Association of Body Mass Index and Mortality After Acute Ischemic Stroke

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Background—The prevalence of severe obesity is rising in the United States. Although mild to moderately elevated body mass index (BMI) is associated with reduced mortality after acute ischemic stroke, less is known about severe obesity.

Methods and Results—Patients with acute ischemic stroke (n=1791) ≥45 years were identified from the biethnic population–based Brain Attack Surveillance in Corpus Christi (BASIC) study from June 1, 2005, to December 31, 2010. Median follow-up was 660 days. BMI was abstracted from the medical record. Survival was estimated by BMI category (underweight, normal weight, overweight, class 1 obesity, class 2 obesity, and severe obesity) using Kaplan-Meier methods. Hazard ratios for the relationship between BMI modeled continuously and mortality were estimated from Cox regression models after adjustment for patient factors. The median BMI was 27.1 kg/m² (interquartile range, 23.7–31.2 kg/m²), and 56% were Mexican American. A total of 625 patients (35%) died during the study period. Persons with higher baseline BMI had longer survival in unadjusted analysis (P<0.01). After adjustment for demographics, stroke severity, and stroke and mortality risk factors, the relationship between BMI and mortality was U shaped. The lowest mortality risk was observed among patients with an approximate BMI of 35 kg/m², whereas those with lower or higher BMI had higher mortality risk.

Conclusions—Severe obesity is associated with increased poststroke mortality in middle-aged and older adults. Stroke patients with class 2 obesity had the lowest mortality risk. More research is needed to determine weight management goals among stroke survivors. (Circ Cardiovasc Qual Outcomes. 2014;7:00-00.)

Key Words: mortality ▪ obesity ▪ stroke

More than 35% of US adults are obese. Obesity accounts for almost 10% of all medical spending, reaching as high as $147 billion annually in the United States. In 2008, 35% of Americans were severely obese (body mass index [BMI] ≥40 kg/m²), which corresponds roughly to 100 lb (45 kg) or more overweight. More than 50% of severely obese Americans have hypertension, the most important stroke risk factor. Increasing BMI is associated with an increased risk of incident stroke and an increased risk of all-cause mortality in the general population. In contrast to the general population, research has shown that higher BMI may be neutral or have a protective association with mortality in patients with clinical cardiovascular disease, including patients with stroke, a phenomenon described as the obesity paradox. However, less is known about the relationship between severe obesity and mortality in patients with stroke. Moreover, little is known about the relationship between obesity and poststroke mortality among Latinos, particularly Mexican Americans (MAs), a subgroup with high rates of severe obesity and incident stroke. For these reasons, we sought to explore the association of BMI and all-cause mortality among patients with acute ischemic stroke (AIS) in a biethnic population–based stroke surveillance study. We hypothesized that all-cause mortality would be higher in severely obese patients with AIS compared with normal-weight patients with AIS.

Methods
The Brain Attack Surveillance in Corpus Christi (BASIC) study is a population-based complete case stroke surveillance study in the biethnic community of Nueces County, Texas. Nueces County is a geographically isolated, urban area. Ninety percent of the population of Nueces County (population, 340,223) resides in Corpus Christi. The BASIC methods of stroke case capture have been detailed previously. Briefly, patients with stroke who were aged ≥45 years were identified by active surveillance of hospital admission and emergency department logs of the 7 hospitals in the community. Passive surveillance of stroke hospital and emergency department discharges using International Classification of Disease, Ninth Revision code
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- Previous studies have found that higher body mass index (BMI) may have a neutral or protective association with mortality in patients with stroke, a phenomenon described as the obesity paradox.

WHAT THE STUDY ADDS

- In this population-based, biennial stroke surveillance study, there is a U-shaped relationship between BMI at stroke onset and all-cause mortality in patients with acute ischemic stroke.
- After adjustment, a 1-unit-higher BMI had a protective association with mortality when BMI was <31 kg/m². Higher BMI >31 kg/m² did not render significant protective associations, and higher values of BMI >38 kg/m² were associated with higher mortality in the fully adjusted model.

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Covariates

Our primary predictor of interest was BMI. Patients’ height and weight were abstracted from the medical records, and index BMI was calculated. For descriptive analyses, underweight was defined as BMI <18.5 kg/m², normal weight as 18.5 to 24.9 kg/m², overweight as 25 to 29.9 kg/m², class 1 obesity as 30 to 34.9 kg/m², class 2 obesity as 35 to 39.9 kg/m², and severe obesity as ≥40 kg/m². BMI was modeled as a continuous variable in evaluations of the association with all-cause mortality in multivariable models.

A review of the literature and our previous work was used to identify potential confounders of the association between BMI and all-cause mortality in patients with AIS. From this assessment, the following covariates were abstracted from the stroke hospitalization medical record and included in the multivariable model: age, race/ethnicity, sex, stroke severity, history of stroke or transient ischemic attack, hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, heart failure, high cholesterol, chronic obstructive pulmonary disease, dementia, end-stage renal disease, cancer, history of stroke or transient ischemic attack (before the BASIC study), excessive alcohol use, and smoking. Second stroke during the study period was identified through BASIC stroke surveillance. Stroke severity was defined as the National Institutes of Health Stroke Scale (NIHSS) at the time of the index stroke and was taken from the medical record or abstracted from the medical record using the validated Williams method. Outcome

All-cause mortality was ascertained from the time of the first AIS through December 31, 2010. In-hospital deaths were identified using the hospital medical record. Out-of-hospital deaths were identified using outcome assessments at 90 days, the Social Security Death Index, and the Texas Department of Health death certificate database. The Texas Department of Health death certificate database was not available for 2010 at the time of analysis. However, judging from previous years of data, <3% of deaths in our population are based on this data source alone, and thus few mortality cases for this year should have been missed. Mortality is ascertained from multiple sources, and the date of death for patients with stroke who died outside of Nueces county is still obtained.

Statistical Analysis

Patients’ demographics and stroke risk factors were summarized using frequencies/percentages and medians/interquartile ranges and compared across BMI groups using nonparametric Kruskal-Wallis tests for continuous variables and χ² tests for categorical variables. Kaplan-Meier curves and a log-rank test were used to assess the crude association between categorical BMI (underweight, normal weight, overweight, class 1 obesity, class 2 obesity, and severe obesity) and all-cause mortality. Cox proportional hazards models were then used to analyze the association of BMI modeled as a continuous covariate and mortality, accounting for demographics and risk factors. All covariates were added simultaneously to the multivariable Cox regression model. Second stroke identified during BASIC was modeled as a time-varying covariate.

Scatterplots of martingale residuals were used to determine the appropriate form of the continuous variables and to investigate outliers. In the fully adjusted model, the functional forms (ie, linear versus nonlinear) of BMI, age, and NIHSS score were assessed. Visual inspection of a smoothed Martingale residuals plot showed that BMI was nonlinearly associated with all-cause mortality and that 11 observations with a BMI >50 kg/m² could potentially drive the nonlinear association. Thus, a penalized cubic spline model with degrees of freedom selected via the Akaike information criteria was used to model the BMI-mortality association, with the 11 patients with BMI >50 kg/m² removed from our analyses. Using similar methods, it was determined that NIHSS score was best fit using natural log NIHSS score plus 1, and age was best modeled linearly. Using Schoenfeld residuals, we determined that the natural log of NIHSS score violated the assumption of proportional hazards, and thus we modeled this variable as having a time-dependent coefficient. No other violations of model assumptions were identified.

The fully adjusted model was used to determine predicted mortality risk at 1, 2, and 3 years for individuals with otherwise average characteristics but various baseline BMI values. For a range of baseline BMI values, we then computed hazard ratios associated with a 1-kg/m² difference in BMI to determine at what BMI individuals with higher weight have higher mortality (eg, mortality hazard ratio comparing those with BMI of 25 versus 24 kg/m², 26 versus 25 kg/m², etc). In the fully adjusted model, we also tested whether age modified the association of BMI with all-cause mortality by estimating a model in which the BMI spline term differed by age and comparing it with the model without the interaction using a likelihood ratio test. On the basis of the significant association, we stratified by age to visualize the nature of the effect modification by age. The same methods were used to assess whether smoking modified the association of BMI with all-cause mortality.

We then performed a series of sensitivity analyses to determine the robustness of our main findings. First, because modeling BMI as a continuous predictor can sometimes exaggerate its relationship with mortality, we repeated the fully adjusted analysis with BMI coded in 1-unit categories compared with a reference group of normal-weight (BMI=24 kg/m²) patients with stroke. To ensure that all categories had a sufficient number of individuals, some BMI categories were collapsed. Second, to explore the possibility that the results are influenced by including patients with prior history of stroke/transient ischemic attack, we ran the fully adjusted model excluding patients with stroke who reported a history of stroke or transient ischemic attack. Because recurrent stroke may be on the causal pathway from BMI to mortality, we ran the fully adjusted model excluding recurrent stroke as a covariate. Finally, to ensure that truncating the distribution of the primary predictor by excluding the 11 patients with BMI >50 kg/m² did not bias the model estimates, the fully adjusted model was re-run including these observations. This project was approved by the Institutional Review boards at the University of Michigan and both of the Nueces County hospital systems.
Results

From June 1, 2005, to December 31, 2010, a total of 1870 patients were identified with an AIS during BASIC surveillance. Sixty-five patients (4%) were excluded because of missing height and weight data, 11 patients (0.6%) were excluded because their BMI was >50 kg/m², 1 patient was excluded for inaccurate recording of weight (weight was recorded as 20 pounds), or 2 patients were excluded because of missing multiple data fields. There was no difference in age or stroke severity among those with and without BMI data (data not shown). The median BMI of the 1791 patients in our study population was 27.1 kg/m² (interquartile range, 23.7–31.2 kg/m²). Of these, 54 (3%) were underweight, 543 (30%) were normal weight, 629 (35%) were overweight, 311 (17%) had class 1 obesity, 157 (9%) had class 2 obesity, and 97 (5%) had severe obesity.

The median age was 72 years (interquartile range, 60–81 years), and 56% of the patients with AIS were MA. Baseline characteristics of the cohort are reported in the Table. As obesity increased, the age of patients with AIS decreased (P<0.01). MAs made up 73% of the severely obese patients with AIS and 65% of the class 2 obesity patients. Women were more likely to be underweight (5% versus 1%; P<0.01), to be normal weight (34% versus 26%; P<0.01), and to have class 2 obesity (11% versus 7%; P<0.01) compared with men. Men were more likely to be overweight compared with women (42% versus 28%; P<0.01). There was no difference in class 1 obesity (P=0.15) or severe obesity (P=0.10). Underweight patients with AIS had a higher NIHSS score compared with the other groups. Those with higher BMI were more likely to have diabetes mellitus. In contrast, underweight patients were more likely to have atrial fibrillation.

The median follow-up was 660 days (range, 0–2038 days). A total of 625 patients (35%) died during the study period. Survival was different among the 6 BMI groups (log-rank P≤0.001; Figure 1), with higher survival among those with higher BMI. After adjustment for demographics, stroke severity, and stroke and mortality risk factors, the relationship between BMI and mortality was U shaped (Figure 2). For BMI levels ranging from 17 to ≈35 kg/m², mortality risk was lower among those with higher BMI. The lowest mortality risk was observed at an approximate BMI of 35 kg/m². At BMI levels >35 kg/m², mortality risk was higher among those with higher BMI. Results of the fully adjusted with BMI modeled categorically did not differ from the spline model (Figure 3).

To further explore the U-shaped phenomenon, we sought to determine the threshold at which a 1-unit higher BMI was no longer associated with lower mortality and it became

<table>
<thead>
<tr>
<th>Table. Sociodemographic Characteristics and Stroke Risk Factors</th>
<th>Underweight (n=54, 3%), n (%)</th>
<th>Normal Weight (n=543, 30%), n (%)</th>
<th>Overweight (n=629, 35%), n (%)</th>
<th>Class 1 Obesity (n=311, 17%), n (%)</th>
<th>Class 2 Obesity (n=157, 9%), n (%)</th>
<th>Severe Obesity (n=97, 5%), n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>85 (76–90)</td>
<td>79 (67–85)</td>
<td>72 (60–81)</td>
<td>67 (57–77)</td>
<td>63 (54–73)</td>
<td>57 (52–65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mexican Americans</td>
<td>19 (35)</td>
<td>252 (46)</td>
<td>363 (58)</td>
<td>195 (63)</td>
<td>108 (65)</td>
<td>71 (73)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women</td>
<td>43 (80)</td>
<td>309 (57)</td>
<td>257 (41)</td>
<td>95 (61)</td>
<td>152 (60)</td>
<td>57 (59)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td>7 (2–14)</td>
<td>5 (2–9)</td>
<td>4 (2–8)</td>
<td>4 (2–8)</td>
<td>3 (2–7)</td>
<td>3.5 (1–6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (80)</td>
<td>407 (75)*</td>
<td>495 (79)</td>
<td>267 (86)</td>
<td>141 (90)</td>
<td>90 (93)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16 (30)</td>
<td>133 (25)*</td>
<td>96 (15)</td>
<td>35 (11)</td>
<td>19 (12)</td>
<td>6 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CAD</td>
<td>22 (41)</td>
<td>177 (33)*</td>
<td>222 (35)</td>
<td>106 (34)</td>
<td>54 (34)</td>
<td>35 (36)</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (26)</td>
<td>161 (30)*</td>
<td>245 (39)</td>
<td>166 (53)</td>
<td>105 (67)</td>
<td>76 (78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>17 (31)</td>
<td>191 (35)*</td>
<td>272 (43)</td>
<td>159 (51)</td>
<td>73 (47)</td>
<td>43 (44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>20 (37)</td>
<td>92 (17)*</td>
<td>87 (14)</td>
<td>41 (13)</td>
<td>23 (15)</td>
<td>22 (23)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cancer</td>
<td>8 (15)</td>
<td>75 (14)*</td>
<td>80 (13)</td>
<td>32 (10)</td>
<td>9 (6)</td>
<td>8 (8)</td>
<td>0.06</td>
</tr>
<tr>
<td>ESRD</td>
<td>1 (2)</td>
<td>33 (6)*</td>
<td>35 (6)</td>
<td>15 (5)</td>
<td>9 (6)</td>
<td>7 (7)</td>
<td>0.77</td>
</tr>
<tr>
<td>COPD</td>
<td>9 (17)</td>
<td>70 (13)*</td>
<td>56 (9)</td>
<td>28 (9)</td>
<td>18 (11)</td>
<td>9 (9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dementia</td>
<td>14 (26)</td>
<td>79 (15)*</td>
<td>53 (8)</td>
<td>14 (5)</td>
<td>5 (3)</td>
<td>1 (1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>21 (39)</td>
<td>157 (29)*</td>
<td>182 (29)</td>
<td>80 (26)</td>
<td>41 (26)</td>
<td>21 (22)</td>
<td>0.24</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>4 (7)</td>
<td>63 (12)</td>
<td>67 (11)</td>
<td>35 (11)</td>
<td>23 (15)</td>
<td>12 (12)</td>
<td>0.71</td>
</tr>
<tr>
<td>Excessive alcohol use</td>
<td>3 (6)</td>
<td>38 (7)*</td>
<td>38 (6)</td>
<td>20 (6)*</td>
<td>7 (4)</td>
<td>3 (3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Smoker</td>
<td>11 (20)</td>
<td>117 (22)*</td>
<td>125 (20)†</td>
<td>57 (18)*</td>
<td>30 (19)</td>
<td>17 (18)*</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Sociodemographic characteristics and stroke risk factors among patients with acute ischemic stroke (n=1791) from the Brain Attack Surveillance in Corpus Christi (BASIC) project, June 1, 2005, to December 31, 2010, are presented. CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease, IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*1 missing.
†2 missing.
‡6 missing.
associated with higher mortality. Using the fully adjusted Cox model, we compared the relative difference in mortality risk associated with 1-kg/m²-higher baseline BMI using hazard ratios for a range of baseline BMIs (Figure 4). The loss of a protective association between BMI and mortality occurred when comparing a baseline BMI of 31 kg/m² with a baseline BMI of 32 kg/m² (hazard ratio, 0.98; 95% confidence interval, 0.96–1.01). Conversely, the transition to a harmful association between BMI and mortality occurred at the point of comparing baseline BMIs of 38 and 39 kg/m² (hazard ratio, 1.04; 95% confidence interval, 1.00–1.08).

Using the fully adjusted model, we found evidence that age modified the association of BMI with mortality (P=0.001). The above-described BMI-mortality association was strongest among younger patients compared with older patients. That is, higher age at stroke onset attenuated the BMI-mortality association. There was no suggestion that smoking status modified the association of BMI with mortality (P=0.15). Limiting the population to patients with first stroke, removing the recurrent stroke covariate, or including those with a BMI ≥50 kg/m² did not meaningfully alter the main results (data not shown).

Discussion

In this population-based stroke surveillance study, we found a U-shaped relationship between BMI at stroke onset and all-cause mortality in patients with AIS. After accounting for demographics, stroke severity, and stroke and mortality risk factors, a 1-unit higher BMI had a protective association with mortality when BMI was <31 kg/m². Higher BMI >31 kg/m² did not render significant protective associations, and higher values of BMI >38 kg/m² were associated with higher mortality in the fully adjusted model. The large number of severely obese patients with AIS in our study population allowed us to differentiate the detrimental association of severe obesity from the beneficial association of class 1 obesity on the risk of poststroke mortality.

Some previous studies suggest that the association of obesity and poststroke mortality is age dependent, although the direction of the interaction has not been consistent across studies.8,9,12 Our results are similar to work in the United States and Korea showing that stroke patients with younger ages have a stronger BMI-mortality association than older stroke patients.8,12 In addition, our findings are in general agreement with previous studies showing a protective association of obesity on poststroke mortality,8–12 but we were able to address some of the limitations of previous work in this area.8–12,26 First, we conducted a population-based study limited to patients with AIS and performed a comprehensive adjustment for possible confounders, including the nonlinear association of NIHSS score with mortality and the time-dependent effect of recurrent stroke. Second, we avoided potential misclassification bias by treating BMI as a continuous predictor and by not combining obese and severely obese patients and normal-weight and underweight patients for analyses, which could introduce bias. For example, lumping underweight individuals who have higher risk with normal-weight individuals to define the normal-weight comparison group would overestimate the protective association between obese and normal-weight groups. In addition, we were able to
adjust for potential factors related to mortality in underweight patients with AIS, including cancer, smoking status, dementia, and end-stage renal disease.27 Reasons for the reduced mortality among obese patients with stroke are unknown. Researchers have speculated that the reason may be the more frequent use of antihypertensive medications among obese patients with stroke, but this requires additional research.9

Severe obesity is associated with increased all-cause mortality in the general population.6,28 Data suggest that the prevalence of vascular risk factors, including diabetes mellitus, hypertension, and hyperlipidemia, among severely obese people mediates the increased mortality risk.28 However, in our study of patients with AIS, severely obese patients with AIS continued to have increased mortality after accounting for these conditions. Another possibility to explain our results is that, similar to the general population,29 severely obese patients with AIS may have more depressive symptoms, which in turn are associated with increased poststroke mortality.30 We did not explore depressive symptoms in our study population. Alternative explanations for the increased mortality among severely obese patients with AIS may include decreased diagnostic testing because of size limitations of diagnostic equipment (MRI scanners), decreased use or intensity of poststroke rehabilitation because of the difficulty of therapists working with larger patients or weight limits of rehabilitation equipment, or missed follow-up appointments because of difficulty using standard transportation for larger patients. More research is needed to explore ways in which severe obesity is associated with increased poststroke all-cause mortality.

Our findings have important clinical implications. The current secondary stroke prevention guidelines recommend weight loss as part of the comprehensive therapy for hypertension and metabolic syndrome.31 To date, however, there is no randomized, controlled trial evidence that weight management or reduction prevents recurrent stroke or death after AIS. In addition, weight management by calorie restriction and physical activity poses potential risks in adults with AIS, particularly those with older age, diabetes mellitus, or neurological disability. Thus, in the absence of hypertension and metabolic syndrome, providers, health systems, and payers may focus their efforts on improving currently suboptimal adherence to secondary stroke preventive strategies with proven efficacy such as statins and antithrombotic drugs.31

Limitations of this study warrant discussion. BMI may not accurately reflect obesity among the elderly and does not account for body fat distribution.32 We studied BMI (a measure of overall obesity) and did not examine the role of body composition or abdominal adiposity. BMI was abstracted from the medical record and is dependent on the accuracy of medical documentation. We cannot exclude that weight may be difficult to obtain in obese patients with stroke, particularly those with severe disabilities, and therefore, measurement error is possible. BMI measures over time in individual patients were not available. Thus, we cannot determine the influence of changes in BMI on mortality. In addition to BMI, other factors that have been shown to influence poststroke mortality and that may be associated with BMI such as admission to a stroke unit, depression, and social support were not available. Our model may be
overadjusted given that recurrent stroke may be on the causal pathway between BMI and poststroke mortality. However, a recent study showed no association between obesity and recurrent stroke, and our sensitivity analysis excluding recurrent stroke did not meaningfully change the study results. Our study population is limited to MA and non-Hispanic white patients with AIS who were aged >45 years. Thus, our results are not generalizable to the entire US AIS population. Like most studies of AIS who were aged >45 years. Thus, our results are not generalizable to the entire US AIS population. Like most

Conclusions
In conclusion, in this population-based stroke surveillance study, we demonstrated a heterogeneous association of BMI with all-cause mortality in middle-aged and older adults with AIS, with a protective association for obesity and a detrimental association for severe obesity. Further study is needed to confirm these findings and to determine the safety and effectiveness of weight loss interventions among obese and severely obese patients with AIS.

Sources of Funding
This study was funded by National Institutes of Health/NINDS R01NS038916, K23NS058359 (Dr Kerber), K23NS073685 (Dr Skolarus), and K23AG040278 (Dr Levine).

Disclosures
None.

References
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Circ Cardiovasc Qual Outcomes. published online December 10, 2013;
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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