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.

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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 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] In children with genetically confirmed FH, undertreatment is common as well.[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,[2,12,13] which makes early identification of children with FH clinically relevant.[14] To date's reference ranges are, however, based on old or small-case studies.[15–21]

To provide such reference ranges, we used data of Lifelines, a prospective population-based cohort study, which was initiated in 2006.[22,23] 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.[24] 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 have been described previously.[22,23] 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.[24] LDL-c levels were also calculated using the Friedewald formula,[25] 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.[26] Let $Y(t)$ be an outcome variable at age t. We used the

Box-Cox-t power transformation with parameters $\mu(t)$, $\sigma(t)$, and $v(t)$ to transform $Y(t)$ to $Z(t)$ with the following formula[27]:

$$Z(t) = \begin{cases} \dfrac{1}{\sigma(t)v(t)}\left(\left[\dfrac{Y(t)}{\mu(t)}\right]^{v(t)} - 1\right) & if\ v(t) \neq 0, \\[2ex] \dfrac{1}{\sigma(t)}\log\left[\dfrac{Y(t)}{\mu(t)}\right] & if\ v(t) = 0. \end{cases}$$

The transformed variable $Z(t)$ then follows a student t-distribution with $\tau(t)$ degrees of freedom. The relations between the age t and all 4 parameters were modeled with P-splines functions.

To compare our results to previously reported age- and gender-based percentiles, we also calculated age- and gender-based specific percentiles with corresponding age groups. All analyses were performed stratified by sex and carried out using IBM SPSS Statistics, version 22.0 (Armonk, NY: IBM Corp.) or the statistical software R (version 3.2.2).

Results

Study population

As clarified in the methods section, a total of 8071 children were included in our study. Demographic and clinical characteristics of the study population are shown in Table 1. Mean age was, for both boys and girls, 12 years. Furthermore, Table 1 shows that boys and girls have on average similar lipid profiles, blood pressure, and glucose levels. Supplementary Table 1 shows the number of included children per year of age.

Table 1 Demographics and clinical characteristics

Characteristics	Boys (n = 3823)	Girls (n = 4248)
Age (y)	12 ± 2.7	12 ± 2.8
Lipid profile (mg/dL)		
Total cholesterol	155 ± 27	162 ± 27
LDL-c	89 ± 23	93 ± 23
HDL-c	58 ± 12	62 ± 12
Triglycerides	52 (40–71)	62 (47–82)
SBP (mm Hg)	107 ± 11	106 ± 11
DBP (mm Hg)	59 ± 6	60 ± 6
Glucose (mmol/L)	4.7 ± 0.5	4.6 ± 0.5
HbA1c (%)	5.4 (3.0)	5.4 (0.3)

DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Data are expressed as mean ± standard deviation but triglycerides as interquartile range.

The associations between age and fasting lipid parameters are depicted in Figure 1 for boys and girls separately, using the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. Supplementary Table 2 shows age- and gender-specific lipid percentiles, including the 5th, 10th, 50th, 90th, and 95th percentiles. In the following sections, we briefly describe the main finding for different components of the lipid profile.

Age, gender, and LDL-c levels

Boys aged 8 years presented with a median LDL-c of 89 mg/dL (95th percentile: 125 mg/dL). Over the age range studied, LDL-c dropped in boys starting at approximately 12 years of age, with the lowest values around 15 years of age. Interestingly, at ages 17 and 18 years, LDL-c appears to increase marginally.

In girls, LDL-c levels appeared to be slightly higher compared with boys. As in the boys, a drop in LDL-c was noted starting at 10 years of age, with the lowest values around 14 years of age, thus a little earlier than in boys. The increase in LDL-c at later ages (15.0–17.9) was more pronounced in girls than boys. This is clearly illustrated at 17 years of age, when LDL-c is substantially higher in girls compared with boys for both median (95 mg/dL vs 82 mg/dL) and the 95th percentile (144 mg/dL vs 126 mg/dL).

In clinical practice, LDL-c levels are often calculated using the Friedewald formula (f-LDL-c).[25] Supplementary Figure 1 shows the absolute difference between f-LDL-c and direct measurement of LDL-c. Negative values indicate lower f-LDL-c in comparison with direct measurement of LDL-c and *vice versa* for positive values. Supplementary Figure 1 indicates that the population distribution of f-LDL-c is slightly lower in both boys and girls. Overall, f-LDL-c was approximately 6 mg/dL lower as compared with direct measurement of LDL-c. Clearly, with increasing triglyceride levels, the discrepancy between direct measurement and f-LDL-c increases.

Age, gender, and HDL-c levels

At 8 years of age, HDL-c levels are very similar in boys and girls; however, our cross-sectional data show markedly different HDL-c dynamics between genders with aging. HDL-c increases in boys aged 8.0 to 10.9 years followed by a strong decrease between ages 11.0 and 14.9 years, and a subsequent stabilization. In girls, by contrast, HDL-c is generally slowly decreasing with age.

Age, gender, and triglyceride levels

At 8 years of age, triglyceride levels are lower in boys (median: 45 mg/dL; 95th percentile: 96 mg/dL) than in girls (median: 52 mg/dL; 95th percentile: 105 mg/dL). In both boys and girls, triglycerides levels increase with age over
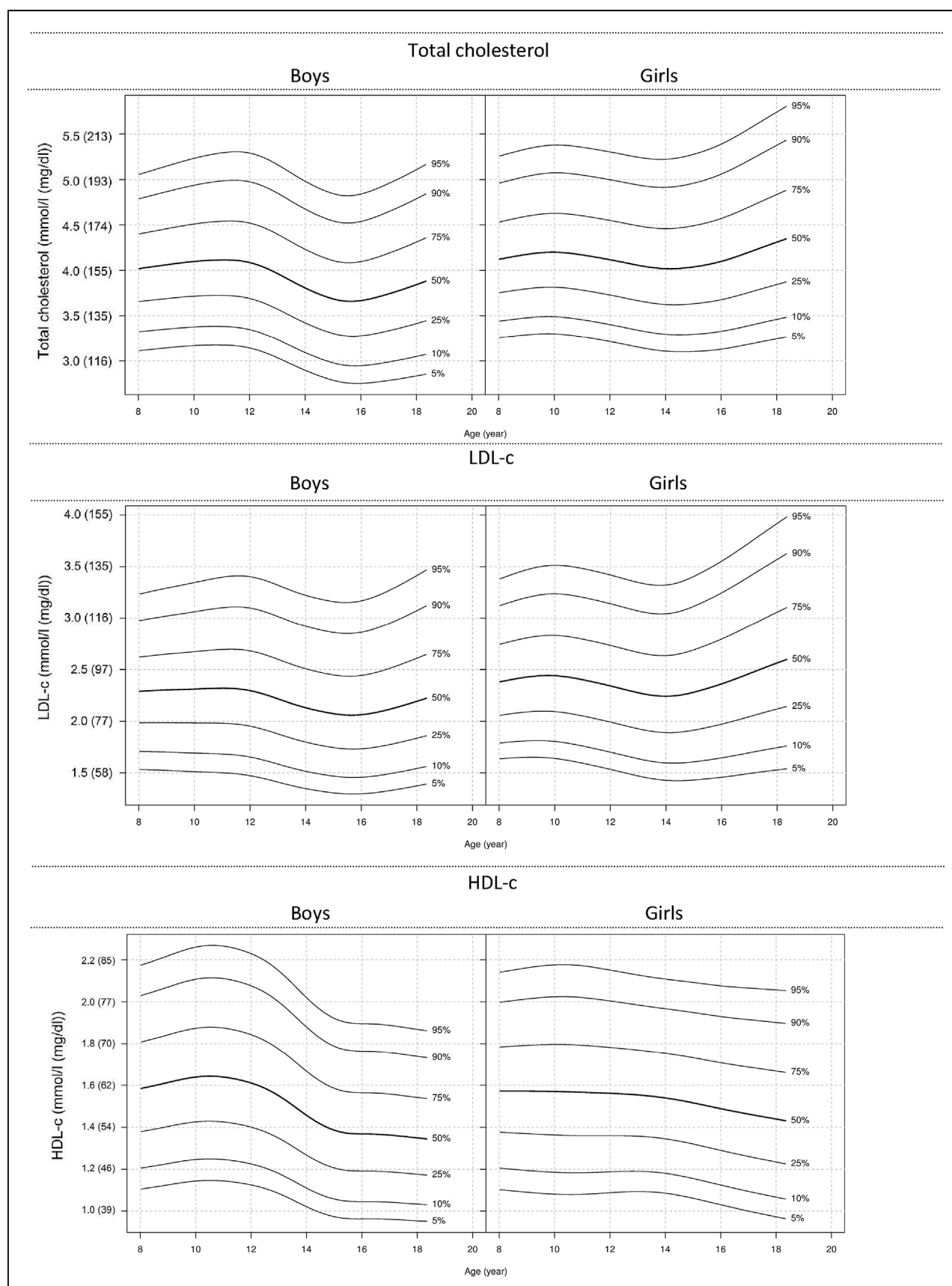
Figure 1   Relation between age, gender, and lipid parameters. Age- and gender-based smoothed percentile curves (5th, 10th, 25th, 50th, 75th, 90th, and 95th) for total cholesterol, LDL-c, HDL-c, and triglycerides for boys and girls separately. LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol.
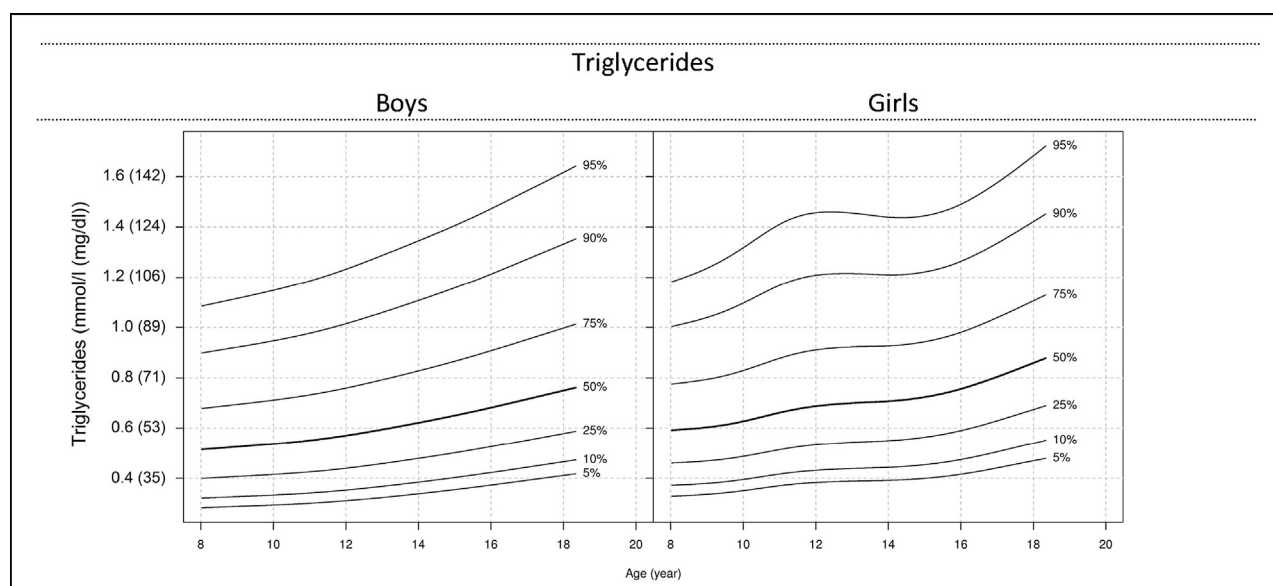
Figure 1 (*continued*).

all percentiles studied. At the age of 18 years, median triglycerides were 47% higher in boys and 46% higher in girls compared with the boys and girls aged 8 years.

Extremes

In our study population, a considerable number of children presented with severe hypercholesterolemia: 375 (4.6%) children presented with LDL-c levels >130 mg/dL. Eighty (1.0%) children showed LDL-c >160 mg/dL, which is a strong indicator of having FH. Eighteen children (0.22%) presented with LDL-c levels >190 mg/dL and could be considered as having FH (Table 2).

Discussion

This study provides tables with age- and gender-based percentiles for lipid and lipoprotein levels in children and adolescents, which can aid clinicians in the diagnosis of dyslipidemia, and in their decisions if additional diagnostic evaluations are indicated. This will allow to distinguish severe dyslipidemia, where pharmacological therapy might be indicated, from lipid abnormalities in

need of lifestyle advice. We believe that the presented reference ranges are a prerequisite for effective screening and identification of children and adolescents with FH. In our study population (children and adolescents of Caucasian descent), we identified a prevalence of 1:450 for FH (LDL-C > 190 mg/dL).

Importance of lipid reference values in clinical practice

Several studies have shown that young children with increased total cholesterol levels, for example above the 90th percentile, will maintain their percentile ranking over time.[29,30] This is why timely identification and treatment of children and adolescents with severely elevated cholesterol levels, can be an important step in reducing cardiovascular events. The recommended diet of children with FH should include less consumption of total fat (<30% of calories), saturated fat (<7% of calories), and less than 200 mg of cholesterol/d. Furthermore, the consumption of heart-healthy foods such as fruit, vegetables, and whole grain should be encouraged.[2] Besides diet intervention, cost-effective interventions using low-cost generic

Table 2 Prevalence of dyslipidemia in lifelines, compared with Germany and the United States

Dyslipidemia	Prevalence in Lifelines n (%)	Prevalence in Germany[16]	Prevalence in the United States[17,19]	Prevalence in Brazil[28]
Total cholesterol > 200 mg/dL	412 (5.1%)	7.8%	8%	–
LDL-c > 130 mg/dL	375 (4.6%)	6.1%	7%	–
LDL-c > 160 mg/dL	80 (1.0%)	–	–	–
LDL-c > 190 mg/dL	18 (0.22%)	0.23%	–	0.12%
HDL-c < 40 mg/dL	362 (4.5%)	8%	13%–15%	–
Triglycerides > 133 mg/dL	282 (3.5%)	11.7%	12%	–

HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.
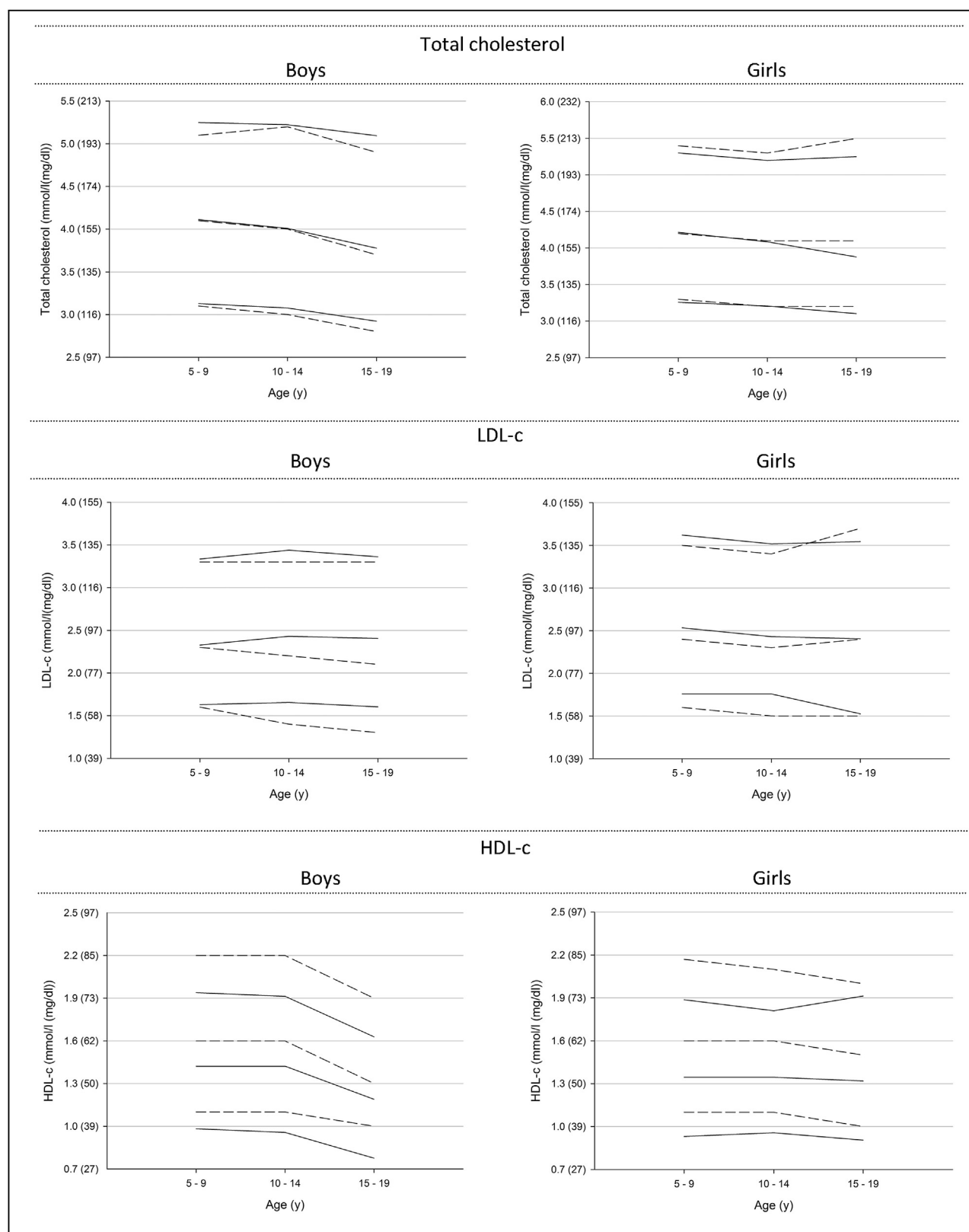
Figure 2   Comparison between lipid parameters between Lifelines and the LRC Prevalence study. Comparison of total cholesterol, LDL-c, HDL-c, and triglycerides between Lifelines (dotted line) and LRC Prevalence study (solid line). The lines correspond to the 5th, median and 95th percentile. LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol.
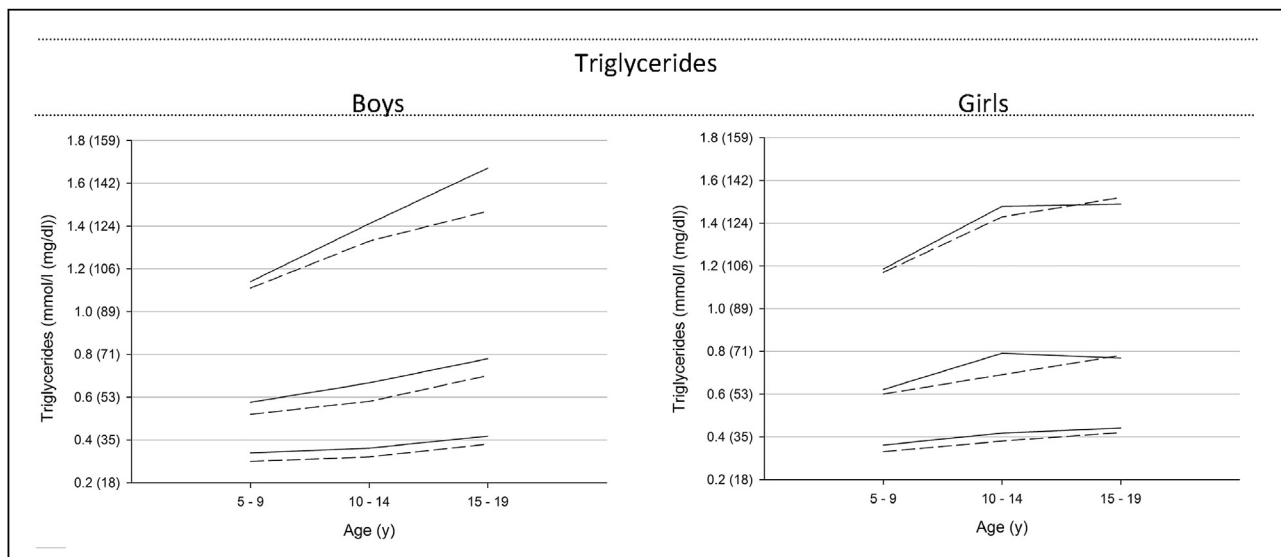
Figure 2   (*continued*).

statins combined with cholesterol absorption inhibitors are fundamental to FH management.[31] Current guidelines advocate initiating statin treatment in children with FH from the age of 8 years onward.[2,13] Although long-term data on safety and cardiovascular outcomes for statin treated children are limited, follow-up studies showed normalization of progression of carotid intima-media thickness in statin-treated FH children.[31,32] Importantly, side-effects have been reported to be rare.[33,34]

Screening for FH is a worldwide challenge. The most commonly used diagnostic criteria for FH (ie, Dutch Lipid Clinic Network and Simon Broome criteria) are however not applicable to children. Currently, 2 times plasma LDL-c levels >190 mg/dL is used as diagnostic criterion, whereas a threshold of 130 mg/dL is used in case of affected family members.[2] Universal pediatric screening of FH (phenotype-based screening) could be effectively incorporated in infant health checkups such as immunization programs.[35] This has been proven to be a highly effective approach, especially if reverse cascade screening to identify affected family members is integrated (genotype-based screening).[9,36–38] Age-specific diagnostic LDL-c cutoff criteria for diagnosis of relatives with FH have been published previously.[39]

In line with other cross-sectional studies, we show that lipid distributions change with age.[17,18,40,41] When studying adolescents around 11–16 year of age with a pronounced fall in cholesterol levels (see Fig. 1), the use of a fixed LDL-c level for a diagnosis of FH can easily result in a misdiagnosis. In case of a clinical suspicion of FH because of, for example, familial presence of hypercholesterolemia or premature CVD, genetic testing can also provide a better tool for diagnosis. Finally, using age- and gender-specific LDL-c cutoff values can also help to identify subjects with FH as we recently showed in young premenopausal women.[42]

Comparison with the LRC prevalence study

The LRC Prevalence study, conducted in the United States in 1970s,[40] has provided clinicians and researchers with cross-sectional lipid reference values.[43] Because of differences in lifestyle, cholesterol analysis methods, time of inclusion (~30 year difference), and ethnicity, dissimilarities in the distribution of lipid parameters were anticipated. After matching age groups, we compared the age- and gender-based percentiles from LRC Prevalence study with the Lifelines study (Fig. 2). LDL-c levels were lower in boys (~8 mg/dL) of the Lifelines cohort during adolescence while this discrepancy was not observed in girls. HDL-c levels were higher in both boys and girls in Lifelines compared with the LRC study, whereas triglycerides were slightly lower. The US National Health and Nutrition Examination Surveys previously showed an initial decline of total cholesterol levels in children and young adults (aged 4–19 years) between 1966 and 1970 and 1988 and 1994.[15] The detrimental increase in overweight and obesity in children over the past decades,[44] which is associated with dyslipidemia,[28] may have reversed the initial lowering of LDL-c levels observed at that time.

Frequency of pediatric hypercholesterolemia

In our study population, 4.6% of the children presented with LDL-c levels >130 mg/dL. In the United States[19,21] and Germany,[18] higher percentages were reported, 7.0% and 6.1%, respectively (Table 2). It is possible that the lower frequency of hypercholesterolemia in our cohort is related to the use of lipid-lowering drugs, but we cannot verify this as Lifelines pediatrics questionnaires do not cover medication use. By contrast, in a pediatric Brazilian cohort (age 12–17 year),[45] the prevalence of LDL-c

>190 mg/dL was lower compared with Lifelines, but this could also be a consequence of declining LDL-c levels in adolescence. It may be noted that statements about frequencies of FH in our population are hampered by 1 time point measurements, instead of recommended repeated measurements.

Strengths and limitations

The strengths of our study are the large number of children included and that the measurement of lipid levels was performed on fresh samples in a single central laboratory. We cannot ensure that our study population is representative of the Dutch pediatric population. The adult Lifelines study cohort has, however, been described to be slightly healthier compared with the larger Dutch population,[22] and it is thus likely that our pediatric cohort population is also healthier. Another limitation is that almost all Lifelines participants are of Caucasian descent, and therefore, our reference ranges may be not applicable to other ethnicities. We could not asses the relationship between pubertal stage and lipid levels as the Tanner stages of pubertal development have not been evaluated in the Lifelines cohort.

Conclusions

Our study provides contemporary age- and gender-based reference values for plasma lipid and lipoprotein levels in children and adolescents. We expect that these lipid and lipoprotein values, translated into age- and gender-specific percentiles, can serve clinicians as an effective and reliable instrument to help identifying children and adolescents with dyslipidemia, especially FH.

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Supplementary data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jacl.2018.05.011.

References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385: 117–171.
2. Wiegman A, Gidding SS, Watts GF, et al, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36:2425–2437.
3. Nordestgaard BG, Chapman MJ, Humphries SE, et al, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European atherosclerosis society. *Eur Heart J*. 2013;34:3478–3490.
4. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650–1656.
5. Humphries SE, Cooper J, Dale P, Ramaswami U, FH Paediatric Register Steering Group. The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and 1-year growth data. *J Clin Lipidol*. 2018;12:25–32.
6. Bogsrud MP, Langslet G, Wium C, Johansen D, Svilaas A, Holven KB. Treatment goal attainment in children with familial hypercholesterolemia: A cohort study of 302 children in Norway. *J Clin Lipidol*. 2017;12(2):375–382.
7. Khera AV, Won HH, Peloso GM, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol*. 2016; 67:2578–2589.
8. Huijgen R, Hutten BA, Kindt I, Vissers MN, Kastelein JJ. Discriminative ability of LDL-cholesterol to identify patients with familial hypercholesterolemia: a cross-sectional study in 26,406 individuals tested for genetic FH. *Circ Cardiovasc Genet*. 2012;5:354–359.
9. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ*. 2007;335:599.
10. Knowles JW, Rader DJ, Khoury MJ. Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing. *JAMA*. 2017; 318:381–382.
11. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet*. 2001;357:165–168.
12. Braamskamp MJ, Kastelein JJ, Kusters DM, Hutten BA, Wiegman A. Statin initiation during childhood in patients with familial hypercholesterolemia: consequences for cardiovascular risk. *J Am Coll Cardiol*. 2016;67:455–456.

13. Martin AC, Coakley J, Forbes DA, Sullivan DR, Watts GF. Familial hypercholesterolaemia in children and adolescents: a new paediatric model of care. *J Paediatr Child Health*. 2013;49:E263–E272.

14. Martin AC, Gidding SS, Wiegman A, Watts GF. Knowns and unknowns in the care of pediatric familial hypercholesterolemia. *J Lipid Res*. 2017;58:1765–1776.

15. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: data from the third national health and nutrition examination survey. *Prev Med*. 1998;27:879–890.

16. Porkka KV, Raitakari OT, Leino A, et al. Trends in serum lipid levels during 1980-1992 in children and young adults. The cardiovascular risk in young Finns study. *Am J Epidemiol*. 1997;146:64–77.

17. Azizi F, Rahmani M, Madjid M, et al. Serum lipid levels in an Iranian population of children and adolescents: Tehran lipid and glucose study. *Eur J Epidemiol*. 2001;17:281–288.

18. Dathan-Stumpf A, Vogel M, Hiemisch A, et al. Pediatric reference data of serum lipids and prevalence of dyslipidemia: Results from a population-based cohort in Germany. *Clin Biochem*. 2016;49: 740–749.

19. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr*. 2015;169:272–279.

20. Yip PM, Chan MK, Nelken J, Lepage N, Brotea G, Adeli K. Pediatric reference intervals for lipids and apolipoproteins on the VITROS 5,1 FS Chemistry System. *Clin Biochem*. 2006;39:978–983.

21. 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;308:591–600.

22. Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the LifeLines Cohort Study. *PLoS One*. 2015; 10:e0137203.

23. Scholtens S, Smidt N, Swertz MA, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2015;44: 1172–1180.

24. Balder JW, de Vries JK, Nolte IM, Lansberg PJ, Kuivenhoven JA, Kamphuisen PW. Lipid and lipoprotein reference values from 133,450 Dutch Lifelines participants: age- and gender-specific baseline lipid values and percentiles. *J Clin Lipidol*. 2017;11:1055–1064.

25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.

26. Stasinopoulos DM, Rigby RA. Generalized additive models for location scale and shape (GAMLSS) in R. *J Stat Softw*. 2007;23:1–46.

27. Rigby RA, Stasinopoulos DM. Using the Box-Cox t distribution in GAMLSS to model skewness and kurtosis. *Stat Model*. 2006;6: 209–229.

28. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med*. 2015;373:1307–1317.

29. Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. *Am J Epidemiol*. 1991;133:884–899.

30. Lauer RM, Clarke WR. Use of cholesterol measurements in childhood for the prediction of adult hypercholesterolemia. The Muscatine Study. *JAMA*. 1990;264:3034–3038.

31. Kusters DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA*. 2014;312:1055–1057.

32. Braamskamp MJAM, Langslet G, McCrindle BW, et al. Effect of Rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: The CHARON Study (hypercholesterolemia in children and adolescents taking rosuvastatin open label). *Circulation*. 2017;136:359–366.

33. Avis HJ, Vissers MN, Stein EA, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2007;27:1803–1810.

34. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2017;(7): CD006401.

35. Martin AC, Bell DA, Brett T, Watts GF. Beyond cascade screening: detection of familial hypercholesterolaemia at childhood immunization and other strategies. *Curr Opin Lipidol*. 2017;28:321–327.

36. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-parent familial hypercholesterolemia screening in primary care. *N Engl J Med*. 2016;375:1628–1637.

37. Martin AC, Allen C, Pang J, Watts GF. Detecting familial hypercholesterolemia: the jack and the beanstalk principle. *J Clin Lipidol*. 2017;11:575–578.

38. Klancar G, Groselj U, Kovac J, et al. Universal screening for familial hypercholesterolemia in children. *J Am Coll Cardiol*. 2015;66: 1250–1257.

39. Starr B, Hadfield SG, Hutten BA, et al. Development of sensitive and specific age-and gender-specific low-density lipoprotein cholesterol cut-offs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clin Chem Lab Med*. 2008;46:791–803.

40. Plasma lipid distributions in selected North American populations: the lipid research clinics program prevalence study. The lipid research clinics program epidemiology committee. *Circulation*. 1979;60:427–439.

41. Holven KB, Narverud I, van Lennep JR, et al. Sex differences in cholesterol levels from birth to 19 years of age may lead to increased cholesterol burden in females with FH. *J Clin Lipidol*. 2018;12:748–755.

42. Balder JW, Rimbert A, Zhang X, et al. Genetics, lifestyle, and low-density lipoprotein cholesterol in young and apparently healthy women. *Circulation*. 2018;137:820–831.

43. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents, national heart, lung, and blood institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(Suppl 5):S213–S256.

44. Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. *JAMA Pediatr*. 2014;168:561–566.

45. Kaestner TL, Bento VF, Pazin DC, et al. Prevalence of high cholesterol levels suggestive of familial hypercholesterolemia in Brazilian adolescents: data from the study of cardiovascular risk in adolescents. *J Clin Lipidol*. 2017;12(2):403–408.