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Predictors of Cholesterol and Lipoprotein(a) Testing in Children with Arterial Ischemic Stroke

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Abstract

Objective—Professional societies recommend screening lipids in healthy children. Dyslipidemia and elevated lipoprotein(a) are risk factors for adult cardiovascular disease and stroke. Their role in childhood arterial ischemic stroke is unexplored. Inconsistencies in testing limit analysis of existing lipid data. The objective of this study is to identify predictors and modifiable barriers to lipid testing in pediatric stroke.

Methods—In this cross-sectional analysis, children (28days–18yrs) with arterial ischemic stroke were identified from the International Pediatric Stroke Study registry (1/2003–4/2012). Analyzed

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predictors of recorded lipid or Lp(a) testing were: age, sex, race, ethnicity, BMI category, other stroke risk factors, country, US region and recurrent thrombosis.

Results—Among 1652 participants [median, 6yrs (interquartile range 1.7–12.7); 59.0% male; 40.8% white; 7.0% black], at least one lipid parameter or Lp(a) was available for 461 (27.9%). Compared with infants, testing was incrementally higher for older age categories. Compared with whites, testing was lower in blacks [adjusted OR 0.5, (95%CI 0.4–0.5), $p<0.0001$]. Hispanic ethnicity only predicted testing within the US [OR 2.2 (95%CI 1.4–3.4), $p=0.001$]. Testing was lower in the US and Australia, and higher in Chile. Any thrombotic recurrence and recurrent symptomatic arterial ischemic stroke were associated with testing, unlike male sex, BMI, other stroke risk factors, and region in the US.

Conclusions—Only a quarter of children with stroke had recorded lipid testing. Older age, white race and recurrence predicted testing. In future study adjusting for these predictors may be necessary. Standardized lipid testing in children with arterial ischemic stroke may further our understanding of this potential risk factor.

Keywords

pediatric stroke; cholesterol; lipids; lipoprotein(a); prevention; risk factors

Introduction

Important risk factors and interactions between risk factors are continuing to be discovered in childhood arterial ischemic stroke (AIS).^{1, 2} While extensive literature addresses dyslipidemia and elevated Lp(a) in adult vascular disease there is a scarcity of studies on dyslipidemia in childhood AIS.³ The pathology of steno-occlusive arteriopathy, the most common cause of childhood AIS, is currently thought to be non-arteriosclerotic but without histopathologic data, we cannot be certain of this.⁴ Arteriopathy is also the main predictor of recurrent childhood AIS.^{5, 6} Arterial disease or the underlying condition associated with arterial disease may be an important determinant of long term wellness that extends even to different phenotypes of childhood arteriopathy, such as focal cerebral arteriopathy, dissection, and moyamoya disease.

A recommendation for routine cholesterol screening for children aged 9 to 11 (prepubertal) and 17 to 21 years was recently issued by the National Heart Lung and Blood Institute (NHLBI) with American Academy of Pediatrics (AAP) endorsement in the US.⁷ The 9–11 year range was chosen to mark stable lipid levels before the pubertal 10–20% decrease in levels. Screening children is intended to reduce adult cardio- and cerebrovascular disease because even young children have aortic atherosclerosis and lipid levels in childhood predict adult atherosclerosis.^{8, 9, 10} It is striking that among guidelines on stroke in infants and children: UK (2004), AHA (2008) and CHEST guidelines (2012), there is no discussion of lipids.^{11, 12}

Experts in pediatric stroke are uncertain about the clinical utility of cholesterol testing and practice is inconsistent. (unpublished data: Capano L HJ, Chan N, Fullerton H, et al. Arterial health and secondary stroke prevention in children: Expert beliefs and practices 2011) This

uncertainty has led to a paucity of data with which to answer important questions on the role of dyslipidemia in pediatric AIS. Dyslipidemia may have its greatest impact before puberty and in late adolescence when levels are naturally highest.^{13, 14} It may be a risk factor for stroke only through an interaction with inflammation or an infectious state and it may be a risk factor only when the stroke is associated with steno-occlusive arteriopathy. Systematic testing among children with stroke will help to address these questions and may even elucidate new causal pathways in mechanisms of stroke in children.

Incomplete available recorded testing suggests that there may be biases in a clinician's decision to test for lipid levels. Biases may be based on the presence of other factors traditionally associated with atherosclerosis, such as older age, male sex, obesity, and black race. Among young adults in the 15 Cities Young Stroke Study (n=3,944, age 15–49yrs) dyslipidemia was seen in 45.8%.¹⁵ Young adults share traditional risk factors, such as diabetes, hypertension and smoking, with older adults and stroke prevalence increases with age.¹⁶ Stroke incidence, mortality and the prevalence of traditional risk factors are higher among young adult men than women.^{16–18} Obesity became widespread among children at the turn of the 21st century and obesity is associated with dyslipidemia.¹⁹ Stroke incidence is approximately twice as high in blacks compared with whites, even among young adults.^{20, 21} Approximately half of the racial disparity in stroke can be attributed to traditional and socioeconomic risk factors.²²

Identified stroke risk factors and region of enrollment may influence recorded testing. The absence of another identified risk factor may positively influence testing in an effort to determine cause. In the few available studies on lipids in children with AIS, only patients with cryptogenic stroke were included.^{23–25} The presence of arteriopathy, a risk factor that could theoretically be associated with dyslipidemia, might also positively influence testing. One provider's bias in testing would have an apparent influence on testing at enrolling centers where only one or few investigators are caring for children with stroke. In a registry with limited numbers of investigators and enrolling centers, a provider bias would result in variable testing by region and country. In some regions, a high prevalence of adult stroke might positively influence testing. The Stroke Belt in the southeastern US, has a higher prevalence of stroke and stroke risk factors compared with other regions in the US. The higher black/white ratio, socioeconomic disparity in income and education has been used to explain this disparity in stroke prevalence.²⁶

The aim of this study is to characterize the frequency, patterns and predictors of lipid testing recorded in the International Pediatric Stroke Study (IPSS), the largest international registry of children with stroke, in order to learn about what might be a current conception of how lipids interact in pediatric stroke, and to validate future analysis of the results of recorded testing. We hypothesized that older age, male sex, black race, higher body mass index (BMI), the absence of another identified stroke risk factor, and origin from the Southeastern US, would be associated with lipid and Lp(a) testing. We hypothesized that children who would have a recurrent event were more likely to be identified as higher risk patients and were more likely to have recorded testing.

Methods

Study Design

This was a cross sectional analysis of participants in the IPSS, a prospective international registry of neonates and children with AIS and cerebral sinovenous thrombosis (CVST). The design and characteristics of the IPSS have been described previously.²⁷

Participants

The registry was queried from January, 2003 through April, 2012 for children with AIS. Participants were included if their age at stroke occurred at at least 28 days of age and less than 19 years. The query yielded 1652 subjects. Subjects originated from 72 centers in 20 countries (Argentina, Australia, Austria, Canada, Chile, China, Estonia, France, Germany, Greece, Malaysia, Netherlands, Philippines, Poland, Serbia, Spain, Switzerland, Thailand, the United Kingdom, and the United States.) The IPSS registry has institutional ethics approval at each of the participating sites and at the coordinating center at the Hospital for Sick Children, in Toronto, CA.

Baseline Characteristics

Data were entered into the registry by local investigators.⁴ Recorded testing for lipids was defined as a minimum of one value recorded for any of: total cholesterol (TC), LDL-c, HDL-c or lipoprotein a (Lp(a)). Age at stroke was analyzed as a continuous and categorical variable. Categorical age was defined as infancy (28 days to <2 years), young childhood (2 years to <5 years), childhood (5 years to <12 years), and adolescence (12 years to <19 years.) BMI recorded at the time of the index stroke was defined according to the World Health Organization classification of weight by age and sex for children 5–19 years: overweight= > +1SD (equivalent to 25 kg/m² at 19 years), obesity= >+2SD (equivalent to 30 kg/m² at 19 years), thinness= <-2SD (<18.5 kg/m² at 19 years), and severe thinness= <-3SD. Normal weight is <+1 and >-2 SD.²⁸ Subjects at least 5 years, who could be categorized by the WHO classification system, and who had relevant data points entered were assigned BMI categories appropriate to age and sex (1=severe thinness, 2=thinness, 3=normal, 4=overweight, 5=obesity).

Race was defined as white, black and other (East Indian/South Asian, First Nations/Aboriginal, Middle Eastern, Southeast Asian.). Ethnicity was defined as Hispanic and non-Hispanic. Children were coded as black and Hispanic or Latino if at least one parent was of that racial/ethnic origin. Risk factors for arterial stroke were previously identified by experts in the field: cardiac, arteriopathy, chronic disorder, acute systemic illness, chronic head and neck disorders, and acute head and neck disorders.⁴ If none of these categories was selected, the subject was classified as having unidentified risk factors. Participants were classified by enrolling country as: the US, Canada, Chile and Australia (the four top enrolling countries) or “other country”. US centers were categorized by region (Southwest, Southeast, Northeast, West and Midwest).

Recurrent thrombotic events that occurred during the acute hospitalization for the index stroke or discovered on follow-up were classified as AIS (silent or symptomatic); transient

ischemic attack (TIA); CSVT, new or extension; intracardiac clot; pulmonary embolism; and systemic arterial or venous thrombosis. Investigators were encouraged to enter follow-up data on their subjects.

Statistical Analysis

Analyses were performed using statistical software (SPSS 19.0, IBM). Subject demographics are reported as a median and interquartile range (25th–75th) or by proportion with and without testing for each predictor variable. Differences between the lipid- tested and untested groups were explored with Chi-square tests and the Wilcoxon test. Univariable logistic regression was used to identify significant predictors of recorded testing. Predictors included, continuous and categorical age, male sex, race, ethnicity, BMI, other stroke risk factor category, country of enrollment, and among participants from the US, region in the country. Logistic regression was also used to determine if at least one recurrent thrombotic event predicted a record of testing. Multivariable regression was used to measure the association between predictor variables and the dependent variable in an adjusted regression.

For categorical variables, the reference category was the category hypothesized to have the lowest proportion of testing. This corresponded to the categories: infancy, white race, Hispanic ethnicity, BMI category of severe thinness, and other enrolling country. For region in the US, the reference category, Southeast, was selected as a region where we expected the highest testing. The association between any form of thrombotic recurrence and between recurrent symptomatic AIS with recorded lipid testing was measured using logistic regression. Subjects with one or more than one recurrence were not differentiated.

Relatively few participants ($n < 57$ per category) were of a race other than black or white so these subjects were excluded from the analysis for race. If there was missing data for height and weight, race or ethnicity, those participants were excluded from the analysis of those variables. Participants without selected stroke risk factors were classified as having “no identified” risk factor and were analyzed in the “unidentified” risk factor category.

The proportion of participants with recorded testing by site was analyzed to create several scenarios for restricting data from only sites with higher proportions of recorded testing. Scenarios were modeled for sites with 25%, 45%, 60% and 65% of participants with recorded testing, based on the distribution of the data.

Results

From 72 sites in 20 countries, there were 1652 participants included in the final analysis. Age was not normally distributed. The median (interquartile range) age was 6.0 years (1.7–12.7). The cohort was 59.0% male. Race was Caucasian in 40.8%, black in 7.0%, other (East Indian/South Asian, First Nations/Aboriginal, Middle Eastern, Southeast Asian) in 8.2% and not selected in 44.0%. Ethnicity was non-Hispanic in 48.5%, Hispanic in 13.2% and not selected in 38.3%. Recorded testing was available for participants from 34 sites and 74.0% of the recorded testing was from 13 sites. The majority (85.0%, 1404/1652) of participants originated from 4 countries: the United States (52.8%), Canada (19.6%), Chile (7.3%) and Australia (5.3%). Variables for BMI assessment were available in 324 (36.2%) of 896

subjects 5–18 years. By BMI category, 2.8% were severely thin, 2.5% were thin, 61.4% were normal, 20.4% were overweight and 13.0% were obese. There was no identified risk factor in 28.9% of the cohort.

Recorded testing of at least one lipid parameter was available for 461 (27.9%) subjects from 34 sites. Among subjects with recorded testing, 193 (41.9%) had only one parameter, 51 (11.1%) had two parameters, 120 (26.0%) had three parameters, and 97 (21.0%) had all four parameters. Where only one parameter was recorded the parameter was Lp(a) in 127 (65.8%) subjects.

The likelihood of recorded testing increased with increasing age [OR 1.1 per year (95% CI 1.0–1.1), $p<0.0001$]. Compared with infancy, the odds of recorded testing was higher in children (5–<12yrs) [OR 1.8 (95% CI 1.3–2.5), $p<0.0001$] and adolescents (12–<19 yrs) [OR 2.2 (95% CI 1.7–3.0), $p<0.0001$]. Black children were less likely to have recorded testing than white children [OR 0.4 (95% CI 0.3–0.6), $p<0.0001$]. Hispanic participants in this cohort were not more likely to have recorded testing, but among Hispanic participants from only the US, recorded testing was more likely [OR 2.2 (95% CI 1.4–3.4), 0.001]. Adjustment for participants with overweight and obese BMIs attenuated the association between ethnicity and testing in the US ($p=0.53$). Enrollment from the US [OR 0.6 (95% CI 0.5–0.8), $p=0.002$] or Australia [OR 0.4 (95% CI 0.2–0.8), $p=0.006$] conferred a lower likelihood of recorded testing compared with other countries. Males, participants with higher BMI category, any other stroke risk factor including no identified risk factor, and US southeastern participants were not more likely to have recorded testing. (Tables 1&2)

A recurrent thrombotic event from January, 2003 through April, 2012, was recorded for 106 (6.4%) of participants. The most common recurrent thrombotic events among participants were symptomatic AIS ($n=56$), TIA ($n=22$), and silent AIS ($n=17$). Other forms of recurrence were rare: systemic venous thrombosis ($n=5$); systemic arterial thrombosis ($n=3$); new CSVT ($n=3$); extension of CSVT ($n=1$); and intracardiac clot ($n=1$). No participant had a pulmonary embolism. Among children with any form of thrombotic recurrence, recording testing was more than twice as high as among children without recurrence [OR 2.7 (95% CI 1.8–4.0), $p<0.0001$]. Among only participants with recurrent symptomatic AIS, the association with recorded testing was similar [OR 2.1 (95% CI 1.3–3.7), $p=0.005$]. (Tables 1&2)

On multivariable analysis, recorded testing remained positively associated with older age, white race, country of origin and recurrence. Compared with infants, recorded testing was more likely for young children (2–<5yrs) [adjusted OR 1.7 (95% CI 1.2–2.5), $p=0.004$], children (5–<12yrs) [adjusted OR 1.9 (95% CI 1.4–2.6), $p<0.0001$] and adolescents (12–<19 yrs) [adjusted OR 2.4, (95% CI 1.7–3.3), $p<0.0001$] and black participants were less likely to have recorded testing than white participants [adjusted OR 0.5, (95% CI 0.4–0.5), $p<0.0001$]. Recorded testing was decreased among participants enrolled from the US [adjusted OR 0.5 (95% CI 0.4–0.7), $p<0.0001$] and Australia [adjusted OR 0.5 (95% CI 0.2–0.9), $p=0.02$], and increased among participants enrolled from Chile [adjusted OR 2.5 (95% CI 1.5–4.2), $p<0.0001$] compared with other countries. Among participants with any form of thrombotic recurrence, recorded testing was more than twice as likely [adjusted OR 2.5

(95% CI 1.6–3.9), $p < 0.0001$], adjusted for age, race and country of origin. The variation in recorded testing explained by age, race, country of origin and recurrence was 13% ($R^2 = 0.13$; Table 3). Another approach to address selection bias in the tested sub cohort is to limit future analysis to sites with a higher proportion tested. If, for example, the analysis is limited to sites with 45% of participants tested, the analysis would include 20 sites with a total of 202 participants, where the overall proportion tested is $> 75\%$. (Table 4)

Discussion

The predictors of recorded testing for lipid levels in the IPSS registry were older age and white race. A recurrent thrombotic event during the acute hospitalization or during the follow-up period for each participant was highly associated with recorded testing. Preferred testing in older children is consistent with conceptualization of dyslipidemia as an adult risk factor, but more limited data among young children may obscure a real association with stroke if dyslipidemia is influential in younger childhood. Incident pediatric AIS peaks in early/mid-childhood.²⁹ There is a similar pre-adolescent peak in lipids, and following a peak at 7–12 years, early adolescent cholesterol levels drop and then slowly increase towards adult levels by late adolescence.^{13, 14}

There is extensive literature on racial disparities in young and older adult stroke incidence.^{21, 22} In the IPSS registry, recorded testing for lipids was higher for white compared with black children. Among black children, sickle cell anemia is a prominent risk factor for stroke. Providers caring for children with sickle cell anemia might not conceive that the mechanism of stroke includes a role for dyslipidemia. This reasoning, however, may not be valid. Like other stroke risk factors, there is emerging literature for pro-inflammatory and hypertension-related genetic polymorphisms among patients with sickle cell disease at higher risk for stroke and large vessel disease.^{30, 31} Adults with sickle cell anemia and higher than median triglyceride/HDL-C values had blunted vascular dilatory responses to acetylcholine, suggesting that there may be a role for dyslipidemia in sickle cell-related vascular disease.³²

Other reasons for racial disparities in recorded testing may be due to reduced awareness of stroke symptoms and the advantages of early treatment, cultural and language barriers. There may be differences in socioeconomic status, insurance coverage, trust in the healthcare system and information on how to access the system may also be limited.³³ Black participants contributed only a small proportion to this cohort (7%). To our knowledge, racial disparity has not been reported in incident childhood stroke, as contrasted with young adult stroke. As the field moves forward to reduce stroke-related disability and recurrence, racial disparities in pediatric stroke require further study. Regarding ethnicity, recorded testing was more likely among US Hispanic participants. In the full cohort the lack of association between testing and ethnicity was likely due to the influence of Chile from where 95% of participants were Hispanic. In the US, the association between recorded testing and ethnicity was at least partly explained by the patient's being in overweight and obese BMI categories, providing indirect evidence that physicians were more likely to obtain lipid levels in overweight or obese children.

Sex, BMI, region in the US and other stroke risk factors were not associated with recorded testing after multivariable adjustment. These were unexpected findings and may reflect the strong provider bias in this cohort. While testing was performed and recorded at 48 of 71 sites, 74.0% of the participants with recorded testing originated from 13 sites. The patient-related predictors in our final model accounted for only 13% of the variation in recorded testing. This suggests a large contribution of non-patient related determinants of testing. An important barrier to testing is the absence of an advisory recommendation on whether or not and in whom testing should be performed. This stems from a lack of research on this topic and possibly a low awareness of the high prevalence of risk factors for atherosclerosis in children, particularly in the US. Low frequencies of testing perpetuate our limited understanding of the role lipids in pediatric stroke.

Mechanisms of childhood AIS are still being understood. There is evidence for early atherosclerotic disease in children and a relationship between childhood dyslipidemia and adult atherosclerosis. Aortic fatty streaks and atherosclerosis was found in nearly all children as young as 2 years, who died largely of trauma and atherosclerotic changes correlate with high low-density lipoprotein cholesterol (LDL-c) and low high-density lipoprotein cholesterol (HDL-c).^{8, 9} High childhood levels in childhood predicted increased carotid intimal-medial thickness, a marker of atherosclerotic disease, in adulthood, in one prospective longitudinal study.¹⁰

A theory on how lipids might influence stroke is through a shared mechanism with infection and an inflammatory state. In animal studies an induced inflammatory state with high lipid levels leads to accelerated atherosclerosis.³⁴⁻³⁶ Another possibility is that dyslipidemia might be more important in stroke recurrence. Arteriopathy has recently been shown to be associated with markers of endothelial injury.³⁷ Endothelial injury is also considered an inciting event in the development of atherosclerosis.³⁸ Atherosclerotic changes may be a late effect of an endothelium that fails to heal normally and may predispose to recurrent childhood stroke.

Our study has several strengths. First, the IPSS represents an international registry of patients, so that we were able to explore differences among countries in prevalence of testing. Second, the involvement of pediatric stroke investigators suggests that our data likely represents patients who are most likely to have testing performed. We studied a large cohort (n=1652) of children with AIS. The absolute number of children (n=461) with lipid testing is higher than has been reported in other childhood stroke cohorts.

There are also a number of limitations to this study. The primary limitation is the absence of uniform recorded testing; only one quarter of the children with acute ischemic strokes had any recorded lipid testing. The registry is voluntary and there are few mandatory data fields. Second, providers with an interest in pediatric stroke populate the registry. The registry is not designed to sample a population so participants may not be representative of all strokes in these different regions and is not necessarily indicative of regional practices. For example, in Canada 48% of participants (156/324) were enrolled at one site, the IPSS registry core at which 44% of enrollees had recorded testing. Third, there was a low recruitment of racial and ethnic minorities. Fourth, the timing of lipid testing relative to the index stroke event

was not analyzed. We assume that testing was performed by the stroke provider in response to the stroke. In fact testing may have been performed by the primary care provider even before the admission for stroke. In that case the pediatric stroke investigator would only have been responsible for recording the data. In addition, recorded testing is a surrogate for testing but it may poorly reflect actual testing. If recording of performed testing is less than true performed testing there is misclassification of subjects in the untested group. The effect of this would be to reduce a true difference between the tested and untested cohorts and this would have limited our ability to identify true predictors of testing. Fifth, data points necessary for BMI calculation were missing for the majority of eligible subjects 5–18 years, and ethnic/racial data was missing for ~40% of the cohort. Finally, we may have been underpowered to detect an association with Hispanic ethnicity.

As we continue to explore this potential risk factor we will either support or disprove a rationale for the trends in current practice. Future analyses may need to adjust for age and race, or to limit analyses to those sites that include a reasonably high proportion of individuals tested for lipids. Ideally we would study a cohort with prospective standard lipid testing by age and incident stroke. Dyslipidemia as a risk factor for childhood stroke would have immediate clinical relevance. Diet, exercise, and lipid lowering medication could impact the long-term health of children with stroke.

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References

1. Hills NK, Johnston SC, Sidney S, et al. Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke. *Ann Neurol*. 2012; 72:850–858. [PubMed: 23280836]
2. Rodan L, McCrindle BW, Manlhiot C, et al. Stroke recurrence in children with congenital heart disease. *Ann Neurol*. 2012; 72:103–111. [PubMed: 22829272]
3. Sultan SM, Schupf N, Dowling MM, et al. Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. *Int J Stroke*. 2014; 9:79–87. [PubMed: 24148253]
4. Mackay MT, Wiznitzer M, Benedict SL, et al. Arterial ischemic stroke risk factors: The international pediatric stroke study. *Ann Neurol*. 2011; 69:130–140. [PubMed: 21280083]
5. Braun KP, Bulder MM, Chabrier S, et al. The course and outcome of unilateral intracranial arteriopathy in 79 children with ischaemic stroke. *Brain*. 2009; 132:544–557. [PubMed: 19039009]
6. Darteyre S, Chabrier S, Presles E, et al. Lack of progressive arteriopathy and stroke recurrence among children with cryptogenic stroke. *Neurology*. 2012; 79:2342–2348. ; discussion 2346. [PubMed: 23197751]
7. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. *Pediatrics*. 2011; 128(Suppl 5):S213–256. [PubMed: 22084329]
8. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The bogalusa heart study. *N Engl J Med*. 1998; 338:1650–1656. [PubMed: 9614255]
9. McGill HC Jr, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The pday research group. Pathobiological determinants of atherosclerosis in youth. *Arterioscler Thromb Vasc Biol*. 1997; 17:95–106. [PubMed: 9012643]
10. Davis PH, Dawson JD, Riley WA, et al. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The muscatine study. *Circulation*. 2001; 104:2815–2819. [PubMed: 11733400]

11. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: A scientific statement from a special writing group of the american heart association stroke council and the council on cardiovascular disease in the young. *Stroke*. 2008; 39:2644–2691. [PubMed: 18635845]
12. Group PSW. Stroke in childhood: Clinical guidelines for diagnosis, management and rehabilitation. 2004
13. Skinner AC, Steiner MJ, Chung AE, et al. Cholesterol curves to identify population norms by age and sex in healthy weight children. *Clin Pediatr (Phila)*. 2012; 51:233–237. [PubMed: 22157422]
14. Brotons C, Ribera A, Perich RM, et al. Worldwide distribution of blood lipids and lipoproteins in childhood and adolescence: A review study. *Atherosclerosis*. 1998; 139:1–9. [PubMed: 9699886]
15. Putaala J, Yesilot N, Waje-Andreassen U, et al. Demographic and geographic vascular risk factor differences in european young adults with ischemic stroke: The 15 cities young stroke study. *Stroke*. 2012; 43:2624–2630. [PubMed: 22798330]
16. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, et al. Long-term mortality after stroke among adults aged 18 to 50 years. *JAMA*. 2013; 309:1136–1144. [PubMed: 23512060]
17. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: A report from the american heart association. *Circulation*. 2012; 125:e2–e220. [PubMed: 22179539]
18. Ji R, Schwamm LH, Pervez MA, et al. Ischemic stroke and transient ischemic attack in young adults: Risk factors, diagnostic yield, neuroimaging, and thrombolysis. *JAMA Neurol*. 2013; 70:51–57. [PubMed: 23108720]
19. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among us adults, 1999–2008. *JAMA*. 2010; 303:235–241. [PubMed: 20071471]
20. Jacobs BS, Boden-Albala B, Lin IF, et al. Stroke in the young in the northern manhattan stroke study. *Stroke*. 2002; 33:2789–2793. [PubMed: 12468771]
21. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012; 79:1781–1787. [PubMed: 23054237]
22. Howard G, Cushman M, Kissela BM, et al. Traditional risk factors as the underlying cause of racial disparities in stroke: Lessons from the half-full (empty?) glass. *Stroke*. 2011; 42:3369–3375. [PubMed: 21960581]
23. Abram HS, Knepper LE, Warty VS, et al. Natural history, prognosis, and lipid abnormalities of idiopathic ischemic childhood stroke. *J Child Neurol*. 1996; 11:276–282. [PubMed: 8807416]
24. Glueck CJ, Daniels SR, Bates S, et al. Pediatric victims of unexplained stroke and their families: Familial lipid and lipoprotein abnormalities. *Pediatrics*. 1982; 69:308–316. [PubMed: 6977760]
25. Nowak-Gottl U, Junker R, Hartmeier M, et al. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. *Circulation*. 1999; 100:743–748. [PubMed: 10449697]
26. Liao Y, Greenlund KJ, Croft JB, et al. Factors explaining excess stroke prevalence in the us stroke belt. *Stroke*. 2009; 40:3336–3341. [PubMed: 19679841]
27. Golomb MR, Fullerton HJ, Nowak-Gottl U, et al. Male predominance in childhood ischemic stroke: Findings from the international pediatric stroke study. *Stroke*. 2009; 40:52–57. [PubMed: 18787197]
28. http://www.who.int/growthref/who2007_bmi_for_age/en/index.html
29. Pavlakis SG, Levinson K. Arterial ischemic stroke: Common risk factors in newborns and children. *Stroke*. 2009; 40:S79–81. [PubMed: 19064805]
30. Hoppe C, Klitz W, D'Harlingue K, et al. Confirmation of an association between the tnfr(–308) promoter polymorphism and stroke risk in children with sickle cell anemia. *Stroke*. 2007; 38:2241–2246. [PubMed: 17600229]
31. Flanagan JM, Frohlich DM, Howard TA, et al. Genetic predictors for stroke in children with sickle cell anemia. *Blood*. 2011; 117:6681–6684. [PubMed: 21515823]
32. Zorca S, Freeman L, Hildesheim M, et al. Lipid levels in sickle-cell disease associated with haemolytic severity, vascular dysfunction and pulmonary hypertension. *Br J Haematol*. 2010; 149:436–445. [PubMed: 20230401]

33. Cruz-Flores S, Rabinstein A, Biller J, et al. Racial-ethnic disparities in stroke care: The american experience: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011; 42:2091–2116. [PubMed: 21617147]
34. Kritchevsky D, Tepper SA, Kim HK, et al. Experimental atherosclerosis in rabbits fed cholesterol-free diets. 4. Investigation into the source of cholesteremia. *Exp Mol Pathol*. 1975; 22:11–19. [PubMed: 1116563]
35. Minick CR, Murphy GE, Campbell WG Jr. Experimental induction of athero-arteriosclerosis by the synergy of allergic injury to arteries and lipid-rich diet. I. Effect of repeated injections of horse serum in rabbits fed a dietary cholesterol supplement. *J Exp Med*. 1966; 124:635–652. [PubMed: 5922287]
36. Van Winkle M, Levy L. Effect of removal of cholesterol diet upon serum sickness-cholesterol-induced atherosclerosis. *J Exp Med*. 1968; 128:497–515. [PubMed: 5666961]
37. Eleftheriou D, Ganesan V, Hong Y, et al. Endothelial injury in childhood stroke with cerebral arteriopathy: A cross-sectional study. *Neurology*. 2012; 79:2089–2096. [PubMed: 23077025]
38. Mannarino E, Pirro M. Molecular biology of atherosclerosis. *Clin Cases Miner Bone Metab*. 2008; 5:57–62. [PubMed: 22460847]

Table 1

Demographics by Proportion Reported Tested and Untested

		Untested (n=1191)	Tested (n=461)	p-value ^a
Median age (yrs) at stroke(interquartile range)		5.4 (1.4, 11.8)	8.5 (3.1, 13.9)	<0.0001 ^{b*}
Male/total (%)		694/1189 (58.3)	279/461 (60.5)	0.388
Stroke Risk Factor ^{**}		N (N/1191)	N (N/461)	
	Cardiac	348 (29.2)	117 (25.4)	0.12
	Vasculopathy	338 (28.4)	136 (29.5)	0.65
	chronic disorder	338 (28.4)	136 (29.5)	0.65
	acute systemic illness	322 (27.0)	119 (25.8)	0.61
	chronic head and neck disorders	104 (8.7)	45 (9.8)	0.51
	acute head and neck disorders	250 (21.0)	108 (23.4)	0.28
	Unidentified	331 (27.8)	147 (31.9)	0.10
Form of Recurrence ^{**}				
	Symptomatic AIS ^c	31 (2.6)	25 (5.4)	0.004 [*]
	Silent AIS ^c	7 (0.6)	10 (2.2)	0.004 [*]
	TIA ^d	9 (0.8)	13 (2.8)	0.001 [*]
	CSVT ^e -new	2 (0.2)	1 (0.2)	0.83
	CSVT ^e -extension	1 (0.1)	0 (0.0)	0.53
	Intracardiac clot	0 (0.0)	1 (0.2)	0.11
	pulmonary embolism	0 (0.0)	0 (0.0)	–
	systemic arterial thrombosis	2 (0.2)	1 (0.2)	0.83
	systemic venous thrombosis	1 (0.1)	4 (0.9)	0.009 [*]
	Any form of recurrence	54 (4.5)	52 (11.3)	<0.0001 [*]
Age category				
	infancy= 28 days- <2	365 (30.6)	87 (18.9)	<0.0001 [*]
	young childhood= 2 -<5	221 (18.6)	83 (18.9)	

		Untested (n=1191)	Tested (n=461)	p-value ^a	
	childhood= 5 -<12	311 (26.1)	135 (29.3)		
	adolescence= 12 -<19	292 (24.5)	156 (33.8)		
Country of origin (top 4)					
	United States	661 (55.5)	212 (46.0)	<0.0001 [*]	
	Canada	219 (18.4)	105 (22.8)		
	Chile	77 (6.5)	43 (9.3)		
	Australia	71 (6.0)	16 (3.5)		
	Other	163 (13.7)	85 (18.4)		
Race		N (N/475)	N (N/315)		
	White	386 (81.3)	288 (91.4)	<0.0001 [*]	
	Black (one parent)	89 (18.7)	27 (8.6)		
	[Other/None] ^f	716	146]		
Ethnicity		N (N/624)	N (N/395)		
	Non-Hispanic or Latino	491 (78.7)	310 (78.5)	0.94	
	Hispanic or Latino (one parent)	133 (21.3)	85 (21.5)		
	[None	567	66]		
BMI, category (5–18 yrs)		N (N/139)	N (N/185)		
	severely thin	4 (2.9)	5 (2.7)	0.47	
	Thin	5 (3.6)	3 (1.6)		
	Normal	90 (64.7)	109 (58.9)		
	Overweight	23 (16.5)	43 (23.2)		
	Obese	17 (12.2)	25 (13.5)		
Region in the US		N (N/661)	N (N/212)		
	Southeast	21 (3.2)	7 (3.3)	0.0002 [*]	
	Southwest	127 (19.2)	38 (17.9)		
	Northeast	210 (31.8)	72 (34.0)		
	West	150 (22.7)	70 (33.0)		
	Midwest	153 (23.1)	25 (11.8)		

^a p values for Chi-square tests

^bWilcoxon test

^cArterial ischemic stroke

^dTransient ischemic attack

^eCerebral sinovenous thrombosis

^fEast Indian/South Asian, First Nations/Aboriginal, Middle Eastern, Southeast Asian, none

^{*}significant

^{**}risk factors and recurrence are not mutually exclusive

Table 2

Univariable Analysis of Predictors of any Recorded Lipid Testing

Predictor		OR	95% CI	p value
Age (continuous)		1.1	1.0–1.1	<0.0001 *
Age (categorical)	constant [ref=infancy (28 days–<2yrs)]	0.2		
	young childhood (2 – <5yrs)	1.6	1.1–2.2	0.01 *
	childhood (5 – <12yrs)	1.8	1.3–2.5	<0.0001 *
	adolescence (12 – <19yrs)	2.2	1.7–3.0	<0.0001 *
Male Gender		1.1	0.9–1.4	0.388
Race	Black (ref=white)	0.4	0.3–0.6	<0.0001 *
Ethnicity	Hispanic or Latino (ref= Non-Hispanic or Latino)	1.0	0.7–1.4	0.94
	US only, Hispanic or Latino	2.2	1.4–3.4	0.001
BMI (categorical)	constant [ref=severe thinness]	1.3		
	thin	0.5	0.1–3.4	0.46
	normal	1.0	0.3–3.7	0.96
	overweight	1.5	0.4–6.1	0.58
	obese	1.2	0.3–5.0	0.83
Country of origin	constant [ref=other]	0.5		
	US	0.6	0.5–0.8	0.002 *
	CA	0.9	0.6–1.3	0.64
	Chile	1.1	0.7–1.7	0.77
	Australia	0.4	0.2–0.8	0.006 *
Region in the US	constant [ref=Southeast]	0.3		
	Southwest	0.9	0.4–2.3	0.82
	Northeast	1.0	0.4–2.5	0.95
	West	1.4	0.6–3.4	0.46
	Midwest	0.5	0.2–1.3	0.14
Stroke Risk Factor ^a				
	cardiac	0.8	0.6–1.1	0.12
	vasculopathy	1.1	0.8–1.3	0.65
	chronic disorder	1.1	0.8–1.3	0.65
	acute systemic illness	0.9	0.7–1.2	0.61
	chronic head and neck disorder	1.1	0.8–1.6	0.51
	acute head and neck disorder	1.2	0.9–1.5	0.28
	unidentified	1.2	1.0–1.5	0.10
Recurrence				
	Any thrombotic event ^b	2.7	1.8–4.0	<0.0001 *
	Symptomatic AIS ^c only	2.1	1.3–3.7	0.005

* significant

^aStroke risk factor analyses are univariable because there are multiple risk factors per subject. The reference category for each risk factor is the absence of that risk factor.

^bAIS (silent or symptomatic), transient ischemic attack (TIA), cerebral sinovenous thrombosis, intracardiac clot, and systemic arterial or venous thrombosis

^cArterial ischemic stroke

Table 3

Multivariate Analysis of Predictors of any Recorded Lipid Testing

Model Summary			
-2 Log likelihood		Cox & Snell R ²	
1732.3		0.13	
	OR	95% CI	p value
Age (ref=infancy, 28 days-<2yrs)			
young childhood (2 – <5yrs)	1.7	1.2–2.5	0.004*
childhood (5 – <12yrs)	1.9	1.4–2.6	<0.0001*
adolescence (12 – <19yrs)	2.4	1.7–3.3	<0.0001*
Black Race (ref=white)	0.5	0.4–0.5	<0.0001*
Country of origin (ref=other)			
US	0.5	0.4–0.7	<0.0001*
CA	0.8	0.5–1.2	0.2
Chile	2.5	1.5–4.2	<0.0001*
Australia	0.5	0.2–0.9	0.02*
Recurrence	2.5	1.6–3.9	<0.0001*

Table 4

Samples that will yield a higher proportion tested by site

Inclusion of sites with (%) tested	total subjects	number of sites	mean proportion % tested across sites
25	368	29	63.0
45	202	20	75.6
60	166	16	81.4
65	111	14	84.2