Obesity and the Risk of Intracerebral Hemorrhage
The Multicenter Study on Cerebral Hemorrhage in Italy

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Background and Purpose—The effect of obesity on the risk of intracerebral hemorrhage (ICH) may depend on the pathophysiology of vessel damage. To further address this issue, we investigated and quantified the correlations between obesity and obesity-related conditions in the causal pathways leading to ICH.

Methods—A total of 777 ICH cases ≥55 years of age (287 lobar ICH and 490 deep ICH) were consecutively enrolled as part of the Multicenter Study on Cerebral Hemorrhage in Italy and compared with 2083 control subjects by a multivariate path analysis model. Separate analyses were conducted for deep and lobar ICH.

Results—Obesity was not independently associated with an increased risk of lobar ICH (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.58–1.01) or deep ICH (OR, 1.18; 95% CI, 0.95–1.45) when compared with control subjects. The path analysis confirmed the nonsignificant total effect of obesity on the risk of lobar ICH (OR, 0.77; 95% CI, 0.58–1.02) but demonstrated a significant indirect effect on the risk of deep ICH (OR, 1.28; 95% CI, 1.03–1.57), mostly determined by hypertension (OR, 1.07; 95% CI, 1.04–1.11) and diabetes mellitus (OR, 1.04; 95% CI, 1.01–1.07). Obesity was also associated with an increased risk of deep ICH when compared with lobar ICH (OR, 1.62; 95% CI, 1.14–2.31).

Conclusions—Obesity increases the risk of deep ICH, mostly through an indirect effect on hypertension and other intermediate obesity-related comorbidities, but has no major influence on the risk of lobar ICH. This supports the hypothesis of different, vessel-specific, biological mechanisms underlying the relationship between obesity and cerebral hemorrhage. (Stroke. 2013;44:1584-1589.)

Key Words: hemorrhage • obesity • stroke
of several predisposing conditions, including hypertension, diabetes mellitus, and their complications, obesity might be involved in the biological mechanisms of brain hemorrhage. In apparent contrast with this, a recent meta-analysis of prospective studies, as well as data from a large Chinese population cohort documented no independent effect of obesity on the rate of ICH, thus questioning the relationship between the 2 conditions and leaving some issues open. In this regard, several limitations of the previous studies on this topic should be noted. First, they often neglect the likely differential effect of individual body weight on the specific pathogenic subtype of ICH. Factors that damage small penetrating arteries leading to the clinical phenotype of hemorrhage in the deep subcortical regions are probably different from those favoring lobar hemorrhages related to cerebral amyloid angiopathy. In line with this view, 2 recent reports suggested that extreme body mass index (BMI) values might have a differential influence on brain vessels, with a prominent effect on hypertensive deep ICH. Second, although there is theoretical support in the literature for the role of specific vascular risk factors as mediators of the effects of obesity on brain hemorrhage, this relationship has yet to be explicitly tested, and relatively little has been published on the explanatory pathways underlying such an eventual relationship.

To address these issues, we used hemorrhage location (deep versus lobar) to categorize the likely pathogenesis of ICH and conduct a case–control analysis aimed at (1) investigating the differential influence of obesity on the occurrence of the 2 pathogenic subtypes of ICH, and (2) elucidating the relationship between obesity and comorbidities in the biological pathways leading to ICH development by multivariate path analysis.

Methods

Study Group

Cases

The Multicenter Study on Cerebral Hemorrhage in Italy is a countrywide network of neurological centers aimed at recruiting patients with cerebral hemorrhage in the setting of a hospital-based, multi-center, observational study. Centers are included in the network provided that the recruitment process of cases takes place prospectively. The study was approved by relevant local authorities at each study site. For the purpose of the present analysis, we screened data sets from patients with acute ICH ≥5 years of age consecutively admitted to 4 hospitals between January 2002 and July 2011. Eligibility for study participation required neuroimaging (computed tomography or MRI) confirmation of hemorrhagic stroke. Exclusion criteria included the presence of trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other perceived cause of secondary ICH. ICH location was assigned on the basis of admission computed tomography scan by stroke neurologists at each participating center. ICH isolated to the cortex (with or without involvement of subcortical white matter) and cerebellar hematomas were defined as lobar ICH, whereas ICH selectively involving the thalamus, basal ganglia, or brain stem was defined as deep (nonlobar) ICH. Multiple concurrent bleeds involving deep and lobar territories were defined as mixed ICH and represented an exclusion criterion. Demographic and clinical information, as well as neuroimaging data, were collected prospectively in each center.

Control Subjects

Control subjects were enrolled from the Moli-sani project, an Italian population-based study aimed at investigating the equilibrium between genetics and environment in the pathogenesis of cardiovascular and cancer disease and included individuals ≥55 years of age at the time of enrollment, frequency-matched with cases by sex. Control subjects were confirmed to have no medical history of stroke through interview and review of medical records.

Risk Factor Definition

Subjects were classified as current smokers if they were currently smoking ≥1 cigarettes per day on a regular basis. Hypertension was defined as systolic blood pressure (BP) >140 mm Hg and diastolic BP ≥90 mm Hg, or using pharmacological treatment for hypertension. Hypercholesterolemia was considered as cholesterol ≥240 mg/dL or using pharmacological treatment to lower blood lipids. Diabetes mellitus was defined as fasting glucose levels >125 mg/dL or current treatment with antidiabetic drugs. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m²) and subjects dichotomized into obese (BMI ≥30.0 kg/m²) and nonobese (BMI <30.0 kg/m²). On the basis of daily alcohol consumption, subjects were dichotomized into excessive drinkers (>45 g of alcohol) and light-to-moderate drinkers or nondrinkers. We also collected information on atrial fibrillation (medication history or electrocardiographic findings at admission), atherosclerotic peripheral arterial disease (medical history), coronary artery disease (medical history of angina, myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty), history of previous stroke or transient ischemic attack (based on clinical history), and pre-ICH medications (warfarin, aspirin or other antplatelet agents, antihypertensive agents, oral hypoglycemic agents or insulin, and statins).

Statistical Analyses

Descriptive differences between groups were examined with the \( \chi^2 \) test, and 1-way ANOVA \( F \) test, when appropriate. To explore the mechanisms involved in the development of ICH, we designed a multivariate path model based on clinical evidence. In particular, we investigated the recursive relationships between the following sequence of binary variables: obesity, diabetes mellitus, hypertension, hypercholesterolemia, and ICH (deep ICH versus control subjects; lobar ICH versus control subjects; deep ICH versus lobar ICH) adjusted for confounding variables (age, sex, smoking, oral anticoagulants, and alcohol; Figure 1). The same analysis was conducted entering continuous variables (serum glucose and cholesterol levels, and mean BP values on admission) into the model.

Path analysis is a special type of structural equations modeling, a multivariate approach based on the use of a system of simultaneous equations to describe a priori path relationships that generate the data. The causal mechanism of a path analysis model distinguishes 3 types of effects: direct effect (DE), indirect effect (IE), and total effect (TE) with respect to a specific model. The DE of an explanatory (exogenous) variable on a response (endogenous) variable is the net effect of a predictor compared with the other predictors in the built-in equations, the indirect effect (IE) is the effect mediated by the pathway relationships of the other variables, and the TE is the sum of both the DE and IE (TE=DE+IE). A variable is exogenous if its causes lie outside the model, and endogenous when it is determined by other variables within the model. In our model, obesity was an exogenous variable and the others were endogenous variables. The structural equations parameters are estimated by optimizing the log-likelihood function of multivariate binary variables using the latent-response formulation. Maximum likelihood estimates with robust SE of the structural equations parameters were computed. For convenience, the parameter estimates were re-expressed in odds ratios (ORs) of binary response variables on predictor variables. The \( P \) values of the DE, IE, and TE were evaluated by \( z \) tests (\( \text{est/SE} \)). \( P \) values <0.05 in 2-sided tests were considered statistically significant. Descriptive statistics were evaluated by the SPSS v.15 software (http://www.spss.com). Structural equations modeling was fitted with Mplus v.7 software (http://www.statmodel.com).
Results
A total of 777 patients with ICH fulfilled the inclusion criteria (mean age, 75.5±9.4 years; men, 55.3%). Two-hundred eighty-seven patients (36.9%) had lobar ICH, whereas 490 (63.1%) had deep ICH.

This cohort was matched with 2083 selected control subjects in case–control analysis. The characteristics of the study group are shown in Table 1. As expected, cases were more likely to have a history of hypertension, diabetes mellitus, and to be prescribed antiplatelets or oral anticoagulants, but had a lower rate of hypercholesterolemia and untreated high levels of cholesterol. History of atherosclerotic peripheral arterial disease, ischemic heart disease, and atrial fibrillation were also more common among cases than among control subjects. In contrast, the prevalence of obesity was not significantly different in the 2 groups.

Table 1. Demographic and Clinical Characteristics of the Study Group

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=777)</th>
<th>Control Subjects (n=2083)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>75.5±9.4</td>
<td>74.0±8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, female</td>
<td>347 (44.7)</td>
<td>869 (41.7)</td>
<td>Ns</td>
</tr>
<tr>
<td>BMI, ≥30 kg/m²</td>
<td>279 (35.9)</td>
<td>715 (34.3)</td>
<td>Ns</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>129 (16.6)</td>
<td>197 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>117 (15.1)</td>
<td>53 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>24 (3.1)</td>
<td>33 (1.6)</td>
<td>0.010</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td>171 (22.0)</td>
<td>867 (41.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive under treatment</td>
<td>500 (64.4)</td>
<td>1149 (55.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive not under treatment</td>
<td>106 (13.6)</td>
<td>67 (3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>626 (80.6)</td>
<td>1798 (86.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic under treatment</td>
<td>109 (14.0)</td>
<td>254 (12.2)</td>
<td>Ns</td>
</tr>
<tr>
<td>Diabetic not under treatment</td>
<td>42 (5.4)</td>
<td>31 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterolemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhypercholesterolemic</td>
<td>623 (80.2)</td>
<td>1565 (75.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypercholesterolemic under treatment with statins</td>
<td>92 (11.8)</td>
<td>267 (12.8)</td>
<td>Ns</td>
</tr>
<tr>
<td>Hypercholesterolemic not under treatment</td>
<td>60 (7.7)</td>
<td>251 (12.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>93 (12.0)</td>
<td>234 (11.2)</td>
<td>Ns</td>
</tr>
<tr>
<td>Alcohol, excessive drinking</td>
<td>116 (14.9)</td>
<td>301 (14.5)</td>
<td>Ns</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>221 (28.4)</td>
<td>355 (17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>76 (9.8)</td>
<td>19 (0.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and Ns, nonsignificant.
Deep ICH Versus Control Subjects
As opposed to what was observed in the subgroup of lobar ICH, both hypertension and diabetes mellitus had a significant DE on the risk of deep ICH (OR, 2.72; 95% CI, 2.10–3.50 for hypertension; OR, 1.62; 95% CI, 1.25–2.11 for diabetes mellitus), and a similar protective DE was detected for hypercholesterolemia (OR, 0.58; 95% CI, 0.44–0.75). Obesity had a DE on the development of hypertension (OR, 1.65; 95% CI, 1.37–1.98) and diabetes mellitus (OR, 1.71; 95% CI, 1.37–2.13), but not on ICH (OR, 1.18; 95% CI, 0.95–1.45). Overall, the significant paths indicated that obesity increases the risk of deep ICH through an IE on hypertension and diabetes mellitus, with a TE for these paths corresponding to an OR of 1.28 (95% CI, 1.03–1.57; Table 2; Figure 2B).

Deep ICH Versus Lobar ICH
When we compared the 2 pathogenic subtypes of ICH, we observed a significant DE of obesity in increasing the risk of deep ICH (OR, 1.53; 95% CI, 1.07–2.17), but no IE by intermediate comorbidities (OR, 1.06; 95% CI, 0.98–1.13), with a TE corresponding to an OR of 1.62 (95% CI, 1.14–2.31, Table 2; Figure 2C).

The results of the analysis did not change when predictors were entered into the model as continuous variables (Table III and Figure III in the online-only Data Supplement).

Discussion
The main findings of the present analysis among people ≥55 years of age were (1) the lack of any independent association between obesity and ICH; (2) an IE of obesity on the risk of ICH, which seemed stronger for hemorrhage located in the deep cerebral structures than for lobar ICH; and (3) the evidence that the complex relationships between factors that are intermediate in the causal pathway linking obesity to cerebral bleeding significantly increase the risk of deep ICH, as opposed to the nonsignificant effect on lobar ICH.
In particular, whereas arterial hypertension was responsible for most of the IE of obesity on both the pathogenic subtypes of ICH, diabetes mellitus did not account for any significant effect of obesity on lobar ICH. This supports the intriguing hypothesis that the specific biological mechanisms underlying the relationship between obesity and ICH may depend on the pathogenesis of vascular damage and, overall, provides evidence for a major role of obesity as modifiable determinant of deep ICH.

In the Context of the Current Literature

The question of whether the risk of stroke and cardiovascular diseases in obese subjects is independent of other factors has been matter of long debate. Because obese subjects, on average, have higher BP, higher cholesterol, and higher blood glucose levels than lean persons, it is likely that obesity exerts much of its effect through the enhancement of these factors. However, this effect is difficult to estimate. Most statistical models based on 1 equation include these potential consequences of obesity as covariates. These approaches allow to quantify the strength of the association of each factor with outcome but do not allow to evaluate the correlations between factors. Furthermore, accounting for these potential confounding may lead to overadjustment. Other models omit them from the analysis and thus evaluate the overall role of BMI on stroke risk. What distinguishes our study from others is the application of a path analysis instead of a 1-regression modeling approach. Path analysis is a structural equations model that allows to extend the traditional regression analyses by exploring and quantifying the complex internal relationships between factors and to illustrate how these relationships influence outcome, in the context of a biologically rational model. On the basis of these considerations and on our own findings, we speculate that the results of a recent meta-analysis, and of several epidemiological studies indicating a lack of any significant effect of obesity on the risk of ICH, should be regarded with caution because they do not necessarily preclude that other undetected IEs might be operant. The same is true for the relationship of obesity with each specific pathogenic subtype of ICH. In this regard, our findings confirm and extend those of recent case–control analyses that pointed toward a negligible effect of obesity on the risk of cerebral amyloid angiopathy–related ICHs, as opposed to an independent influence on those related to hypertensive vasculopathy. Actually, although we were not able to detect any significant independent contribution of obesity on the risk of deep ICH, we observed a significant IE as a result of the relationships between obesity and its comorbidities. Taken together with previous reports, our data suggest a complex relationship between obesity and cerebral hemorrhage, with different contributions of obesity-related conditions and, indirectly, support the prevailing idea that metabolic factors play a much larger role in the pathogenesis of deep ICH than in cerebral amyloid angiopathy–related hemorrhages. Obviously, because of the design of the present study, we can only speculate on the mechanisms underlying such a relationship. Insulin resistance, the renin-angiotensin system, and the adipocyte-derived resistin and leptin are likely to play a role. The elevated inflammatory state observed in obese subjects might also contribute. Finally, we cannot exclude the involvement of obesity-specific genetic determinants in the pathophysiology of the microvascular damage leading to cerebral bleeding.

Implications

Body weight control seems to be an effective way to prevent brain hemorrhage. Although the direct effect of excess body weight on disease risk is modest, its close relationship with established risk factors supports the hypothesis that obese subjects might benefit from a reduction in weight of such magnitude as to better control specific comorbidities. This seems especially true for hypertension and much less for diabetes mellitus and hypercholesterolemia.

Limitations

Some limitations of our analysis are worthy of consideration. First, because we dichotomized subjects into obese and nonobese, we lack information about the relationship between body weight and ICH rate in other BMI categories. Noteworthy, in line with the observed J-shaped relationship between BMI and stroke mortality, both very high and low BMI values have been recently associated with increased risk of deep ICH. Second, there may be patient characteristics that selectively influence the risk of ICH that we cannot take into account. In particular, we cannot analyze the differential effect of visceral and peripheral adiposity and of individual dietary habits on the risk of disease. The same is true for severity of prestroke obesity-related conditions. The hospital-based setting of our study prevents the possibility to know the exact BP values, as well as serum cholesterol and glucose levels just before ICH occurrence. Other considerations include the potential survival effect, which may have biased risk toward the null. Finally, because of the observational nature of the study, we cannot exclude that unmeasured or unknown variables not included in the present analysis may have confounded our results.

Conclusions

Our findings confirm that, despite its modest direct effect, obesity has a significant impact on the risk of ICH. In particular, such an effect is mainly mediated by hypertension and is higher for hemorrhages related to hypertensive vasculopathy. The role of specific obesity-related conditions as intermediate in this relationship supports the notion that body weight normalization should not be the primary target but rather some weight loss, which can lead to substantial improvements in these factors. The differential effect they seem to have according to the location of the hemorrhage further suggests that the mechanisms linking obesity to cerebral bleeding might vary and depend on the specific pathogenic subtype of ICH.

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Author Contributions
Drs Pezzi, Grassi, Paciaroni, Zini, Silvestrelli, and Iacoviello helped in manuscript drafting/revising, study design, data analysis and interpretation, data acquisition, statistical analysis, and study supervision; Drs Di Castelnuovo, Del Zotto, Caso, Nichelli, Giossi, Volonghi, Simone, Lanari, Costa, Poli, Pentore, Falzone, Gamba, Morotti, Ciccone, Ritelli, Colombi, de Gaetano, and Agnelli helped in manuscript drafting/revising, data analysis and interpretation, data acquisition, and study supervision; Dr Padovani helped in manuscript drafting/revising, data analysis and interpretation, data acquisition, and study supervision.

Disclosures
None.

References
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**Table 3.**

Odds Ratios (OR) and 95% Confidence Intervals (CI) estimates of the direct, indirect and total effects of the obesity on the risk of ICH, based on continuous variables (glucose and cholesterol levels, and mean blood pressure values at admission) and adjusted for confounding variables (sex, age, smoking, oral anticoagulants, and alcohol).

<table>
<thead>
<tr>
<th>Obesity → ICH</th>
<th>Lobar ICH vs control subjects</th>
<th>Deep ICH vs control subjects</th>
<th>Deep ICH vs Lobar ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct effect (DE)</strong></td>
<td>0.66 (0.49 to 0.90)</td>
<td>1.05 (0.84 to 1.32)</td>
<td>1.69 (1.19 to 2.40)</td>
</tr>
<tr>
<td><strong>Indirect effect (IE)</strong></td>
<td>1.14 (1.05 to 1.23)</td>
<td>1.27 (1.16 to 1.39)</td>
<td>1.03 (0.96 to 1.10)</td>
</tr>
<tr>
<td>obesity → blood pressure → ICH</td>
<td>1.05 (1.01 to 1.10)</td>
<td>1.10 (1.005 to 1.16)</td>
<td>1.05 (0.99 to 1.11)</td>
</tr>
<tr>
<td>obesity → cholesterol → ICH</td>
<td>1.01 (0.95 to 1.07)</td>
<td>1.07 (1.00 to 1.14)</td>
<td>0.99 (0.97 to 1.01)</td>
</tr>
<tr>
<td>obesity → blood glucose → ICH</td>
<td>1.07 (1.03 to 1.10)</td>
<td>1.08 (1.04 to 1.12)</td>
<td>0.99 (0.97 to 1.02)</td>
</tr>
<tr>
<td><strong>Total effect (TE)</strong></td>
<td>0.75 (0.55 to 1.02)</td>
<td>1.34 (1.05 to 1.70)</td>
<td>1.74 (1.22 to 2.48)</td>
</tr>
</tbody>
</table>
Figure 3
Path diagrams of the statistically significant links ($P<0.05$) of the fitted ICH pathways based on continuous variables (glucose and cholesterol levels, and mean blood pressure values at admission) re-expressed in odds ratios (ORs) adjusted for confounding variables (sex, age, smoking, oral anticoagulants, and alcohol: A) lobar ICH vs control subjects; B) deep ICH vs control subjects; C) deep ICH vs lobar ICH.

A)

B)