Article details: 2022-0163
Title: Evaluating the prevalence of lipid assessments in children in Alberta, Canada
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Reviewer 1: Dr. Brian McCrindle
Institution: The Hospital for Sick Children
General comments (author response in bold)

1. The authors should emphasize one of the great strengths of their study that, despite the lack of granularity with administrative data, their study related to a well-defined geographic population completely enumerated and captured into a single payor universal health care system, which gives their findings greater generalizability.
This description has been added to the Interpretation section.
Interpretation section: "These findings- from a well-defined geographic population and single payor universal health care system-highlight the need for dedicated strategies to promote the early and systematic detection of inherited lipid disorders in Canadian children."

2. Please give the data source for the denominators.
We have added a Supplementary Table providing the data sources for each data point.

3. If you had postal code, why did you not look at SES, which might be an important explanatory factor?
We agree that this analysis would be interesting, however, we only collected the first 3 digits of the postal code for children. Statistics Canada produces two products that attach six-character postal codes to units of census geography, therefore this analysis is not possible without additional pooling of the census data.

4. I would suggest a further analysis using a cutpoint of LDL >3.5 mmol/L, which has been shown in a large Dutch cohort to be predictive of FH. I am not sure why the 3.4 cutpoint was used.
Thank you for this comment. Table 2 has been corrected to indicate the number of children with an LDL-C >3.5 mmol/L.

5. Not sure that the stats are relevant, but confidence intervals are needed around the prevalence estimates.
95% confidence intervals have been included for all odds ratios presented in manuscript. Most other prevalence data presented are not estimates but rather are calculated prevalence outputs.

6. What proportion of children by age with presumed FH were associated with a statin prescription? This would be important information.
Thank you for this comment. We have modified the Results section to include this information "Three children in cohort 1 with LDL-C levels ≥4.0 mmol/L had a statin dispensed (13%; n=3/23). Thirteen children in cohort 2 had a statin dispensed, 8 of these children had an LDL-C ≥4 mmol/L within the study period (9%; n=8/86) and 1 child had no LDL-C value reported but had a total cholesterol level of 5.14 mmol/L."

7. Unfortunately, the reasons for the lipid assessments are unknown. It would be important to know if these were obtained for universal screening, targeted screening, or for evaluation of some other condition, notably obesity.

We agree with the reviewer, however, indication for assessment was not available. As outlined in our response to the Editors, we have highlighted this in our Limitations section.

8. The authors might provide a table with suggested strategies to improve screening, evaluation and treatment.

Thank you for this comment. As outlined in our response to the Editors, we have included a new paragraph outlining strategies to improve screening, evaluation, and treatment. Moreover, we have included a new Table (Table 3) further outlining strategies as well.

Reviewer 2: Dr. Sarah De Ferranti
Institution: Children's Hospital Boston
General comments (author response in bold)

1.The approach is creative, and there is a definite gap in the literature. However, I believe the authors can use the data in a bit more straightforward fashion to accomplish their goals. Or, alternatively, the reasons behind their approach could be explained more clearly to the reader. For example, I am not sure why the authors chose to use 2 cohorts and why do they overlap?

We thank the Reviewer for her insightful comments. We have addressed our rationale for using two study cohorts in our response to the Editors and have elaborated the rationale in the Methods section (paragraph 2).

2. Given that FH is a disease with public health impact, that identifying it early is of importance to initiate treatment, and that lipid screening is an important way to identify FH. Describe the frequency of lipid testing of children and adolescents in Alberta over the past 20 years. Table 1 could be based on all available data over 20 years, and then could be divided by lipid screening age group (2-8, 9-11, 12-6, and 17+). Are there differences based on age, gender, setting (rural vs. urban)? (combine all available data to answer these questions) Are there temporal trends 2000-2021? (use 2 subsets, 2000 and 2021 as you have done for Figure but would try to include individuals of all ages as much as is available). Could also divide the data based on screening eras (pre-post 2011) although not sure if Canadian practitioners were very aware of the 2011 US NHLBI Expert Panel guidelines.

We agree with the comments from the reviewer that the questions raised are of great importance. However, data were only available from April 2012 to December 2021. and thus we were unable to address these important questions within this study. We have highlighted limitations of the available data sources in the Limitations section.

3. Based on this lipid testing, what is the frequency of children with lipid levels in the range for FH identified, and how appropriately is it being treated?

1% (1/100) of children in both cohorts had an LDL level suggestive of FH. This is described in the Result section. "Total cholesterol was ≥5.2 mmol/L for 7% (n=112) of children in cohort 1 and 7% (n=448) children in cohort 2, while 1% (n=23) in cohort 1 and 1% (n=86) in cohort 2, had an LDL-C value ≥4.0 mmol/L (Table 2)."

A key finding from the present study was that the majority of children with severe elevations in LDL-C (>4.0 mmol/L) did not receive statin therapy. This is outlined in the Results and Interpretation section and is reviewed in our response to the Editors (response #24).

4. It would be helpful to describe the denominator of the individuals identified with lipid levels in the range of FH, and also of those with lipid levels in the FH range that are treated with statin.

Thank you for this comment. As per above, we have modified the Results section to include this information "Three children in cohort 1 with LDL-C levels ≥4.0 mmol/L had a statin dispensed (13%; n=3/23). Thirteen children in cohort 2 had a statin dispensed, 8 of these children had an LDL-C ≥4 mmol/L within the study period (9%; n=8/86) and 1 child had no LDL-C value reported but had a total cholesterol level of 5.14 mmol/L."

5. Testing for lipids is not entirely equivalent to lipid screening, which is not entirely equivalent to FH screening. These points are raised but could probably be emphasized in the Discussion/Limitations a bit more.

We have emphasized these discrepancies in the Limitations section, specifically highlighting that this study comments on lipid assessments. We could not directly assess lipid screening rates (as we did not know if the lipid assessments in the data collection were initial assessments) and we did not know the purpose of lipid assessments (i.e. FH screening or assessments for another purpose). We have tried to clearly outline this in the Limitations section.

6. It should be acknowledged that it can be difficult to exclude secondary causes of lipid disorders in admin databases.

A sentence has been added to the Limitation section "In addition, we were unable to determine if the cause of severe hypercholesteremia was FH or secondary to another condition."

7. I like Table 2 but I would again divide it by 2 non-overlapping ages

We thank the reviewer for this suggestion but do want to highlight again that these are not overlapping children in the same study, but rather overlapping ages from two different eras. As we have indicated in the manuscript (with increased emphasis in response to the Editor and Reviewer comments), two cohorts were studied to span the full pediatric age range (2-18 years old) with only about 9 years of data available. Thus, we have maintained Table 2 to depict Cohorts 1 and 2.

8. Figure 1 could just describe testing by age using as much data as the authors have available, not divided by cohorts.

We appreciate that a single cohort covering the entire span of childhood would make interpretation of the data easier. However, data was only available going back to April 1, 2012 which only covers a span of 10 years.