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Dyslipidemia in Children with Arterial Ischemic Stroke: Prevalence and Risk Factors

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Abstract

Background—Risk factors for pediatric stroke are poorly understood and require study to improve prevention. Total cholesterol (TC) and triglyceride (TG) values peak to near-adult levels before puberty, a period of increased stroke incidence. The role of lipids in childhood arterial ischemic stroke (AIS) has been minimally investigated.

Subjects/Methods—We performed a cross-sectional analysis of lipid and Lp(a) concentrations in children with AIS in the International Pediatric Stroke Study (IPSS) to compare the prevalence of dyslipidemia and high or low ranking lipid values in our dataset to reported population values.

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We tested sex, BMI, race, ethnicity, family history and stroke risk factors for associations with dyslipidemia, high non-HDL-c and hypertriglyceridemia.

Results—Compared with the National Health and Nutrition Examination Survey, a higher proportion of children ≥5 years with AIS had dyslipidemia (38.4% vs 21%), high-TC (10.6% vs 7.4%), high non-HDL-c (23.1% vs 8.4%) and low-HDL-c (39.8% vs 13.4%). The lipid values that corresponded to one standard deviation above the mean (84.13th%tile) in multiple published national studies generally corresponded to a lower ranking percentile in children ≥5 years with AIS. Dyslipidemia was more likely associated with an underweight, overweight or obese BMI compared with a healthy weight. Ethnic background and an acute systemic illness were also associated with abnormal lipids.

Conclusions—Dyslipidemia and hypertriglyceridemia may be more prevalent in children with arterial ischemic stroke compared with stroke-free children.

Keywords

pediatric stroke; lipids; risk factors; prevalence; body mass index

Introduction

The National Heart, Lung, and Blood Institute (NHLBI) guidelines cite dyslipidemic patterns associated with atherosclerosis in children and adults: elevated triglycerides (TG) levels, low high-density lipoprotein cholesterol (HDL-c) levels and normal or only mildly elevated low-density lipoprotein cholesterol (LDL-c) levels. A non-HDL-c value is the result of subtracting HDL-c from total cholesterol (TC) and results in a combination of LDL-c, triglyceride-rich lipoprotein cholesterol, and atherogenic lipoproteins such as intermediate-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol. In adults this value correlates better than other lipid parameters with cardiovascular risk score and future major cardiovascular events.(1, 2) In children the value has better correlation with overweight and obesity than TC and LDL-c.(3, 4) In the Bogalusa Heart Study longitudinal cohort, childhood non- HDL-c was a better predictor than LDL-c of adult dyslipidemia and other non-lipid cardiovascular risk factors.(5) Non-HDL-c can also be accurately calculated from nonfasted samples.

Lipoprotein(a) (Lp(a)) reaches adult levels by the second year of life.(6) Lp(a) is an adult cardiovascular risk factor, and data are limited for pediatric ischemic stroke.(7, 8) A recent prospective cohort study found that baseline Lp(a) values were not higher in children with arterial ischemic stroke (AIS) than healthy controls, and Lp(a) did not predict incident stroke, but high Lp(a) was associated with recurrent stroke.(9)

Four factors that should be considered in childhood dyslipidemia include age, sex, body mass index (BMI), and race. Large population surveys show a prepubertal peak in cholesterol levels, but not triglycerides in boys. Cholesterol values are generally higher for girls, and peak at a slightly younger age.(10–12) Children (≥5 years) and adolescents, with a BMI >95th percentile or increased skin-fold thickness have higher dyslipidemic lipid patterns, blood pressure and fasting insulin levels.(13–15) There is limited data regarding

lipids in underweight children, but young underweight children may have poorer general health and increased health care needs.(16) Lipid values v ary by race and country of origin. Children from northern European countries including black children have similar average lipid values whereas Asian children and black children living in Africa have lower values. (10)

Pediatric stroke often occurs in previously healthy children and identification of risk factors can be difficult. We have limited knowledge about the prevalence of dyslipidemia and influence of cerebral ischemia on lipid and Lp(a) values in children with AIS. In our review of dyslipidemia in childhood AIS, we found few studies with a healthy comparison group. (8) The IPSS is the largest international registry of children with stroke. From this cohort (through April 2012) we published predictors of lipid and Lp(a) testing. Compared with children who did not have a recorded cholesterol parameter, those with recorded testing were more likely to be older and white.(17)

Modern lifestyle, diet and environment influences pediatric health. Recent NHLBI guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents reflect interval data on atherosclerosis in children and adolescents and the high prevalence of childhood obesity.(18–20) A role for early atherosclerosis and abnormal lipids in childhood stroke would be consistent with this recent data. We hypothesized that dyslipidemia is more prevalent in children with AIS compared with published national values. Here we compare prevalence of dyslipidemia in children with AIS to healthy children, and we evaluate risk factors for dyslipidemia in children with AIS.

Methods

Study Design

This was a cross-sectional analysis of participants in the IPSS, a prospective international study in children and adolescents with AIS and cerebral sinus venous thrombosis (CSVT), whose design has been described.(21)

Participants

The registry was queried from January, 2003–October, 2013 for recorded testing of at least one cholesterol parameter: TC, HDL-c, LDL-c, TG or Lp(a). The total population with AIS in the registry was 2 638, of whom 1 877 were children and adolescents >28 days-<19years. Of the children and adolescents with AIS 482 (25.7%) had at least one recorded cholesterol or Lp(a) parameter.

Baseline Characteristics

Data was entered by local investigators at each site into the registry. Entry of most data points including lipids is optional. Age was analyzed as both a continuous and categorical variable. Categorical age was defined as infancy (28 days -<2 years,) young childhood (2-<5 years,) childhood (5-<12 years,) and adolescence (12-<19 years.) For children at least 5 years old BMI was calculated and classified as a percentile and weight category by age and sex using the Centers for Disease Control and Prevention (CDC) BMI Percentile Calculator

for Child and Teen.(22). BMI is a valid measure for children 2 years and older, but dyslipidemia and BMI is generally studied in children 5 years and older. The CDC defines underweight as <5th percentile; healthy weight as the ≥5th –85th percentile; overweight as the >85th -<95th percentile; and obesity as ≥95th percentile for age and sex.(23) Race was defined as white, black, Asian, and other/not available. Ethnicity was defined as Hispanic or Latino or non-Hispanic or Latino. If black, Asian or Hispanic/Latino applied to at least one parent it was applied to the child.

All subjects had recorded testing of at least one lipid value (TC, LDL-c, HDL-c, TG) or Lp(a). Non-HDL-c is calculated by subtracting HDL-c from TC. Lipid thresholds recommended by the NHLBI expert panel are: high TC ≥200mg/dL, LDL-c ≥130mg/dL, non-HDL-c ≥145mg/dL, and low HDL-c <40mg/dL. For children 0–9 years high TG were ≥100mg/dL, and for children 10–19 years, ≥130mg/dL.(18) The National Health and Nutrition Examination Survey (NHANES) by the CDC used these thresholds.(24, 25) We defined dyslipidemia as either TC ≥200mg/dL, or HDL-c <40mg/dL, or non-HDL-c ≥145 mg/dL. High Lp(a) was >30mg/dL because this was found to be the upper quartile threshold value for increased risk of venous thromboembolism in childhood.(26)

We compared the proportion of all children and children ≥5 years with abnormal values in our study to proportions reported in two large national studies: NHANES and the Turkish school-children study.(24, 27) Other national studies reported average values. In our sample the lipid values were generally not normally distributed and our average values were calculated as medians and interquartile ranges. To compare this with national samples reporting means and standard deviations we looked at the ranking of high values identified in national samples in our sample of children ≥ 5 years. We compared values for TC, non-HDL-c, LDL-c, TG, and Lp(a) representing the mean plus one standard deviation, the 84.13th percentile, and the value for HDL-c representing the mean minus one standard deviation, the 15.87th percentile, from national studies to corresponding values with their percentiles in our sample. Where there was not an exact corresponding value we estimated to the next higher value for all lipids and Lp(a) except HDL-c where we estimated to the next lower value. We looked to see if the high ranking values for TC, non-HDL-c, LDL-c, TG, and Lp(a) corresponded to a lower rank in our study population ≥ 5 years and if the low ranking HDL-c value corresponded to a higher rank. Other comparison studies included the CASPIAN I study, the Cardiovascular Risk in Young Finn Study, the Slovak Lipid Community Study, the Calabrian Sierras Community Study, and the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS).(28–33). Characteristics of these studies are detailed (Table 3).

Risk factors for AIS as defined in IPSS are: cardiac, vasculopathy, chronic disorder, acute systemic illness, chronic head and neck disorders, and acute head and neck disorders.(34) Stroke risk factors are not mutually exclusive. Forms of recurrence were symptomatic AIS, silent AIS, and transient ischemic attack (TIA). A positive family history indicated that a first or second-degree relative had a history of early (<60years) deep venous thrombosis, stroke (ischemic or hemorrhagic), cerebral vascular disease, heart attack or pulmonary embolus.

Statistical Analysis

For continuous variables normality was tested with the Shapiro-Wilk test. Univariate logistic regression was used to calculate odds ratios and 95% confidence intervals for the association of risk factors with dyslipidemia, non-HDL-c, and hypertriglyceridemia. The analysis was performed using statistical software (SPSS 23.0, IBM).

Results

There were 482 children with AIS and at least one lipid parameter or Lp(a) included in our analysis. The cohort was 59.8% male. Age was not normally distributed. The median age was 6.1 (interquartile range, 8.7) years. Approximately 80% of the sample was <12 years, and more than one third was 5-<12 years. Data was available to calculate BMI in 69.8% (187/268) of children ≥5 years in whom 33% (62/187) were overweight or obese. More than half of the sample was white and less than 10% were black or Asian. Only one fifth of the sample had at least one Hispanic or Latino parent. Between 3 and 7% of the available lipids were obtained prior to the index stroke. The majority of the analyzed lipids were obtained after the stroke. Only 5.6% had a recurrent AIS (silent or symptomatic) or TIA. (Table 1) Most lipid values were not normally distributed. The median lipid parameter concentrations for the full sample and by sex do not cross abnormal thresholds but the interquartile ranges are wide and do cross abnormal lipid thresholds. (Table 2)

Using the same threshold values, the proportion of children with dyslipidemia was higher in our full sample (36%), and in children ≥5 years (38.4%) compared with NHANES (21%), where children were 6–19 years. The proportion with high non-HDL-c was similarly higher in our full sample (19.1%), and in children ≥5 years (23.1%) compared with NHANES (8.4%), as was the proportion with low HDL-c in our full sample (39.9%), and in children ≥5 years (39.8%) compared with NHANES (13.4%). The proportion with high TC was also higher in our sample.

The Turkish school-children study, in children 7–18 years, used slightly higher thresholds for abnormal non-HDL-c and TG and a slightly lower threshold for HDL-c. The proportion of children with high non-HDL-c in our full sample (19.1%) and ≥5 years (23.1%) was higher than Turkish school-children study (10.4%). The proportion with low HDL-c overall (39.9%) and in children ≥5 years (39.8%) was also higher than Turkish school-children (6.6%), and the proportion with high LDL-c was only higher in children ≥5 years (15.4%) compared with the Turkish school-children (11.9%). The proportion with high TC was similar in the two samples. For all lipid parameters except for Lp(a) in our sample, there was a higher proportion of girls with abnormal values.(Table 4)

The lipid value representing the 84.13th percentile (mean +1 SD) in national studies, corresponded to a lower percentile in our sample for 3 out of 5 studies that reported TC; for all 3 studies reporting non-HDL-c; for 5 out of 6 studies reporting LDL-c; for all 6 studies reporting TG; and for 2 out of 3 studies where Lp(a) was reported. The 15.87th percentile (mean −1 SD) value for HDL-c in all 6 studies corresponded to a higher percentile in our sample.(Table 5)

In univariate analyses in children with AIS there were trends towards associations between individual abnormal BMI categories and dyslipidemia, or high non-HDL-c or hypertriglyceridemia but only when subjects categorized as having abnormal weights were combined compared with healthy weight children did the associations have significance. Children with either an underweight, overweight or obese BMI, compared with a healthy weight was more likely to be associated with dyslipidemia [OR 2.2 (95%CI 1.0–4.6), p=0.04]. High non-HDL-c (≥145 mg/dL) was more likely in children with an underweight or obese BMI compared with healthy weight [OR 3.7 (95%CI 1.1–11.8), p=0.03], and in children with at least one Hispanic or Latino parent [OR 2.9 (95%CI 1.1–7.7), p=0.03], and was less likely when there was a cardiac stroke risk factor [OR 0.2 (95%CI 0.04–0.8), p=0.03]. Hypertriglyceridemia was more likely in children with an underweight or obese BMI compared with healthy weight [OR 4.4 (95%CI 1.2–16.4), p=0.03], in children with at least one Hispanic or Latino parent [OR 1.9 (95%CI 1–3.8), p=0.04], and in children with an acute systemic illness risk factor [OR 2.4 (95% CI 1.4–4.1), p=0.001]. Vasculopathy was not associated with dyslipidemia, high non-HDL-c or hypertriglyceridemia.(data not shown)

Discussion

Dyslipidemia is well studied in other disease processes in adults and there are safe and effective treatments. Compared to children in NHANES and Turkish school-children study, we found a higher proportion of children with AIS to have dyslipidemia, high non-HDL-c, and low HDL-c. The high values identified in six national studies where children were typically ≥6 years generally corresponded to lower ranking values for TC, non-HDL-c, LDL-c, TG and Lp(a), and the low values for HDL-c generally corresponded to a higher rank in our sample of children ≥5 years. In this way we were able to compare high and low ranking values in normally distributed samples to our sample. We found that the high values for TC, non-HDL-c, LDL-c, TG and Lp(a) did not rank as high in children with AIS implying that there is a greater representation of high values for these lipids in our sample. Similarly the low HDL-c values in national studies ranked higher in children with AIS implying a greater representation of low HDL-c values in our sample.

Similar to cholesterol curves by sex in healthy children, we found a higher proportion of girls with AIS had abnormal lipid values compared with boys. Similar findings were not seen for Lp(a). One third of children 5 years and older with available BMI data in our sample were overweight or obese. This is similar to recently reported United States trends.(35) Of the few risk factors that were significantly associated with dyslipidemia, high non-HDL-c or hypertriglyceridemia in our study, we found a consistent association with underweight and obese BMI. The association between underweight BMI and dyslipidemia has limited precedent and may imply underlying illness or inflammatory state but should be confirmed in other samples and investigated further. Our sample had a higher than expected proportion of underweight children (7.8%). National proportions are 3.5–5% in healthy children and adolescents.(36) Having at least one Hispanic or Latino parent was associated with high non-HDL-c and hypertriglyceridemia, and hypertriglyceridemia was more likely in children with an acute systemic illness.

Inflammation has been significantly associated with childhood AIS.(37) Inflammation contributes to the effect of dyslipidemia in the production of atherosclerotic plaques.(38) If these two factors interact in children to produce vascular disease we might have also expected an association with vasculopathy but that was not found. Early in the development of atherosclerosis, impaired vessel wall reactivity could contribute to stroke risk in children.(39) Perhaps with higher resolution vessel wall imaging we might see more early vascular abnormality in children with stroke.

Our study is one of the first to compare the prevalence of dyslipidemia in a large international childhood stroke sample with population studies. Our findings suggest further study and identification of subgroup of children with AIS who might benefit from lipid intervention, such as in children with underweight and obese BMI and possibly in children with a high inflammatory state. There are a number of limitations to this study. Our sample was small and lipid values were not normally distributed. Instead of comparing means we could only compare percentile values in our data set with similarly ranked values from population studies. This method is not as straightforward and intuitive as a comparison of means. Lipids were typically measured after the stroke occurred and in order to test dyslipidemia as a risk factor we would want prospective, uniform testing. The specific time interval of testing from an AIS may additionally influence the lipid value. Adults who suffer non-cerebral ischemia show an early decrease in lipid values, followed by an increase beginning at one week and then reduced but still elevated values at 3 months.(40) In another study the lowest values were at 2 days.(41) The data is more limited for cerebral ischemia in adults and is not available for childhood AIS. After acute cerebral ischemia in adults one study found no significant changes in lipid or Lp(a) levels on repeated measures within 4 weeks from stroke.(42) Serial lipid testing was not available for most of our cohort. This limited our ability to analyze the lipids by time interval of testing from stroke.

In our cohort it is not known how decisions were made for lipid testing. Only 25% of the eligible subjects for this study had available testing. Given this small number we previously looked at predictors of lipid testing in this cohort and how well the tested cohort represented the registry population. Among the predictors that we thought might influence testing, including age, sex, race, ethnicity, BMI category, other stroke risk factors, country, US region, and recurrent thrombosis, w e found that older age, white race, and recurrence predicted testing. To account for that we analyzed some of these variables here as they relate to dyslipidemia.

We are not able to confirm the conditions of testing including whether or not these were fasted samples. If a significant number of samples were obtained from non-fasted patients lipid values might be falsely elevated. This is one reason that we focus here on the non-HDL-c value which can be accurately calculated from nonfasted samples. An ideal comparison group is healthy children. Our sample did not have a stroke-free subgroup for comparison. Instead we chose to compare our sample to published national samples. There was some variability in the years of enrollment and age of participants among the studies. We stratified our sample for children ≥5 years for greater symmetry with published studies but we also included our full sample in other analyses because lipid values after the age of 2 years are thought to approximate adult values, and current screening guidelines for healthy

children begin after this age.(43). We found that children ≥5 years were similar in proportion with abnormal lipid values to our full sample. Future, larger samples might focus on children ≥2 years.

In our comparison of proportions of children with abnormal values, our threshold values were the same as the values used in NHANES, but the Turkish school-children study used slightly higher thresholds for non-HDL-c, HDL-c, and TG. This would have an effect of minimizing a true difference. Trending lipid values over time is best done with repeated sampling of a cohort. Our data was generally limited to single values for participants and each time interval represented different groups of participants. This introduces the possibility that the differences seen with time were due to differences in the sample at each time interval. Our sample did not well represent racial groups other than white children. Dyslipidemia by racial and ethnic group is an important area of research in healthy children and should be further studied in children with stroke.

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References

1. van Deventer HE, Miller WG, Myers GL, Sakurabayashi I, Bachmann LM, Caudill SP, et al. Non-HDL cholesterol shows improved accuracy for cardiovascular risk score classification compared to

direct or calculated LDL cholesterol in a dyslipidemic population. Clin Chem. 2011; 57(3):490–501. [PubMed: 21228254]

2. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012; 307(12):1302–9. [PubMed: 22453571]
3. Miyazaki A, Oguri A, Ichida F. Non-high-density lipoprotein cholesterol as a cardiovascular risk screening tool in children. Pediatr Int. 2015
4. Srinivasan SR, Myers L, Berenson GS. Distribution and correlates of non-high-density lipoprotein cholesterol in children: the Bogalusa Heart Study. Pediatrics. 2002; 110(3):e29. [PubMed: 12205279]
5. Srinivasan SR, Frontini MG, Xu J, Berenson GS. Utility of childhood non-high-density lipoprotein cholesterol levels in predicting adult dyslipidemia and other cardiovascular risks: the Bogalusa Heart Study. Pediatrics. 2006; 118(1):201–6. [PubMed: 16818566]
6. Rifai N, Heiss G, Doetsch K. Lipoprotein(a) at birth, in blacks and whites. Atherosclerosis. 1992; 92(2–3):123–9. [PubMed: 1385953]
7. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol. 2014; 64(9):851–60. [PubMed: 25169167]
8. Sultan SM, Schupf N, Dowling MM, Deveber GA, Kirton A, Elkind MS. Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. Int J Stroke. 2014; 9(1):79–87. [PubMed: 24148253]
9. Goldenberg NA, Bernard TJ, Hillhouse J, Armstrong-Wells J, Galinkin J, Knapp-Clevenger R, et al. Elevated lipoprotein (a), small apolipoprotein (a), and the risk of arterial ischemic stroke in North American children. Haematologica. 2013; 98(5):802–7. [PubMed: 23349301]
10. Brotons C, Ribera A, Perich RM, Abrodos D, Magana P, Pablo S, et al. Worldwide distribution of blood lipids and lipoproteins in childhood and adolescence: a review study. Atherosclerosis. 1998; 139(1):1–9. [PubMed: 9699886]
11. Skinner AC, Steiner MJ, Chung AE, Perrin EM. Cholesterol curves to identify population norms by age and sex in healthy weight children. Clin Pediatr (Phila). 2012; 51(3):233–7. [PubMed: 22157422]
12. Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. J Pediatr. 2009; 155(3):S6 e15–26.
13. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. Pediatrics. 1999; 103(6 Pt 1):1175–82. [PubMed: 10353925]
14. Freedman DS, Burke GL, Harsha DW, Srinivasan SR, Cresanta JL, Webber LS, et al. Relationship of changes in obesity to serum lipid and lipoprotein changes in childhood and adolescence. JAMA. 1985; 254(4):515–20. [PubMed: 3859672]
15. Reuter CP, da Silva PT, Renner JD, de Mello ED, Valim AR, Pasa L, et al. Dyslipidemia is Associated with Unfit and Overweight-Obese Children and Adolescents. Arq Bras Cardiol. 2016; 106(3):188–93. [PubMed: 26885973]
16. Wake M, Clifford SA, Patton GC, Waters E, Williams J, Canterford L, et al. Morbidity patterns among the underweight, overweight and obese between 2 and 18 years: population-based cross-sectional analyses. Int J Obes (Lond). 2013; 37(1):86–93. [PubMed: 22689070]
17. Sultan S, Schupf N, Dowling M, DeVeber G, Kirton A, Elkind MS, et al. Predictors of cholesterol and lipoprotein(a) testing in children with arterial ischemic stroke. J Stroke Cerebrovasc Dis. 2014; 23(9):2405–13. [PubMed: 25174567]
18. Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011; 128(Suppl 5):S213–56. [PubMed: 22084329]

19. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics. 2007; 120(2):340–5. [PubMed: 17671060]
20. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. JAMA. 2010; 303(3):242–9. [PubMed: 20071470]
21. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G, International Pediatric Stroke Study G. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke. 2009; 40(1):52–7. [PubMed: 18787197]
22. CDC DoN. Physical Activity, and Obesity BMI Percentile Calculator for Child and Teen Metric Version. [Available from: https://nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric
23. CDC. Healthy Weight, Assessing Your Weight, About Child & Teen BMI. [updated May 15, 2015. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html
24. Nguyen D, Kit B, Carroll M. Abnormal Cholesterol Among Children and Adolescents in the United States, 2011–2014. NCHS Data Brief. 2015; (228):1–8.
25. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988–2010. JAMA. 2012; 308(6):591–600. [PubMed: 22871871]
26. Nowak-Gottl U, Junker R, Hartmeier M, Koch HG, Munchow N, Assmann G, et al. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. Circulation. 1999; 100(7):743–8. [PubMed: 10449697]
27. Ucar B, Kilic Z, Dinleyici EC, Colak O, Gunes E. Serum lipid profiles including non-high density lipoprotein cholesterol levels in Turkish school-children. Anadolu Kardiyol Derg. 2007; 7(4):415–20. [PubMed: 18065339]
28. Kelishadi R, Ardalan G, Gheiratmand R, Ramezani A. Is family history of premature cardiovascular diseases appropriate for detection of dyslipidemic children in population-based preventive medicine programs? CASPIAN study. Pediatr Cardiol. 2006; 27(6):729–36. [PubMed: 17111289]
29. Buscot MJ, Magnussen CG, Juonala M, Pitkanen N, Lehtimaki T, Viikari JS, et al. The Combined Effect of Common Genetic Risk Variants on Circulating Lipoproteins Is Evident in Childhood: A Longitudinal Analysis of the Cardiovascular Risk in Young Finns Study. PLoS One. 2016; 11(1):e0146081. [PubMed: 26731281]
30. Alberty R, Albertyova D, Ahlers I. Distribution and correlations of non-high-density lipoprotein cholesterol in Roma and Caucasian children: the Slovak Lipid Community Study. Coll Antropol. 2009; 33(4):1015–22. [PubMed: 20102043]
31. Alberty R, Albertyova D. Lipoprotein(a) in Children of Asian Indian Descendants and Their Caucasian Neighbors: The Slovak Lipid Community Study. Indian J Clin Biochem. 2012; 27(3): 231–8. [PubMed: 26405380]
32. Martino F, Puddu PE, Pannarale G, Colantoni C, Zanoni C, Martino E, et al. Arterial blood pressure and serum lipids in a population of children and adolescents from Southern Italy: the Calabrian Sierras Community Study (CSCS). Int J Cardiol. 2013; 168(2):1108–14. [PubMed: 23201079]
33. Spinneker A, Egert S, Gonzalez-Gross M, Breidenassel C, Albers U, Stoffel-Wagner B, et al. Lipid, lipoprotein and apolipoprotein profiles in European adolescents and its associations with gender, biological maturity and body fat--the HELENA Study. Eur J Clin Nutr. 2012; 66(6):727–35. [PubMed: 22252104]
34. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V, et al. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Ann Neurol. 2011; 69(1):130–40. [PubMed: 21280083]
35. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA. 2012; 307(5):483–90. [PubMed: 22253364]
36. Cheryl, D. Fryar MSPH, and Cynthia L. Ogden, Ph.D., Division of Health and Nutrition Examination Surveys. Prevalence of Underweight Among Children and Adolescents Aged 2–19 Years: United States, 1963–1965 Through 2007–2010: CDC, National Center for Health Statistics.

[updated September 11, 2012. Available from: http://www.cdc.gov/nchs/data/hestat/underweight_child_07_10/underweight_child_07_10.htm

37. Fullerton HJ, deVeber GA, Hills NK, Dowling MM, Fox CK, Mackay MT, et al. Inflammatory Biomarkers in Childhood Arterial Ischemic Stroke: Correlates of Stroke Cause and Recurrence. Stroke. 2016; 47(9):2221–8. [PubMed: 27491741]
38. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002; 105(9):1135–43. [PubMed: 11877368]
39. Zeiher AM, Schachlinger V, Hohnloser SH, Saurbier B, Just H. Coronary atherosclerotic wall thickening and vascular reactivity in humans. Elevated high-density lipoprotein levels ameliorate abnormal vasoconstriction in early atherosclerosis. Circulation. 1994; 89(6):2525–32. [PubMed: 8205660]
40. Andreassen AK, Berg K, Torsvik H. Changes in Lp(a) lipoprotein and other plasma proteins during acute myocardial infarction. Clin Genet. 1994; 46(6):410–6. [PubMed: 7534219]
41. Shrivastava AK, Singh HV, Raizada A, Singh SK. Serial measurement of lipid profile and inflammatory markers in patients with acute myocardial infarction. EXCLI J. 2015; 14:517–26. [PubMed: 26535040]
42. Kargman DE, Tuck C, Berglund L, Lin IF, Mukherjee RS, Thompson EV, et al. Lipid and lipoprotein levels remain stable in acute ischemic stroke: the Northern Manhattan Stroke Study. Atherosclerosis. 1998; 139(2):391–9. [PubMed: 9712347]
43. Daniels SR, Greer FR. Committee on N. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008; 122(1):198–208. [PubMed: 18596007]

Table 1

Demographics

		AIS (n=482) N(%)
Male		288 (59.8)
Median age (years) at stroke(IQR)		6.1 (8.7)
Age category		
	infancy, 28 days- <2 yrs	114 (23.7)
	young childhood, 2 - <5 yrs	100 (20.7)
	childhood, 5 - <12 yrs	173 (35.9)
	adolescence, 12 -<19 yrs	95 (19.7)
BMI classification by age (≥ 5years) and sex (%tiles)[a]		**(subjects with data)**
	underweight, < 5th	21 (7.8)
	healthy weight, ≥5th – 85th	104 (38.8)
	overweight, >85th – <95th	30 (11.2)
	obese, ≥95th	32 (11.9)
Race		
	White	301 (62.4)
	Black (≥ one parent)	31 (6.4)
	Asian (≥ one parent)	19 (3.9)
	Other/NA (both parents)[b]	131 (27.2)
Ethnicity		
	Non-Hispanic or Latino	383 (79.5)
	Hispanic or Latino (≥ one parent)	99 (20.5)
Lipids tested		
	Total cholesterol	306 (63.5)
	LDL-c	176 (36.5)
	HDL-c	218 (45.2)
	Triglycerides	293 (60.8)
	Lp(a)	237 (49.2)
Pre-stroke Lipid testing		**(% of tested)**
	Total cholesterol	22 (7.2)
	LDL-c	10 (5.1)
	HDL-c	11 (5)
	Triglycerides	16 (5.4)
	Lp(a)	8 (3.1)
Follow-up Lipid Testing		
	Yes	18 (3.7)
Stroke Risk Factor [c]		
	Cardiac	117 (24.3)

		AIS (n=482) N(%)
	Vasculopathy	137 (28.4)
	Chronic disorder	136 (28.2)
	Acute systemic illness	133 (27.6)
	Chronic head and neck disorder	40 (8.3)
	Acute head and neck disorder	103 (21.4)
Recurrence [d]		
	Any	27 (5.6)
	Symptomatic AIS	18 (3.7)
	Silent AIS	6 (1.2)
	TIA	4 (0.8)
Family history [e]		
	Reported positive history	55 (11.4)

AIS= arterial ischemic stroke; TIA= transient ischemic attack; LDL-c= low density lipoprotein cholesterol; HDL-c= high density lipoprotein cholesterol; Lp(a)= lipoprotein(a); IQR= interquartile range

[a] CDC, (23)

[b] East Indian/South Asian, First Nations/Aboriginal, Middle Eastern, Southeast Asian; NA= not available in the registry

[c] Stroke risk factors are not mutually exclusive.

[d] For multiple recurrences, the first is used. One patient is recorded as having a TIA and Silent AIS for their first event.

[e] Family (first and second-degree relative) History of early (<60yrs) DVT, stroke (ischemic or hemorrhagic)/cerebral vascular disease/heart attack or pulmonary embolus

Table 2

Median Lipid Parameter Concentrations (mg/dL)

	overall [median (IQR, N)]	
	boys	**girls**
Total cholesterol	156 (51.3, 306)	
	147 (54, 185)	160 (49, 121)
non-HDL-c	111 (43, 204)	
	105 (43.9, 116)	118.5 (45, 88)
LDL-c	88.5 (39.8, 196)	
	83 (39.5, 113)	93 (42, 83)
HDL-c	44 (20, 218)	
	46 (22, 125)	42 (17, 93)
Triglycerides	91 (82, 293)	
	90 (80.3, 170)	95 (84, 123)
Lp(a)	10 (20, 237)	
	10 (21, 139)	8 (20, 98)

LDL-c= low density lipoprotein cholesterol; HDL-c= high density lipoprotein cholesterol; Lp(a)= lipoprotein(a); IQR= interquartile range

Table 3

Comparative features of present study and population studies

	Study Design	Years of enrolment (or publication year)	Location of study	Age of participants (years)	Threshold values (mg/dL)
present study	cross sectional	2003–2013	international	28 days - < 19	TC ≥200; LDL-c ≥130; non- HDL-c ≥145; HDL-c <40; TG ≥100 (0–9 years) and ≥130 (10–19 years)
National Health and Nutrition Examination Survey cross sectional analysis[a,b]	cross sectional	average values 2007–2010[a] proportions 2011–2014[b]	United States	6–19 (TG 12–19)	TC ≥200; LDL-c ≥130; non- HDL-c ≥145; HDL-c <40; TG ≥100 (0–9 years) and ≥130 (10–19 years)
Turkish school-children[c]	cross-sectional	published in 2007	Eskisehir, Turkey	7–18	TC >200; LDL-c >130; non-HDL-C > 150; HDL-c <35; TG >140
CASPIAN I study[d]	population-based sample	2003–2004	Iran	6–18	age and gender-specific 95th %tile of LRC standards[e], HDL-C < 5th percentile
Young Finns Study[f]	population-based prospective cohort	1980	Finland	3–15	NCEP for cholesterol (1992)(1741227); AAP and AHA guidelines for TG (2003)(12654618)
Slovak Lipid Community Study[g,h]	cross-sectional biracial	10/2005–1/2007	Central Slovakia	7–17; non-HDL-c 7–11; Lp(a) study 7–18	summary values only
Calabrian Sierras Community Study[I]	cohort sample	published in 2013	Southern Italy (14-town community)	6–14	age and sex specific 95th percentileof this sample
European adolescents - HELENA Study[j]	multicenter cross-sectional	published in 2012	10 European centers	12.5–17.5	summary values and percentile distribution of this sample

[a](25)

[b](24)

[c](27)

[d](28);

[e]Lipid Research Clinic standards, Nelson Textbook of Pediatrics 17th edn. Saunders, Philadelphia, pp 445–459

[f](29)

[g](30);

[h]Lp(a) study (31)

[I](32)

$j_{(33)}$

Table 4

Proportion with lipid or Lp(a) abnormality in our study and representative population-based studies

	AIS (%) (n/n)		AIS ≥5 years (%) (n/n)		National Health and Nutrition Examination Survey[b] (n=4638)(%)		Turkish school-children[c] (n= 2896) (%)	
	overall		overall		overall		overall	
	boys	girls	boys	girls	boys	girls	boys	girls
Dyslipidemia[a]	36 (115/319)		38.4 (68/177)		21			
	32 (62/194)	42.4 (53/125)	33 (34/103)	45.9 (34/74)	20.9	21		
High TC (≥200mg/dL)	10.8 (33/306)		10.6 (18/170)		7.4		11.8	
	10.3 (19/185)	11.6 (14/121)	10.2 (10/98)	11.1 (8/72)	5.9	8.9	9.5	14.1
High non- HDL-c (≥145 mg/dL)	19.1 (39/204)		23.1 (28/121)		8.4		10.4	
	16.4 (19/116)	22.7 (20/88)	19.7 (13/66)	27.3 (15/55)	7.5	9.4	13.2	8.9
High LDL-c (≥130 mg/dL)	10.7 (21/196)		15.4 (18/117)				11.9	
	8 (9/113)	14.5 (12/83)	10.8 (7/65)	21.2 (11/52)			9.1	14.5
Low HDL-c (<40mg/dL)	39.9 (87/218)		39.8 (51/128)		13.4		6.6	
	37.6 (47/125)	43 (40/93)	36.6 (26/71)	43.9 (25/57)	14.8	12	5.5	7.7
High TG, 0- <10 yrs (≥100mg/dL)	44.5 (94/211)		40.6 (28/69)					
	42.6 (52/122)	47.2 (42/89)	40.5 (15/37)	40.6 (13/32)				
High TG, 10- <19 yrs (≥130mg/dL)	32.9 (27/82)		32.9 (27/82)				7.5	
	31.3(15/48)	35.3 (12/34)	31.3(15/48)	35.3 (12/34)			8.1	8.9
Lp(a): abn high (>30mg/dL)	20.3 (48/237)		24.3 (35/144)					
	20.9 (29/139)	19.4 (19/98)	28.7 (22/79)	20 (13/65)				

TC= total cholesterol; HDL-c= high density lipoprotein cholesterol; LDL-c= low density lipoprotein cholesterol; TG= triglycerides; Lp(a)= lipoprotein(a)

*significant

[a]TC ≥200mg/dL or HDL-c <40mg/dL or non-HDL-c ≥145 mg/dL

[b](24)

[c](27)

Table 5

Comparison of values representing a fixed percentile in published national values to the percentile of the corresponding value among children with AIS ≥ 5 years

		Turkish school-children[b]		CASPIAN I study[c]	Young Finns Study[d]		Slovak Lipid Community Study[e,f]		Calabrian Sierras Community Study[g]	European adolescents - HELENA Study[h]	
		Mean+ 1SD (84.13th %tile), [Mean-1SD for HDL-c (15.87th %tile)] (mg/dL)[a]									
		Males	Females		Males	Females	Males	Females		Males	Females
Corresponding percentile of the value among similar children with AIS ≥ 5 years in our study (%tile)	TC	189.7	199.9	182.7			175.2		184	179	195
		86.7	***90.3***	***78.2****			***72.9****		***78.2****	***77.6****	***84.7***
	nonHDL-c	136.9	147				75th%tile, 116.4	75th%tile, 130.7	132		
		78.8*	***80****				***65.2****	***61.8****	***68.6****		
	LDL-c	118.1	128	115.4	152.7	160.9	108.3		116	114	123
		83.1*	***78.8****	***77.8****	***>98.5***	***96.2***	***74.4****		***77.8****	***81.5****	***75****
	HDL-c	37.6	38.2	31.8	48	49.1	32.5		39	43	46
		31*	***36.8****	***18****	***59.2****	***73.7****	***18.8****		***39.8****	***42.3****	***68.4****
	TG	125.6	128.2	118	93	100.1	127.5		90	97	112
		71.8*	***68.2****	***65.6****	***54.1****	***56.1****	***68.9****		***51****	***57.6****	***63.6****
	Lp(a)						39.9			38.8	46.4
							81.9*			***78.5****	***89.2***

SD= standard deviation; TC= total cholesterol; HDL-c= high density lipoprotein cholesterol; LDL-c= low density lipoprotein cholesterol; TG= triglycerides; Lp(a)= lipoprotein(a)

[a] For TC, non-HDL-c, LDL-c, TG, and Lp(a), mean + 1SD = 84.13th percentile; for HDL-c, mean - 1SD= 15.87th percentile

* Corresponding percentile in our study is lesser than 84.13%tile for TC, non-HDL-c, LDL-c, TG, and Lp(a), or greater than 15.87%tile for HDL-c 525

[b] (27)

[c] (28)

[d] (29)

[e] (30);

[f] Lp(a) study (31)

[g] (32)

[h] (33)