Obesity Increases Stroke Risk in Young Adults

Opportunity for Prevention

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See related article, p 1690.

A debate has been smoldering over the meaning of obesity in reducing the world burden of stroke. Like so many debates in medicine, it begins with disagreements about the interpretation of evidence, the meaning of statistical test results, and the role of bias. In one camp, are those who see that obesity is associated with increased risk for stroke and say that it as an important target for primary and secondary prevention. In the other, are those who agree that obesity increases stroke but say that it is more effective to treat the consequence of obesity that are responsible for stroke risk (i.e., hypertension and dyslipidemia) than obesity itself.

What everyone can agree on is that obesity is epidemic. In the United States, the prevalence of obesity (i.e., body mass index [BMI] >30 kg/m²) increases with age from 17% for children aged <20 years to 32% to 33% among adults 20 to 39 years, and 36% to 42% for adults ≥40 years.1,2 In adults, the evidence that obesity is associated with increased risk for ischemic stroke is consistent and compelling.3 In fact, risk for ischemic stroke increases almost linearly starting at a BMI of ≈20 and adults with a BMI of >30 kg/m² have about a 70% increased risk for ischemic stroke compared with patients with a BMI <25 kg/m².4,5

In this issue of Stroke, Mitchell et al6 raise further concern about obesity by showing an association with increased stroke risk in a study composed exclusively of young adults. Mitchell et al6 studied men and women aged 15 to 49 years who participated in 3 separate case–control studies. A total of 1201 case subjects with ischemic stroke were identified from 59 hospitals in the Maryland/Washington, DC, area. A total of 1154 control subjects were identified by random-digit dialing and frequency matched to case subjects for age (within 10 years), region of residence, and ethnicity.7 Despite the young age of the case subjects, 42% had hypertension, 17% had diabetes mellitus, and 40% were obese. In an analysis adjusted for age, sex, race, and smoking, obesity was associated with a 65% increased risk for ischemic stroke (odds ratio, 1.65; 95% confidence interval, 1.33–2.04), but the association was substantially attenuated by further adjustment for hypertension, and diabetes mellitus (odds ratio, 1.21; 95% confidence interval, 0.96–1.51).

This finding of Mitchell et al6 on hypertension and diabetes mellitus is consistent with research among older populations. In fact, there is broad agreement that these factors partially mediate the observed association between obesity and risk for vascular disease. Other mediators include vascular inflammation, insulin resistance, and dyslipidemia. Herein lies the controversy on the interpretation of obesity research. In statistical terms, a mediator is something that is on the causal pathway between an independent variable and a dependent variable. For example, obesity causes the hypertension (the mediator) that causes the stroke. Adjustment for a mediator will always attenuate a measure of association, but whether it affects the importance of the unadjusted finding is a matter of interpretation.

In the case of obesity among young adults, some will highlight the unadjusted findings of Mitchell et al6 to say we should treat the obesity to prevent the mediators which result in stroke. Others will say, treat the mediators and leave the obesity alone. If we had better therapy for obesity, there would probably be no controversy and we would all agree that treating obesity is the best first option. A justification for this approach is that the adjusted odds ratio of Mitchell et al6 was still 1.21 overall (95% confidence interval, 0.96–1.51) and 1.34 in men (95% confidence interval, 0.96–1.88). This elevated odds ratio suggests that residual risk may remain and that even optimal prescription of risk-reducing therapy (eg, hypertension therapy) would still leave many young obese patients exposed to untreated risk. This is particularly true because the only practical risk-reducing therapy for mediators of vascular disease in obesity is hypertension therapy. Research has not firmly established that tight control of diabetes mellitus reduces risk for vascular disease; there are no specific therapies recommended for treating the inflammation of obesity, and many young patients are not currently considered candidates for lipid-lowering therapy.

Another argument in favor of treating obesity in young adults (and not just the mediators) is that young adults carry the burden of obesity for more years than older patients and, therefore, may realize a larger lifetime benefit from weight reduction. Treatment of obesity, furthermore, would have benefits beyond stroke reduction, including a possible reduction in risk for vascular cognitive impairment and dementia through mechanisms that include modulation of inflammation, hypertension, hyperglycemia, dyslipidemia, and insulin resistance.9

How reliable are the findings by Mitchell et al6? Case–control studies achieve reliability by enrolling unbiased samples of cases and controls from the underlying population and accurately classifying clinical characteristics, including exposure status. Mitchell et al6 accepted case subject referrals7 and did not report their enrolled fraction, thus raising the possibility.
that their sample may not be fully representative of patients with ischemic stroke in their area. There is no obvious reason, however, why patients with obesity would be differentially enrolled. Control subjects were identified by random-digit dialing and, again, we are not told about the fraction of enrolled to eligible. Perhaps more concerning are the matching method and the method for classifying weight and height by self-report. Frequency matching did not result in case and control groups that were fully matched for age, sex, or race and this might have resulted in some residual confounding. Although self-report weight typically underestimates actual weight, there is no obvious reason that the error would be differential between case and control subjects. Ideally, the authors would have measured weight and obtained data on waist circumference, which may be more accurate than BMI in characterizing cardiovascular disease risk. Overall, however, the study is fairly well designed, and the results are likely to be reliable.

The study by Mitchell et al was not designed to measure the effect of obesity on risk for recurrent stroke, but other research has stirred uncertainty by reporting that stroke patients with obesity may have a lower risk for major vascular events after ischemic stroke. This apparent protective effect of obesity in developing observational research, termed the obesity paradox, may be the result of a form of selection bias. In short, developing stroke as a consequence of obesity may be less harmful than developing a stroke as a result of other factors.

The findings by Mitchell et al have implications for clinical and public health approaches to stroke prevention. In the United States alone, the data from this study suggests that many strokes may be attributable to obesity annually among young adults. The worldwide burden would be much greater. To prevent obesity-associated stroke among young adults, clinical approaches include community and office-based screening to identify obese patients for weight loss and treatment of risk factors, such as hypertension. Obese young adults should be seen regularly by primary care providers who are trained to recognize stroke risk factors and prescribe appropriate preventive therapy. Weight loss is trickier because we do not have highly effective ways to treat obesity in the office. The American Heart Association and others recognize this and recommend referring obese patients to programs that can provide intensive counseling. Some young adults will be successful, but on a large scale, available research suggests that the modest average weight loss accomplished with intensive counseling may not substantially affect cardiovascular risk. More effective approaches to weight loss are likely to emerge from science examining the biochemistry of appetite and obesity, and from public policy initiatives that encourage healthier eating and more physical activity in communities. Until biochemical research fuels translational research and more effective obesity treatment, the study by Mitchell et al supports a clear message to young adult patients and the public that the harmful effects of obesity on the brain start early in life.

Disclosures

None.

References


Key Words: Editorials obesity prevention & control stroke
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Stroke. 2015;46:1435-1436; originally published online May 5, 2015;
doi: 10.1161/STROKEAHA.115.009347
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/46/6/1435

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