Persistent High Non-High-Density Lipoprotein Cholesterol in Early Childhood: A Latent Class Growth Model Analysis

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Objectives To examine patterns of non–high-density lipoprotein (HDL) cholesterol in early childhood and identify factors associated with persistent high non-HDL cholesterol in healthy urban children.

Study design We identified all children enrolled in a primary care practice-based research network called TARGet Kids! (The Applied Research Group for Kids) with ≥3 laboratory measurements of non-HDL cholesterol. Latent class growth model analysis was performed to identify distinct trajectory groups for non-HDL cholesterol. Trajectory groups were then categorized into "normal" vs "persistent-high" non-HDL cholesterol based on guideline cut-off values and logistic regression was completed to examine the association between trajectory group and the presence of anthropometric and cardiometabolic risk factors.

Results A total of 608 children met inclusion criteria for the trajectory analysis (median age at enrolment = 18.3, IQR = 27.9 months). Four trajectory groups were identified with 2 groups (n = 451) categorized as normal non-HDL cholesterol and 2 groups (n = 157) as persistent high non-HDL cholesterol. Family history of high cholesterol (OR 2.04, 95% CI 1.27-3.28) was associated significantly with persistent high non-HDL cholesterol, whereas East/Southeast Asian vs European ethnicity (OR 0.33, 95% CI 0.14-0.78), longer breastfeeding duration (OR 0.96, 95% CI 0.93-1.00), and greater birth weight (OR 0.69, 95% CI 0.48-1.00) were associated with lower odds of persistent high non-HDL cholesterol.

Conclusions Patterns of non-HDL cholesterol are identified during early childhood, and family history of high cholesterol was associated most strongly with persistent high non-HDL cholesterol. Future research should inform the development of a clinical prediction tool for lipids in early childhood to identify children who may benefit from interventions to promote cardiovascular health. *(J Pediatr 2017;191:152-7).*

Cardiovascular disease (CVD) is the leading cause of death in adults worldwide,[1] and the pathogenesis of CVD is mediated primarily through the development of atherosclerosis.[2] The appearance of atherosclerotic lesions has been shown to originate in childhood,[3] and the number and intensity of childhood risk factors (eg, obesity/overweight, diabetes mellitus, high low-density lipoprotein [LDL] cholesterol, low high-density lipoprotein [HDL] cholesterol, etc) are linked with onset and severity of CVD.[3-6] Fortunately, risk reduction during childhood in the form of primary prevention (future CVD prevention through management of risk factors) can delay progression to clinical disease.[2]

Non-HDL cholesterol is a significant determinant of future cardiometabolic health that has been shown to track well from late childhood into adulthood[7,8] and represents a critical opportunity for lifestyle and medical intervention. Several socioeconomic and lifestyle factors, as well as family history of CVD, have been associated with non-HDL cholesterol,[9-12] yet these alone have been shown to be poorly sensitive and specific predictors of cardiovascular risk in young children.[13,14] To date, no study has examined their relationship to longitudinal measurements of non-HDL cholesterol over time. Thus, the primary objective of this study was to examine patterns of non-HDL cholesterol in early childhood, and the secondary objective was to explore factors associated with persistent high non-HDL cholesterol among healthy children in a primary care cohort of young children.

Methods

This was a cohort study involving healthy children who received primary care at the Applied Research Group for Kids (TARGet Kids!) participating

BMI	Body mass index
CVD	Cardiovascular disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
TARGet Kids!	The Applied Research Group for Kids

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pediatrician's office or family medicine practice and whose parents consented to participate between July 2008 and January 2016. TARGet Kids! is a primary care practice-based research network (www.targetkids.ca) based in Toronto, Canada. Study participants were recruited by research personnel embedded within 10 large participating pediatric and family medicine practices. On enrollment, TARGet Kids!-trained research assistants at each site enter the subject ID and identifying personal information into a Web-based remote data entry system using the MediData RaveTM platform (MediData Solutions, New York, New York). All study documents are then transported to the Methods Centre, where trained research assistants enter the remaining data and ensure secure document storage. Complete data collection protocol and details of this cohort have been described elsewhere.[15]

Children with severe developmental delay or chronic medical conditions (except asthma), as well as children whose families were unable to complete questionnaires in English, were excluded. For the purposes of this study, we also excluded participants with <3 laboratory measurements of non-HDL cholesterol because a minimum of 3 time points is required for the most accurate estimation of trajectories.[16] All laboratory measurements were taken during routine care for research purposes. Consent was obtained from parents, and ethical approval was obtained from the research ethics boards at The Hospital for Sick Children and St. Michael's Hospital.

Nonfasting serum venous blood samples were collected in the primary care offices by pediatric phlebotomists at the time of the child's scheduled visit, and the time since last oral intake was recorded. Nonfasting values of non-HDL cholesterol (total cholesterol minus HDL cholesterol) have been shown to represent accurately atherogenic serum lipid levels in children.[17] Specimens were transported by research assistants to Mount Sinai Services Laboratory (http://www.mountsinaiservices.com) and laboratory lipid analysis (total cholesterol and HDL) was performed with enzymatic colorimetric on the Roche Modular platform.[15] Cut points for cardiometabolic risk based on non-HDL cholesterol were derived from the 2011 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[2]

A group-based trajectory modeling approach (implemented through SAS Proc Traj (Carnegie Mellon University, Pittsburgh, PA),[18] available for download at: https://www.andrew.cmu.edu/user/bjones/), was used to identify subgroups of children with a similar underlying trajectory of non-HDL cholesterol from birth to age 8 years. Group-based trajectory modeling is a useful method to identify distinct clusters of individuals who share similar developmental trajectories with respect to a single longitudinal variable.[19] This method fits longitudinal data as a discrete mixture of multiple latent trajectories using the maximum likelihood method.

In this study, a censored normal model was fit as a polynomial function of age. As this is the first study to examine repeated measures of non-HDL cholesterol in children, there was no a priori knowledge of number of trajectories or potential trajectory shape. Thus, these parameters were assessed via the 2-stage Bayesian Information Criterion approach for data sets with 3 time points as described by Andruff et al.[19] Beginning with a single quadratic trajectory model, groups were added in a step-wise manner until the subsequent Bayesian Information Criterion and the log Bayes factor provided no further evidence for a better model fit.[18] This method resulted in a final model with 4 trajectories, 3 of which were carried out using a linear function, and 1 using a quadratic function. Because all trajectories demonstrated a similar shape, trajectories were labeled 1 (lowest non-HDL cholesterol) through 4 (highest non-HDL cholesterol).

The posterior predicted probabilities for every individual's inclusion in each of the 4 trajectories were calculated, and subjects were assigned to the trajectory for which their posterior probability was the highest. Although it generally is recommended that each trajectory group hold a group membership of at least 5%, it has been noted that clinical samples may yield groups with a smaller proportion because of the distinct biological profile of some subjects.[19]

Standing height and weight were measured at each well-child visit by trained research staff with a stadiometer (SECA, Hamburg, Germany) and a precision digital scale (SECA), respectively. For children <2 years old, length was measured with a length board. Body mass index (BMI) z scores were calculated with the World Health Organization growth standards and reference data.[20]

Sociodemographic (child age, maternal age, maternal ethnicity, maternal education, self-reported before tax income), nutritional (child birth weight, breastfeeding duration, parent BMI), and health (parents' smoking, gestational smoking, gestational diabetes) information was collected during scheduled primary health care visits through a standardized parent-completed survey instrument. Self-reported family history of cardiometabolic disease (diabetes, heart disease, hypertension, and high cholesterol) in parents also was obtained. Items in the survey were based on the Canadian Community Health Survey.

Maternal ethnicity was categorized as European, East/Southeast Asian (eg, China, Korea, Japan, Vietnam), South Asian (eg, India, Pakistan, Sri Lanka), and other (Arab, African, Latin, mixed, and other),[21] and maternal education was dichotomized to college/university and high school/elementary school. All numeric variables were examined as continuous.

Descriptive statistics were summarized by trajectory group for all subjects. Based on predetermined cut-offs for cardiovascular risk,[2] trajectory groups 1 and 2 were then combined to form the "normal non-HDL cholesterol" group, and trajectory groups 3 and 4, which both exceeded the cut-off value for high non-HDL cholesterol, were combined to form the "persistent high non-HDL cholesterol" group. Multivariable logistic regression, using the dichotomization of trajectory group as the outcome, was conducted to examine the association with each exposure variable measured at cohort entry. Covariates with missing values were imputed using multiple imputation[22] (all variables <10% missing) and all covariates were included in the final adjusted model. Sensitivity analysis was completed by excluding group 4 from our regression analysis and by examining BMI z score and birth weight as categorical vari-