Background and Purpose—Subarachnoid hemorrhage (SAH) caused by ruptured intracranial aneurysm affects approximately 16,000 Americans annually, and almost 40% of affected patients die within 30 days despite the best current therapy. Prevention of SAH is therefore of paramount importance. We present a preliminary analysis of risk factors for SAH from our population-based, case-control study.

Methods—Cases were prospectively collected and matched 2:1 by age, race, and gender to controls using random digit dialing. Personal risk factor history, family history, neuroimaging data, and genetic samples were obtained. Univariate and bivariate analyses were performed and population-attributable risks estimated. Multivariable analysis was performed using conditional logistic regression.

Results—Between June 1997 and February 2000, 107 cases and 197 controls were enrolled. In bivariate analyses, a large proportion of population-attributable risk for SAH could be explained by modifiable risk factors: smoking, hypertension, and heavy alcohol use. In multivariable analysis, current cigarette smoking, history of hypertension, frequent alcohol use, lower body mass index, and a family history of a relative with SAH or intracranial aneurysm were found to be significant, independent risk factors for SAH.

Conclusion—Our data confirm previous reports that SAH clusters within some families independent of environmental risk factors, suggesting that SAH has a significant genetic component. Yet, even among families at increased risk of SAH, smoking cessation, treatment of hypertension, and reduced alcohol intake may substantially decrease SAH risk. The independent associations with heavy alcohol use and low body mass index with SAH may be confounded by smoking and require further study. (Stroke. 2002;33:1321-1326.)

Key Words: risk factors • stroke • subarachnoid hemorrhage
Subjects and Methods

All patients in the Greater Cincinnati/Northern Kentucky region with a potential ICH or SAH are identified by surveillance of 16 hospital emergency and radiology departments and through hospital discharge diagnoses (ICD-9: 430 to 432). Cases are eligible if they are ≥18 years old, have SAH or ICH, and reside within a 50-mile radius of the University of Cincinnati. Cases cannot have trauma or brain tumor as the cause of hemorrhage and must give informed consent to participate in the study (personally or through their legal representative). Two controls matched by age (±5 years), race, and gender are obtained from the general population within the same 50-mile radius of the University of Cincinnati using random digit dialing. The Institutional Review Board at all participating hospitals approved this study.

The definition for SAH is adapted from the Classification of Cerebrovascular Disease III—1989.37 SAH is defined as the non-traumatic abrupt onset of severe headache or altered level of consciousness associated with blood in the subarachnoid space, as observed on CT or at autopsy, or a clinical history and examination consistent with SAH in which xanthochromia and increased red blood cells are found in the cerebrospinal fluid.

Study physicians review all imaging studies for each potential case. The physician confirms that it is a case and determines the most likely mechanism for the SAH. In this way, cases of SAH due to AVM or cases believed to be primary ICH without aneurysmal cause are excluded. Cases of massive SAH without angiography to document an aneurysm but without other identified cause are presumed to be a result of IA rupture and are included in this analysis.

To determine their ability to be interviewed, every patient must pass a 7-question screening test regarding orientation, ability to follow commands, and attention. For each case, a proxy knowledgeable about the patient is interviewed. The first choice for proxy is the spouse or live-in companion. If this person is not available or cannot provide accurate information, a child, parent, sibling, or close personal friend (with preference in this order) is interviewed. Proxy information is used when the patient does not pass the screening test and cannot provide his/her full medical history because of neurological impairment. If a patient requires proxy interview, then proxies are identified for the matching controls to ensure the validity of this approach. Agreement between patients and proxies on interview questions was measured, as was the agreement between controls and proxies. Because proxies and controls had excellent agreement because of the difficulty in obtaining these proxies, the practice of obtaining proxies for controls was discontinued in June 1999.

After informed consent is obtained, each hemorrhage patient, control, and/or proxy is interviewed face-to-face in a highly structured and identical manner. Questions were adapted from the National Health and Nutritional Examination Survey III.38 A detailed abstraction of risk factor information from the medical record is also performed for each case, and the consistency between the risk factors reported in the interview and the medical record is assessed. Data obtained from interviews were used for this case-control analysis, because only interview information is available for the controls.

Some eligible patients cannot be enrolled in the study in a timely fashion because they die before enrollment or refuse to participate (14% of all approached cases refused). For all noninterviewed cases of SAH in the study region, a retrospective medical record and imaging review is performed in the same manner as for interviewed cases. Noninterviewed patients are identified and counted for epidemiological purposes, but the analyses below include only those cases who participated in the direct interview and from whom a genetic specimen was collected.

A Certificate of Confidentiality was obtained from the Department of Health and Human Services because of the sensitive information recorded, including genetic information and the use of illicit drugs.

Alpha-1 Antitrypsin Genotyping

From each interviewed case and control, we obtain 4 buccal brush samples that are stored at 4°C. After DNA is extracted and checked for purity and quantity, 5 µl is used for each polymerase chain reaction of the alpha-1 antitrypsin gene, using established protocols to test for S and Z mutations.39 Annealing and extension cycles are performed 36 times in each protocol. Amplified products are cut into fragments by the restriction endonuclease Xmn I for the S mutation protocol and Taq I for the Z mutation protocol, and separated using acrylamide gel electrophoresis. Staining with ethidium bromide allows visualization of the discrete bands.

Data Analyses

The data were managed and analyzed using SAS (SAS Institute). Kappa statistics were used to test the agreement of responses between interviewed subjects and their proxies. This analysis was performed to assess the validity of including proxy information to represent subjects with severe neurological impairment.

Medical record data from interviewed patients were compared with data from noninterviewed patients during the first year of the study (1998). Since all eligible patients were not interviewed, this analysis was performed to see whether interviewed cases were representative of all eligible patients. Kappa statistics were used to test agreement between interview responses and information from the medical record review.

Association between each risk factor of interest and SAH was performed using a conditional logistic approach utilizing PROC PHREG to account for the matching of controls. Odds ratios and corresponding confidence intervals were calculated. The odds ratios and prevalence rates of risk factors from matched controls were used to calculate the attributable risk; 95% confidence intervals were also calculated by invoking asymptotic normality. The attributable risks are generalizable to a population that is similar in age, race, and gender to those at risk for SAH.

A multivariable, matched, linear, logistic regression analysis was performed. All variables that were associated with SAH in bivariate analysis (P<0.20) were included in the initial model and then backward eliminated in a stepwise fashion. Because our specific hypothesis involved the association of alpha-1-antitrypsin S or Z mutations with SAH, this variable (presence of mutation) was forced into the model even though it was nonsignificant in bivariate analysis. The other associated risk factors were treated as covariates in looking at the associations with the gene. Significance in the final model was considered at P<0.05. At this time, the sample size is not adequate to consider interactions.

Results

Study Population Characteristics

This analysis consisted of 107 cases of SAH and 197 matched controls enrolled between June 1997 and February 2000. The majority of cases were women (70%). Whites and other races comprised 76% and blacks 24% of cases. Of the 107 cases, 103 (96.2%) had SAH alone, 1 (0.9%) had both SAH and ICH, 2 (1.9%) had only intraventricular hemorrhage, and 1 (0.9%) had ICH that was associated with aneurysmal rupture. For 96 cases, the presence of an aneurysm was angiographically confirmed, whereas 11 died before angiogram. Ninety cases had 2 matched controls, whereas 17 had 1. Proxy interviews were required for 25 (23%) of the 107 cases.

Validity of Study Methods and Applicability to the Population at Large

Kappa statistics were calculated to test the agreement of responses between interviewed subjects and their proxies, as well as for controls and their proxies. Agreement was excellent (K>0.7) or good (K=0.5 to 0.7) for most variables (data not shown). Fair agreement (K<0.5) was seen for marijuana use and the use of aspirin, acetaminophen, or other anti-inflammatory drugs. A kappa statistic was not estimable for purity and quantity, 5 µl is used for each polymerase chain reaction of the alpha-1 antitrypsin gene, using established protocols to test for S and Z mutations.39 Annealing and extension cycles are performed 36 times in each protocol. Amplified products are cut into fragments by the restriction endonuclease Xmn I for the S mutation protocol and Taq I for the Z mutation protocol, and separated using acrylamide gel electrophoresis. Staining with ethidium bromide allows visualization of the discrete bands.

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for cocaine use in cases and for marijuana or cocaine use in controls.

Risk factor data from the medical record were compared with data obtained by interview. Percent agreement and kappa scores indicated excellent agreement (K=0.7) for hypertension, diabetes, prior stroke, current smoking, and heart disease. Family history of hemorraghic stroke, heavy alcohol use, and any history of smoking were reported with lower frequency in the medical record as compared with interview but still demonstrated good agreement (K=0.5 to 0.7; data not shown).

The age-adjusted rates of risk factors for interviewed and noninterviewed cases during the first year of the study (1998) are shown in Table 1. The noninterviewed cases were significantly older than those interviewed (59.1±18.0 versus 48.9±14.7 years, P=0.003). Because risk factor prevalence varies by age, age-adjustment was performed to accurately compare risk factor rates among interviewed and noninterviewed cases. After age-adjustment, no significant differences in risk factor prevalence were found except that noninterviewed cases had a 49% mortality rate compared with 2% among interviewed cases.

### Bivariate and Multivariable Analyses

Demographic and risk factor characteristics for cases and controls, and odds ratios from the bivariate analysis, are shown in Table 2. Hypertension, family history of SAH or IA, smoking (current or ever), heavy alcohol use (more than 2 drinks per day), lower education level, lower body mass index (BMI), and low estrogen status (postmenopausal or surgically menopausal) were associated with SAH at the P<0.05 level. Notably, the S and Z mutations in the alpha-1-antityrpsin gene were not associated with increased risk for SAH. Population-attributable risks were calculated for bivariately significant variables where community risk factor data were available and were 56% for ever smoking (38% for current smoking), 20% for hypertension, and 15% for heavy alcohol use. The sum of the calculated population-attributable risks is greater than 100%, indicating overlap of these risk factors among cases.

Table 3 presents the results of the multivariable regression analysis. A history of hypertension, current cigarette smoking, heavy alcohol use, lower BMI, and a family history of SAH or IA were found to be significant risk factors for SAH at the P<0.05 level.

Several independent and significant risk factors from the multivariable analysis were noted to exhibit collinearity. There were 20 SAH patients with heavy alcohol use in this analysis, of whom 13 were current smokers and 5 were previous smokers. Current smoking was associated with a lower BMI (26.5 for current smokers versus 28.6 for previous smokers and nonsmokers, P<0.01).

### Discussion

This analysis has identified the most significant environmental risk factors associated with SAH from ruptured IA. Cigarette smoking, hypertension, and frequent alcohol use are risk factors that, if modified, could lead to reduced incidence of SAH. The increased risk with a positive family history implies that genetic factors may be associated with SAH, and further study is necessary to define the biological cause of heritability.

Cigarette smoking has been consistently identified as one of the most important risk factors for SAH. Smoking reduction or cessation has been proven to lessen the risk of SAH. Our data confirm this effect, in that former smokers had less risk for SAH than current smokers.

Alcohol use has been associated with increased risk of SAH in previous studies. The strong association of SAH with heavy alcohol use in our study confirms its importance as a risk factor, although this may be confounded by its relationship to smoking because only 2 of the 20 SAH patients with heavy alcohol use were nonsmokers. Thus, it is not clear whether there is any independent risk associated with heavy alcohol use or whether it is a surrogate for smoking. No increased risk for mild to moderate alcohol use was identified.

Data from previous studies are conflicting with regard to the association of hypertension with SAH. Our study suggests that hypertension is indeed associated with increased risk of SAH. There is no evidence available to show that improved blood pressure control or reduction in alcohol intake reduces SAH risk, although treatment of hypertension lowers the risk of ischemic strokes and ICH. Thus, it is reasonable to assume that control of hypertension would lower the risk of SAH.

The use of population-attributable risk gives an estimate of the public health impact of a risk factor and takes into account the prevalence of the risk factor in a population similar to that at risk for SAH. As seen in Table 2, much of the population-attributable risk can be accounted for by smoking, hypertension, and alcohol use. Therefore, SAH is a disease in which patient education and risk factor modification may have a large impact.

Most studies of SAH have not had demographically matched controls or were not population based. Two previous population-based studies of similar design in New
Zealand and King County, Washington had representative controls and also estimated population-attributable risks. In these studies, 38% to 43% of SAH cases could be attributed to the effect of smoking, 28% to the effect of hypertension, and 5% to familial factors.22,24,33 Our population-attributable risks are similar to these studies and to a recently published meta-analysis.44 Our completed study will provide greater power to study attributable risk information for individual risk factors but will also be the first to consider the complex interactions between environmental and genetic risk factors.

The association of low BMI with SAH has been previously reported.20 It is possible that this association is confounded by smoking, because smokers had significantly lower BMIs than previous smokers or nonsmokers in our population. It is important to note that body height and weight, necessary for calculating the BMI, were self-reported. If patients or proxies overestimate height or underestimate weight consistently as

<table>
<thead>
<tr>
<th>Variable</th>
<th>SAH (%) (n=107)</th>
<th>Control (%) (n=197)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>PAR 95% CI for PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>70.1</td>
<td>71.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>24.3</td>
<td>23.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.9</td>
<td>27.4</td>
<td>2.4 (1.4–4.2)</td>
<td>0.002</td>
<td>0.24 0.12–0.34</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.6</td>
<td>9.1</td>
<td>0.6 (0.2–1.6)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Relatives with SAH or IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree</td>
<td>9.4</td>
<td>4.1</td>
<td>2.4 (0.9–6.3)</td>
<td>0.08</td>
<td>0.06 0.00–0.10</td>
</tr>
<tr>
<td>Second degree</td>
<td>14.0</td>
<td>6.1</td>
<td>2.3 (1.0–5.0)</td>
<td>0.04</td>
<td>0.08 0.02–0.14</td>
</tr>
<tr>
<td>Any</td>
<td>23.4</td>
<td>8.6</td>
<td>2.9 (1.5–5.6)</td>
<td>0.001</td>
<td>0.16 0.08–0.23</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>55.1</td>
<td>26.4</td>
<td>4.6 (2.5–8.4)</td>
<td>&lt;0.0001</td>
<td>0.39 0.26–0.49</td>
</tr>
<tr>
<td>Ever</td>
<td>79.4</td>
<td>57.9</td>
<td>3.0 (1.7–5.5)</td>
<td>0.0002</td>
<td>0.51 0.31–0.65</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>18.7</td>
<td>3.6</td>
<td>8.5 (2.9–25.1)</td>
<td>0.0001</td>
<td>0.16 0.09–0.22</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>28.0</td>
<td>33.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>8.4</td>
<td>4.1</td>
<td>2.2 (0.8–5.6)</td>
<td>0.1</td>
<td>0.04 0.01–0.09</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.9</td>
<td>0.5</td>
<td>4.0 (0.4–44.1)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12th grade</td>
<td>21.5</td>
<td>8.6</td>
<td>3.5 (1.6–7.5)</td>
<td>0.001</td>
<td>0.14 0.07–0.21</td>
</tr>
<tr>
<td>12th grade</td>
<td>40.2</td>
<td>32.5</td>
<td>1.6 (1.0–2.7)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>&gt;12th grade</td>
<td>38.3</td>
<td>58.9</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;23</td>
<td>33.3</td>
<td>22.8</td>
<td>2.6 (1.2–5.4)</td>
<td>0.01</td>
<td>0.14 0.03–0.23</td>
</tr>
<tr>
<td>23–25.9</td>
<td>21.6</td>
<td>20.3</td>
<td>1.8 (0.8–4.0)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>26–30.9</td>
<td>28.4</td>
<td>28.4</td>
<td>1.7 (0.8–3.6)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>≥31</td>
<td>16.7</td>
<td>28.4</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin use</td>
<td>27.1</td>
<td>24.9</td>
<td>1.1 (0.6–2.0)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen use</td>
<td>36.4</td>
<td>26.4</td>
<td>1.6 (1.0–2.6)</td>
<td>0.07</td>
<td>0.14 0.03–0.23</td>
</tr>
<tr>
<td>NSAID use</td>
<td>34.6</td>
<td>25.9</td>
<td>1.6 (0.9–2.6)</td>
<td>0.09</td>
<td>0.12 0.01–0.21</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>1.9</td>
<td>1.5</td>
<td>1.2 (0.2–7.0)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Low estrogen state</td>
<td>45.3</td>
<td>30.7</td>
<td>2.4 (1.2–5.0)</td>
<td>0.02</td>
<td>0.21 0.06–0.34</td>
</tr>
<tr>
<td>Heart disease</td>
<td>10.3</td>
<td>10.7</td>
<td>1.0 (0.4–2.0)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Prior stroke</td>
<td>5.6</td>
<td>2.0</td>
<td>2.8 (0.8–10.0)</td>
<td>0.1</td>
<td>0.04 0.01–0.07</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>6.5</td>
<td>6.1</td>
<td>1.1 (0.4–3.0)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Z</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0 (0.1–11.0)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>S or Z</td>
<td>7.5</td>
<td>6.6</td>
<td>1.2 (0.5–3.0)</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratio; PAR, population-attributable risk; IA, intracranial aneurysm; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.
TABLE 3. Risk Factors for SAH Due to Ruptured IA (Matched Logistic Regression)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td>4.4</td>
<td>1.9, 10.1</td>
<td>0.0004</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4.4</td>
<td>1.9, 10.1</td>
<td>0.0005</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.7</td>
<td>0.8, 4.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>11.1</td>
<td>2.8, 43.5</td>
<td>0.0006</td>
</tr>
<tr>
<td>Body mass index (4 categories)</td>
<td>0.6</td>
<td>0.4, 0.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Relative with SAH or brain aneurysm</td>
<td>3.2</td>
<td>1.5, 6.9</td>
<td>0.003</td>
</tr>
<tr>
<td>S or Z mutation of alpha-1-antitrypsin</td>
<td>1.3</td>
<td>0.4, 4.1</td>
<td>0.7</td>
</tr>
</tbody>
</table>

direct interview is more informative than retrospective chart review. This suggests incomplete history taking or under-documentation of certain variables in the medical record. Since family history of IA or SAH was one risk factor that was recorded less frequently in the medical record, studies using only medical record review will underestimate the importance of genetic risk for SAH due to IA.

In summary, our study to date has confirmed the importance of several environmental risk factors for SAH including cigarette smoking, hypertension, and alcohol intake, which can account for a large portion of the population-attributable risk. The importance of low BMI as a risk factor may be confounded by an association with smoking, but this requires further study. Lower education level and estrogen deficiency show trends toward significance and may emerge as important risk factors as we gain statistical power. This analysis cannot exclude a significant relationship between mutations in the alpha-1-antitrypsin gene and SAH; but based on our current calculated odds ratio, alpha-1-antitrypsin gene mutations would account for very few cases of SAH. Family history is demonstrated to be a highly significant independent risk factor, which implies a heritable component for SAH that must be further studied on a larger scale.

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