Stroke is a leading cause of premature death and disability, and one of its major risk factors—obesity—is worrisomely increasing in prevalence across the world. The study results reported by Pillay et al1 provide a fresh perspective on the differential risks for the main pathological stroke types associated with different measures of adiposity and body fat distribution. Using data from the UK Biobank, a prospective study of 500,000 adults recruited between 2006 and 2010 who were followed up for a median of 12 years, they show that after mutual adjustment of body mass index (BMI) and waist circumference together with recognized confounders, BMI was not associated with ischemic stroke (hazard ratio [HR], 1.04; 95% CI, 0.97-1.11 per 5-unit higher BMI) but was inversely associated with intracerebral hemorrhage (HR, 0.85; 95% CI, 0.74-0.96) and subarachnoid hemorrhage (HR, 0.82; 95% CI, 0.69-0.96). Conversely, waist circumference, which is a better measure of body fat and particularly of internal fat deposits, was positively correlated with both ischemic stroke (HR, 1.19; 95% CI, 1.13-1.25 per 10 cm higher waist circumference) and intracerebral hemorrhage (HR, 1.17; 95% CI, 1.05-1.30) but not associated with subarachnoid hemorrhage (HR, 1.07; 95% CI, 0.93-1.22).

A BMI of 30 or higher is commonly used to define obesity, which is known to interact with other cardiovascular factors associated with risk that include elevated blood pressure, dyslipidemia, poor glycemic control, sleep apnea, left ventricular hypertrophy, and atrial fibrillation. A BMI of 30 or higher also activates cytokines and inflammatory responses, which can influence the sympathetic nervous system, renin-angiotensin axis, endothelial function, and microcirculation.2 However, as BMI is a rather blunt measure of body fat and its distribution in the body, and the association between obesity and stroke is much better defined for ischemic than hemorrhagic forms of stroke,3 there are considerable gaps in our understanding of the modulating mechanisms and pathophysiology of stroke and other cardiovascular diseases.

Pillay et al1 aimed to address uncertainty over the associations of general and central adiposity with the major stroke types. Key strengths of their approach were the large number of person-years of observation that allowed large numbers of hemorrhagic stroke events to be accrued alongside the more common acute ischemic stroke, with high levels of completeness of case ascertainment through record linkage and reliable diagnoses. Together with an examination of 2 key obesity measures and mutual adjustment of multiple confounders and sensitivity approaches, their analyses allowed reliable assessments of independent associations.

These data pertain to adult risk exposures, but atherosclerosis begins early in life where an overlap between biological and developmental factors likely determine future cardiometabolic health. Key determinants of this risk are anthropometric measures. In addition to measuring obesity, BMI also reflects height in relation to nutrition as well as biological variables, while mounting evidence exists that central obesity promotes an inflammatory response that plays a crucial role in the pathogenesis of cardiovascular diseases by driving endothelial cell activation/dysfunction.4 Thus, the findings of Pillay et al1 in relation to the risks of central obesity and ischemic stroke are not too surprising, as most of these events are due to atherosclerosis, either directly (eg, increased carotid intima-media thickness) or indirectly (eg, coronary artery disease). On the other hand, the positive, albeit shallower, association of central obesity with intracerebral hemorrhage is intriguing, given that chronic hypertension rather than atherosclerosis drives the risk of this serious disease. Does this suggest an interaction between obesity and hypertension through endothelial dysfunction from inflammatory effects that promote cerebral small vessel disease? Recent studies5 suggest an...
overlapping pathophysiology between ischemic stroke and intracerebral hemorrhage, whereby patients with a history of intracerebral hemorrhage carry a similar risk of serious ischemic events (cerebral and cardiac) as they do for recurrent intracerebral hemorrhage. Moreover, the use of aspirin reduces the risks of both, although it is uncertain how much of this is from antithrombotic or anti-inflammatory effects.

Even more intriguing is the association between obesity and subarachnoid hemorrhage. Higher BMI has consistently been shown to be associated with a lower risk of subarachnoid hemorrhage in several population-based cohort studies, which may in part be explained by residual confounding from cigarette smoking and hypertension. However, Pillay et al found none of these or other intermediate factors changed the associations of adiposity measures and subarachnoid hemorrhage, raising again the potential for developmental risk factors associated with height and vascular biology and propensity to form cerebral aneurysm. This may also explain the well-recognized female excess sex-risk disparity toward subarachnoid hemorrhage.

Stroke is a devastating condition that is associated with modifiable risk factors, including obesity. However, implementing lifestyle changes at the individual-level to address sedentary behavior, poor diet, and obesity is particularly challenging. Managing risk factors in early life through education programs and healthy community participation activities has stronger potential to improve health and offer a host of other benefits. The findings of Pillay et al suggest abdominal obesity is an independent and direct, rather than intermediary, factor associated with risk for stroke, both ischemic and intracerebral hemorrhage. They also provide a clear message for public health policies toward improving the ability of people to adopt active lifestyles and healthy diets that act positively on obesity metrics beginning early in life.
