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Association of Non-High-Density Lipoprotein Cholesterol with Low-Density Lipoprotein Cholesterol in Korean Children and Adolescents: The Korean National Health and Nutrition Examination Surveys 2008 - 2014

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Abstract

Background: The aim of this study was to identify the association between non-high-density lipoprotein cholesterol (non-HDL-C) and low-density-lipoprotein cholesterol (LDL-C) according to age and gender in apparently healthy Korean children and adolescents.

Methods: A total of 6,255 subjects aged 10-19 years from the 2008-2014 Korean National Health and Nutrition Examination Survey were analyzed. Serum non-HDL-C, LDL-C, and their association were evaluated according to age and gender.

Results: The means of the 75th percentile and 95th percentile concentrations for non-HDL-C were 117.0 mg/dL and 148.0 mg/dL in males, respectively, and 121.0 mg/dL and 151.0 mg/dL in females, respectively. The means of the 75th percentile and 95th percentile concentrations for LDL-C were 99.2 mg/dL and 125.0 mg/dL in males, respectively, and 102.8 mg/dL and 128.9 mg/dL in females, respectively. The mean age- and gender-specific difference between non-HDL-C and LDL-C was approximately 15-20 mg/dL in all age groups. The mean difference between non-HDL-C and LDL-C was 16.8 mg/dL in males and 17.0 mg/dL in females (P=0.370). In the subgroup analyses, the mean difference between non-HDL-C and LDL-C was higher in boys and girls with TG levels ≥ 150 mg/dL than in those with TG levels <150 mg/dL (39.93 mg/dL vs 14.50 mg/dL, P < 0.001 in males and 39.28 mg / dL vs 15.13 mg/dL, P<0.001 in females).

Conclusions: In apparently healthy Korean children and adolescents, the mean difference between non-HDL-C and LDL-C was approximately 20 mg/dL among both genders.

Keywords: Cardiovascular disease; Atherosclerosis; Dyslipidemia; Non-high-density lipoprotein cholesterol; Low-density lipoprotein cholesterol; Children; Adolescents

Introduction

Cardiovascular diseases (CVDs) are one of the most common causes of morbidity and mortality worldwide, including in the Republic of Korea [1,2]. It has been well established that atherosclerosis is closely related to CVDs and that hypercholesterolemia is one of the major risk factors for the development of atherosclerosis [3]. Atherosclerosis can begin early in a lifetime, even among children and adolescents [4]. Early recognition and age-specific intervention for the modifiable risk factors, such as hypercholesterolemia, are important to prevent the development of CVDs later in life.

Non-high-density lipoprotein cholesterol (non-HDL-C), which is estimated total cholesterol (T-C) minus high-density lipoprotein cholesterol (HDL-C), has been considered to be a predictor of atherosclerosis [5]. Recent studies have demonstrated that non-HDL-C can be used as an accurate predictor of CVD risk in adults [6,7]. It has been proposed as a potential substitute for low-density lipoprotein cholesterol (LDL-C) in terms of risk prediction of CVDs. To date,

LDL-C is considered to be a key parameter in CVD risk estimation and a primary target in CVD prevention in current clinical guidelines [8]. These guidelines recommended that non-HDL-C can be used when the concentration of triglyceride is high or as a secondary target after achieving the primary target, the concentration of LDL-C levels. The guidelines also suggest that non-HDL-C targets should be defined as the corresponding LDL-C targets + 30 mg/dL in adults. On the other hand, non-HDL-C in children and adolescents is considered to be a good or better predictor of adult dyslipidemia and subclinical atherosclerosis than other lipid measures, including LDL-C [9]. A recent US guideline, from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, recommended that non-HDL-C can be used in non-fasting children and adolescents as a universal screening tool for dyslipidemia [10]. However, the distribution of serum lipids varies with age and gender, ethnicity, and obesity [11]. It should be carefully applied the references from other nations and ethnicities. In addition, increasing evidence indicates that the difference between non-HDL-C and LDL-C (non-HDL-C – LDL-C) is lower than the expected 30 mg/dL difference in a general population [12]. However, there are scarce reports that evaluate the relationship between non-HDL-C and LDL-C in children and adolescents.

The current study aimed to identify the association between non-HDL-C and LDL-C according to age and gender in Korean children and adolescents aged 10-19 years old. Additionally, we evaluated the factors that can affect the difference between non-HDL-C and LDL-C using a nationally representative survey.

Methods

Subject

The present study was performed using data from the Korean National Health and Nutrition Examination Survey (KNHANES) from 2008-2014. The KNHANES is a cross-sectional, nationwide and population-based surveillance system and has been conducted annually since 1998 to evaluate the health and nutritional status of civilians or the non-institutionalized population of Republic of Korea [13]. The survey is undertaken by the Division of Chronic Disease Surveillance at the Korean Centers for Disease Control and Prevention. This nationally representative survey uses a stratified, multistage probability sampling design to select household units. The participants not only complete questionnaires, including a health interview survey, a health behavior survey, and a nutrition survey, but they also undergo a health examination survey that includes glucose and lipid profiles in a fasting state.

There are a total of 7,709 subjects aged 10 to 19 years old in the KNHANES from 2008-2014. Among these, 6,271 participants had complete anthropometric measurements and serum lipid levels from a fasting blood sample. Subjects who were diagnosed with type 1 or 2 diabetes mellitus (DM) or thyroid disease were excluded from this study. The presence of type 1 or 2 DM and thyroid disease were assessed using a self-reported questionnaire that the respective subjects had provided during the health interview. Children and adolescents who received current medication for hyperlipidemia were excluded. The administration of a relevant drug for more than 20 days each month was defined as current medication for hyperlipidemia. Additionally, the participants with serum TG concentrations ≥ 400 mg/dL were excluded because LDL - C was calculated using Friedewald's equation (LDL-C = total cholesterol – HDL - C – TG/5); this equation cannot be used when the triglyceride concentration is ≥ 400 mg/dL [14]. Finally, 6,255 children and adolescents (3,301 boys and 2,954 girls) were included in this study. Informed consent was provided by all participants of the KNHANES.

Anthropometric and Laboratory Measurements

Height, weight, waist circumference (WC), body mass index (BMI), and blood pressure (BP) were included in the anthropometric data. BMI was assessed using the following equation: the weight in kilograms divided by the square of the height in meters (kg/m^2). WC was determined at the area between the lower rib margins and the iliac crest to the nearest 0.1 cm. Systolic BP (SBP) and diastolic BP (DBP) were determined three times on the right upper arm using a calibrated sphygmomanometer with an appropriately sized cuff. Then, the mean of last two measurements was used for analysis.

Blood samples were obtained from all subjects after ≥ 8 hr of fasting. The collected specimens were centrifuged, frozen at -70°C and transported to a central laboratory (NeoDIN Medical Institute, Seoul,

Korea since 2008), where they were evaluated within 24 hr. Serum lipid concentrations, including T-C, HDL-C, and TG, were analyzed by an enzymatic method using an automated analyzer (Hitachi Automatic Analyzer 7600, Hitachi). The total coefficient of variation (CVs) for total cholesterol was 1.0% - 2.8%. The total CV for HDL-C was 0.9% -3.2%, and the total CV for triglycerides was 0.9% - 3.1%. The concentrations of LDL-C were determined using Friedewald's formula. Non-HDL-C was calculated as T-C – HDL-C. The difference between non-HDL-C and LDL-C was calculated as non-HDL-C – LDL-C.

Data collection of lifestyle characteristics

The lifestyle characteristics included smoking, alcohol drinking, and physical activity. Smoking was categorized into two groups: yes or no. Smoking was defined as ≥ 5 packs in one's lifetime. Alcohol drinking was divided into two groups: yes or no. Alcohol drinking was defined as ≥ 2 alcoholic beverages consumed in a week during the previous year. Physical activity was categorized into two groups: exercise or no exercise. Exercise was defined as intense physical activity for 20 min on ≥ 3 days/week, moderate physical activity for 30 min on ≥ 5 days/week, or walking for 30 min on ≥ 5 days/week.

Statistics

The data were analyzed using SPSS for Windows version 22 (IBM SPSS Inc., Chicago, IL, USA). The data are reported as the mean ± SD for the continuous variables and as percentages (%) for categorical variables. The differences in continuous variables were analyzed using a T-test and the differences in categorical variables were analyzed using a chi-squared test. LDL-C concentrations were divided into three groups: approximately < 75th, 75-94th, and ≥ 95th percentile concentration of LDL-C in this study. The mean of non-HDL-C – LDL-C was evaluated according to LDL-C concentration groups. To evaluate the association of non-HDL-C with LDL-C, we used a cross-table, and non-HDL-C levels were divided into three groups according to the aforementioned LDL-C group + approximate mean of non-HDL-C – LDL-C mg/dL. Two-tailed P values less than 0.05 were considered statistically significant.

Results

Clinical characteristics of the study population

The clinical characteristics of the participants are shown in Table 1. The males had a significantly higher mean height (164.13 cm vs 157.11 cm, P<0.001), weight (57.38 kg vs 50.26 kg, P<0.001), WC (71.48 cm vs 66.96 cm, P<0.001), BMI (20.97 kg / m^2 vs 20.19 kg/m^2, P<0.001), SBP (108.67 mmHg vs 103.76 mmHg, P < 0.001). DBP (66.85 mmHg vs 65.67 mmHg, P<0.001), and fasting glucose (90.17 mg/dL vs 88.98 mg/dL, P<0.001) than females and were more likely to be smokers (P<0.001), and individuals who perform physical activity (P=0.015).

The females had significantly higher mean age (14.25 years old vs 14.10 years old, P<0.036), T-C (162.46 mg/dL vs 154.74 mg/dL, P<0.001), HDL-C (55.49 mg/dL vs 52.43 mg/dL, P<0.001), LDL-C (89.89 mg/dL vs 85.53 mg/dL , P<0.001), and non-HDL-C (106.97 mg/dL vs 102.31 mg/dL , P<0.001) than males (Table 1).

	All subjects	Males	Females	P
	(n=6,255)	(n=3,301)	(n=2,954)	
Age (years)	14.2 ± 2.8	14.1 ± 2.7	14.2 ± 2.8	0.036
Height (cm)	160.8 ± 11.4	164.1 ± 12.7	157.1 ± 8.3	<0.001
Weight (kg)	54.0 ± 14.0	57.4 ± 15.6	50.3 ± 10.9	<0.001
WC (cm)	69.3 ± 9.8	71.5 ± 10.6	67.0 ± 8.2	<0.001
BMI (kg/m2)	20.6 ± 3.6	21.0 ± 3.8	20.2 ± 3.3	<0.001
SBP (mmHg)	106.4 ± 10.5	108.7 ± 11.0	103.8 ± 9.4	<0.001
DBP (mmHg)	66.3 ± 9.2	66.8 ± 9.9	65.7 ± 8.4	<0.001
Glucose (mg/dL)	89.6 ± 8.4	90.2 ± 7.2	89.0 ± 9.4	<0.001
Hb A1c (%)	5.5 ± 0.3	5.5 ± 0.3	5.5 ± 0.4	0.11
T-C (mg/dL)	158.4 ± 26.6	154.7 ± 27.0	162.5 ± 25.7	<0.001
HDL-C (mg/dL)	53.9 ± 10.7	52.4 ± 10.5	55.5 ± 10.6	<0.001
TG (mg/dL)	84.4 ± 46.2	83.9 ± 48.1	85.0 ± 44.0	0.367
LDL-C (mg/dL)	87.6 ± 22.8	85.5 ± 23.1	90.0 ± 22.2	<0.001
Non-HDL-C (mg/dL)	104.5 ± 25.2	102.3 ± 25.8	107.0 ± 24.4	<0.001
Smoker (%)	83 (1.3%)	62 (1.9%)	21 (0.7%)	<0.001
Alcohol drinker (%)	472 (7.5%)	251 (7.6%)	221 (7.5%)	0.886
Physical activity (%)	1,296 (20.7%)	723 (21.9%)	573 (19.4%)	0.015
The data are presented as the means ± standard deviations.				
WC: Waist Circumference; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; T-C: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglyceride; LDL-C: Low-Density Lipoprotein Cholesterol; Non-HDL-C: Non-High-Density Lipoprotein Cholesterol.				

Table 1: Clinical characteristics of the study population (n=6,255).

Non-HDL-C, LDL-C, and Non-HDL-C – LDL-C according to age and gender

The non-HDL-C, LDL-C, and non-HDL-C – LDL-C were investigated according to age and gender. The means, the standard deviations, and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of non-HDL-C, LDL-C, and non-HDL-C – LDL-C according to age and gender are expressed in Table 2. The mean non-HDL-C concentration was 102.3 mg/dL in males and 107.0 mg/dL in females (P<0.001). The mean non-HDL-C concentration was 110.5 mg/dL in 10-year-old boys, decreased to 96.4 mg/dL in 14-year-old boys and increased to 109.9 mg/dL in 19-year-old boys. In girls, the mean non-HDL-C concentration was 112.0 mg/dL in the 10-year-old age group and decreased modestly to 105.2 mg/dL in the 19-year-old age group. The 75th percentile of non-HDL-C concentrations was 117.0 mg/dL in boys and 121.0 mg/dL in girls, whereas the 95th percentile of non-HDL-C concentrations was 148.0 mg/dL in boys and 151.0 mg/dL in girls (Table 2).

Males										
Non-HDL-C										
Age	n	mean	SD	Percentile						
				5	10	25	50	75	90	95
10	347	110.5	23.1	78	83	94	109	123	143.2	151.6
11	374	107.2	24.7	71.8	77	88	105	123	142.5	151

Age	n	mean	SD	percentile						
12	381	103.3	27.6	67.2	74.2	86	97	116	136.8	151.7
13	377	99.6	24.4	63	70.8	83	97	112	133	143
14	396	96.4	24.8	58.9	69	79	94	111	126	138
15	346	98.5	25.2	61.4	68	80	96	115	128	143
16	296	100.4	28.2	62	69	81	97	113	135.9	154
17	298	97.7	24.2	63	68	80.8	97.5	112	128.1	137.1
18	270	101.9	26.5	64.6	71.1	81.8	99.5	116.3	133.9	149
19	216	109.9	25.6	70	78.7	93.3	108	125	147	155
Total	3,301	102.3	25.8	66	72	84	100	117	135	148
LDL-C										
10	347	95.2	21.5	63.6	70.2	79.8	94	107.8	124.5	133.6
11	374	91.2	22.3	84	65	74.4	89.8	107	122.4	129
12	381	87.3	25.1	53.3	60	70.9	84	89.6	117.2	129.1
13	377	82.3	20.8	52.2	57.1	68.6	80	93.8	111.2	120.4
14	396	80.7	22.5	47.4	56	65.5	77.8	94.6	108.1	117.6
15	346	81.5	22.4	48.2	54.7	65.8	78.5	95.9	110.6	117.8
16	296	83	25.1	46.5	56	66.4	81.1	94.6	111.2	128.4
17	298	80.5	21.8	47.7	54.8	65.2	79.1	94.8	107.9	119.8
18	270	84.5	22.9	49.9	57	68	82.5	98.9	114.6	124.5
19	216	89.7	21.8	56	62.8	76.3	88.5	103.2	117.5	125.1
Total	3,301	85.5	23.1	51.8	58.4	70	83.6	99.2	114.8	125
Non-HDL-C – LDL-C										
10	347	15.3	8.8	5.9	7.2	9.2	12.8	19.4	26.4	34.3
11	374	16.1	10.2	6	7.1	9.4	13.2	18.8	29.2	37.8
12	381	16	9.8	6.2	7.2	9.6	13.6	18.8	28	36.7
13	377	17.3	10.2	6.6	7.6	10.4	14.8	21.1	30.2	40
14	396	15.7	8.6	6.4	7.7	9.4	13.2	19.2	27.7	32.8
15	346	17	9.6	7.1	8	10.8	14.6	20.1	29.3	36.7
16	296	17.5	9.5	6.9	7.8	10.6	15.5	22.1	30.4	37.2
17	298	17.2	9.2	7.6	8.8	11	14.8	20.3	29.2	35
18	270	17.3	9.4	7.6	8.6	11	24.7	20.8	28.5	34.4
19	216	20.2	10.4	8.6	10.3	13	17.6	24.4	34.6	41.4
Total	3,301	16.8	9.6	6.6	7.8	10.2	14.4	20.4	29.2	35.8
Females										
Non-HDL-C										
Age	**n**	**mean**	**SD**	**percentile**						

				5	10	25	50	75	90	95
10	298	112	23.5	76	84	94	111	129	142	152
11	331	107.1	23.8	70.6	78	92	106	121	140	144.4
12	311	107.2	24.2	69.6	77	90	106	121	141	155.8
13	338	107	24.5	72	80.9	91.8	103	122	136.2	154.1
14	341	106.4	22.3	73	79	91	105	120	136	148
15	279	103.8	24.4	68	77	87	101	117	135	149
16	280	107.3	26.8	69	77	90	104	120.8	140	155
17	303	105.9	25	70.2	75.4	88	102	121	142.6	153
18	227	107.3	24.7	72.8	77.8	90	105	121	142.2	152
19	246	105.2	24.4	71	76	88.8	103	121.3	133.3	145
Total	2,954	107	24.4	71	78	90	105	121	139	151
LDL-C										
10	298	94.6	22.3	59.6	66.8	78	94	110.3	122	132.1
11	331	88	20.8	53.9	62.9	74.6	88	100.2	116	125.3
12	311	88.6	22.2	52.6	61.6	73	87	99.4	118.4	129.8
13	338	89.8	22.7	58.6	64.5	76.2	86	103.1	116.8	132.8
14	341	89	20.9	56.9	63.3	75.8	89	101.2	115.3	127.5
15	279	87.3	21.5	55.6	63.8	72	86	99.2	116.2	127.2
16	280	91.4	24	58.2	62.6	75.4	89	104.7	122.8	131.4
17	303	90.8	22.8	59.1	65.3	74.4	88	103.4	121.6	135.6
18	227	91.6	22.2	61.7	65.6	75.4	89	104.6	120.8	134.6
19	246	89.4	21.7	57.6	63.3	75.5	88	102.9	116.5	122.7
Total	2,954	90	22.2	54.6	64	75	88	102.8	118.5	128.9
Non-HDL-C – LDL-C										
10	298	17.4	8.6	6.8	8.4	11.4	16	21.4	28.2	32
11	331	19.1	10.3	7.6	8.8	11.8	17	24	32.2	39.6
12	311	18.7	9.3	8	9.4	12.8	17	22.2	29.3	34.6
13	338	17.2	8.9	7.4	8.8	11.4	15	20.6	26.3	35.4
14	341	17.5	8.9	7.6	9.2	11.4	15	21.3	29.6	36.1
15	279	16.5	8.9	7.4	8.6	10.6	14	20	26.2	32.6
16	280	15.9	8	7	8.2	10.6	14	18.7	24.8	33.3
17	303	15.1	7.4	6.6	7.6	9.6	14	18.4	23.6	29.6
18	227	15.8	7.1	7.6	8.6	11	14	18.8	25.4	30.1
19	246	15.8	8.9	6.7	7.8	10.2	14	18.6	25.9	31.3
Total	2,954	17	8.8	7.4	8.4	11	15	20.4	27.6	33.4

SD: Standard Deviation; **non-HDL-C**: Non-high-density Lipoprotein Cholesterol; **LDL-C**: Low-Density Lipoprotein Cholesterol

Table 2: Means and standard deviations for non-HDL-C – LDL-C according to age and gender in Korean children and adolescents aged 10-19 years (n=6,255).

The mean LDL-C concentration was 85.5 mg/dL in males and 90.0 mg/dL in females (P<0.001). The mean LDL-C concentration was 95.2 mg/dL in the 10-year-old group, decreased to 80.7 mg/dL in the 14-year-old age group and increased modestly to 89.7 mg/dL in the 19-year-old age group among boys. The mean LDL-C concentration was 94.6 mg/dL in 10-year-old girls, decreased to 87.3 mg/dL in 15-year-old girls and increased modestly to 89.4 mg/dL in 19-year-old girls. The 75th percentile of LDL-C concentrations was 99.2 mg/dL in boys and 102.8 mg/dL in girls, whereas the 95th percentile of LDL-C concentrations was 125.0 mg/dL in boys and 128.9 mg/dL in girls.

The mean of non-HDL-C – LDL-C was 16.78 mg/dL in males and 16.99 mg/dL in females (P=0.370). The mean of non-HDL-C – LDL-C was 15.34 mg/dL in 10-year-old boys and increased modestly to 20.23 mg/dL in 19-year-old boys. In girls, the mean of non-HDL-C – LDL-C was 17.41 mg/dL in the 10-year-old age group and decreased modestly to 15.84 mg/dL in the 19-year-old age group. The 50th percentile of non-HDL-C – LDL-C was 14.4 mg/dL in males and 15.2 mg/dL in females. The 75th percentile of non-HDL-C – LDL-C was 20.4 mg/dL in boys and 20.4 mg/dL in girls, whereas the 95th percentile of non-HDL-C – LDL-C was 35.8 mg/dL in boys and 33.4 mg/dL in girls.

The mean concentration of non-HDL-C and non-HDL-C – LDL-C according to LDL-C concentration

The mean concentrations of non-HDL-C and non-HDL-C – LDL-C according to the LDL-C concentration were examined in all participants. The LDL-C levels were categorized into three groups: approximately < 75th, 75-94th, and ≥ 95th percentile. The 75th and 95th percentiles of LDL-C concentrations were 100 mg/dL and 130 mg/dL for both genders. The mean concentrations of non-HDL-C were 92.0 mg/dL for boys with LDL-C concentrations < 100 mg/dL, 129.1 mg/dL for boys with LDL-C concentrations from 100-129 mg/dL, and 166.5 mg/dL for boys with LDL-C concentrations ≥ 130 mg/dL. In girls, the mean concentrations of non-HDL-C were 95.7 mg/dL for those in the LDL-C <100 mg/dL group, 128.8 mg/dL for those in the LDL-C 100-129 mg/dL group, and 163.8 mg/dL for those in the LDL-C ≥130 mg/dL group (Table 3).

	Male			**Female**		
	<100	100-129	≥130	<100	100-129	≥130
	n=2,508	n=671	n=122	n=2,098	n=713	n=143
Non-HDL-C	92.0 ± 17.4	129.1 ± 13.0	166.5 ± 25.5	95.7 ± 16.0	128.8 ± 12.0	163.8 ± 17.7
Non-HDL-C – LDL-C	16.3 ± 9.3	18.2 ± 9.6	20.2 ± 10.5	16.78 ± 8.9	17.3 ± 8.1	19.9 ± 10.2
The data are presented as the means ± standard deviations						
LDL-C: Low-density Lipoprotein Cholesterol; **non-HDL-C**: Non-high-density Lipoprotein Cholesterol						

Table 3: Means and standard deviations for non-HDL-C and non-HDL-C – LDL-C according to the 75th and 95th percentile concentrations of LDL-C from the current study in Korean children and adolescents aged 10-19 years (n=6,255).

For boys, the mean concentrations of non-HDL-C – LDL-C were 16.3 mg/dL for those in the LDL-C < 100 mg/dL group, 129.1 mg/dL for those in the LDL-C 100-129 mg/dL group, and 166.5 mg/dL for those in the LDL-C ≥130 mg/dL group. The mean concentrations of non-HDL-C were 95.7 mg/dL in girls with a LDL-C concentration < 100 mg/dL, 128.8 mg/dL in girls with a LDL-C concentration from 100-129 mg/dL, and 163.8 mg/dL in girls with a LDL-C concentration ≥ 130 mg/dL.

Association between non-HDL-C and LDL-C

The relationship between non-HDL-C and LDL-C was evaluated in all participants. The results are presented in Table 4 under the assumption that non-HDL-C was estimated as the 75th and 95th percentile concentrations of LDL-C + the approximate mean of non-HDL-C – LDL-C (20 mg/dL). In this study, estimated non-HDL-C agreed with the 75th and 95th percentile concentrations of non-HDL-C, which were 120 mg/dL and 150 mg/dL, respectively. In the lowest LDL-C concentration (LDL-C <100 mg/dL) group, the greatest overlap was observed between LDL-C and non-HDL-C corresponding to LDL-C + 20 mg/dL in males and females (Table 4).

Males and females with a LDL-C concentration from 100-129 mg/dL exhibited the greatest overlap with non-HDL-C concentrations from 120-149 mg/dL, corresponding to LDL-C + 20 mg/dL. A total of 25.2% of males and 24.1% of females with LDL-C levels from 100-129 mg/dL were classified into the non-HDL-C < 120 mg/dL group, whereas 66.9% of males and 70.1% of females were classified into the non-HDL-C 120-149 mg/dL group. Additionally, 78.7% of males and 82.5 % of females with LDL-C levels ≥ 130 mg/dL had non-HDL-C levels ≥ 150 mg/dL, corresponding to LDL-C + 20 mg/dL. A total of 25.2% of males and 24.1% of females with LDL-C levels ≥ 130 mg/dL were classified into the non-HDL-C 120-149 mg/dL group, which did not correspond to LDL-C + 20 mg/dL.

Non-HDL-C (mg/dL)						
	< 120	120-149	≥ 150		< 120	120-149	≥ 150
Males				**Females**			
LDL-C (mg/dL)				**LDL-C (mg/dL)**			
<100 (n=2,508)	2,397 (95.6%)	108 (4.3%)	3 (0.1%)	<100 (n=2,098)	1,986 (94.7%)	109 (5.2%)	3 (0.1%)
100-129 (n=671)	169 (25.2%)	449 (66.9%)	53 (7.9%)	100-129 (n=713)	172 (24.1%)	500 (70.1%)	41 (5.8%)
≥130 (n=122)	0 (0%)	26 (21.3%)	96 (78.7%)	≥130 (n=143)	0 (0%)	25 (17.5%)	118 (82.5%)

The data are expressed as the number of subjects (percentage) who were classified into their respective non-HDL-C group according to their LDL-C concentration. In the shaded cells, the number (percentage) of non-HDL-C is shown in accordance with LDL-C concentration + 20 mg/dL.

Non-HDL-C: Non-high-density Lipoprotein Cholesterol; **LDL-C**: Low-density Lipoprotein Cholesterol

Table 4: Cross-table between LDL-C and non-HDL-C corresponding to LDL-C + 20 mg/dL in Korean children and adolescents aged 10-19 years (n=6,255).

Association of non-HDL-C with LDL-C according to TG concentration

Further analyses were performed to determine whether the relationship between non-HDL-C and LDL-C was affected by TG levels (normal: TG < 150 mg/dL vs high: TG ≥ 150 mg/dL). The means ± standard deviations of non-HDL-C – LDL-C were 14.50 ± 5.92 mg/dL in males with normal TG levels and 15.13 ± 5.66 mg/dL in females with normal TG levels. In children and adolescents with a high TG, the means ± standard deviations of non-HDL-C – LDL-C were 39.93 ± 5.92 mg/dL in males and 39.28 ± 9.21 mg/dL in females. Additionally, the sub analyses were stratified according to a TG concentration of 150 mg/dL, as shown in supplementary Table 1 and 2. In males and females with TG <150 mg/dL and who were in the lowest LDL-C concentration (LDL-C < 100 mg/dL) group, the greatest overlap was observed between LDL-C and non-HDL-C concentrations that corresponded with LDL-C + 20 mg/dL (Supplementary Table 1).

The greatest overlap was found between males and females who had a LDL-C concentration from 100-129 mg/dL, normal TG levels and a non-HDL-C concentration < 150 mg/dL. A total of 70.0% of males and 72.1% of females with a LDL-C concentration from 120-139 mg/dL and a normal TG concentration exhibited a non-HDL-C concentration from 120-149 mg/dL, corresponding to LDL-C + 20 mg/dL, whereas 28.5% of males and 26.4% of females had a non-HDL-C concentration <120 mg/dL, which did not correspond to LDL-C + 20 mg/dL. In males and females with a high TG, the greatest overlap was observed between those who had a LDL-C concentration < 100 mg/dL and who were in the non-HDL-C group, corresponding to LDL-C + 20 mg/dL (Supplementary Table 2). The greatest overlap for those with a LDL-C concentration ≥130 mg/dL was with a non-HDL-C concentration ≥ 150 mg/dL; the greatest overlap for those with a LDL-C concentration from 100-129 mg/dL was with a non-HDL-C concentration ≥ 150 mg/dL, which did not correspond with LDL-C + 20 mg/dL.

Discussion

The current study identified the age- and gender-specific difference between non-HDL-C and LDL-C concentrations in Korean children and adolescents. The mean 75th percentile and 95th percentile concentrations among both genders were approximately 120 mg/dL and 150 mg/dL for non-HDL-C, respectively, and 100 mg/dL and 130 mg/dL for LDL-C, respectively. The mean age- and gender-specific difference between non-HDL-C and LDL-C was approximately 15-20 mg/dL in all age groups from 10 to19 years old among boys and girls. The mean of non-HDL-C – LDL-C was 16.78 mg/dL in males and 16.99 mg/dL in females, which was lower than the 30 mg/dL difference indicated in most clinical guidelines; there was no significant difference in the mean of non-HDL-C – LDL-C between males and females. The mean difference between non-HDL-C and LDL-C was significantly higher in children and adolescents with TG concentrations ≥ 150 mg/dL than in those with TG concentrations < 150 mg/dL. Non-HDL-C has some advantages in clinical practice. Non-HDL-C is not affected by the fasting state, whereas LDL-C can be determined only in a non-fasting condition. Non-HDL-C includes all atherogenic lipoproteins, such as LDL, lipoprotein (a), intermediate-density lipoprotein (IDL), and very-low-density lipoprotein (VLDL) remnants [14]. Non-HDL-C is convenient to calculate because it is simply T-C minus HDL-C. It may be more appropriate to educate children and adolescents with dyslipidemia, their parents, and the general population. Non-HDL-C can be understood as a marker that means "all but the good cholesterol", whereas LDL-C is considered to be "a type of bad cholesterol". In addition, recent reports have suggested that non-HDL-C is considered to be good or better than other cholesterols, such as LDL-C or T-C, in children, adolescents [9,15], and adults [16]. In contrast to adult non-HDL-C, which is not used as screening index during health checkups for the identification and treatment of high risk for CVDs in guidelines of the US [8], Europe [14] and Japan [15], childhood non-HDL-C is recommended for use in non-fasting children and adolescents as a screening tool for dyslipidemia in recent US guidelines [10]. The guidelines recommended universal screening with non-fasting non-HDL-C among children and adolescents, first at ages 9-11 years and again at ages 17-21 years, as the first step to identify children and adolescents with lipid disorders that predispose them to accelerated atherosclerosis. With the exception of US guidelines, other guidelines do not recommend non-HDL-C for dyslipidemia screening in children and adolescents. However, recent reports from Korea and Japan demonstrated the distribution of non-HDL-C in children and adolescents [17,18]. In another Japanese study, the mean concentration of non-HDL-C was 112.9 mg/dL in boys with abdominal obesity, 135.4 mg/dL in boys with pre-MetS (abdominal obesity plus one component of MetS), and 149.0 mg / dL in boys with MetS [19]. In a report of Japanese schoolchildren, approximately 15% (26 of 176) of subjects who were screened using T-C criteria were mis categorized as having hyperlipidemia because they had high HDL-C levels (≥ 90 mg / dL) [20]. In their study, none of those who were screened with the non-HDL-C criteria were mis categorized as hyperlipidemic. Based on these studies, non-HDL-C may be applicable for the screening of dyslipidemia in children and adolescents from other countries, including Korea and Japan.

The target level of non-HDL-C for the management of hypercholesterolemia in adults is set at a concentration of LDL-C + 30 mg/dL according to the guidelines of the NCEP-ATP III, the ESC/EAS and the JAS [9,14,15]. However, there are some limitations of these guidelines regarding the screening of dyslipidemia in the general

population, including children, adolescents and adults. Because the guidelines were established using results from patients with dyslipidemia, non-HDL-C for the screening of dyslipidemia may not be valid for practical use in a general population. A recent report suggests that in apparently healthy adults, LDL-C levels of 70 mg/dL and 100 mg/dL correspond to non-HDL-C levels of 93 mg/dL and 125 mg/dL, respectively [21]. In a study from the limiting under treatment of lipids in ACS with rosuvastatin (LUNAR) trial, an LDL-C value of 74 mg/dL corresponded to a non-HDL-C value of 92 mg/dL in subjects with acute coronary syndrome who were treated with high-dose statin therapy [22]. A recent Japanese study reported that the mean difference between non-HDL-C and LDL-C concentrations was approximately 20 mg/dL for men and women in two different regions [23]. In the pediatric field, Abe et al. reported that a non-HDL-C concentration ≥ 122 mg/dL in males and ≥ 125 mg/dL in females was considered borderline high risk (highest 75th percentile) and a non-HDL-C concentration ≥ 152 mg/dL in males and ≥159 mg/dL in females indicates high risk (highest 95th percentile) in non-fasting children and adolescents aged 9-16 years [18]. This Japanese study suggested that non-HDL-C levels may be below LDL + 30 mg/dL [18]. In the present study, the difference between non-HDL-C and LDL-C concentrations was less than 30 mg / dL and was approximately 20 mg/dL in Korean children and adolescents aged 10-19 years. Moreover, the borderline high risk (highest 75th percentile) and high risk (highest 95th percentile) concentrations of non-HDL-C were in accordance with the corresponding LDL-C concentration + 20 mg/dL in our study. These results agreed with the results of a previous adult study.

In our study, approximately 20% of children and adolescents with LDL ≥ 130 mg/dL exhibited non-HDL-C concentrations from 120-149 mg/dL, which is considered as borderline high risk. However, they cannot be identified when non - HDL - C is used without other cholesterol profiles. To identify children and adolescents with low non-HDL-C but high LDL-C, the cut-off values of non-HDL-C should be set below LDL - C + 20 mg/dL (Supplementary Table 3). Non-HDL-C levels ≥ 145 mg/dL correspond to LDL-C + 15 mg/dL, which was the lowest difference between non – HDL - C and LDL - C concentrations according to age and gender; when this criterion was applied as a cut-off value, 8% of boys and girls with LDL - C levels ≥ 130 mg/dL were classified as having borderline high non - HDL - C (110 - 144 mg/dL). Approximately 45% of boys and 35% of girls who were classified as having high non - HDL - C (≥ 145 mg/dL) did not exhibit LDL-C levels ≥ 130 mg/dL. The cut-off value of non- HDL - C ≥ 145 mg/dL may be related to an increased need for a lipid profile in an individual perspective and to increased medical expenses in a social perspective compared with a cut-off value of non-HDL-C ≥150 mg/dL. From a personal to a national aspect, the best cut-off value of non-HDL-C for the prevention and control of cholesterol in children and adolescents should be determined with caution.

There were several limitations of this study. The results were based on cross-sectional data. We can only evaluate the association between non - HDL - C and LDL - C concentrations at one point, but we cannot trace the fluctuations in cholesterol for a given child according to age. We were unable to evaluate the relationship of the difference between non - HDL - C and LDL - C concentrations with pubertal stage. We could not assess the BMI standard deviation score (SDS) but could present raw BMI because KNHANES does not provide the exact chronological age, which is needed to determine the BMI SDS. We could not evaluate the relationship between non – HDL - C and LDL - C according to obesity or overweight, which can influence the non -

HDL - C concentration [24]. Finally, the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents defined non-HDL-C levels < 120 mg/dL as acceptable, non-HDL-C levels from 120-144 mg/dL as borderline high, and non-HDL-C levels ≥ 145 mg/dL as high [10]. The definitions for non-HDL-C are based on the Bogalusa Heart Study [9,15]. The distributions of cholesterol level were different from those reported in a local biracial community study; the 75th percentile concentration of non - HDL - C was 123 mg/dL in boys aged 6 - 19 years and 123 mg/dL in girls aged 6 - 19 years, and the 95th percentile concentration of non-HDL-C was 161 mg/dL and 156 mg/dL in boys and girls, respectively [24]. A large-scale prospective study should be conducted to determine the validity of non-HDL-C cut-off values for the screening of Korean children and adolescents.

In conclusion, a nationally representative and cross-sectional study evaluated the association between non-HDL-C and LDL-C according to age and gender in Korean children and adolescents aged 10-19 years. The 75th and 95th percentile concentrations of non-HDL-C in both genders were approximately 120 mg/dL and 150 mg/dL, respectively. The 75th and 95th percentile concentrations of LDL-C for boys and girls were approximately 100 mg/dL and 130 mg/dL, respectively. The age- and gender-specific difference between non-HDL-C and LDL-C ranged approximately from 15 mg/dL to 20 mg/dL in all age groups. The mean difference between non - HDL - C and LDL - C was approximately 20 mg/dL in both genders. The 75th and 95th percentile concentrations of non-HDL-C were 120 mg/dL and 150 mg/dL, which corresponded to LDL - C + 20 mg/dL. The difference between non-HDL-C and LDL-C was greater in children and adolescents with TG levels ≥ 150 mg/dL than in those with TG levels < 150 mg/dL. Our results may provide valuable information for strategies that seek to identify children and adolescent with dyslipidemia.

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