In 2007, national estimates from the Nationwide Inpatient Sample reported that 4.9% of all strokes in the United States were in adults aged between 18 and 44 years. Stroke in this young age group is associated with higher societal costs compared with older age groups. More worrisome, stroke in this age group appears to be increasing. In our population-based stroke study of Northern Kentucky and Southern Ohio, the stroke incidence in those aged 20 to 54 years significantly increased from 1993 to 2005. The reasons for this increase are unclear but may involve earlier age of onset and increasing prevalence of traditional risk factors, such as diabetes mellitus, hypertension, and obesity. It also may be secondary, in part, to increased use of illicit drugs, a more common cause of stroke among the young.

In the Baltimore–Washington Cooperative Young Stroke Study that included patients aged 18 to 44 years old, the use of illicit drugs was found to be the fifth most common etiology for ischemic stroke (9% of the study population). However, this study included only ischemic strokes and likely underestimates the contribution of substance abuse as an etiology for all strokes in this population, because hemorrhagic stroke also is associated with substance abuse. Smoking, cocaine, and alcohol are associated with both ischemic and hemorrhagic strokes, whereas amphetamines are associated mostly with hemorrhagic events. The relationship between marijuana and stroke is less clear.

In the present study, we sought to identify trends in substance abuse detection among persons aged 18 to 54 years who had a diagnosis of stroke during the periods of July 1, 1993 to June 30, 1994, 1999, and 2005, who live in the Greater Cincinnati and Northern Kentucky areas.

Background and Purpose—Approximately 5% of strokes occur in adults aged 18 to 44 years. Substance abuse is a prevalent risk factor for stroke in young adults. We sought to identify trends in substance abuse detection among stroke patients.

Methods—Using a population-based design, we sought to identify all patients aged 18 to 54 years experiencing a stroke (ischemic or hemorrhagic) in the Greater Cincinnati and Northern Kentucky Study region during 1993 to 1994, 1999, and 2005. Demographic and clinical characteristics and substance use data were obtained retrospectively from chart review and adjudicated by physicians.

Results—The number of young patients identified with a stroke increased from 1993 to 1994 (297) to 2005 (501). Blacks (61% vs 51%; P<0.02) and men (61% vs 47%; P<0.002) reported substance abuse (current smoking, alcohol, or illegal drug use) more frequently than did whites and women. Overall use of substances increased across study periods, 45% in 1993 versus 62% in 2005 (P=0.003). The trend was significant for illegal drug use (3.8% in 1993 vs 19.8% in 2005) and ever smoking (49% in 1993 vs 66% in 2005). Documentation of both cocaine and marijuana use increased over time. In 2005, half of young adults with a stroke were current smokers, and 1 in 5 abused illegal drugs.

Conclusions—Substance abuse is common in young adults experiencing a stroke. The observed increase in substance abuse is contributing to the increased incidence of stroke in young adults. Patients aged younger than 55 years who experience a stroke should be routinely screened and counseled regarding substance abuse.
Methods

The Greater Cincinnati and Northern Kentucky regions include 2 southern Ohio counties and 3 Northern Kentucky counties that abut the Ohio River. This represents a large, 1.3-million, biracial, metropolitan population, with similar proportions of blacks and similar demographic and socioeconomic status indicators to the US population in general, except that the Hispanic population is relatively underrepresented. Although residents of nearby counties seek care at the 17 to 19 acute care hospitals in the study region, dependent on study year, only residents of the 5 study area counties and aged 18 to 54 years are included in this analysis (identified as being from the study area based on their zip code). Study periods are July 1, 1993 to June 30, 1994, January 1, 1999 to December 31, 1999; and January 1, 2005 to December 31, 2005. The screening of cases has been described elsewhere.9

Briefly, study nurses reviewed the medical records of all patients with International Classification of Diseases, 9th revision, codes 430 to 436 as primary or secondary discharge diagnoses from the acute care hospitals in the study region. Strokes not found by the latter screening were ascertained by monitoring all stroke-related visits to all local public health clinics, hospital-based outpatient clinics, and the 5 county coroners’ offices. Further monitoring was performed by examining the records of potential stroke cases in a random sample of primary care physicians’ offices and nursing homes in the Greater Cincinnati and Northern Kentucky regions. Sampling was necessary given the large number of physician offices and nursing homes in the region. Nonhospital sites were selected randomly for each study period by the study statistician from a list generated from a combination of the local yellow pages and the American Medical Association listing of physicians in the region. All events were cross-checked within and between sources to prevent double counting. Institutional Review Board approval was obtained at each participating study site during all study periods. Abstracted information and all available neuroimages were then reviewed by a study physician who decided whether the patient met the case definition of stroke. The events were classified as ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or subarachnoid hemorrhage according to definitions adapted from the Classification of Cerebrovascular Diseases III.10

All ischemic strokes, hemorrhagic strokes, and strokes of unknown subtype during the study period were included in this analysis. Events classified as transient ischemic attacks were not included. Results of serum or urine drug testing were noted when performed, but because this study is based on retrospective medical record review, drug testing was not mandated.

Race was identified by the patient’s self-assessment in the medical record. Traditional risk factors were assigned based on historical diagnosis. Patient who did not report previous diagnosis of hypertension but were using blood pressure medications were considered hypertensive. Alcohol abuse was considered present if subjects consumed more than 3 servings per day (where 1 serving equals 1 oz of hard liquor, 4 oz of wine, or 12 oz of beer); this threshold level has been identified to be the minimum intake required to increase the risk of ischemic stroke.11 Alcohol abuse also was considered present if documented as heavy in the chart. Smoking was defined as current if present within the last 3 months. Illicit drugs (marijuana, cocaine or crack, others) were recorded as present if found on routine urine or blood drug tests, or if self-reported in the medical chart. Information regarding illicit drug use within 24 hours of stroke onset also was abstracted if noted in the medical chart.

Statistical Methods

Data management and descriptive and comparative analyses were performed using SAS versions 8.02 and 9.3, respectively (SAS Institute). Proportions are reported using the weighted estimates that were obtained by including the sampling weights in all analyses as dictated by the study design. A detailed description of the sample weights has been described elsewhere.12 Generalized estimating equations methods13 were used to examine the differences over time. This methodology also accounted for those patients with >1 event within a study time period. The working correlation structure giving the best model fit was obtained. A binary or multinomial distribution was specified for categorical variables, as appropriate.

Results

In 1993 to 1994, 1999, and 2005, there were totals of 2735, 2875, and 2697 patients aged 18 years or older who experienced a stroke (ischemic or hemorrhagic). The number of patients aged 18 to 54 years who experienced a stroke increased from 1993 to 1994 to 2005; there were 297, 376, and 501 strokes for each of the periods (1993–1994, 1999, and 2005, respectively). Baseline patient and stroke characteristics and an overview of the percentage of substance abuse across study periods are given in Table 1. There was a decrease in the percentage of ischemic strokes over time, but this did not achieve statistical significance. Blacks reported

<table>
<thead>
<tr>
<th>Race</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=297</td>
<td>N=376</td>
</tr>
<tr>
<td>White</td>
<td>189 (69%)</td>
</tr>
<tr>
<td>Black</td>
<td>103 (30%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (1.4%)</td>
</tr>
</tbody>
</table>

*Substance abuse†

Present | 138 (45%) | 206 (52%) | 286 (62%)

Alcohol or drugs within 24h of stroke* | 5 (1.4%) | 25 (6.3%) | 72 (12.8%)

Stroke type

Ischemic | 219 (78%) | 260 (71%) | 374 (69%) |

Hemorrhagic | 78 (22%) | 114 (29%) | 121 (22%) |

Unknown | 0 (0%) | 2 (0.5%) | 6 (0.2%)

Data presented as raw n (weighted %).

*Change over time, P<0.05.
†Substance abuse combined (current smoking, alcohol, and illicit drug use).
Table 2. Trends in Substance Use Over Time Among Stroke Patients

<table>
<thead>
<tr>
<th>Strokes Only</th>
<th>1993–1994 (n=297)</th>
<th>1999 (n=376)</th>
<th>2005 (n=501)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current*</td>
<td>129 (42%)</td>
<td>187 (47%)</td>
<td>245 (52%)</td>
</tr>
<tr>
<td>Past</td>
<td>24 (7%)</td>
<td>29 (7%)</td>
<td>61 (14%)</td>
</tr>
<tr>
<td>†Never</td>
<td>144 (51%)</td>
<td>160 (46%)</td>
<td>195 (35%)</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (8%)</td>
<td>48 (12%)</td>
<td>52 (15%)</td>
</tr>
<tr>
<td>‡Illicit drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (3.8%)</td>
<td>39 (9.8%)</td>
<td>96 (19.8%)</td>
</tr>
</tbody>
</table>

Data presented as raw n (weighted %).
*Current if present within the last 3 mo.
†Change over time, *P*<0.01.
‡Change over time, *P*<0.001.

We showed an increase in the overall use of substances (current smoking, alcohol, and illicit drug use combined) from 1993 (45%) and 1999 (52%) to 2005 (62%) (*P*=0.003). This paralleled an increase in the documented use of substances within 24 hours of stroke (1.4% in 1993–1994; 6.3% in 1999 and 12.8% in 2005; *P*<0.0001). Across all study periods, 28 patients had laboratory evidence of abusing illicit drugs; the percentage was lower in 1993 to 1994 (8%), increasing in 1999 (15%) and 2005 (19%); this was not statistically significant. The absolute number of patients detected only by self-report on the medical chart increased across study periods (9 in 1993–1994 to 22 in 1999 and 34 in 2005); however, the percentage of patients detected by the combination of self-report and testing, although increasing, showed no statistically significant change over time (23% for 1993; 28% for 1999, and 37% for 2005). When each substance is analyzed separately, the trend is statistically significant for both illicit drug use and ever smoking (Table 2), with illicit drug use showing the most marked increase over time (3.8%, 9.8%, and 19.8% for 1993–1994, 1999; and 2005, respectively; *P*=0.001). Documented cocaine use increased from 2.0% in 1993 to 4.5% in 1999 and to 6.6% in 2005 (*P*<0.01), and documented marijuana increased from 0.6% in 1993 to 5.5% in 1999 and to 11.4% in 2005 (*P*<0.01). Across study periods, the highest percentage of patients who had documented abuse of illicit drugs were aged younger than 35 years, 19% compared with 12% for those aged 35 to 54 years (*P*=0.06). Statistically significant increase in documented use over time was only evident for those aged 35 to 54 years (*P*<0.01).

In contrast to Illicit drug use, there was a trend toward smoking being more common in those aged 35 to 54 years (49%) vs those aged 20 to 34 years (39%) (*P*=0.06). Current smoking did not significantly change over time (Table 3). Substance abuse was found in both ischemic and hemorrhagic events. Compared with intracerebral hemorrhage patients with subarachnoid hemorrhage and ischemic stroke, the older rates of documented current tobacco use (33% vs 52% and 49%, respectively; *P*<0.01), and subarachnoid hemorrhage patients reported less alcohol abuse than intracerebral hemorrhage patients (13% vs 6% and 10% for intracerebral hemorrhage, subarachnoid hemorrhage, and ischemic stroke, respectively; *P*=0.02). There was no significant difference between type of event and illicit drugs use.

### Discussion

Illicit drug use and ever smoking among young adults with a diagnosis of acute stroke is common and is being more frequently detected within our study population across study periods. It is worrisome that in 2005, half of young adults with stroke were current smokers and 1 out of 5 abused illicit drugs. Tobacco is a well-known risk factor for stroke; the relative risk of stroke associated with cigarette smoking has been calculated at 2.9 for ischemic events (in those aged <55 years old) and 1.31 for intracerebral hemorrhage. In the period of 2000 to 2004, cigarette smoking resulted in an estimated yearly 443,000 premature deaths. Smoking increases cardiovascular risk by inducing a proinflammatory state, arterial endothelial dysfunction, oxidative stress, increased platelet aggregability, blood viscosity, and coagulability, as well as impaired insulin and lipid metabolism. Similarly, many illicit drugs have been linked to increased stroke risk (cocaine, amphetamines, opiates, phencyclidine, and marijuana). In our

| Table 3. Substance Use by Age in Stroke Patients Across Study Periods |
|------------------------|------------------|------------------|------------------|------------------|
| Age                    | Current Smoker | Illicit Drug Abuse | Current Smoker | Illicit Drug Abuse |
| 18–35 y                | 15 (38%) | 17 (44%) | 17 (36%) | 5 (12%) | 6 (15%) | 13 (28%) |
| 35–44 y                | 26 (41%) | 45 (48%) | 66 (55%) | 2 (3%) | 15 (16%) | 24 (20%)* |
| 45–54 y                | 88 (43%) | 125 (47%) | 162 (53%) | 6 (2%) | 18 (7%) | 59 (19%)† |

Data presented as raw n (weighted %).
†Change from 1993 to 1994 and 1999 to 2005, *P*<0.01.
study, marijuana was the most commonly detected illicit drug, followed by cocaine. Marijuana may increase stroke risk, but the evidence is more robust for cocaine. Petitti et al reported an odds ratio of 13.9 for cocaine use associated with stroke in a case control study of women aged 15 to 44 years in the Kaiser Permanente Medical Care Program. Postulated stroke mechanisms include cocaine-induced vasospasm, cerebral vasculitis, enhanced platelet aggregation, hypertensive crisis associated with altered cerebral autoregulation, and cardioembolism. Amphetamines also have been associated with acute intracranial hypertension and possibly vasculitis.

Our findings build on those reported by George et al. Using data from 1995 to 2008, from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, they found increasing use of substances, alcohol, and tobacco, as well as other traditional stroke risk factors, in adolescents and young adults hospitalized with acute ischemic stroke. We, however, found a high prevalence, but no increasing trends, for current tobacco and heavy alcohol use. This likely reflects state-specific trends, because our findings are similar to what has been reported for the states of Ohio and Kentucky. From 1995 to 2005, the Behavioral Risk Factor Surveillance System did not report an increase in adult current smokers or heavy drinkers.

Even though illicit drug use was more commonly found in those aged 18 to 35 years, increased documentation (and thus detection) across study periods was evident only in the group of those 35 to 54 years old. In our study, both blacks and men had increased association with overall use of substances (current smoking, alcohol, and illicit drug use combined). Alcohol intake in small amounts appears to be protective against cardiovascular events, whereas consumption at higher amounts is associated with increased risk of atrial fibrillation, ventricular fibrillation, dilated cardiomyopathy, hypertension, dyslipidemia, and a systemic anticoagulant effect, all of which increase the risk of stroke. An analysis of a national survey reported an increased use of cocaine among men and blacks, and the Baltimore–Washington Young Stroke Study found more illicit drug use among blacks (but no sex differences). Our analysis incorporated a retrospective design and cannot correct for testing or diagnosis bias. During all study periods, only 28 patients were identified solely on the basis of illicit drug test results. It is impossible to tell from our data if there were truly higher rates of use, or higher rates of testing, or higher rates of documentation over time. It is possible that black men were singled out in particular for questioning and drug testing, leading to a higher rate of documented use. We are not aware of any guideline or national recommendation that advocated for more aggressive drug questioning and testing in the setting of acute stroke in young adults.

Another finding of our study was the significant increased detection of cocaine and marijuana from 1993 to 2005. Unfortunately, population data regarding trends of recreational substance use, from the early 1990s to 2005, are lacking. The National Survey on Drug Use and Health conducts periodical surveys on the use of substances by those aged ≥12 years, but because of changes in methodology starting in 2002, it is not possible to compare reports older than this date with newer ones. Nevertheless, at a national level, no significant increase was reported by the National Survey on Drug Use and Health in the use of substances (including alcohol, tobacco, and marijuana) from 2002 to 2005, although a slight (not statistically significant) increase in the use of cocaine is mentioned. National trend analysis of the period from 1992 to 2002 showed a national decrease in cocaine and an increase in marijuana substance abuse treatment admission rates, but data were incomplete for many states and no trends could be specified for the states of Ohio and Kentucky. In a younger population, the National Youth Risk Behavior Survey reported no change in marijuana use and an increase in cocaine use between 1993 and 2005 for 9th through 12th grade students in public and private schools throughout the United States. Alternatively, an increased intensity of substance use or adulterated drugs with components that could pose further health hazards also could explain our study findings without an overall change in the use of recreational substances at a population level. Ultimately, the design of our study does not allow us to draw conclusions on substance abuse incidence rates given its observational nature and retrospective design. We cannot correct for testing or diagnosis bias, because we did not uniformly record both negative and positive drug test results across study periods, and the testing performed was not systematic. It is also possible that those who experienced a stroke and abused substances in 1993 to 1994 were less inclined to seek medical care than their 1999 and 2005 counterparts.

It would have been useful to identify trends for the consumption of amphetamines or amphetamine-like substances (mephedrone, pyrovalerone, methylenedioxypyrovalerone), because consumption of these substances is presumed to be on the rise and because amphetamines are associated with hemorrhagic stroke. Another limitation of our study is that we were unable to further classify smoking status by the number of cigarettes consumed, but it is known that the risks of stroke and cardiovascular disease increase even with small exposures. Strengths of our investigation include its population-based design that is comparable with that of the United States, in general, in its proportion of blacks, demographic, and socioeconomic status, the large number of subjects undergoing study, and the availability of data from 3 study periods with consistent methodology allowing for testing trends over time.

Substance abuse is 1 of many risk factors for stroke. It is likely that no single factor, but rather a mixture of them, is responsible for the increased incidence of stroke observed among young adults in our population. As an example, unpublished analysis of our data shows an increasing prevalence of dyslipidemia across study periods (13.1% in 1993–1994; 18.8% in 1999; and 24.2% in 2005; \( P<0.047 \)), but no trend is evident for hypertension, diabetes mellitus, or atrial fibrillation.

In summary, substance abuse is a common and important risk factor for stroke. In our population, detection of both illicit drug use and ever smoking among young adults with a diagnosis of stroke increased from 1993 to 2005, preferentially in those aged 35 to 54 years. The observed increase in substance abuse is contributing to the increased incidence of stroke in young adults. All patients aged <55 years who experience a stroke should be routinely screened and counseled regarding substance abuse.
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References
Trends in Substance Abuse Preceding Stroke Among Young Adults: A Population-Based Study

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