Title: Evaluating the Prevalence of Lipid Assessments in Children in Alberta, Canada

Authors: Christian S[1], Ridsdale R[1], Mu L[2], Khoury, M[1]

Affiliation:
[1]University of Alberta, Edmonton, AB
[2]Alberta Health Services, Edmonton, AB

Corresponding Author:
Susan Christian, MSc PhD CGC
Department of Medical Genetics
University of Alberta
826 Medical Sciences Building, University of Alberta
Edmonton, Alberta T6G 2H7
t) 780-407-1015/ f) 780-407-1761
Email: smc12@ualberta.ca
ORCID: 0000-0001-5248-3049

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Abstract

Background: Familial hypercholesterolemia (FH) is common, inherited, life-threatening, and treatable. It is characterized by marked elevations of low-density lipoprotein-cholesterol (LDL-C) resulting in a high risk of cardiovascular disease. Early diagnosis is paramount and treatment starting in childhood dramatically reduces the risk of cardiovascular disease. We sought to evaluate the prevalence of pediatric lipid assessments in Albertan children.

Method: Laboratory and administrative data from Alberta Health were reviewed between April 1, 2012 and December 31, 2021. Two separate pediatric cohorts were evaluated to allow for longitudinal assessments throughout the pediatric period (2-18 years old). Annual lipid assessment frequencies were also reviewed for all children (2-18 years) between 2013 and 2021.

Results: Pediatric lipid assessments were performed in 4.3% (1,972/46,170) of children between 2 and <11 years old and 20% (8,158/40,926) of children between 9 and <18 years. Female children ages 2- <11 years old (odds ratio (OR) 0.8, 95% confidence interval (CI) 0.69, 0.83) and those living in rural communities (OR 0.6, 95% 0.48, 0.66 for 2 - <11 year olds; OR 0.6, 95% CI 0.55, 0.65 for 9 - <18 year olds) were significantly less likely to have a lipid assessment, compared with male children and those in non-rural communities, respectively. Among those with lipid assessments, 1.2% (109/9,353) had an LDL-C level suggestive of probable FH (≥4.0 mmol/L). Statin therapy was prescribed in 16 children total during the study period. The frequency of lipid assessments was relatively stable with the exception of a decrease in 2020 (range 10,318 to 15,639 assessments per year).

Interpretation: Pediatric lipid assessment rates in Alberta is sub-optimal. These findings highlight the need to increase awareness of the benefits of early diagnosis and treatment of FH with regard to long-term health as well as identify and overcome barriers to diagnosis and treatment.

Introduction

Pediatric lipid screening is a simple and effective tool to identify children with inherited lipid disorders, such as familial hypercholesterolemia (FH).(1) FH is an autosomal co-dominant, life-threatening, and treatable disease characterized by lifelong marked elevations of low-density lipoprotein cholesterol (LDL-C). If untreated, individuals with FH have an 18-fold increased risk of cardiovascular disease.(2) Early diagnosis is paramount and treatment starting in childhood dramatically reduces atherosclerotic progression and subsequent risk for manifesting cardiovascular disease.(3) To this end, U.S.-based recommendations from the National Heart, Lung, and Blood Institute and endorsed by the American Academic of Pediatrics recommend universal lipid screening for children 9-11 years and again between 17-21 years.(4) However, research has shown that less than 10% of individuals with FH are diagnosed and less than 5% of Canadian pediatricians report routinely performing lipid assessments on healthy children.(1,5) Rather, lipid assessments are more often performed in the presence of other identified cardiovascular risk factors, such as obesity.(5) The real-world practice patterns of primary care physicians (including family physicians) with respect to pediatric lipid assessments of Canadian youth require evaluation in order to gain insights regarding the current detection of FH and other inherited lipid disorders in youth. Thus, we sought to evaluate the prevalence of pediatric lipid assessments in Albertan children, and factors associated with lipid assessments, using data available from Alberta Health.

Methods

Data Sources and Cohorts

Data were retrieved from five Alberta Health databases including the Provincial Registry, the Lab Database, the Pharmaceutical Information Network, Connect Care, Discharge Abstract Database, and the National Ambulatory Care Reporting System. Individuals are assigned a unique ID number that permits linking across the databases. Children were excluded from all data sets if they had an underlying diagnosis that would predispose them to routine lipid screening independent of universal screening practices based on ICD-10 codes. Diagnoses excluded are provided in Supplementary Table 1.(4) All data were de-identified and Research Ethics Board approval was obtained through the University of Alberta.

Administrative, pharmaceutical and laboratory data, including lipid parameters, were included between April 1, 2012 (onset of data availability) and December 31, 2021. Two separate pediatric cohorts were evaluated to allow for longitudinal assessments throughout the pediatric period within the available data timeline. The first cohort ("cohort 1") comprised Albertan children born between April 1, 2010 and December 31, 2010 (longitudinal follow-up from 2 to <11 years) and the second cohort ("cohort 2") comprised Albertan children born between April 1, 2003 and December 31, 2003 (longitudinal follow-up from 9 to <18 years). Lipid panel data were evaluated, including total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides. Sex, residence (rural vs non-rural), age at lipid panel assessment, and initiation, age and type of statin treatment were also collected. Annual lipid assessment trends (i.e. the total number of pediatric lipid assessments per year) were also reviewed between January 1, 2013 to December 31, 2021 for Albertan children 2 years to <18 years.

Data analysis

Continuous variables were presented as means with standard deviations. Categorical variables were presented as counts and percentages. Lipid assessment was defined as the reporting of an LDL-C and/or total cholesterol value. The presence of a lipid assessment was evaluated based on sex, age, and residence (rural vs non-rural) using logistic regression or Pearson correlation. Rural was defined by a zero in the second character of the postal code.(6) An LDL-C level of ≥4.0 mmol/L was considered indicative of severe hypercholesterolemia or probable FH based on the simplified Canadian definition for familial hypercholesterolemia.(7) A total cholesterol level of ≥5.2 mmol/L was considered abnormal.(4) Statistical analyses were performed on Stata 17.0.(8) Due to the large sample size, a p-value of < 0.0001 defined statistical significance.

Results

The study cohorts included 46,170 children followed from 2 to <11 years old (cohort 1) and 40,926 children followed from 9 to <18 years old (cohort 2). Children with a diagnosis that may influence lipid metabolism (Supplementary Table 1) were excluded (n = 346 and n = 455 in cohorts 1 and 2, respectively).

Demographic data for each cohort is described in Table 1. At least one lipid assessment was performed on 4% (n = 1,972) of children in cohort 1 and 20% (n = 8,158) of children in Cohort 2. Male children in cohort 1 had 1.3 (95% CI 1.20, 1.45; p<0.0001) times increased odds of having a lipid assessment compared with females, whereas male children in cohort 2 had 0.9 (95% CI 0.86, 0.95; p<0.0001) times decreased odds of having an assessment compared with females. Children living in rural Alberta in both cohorts were less likely to have a lipid assessment compared to children living in non-rural communities (cohort 1: OR 0.56; 95% CI 0.48, 0.66; p<0.0001 and cohort 2: OR 0.6; 95% CI 0.55, 0.65; p<0.0001).

Lipid assessment results are shown in Table 2. Overall, 7% (n=112) of 1,723 children in cohort 1 and 7% (n=448) of 7,185 children in cohort 2 that had a total cholesterol value had a result ≥5.2 mmol/L. In addition, 1% (n=23) of 1,836 children in cohort 1 and 1% (n=86) of 7,517 children in cohort 2 that had an LDL-C value, had a result ≥4.0 mmol/L.

Three children in cohort 1 with LDL-C levels ≥4.0 mmol/L were prescribed a statin (1 atorvastatin and 2 rosuvastatin). Thirteen children in cohort 2 were prescribed a statin, 8 of these children had an LDL-C ≥4 mmol/L within the study period and 1 child had no LDL-C value reported but had a total cholesterol level of 5.14 mmol/L. Although 4 children that were prescribed statins had initial LDL-C levels <4.0 mmol/ L and total cholesterol levels <5.2 mmol/L, the date of the statin prescription was several years after the initial lipid assessment was performed. Follow-up lipid assessment data were not available as part of this study and as such the LDL-C values at the time of statin prescription are not known for these children. The most common statin prescribed was atorvastatin (n=8) followed by rosuvastatin (n=3), simvastatin (n=1) and lovastatin (1).

Lipid assessments increased with age in both cohorts (Pearson correlation: 0.96; p<0.0001 and 0.97; p<0.0001 for cohort 1 and 2, respectively) and ranged from 0.1% of 2-year-old children to 3.9% of 17-year-old adolescents (Figure 2). There was a 2-year overlap in age between the two cohorts when children were 9 and 10 years of age. Children in cohort 1 were 9 and 10 years of age in 2020 and 2021 and children in cohort 2 were 9 and 10 years of age in 2012 and 2013. Of 9-year-old children, 0.73% (n=338) in cohort 1 had a lipid assessment compared to 1.02% (n=419) of 9-year-old children in cohort 2, whereas, 1.15% (n=532) of 10-year-old children in cohort 1 had a lipid assessment compared to 1.07%

(n=436) of 10-year-old children in cohort 2. The difference between cohorts was significant for 9-year-old children (OR 0.71; 95% CI 0.61, 0.81; p<0.0001 for cohort 1 compared with cohort 2) but not for 10-year-old children (OR: 1.07; 95% CI 0.94, 1.21 p=0.33 for cohort 1 compared with cohort 2).

A total of 117,130 initial lipid assessments were performed in children between the ages of 2 and 18 years between January 1, 2013 and December 31, 2021. Lipid assessment rates were relatively constant overtime time with the exception of slightly less lipid screening in 2020, followed by a return to assessment rates in keeping with prior years in 2021 (Figure 2).

Interpretation

Inherited lipid disorders such as FH are common and are typically clinically silent throughout childhood.(9) Thus, systematic strategies that incorporate universal, targeted, and cascade screening are needed to optimize the detection of cases.(10) The findings in this study indicate that lipid assessments are infrequently and sub-optimally utilized in the care of Albertan children; only 4% of children had a lipid assessment performed between 2 to <11 years and 20% of children had a lipid assessment performed between 9 to <18 years. Approximately 1% of children that had a lipid assessment performed had an LDL-C level that was severely elevated and suspicious of FH, however, very few children were prescribed statin therapy. These findings highlight the need for dedicated strategies to promote the early and systematic detection of inherited lipid disorders in Canadian children and to incorporate support systems to facilitate the evidence-based treatment of identified cases.

The finding of infrequent lipid assessments in the first decade of life is well aligned with previous work. For example, Khoury et al., in a survey administered through the Canadian Pediatric Surveillance Program, demonstrated that only about 3% of Canadian pediatricians who provide primary care reported performing lipid screening on otherwise healthy 9 to 11 year old children most/all of the time.(5) Although, to the best of the authors' knowledge, there are no other evaluations of lipid assessment rates in Canadian children, evaluations of U.S. children have similarly demonstrated sub-optimal lipid screening practices. While some evaluations of US screening rates have identified rates of ~20%(11,12), other analyses have identified lower screening rates in otherwise healthy children of 2-7%.(13–16) Given that we were unable to evaluate the indication for screening in the present study, the true universal screening frequency cannot be inferred, but likely comprises a small fraction of the 4% of 2-11 year-old Albertan children who received a lipid assessment. Assessments may have been performed in large part due to other cardiovascular risk factors or the diagnosis of dyslipidemia or premature cardiovascular disease in family members, as suggested by current guidelines.(10) Supporting this, lipid assessment frequencies increased gradually with age, from 0.09% in 2-year-olds to 3.9% in 17-year-olds, suggesting that assessments may have been performed due to the presence of other identified risk factors which accumulated with time. Further supporting the hypothesis that many of the assessments performed were targeted on the basis of dyslipidemia risk factors rather than universal screening is the finding that assessments were more common in males compared to females between the ages of 2-11 years. The 1.3 increased odds of a lipid assessment in males relative to females may be related to the increased prevalence of obesity (which in turn may trigger lipid assessments) in school-aged males compared with females.(17,18) Conversely, for children and adolescents between 9-18 years of age, females had slightly increased odds of receiving a lipid assessment compared with males (OR 0.9). The cause for this slight difference is not known, but may be due in part to unidentified screening that may have occurred at earlier time points (<9 years old). Prior work evaluating U.S. children did not

identify a difference in lipid screening rates between male and female children(13,16), while other work has demonstrated increased odds of screening in males.(15) Further studies are needed to explore factors that may contribute to the lipid assessment gender disparities observed in the first decade of life.

Further compounding the finding of sub-optimal lipid assessments was the observation that children residing in rural communities undergo less frequent assessments compared with their urban counterparts. This may be due to a lack of access to primary care in geographically dispersed and under-resourced locations. Prior work has similarly demonstrated that limitations of access to care naturally impede routine health assessments, including pediatric lipid assessments. For example, Sriram et al. previously demonstrated that, in children in Olmstead County, Minnesota, children with government health insurance policies had an adjusted OR of 0.47 (95% CI 0.41, 0.53) to receive a pediatric lipid assessment, compared with children with private health insurance.(16) Moreover, children with no insurance at all had an OR of 0.14 (95% CI 0.10, 0.21). Conversely, an analysis of commercial and Medicaid insurance claims of a representative US sample did not demonstrate a difference in lipid screening rates based on census region, race, ethnicity, or insurance type.(12) Further assessments evaluating impediments to access of care for Canadian children are needed.

We leveraged an overlap of ages between cohorts 1 and 2 (9 and 10 year old children) to evaluate changes in lipid assessment practices between the cohort periods (2012-2013 for cohort 2 vs 2020-2021 for cohort 1). We found that lipid assessment practices were significantly lower for 9-year old children in 2020 compared with 9-year old children in 2012. Conversely, lipid assessment practices for the 10- year-old children were no different between 2021 and 2013. The lower number of assessments in 2020 may have been due in part to the impact from the COVID-19 pandemic and decreased health care assessments during this period. Supporting this was our finding that lipid assessment frequency by year was relatively consistent between 2013-2019 and then decreased in 2020 (Figure 2). Fortunately, lipid assessments increased again in 2021. However, the findings in this study indicate that Canadian lipid assessment practices have generally not changed in the last 8 years.

Of children who underwent screening, about 1% in both cohorts had an LDL-C value ≥4 mmol/L (109 children and adolescents in total). In childhood, an LDL-C of ≥4 mmol/L corresponds with a high likelihood of FH, and is used in the simplified Canadian definition of FH incorporated by Ruel et al.(7) Despite this, and evidence supporting the beneficial long-term effects of early treatment for youth with FH(3,19,20), only 16 children across the two cohorts were prescribed statin therapy. This highlights the need to not only incorporate strategies to improve widespread pediatric lipid screening strategies, but also implement strategies to facilitate recognition and timely management of abnormal findings.

Limitations

While this study represents the first evaluation of pediatric lipid assessment practices within a Canadian context, certain limitations should be considered. First, while we were able to comprehensively assess lipid assessments in Albertan children, this may not be representative of assessment patterns in other provinces or territories across Canada. In addition, we were unable to evaluate longitudinal lipid assessment patterns across the full pediatric age range (2-18 years old). Therefore, we generated two cohorts within the available data period to evaluate screening practices between 2-<11 years old and 9-<18 years old. This approach did, however, provide the distinct advantage of permitting overlap of 9- and 10-year-old children to evaluate for an era effect. We were unable to assess the reason for lipid

assessments. While patients with conditions known to be associated with dyslipidemia were excluded from this analysis, we were unable to ascertain if a lipid panel was performed as part of universal screening practices or due to the presence of cardiovascular risk factors, such as obesity, or the presence of a positive family history. While we may infer that most lipid assessments were targeted in nature rather than universal for reasons outlined above, we cannot be certain and further study is required. We were unable to assess if children had screening performed outside the available data period (<2 years old in cohort 1 and <9 years old in cohort 2). While our trends suggest that screening children <2 years old may have been quite rare, it is possible that children in cohort 2 had assessments prior to their 9th birthday and were not captured as having been screened. Finally, we did not evaluate repeated assessments of dyslipidemia over time. Therefore, the true prevalence of dyslipidemia, as well as responses to therapy cannot be determined from the available data.

Conclusion

Pediatric lipid assessments for Albertan children and adolescents are sub-optimal, particularly in the first decade of life and in children living in rural communities. Assessment practices have not changed substantially in the last 8 years, apart from a noticeable decrease in assessments in 2020. Children identified to have severe dyslipidemia appear to be under treated, though further evaluation of this population of children on a more granular level is needed. In order to optimize the primary prevention of cardiovascular disease, it is imperative that strategies are incorporated to improve the detection and management of children with dyslipidemia, particularly those children with inherited lipid disorders.

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Table 1: Demographic data for each cohort

Characteristics	Cohort 1 (2-<11 years)		Cohort 2 (9-<18 years)	
	Screening	*No screening*	*Screening*	*No screening*
Total children	1,972 (4%)	44,198 (96%)	8,158 (20%)	32,768 (80%)
Male Female	1,146 (58%) 826 (42%)	21,546 (49%) 22,652 (51%)	4,024 (49%) 4,134 (51%	16,992 (52%) 15,776 (48%)
Rural Non rural	177 (9%) 1,795 (91%)	6,585 (15%) 37,611 (85%)	863 (11%) 7,195 (89%)	5,429 (17%) 27,339 (83%)
Age at lipid screening	7.70 (2.15) years	N/A	12.19 (2.37) years	N/A

Table 2: Summary of lipid screening results

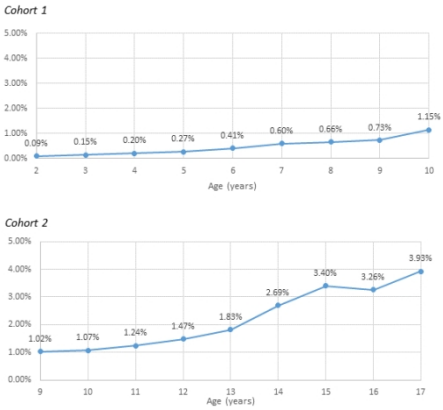
Lipid screening results	Cohort 1 (2-<11 years)	Cohort 2 (9-<18 years)
Mean Total cholesterol	4.01 (0.78) mmol/L	3.96 (0.79) mmol/L
Mean LDL cholesterol	2.21 (0.69) mmol/L	2.15 (0.67) mmol/L
Mean HDL cholesterol	1.35 (0.59) mmol/L	1.29 (0.31) mmol/L
Mean Non-HDL cholesterol	2.74 (0.76) mmol/L	2.67 (0.78) mmol/L
Mean Triglycerides	1.18 (0.78) mmol/L	1.16 (0.70) mmol/L
Children with Total cholesterol >5.2 mmol/L	112 (7%)	448 (6%)
Children with LDL cholesterol >3.4 mmol/L	85 (4%)	296 (4%)
Children with LDL cholesterol >4.0 mmol/L	23 (1%)	86 (1%)
Children with LDL cholesterol >5.0 mmol/L	7 (0.4%)	18 (0.2%)
Statin prescribed	3	13

Supplementary Table 1: Diagnoses excluded from analysis due to increased risk of dyslipidemia based on ICD codes

Diagnosis
Hypothyroidism
Diabetes
Chronic kidney disease
Hemolytic uremic syndrome
Nephrotic syndrome,
Alagille syndrome
Systemic lupus erythematosus
Juvenile rheumatoid arthritis
Glycogen-storage disease
Gaucher disease
Cystine-storage disease
Juvenile Tay-Sachs disease,
Niemann-Pick disease
Organ transplantation
Progeria
Childhood cancer

Figure 1: Percent of initial lipid assessments performed based on age

Figure 2: Number of lipid assessments performed for children 2-18 years of age over time



Percent of initial lipid assessments performed based on age

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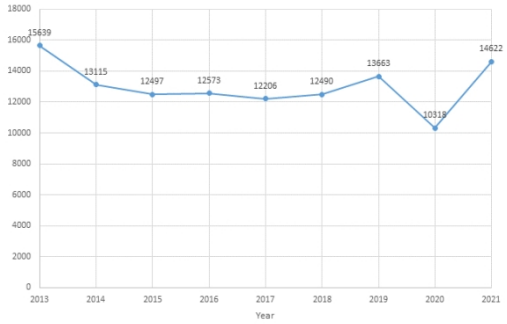

Number of lipid assessments performed for children 2-18 years of age over time

855x481mm (38 x 38 DPI)