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JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Stroke 2009;40;2704-2708; originally published online Jun 18, 2009;

DOI: 10.1161/STROKEAHA.109.550228

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ISSN: 1524-4628

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The Impact of Body Mass Index on Mortality After Stroke

Amytis Towfighi, MD; Bruce Ovbiagele, MD

Background and Purpose—Little is known about the contribution of obesity to the higher mortality risk among stroke survivors. We assessed the independent association between body mass index (BMI) and mortality among stroke survivors.

Methods—Cross-sectional and prospective data from a nationally representative survey of noninstitutionalized civilian U.S. population aged 25 or older (n=20 050) with a baseline history of stroke (n=644) followed up from survey participation (1988–1994) through mortality assessment in 2000. Relationships between BMI and mortality attributable to all causes or cardiovascular causes were examined after adjusting for established prognosticators after stroke.

Results—Stroke survivors were more likely to be overweight (BMI 25 to 29 kg/m²) or obese (BMI ≥30 kg/m²) than those without stroke (64.3% versus 53.2%, *P*=0.003). In multivariable analysis, overall risk for all-cause mortality increased per kg/m² of higher BMI (*P*=0.030), but an interaction between age and BMI (*P*=0.009) revealed that the association of higher BMI with mortality risk was strongest in younger individuals and declined linearly with increasing age, such that in the elderly, overweightness and obesity had a protective effect. The results were similar for the cardiovascular mortality outcome.

Conclusions—Higher BMI after stroke is associated with a greater risk of all-cause and cardiovascular death among younger individuals. Younger stroke survivors may especially benefit from more vigorous efforts to monitor and treat obesity. (*Stroke*. 2009;40:2704-2708.)

Key Words: stroke ■ mortality ■ obesity ■ body mass index ■ cardiovascular deaths

Although mortality after stroke is highest in the first month, survivors have a higher mortality risk than individuals in the general population for several years after the stroke.^{1–3} Most deaths in the first month are attributable to the stroke itself; however, most later deaths are attributable to general cardiovascular causes, including recurrent stroke. Identifying predictors of later death may open avenues for mitigating this risk among stroke survivors.

Obesity, a growing pandemic, is an established stroke risk factor^{4,5} and an important predictor of death in the general population^{6–9}; however, little is known about its effect on mortality after stroke. Although one prospective study showed that obese men were more likely to die from stroke than normal-weight men,¹⁰ no study to our knowledge has assessed the effect of obesity on mortality after stroke.

Our goal was to assess the association between higher adiposity and cardiovascular and all-cause mortality among stroke survivors.

Methods

Population for Study

The Third National Health and Nutrition Examination Surveys (NHANES III) was a nationally representative survey of 33 199 civilian noninstitutionalized U.S. individuals, conducted from 1988 to 1994.

The study outcomes—all-cause and cardiovascular mortality—were recorded from NHANES III mortality follow-up data, which

relied on a probabilistic match between NHANES III and National Death Index (National Center for Health Statistics [NCHS] 2006) death certificate records. Mortality records were available for 20 024 of 20 050 adults who completed interviews and medical examinations. Mortality assessments, including cause-specific mortality and mortality dates, were conducted from baseline interview through December 31, 2000. Cause-specific mortality was coded using the ninth revision of the International Classification of Diseases, Injuries, and Causes of Death (ICD-9) for deaths occurring between 1988 and 1998 and tenth revision (ICD-10) for deaths occurring between 1999 and 2000. The Underlying Cause of Death 113 Groups All Years (UCOD-113) variable recoded all deaths before 1999 coded under ICD-9 guidelines into comparable ICD-10 codes.¹¹

Of all participants, 644 who met inclusion criteria (age >25, not pregnant) reported a physician diagnosis of stroke and had mortality data available. Of these, 97 were missing BMI measurements and 123 to 135 (depending on the model) were missing covariate values, leaving a total of 424 subjects for the multivariable model for cardiovascular mortality and 412 subjects for the multivariable model for all-cause mortality.

Study Variables

Primary Predictor Variables

BMI was calculated from height and weight (kg/m²) measured using standardized protocols. BMI was investigated as a continuous variable after confirming the assumption of linearity for continuous BMI versus the log mortality rate outcomes and a categorical variable using established cutoffs. Individuals were categorized as nonoverweight (BMI <25 kg/m²), overweight (BMI 25 to 29.9 kg/m²), obese (BMI 30.0 to 39.0 kg/m²), and morbidly obese (BMI

Received February 23, 2009; final revision received May 26, 2009; accepted May 27, 2009.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.109.550228

>39 kg/m²). Nonoverweight was the referent category. The obese and morbidly obese categories were collapsed together because the latter category was relatively rare.

Because 38% of the waist circumference (WC) observations were missing, and the missingness was probably not at random (those with a missing value were more likely to be older and had worse mortality outcomes), WC was not considered as a primary predictor variable. Nonetheless, among those with recorded WC values, WC and BMI were highly positively correlated (Spearman $r=0.87$, $P<0.001$).

Primary Outcome Variable

The primary study outcome variable was all-cause mortality, analyzed as a time to event outcome (event was deceased from all causes versus alive).

Secondary Outcome Variable

The secondary outcome variable was cardiovascular mortality, analyzed as a time to event outcome (event was deceased attributable to cardiovascular causes versus alive or deceased attributable to competing noncardiovascular causes). Cardiovascular deaths included deaths from any heart disease, cerebrovascular cause, atherosclerosis, or hypertension (UCOD-113 codes 054 to 074). Stroke mortality (deaths from any cerebrovascular cause, UCOD-113 code 070) was not used as a primary outcome as it was too rare to formally control for covariates.

Covariates

Covariates included variables known to be associated with obesity and mortality after stroke. Hypertension was defined by self-reported physician diagnosis, self-reported current antihypertensive medication use, or a mean of the first 3 blood pressure readings >140 mm Hg systolic or 90 mm Hg diastolic. Diabetes mellitus (DM) was defined by self-reported physician diagnosis, self-reported current medical therapy, or glycosylated hemoglobin >7%. Hypercholesterolemia was defined by self-reported physician diagnosis, self-reported current medical therapy, or total cholesterol level >200 mg/dL. Elevated LDL was defined as LDL >100 mg/dL. Hypertriglyceridemia was defined as triglyceride level >150 mg/dL. Low HDL was defined as HDL <50 mg/dL in women and 40 mg/dL in men. Hyperhomocysteinemia was defined as homocysteine ≥ 8.5 micromol/L. Smoking was defined by self-reported history of smoking more than 100 cigarettes. History of myocardial infarction (MI) was defined by self-reported physician diagnosis of "heart attack." Elevated LDL and hyperhomocysteinemia were not included in the multivariable analysis because of the large number of missing observations. Time from stroke occurrence to baseline NHANES interview was also considered as a covariate.

Statistical Analysis

Weighted estimates were applied to the descriptive prevalence analysis using NHANES mobile examination center-examined sample weight values, adjusting for differential probabilities of selection and nonresponse, poststratified to 1990 U.S. Census total population estimates. To account for the effect of the NHANES clustering design on the Cox hazard model, the primary sampling unit variable was included as a stratification variable. Both the weighting and stratification by primary sampling unit were negligible in this subsample; therefore, stratification by primary sampling unit was subsequently dropped without changes in results. Tests based on the correlation matrix were conducted to rule out collinearity before running all multivariable regression analyses. Data analyses were conducted using SAS (version 9.1; SAS Institute Inc) and the R "cmprsk" competing risk library (R 2.7.1, R foundation for Statistical Computing). Statistical hypotheses were tested using $P<0.05$ as the level of statistical significance except as noted.

Bivariate Analysis

Cox regression models for time to event outcomes were used to bivariate analyze the influence of categorical and continuous BMI on cardiovascular and all-cause mortality. For cardiovascular mortality, the Cox model was expanded to a competing risk Cox model

(implemented via R function 'crr') because noncardiovascular mortality was a simultaneous competing risk.

Comparison of Clinical Characteristics Across BMI Groups

All covariates were assessed across BMI groups. Continuous variables were compared across the groups using the nonparametric Wilcoxon rank sum test. Categorical variables were compared using the χ^2 test.

Multivariable Analyses

The multivariable Cox regression model was used to analyze the simultaneous effect of either continuous or categorical BMI and all covariates including age on all-cause mortality. The cardiovascular mortality outcome was analyzed similarly using an expanded Cox regression model allowing for the competing risk of noncardiovascular death. Both models considered all covariates simultaneously including all interactions between BMI and each covariate. For variable selection, the backwards stepwise procedure with a liberal $P<0.25$ level of significance was used. The main effect of a given covariate was retained if there was a significant interaction involving the covariate.

Because the continuous BMI model showed significant interactions of BMI with age, for logical consistency, the interactions of BMI category with age in categorical BMI models were included even when not statistically significant. The interaction effects in the categorical BMI models qualitatively resembled the continuous BMI models; therefore, we deemed it biologically unreasonable not to include these effects.

Results

Of 20 050 subjects, 17 648 (88%) had complete BMI and stroke history data. Stroke survivors were more likely to be overweight/obese than those without a history of stroke (64.3% versus 53.2%, $P=0.003$). Among stroke survivors, those with higher BMI were more likely to be women, younger, diabetic, hypertensive, and to have lower HDL levels (Table 1). The mean and median times from stroke occurrence to mortality or follow-up were 14.1 years (standard deviation: 10.1 years) and 11.5 years (interquartile range: 7.5 to 18.3 years). Time from index event to baseline assessment did not differ between BMI groups (Table 1).

In multivariable analysis, older age, history of smoking, history of MI, and DM were associated with higher all-cause mortality, whereas female sex was associated with lower all-cause mortality (Table 2). Similarly, older age, history of MI, DM, and hypercholesterolemia were associated with higher cardiovascular mortality, whereas female sex was associated with lower cardiovascular mortality (Table 3).

The bivariate (unadjusted) results showed that BMI increases were associated with lower all-cause mortality (per kg/m² HR 0.96, 95% CI 0.94 to 0.98, $P<0.001$) and cardiovascular mortality (per kg/m² HR 0.95, 95% CI 0.92 to 0.98, $P<0.001$). However, on multivariable adjustment, there were interaction effects between age and continuous BMI ($P=0.009$ for all-cause mortality and $P=0.044$ for cardiovascular mortality) such that BMI was a risk factor in younger but not older subjects (Tables 2 and 3). For example, keeping age constant, for a 40-year-old stroke survivor, a 1-kg/m² increase in BMI resulted in a marginally significant 5% increase in all-cause mortality (HR 1.05, 95% CI 0.99 to 1.11) and a marginally significant 4% increase in cardiovascular mortality (HR 1.04, 95% CI 0.97 to 1.11), whereas for an 80-year-old stroke survivor, a 1-kg/m² increase in BMI resulted in a 5% decrease in all-cause mortality (HR 0.95,

Table 1. Comparison of Clinical Characteristics of Stroke Survivors Across BMI Groups

Characteristics	Nonoverweight* n=205	Overweight† n=211	Obese‡ n=108	Morbidly Obese§ n=23	P Value
F, n (%)	94 (45.9)	101 (47.9)	61 (56.5)	19 (82.6)	0.004
Race/ethnicity					
Hispanic/other¶	29 (14.2)	37 (17.5)	27 (25.0)	4 (17.4)	0.110
Non-Hispanic white	124 (60.5)	121 (57.4)	49 (45.4)	10 (43.5)	
Non-Hispanic black	52 (25.4)	53 (25.1)	32 (29.6)	9 (39.1)	
Age, mean (SD)	73.5 (13.2)	73.3(12.2)	67.8 (12.1)	64.4 (14.0)	<0.001
Diabetes mellitus, n (%)	46 (24.6)	56 (28.3)	38 (37.3)	11 (55)	0.010
Hypertension, n (%)	140 (73.3)	172 (85.1)	88 (83.8)	20 (87)	0.015
History of myocardial infarction, n (%)	48 (23.4)	51 (24.4)	28 (25.9)	6 (26.1)	0.964
History of smoking, n (%)	122 (59.5)	111 (52.6)	70 (64.8)	11 (47.8)	0.130
Hypercholesterolemia, n (%)	146 (83.4)	133 (74.3)	83 (79.8)	20 (90.9)	0.094
Low HDL, n (%)	68 (37)	100 (51.3)	38 (50.5)	12 (60)	0.014
Hypertriglyceridemia, n (%)	72 (39.1)	93 (47.7)	54 (55.1)	10 (50)	0.068
Time from stroke to interview in years, mean (SD)	8.4 (11.2)	7.7 (8.4)		7.9 (8.5)	0.573

*BMI <25.0 kg/m².†BMI 25.0–29.9 kg/m².‡BMI 30.0–39.0 kg/m².§BMI >39.0 kg/m².

¶18 subjects were classified as “other” race/ethnicity.

HDL indicates high density lipoprotein cholesterol.

95% CI 0.92 to 0.98) and a 6% decrease in cardiovascular mortality (HR 0.94, 95% CI 0.90 to 0.99; Table 4).

When we used our continuous BMI model to estimate mortality risk at 5 years according to age group and BMI, we found that in younger individuals, an increase in BMI was marginally significantly associated with a higher risk of overall and cardiovascular mortality, and in the elderly, an increase in BMI was associated with a modest decrease in overall and cardiovascular mortality (Table 5). Considering BMI as a categorical variable yielded similar results, with a significant interaction effect between age and obesity ($P=0.016$) for overall mortality, but no significant effect for cardiovascular mortality.

When we compared all-cause mortality rate ratios in overweight/obese individuals versus normal-weight individuals of similar age, we found a trend among individuals

younger than 70, showing that overweight/obese individuals had a higher risk (point estimate) of all-cause mortality than normal-weight individuals (Figure). As expected, obesity conferred a higher risk than overweightness. For example, an obese 30-year-old stroke survivor had a 6-fold higher risk of overall mortality compared to a similarly aged normal-weight stroke survivor, approaching statistical significance (HR 5.96, 95% CI 0.98 to 36.18), whereas an overweight 30-year-old stroke survivor had nearly a 2-fold risk of overall mortality compared to a similarly aged normal-weight stroke survivor, although not significant (HR 1.77, 95% CI 0.34 to 9.30) (Figure). Similar findings were noted for cardiovascular mortality, albeit to a lesser degree.

Whereas overweightness/obesity had a mild deleterious effect on cardiovascular and all-cause mortality in individuals under age 70, they conferred a modest protective effect in older individuals (Figure). For example, an 80-year-old obese stroke survivor had a significant 42% lower chance of dying from all causes than a normal-weight stroke survivor of same

Table 2. Continuous BMI Model for All-Cause Mortality

Variable	Beta	SE	HR (95% CI)	P Value
BMI	0.14	0.07	...	0.030
Age (per year)	0.14	0.03	...	<0.001
BMI * age	−0.002	0.001	...	0.009
Low HDL	0.24	0.14	1.27 (0.97–1.68)	0.079
History of smoking	0.32	0.15	1.38 (1.03–1.86)	0.029
History of myocardial infarction	0.37	0.15	1.45 (1.07–1.96)	0.014
Female	−0.47	0.14	0.62 (0.47–0.83)	0.001
Hypertension	0.31	0.18	1.36 (0.95–1.94)	0.089
Diabetes mellitus	0.72	0.16	2.05 (1.49–2.83)	<0.001
Hypercholesterolemia	0.31	0.18	1.36 (0.96–1.93)	0.081
Hispanic	−0.18	0.20	0.83 (0.56–1.23)	0.349
Black	0.30	0.17	1.35 (0.95–1.91)	0.083

Table 3. Continuous BMI Model for Cardiovascular Mortality

Variable	Beta	SE	HR (95% CI)	P Value
BMI	0.133	0.081	...	0.100
Age (per year)	0.126	0.032	...	<0.001
BMI * age	−0.002	0.001	...	0.044
History of myocardial infarction	0.418	0.185	1.52 (1.05–2.20)	0.024
Female	−0.395	0.166	0.67 (0.48–0.94)	0.018
Hypertension	0.368	0.237	1.44 (0.90–2.32)	0.120
Diabetes mellitus	0.745	0.187	2.11 (1.45–3.06)	<0.001
Hypercholesterolemia	0.463	0.232	1.59 (1.00–2.53)	0.046

Table 4. Mortality Rate Ratios per kg/m² Relative to Person of Same Age

Age	Adjusted All-Cause Mortality Hazard Ratio (95% CI)	Adjusted Cardiovascular Mortality Hazard Ratio (95% CI)
30	1.07 (0.99–1.16)	1.06 (0.98–1.17)
40	1.05 (0.99–1.11)	1.04 (0.97–1.11)
50	1.02 (0.98–1.07)	1.01 (0.96–1.07)
60	1.00 (0.97–1.03)	0.99 (0.96–1.03)
70	0.97 (0.95–1.00)	0.97 (0.94–1.00)
80	0.95 (0.92–0.98)	0.94 (0.90–0.99)
90	0.93 (0.89–0.97)	0.92 (0.87–0.98)

age (HR 0.58, 95% CI 0.36 to 0.93) and an 80-year-old overweight stroke survivor had a modest 20% lower chance of dying from all causes than a normal-weight stroke survivor of same age (HR 0.80, 95% CI 0.59 to 1.10; Figure), although these latter findings were not significant. Similar but less robust trends were seen for cardiovascular mortality.

Discussion

We found that the effect of obesity on mortality after stroke was age-dependent; overweight/obese individuals under age 70 were more likely to die from cardiovascular or all causes over an average of 14 years after index stroke than their normal-weight counterparts, whereas older individuals had lower cardiovascular and all-cause mortality. Although previous studies have shown an age differential effect of obesity on stroke incidence¹² and cardiovascular mortality,¹³ we are unaware of prior studies showing an age differential impact of obesity on mortality after stroke.

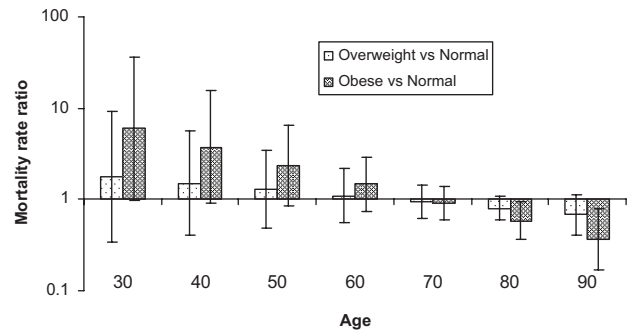
Our continuous BMI models indicated that BMI increases were associated with modestly lower cardiovascular and all-cause mortality in the elderly and modestly higher cardiovascular and all-cause mortality in younger individuals. For example, as shown in Table 5, at 5 years follow-up, a typical 80-year-old stroke survivor had a 35%, 27%, or 18% risk of cardiovascular death if he/she was nonoverweight, overweight, or obese. A typical 40-year-old stroke survivor had a 2.2%, 2.6%, or 3.6% risk of cardiovascular death if he/she was nonoverweight, overweight, or obese. Similar trends were seen for all-cause mortality.

The association of obesity with mortality among younger stroke survivors was of borderline statistical significance,

Table 5. Estimated Mortality Risks at 5 Years Follow-Up*

Age	All-Cause Mortality Risk			Cardiovascular Mortality Risk		
	BMI=22	BMI=27	BMI=35	BMI=22	BMI=27	BMI=35
30	1.1%	1.5%	2.7%	1.1%	1.4%	2.3%
40	2.5%	3.2%	4.5%	2.2%	2.6%	3.6%
50	5.8%	6.5%	7.6%	4.5%	4.9%	5.4%
60	13.1%	13.0%	12.7%	9.2%	8.8%	8.2%
70	28.1%	25.1%	20.8%	18.3%	15.7%	12.3%
80	53.8%	45.1%	32.9%	34.5%	27.2%	18.2%
90	83.6%	71.2%	49.5%	58.7%	44.5%	26.5%

*Risk estimates are derived from the continuous BMI models.

**Figure.** All-cause mortality rate ratios vs age in overweight/obese vs normal-weight stroke survivors of similar age.

whereas the effect of overweightness was not significant. The lack of significance was, not surprisingly, particularly a problem in the categorical BMI model compared to the continuous model. Although it is difficult to know whether the lack of significance was attributable to poor power versus lack of true effect, a resampling simulation suggests that it was the former. For example, the hazard ratio for cardiovascular mortality in 30-year-old overweight stroke survivors was 1.36 compared to 30-year-old nonoverweight stroke survivors. The 95% confidence interval was 0.19 to 9.71, a range that includes the null value of 1.0. A resampling (bootstrap) simulation using 1000 resamplings shows that our power for testing the null hypothesis of HR=1 is only 8.1% with the current sample of n=424. By simulation, to obtain at least 80% power, the sample size would need to be at least 2697. This is an indication that our sample size is inadequate, making our finding inconclusive rather than negative. With the current sample size of 424, the HR point estimate in this example would need to be at least 7.1, not 1.36 (computed using asymptotic theory).

Although our study may be underpowered, we believe the associations were real for several reasons. First, the results were consistent whether BMI was assessed as a categorical or continuous variable and for both all-cause and cardiovascular mortality. Secondly, the relationship between higher adiposity and mortality declined linearly across the board with increasing age. Thirdly, the differential effect of age on the relationship between obesity and mortality among stroke survivors is in accord with general population studies.^{7,14}

There are multiple potential explanations for the age differential effect of obesity on mortality, including selective survival, increased mortality rates, and increased prevalence of other diseases among older populations. In addition, because lean mass and height decline with aging, BMI may not be an accurate marker of body fatness in elderly individuals¹⁵; waist-to-hip ratio or WC may be better markers of body fatness and may be better predictors of mortality in the elderly.^{6,16,17}

As previously noted, general population studies have shown a deleterious influence of obesity on survival; however, the exact mechanisms of this effect are unknown. Obesity is associated with proinflammatory and prothrombotic states,^{18–23} both of which are involved in atherothrombosis.

Fortunately, BMI assessment is simple and obesity eminently modifiable. Several studies have shown that weight loss improves cardiovascular risk factors.^{24,25} Preclinical

animal data²⁶ and one human cohort study have shown mortality reduction with intentional weight loss.²⁷ However, conflicting observational studies have indicated that weight loss may be associated with increased mortality^{28,29}; those results were likely confounded by effects of occult disease causing unintentional weight loss.

This study has limitations. First, NHANES relies on self-reported history of stroke. However, whereas NHANES has not validated self-reporting of stroke, other studies have found this method to have a sensitivity ranging from 80% to 95% and a specificity of 96% to 99%.^{30,31} Second, the effect of obesity on cardiovascular and all-cause mortality may differ in individuals with ischemic versus hemorrhagic strokes; however, the majority of strokes in this study were likely ischemic. Third, we were unable to adjust for elevated LDL levels and hyperhomocysteinemia in our multivariable analysis because of the large number of missing observations.

In conclusion, our study should add further impetus to clinicians to incorporate simple measures of obesity, including BMI, in their routine assessment of stroke patients. Beyond the potential adverse influence of obesity on vascular events, obesity appears to confer a higher risk of death. Relatively younger obese stroke patients seem to be affected the most and may benefit from timely comprehensive interventions geared at promoting weight loss.

Acknowledgments

Statistical analyses performed by Daniela Markovic, MS and Jeffrey Gornbein, DrPH, Department of Biomathematics, University of California at Los Angeles.

Disclosures

None.

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