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Original Article

Pediatric lipid reference values in the general population: The Dutch lifelines cohort study

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BACKGROUND: Atherosclerosis starts in childhood and its progression is influenced by lifelong low-density lipoprotein cholesterol (LDL-c) exposure, the so-called cholesterol burden. Early identification of children and adolescents with severely elevated LDL-c is thus of major clinical significance. This is especially true for children with familial hypercholesterolemia (FH), a frequent but undertreated genetic disorder. To identify children with possible FH, insight in the distribution of lipid levels in children is a prerequisite.

OBJECTIVE: To provide health care professionals with contemporary age- and gender-based pediatric reference values for lipid and lipoprotein levels to help the identification of children with dyslipidemia, especially FH.

METHODS: Lifelines is a large prospective population-based Dutch cohort study. Children from 8 till 18 years of age were included and fasting lipid levels were measured. Smoothed reference curves and percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) were generated using the Generalized Additive Models for Location, Scale and Shape package in the statistical software R.

RESULTS: A total of 8071 children (3823 boys and 4248 girls) were included. In the total cohort, we noted marked dynamic changes in lipid and lipoprotein levels over age, which were in part gender specific. Our data highlight a high and unexpected prevalence of severely elevated LDL-c (>190 mg/dL) in both boys and girls.

CONCLUSION: Our cross-sectional data provide contemporary reference ranges for plasma lipids that can assist physicians in identifying children at increased risk of premature atherosclerosis, especially FH.

Introduction

Cardiovascular disease (CVD) represents a leading cause of death globally.[1] Most often men and women above 55 and 65 years of age, respectively, are affected, but fatty streaks start developing at a very young age and the progression of atherosclerosis is positively associated with

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plasma low-density lipoprotein cholesterol (LDL-c) exposure.[2–4] This progression is accelerated in individuals with familial hypercholesterolemia (FH), a genetic disorder characterized by elevated LDL-c levels and premature CVD. Mutations in *LDLR*, *APOB*, and *PCSK9* have been shown to cause FH. The prevalence of FH is estimated to be 1 per 200 to 250 individuals but this lipid disorder is severely underdiagnosed and undertreated.[2,3] Also in children with genetically confirmed FH, undertreatment is common.[5,6] Carriers of FH mutations suffer from increased cardiovascular risk, related to a lifelong exposure to increased LDL-c levels.[7] In adults, and to a lesser extent in children, identification of FH affected individuals is difficult because of the overlap of LDL-c levels in both FH and non-FH individuals.[8,9] In this context, genetic testing can help in the clinical diagnosis of FH and in the screening of affected family members, known as cascade screening.[10,11]

Childhood is the best period to discriminate between mutation-positive and mutation-negative hypercholesterolemia on the basis of plasma LDL-c levels only.[9] Children with LDL-c levels twice >190 mg/dL should be considered as having FH, whereas 2 consecutive LDL-c levels >160 mg/dL in combination with a family history of hypercholesterolemia or premature CVD are highly suggestive of FH. Finally, children of affected parent(s) with an LDL-c >130 mg/dL are likely to have inherited the mutation.[2]

Initiation of statin treatment early in life (around 8 years) is an accepted strategy in clinical practice,[2,14] which makes early identification of children with FH clinically relevant.[15] To date's reference ranges are, however, based on old or small-case studies.[16–22]

To provide such reference ranges, we used data of Lifelines, a prospective population-based cohort study, which was initiated in 2006.[23,24] Using the same cohort, we recently reported that lipid levels in adults are strongly age- and gender-dependent, whereas the data of participants below the age of 18 years were not yet released.[25] For the present study, we have generated age- and gender-based reference values for lipid levels in children, aged 8 till 18 years. These data can help the identification of children at increased risk of atherosclerosis such as children with FH and assist cascade screening in families.[2]

Methods

Study population

The study protocol was approved by the Medical Ethical Committee of the University Medical Center Groningen in the Netherlands, and all participants provided written informed consent. The rationale and design of Lifelines has been described previously.[23,24] In short, Lifelines is an ongoing prospective population-based cohort study. Between 2006 and 2013 inhabitants from the 3 northern provinces of the Netherlands (Groningen, Friesland, and Drenthe) between 25 and 50 years of age were approached by their general practitioner to participate. On a positive response, relatives (first-degree family members, including children [≥6 months], partner, and parents-in-law) were also invited. Individuals could also participate through self-registration. Of the 167,729 almost exclusively Caucasian participants, 14,801 are children. This multiple-generation design offers the unique opportunity to study the origins of multifactorial diseases. In total, 85,000 (51%) participants are part of a 2-generation family and 20,000 (12%) of a 3-generation family.

For the present study, we provide cross-sectional population distributions of plasma lipid levels of children screened at the baseline visit. Of the total 14,801 children, 6730 were excluded because of (1) age <8 years (n = 5137), because blood sampling was only performed in children aged ≥8 years; (2) nonfasting (defined as an overnight fast) lipid measurements (n = 490); and (3) missing lipids measurements (n = 1103). In total, 8071 children (3823 boys and 4248 girls) were included. Supplementary Table 1 provides the number of children included for each year of age.

Questionnaires, physical examination, and biomaterial collection

The parents of the children received questionnaires specifically suited for the child's age. The questionnaires covered topics on lifestyle, health, nutrition, and development. A physical examination was performed including anthropometry, blood pressure measurement (10 measurements during 10 minutes using Dinamap registration), and pulmonary function tests. Fasting blood samples were drawn after an overnight fast. Fresh samples were transferred to the central laboratory of University Medical Center Groningen for routine clinical chemistry.

Cholesterol measurements

Total cholesterol, LDL-c, high-density lipoprotein cholesterol (HDL-c), and triglycerides were directly measured and were standardized against appropriate controls as described.[25] LDL-c levels were also calculated using the Friedewald formula,[26] but only when triglyceride levels did not exceed 400 mg/dL.

Statistics

Baseline characteristics that follow a normal distribution were reported as mean and standard deviation. Baseline characteristics with a skewed distribution were reported as median and interquartile range.

Smoothed reference curves were generated using Generalized Additive Models for Location, Scale and Shape.[27] Let $Y(t)$ be an outcome variable at age t. We used the Box-Cox-t power transformation with parameters $\mu(t)$,