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Research Article

Importance of detecting hyperlipidemia in children and adolescents to manage cardiovascular risk: A cross-sectional study

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Abstract

Objectives: As childhood and adolescence are the periods when cardiovascular risk factors begin to emerge, this study aimed to investigate the serum lipid profiles of the pediatric population in age- and sex-specific partitions.

Methods: The serum lipids were measured in 9613 pediatric samples from residual material in the Istanbul Public Health Laboratory with age groups stratified as 1-4 years, 5-9 years, 10-14 years, and 15-19 years.

Results: The total-C and LDL-C were significantly high in girls aged 1-4 years, and total-C and LDL-C were significantly low in boys aged 15-19 years. Total-C levels of girls were also different at ages 1-4 and 15-19 years compared with boys. The girls also showed higher LDL-C levels at 1-4 and 15-19 years, non-HDL-C levels at 1-4 years, 5-9 years, and 15-19 years, and HDL-C at 15-19 years compared with the boys of the same age group. The prevalence of hypertriglyceridemia, hypercholesterolemia, and high LDL-C in the 15-19 age groups was significantly different between boys and girls.

Conclusion: This study emphasizes the importance of determining lipid profiles during childhood and adolescence and taking preventive actions for cardiovascular diseases by implementing reliable age- and sex-specific cut-off values.-

Keywords: Cardiovascular risk, LDL-cholesterol, non-HDL-cholesterol, pediatric reference intervals, Turkish children

Cardiovascular disease (CVD) is a major cause of death around the world. Nowadays, the priority in the prevention of CVDs is to evaluate risk factors such as total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and hypertension and obesity [1]. The risk stratification has been reported to reduce the development of CVD using clinical and risk scores together with lifestyle changes and pharmacotherapy [2-4]. For early diagnosis, the use of age- and sex-specific reference intervals is essential.

Growth, organ maturation, and metabolic, immune, and hormonal changes in the pediatric population cause differences in the reference ranges of childhood and adolescence. Population-based studies, clinical trials, and practices indicate that the early detection of individuals at risk of atherosclerosis and the gradual reduction of serum lipid levels in the optimal range may have a protective effect on the prevention of CVD [5, 6].

It has been shown that atherosclerotic changes can be detected in the arterial wall, even at the age of 2, particularly in populations who have high fat and energy-intensive dietary habits and have adopted sedentary lifestyles [7]. For this reason, it is important to take into account lifestyle changes, and screening procedures must be carried out in childhood to prevent chronic diseases that may occur in adulthood [8, 9]. In addition, numerous studies have demonstrated the differences in biomarker concentration between ethnic groups, geographical location, and nations, as well as differences in instrument/analytical methods [10]. In recent years, among other lipid parameters, non-HDL-C has been presented as a

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more reliable marker than LDL-C because the assessment of all atherogenic lipoprotein groups cannot be done with LDL-C measurement, and overnight fasting is required for accurate measurement [11]. Therefore, the 2011 National Heart, Lung, and Blood Institute (NHLBI) expert panel recommends screening for non-fasting HDL-C levels in the detection of dyslipidemia in childhood and adolescence at-risk groups: first between 9 and 11 years of age and second between 18 and 21 years of age [1]. This shows the importance of using reliable age- and sex-matched appropriate reference intervals for the correct interpretation of laboratory test results and clinical decision-making. Unfortunately, there are no reliable reference intervals and cut-off values for fasting or non-fasting serum lipids with consensus among Turkish children and adolescents yet.

Because childhood and adolescence are the periods when cardiovascular risk factors begin to emerge, this cross-sectional study aimed to investigate the lipid parameters, including total-C, HDL-C, non-HDL-C, LDL-C, and triglyceride concentrations of the pediatric population in age- and sex-specific partitions, and to detect the prevalence of dyslipidemia among Turkish children.

Materials and Methods

Study population

The study comprised venous blood samples from residual material of 9613 children and adolescents (5382 girls and 4231 boys) aged 1-19 years, who were presented to the general pediatric clinics and to family medicine clinicians for an annual well-child exam from January 2019 to March 2019. Children, regardless of age, who attended the clinic for acute visits and chronic or metabolic diseases, as well as those taking medications, were excluded. Informed consent was obtained from parents and sometimes from children who were able to understand the form.

Biochemical analysis

The venous blood samples were collected into serum separator tubes (SST, Becton Dickinson) and centrifuged for 10 min at 2000g. Serum fractions were separated in 4 h. Fasting was not required as the majority of the subjects were children. Total-C, HDL-C, and triglyceride concentrations of the serum samples were measured using the enzymatic/colorimetric method on Beckman-Coulter® AU5800 chemistry analyzer using the Beckman-Coulter test kits (Beckman Coulter, Brea, CA) in the Istanbul Public Health Laboratory #1. The non-HDL-C concentration was calculated by subtracting HDL-C from total-C. The following cut-off values were used to define dyslipidemia in children and adolescent according to the American Heart Association guidelines; total-C ≥200 mg/dL, LDL-C ≥130 mg/dL, HDL-C ≤40 mg/dL, and non-HDL-C ≥ 145 mg/dL [12].

Statistical analysis

Subjects in the study group were stratified by age and sex. Age stratification was performed based on the guidelines from the National Institutes of Health as follows: Group I (1-4 years), Group II (5-9 years), Group III (10-14 years), and Group IV (15-19 years). The data were analyzed using the Statistical Package for the Social Sciences 21 software (SPSS, Chicago, IL, USA). The results are expressed as mean±standard deviation. The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. The Chi-square (χ^2) test, Kruskal-Wallis variance analysis, and a post hoc analysis using the Mann-Whitney U test were performed for unequal variances. Correlation analyses were performed using the Spearman's test. Statistical significance was defined as $p<0.05$.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by Ethics Committees of the Turkish Ministry of Health, Health Directorate of Istanbul (Approval no. 2020/34) and Istanbul Faculty of Medicine Ethics Committee for Clinical Research (Approval no: 2020/04).

Results

Age- and sex-specific serum lipid levels of the 9613 children are presented in Table 1. The mean age was 13.5±4.4 years for girls and 12.4±4.5 years for boys. The serum lipid ranges were 26-397 mg/dL for triglyceride, 26-324.2 mg/dL for LDL-C, 33-357 mg/dL for non-HDL-C, 21-108 mg/dL for HDL-C, and 77-417 mg/dL for total-C in all groups.

When lipid parameters in all age groups of boys and girls were compared, it was found that total-C and LDL-C levels were significantly high in girls aged 1-4 years and total-C and LDL-C levels except non-HDL-C were significantly low in boys aged 15-19 years. Total-C and LDL-C levels of girls aged 5-9 years were higher than all groups aged above 10 years; only HDL-C levels in boys aged 5-9 years were higher than those in the group 10-14 years. Non-HDL-C levels of boys and girls aged 5-9 years were also higher than the levels of those in the age group 15-19 years. Decreased HDL-C levels in girls were found in the age group 10-14 years compared with the age groups 5-9 and 15-19 years. Triglyceride levels were the highest in girls aged 10-14 years, significantly higher in those aged 15-19 years than in girls aged 5-9 years. However, triglyceride levels were significantly lower in boys younger than 10 years compared with the other age groups.

When we compared lipid parameters between boys and girls, total-C levels were significantly different in girls aged 1-4 years and 15-19 years compared with the levels of boys (171.9±32.9 vs. 187.8±40.6 mg/dL, $p=0.003$; 161.3±33.4 vs. 171.3±31.7 mg/dL, $p<0.001$, respectively). Girls in the age groups 1-4 and 15-19 years showed significantly higher LDL-C levels ($p<0.001$, $p<0.001$), those in the age groups 1-4, 5-9, and 15-19 years showed higher non-HDL-C levels ($p=0.001$, $p=0.047$, $p<0.001$),

Table 1. Age- and sex-specific serum triglyceride, total cholesterol, LDL-cholesterol, HDL- and, non-HDL cholesterol levels of Turkish children

	Boys						Girls					
	Age (years)	n	Lower-Upper Limit	Mean±SD	Median	Lower-Higher 90% CI	Age (years)	n	Lower-Upper Limit	Mean±SD	Median	Lower-Higher 90% CI
Triglyceride (mg/dL)	1-4	118	32-213	72.76±34.61	64	67.48-78.05	1-4	112	34-362	80.43±45.93	67	73.23-87.63
	5-9	1167	17-356	73.32±35.91	64	71.59-75.05	5-9	1057	25-341	78.16±34.42	71	76.42-79.91
	10-14	1222	26-393	90.63±49.23	78	88.31-92.95	10-14	1329	24-382	91.20±43.05	82	89.26-93.15
	15-19	1724	26-397	93.95±49.47	82	91.99-95.91	15-19	2884	23-384	82.87±37.46	74	81.72-84.02
Total Cholesterol (mg/dL)	1-4	118	80-270	171.86±32.88	166	166.84-176.88	1-4	112	102-309	187.82±40.57	179	181.46-194.18
	5-9	1167	85-306	172.85±30.94	171	171.36-174.34	5-9	1057	83-319	173.84±30.84	171	172.28-175.41
	10-14	1222	81-330	168.34±32.19	165	166.83-169.86	10-14	1329	77-305	169.20±29.90	167	167.85-170.56
	15-19	1724	77-417	161.33±33.38	157	160.01-162.66	15-19	2884	80-397	171.33±31.83	168	170.35-172.31
LDL Cholesterol (mg/dL)	1-4	118	37-193	105.31±28.20	100	101.00-109.61	1-4	112	54-224	119.70±32.90	113	114.55-124.86
	5-9	1167	24-234	103.48±25.99	102	102.23-104.74	5-9	1057	38-235	105.01±25.81	103	103.71-106.32
	10-14	1222	13-246	98.78±26.79	97	97.52-100.04	10-14	1329	12-222	99.32±24.96	97	98.20-100.45
	15-19	1724	26-324	96.78±28.34	93	95.66-97.90	15-19	2884	13-330	101.83±26.52	99	101.02-102.64
HDL Cholesterol (mg/dL)	1-4	118	31-100	52±11.50	52	50.24-53.75	1-4	112	26-94	52.02±10.81	51	50.33-53.72
	5-9	1167	27-98	54.70±11.14	54	54.16-55.23	5-9	1057	24-91	53.19±10.96	53	52.64-53.75
	10-14	1222	25-108	51.43±11.06	50	50.91-51.95	10-14	1329	22-106	51.63±10.51	50	51.16-52.11
	15-19	1724	21-82	45.76±8.80	45	45.41-46.10	15-19	2884	26-97	52.92±10.09	52	52.61-53.23
Non-HDL Cholesterol (mg/dL)	1-4	118	46-221	119.86±28.94	115.5	115.45-124.28	1-4	112	62-259	135.79±36.91	128.5	130.01-141.58
	5-9	1167	33-266	118.15±28.13	116	116.8-119.51	5-9	1057	44-247	120.65±27.73	118	119.25-122.05
	10-14	1222	26-271	116.91±30.0	114	115.5-118.33	10-14	1329	26-246	117.57±27.50	115	116.33-118.81
	15-19	1724	33-357	115.57±32.15	111	114.3-116.85	15-19	2884	27-344	118.41±29.36	115	117.51-119.31

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; SD: Standard deviation; CI: Confidence interval.

and those in the group 15-19 years exhibited higher HDL-C levels (p<0.001) compared with the same age groups of boys. However, HDL-C levels were significantly lower in girls aged 5-9 years (p=0.002). Increased triglyceride levels were found in girls aged 5-9 years and 10-14 years (p<0.001, p=0.01) compared with boys of the corresponding age groups, whereas increased triglyceride levels were found in boys aged 15-19 years compared with girls of the same age group (p<0.001).

The prevalence of dyslipidemia is shown in Figure 1a-e. The prevalence of dyslipidemia in girls and boys in the age group 15-19 years was 16.9% and 11.4% for total-C, 13.5% and 10.5% for LDL-C, 13.9% and 13.3% for non-HDL-C, 7.1% and 14.1% for triglyceride, and 2.4% and 10.7% for HDL-C. For the girls and boys in the age group 10-14 years, the dyslipidemia prevalence was 15.2% and 15% for total-C, 10.5% and 11.9% for LDL-C, 10.8% and 12.8% for non-HDL-C, and 3.2% and 4.9% for HDL-C. The prevalences for hypertriglyceridemia, hypercholesterolemia, and high LDL-C results in the age group 15-19 years were significantly different between boys and girls (p<0.001, p<0.001, p=0.003). For HDL-C results, significantly lower levels were obtained in girls aged 10-14 years and 15-19 years compared with boys of the same age groups (p=0.024, p<0.001). No significant differences were found in non-HDL-C levels between boys and girls in all age groups.

The results of correlation analysis in all groups were as follows: significant correlations existed between triglyceride and other parameters (with HDL-C: r=-0.236, p<0.001; with non-HDL-C: r=0.497, p<0.001; with total-C: r=0.400, p<0.001; with LDL-C: r=0.290, p<0.001). Strong correlations existed between non-HDL-C and triglyceride, total-C, and LDL-C (r=0.497, p<0.001; r=0.963, p<0.001; and r=0.974, p<0.001; respectively), HDL-C correlated weakly with both total-C and LDL-C (r=0.371, p<0.001 and r=0.178, p=0.009, respectively). LDL-C strongly correlated with both non-HDL-C and total-C (p<0.001 for both) and also with HDL-C (p=0.001). Non-HDL-C and LDL-C levels negatively correlated with age in girls (r=-0.201, p=0.003, r=-0.202, p=0.003); however, only triglyceride concentrations were associated with age in boys (r=0.206, p=0.005).

Discussion

In this study, we evaluated total-C, HDL-C, LDL-C, non-HDL-C levels, and triglyceride con-

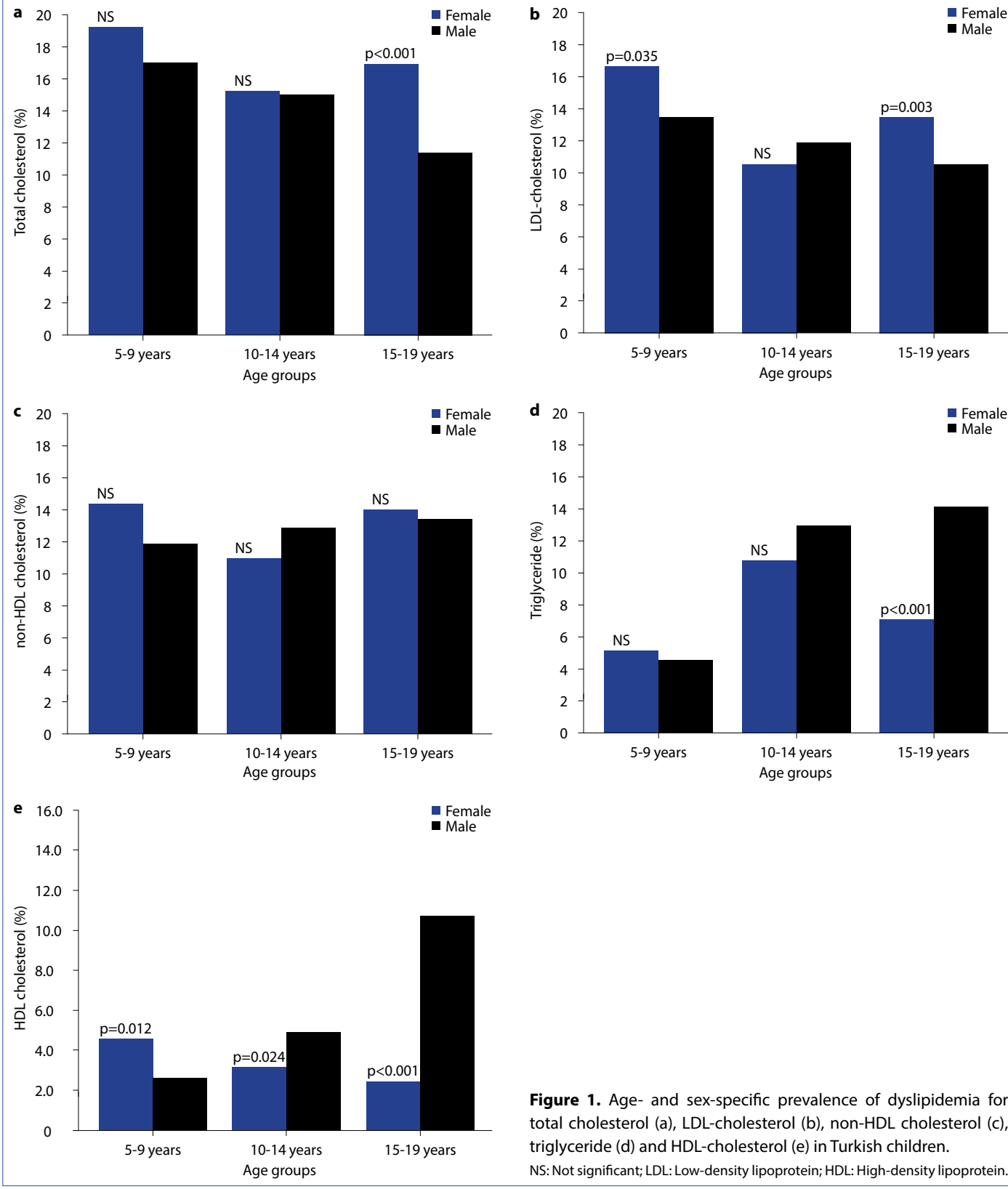

Figure 1. Age- and sex-specific prevalence of dyslipidemia for total cholesterol (a), LDL-cholesterol (b), non-HDL cholesterol (c), triglyceride (d) and HDL-cholesterol (e) in Turkish children.

NS: Not significant; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

centrations in 9613 children aged 1-19 years. Lipid levels vary with normal growth and maturation such that lipid concentrations in the newborn, although low, increase in the first 2 years. According to our findings, girls in the age groups 1-4 years and 15-19 years had higher serum cholesterol, HDL-C, non-HDL-C, and LDL-C levels than boys in the same age

groups. The serum triglyceride levels of girls in the groups 5-9 years and 10-14 years were also higher than those in boys in the same age groups; however, significantly increased triglyceride levels were obtained in boys in the group 15-19 years. These findings supported the results of studies conducted in 1988-1994 and 2007-2010 in the youth of the United States [13]. In a population-based study, including 16,228 European children aged 2-9 years, increased total-C, LDL-C, and triglyceride levels were reported in girls compared to boys, similar to our results [14]. In a study of Ferranti et al. [15], decrease in total cholesterol and LDL-C levels were reported in puberty, and relatively stable lipid concentrations from two years of age to adolecence period. The results of European children were similar to those we observed, the total-C and LDL-C levels were lower than our findings. Furthermore, there are studies to show lower and higher total-C levels than our findings [16-18]. These sex-specific differences in serum lipids of boys and girls indicate the impacts of hormonal changes on lipid levels, regardless of chronological age.

In our previous population study, including 26,499 adults, higher triglyceride levels and lower HDL-C levels were obtained in men than in women, as observed in adolescent girls and boys aged 15-19 years [19]. Also, the studies with Turkish children and adolescents have reported similar or lower total-C and LDL-C levels than our results [20, 21]. However, lower levels of total-C, LDL-C, and non-HDL-C and higher levels of HDL-C were reported in studies in children and adolescents in China and India [22, 23]. These differences between studies may be largely due to the dietary habits and genetic characteristics of the societies and race.

According to our results, the prevalences of dyslipidemia for non-HDL-C were 13-14% for the age group 15-19 years and 11-13% for the age group 10-14 years. Dyslipidemia arises from genetic causes, dietary conditions, and some diseases such as diabetes and nephrotic syndrome [24]. Our study was a retrospective study with samples transferred from certain districts to the Public Health Laboratory; therefore, it was impossible to control the diet-related characteristics of the patients. However, the National Health and Nutrition Examination conducted between 1999 and 2006 reported higher dyslipidemia prevalence (20.3%) in the age group 12-19 years, and their results in terms of HDL-C and triglyceride for boys and girls aged 15-19 years were similar to our results [25]. In another study, the highest percentage of dyslipidemia using non-fasting samples was obtained for LDL-C and triglyceride, and the percentages of children with dyslipidemia were also higher than our results [26].

For many years, LDL-C had been considered the main cause for the development of atherosclerosis, and reducing LDL-C was targeted to prevent CVD. Later on, non-HDL-C was reported as a major risk factor for coronary atherosclerosis. A 30 mg/dL increase in non-HDL levels was demonstrated to be equivalent to 2 years of vascular aging [27]. The National Cholesterol Education Program (NCEP) guidelines recommend that the target value for non-HDL-C concentration should be 30 mg/dL higher than the LDL-C, even without abnormal LDL levels [6]. Non-HDL-C is metabolically associated with cholesterol within all the apolipoprotein B (apoB) containing lipoproteins, and its measurement represents all the atherogenic apoB particles, including chylomicrons, chylomicron remnants, VLDL, and IDL, as well as LDL and Lp(a) [28]. Therefore, several recent studies have proposed the superiority of non-HDL-C and apoB in predicting the risk of CVD [28, 29]. Also, these studies have reported that the effect of IDL cannot be demonstrated by measuring LDL-C alone [30]; the measurement of non-HDL-C provides an important advantage in determining the risk of CVD is being readily accessible and sensitive in the non-fasting, which is particularly important in screening and monitoring of the pediatric population [31]. Therefore, the majority of children who have abnormal levels of lipids and lipoproteins in childhood have presented persistent elevation in total-C levels and increased intima-media thickness as adults suggest that this condition is directly associated with high non-HDL-C, LDL-C, and total-C levels, and low HDL-C levels in childhood [31, 32]. In this study, non-HDL-C levels of boys and girls aged 5-9 years were higher than those in the age group 15-19 years, and non-HDL-C levels of girls aged 5-9 years were higher than the boys of the same age group. Similar to our findings, a higher reference interval for non-HDL-C levels in girls aged 1-10 years was reported compared to boys in the CALIPER study [33]. In our study, non-fasting samples were used to evaluate lipid parameters. Fasting or non-fasting serum samples can be used for screening. The National Health and Nutrition Examination Surveys demonstrated clinically insignificant differences between non-fasting and fasting statuses [34]. If the non-fasting screening test is abnormal, it is recommended to evaluate fasting lipid parameters and perform at least two measurements. Several population-based studies supported the idea that non-fasting lipid levels are equal or superior to fasting levels [32, 35]. However, Szternel et al. [26] showed false-positive results for triglycerides and false-negative results for LDL-C in non-fasting patients, but they still underlined the usefulness of HDL-C measurement for the diagnosis of dyslipidemia in children. They also noted that a more frequent diagnosis of dyslipidemia in non-fasting children might be due to the lack of appropriate cut-off values. Therefore, a non-fasting lipid profile has been included in several guidelines for the clinical and laboratory practice of CVD risk assessment [36, 37]. Finally, NHLBI guidelines recommend fasting lipid measurements for screening, and non-fasting for non-HDL-C determination together with fasting lipid profiles for confirmation [1]. However, a few studies revealed opposite results on the efficacy of non-HDL-C, demonstrating equal or better predictive ability of apoB compared to non-HDL-C [27, 30]. In a previous meta-analysis in CVD risk prediction, non-HDL-C was shown to have a predictive ratio equal to that of LDL-C, and non-HDL-C had a predictive ratio equal to apoB and apoA1 [35]. Holewijn et al. [30] reported the superiority of apoB over non-HDL-C, indicating that LDL-C was the least effective marker.

This study has some limitations and advantages. The advantage of our study is the inclusion of an almost equal number of subjects of both sexes, with a large sample size in all age groups. The lack of data referring to the influence of some factors associated with lipid levels, such as anthropometric indicators, physical activity, dietary habits, and socioeconomic status, is a limitation of this study. In this cross-sectional study, the distribution of serum lipids and lipoproteins of Turkish children and adolescents of age 1-19 years was analyzed according to age and sex. However, the cross-sectional nature of the data used in this study limits any assumptions about the duration of exposure to these factors and their effects on the serum lipid levels. Longitudinal studies are needed to investigate the complex association of these factors and serum lipids in childhood and adolescence.

Our results highlight the importance of determining lipid profiles during childhood and adolescence and taking preventive actions to minimize or prevent CVD. Although there is no consensus about the screening and strategies for the prevention of CVD, the American Academy of Pediatrics unconditionally recommends screening children who have parents with hyperlipidemia or have CVD risk factors such as obesity, hypertension, and metabolic disorders. We also point to the most important aspect of appropriating screening and taking preventive actions against CVD is implementing reliable reference intervals and accurate cut-off values specific to age and sex and determining country/population-specific reference intervals.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (No: 04, Date: 21/02/2020).

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