	39 (2.51)
Clinical Characteristics			
Qualifying stroke neurological severity			
Mild	1718 (90.14)	2083 (92.29)	1457 (93.94)
Moderate/Severe	188 (9.86)	174 (7.71)	94 (6.06)
Qualifying stroke subtype			
Large vessel atherosclerosis	663 (34.78)	654 (28.99)	388 (25.02)
Cardioembolic	21 (1.10)	27 (1.20)	20 (1.29)
Small vessel disease	1036 (54.35)	1237 (54.83)	873 (56.29)
Other	17 (0.89)	41 (1.82)	45 (2.90)
Unknown	169 (8.87)	297 (13.16)	225 (14.51)
Baseline systolic blood pressure (median, IQR)	142 (130-157)	144 (132-158)	144 (131-158)
Treatment group			
A †	434 (22.90)	588 (26.24)	367 (23.97)
B ‡	509 (26.86)	524 (23.38)	377 (24.62)
C §	497 (26.23)	583 (26.02)	402 (26.26)
D ||	455 (24.01)	546 (24.36)	385 (25.15)
Risk Factors and Comorbidities			
History of previous stroke or TIA			
Yes	547 (28.70)	621 (27.55)	386 (24.89)
History of previous myocardial infarction			
Yes	105 (5.51)	206 (9.14)	178 (11.48)
History of atrial fibrillation			
Yes	27 (1.42)	34 (1.51)	40 (2.58)
History of congestive heart failure			
Yes	34 (1.78)	52 (2.30)	69 (4.45)
History of coronary artery disease			
Yes	252 (13.22)	433 (19.18)	354 (22.82)
History of hypertension			
Yes	1481 (77.70)	1901 (84.23)	1401 (90.33)
History of hyperlipidemia			
Yes	882 (46.35)	1271 (56.39)	959 (61.91)
Smoking status			
Current smoker	982 (51.52)	1275 (56.52)	862 (55.61)
Regular alcohol consumption			
≥ 1 drink/week	467 (24.50)	696 (30.85)	404 (26.06)
Average physical activity prior to qualifying stroke			
Sedentary	694 (36.70)	896 (39.86)	755 (48.96)
Some physical activity	592 (31.31)	696 (30.95)	456 (29.57)
Intense physical activity	605 (31.99)	656 (29.18)	331 (21.47)

*86 participants were excluded due to missing BMI or diabetes information; † Aspirin + Extended Release Dipyridamole/Telmisartan; ‡ Clopidogrel/Telmisartan; §Aspirin + Extended Release Dipyridamole/Placebo; || Clopidogrel/Placebo

Table 3. Adjusted HRs (95% CIs) for All-Cause Mortality following an Ischemic Stroke in Relation to Categorical Indicators of BMI and Diabetes.

All-Cause Mortality	**Obesity Categories**					
	Underweight/normal-weight		Overweight		Obese	
	Deaths/ total	HR (95% CI)	Deaths/ total	HR (95% CI)	Deaths/ total	HR (95% CI)
Diabetes						
No	495/5,958	1.00	337/5,881	0.70 (0.61, 0.81)	126/2,693	0.53 (0.43, 0.66)
Yes	219/1,906	1.46 (1.23, 1.72)	180/2,257	0.94 (0.79, 1.12)	128/1,551	0.97 (0.79, 1.19)
Interaction (additive): RERI * (95% CI), AP † (95% CI)			-0.216 (-0.492, 0.0594), -0.230 (-0.323, -0.137)		-0.0206 (-0.317, 0.276) -0.0213 (-0.113, 0.0708)	
Interaction on multiplicative scale: p-value			*P*=0.5177		*P*=0.1487	

HRs are adjusted for age, gender, race/ethnicity, qualifying stroke neurological severity, ischemic stroke sub-type, baseline systolic blood pressure, hypertension, treatment assignment, history of congestive heart failure, history of atrial fibrillation, history of coronary artery disease, history of previous stroke or TIA, history of myocardial infarction, smoking status, alcohol consumption, and average physical activity prior to qualifying stroke.

*RERI = relative excess risk due to interaction, †AP=attributable proportion due to interaction

Table 4. Adjusted HRs (95% CIs) for Cardiovascular-Related Mortality following an Ischemic Stroke in Relation to Categorical Indicators of BMI and Diabetes.

Cardiovascular-Related Mortality	**Obesity Categories**					
	Underweight/normal-weight		Overweight		Obese	
	Deaths/ total	HR (95% CI)	Deaths/ total	HR (95% CI)	Deaths/ total	HR (95% CI)
Diabetes						
No	288/5,598	1.00	190/5,881	0.72 (0.60, 0.87)	67/2,693	0.54 (0.41, 0.7219)
Yes	136/1,906	1.52 (1.23, 1.88)	111/2,257	1.06 (0.84, 1.33)	95/1,551	1.43 (1.12, 1.84)
Interaction (additive): RERI* (95% CI), AP † (95% CI)			-0.182 (-0.555, 0.190), -0.173 (-0.293, -0.0526)		0.372 (-0.061, 0.806) 0.260 (0.157, 0.362)	
Interaction on multiplicative scale: p-value			*P*=0.8278		*P*=0.0046	

HRs are adjusted for age, gender, race/ethnicity, qualifying stroke neurological severity, ischemic stroke sub-type, baseline systolic blood pressure, hypertension, treatment assignment, hyperlipidemia, history of coronary artery disease, history of previous stroke or TIA, history of myocardial infarction, smoking status, and average physical activity prior to qualifying stroke.

*RERI = relative excess risk due to interaction, †AP=attributable proportion due to interaction

5 Original Manuscript 3

Title: Misclassification and measurement error in exposure assessment of obesity

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Keywords

obesity; anthropometric measures; measurement error; misclassification error; ischemic stroke

5.1 **Abstract**

Obesity is highly prevalent in both the United States and international general populations. Individuals with a history of ischemic stroke tend to have higher rates of obesity. Although obesity is a modifiable risk factor for stroke, the impact of obesity on outcomes (*e.g.*, all-cause mortality) following a stroke is conflicting. Specifically, a number of observational studies have reported that obesity is associated with a decreased risk of all-cause mortality following a stroke, despite biological implausibility and the lack of epidemiological evidence associating obesity with a lower risk of all-cause mortality in the general population.

The measure of obesity has been hypothesized as a potential reason for the paradoxical results. Although body mass index (BMI) is the most widely used measure of obesity, it is susceptible to measurement error. For example, BMI is incapable of distinguishing between muscle and fat mass.

However, it is critical for the construct of obesity to be correctly quantified and defined. Error in the measurement of obesity may impact the estimate of the outcome of interest, such as all-cause mortality, and will not reflect the true magnitude of the problem. As a result, the objective of the current study was to illustrate the extent to which misclassification and measurement error are present in exposure assessment of obesity among a cohort of ischemic stroke survivors using data from the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) clinical trial.

Results of the current study indicated that there was no evidence of mechanical error in measurement as indicated by the comparability of the anthropometric measures (*i.e.*, BMI, waist circumference, waist circumference-to-height ratio) from the PRoFESS

cohort and the anthropometric measures from a population reference standard. Of the three continuous anthropometric measures, BMI was the best at discriminating the patient-relevant clinical outcome of all-cause mortality following an ischemic stroke. However, all of the continuous anthropometric measures were only able to discriminate between subjects with and without the outcome slightly better than chance (area under the curve ≤ 0.60), suggesting evidence of measurement error. Further, there was evidence of misclassification error as indicated by the naïve estimates of diagnostic accuracy for each categorical anthropometric measure at discriminating all-cause mortality within this cohort of ischemic stroke survivors. Stroke is a leading cause of death in the US and international general populations, many of which also have a high prevalence of obesity. Therefore, as shown in the present study, it is imperative to improve calibration of the available measures of obesity and/or to develop alternative methods for determining body adiposity.

5.2 **Introduction**

Obesity is highly prevalent in both the general United States and international populations.[1,2] Since 1980, the prevalence rate of obesity has increased more than 200% in the United States and internationally.[1,132] Obesity, or excess adiposity, is an independent risk factor for a variety of cardiovascular diseases, including stroke.[1,43] In a meta-analysis of data from 25 observational studies, compared with normal-weight individuals, obese individuals had an increased risk for ischemic stroke of 64% (RR: 1.64, 95% CI: 1.36-1.99).[133] This relationship did not hold for hemorrhagic stroke (RR: 1.01, 95% CI: 0.88-1.17).[133] Obesity is also prevalent among individuals with a history of ischemic stroke. It is estimated that between 18% and 44% of individuals who previously had an ischemic stroke are obese.[31]

Stroke is a leading cause of death.[43] Therefore, it is important to target modifiable risk factors such as the precipitating factor of obesity in order to reduce the burden of all-cause mortality following a stroke. Although obesity is a modifiable risk factor for stroke,[6,7] the reported effects of obesity, defined by an elevated body mass index (BMI), on all-cause mortality following a stroke have been conflicting. Specifically, epidemiological studies within this topic area have demonstrated a variety of relationships–including linear, inversely linear, U-shaped, or no relationship–between BMI and the likelihood of all-cause mortality following a stroke.[8–12,14,20,25–27,92,97,98] Whereas observational studies of the general population have found that increasing body mass concurrently increases the risk of all-cause mortality,[100,101] a number of observational studies have reported that obesity is associated with a decreased risk of all-cause mortality following a stroke.[8–12,25,26] This apparent discrepancy is referred to as the

obesity paradox, first documented by Olsen *et al.*[8]. There is some evidence supporting the obesity paradox in the context of other chronic diseases such as myocardial infarction, heart failure, and renal disease.[102,103] However, it is biologically implausible that a risk factor for incident stroke, in addition to all-cause mortality in the general population, could be a protective factor for all-cause mortality among individuals who previously had a stroke. Due to these paradoxical results, there is literature that questions the validity of the obesity paradox.[102–104] In a recent systematic review, Oesch *et al.*[102] questioned the validity of the paradox due to the lack of evidence of a biologically graded or linear relationship between the degree of obesity and mortality following a stroke. They found that overweight individuals, not obese individuals, had the lowest risk of mortality following a stroke.[102] Several investigators have cited methodological issues related to the measurement of obesity and residual confounding as potential explanations of the obesity paradox.[102–104]

The literature within this topic area has consistently utilized BMI to measure obesity; however, the definition and BMI cut points for obesity are heterogeneous. Six studies used one category to denote obesity,[9,10,26,92,97,98] whereas six[8,11,12,20,25,28] other studies subdivided obesity into at least two categories. Additional categories of obesity are based on public health action cut points endorsed by the World Health Organization (WHO).[50] The WHO BMI categories are intended for international use, however there has been growing debate on whether cut points should be specific to an individual's race/ethnicity due to racial/ethnic differences in the distribution of body fat.[50] Among studies that focused on obesity and all-cause mortality following a stroke and used the same number of BMI categories for obesity, cut points for BMI differed based on the

race/ethnicity of the study population. To ascertain the true effect of obesity on all-cause mortality following a stroke, it is important to utilize an accurate and consistent measure and definition of obesity.

In order to ascertain the true effect of obesity on all-cause mortality following a stroke, it is important to utilize an accurate measure of obesity. However, there are multiple methods to measure obesity. For example, obesity can be quantified and defined using BMI, waist circumference (WC), WC-to-height ratio (WHR), WC-to-hip circumference ratio, skinfold thickness, dual x-ray absorptiometry (DEXA), underwater weighing, or air displacement.[77,78] Of these methods, DEXA, underwater weighing, and air displacement offer more precise measures of body adiposity.[77,78] However, these methods are not viable options to be applied at the population or clinical level due to cost and convenience.[77–80] BMI, instead, is the most utilized diagnostic criteria to measure obesity in epidemiologic studies as well as in clinical practice.[77,81,82] Numerous expert panels such as the US Preventive Services Task Force and the American Heart Association/American Stroke Association recommend using BMI to screen for obesity utilizing the BMI $\geq$ 30 kg/m^2 cut point.[5,43,82] Although BMI is the recommended diagnostic measure for obesity, there are several limitations associated with using BMI as a proxy measure to identify or represent obesity. BMI cannot differentiate between excess adipose tissue, the distribution of adipose tissue, or high muscle mass.[77–80] BMI could overestimate adiposity in the case of a muscular individual such as a collegiate athlete. Further, BMI does not account for differences in gender, age, or bone structure.[77–80] As an individual ages, body fat tends to increase whereas muscle mass decreases.[134] As a result, the individual may stay the same weight and his/her BMI remains unchanged

despite changes in body fat and muscle mass. While BMI has relatively high specificity (between 92-95% in men and 93-99% in women), it has poor sensitivity (between 36-41% for men and 32-49% for women) to detect obesity.[79,84] Although BMI is the recommended measure of obesity, it should be recognized as an imperfect reference standard because it misclassifies a large number of individuals who are obese based on a more precise measure of obesity. Further, the number of measures of obesity is concerning. Each measure provides a different piece of the obesity construct, yet there is not a measure of obesity that adequately estimates excess adiposity, predicts the outcome of interest, and can easily be used in epidemiologic studies and clinical practice.

Given that the prevalence of obesity is increasing and that obesity is a leading cause of morbidity and mortality,[106] it is critical for the construct of obesity to be accurately defined and measured. Several consequences occur when using BMI as the reference standard measure of obesity: 1) the estimated diagnostic accuracy (*e.g.,* sensitivity, specificity, *etc*.) of other measures of obesity (index tests) compared to BMI will be biased,[109,110] and 2) the use of BMI as a measure of obesity may lead to biased inferences.[107–110] As such, the diagnostic accuracy (or inaccuracy) of the obesity measure used should not only be recognized but should also be accounted for in the analysis. In order to minimize the impact of bias due to an imperfect reference standard or measurement error, the Agency for Healthcare Research and Quality[109] suggest four alternative methods when determining the diagnostic accuracy of other obesity measures compared to BMI. These options include: 1) assessing the index test's ability to predict patient-relevant clinical outcomes instead of diagnostic accuracy; 2) assessing agreement (*i.e.,* concordance) between each index test and the imperfect reference standard; 3)

calculating diagnostic accuracy estimates and discussing the direction in which the estimates are biased; and 4) adjusting the diagnostic accuracy estimates to account for the imperfect reference standard.[109] Methods such as regression calibration and simulation extrapolation can be used to correct for bias.[108,135] However, these methods require an estimate of the measurement error variance or within-subject variation.[108,135] The current study assesses the extent to which misclassification and measurement error are present in the exposure assessment of obesity using data from the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) clinical trial. To ensure the anthropometric measures of the PRoFESS clinical trial are comparable in dispersion, anthropometric measures of the National Health and Nutrition Examination Survey (NHANES) III cohort are used as a population reference standard.

5.3 **Materials and Methods**

Study population

The data source for the current study is the PRoFESS trial, a double-blind 2-by-2 factorial trial (ClinicalTrials.gov number NCT00153062).[125] Details of the scientific rationale, eligibility requirements, and baseline characteristics of the PRoFESS subjects have been published elsewhere.[37,125–127] Briefly, the objective of the PRoFESS trial was to determine if extended-release dipyridamole and aspirin were superior to clopidogrel, and if telmisartan was superior to placebo, in preventing a recurrent stroke in subjects who were recently diagnosed with an ischemic stroke.[125] Between September 2003 and July 2006, 20,332 subjects were enrolled in PRoFESS at 695 study centers in 35 countries and were followed for a median time of 2.4 years (range 1.5-4.4 years) from

randomization.[37,126,127] To be eligible, subjects had to be at least 55 years and were randomized within 90 days of experiencing an ischemic stroke. Subjects were also eligible if they were between 50 and 54 years with at least two additional risk factors and were randomized between 90 and 120 days after experiencing an ischemic stroke.[125]

Anthropometric measures

Measures of height, weight, and WC were performed at the time of randomization, or baseline. BMI was calculated as weight in kilograms per the square of height in meters (kg/m^2). Additionally, WHR was computed as WC (cm) divided by height (cm).

Ascertainment of the outcome

All-cause mortality, defined as death due to any cause, was the patient-relevant clinical outcome of interest for this study. The outcome was restricted to the first event recorded during follow-up. At the completion of the PRoFESS clinical trial, there were 1,495 deaths which were adjudicated by the PRoFESS trial's Adjudication and Assessment Committee.[125]

Statistical analysis

All statistical analyses were conducted using SAS software package version 9.4 (SAS Institute, Cary, NC). Subjects with missing anthropometric information were excluded from the analysis. All subjects were followed from the date of randomization until the date of death, lost to follow-up, or the end of the clinical trial, whichever occurred first.

The distribution of each continuous anthropometric measure of obesity (*i.e.*, BMI, WC, and WHR) was graphically assessed using a QQ-plot. Categorical baseline

characteristics are presented as a number and proportion, and continuous baseline characteristics are shown as a mean and standard deviation (SD) or as a median and interquartile range.

The coefficient of variation (CV), a measure of dispersion relative to the mean,[136] was calculated for the following continuous anthropometric measures from the PRoFESS cohort: body weight, height, BMI, WC, WHR. The CV of the same anthropometric measures from the NHANES III cohort was also calculated. Anthropometric measures from the NHANES III cohort were considered reference measures, or indicators of a measure's dispersion for a population standard. For each anthropometric measure, the CV with the lowest value was considered a less disperse, or heterogeneous measure.[136] Further, the dispersion of a measure was considered stable if the CV was less than 20%.

Bland-Altman[137] limits of agreement analysis was employed to demonstrate the extent to which WC and WHR agree with BMI. The mean difference (*i.e.*, mean bias) between two continuous measures was estimated by constructing limits of agreement.[137,138] Limits of agreement were calculated using the mean and standard deviation of the differences between the two continuous measures.[137,138] BMI was used as the reference measure because it is recommended to screen and diagnose obesity.[5,43,82,83] Due to the different units of the anthropometric measures of obesity, they were z-standardized for all subjects and by gender. In general, if either of the tested measures (*i.e.*, WC or WHR) agree well with the reference measure (*i.e.*, BMI), Bland and Altman[137] state that the tested measure may replace the reference measure. For the purposes of this illustration, very wide limits of agreement were considered–2 z-scores or more, between 1.5 and 1.99 z-scores as wide, and less than 1.5 z-scores as reasonable

agreement. Pearson correlation coefficients were also calculated to examine linear associations between WC and BMI, and WHR and BMI. Agreement between the continuous anthropometric measures were considered very weak (≤ 0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.00).[139]

Naïve estimates of diagnostic accuracy (*i.e.*, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy[140]) and 95% confidence intervals (95% CI) to discriminate a patient-relevant clinical outcome were calculated for each categorical anthropometric measure of obesity. For this illustration, all-cause mortality following onset of an ischemic stroke was chosen as the outcome of interest because stroke is one of the leading causes of death[43] and it is considered a natural extension of stroke. The following categorizations were used to determine the diagnostic accuracy of BMI, WC, and WHR in discriminating all-cause mortality following an ischemic stroke: obesity (BMI ≥ 30 kg/m^2)[141], abdominal obesity (WC > 102 cm (men) and > 88 cm (women)),[141] and abdominal obesity (WHR ≥ 0.53 (men) and ≥ 0.54 (women)).[142]

Assessing naïve estimates of diagnostic accuracy to discriminate a patient-relevant clinical outcome depends on the cut off for obesity, which may be incorrect due to individual differences in fat distribution. As such, it is important to utilize a diagnostic method that does not rely on calculating diagnostic accuracy based on one cut point and also allows for adjustment of potential confounders. Similar to the naïve estimates of diagnostic accuracy, all-cause mortality following onset of an ischemic stroke was the outcome of interest. Logistic regression models were utilized to estimate the odds ratio (OR) and 95% CI for a one SD increase in each continuous anthropometric measure of

obesity in relation to all-cause mortality following an ischemic stroke for all subjects and by gender. Logistic regression models and gender-stratified logistic regression models were fit to analyze the association between each continuous anthropometric measure and all-cause mortality adjusted for potential confounders. Potential confounders included age, race/ethnicity, qualifying stroke neurological severity, ischemic stroke sub-type, baseline systolic blood pressure, treatment assignment, smoking status, alcohol consumption, average physical activity prior to qualifying stroke, and histories of: hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, previous stroke or TIA, and myocardial infarction.

To determine the discriminatory ability of each continuous anthropometric measure of obesity for all-cause mortality, receiving operating characteristic curve (ROC) analysis was used to determine the area under the curve (AUC). The AUC ranges from 0 to 1.0, with 0 indicating perfectly inaccurate discrimination and discrimination and 1.0 indicating perfect discrimination.[143] In general, an AUC of 0.5 suggests no discrimination, 0.51-0.59 is considered slightly better than chance, 0.6-0.69 is considered good, 0.7-0.8 is considered very good discrimination, 0.8-0.9 is considered excellent discrimination, and ≥ 0.9 is considered outstanding discrimination.[144] To ensure that each model was not poorly calibrated, calibration of each model was analyzed by the Hosmer-Lemeshow (HL) test. A model is considered poorly calibrated if the p-value of the corresponding HL χ^2 is less than 0.05. The well-calibrated anthropometric measure with the highest AUC was considered the best anthropometric measure that best discriminates between those that die and those that do not die from any cause.

5.4 **Results**

Baseline characteristics

Of the 20,332 subjects enrolled in the PRoFESS trial, anthropometric information was not available for 693 subjects (3.42%). As a result, data from 19,639 subjects were analyzed for the current study. Baseline characteristics and the number of deaths due to all causes observed according to gender are presented in **Table 1**. The majority of PRoFESS subjects with complete anthropometric information were men (64.31%), older than 65 years (54.64%), and white (56.51%). They also had a mean BMI of 26.8 kg/m^2 (SD=5.0), mean WC of 96.5 cm (SD=14.1), and mean WHR of 0.58 (SD=0.08). Men had an increased mean WC, whereas women had an increased mean WHR. Men were more likely to have a history of myocardial infarction, be a current smoker, and engage in intense physical activity prior to the qualifying stroke. Conversely, women were more likely to have a history of hypertension and engage in sedentary physical activity.

Relative measure dispersion

The CVs of continuous anthropometric measures for the NHANES III and PRoFESS cohorts according to gender are shown in **Table 2**. For BMI, WC, and WHR, the CVs were lower for all subjects as well as for each gender from the PRoFESS cohort. Although the PRoFESS cohort (*i.e.*, all subjects, men, and women) had higher means of WC and WHR, the CVs for WC and WHR from the PRoFESS cohort were lower. Taken together, measures of central tendency and dispersion between the PRoFESS and NHANES III cohorts are comparable. Additional information related to the means and SDs of each continuous anthropometric measure from both cohorts is also shown in **Table 2**.

Agreement

Table 3 summarizes the mean difference (*i.e.,* mean bias), SD, and the limits for the agreement of BMI and the two other anthropometric measures of obesity for all PRoFESS subjects as well as by gender. All mean differences were near zero, as the distributions were z-standardized. Overall, the limits of agreement in terms of z-scores were very wide, ranging from 2.96 to 3.12, for BMI and WC as well as for BMI and WHR across subjects and genders. Compared with the limits of agreement for BMI and WC, the limits of agreement for BMI and WHR were less for all subjects and men. Pearson correlations between WC and BMI were strong for both men (r=0.70, p-value < 0.0001) and women (r=0.70, p-value < 0.0001). Similarly, the Pearson correlations between WHR and BMI were also strong for men (r=0.71, p-value < 0.0001) and women (r=0.69, p-value < 0.0001). Although these findings demonstrate that WC and WHR each have strong linear associations with BMI by gender, these results also suggest that WC and WHR do not agree well with BMI by gender, indicated by the wide limits of agreement (see **Table 3**).

Naïve estimates of diagnostic accuracy

The WHO endorsed BMI cut point for obesity[141] had extremely poor sensitivities of 14.67% (95% CI: 12.46, 16.94) for men and 20.40% (95% CI: 16.95, 24.20) for women at discriminating between those who died from all-causes and those who survived. Compared with the sensitivities of the other anthropometric measures, BMI defined obesity had the lowest sensitivities. In contrast, the BMI cut point to define obesity had the highest specificities for men (82.25%, 95% CI: 81.55, 82.94) and women (73.24%, 95% CI: 72.14, 74.31). **Tables 4 and 5** display additional details of the

diagnostic performance of BMI, WC, and WHR to discriminate a patient-relevant outcome.

Discriminatory ability using ROC analysis

For all subjects as well as for both genders, BMI appeared to perform slightly better in discriminating those who died from those who survived than the other two continuous anthropometric measures for obesity. Yet, all of the continuous measures are barely better than chance in their discriminatory abilities to correctly differentiate those who died from those who survived after ischemic stroke. The ORs associated with a 1-SD increase in each continuous anthropometric measure and all-cause mortality following an ischemic stroke were similar for BMI and WC across all subjects and by gender. Additional details of the discriminatory ability and the measure of association of each continuous anthropometric measure can be found in **Table 6.**

5.5 Discussion

Several investigators have hypothesized that the paradoxical results of obesity and all-cause mortality following a stroke are partially due to the use of BMI to measure obesity.[102–104] This is the first study to illustrate the extent to which misclassification and/or measurement error are present in exposure assessment of obesity within a cohort of ischemic stroke survivors. Similar to the mean BMI of the NHANES III cohort, the mean BMI of PRoFESS subjects was approximately 27 kg/m^2 (overweight based on the standard WHO BMI categories). In general, the CVs of the continuous anthropometric measures for the PRoFESS cohort were lower than the CVs of the continuous anthropometric measures for the NHANES III cohort. This finding suggests that the

continuous anthropometric measures for the PRoFESS cohort had slightly improved dispersion as compared with the continuous anthropometric measures for the NHANES III cohort. For example, BMI as measured in PRoFESS had a narrower dispersion around the mean (**Table 2**, 18.5% of the mean) in comparison to BMI as measured in NHANES III (**Table 2**, 21.4% of the mean). Compared with continuous anthropometric measures of a population standard (*i.e.,* NHANES III), there is insufficient evidence to determine whether there were flaws inherent to the assessment of these measurements within the PRoFESS cohort. Overall, the continuous anthropometric measures were comparable between both cohorts.

It is important to carefully consider the method used to assess agreement between the continuous anthropometric measures for obesity. Within the PRoFESS cohort, the interpretation of the extent to which WC and WHR agreed with BMI differed based on the method used. The limits of agreement between the continuous anthropometric measures were very wide within this cohort of ischemic stroke survivors, suggesting that WC or WHR cannot replace BMI as the reference standard due to the variability in measurement (**Table 3)**. The same conclusions can be made for the agreement between these measures by gender. In general, these findings suggest that WC and WHR did not agree well with BMI. Conversely, agreement based on Pearson correlation coefficients indicated that WC and WHR each had strong linear associations with BMI. Overall, these results should be interpreted with caution due to the difference in methods used to assess agreement.

Given that BMI is an imperfect reference standard, the ability of each categorical anthropometric measure for obesity to correctly discriminate between those subjects who

did/did not have a patient-relevant clinical outcome (*i.e.*, all-cause mortality following an ischemic stroke) was assessed based on the recommendation of the Agency for Healthcare Research and Quality.[109] All-cause mortality was the ideal patient-relevant outcome because 1) obesity is a risk factor for all-cause mortality in the general population,[100,101] 2) stroke is a leading cause of death,[43] 3) all-cause mortality is a natural extension of stroke, and 4) it is a concrete outcome so there is a reduced chance of outcome assessment misclassification. In general, the positive predictive value (PPV) is directly related to prevalence of the outcome; as the prevalence of the outcome increases the PPV will also increase, assuming that all other factors remain constant.[145] Within the PRoFESS cohort, the prevalence of all-cause mortality was very low within this cohort of ischemic stroke subjects among men and women (7.4%= 934/12630 for men; 7.1%=500/7009 for women, **Table 4**). Hence, it is not surprising that the PPVs were also extremely low. Additionally, the standard WHO cut point for obesity using BMI had the highest overall diagnostic accuracy rate to discriminate between those with and without the outcome of interest for both genders (77.25% for men; 69.47% for women, **Table 5**). In contrast, the cut point for obesity using WHR had the lowest overall diagnostic accuracy rate among men and women (32.32% for men; 29.83% for women, **Table 5**), which suggests that WHR misclassifies men and women approximately 70% of the time. Thus, there is evidence to suggest the presence of misclassification error in the anthropometric measures of obesity.

Overall, results of the ROC analysis indicated that there is evidence of measurement error within this cohort of ischemic stroke survivors. It was determined that BMI showed a slightly higher discriminatory ability overall and by gender in comparison

to WC and WHR. However, the ability of each continuous anthropometric measure of obesity to discriminate between subjects who died and those who survived was far from acceptable, or slightly better than chance as indicated by AUC values less than 0.60 (**Table 6**).[144]

Previous investigators have suggested that measurement and/or misclassification error related to the measure of obesity is present.[102–104] Specifically, several observational studies have found that obesity is associated with a decreased risk of all-cause mortality following a stroke,[8–12,25,26] yet obesity increases the risk of all-cause mortality in the general population.[100,101] The underlying mechanisms of the obesity paradox are not well understood, however investigators have hypothesized several pathways in which obesity could confer a protective effect.[102,146–148] For example, catabolic stress occurs in states such as stroke and other cardiovascular diseases, and obese individuals may have a greater catabolic reserve than their normal-weight counterparts following a catabolic stress event.[102,146,147] Additionally, tumor necrosis factor α (TNF-α) is increased in individuals following a stroke.[149] However, adipose tissue, which secretes soluble TNF-α receptors, may negate the impact of TNF-α following a stroke.[102,147] Thus, obese individuals may be more likely to survive than normal-weight individuals due to their higher levels of catabolic reserve and/or adipose tissue.

Alternatively, the paradoxical findings could be attributed to residual confounding related to the lack of information about subjects' weight history and duration of important confounders (*e.g.*, diabetes, smoking).[150] Without accounting for a subject's weight history or even lifetime maximum weight, it is not possible to determine the true effect of obesity on all-cause mortality following a stroke because the exposure was based on only

one time point. For example, the risk of all-cause mortality following a stroke may differ for a subject whose weight has recently increased above the threshold for obesity compared with a subject whose weight has consistently exceeded the threshold for obesity. The same analogy could also be true for important confounders such as the duration of diabetes and/or the duration of smoking. Thus, it is critical to account for a subject's weight history and duration of important confounders of this relationship to accurately assess the effect of obesity on all-cause mortality following a stroke.

Limitations and strengths

This study has several limitations. This study only assessed the extent of misclassification and measurement error present in the exposure assessment of obesity using BMI, WC, and WHR. The available measures are not as precise in assessing body adiposity in comparison with methods such as DEXA, underwater weighing, or air displacement.[77–80] It would have been beneficial to have compared the diagnostic accuracy of the anthropometric measures using a more precise measure of obesity.

An additional identified limitation is associated with the collection point of the anthropometric measures of obesity. Anthropometric measures were only measured at the time of randomization and it was not possible to determine the impact of weight or WC change between the time of ischemic stroke onset and randomization. Although stroke is a catabolic state and weight loss following a stroke is relatively common, the median weight loss four months following a stroke was found to be only 0.6 kg (or 1.32 lbs) in a previous cohort of first-time stroke subjects.[131] In the PRoFESS cohort, the median time from qualifying stroke to randomization was 15 days and approximately 69% of subjects were randomized within 30 days following the qualifying stroke. Hence, it may be

assumed that the median amount of weight that subjects may have lost between ischemic stroke onset and weight assessment would result in subjects maintaining a relatively consistent BMI and WC between these two time periods. Additionally, the anthropometric measures for obesity available for the PRoFESS cohort are only snapshots of subjects' degree of excess adiposity. As a result, it was not possible to determine the cumulative effect, or allostatic load, of obesity assessed by the available anthropometric measures.

Due to restrictive inclusion criteria of the PRoFESS clinical trial, the generalizability of our results to all ischemic stroke survivors is not known. For example, individuals were excluded if they had a severe disability after the qualifying stroke.[125] The current study used data from the PRoFESS clinical trial to investigate the extent to which misclassification and measurement error were present in the exposure assessment of obesity in order to highlight the need for research efforts to focus on improving calibration of the available measures of obesity and/or developing alternative methods for determining body adiposity. In doing so, future studies could estimate the precision of these measures in accurately assessing the effect of obesity on outcomes following an ischemic stroke.

Regardless of these limitations, the present study includes several notable strengths. This study utilized data from a large clinical trial with prospective ascertainment of the outcome of interest. Unlike other measurement studies that use cross-sectional data, the temporality of the relation between the anthropometric measures of obesity and all-cause mortality following an ischemic stroke could be assessed. In

addition, this is the first study which used data several anthropometric measures of obesity to investigate the effect of obesity on all-cause mortality.

Additionally, the rigorous data collection of the PRoFESS trial reduced information or recall bias. Rather than relying on subjects self-reporting their medical history or anthropometric measures, the PRoFESS trial utilized source documents to verify subjects' medical history. Specifically, subject-reported anthropometric measures of obesity are poor surrogates for objectively-measured measures of obesity.[151] Moreover, the use of clinical trial data ensured good clinical practice, which minimized the potential bias from incorrect documentation of the trial's outcomes. Thus, we assume that the potential for measurement error was minimized related to data collection.

Implications of using an imperfect reference measure

Utilizing a weak proxy measure of obesity will lead to error and therefore will yield biased and inefficient estimates of the effect of obesity on outcomes.[108,135] The effect of the errors related to measuring obesity depends on whether the errors are nondifferential (the relationship between the true and observed exposure is the same for those who do and do not develop the outcome of interest) or differential (the relationship between the true and observed exposure differs between those who do and do not develop the outcome of interest).[80,108] In general, nondifferential measurement error biases the effect estimate towards the null and underestimates the true effect.[80,108,152] If the exposure is observed prior to the outcome of interest, nondifferential measurement error is assumed.[80,108,152] However, the direction of the bias cannot be assumed when the exposure variable consists of multiple categories, such as the case with BMI categories.[153] As a result, the anthropometric measures were restricted to categorical and

continuous variables to illustrate the extent to which misclassification and measurement error were present in exposure assessment of obesity for this study. It is assumed that the measurement error related to anthropometric measures of obesity is nondifferential because these measures were collected prior to the outcome of interest. Overall, it is critical for future studies to detail the diagnostic accuracy of the available anthropometric measure(s) and to also quantify the bias due to misclassification or measurement error associated with these measures. Without determining the bias associated with an imperfect measure of obesity, the estimate of the effect of obesity on outcomes following a stroke may lead to incorrect inferences about the strength, direction of the association, and/or exaggerate the confidence in the accuracy of the results.[80,108,152]

Public health implications

Obesity is highly prevalent in both the US and international populations[1,2] as well as among individuals who have had an ischemic stroke.[31] Despite the high prevalence of obesity among stroke survivors, the current guidelines from the American Heart Association and American Stroke Association only recommend that all individuals who are diagnosed with an ischemic stroke be screened for obesity.[31] Guidelines no longer recommend weight reduction for individuals with a BMI over 25 kg/m^2 due to the unexpected relationship between obesity and prognosis after a stroke and the null results of a weight loss intervention.[31] Hence, it is important to focus research and public health efforts on measures of obesity that accurately quantify excess adiposity and provide unbiased estimates the effect of obesity on outcomes following a stroke.

Future directions

The illustrations related to misclassification and measurement error for anthropometric measures provide valuable information for future studies investigating the effect of obesity on outcomes following an ischemic stroke. Specifically, this study highlights the need for research to determine a better measure of obesity. Rather than a measure of overall adiposity as in BMI, a measure that includes a metabolic health component in addition to fat distribution may be more informative of excess adiposity, and predictive of cardiovascular diseases and all-cause mortality.[142,154] Research has recently supported the heterogeneity of the metabolic profile among obese individuals.[71,72] Thus, indirect measures of abdominal obesity such as WC or WHR should be further investigated for use in clinical practice and research. It is also important for future research to discuss the diagnostic accuracy of the chosen measure(s) of obesity. This information provides transparency to the research community surrounding the precision of the estimates as well as the potential issues related to misclassification and measurement error.

5.6 **Tables and Figures**

Table 1. Baseline Characteristics of 19639 Ischemic Stroke Survivors and by Gender, the PRoFESS trial.

Characteristic	All participants No. (%)	Men No. (%)	Women No. (%)
No. of participants [a]	19639	12630	7009
No. of participants who died from all causes	1434	934	500
BMI (kg/m^2) (mean, SD)	26.8 (5.0)	26.5 (4.5)	27.3 (5.6)
WC (cm) (mean, SD)	96.5 (14.1)	97.4 (13.4)	94.8 (15.0)
WHR (mean, SD)	0.58 (0.08)	0.57 (0.08)	0.60 (0.09)
Sociodemographic Characteristics			
Men	12630 (64.31)		
Age			
≥ 65 years	10731 (54.64)	6417 (50.81)	4314 (61.55)
Race/ethnicity			
White	11098 (56.51)	7144 (56.56)	3954 (56.41)
Black	747 (3.80)	401 (3.17)	346 (4.94)
Asian	6624 (33.73)	4350 (34.44)	2274 (32.44)
Hispanic	966 (4.92)	587 (4.65)	379 (5.41)
Other	204 (1.04)	148 (1.17)	56 (0.80)
Clinical Characteristics			
Qualifying stroke neurological severity			
Moderate/Severe (NIHSS ≥ 8)	1312 (6.68)	820 (6.49)	492 (7.02)
Qualifying stroke subtype			
Large vessel atherosclerosis	5643 (28.75)	3767 (29.85)	1876 (26.77)
Cardioembolic	355 (1.81)	214 (1.70)	141 (2.01)
Small vessel disease	10253 (52.24)	6519 (51.65)	3734 (53.29)
Other	381 (1.94)	234 (1.85)	147 (2.10)
Unknown	2996 (15.26)	1887 (14.95)	1109 (15.83)
Baseline systolic blood pressure (median, IQR)	142 (130-156)	142 (130-156)	142 (130-157)
Treatment group			
A [b]	4869 (24.98)	3154 (25.15)	1715 (24.67)
B [c]	4859 (24.93)	3120 (24.88)	1739 (25.02)
C [d]	4904 (25.16)	3139 (25.03)	1765 (25.39)
D [e]	4861 (24.94)	3129 (24.95)	1732 (24.92)
Risk Factors and Comorbidities			
History of previous stroke or TIA			
Yes	4841 (24.66)	3216 (25.47)	1625 (23.20)
History of previous myocardial infarction			
Yes	1319 (6.72)	1029 (8.15)	290 (4.14)
History of atrial fibrillation			
Yes	523 (2.66)	294 (2.33)	229 (3.27)
History of congestive heart failure			
Yes	525 (2.67)	295 (2.34)	230 (3.28)
History of coronary artery disease			
Yes	3213 (16.36)	2160 (17.10)	1053 (15.03)
History of hypertension			
Yes	14551 (74.10)	9094 (72.00)	5457 (77.87)
History of hyperlipidemia			
Yes	9138 (46.61)	5760 (45.67)	3378 (48.28)
Diabetes			
Yes	5538 (28.20)	3558 (28.17)	1980 (28.25)
Smoking status			
Current smoker	11240 (57.25)	9118 (72.23)	2122 (30.28)
Regular alcohol consumption			
≥ 1 drink/week	6931 (35.30)	5731 (45.39)	1200 (17.12)
Average physical activity prior to qualifying stroke			
Sedentary (walking <1 mile/day)	6954 (35.62)	4196 (33.38)	2758 (39.65)
Some physical activity (20-30 minutes, 3 times/week)	6267 (32.10)	3997 (31.80)	2270 (32.63)
Intense physical activity (> 30 minutes, > 3 times/week)	6304 (32.29)	4376 (34.82)	1928 (27.72)

[a] 693 participants were excluded due to missing anthropometric information; [b] Aspirin + Extended Release Dipyridamole/Telmisartan; [c] Clopidogrel/Telmisartan; [d] Aspirin + Extended Release Dipyridamole/Placebo; [e] Clopidogrel/Placebo

Table 2. Means, Standard Deviations, Coefficient of Variations of Height, Weight, Body Mass Index, Waist Circumference, and Waist-to-Height Ratio in NHANES III and PRoFESS.

	All NHANES III (n=16412)		All PRoFESS (n=19639)		Men NHANES III (n=7727)		Men PRoFESS (n=12630)		Women NHANES III (n=8685)		Women PRoFESS (n=7009)	
Variable	**Mean (SD)**	**CV**	**Mean (SD)**	**CV**	**Mean (SD)**	**CV**	**Mean (SD)**	**CV**	**Mean (SD)**	**CV**	**Mean (SD)**	**CV**
Height (cm)	166.5 (9.8)	5.9	166.4 (10.1)	6.1	173.5 (7.5)	4.3	170.9 (8.3)	4.8	160.4 (7.1)	4.5	158.2 (7.6)	4.8
Weight (kg)	75.0 (17.7)	23.7	74.4 (16.3)	21.9	80.0 (16.4)	20.5	77.6 (15.7)	20.2	70.5 (17.7)	25.1	68.6 (15.8)	23.1
BMI (kg/m^2)	27.0 (5.8)	21.4	26.8 (5.0)	18.5	26.5 (4.8)	18.2	26.5 (4.5)	17.1	27.4 (6.5)	23.6	27.3 (5.6)	20.6
WC (cm)	92.8 (14.6)	15.8	96.5 (14.1)	14.6	94.8 (13.5)	14.3	97.4 (13.4)	13.8	91.0 (15.4)	16.9	94.8 (15.3)	16.1
WHR	0.56 (0.09)	16.1	0.58 (0.08)	14.4	0.55 (0.08)	14.3	0.57 (0.08)	13.2	0.57 (0.10)	17.2	0.60 (0.09)	15.8

NHANES= National Health and Nutrition Examination Survey; PRoFESS= Prevention Regimen for Effectively Avoiding Second Strokes; SD=standard deviation; CV=coefficient of variation in percent; BMI=body mass index; WC=waist circumference; WHR=waist circumference-to-height ratio

Table 3. Summary of Agreement between BMI and WC, and BMI and WHR for all Subjects and by Gender.

	Mean difference	SD	Limits of agreement
All subjects			
BMI and WC	2.57×10^{-14}	0.80	-1.56, 1.56
BMI and WHR	1.208×10^{-13}	0.77	-1.51, 1.51
Men			
BMI and WC	2.31×10^{-14}	0.78	-1.53, 1.53
BMI and WHR	1.35×10^{-13}	0.76	-1.48, 1.48
Women			
BMI and WC	5.6×10^{-15}	0.78	-1.53, 1.53
BMI and WHR	7.27×10^{-14}	0.78	-1.54, 1.54

SD=standard deviation; BMI=body mass index; WC=waist circumference; WHR=waist circumference-to-height ratio

Table 4. Distribution of BMI, WC, and WHR by Gender and All-Cause Mortality following an Ischemic Stroke.

		Outcome		
	BMI[141]	**Dead**	**Alive**	Total
Men	≥ 30 kg/m^2	137	2076	2213
	< 30 kg/m^2	797	9620	10417
Total		934	11696	12630
Women	≥ 30 kg/m^2	102	1742	1844
	< 30 kg/m^2	398	4767	5165
Total		500	6509	7009
	WC[141]	**Dead**	**Alive**	Total
Men	> 102 cm	271	3695	3966
	≤ 102 cm	663	8001	8664
Total		934	11696	12630
Women	> 88 cm	324	4282	4606
	≤ 88 cm	176	2227	2403
Total		500	6509	7009
	WHR[142]	**Dead**	**Alive**	Total
Men	≥ 0.53	628	8242	8870
	< 0.53	306	3454	3760
Total		934	11696	12630
Women	≥ 0.54	380	4798	5178
	< 0.54	120	1711	1831
Total		500	6509	7009

BMI=body mass index; WC=waist circumference; WHR=waist circumference-to-height ratio

Table 5. Classic Indices of Diagnostic Accuracy of BMI, WC, and WHR to Detect All-Cause Mortality following an Ischemic Stroke by Gender.

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%) (95% CI)
BMI*					
Men	14.67 (12.46, 16.94)	82.25 (81.55, 82.94)	6.19 (5.22, 7.28)	92.35 (91.82, 92.85)	77.25 (76.51, 77.98)
Women	20.40 (16.95, 24.20)	73.24 (72.14, 74.31)	5.53 (4.53, 6.67)	92.29 (91.53, 93.01)	69.47 (68.37, 70.54)
WC*					
Men	29.01 (26.12, 32.04)	68.41 (67.56, 69.25)	6.83 (6.07, 7.66)	92.35 (91.77, 92.90)	65.49 (64.66, 66.32)
Women	64.80 (60.44, 68.99)	34.21 (33.06, 35.38)	7.03 (6.31, 7.81)	92.68 (91.56, 93.69)	36.40 (35.27, 37.54)
WHR*					
Men	67.24 (64.12, 70.24)	29.53 (28.71, 30.37)	7.08 (6.55, 7.63)	91.86 (90.94, 92.72)	32.32 (31.50, 33.14)
Women	76.00 (72.01, 79.68)	26.29 (25.22, 27.37)	7.34 (6.64, 8.08)	93.45 (92.21, 94.54)	29.83 (28.76, 30.92)

WC=waist circumference; BMI=body mass index; WHR=waist circumference-to-height ratio; CI= Confidence interval; PPV= Positive predictive value; NPV= Negative predictive value

*Cut points for BMI, WC, and WHR is as noted in Table 4.

Table 6. Summary of Multivariable Adjusted AUROC for anthropometric measures to Discriminate Subjects who Died from All-Causes following an Ischemic Stroke, and Measures of Association for All Subjects, and by Gender.

	AUROC (95% CI)	OR* (95% CI)
All subjects		
BMI	0.5639 (0.5478, 0.5799)	0.949 (0.936, 0.962)
WC	0.5119 (0.4985, 0.5253)	0.827 (0.732, 0.934)
WHR	0.5078 (0.4919, 0.5237)	0.467 (0.230, 0.949)
Men		
BMI	0.5677 (0.5478, 0.5878)	0.949 (0.932, 0.967)
WC	0.5135 (0.4981, 0.5288)	0.843 (0.716, 0.992)
WHR	0.5135 (0.4935, 0.5334)	0.453 (0.170, 1.209)
Women		
BMI	0.5591 (0.5321, 0.5860)	0.945 (0.926, 0.965)
WC	0.5117 (0.4852, 0.5381)	0.992 (0.985, 0.999)
WHR	0.5028 (0.4761, 0.5294)	0.493 (0.170, 1.426)

AUROC=area under the receiving operating curve; BMI=body mass index; WC=waist circumference; WHR=waist circumference-to-height ratio; CI=confidence interval

*ORs are adjusted for age, race/ethnicity, qualifying stroke neurological severity, ischemic stroke sub-type, baseline systolic blood pressure, treatment assignment, smoking status, alcohol consumption, average physical activity prior to qualifying stroke, and histories of: hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, previous stroke or TIA, and myocardial infarction.

6 Overall Discussion

6.1 Specific Aims Revisited

The aims of this dissertation are:

Interventional Management of Stroke (IMS) III Clinical Trial Related Specific Aims

1. To explore the presence of the joint effect of obesity and diabetes on functional disability at 3-months following an ischemic stroke.
2. To explore the presence of the joint effect of obesity and diabetes on all-cause mortality at 1-year following an ischemic stroke.

Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) Clinical Trial Related Specific Aims

3. To evaluate the presence of the joint effect of obesity and diabetes on all-cause mortality following ischemic stroke onset.
4. To evaluate the presence of the joint effect of obesity and diabetes on cardiovascular-related mortality following ischemic stroke onset.

Issues Related to Measures of Obesity Specific Aim

5. To illustrate the extent to which misclassification and measurement error are present in exposure assessment of obesity using data from the PRoFESS clinical trial.

6.2 **Summary and Conclusions**

The research presented in this dissertation examined the joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke (*e.g.,* functional disability, all-cause mortality, and cardiovascular-related mortality). This topic is of interest for several reasons. First, this research is the first to investigate the potential joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke. This research is also built upon the foundation of prior literature which has supported the heterogeneity of the metabolic profile among obese individuals[71,72] in addition to scientific evidence that has determined that the effect of obesity on stroke risk differs by diabetes status.[32] This topic area is also of high national public health relevance since it focused on obesity and diabetes in relation to ischemic stroke. Healthy People 2020 includes several sub-goals targeted at reducing the burden of obesity and diabetes in addition to minimizing the burden associated with ischemic stroke.[41,42] Obesity and diabetes are considered risk factors for ischemic stroke[6,7,60–64] and are also associated with clinical outcomes following a stroke.[8–12,16–26,28–30] Studying this topic area allows us to assess whether certain subgroups of individuals are at higher (or lower) risk for clinical outcomes following an ischemic stroke. Thus, these results can aid in targeting subgroups for which an intervention will be most effective.

The research in this dissertation also illustrated the extent to which misclassification and measurement error were present in exposure assessment of obesity. This topic is significant for several reasons. Stroke is a leading cause of death.[43] Therefore it is important to target modifiable risk factors such as the precipitating factor

of obesity in order to reduce the burden of all-cause mortality following a stroke. Although obesity is a modifiable risk factor for stroke,[6,7] the reported effects of obesity, defined by an elevated body mass index (BMI), on all-cause mortality following a stroke have been conflicting. A number of observational studies have reported that obesity is associated with a decreased risk of all-cause mortality following a stroke,[8–11,25,26] despite biological implausibility and epidemiological evidence that obesity is associated with an increased risk of all-cause mortality in the general population.[100,101] This apparent discrepancy, first documented by Olsen *et al.*[8], is referred to as the obesity paradox. Several investigators have cited methodological issues related to the measurement of obesity as a potential explanation of the obesity paradox.[102–104] Although the literature within this topic area has consistently utilized BMI to measure obesity, the definition and BMI cut points for obesity are heterogeneous. This dissertation sheds light on obesity measures by highlighting the potential issues related to misclassification and measurement error in exposure assessment of obesity.

Summary of the three manuscripts

The first manuscript presented in this dissertation is, to date, the first to explore the potential joint effect of obesity and diabetes on clinical outcomes (*e.g.,* functional disability at 3-months and all-cause mortality at 1-year) following an ischemic stroke in a post-hoc analysis using data from the IMS III trial. For both functional disability and all-cause mortality, there was insufficient evidence to conclude that the effect of obesity differed by diabetes status on the multiplicative or the additive scales. Additionally, there was insufficient evidence to determine that the main effects were not significantly

associated with either clinical outcome following an ischemic stroke in this cohort of acute ischemic stroke patients with at least moderate stroke severity. However, the point estimates for the independent associations between each factor and functional disability at 3-months following an ischemic stroke were consistent with the findings from previous studies.[11,20–24] Namely, obese subjects had lower odds of functional disability[11,20,21] and subjects with diabetes had higher odds of functional disability.[22–24]

The second manuscript focused on evaluating the potential joint effect of obesity and diabetes on mortality-related events (*e.g.,* all-cause mortality and cardiovascular-related mortality) following an ischemic stroke in a post-hoc analysis utilizing data from the PRoFESS trial. There was insufficient evidence to declare that the effect of obesity on all-cause mortality differed by diabetes status on either the multiplicative or additive scales. In contrast, there was evidence that the effect of obesity on cardiovascular-related mortality differed by diabetes status on the multiplicative scale and the attributable proportion due to interaction of the additive scale. However, there was insufficient evidence of an additive interaction for the relative excess risk due to interaction. These findings suggest that obese individuals with diabetes have an increased hazard of cardiovascular-related mortality following an ischemic stroke compared with underweight/normal-weight individuals without diabetes. Thus, these results suggest that future interventions could focus resources on obese individuals with diabetes in order to reduce the excess burden of cardiovascular-related mortality within a cohort of ischemic stroke survivors.

The third manuscript was based on illustrating the extent to which misclassification and measurement error were present in exposure assessment of obesity. Given that the prevalence of obesity is increasing and that obesity is a leading cause of morbidity and mortality,[106] it is critical for the construct of obesity to be accurately quantified and defined. This topic was important because the cut point(s) for obesity using BMI are heterogeneous within the stroke literature, and there is conflicting evidence regarding the effect of obesity on all-cause mortality following a stroke. Although BMI is the recommended measure for obesity,[5,43,82,83] there are several limitations associated with the measure. For example, BMI cannot differentiate between excess adipose tissue, the distribution of adipose tissue, or high muscle mass.[77–80] Hence, BMI is an imperfect reference standard for obesity because it misclassifies a large number of individuals based on a more precise measure of obesity. Error in the measurement of obesity may impact the resulting estimate of the outcome of interest and will not reflect the true magnitude of the problem. To accomplish the objective of this manuscript, several analytic methods were utilized to illustrate the extent to which misclassification and measurement error were present in exposure assessment of obesity measured by BMI, waist circumference (WC), and waist circumference-to-height ratio (WHR) using data from the PRoFESS clinical trial. Results indicated that there was no evidence of mechanical error in terms of measurement as proven by comparability of the anthropometric measures of obesity from the PRoFESS cohort with the anthropometric measures of obesity from a population reference standard. Using BMI, WC, and WHR as continuous variables, it was determined that BMI was best at discriminating the patient-

relevant clinical outcome of all-cause mortality following an ischemic stroke. However, all of the continuous anthropometric measures of obesity were barely able to discriminate between subjects with and without the outcome slightly better than chance (area under the curve ≤ 0.60), suggesting evidence of measurement error. Results also demonstrated evidence of misclassification error as indicated by the naïve estimates of diagnostic accuracy for each categorical anthropometric measure of obesity at discriminating all-cause mortality within this cohort of ischemic stroke survivors. Therefore, as shown in the present study, it is imperative to improve calibration of the available measures of obesity and/or to develop alternative methods for determining body adiposity.

Limitations and strengths

There are several limitations related to this dissertation. Due to the restrictive inclusion criteria of both the IMS III and PRoFESS clinical trials, the generalizability of the results of this dissertation to all acute ischemic stroke patients or ischemic stroke survivors is not known. Additionally, it was not possible to discern whether these results are generalizable to specific racial/ethnic groups who are either acute ischemic stroke patients (IMS III) or ischemic stroke survivors (PRoFESS).

In comparison to non-Hispanic Whites, Blacks have a higher incidence of all stroke types in addition to higher mortality rates.[5] This disparity is especially apparent among young and middle-aged Blacks who are more likely to have hemorrhagic strokes compared with non-Hispanic Whites of the same age.[5] The higher incidence and mortality rates among Blacks may be due to higher prevalence in modifiable/potentially modifiable risk factors (*e.g.*, hypertension, obesity, and diabetes) and contextual-level

factors (*e.g.*, neighborhood characteristics, geography, education, and insurance).[5] Within this dissertation work, only a small proportion of subjects from either the IMS III or PRoFESS clinical trials were Black (*i.e.*, less than 5%). As a result, it was not possible to conduct subgroup analyses related to race/ethnicity and/or age. Future studies should be adequately powered to investigate potential racial/ethnic differences in the presence of the joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke, and in the presence of misclassification and measurement error in the exposure assessment of obesity. It may be of interest for future studies to specifically compare older Blacks with older non-Hispanic Whites, and younger Blacks with younger non-Hispanic Whites.

Other limitations identified are associated with the exposure measurements of obesity and diabetes. The available data pertaining to obesity and diabetes from both data sources were assessed at one time point, which did not provide a measure of the allostatic load of obesity or diabetes over time. Without measuring these exposures over time (*e.g.*, weight histories, measures of abdominal obesity over time, duration of diabetes), it will not be possible to determine the true effect of these exposures on clinical outcomes following an ischemic stroke. Thus, future studies could measure these exposures over time rather than at one time point. Ideally, an ischemic stroke registry that was linked with each subject's medical record would provide longitudinal information prior to the stroke as well as following the stroke.

The IMS III and PRoFESS clinical trials were not designed to answer the research questions of the present dissertation. Examining joint effects, or interactions, is

challenging because tests for interactions are typically underpowered.[123] Although the dissertation work pertaining to the joint effect of obesity and diabetes were most likely underpowered, there was sufficient power to detect an appropriate effect measure for the main effects of obesity and diabetes. Hence, it is critical to utilize an ischemic stroke registry that will provide sufficient resources and power to address these research questions in future studies.

Regardless of these limitations, this dissertation work includes several notable strengths. This was the first dissertation to investigate the potential joint effect of obesity and diabetes on clinical outcomes following an ischemic stroke on the multiplicative and additive scales. In addition, this dissertation was the first to investigate the extent to which misclassification and measurement error were present in exposure assessment of obesity within a cohort of ischemic stroke survivors.

Data from two ischemic stroke clinical trials were used for this dissertation. Although results from a population-based observational study might be more generalizable to acute ischemic stroke patients or ischemic stroke survivors, data from clinical trials provide several strengths to this dissertation. Clinical trial data allowed new hypotheses to be generated and tested by using high-quality, detailed data to develop new knowledge in the interest of public health. Specifically, this dissertation utilized data from clinical trials with prospective ascertainment of the dependent variables of interest. Further, the rigorous data collection of clinical trials reduced information bias. Rather than relying on subjects self-reporting their medical history, both clinical trials utilized source documents to verify subjects' medical history. The use of clinical trial data in this

dissertation helped to ensure good clinical practice, which minimized the potential bias from incorrect documentation of the trials' outcomes.

Future directions

Results of this dissertation show there is evidence that the effect of obesity on cardiovascular-related mortality differed by diabetes status within a cohort of ischemic stroke survivors. Additionally, within a cohort of ischemic stroke survivors, results also suggest that there is evidence of misclassification and measurement error in exposure assessment of obesity. These results could be used to generate hypotheses for future studies evaluating the potential interactions between obesity and diabetes on the risk of clinical outcomes following an ischemic stroke. The dissertation results could also be used by future investigators to develop interventions to reduce the burden of clinical outcomes following ischemic stroke onset.

A limitation of the current work is that it was a post-hoc analysis of two ischemic stroke clinical trials, which were not designed to answer the specific research questions of this dissertation. Therefore, it will be important to re-evaluate the aims of this dissertation in a future study using a population-based observational study that is adequately powered.

The dissertation results support the concept of potential heterogeneity of metabolic profiles among obese individuals.[71,72] Although the underlying mechanisms by which obesity and diabetes may interact to affect clinical outcomes following an ischemic stroke remain unclear, these mechanisms appear to be multifactorial and involve molecular, cellular, neuronal, individual, and environmental factors.[33] Future studies

could differentiate between metabolically healthy and metabolically unhealthy patients within specific BMI categories (or using other measures of obesity) to determine if the effect of obesity on clinical outcomes following an ischemic stroke differs by diabetes (or other measure of metabolic health). To date, there is no standard, guideline-based definition of metabolic health. Hence, it is critical for future research to develop a consistent and accurate definition of metabolic health.

Although the standard WHO BMI categorizations are intended for international use to reflect the risk of type 2 diabetes, hypertension, and cardiovascular disease, there is growing debate on whether different BMI cut points are necessary for different racial/ethnic groups.[50] Despite mounting evidence of the of the differences between BMI, body fat distribution, and percentage of body fat in different racial/ethnic populations, the WHO expert consultation decided to retain the standard WHO BMI cut points for all populaitons.[50] However, future research could focus efforts on better calibration of the available obesity measures within racial/ethnic population groups and/or the development of alternative methods for determining body adiposity in order to accurately quantify and define obesity within these groups.

The obesity and diabetes data available from the IMS III and PRoFESS cohorts showed variability in the definitions and measures used to determine a subject's degree of adiposity (*i.e.*, obesity) and diabetes. Thus, future studies could include systematic reviews of stroke data sources to determine how the constructs of obesity and diabetes are represented. Specifically, data from observational stroke studies, stroke clinical trials, and national stroke registries could be reviewed.

Although several guideline-based methods are used to diagnose diabetes,[155] the limited availability of measures of diabetes within the data sources used in the dissertation precluded assessing the extent of measurement related issues (*e.g.*, misclassification and measurement error) present in exposure assessment of diabetes. However, future work could aim analyze data from an observational stroke data source with multiple measures of diabetes.

In conclusion, this dissertation included a post-hoc analysis of data from two ischemic stroke clinical trials. Results from the dissertation add valuable information to the literature regarding post-ischemic stroke outcomes. These results also highlight the extent to which misclassification and measurement error were present in exposure assessment of obesity within a cohort of ischemic stroke survivors. Accurate measures of excess adiposity and metabolic health that are independent of age, gender, and race/ethnicity are essential for future research. Future population-based stroke registries (or observational cohorts) linked to medical records are needed to examine whether the effect of excess adiposity on clinical outcomes following an ischemic stroke differs by metabolic health.

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