Body Mass Index and Ischemic and Hemorrhagic Stroke
A Prospective Study in Korean Men

Yun-Mi Song, MD, MPH, PhD; Joohon Sung, MD, MPH, PhD;
George Davey Smith, DSc, FFPHM; Shah Ebrahim, DM, FRCP

Background and Purpose—The association between obesity and stroke remains controversial, with earlier studies suggesting that differences might stem from heterogeneous stroke subtype compositions. The association between body mass index (BMI) and stroke subtypes was examined prospectively in a large cohort study.

Methods—A total of 234 863 Korean men aged 40 to 64 years without substantial weight loss over 4 years after baseline examination in 1986 were divided into 8 categories of BMI and were followed up between 1991 and 2000 for fatal and nonfatal stroke events.

Results—There was a positive association across the whole range of BMI and ischemic stroke, with a confounder-adjusted hazard of 11% (95% CI, 1.09 to 1.12) for 1 kg/m² higher BMI. A J-shaped association was observed between BMI and hemorrhagic stroke; groups with a higher BMI than the reference category (22 to 23 kg/m²) had significantly increased risks. Full adjustment for confounders and variables potentially on the causal pathway (ie, blood pressure, blood glucose, and cholesterol) attenuated the association between BMI and stroke subtypes only for those with BMI greater than the reference category. Exclusion of deaths during the first 8 years or stratified analysis according to smoking habit did not change the relation between BMI and stroke subtypes.

Conclusions—BMI is a risk factor for both ischemic and hemorrhagic stroke but shows different relationships with each. When the total burden of stroke is considered, there is an urgent need to find better ways of reducing the trend toward growing obesity in both Western and Asian countries. (Stroke. 2004;35:831-836.)

Key Words: body mass index ■ cerebral hemorrhage ■ cerebral infarction ■ cerebrovascular disorders ■ Korea

The association between obesity and stroke remains controversial, with published studies showing positive,1,2 no,3,4 or negative5 association. While systematic differences in the risk factors for stroke subtypes6,7 and the proposed biological mediators (eg, cholesterol, hypertension, and glucose) influencing the causal pathway between obesity and stroke may occur,8 previous studies have seldom characterized stroke subtypes or adequately examined the influence of such biological mediators. Most studies have been too small to adequately describe the nature of any body mass index (BMI) and stroke relationship.

Compared with Western populations, Asian populations have a lower incidence of coronary heart disease but a higher incidence of stroke. This provides a special strength in the investigation of stroke risk factors because any possible bias from competing risk between stroke and coronary artery disease is greatly reduced. In this study we examined the association between BMI and stroke and specifically examined the relation with stroke subtypes in a large Korean male population cohort.

Subjects and Methods

Subjects and Study Variables
Study participants were Korean male public servants aged 40 to 64 years, who underwent a health examination provided by the Korean National Health System (KNHS) between 1986 and 1990. Details of this study population have been presented previously.9 Among the initial 257 634 men, 22 771 were excluded for the following reasons: weight loss of >5% between 1986 and 1990 (22 182 men); inadequate or missing data needed for calculating BMI (54 men); or nonfatal stroke or death from stroke or other causes (535 men) before 1991. Thus, 234 863 men were included in the study.

In these analyses body weight, blood pressure (BP), and fasting serum total cholesterol and glucose levels measured in 1986 were used. Since height was not measured in 1986, the values of 1991 were used to calculate BMI as weight in kilograms divided by the square of height in meters. Height and weight were measured by trained staff using stadiometers and scales of government-approved quality. A single measurement of BP was made with the use of a standard mercury or electronic sphygmomanometer with the subject in the seated position. To estimate the reliability of the measurements, we calculated the correlations between height and weight measured in 1990 and again in 1992 and found correlations of 0.95 and 0.94 for height and weight, respectively, indicating that BMI was...
estimated accurately. Study subjects were divided into 8 categories according to the level of BMI: <18.0, 18.0 to 19.9, 20.0 to 21.9, 22.0 to 23.9, 24.0 to 25.9, 26.0 to 27.9, 28.0 to 29.9, and ≥30.0 kg/m². Average BMI of study subjects was 23.1 (SD 2.54) kg/m². The boundary for the highest category (≥30.0 kg/m²) approximated the 99.4 percentile of study subjects, and the lowest (<18.0 kg/m²) approximated the 1.42 percentile. We categorized BP according to the sixth report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure¹⁰: normal (<130/<85 mm Hg), high-normal (130 to 139/<85 to 89 mm Hg), stage 1 (140 to 159/<90 to 99 mm Hg), stage 2 (160 to 179/<100 to 109 mm Hg), and stage 3 hypertension (≥180/<110 mm Hg). We divided study subjects into 6 strata of serum total cholesterol: <3.1, 3.1 to 4.0, 4.1 to 5.0, 5.1 to 6.2, 6.3 to 7.1, and ≥7.2 mmol/L. Information on smoking habits and regularity of physical exercise was obtained from a self-administered questionnaire in 1990. Study subjects were classified into 4 groups according to their smoking habits: nonsmoker, ex-smoker, smoking 1 to 19 cigarettes per day, and smoking ≥20 cigarettes per day. For physical exercise, because detailed information was not available, 2 categories were used: engaging in regular exercise or not. We calculated the amount of alcohol consumption using questionnaires administered in 1992 and 1994, in which drinking frequency per week and the amount consumed per drink were queried. The weekly alcohol consumption level was divided into 5 categories: <30, 30 to 104, 105 to 209, 210 to 419, and ≥420 g/wk. We classified economic status into 4 levels by guest on April 7, 2017 http://stroke.ahajournals.org/ Downloaded from
on the basis of quartile distribution of monthly salary in 1990. Information on whether individuals had taken any medication for hypertension, diabetes mellitus, or other chemoprevention purposes was not available.

### Stroke Mortality and Morbidity Follow-Up
All nonfatal and fatal strokes occurring after 1990 were included in this analysis. The following codes in the International Statistical Classification of Diseases, 10th Revision (ICD-10) were used to identify and classify the stroke subtypes: all stroke (I60 to I69), ischemic stroke (I63, I67.8), hemorrhagic stroke (I61), and subarachnoid hemorrhage (I60). Transient ischemic attack was excluded. Stroke deaths of study subjects between January 1991 and December 2000 were ascertained through data linkage with the nationwide death report data of the Korean National Statistical Office and the Stroke Mortality and Morbidity Follow-Up Information on whether individuals had taken any medication for hypertension, diabetes mellitus, or other chemoprevention purposes on the basis of quartile distribution of monthly salary in 1990.

### Statistical Analysis
Follow-up began January 1991, and the participants were censored at the date of stroke admission, stroke death, other causes of death, or December 2000 for the others. Relative risks for stroke subtypes by BMI groups were estimated by the Cox proportional hazard regression analysis. To examine the possible pathways between BMI and stroke occurrence, the findings from a model adjusted for age only, a model adjusted for age plus confounders, and a third model incorporating possible biological mediators of the effects of obesity (cholesterol, glucose, and BP) were compared. To identify the effect of preexisting occult disease, the analysis was repeated after excluding deaths in the first 8 years. Additionally, we performed a stratified analysis according to smoking status to evaluate whether any stroke association with low BMI (common in smokers) was due to smoking. To further explore the overall nature of the association, we used logistic (local regression) smoothers of BMI effects on stroke, using a generalized additive model (GAM).  

### Results
The cohort comprised 234,863 men and 2,253,740 person-years of follow-up. During the follow-up period, 1,720 fatal and 5,724 nonfatal stroke cases occurred. Among stroke events, ischemic stroke accounted for 53.5%, hemorrhagic stroke for 24.3%, subarachnoid hemorrhage for 5.5%, and unspecified stroke for 16.7%.

### Table 2: Incidence Rate per 100,000 Person-Years and Adjusted Hazard Ratio (95% CIs) for Stroke Subtypes by the Level of BMI

<table>
<thead>
<tr>
<th>Type of Stroke (no. of cases)</th>
<th>Model*</th>
<th>&lt;18.0 (n=3330)</th>
<th>18.0–19.9 (n=22,108)</th>
<th>20.0–21.9 (n=53,274)</th>
<th>22.0–23.9 (n=19,553)</th>
<th>24.0–25.9 (n=5,286)</th>
<th>26.0–27.9 (n=23,432)</th>
<th>28.0–29.9 (n=8,146)</th>
<th>≥30.0 (n=1458)</th>
<th>1-kg/m² increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke (7444)</td>
<td>Incidence</td>
<td>316</td>
<td>246</td>
<td>273</td>
<td>319</td>
<td>369</td>
<td>432</td>
<td>496</td>
<td>529</td>
<td>1.07 (0.96–1.08)</td>
</tr>
<tr>
<td>Ischemic stroke (3981)</td>
<td>Incidence</td>
<td>132</td>
<td>112</td>
<td>135</td>
<td>172</td>
<td>206</td>
<td>257</td>
<td>268</td>
<td>239</td>
<td>1.07 (0.96–1.08)</td>
</tr>
<tr>
<td>Hemorrhagic stroke (1806)</td>
<td>Incidence</td>
<td>97</td>
<td>74</td>
<td>68</td>
<td>73</td>
<td>85</td>
<td>102</td>
<td>134</td>
<td>181</td>
<td>1.07 (0.96–1.08)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage (412)</td>
<td>Incidence</td>
<td>13</td>
<td>14</td>
<td>16</td>
<td>19</td>
<td>21</td>
<td>15</td>
<td>24</td>
<td>22</td>
<td>1.07 (0.96–1.08)</td>
</tr>
</tbody>
</table>

*Model I: age was adjusted; model II: age, alcohol consumption, smoking habit, doing exercise, and monthly salary level were adjusted; model III: variables in model II plus blood pressure, glucose, and cholesterol were adjusted; model IV: all variables in model III were adjusted and the stroke occurrence during the first 8 years of follow-up were excluded.
group had an increased risk of hemorrhagic stroke (confounder-adjusted HR, 2.6; 95% CI, 1.7 to 4.0) compared with the reference category before adjustment for the possible effects of obesity. The J-shaped relation was attenuated after adjustment for BP, cholesterol, and glucose levels, although the highest BMI category still showed a fairly strong association (HR, 1.8; 95% CI, 1.1 to 2.7). Subarachnoid hemorrhage showed no significant trend related with BMI. Excluding events during the first 8 years did not materially alter the association of BMI with stroke subtypes.

Figure 1 shows HRs for ischemic and hemorrhagic stroke by level of BMI. Figure 2 shows the shape of the relationship between BMI and all stroke, ischemic stroke, and hemorrhagic stroke adjusted for confounders with the use of GAM with loess smoothing. At the lower end of the BMI distribution, both ischemic stroke and hemorrhagic stroke showed trends consistent with no increase in risk for BMI < 20 kg/m².

**Discussion**

We have demonstrated that BMI is associated with stroke but that the direction and strength of association depend on stroke subtype. The association between ischemic stroke and BMI showed a linear trend, with a protective effect of below-average BMI. In Western populations with higher BMI levels, the reduced ischemic stroke risk of very low BMI level would not be elucidated. Increased risks for both ischemic stroke and hemorrhagic stroke among men with BMI above the reference range (22 to 23 kg/m²) were attenuated by adjustment for cholesterol, glucose, and BP, indicating that

<table>
<thead>
<tr>
<th>Level of BMI, kg/m²</th>
<th>&lt;18.0</th>
<th>18.0–19.9</th>
<th>20.0–21.9</th>
<th>22.0–23.9</th>
<th>24.0–25.9</th>
<th>26.0–27.9</th>
<th>28.0–29.9</th>
<th>≥30.0</th>
<th>1-kg/m² Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker (795)</td>
<td>1.5 (0.8–2.7)</td>
<td>0.8 (0.5–1.1)</td>
<td>0.8 (0.7–1.1)</td>
<td>1</td>
<td>1.3 (1.0–1.5)</td>
<td>1.4 (1.2–1.8)</td>
<td>1.7 (1.2–2.4)</td>
<td>1.7 (1.0–3.1)</td>
<td>1.08 (1.05–1.11)</td>
</tr>
<tr>
<td>Ex-smoker (473)</td>
<td>0.5 (0.2–1.6)</td>
<td>0.8 (0.5–1.1)</td>
<td>0.8 (0.6–1.1)</td>
<td>1</td>
<td>1.0 (0.7–1.2)</td>
<td>1.1 (0.8–1.5)</td>
<td>0.9 (0.5–1.5)</td>
<td>1.2 (0.4–3.1)</td>
<td>1.03 (1.00–1.07)</td>
</tr>
<tr>
<td>Current smoker (2028)</td>
<td>0.6 (0.4–1.0)</td>
<td>0.6 (0.5–0.8)</td>
<td>0.9 (0.6–1.0)</td>
<td>1</td>
<td>1.1 (1.0–1.3)</td>
<td>1.3 (1.1–1.5)</td>
<td>1.1 (0.8–1.4)</td>
<td>0.6 (0.3–1.2)</td>
<td>1.06 (1.04–1.08)</td>
</tr>
</tbody>
</table>

| Hemorrhagic stroke |       |           |           |           |           |           |           |        |                  |
| Nonsmoker (464)    | 1.8 (0.8–3.8) | 0.9 (0.6–1.4) | 0.9 (0.7–1.2) | 1 | 1.0 (0.8–1.2) | 1.1 (0.8–1.5) | 1.2 (0.7–1.8) | 1.2 (0.5–2.7) | 1.02 (0.99–1.06) |
| Ex-smoker (218)    | 1.2 (0.3–4.7) | 1.2 (0.7–2.1) | 1.3 (0.9–2.0) | 1 | 1.3 (0.9–2.0) | 1.4 (0.9–2.1) | 1.4 (0.7–2.9) | † | 1.01 (0.95–1.07) |
| Current smoker (805) | 1.4 (0.8–2.3) | 1.2 (0.9–1.5) | 1.0 (0.8–1.2) | 1 | 1.0 (0.8–1.3) | 1.1 (0.9–1.5) | 1.2 (0.8–1.8) | 2.7 (1.6–4.5) | 1.02 (0.99–1.04) |

*Age, blood pressure, glucose, cholesterol, alcohol consumption, doing exercise, and monthly salary level were adjusted.
†Subjects who had missing values for smoking status and other variables needed for the adjustment were excluded from the analysis.
‡Too few events for analysis.
obesity may have its effect on stroke in part through these mechanisms.

Previous negative studies did not discriminate subtypes or had insufficient stroke cases. Given the different pathogenesis between stroke subtypes, the presence, effect size, or direction of the association between BMI and overall stroke would be substantially influenced by the dominant stroke subtypes in a population. Some studies have reported associations between BMI and stroke subtypes. For ischemic stroke, our findings are in accord with previous Western and Japanese studies. Few studies have examined the relation between BMI and hemorrhagic stroke, and these have given conflicting results. Both inverse and positive associations with BMI have been reported, in addition to a U-shaped relationship.

The overall shape of the association of BMI across its range was graphed with the use of GAM and loess smoother (Figure 2). Although GAM is readily available in a standard software package (R or S-plus), this cannot incorporate censored data, at least in standard packages. Since analyses using Cox proportional hazards models (incorporating time to event and censoring) and logistic regression (only binary outcomes) were very similar in our data, GAM analyses provide a reasonable approach to modeling the nature of the adjusted BMI-stroke association, as more sophisticated spline-based models can do.

The finding of increased risk for hemorrhagic stroke at the lower end of BMI distribution is not uncommon. Two possible mechanisms have been suggested to explain this observation: inadequate control of smoking and preexisting disease. Neither of these explanations seems plausible for our findings. To evaluate the effect of smoking, we adjusted for smoking and additionally performed stratified analysis by smoking status, but the increased risk for hemorrhagic stroke in the lower BMI group remained. We tried to reduce the possible bias due to antecedent illness by excluding the subjects who had not maintained their jobs and who had substantial weight loss over the first 4 years after baseline examination. To further identify the effect of preexisting disease on BMI, we conducted analyses before and after omitting events arising during the first 8 years of follow-up, but these showed no material difference from the main analyses. Weight loss is associated with heavy alcohol use, and because heavy drinking is a known risk factor for stroke, this provides a further possible explanation. Although we considered alcohol intake, self-reports of heavy drinking tend to be unreliable, and this confounding may remain.

Because obesity results in higher BP, diabetes, and hypercholesterolemia, these variables may be mechanisms through which obesity causes atherosclerosis and increased stroke risk. The necessity of controlling these factors when assessing the BMI effects has been debated. In common with our findings for ischemic stroke, adjustment for cholesterol, BP, and glucose level has been found to attenuate BMI-stroke associations. However, in a nonsmoking Japanese-American male cohort study, a trend of increasing risk of stroke with BMI persisted after adjustment for these covariates.

The strength of this study is that a large number of well-characterized stroke events were available for analysis. Consequently, we were able to examine stroke risk across much finer categories of BMI. The relatively low incidence of coronary artery disease among Korean men would have reduced the possible bias from competing risks that may beset studies of stroke conducted in Western populations with early
attrition of participants from coronary heart disease. The availability of a wide range of risk factors, including an indicator of socioeconomic position, allowed us to make good adjustment for potential confounders. Inaccurate stroke diagnosis and subtype classification may incur considerable misclassification bias in any study of this nature. Although we did not perform an independent validation of morbidity data sources, a study using the same KNHS data has demonstrated the accuracy of ischemic stroke diagnosis of 83.4% and 85.7% for hemorrhagic stroke. In that study a total of 626 medical insurance claims indicating a diagnosis of stroke occurring between 1993 and 1997 among approximately 115 600 male public servants were evaluated. The residual inaccuracy would be unlikely to differ between ischemic stroke and hemorrhagic stroke and therefore would not be expected to result in any bias. Measurements of risk factors were not conducted with the same instruments or technicians because these data were collected as part of routine health services. However, the degree of correlation between 2 sequential measurements of height and weight suggests a reasonable quality of measurement.

In conclusion, we have confirmed the importance of BMI as a risk factor for both ischemic stroke and hemorrhagic stroke, which exerts at least part of its effect through BP, blood glucose, and cholesterol. When the total burden of stroke is considered, efforts to reduce obesity are required. Attempting to shift BMI below the average, particularly in Asian countries where the ratio of hemorrhagic to ischemic stroke is relatively high, would not necessarily be rewarded by a greater overall health gain given the increased hazards of hemorrhagic stroke observed. In both Western and Asian countries, there is a strong need to reduce the trend toward growing obesity.

Acknowledgments

This study was supported by the Korea Institute of Environment Science and Technology (2002-02310-0002-0) and by grant HL45522 from the National Heart, Lung, and Blood Institute.

References

Body Mass Index and Ischemic and Hemorrhagic Stroke: A Prospective Study in Korean Men

Yun-Mi Song, Joohon Sung, George Davey Smith and Shah Ebrahim

*Stroke.* 2004;35:831-836; originally published online March 4, 2004;
doi: 10.1161/01.STR.0000119386.22691.1C

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/35/4/831

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/