A 23 year follow-up study of serum lipids change and tracking from adolescence to adulthood: The Kangwha Study

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A 23 year follow-up study of serum lipids change and tracking from adolescence to adulthood: The Kangwha Study

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

A 23 year Follow-up Study of Serum Lipids Change and Tracking from Adolescence to Adulthood: The Kangwha Study

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(Directed by Professor Hyeon Chang Kim)

INTRODUCTION:

Many risk factors of cardiovascular disease (CVD) show tracking pattern from childhood. So, early detection of such risk factors is important for prevention of cardiovascular disease. Serum lipid profile is well-known CVD risk factor. Several studies have examined tracking pattern of lipid profile level during long

follow-up periods in Western countries, but these studies are still rare in East Asia. The objectives of this study are to evaluate tracking pattern of serum lipid profile level from adolescence to adulthood in Korea and to evaluate the association between lipid profile level at adolescence and the incidence of adult dyslipidemia.

METHODS:

A total of 400 adolescents (186 male and 214 female) was enrolled in this study. Total cholesterol, triglyceride, and high density lipoprotein (HDL) cholesterol level of study participants were measured at least once during 1992-1996, and were repeatedly measured at least once during 2005-2015. Body mass index (BMI), waist circumstance, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured, and family history of CVD, smoking history, and presence of adult dyslipidemia was checked. The tracking coefficients of lipid profiles were calculated by Generalized Estimating Equation. The association and predictability between serum lipid profile levels at adolescence and adult dyslipidemia was assessed by multiple logistic regression and area under curve (AUC) value. Additional analyses were performed to find out whether repeated lipid profile measurements during adolescence can enhance the predictability of adult dyslipidemia or not.

RESULTS:

The presence of adult dyslipidemia was 26.3%. When adjusted for age, BMI, waist circumstance, SBP and DBP, tracking coefficient of total cholesterol was 0.64, that of triglyceride was 0.54, and that of HDL cholesterol was 0.58. When adjusted for age, BMI, SBP, family history of CVD, and smoking history, increased total cholesterol level at adolescence was associated with adult dyslipidemia (odds ratio [OR], 1.47; 95% CI, 1.05-2.05, per 1 SD unit increase). Meanwhile, decreased HDL cholesterol level at adolescence was associated with adult dyslipidemia (OR, 0.54; 95% CI, 0.37-0.77, per 1 SD unit decrease). The addition of serum lipid profile level into the model significantly enhanced the AUC value ($p=0.02$ for total participants, $p=0.03$ for male, and $p=0.01$ for female). But the use of the average lipid profile levels of repeated measurements dose not enhanced AUC value ($p \geq 0.26$ for total participants, $p \geq 0.42$ for male, and $p \geq 0.23$ for female).

CONCLUSION:

Moderate tracking patterns of serum lipid profile level were shown in this study. Serum lipid profile measurements at adolescence could help adult dyslipidemia prediction. Increased total cholesterol and decreased HDL cholesterol at

adolescence was associated with adult dyslipidemia. The results of this study supported the importance of lipid profile screening at adolescence for CVD prevention.

Keywords: dyslipidemia, lipid profile, tracking coefficients, predictability

A 23 year Follow-up Study of Serum Lipids Change and Tracking from Adolescence to Adulthood: The Kangwha Study

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I. INTRODUCTION:

1. Background

Dyslipidemia, defined as abnormal blood lipid profile level, is established risk factor of cardiovascular disease (CVD) and premature death (Lewington et al., 2007, Smith, 2007, Di Angelantonio et al., 2009). While the prevalence of dyslipidemia was decreased in Unite States, it has recently increased in Korea (Ha

et al., 2015, Beltrán-Sánchez et al., 2013). And during 2010-2012, hypercholesterolemia prevalence in Korea was 12.6% for male and 14.9% for female, and hypertriglyceridemia prevalence in Korea was 22.9% for male and 10.4% for female, respectively (Ha et al., 2015). Thus, special efforts need to be made to inhibit progress of CVD or to stave off dyslipidemia incidence. Many researches in Western countries have shown that some risk factors of CVD including lipid profile had tracking pattern (Wilsgaard et al., 2001, Ulmer et al., 2003, Bugge et al., 2013, Joshi et al., 2014). Tracking means the correlation between subsequent measurements (Twisk, 2003), which indicates that early detection of abnormal lipid profile level was important for managing adult dyslipidemia (Srinivasan et al., 2006, Nuotio et al., 2015). Generally, serum lipid level was increased up to 2 years old, and is stabilized during 2-10 years old (Wynder et al., 1989). Since puberty stage, serum lipid level decreases at the beginning, but increases gradually later (Kim et al., 2012, Ford et al., 2009).

Recently, the U.S. National Heart, Lung, and Blood Institute (NHLBI), recommended universal lipid screening during 9-11 years and 17-21 years old (National Heart Lung and Blood Institute, 2012). This guideline was adopted at 2015, in Korea (Korean Society of Lipidology and Atherosclerosis, 2015). However, there is little evidence to show that tracking patterns are consistent from childhood to adulthood in East Asian people. There have been only a few studies

that address this issue in East Asia, and these studies had relatively short follow-up periods (Tan et al., 2000, Lee et al., 1997).

2. Objective

The aim of this study is to evaluate tracking pattern of serum lipid profile level from adolescence to adulthood in Korea. Another aim is to evaluate the association and predictability of lipid profile level at adolescence on adult dyslipidemia. In addition, the effects of repeated measurements at adolescence on enhancement of the predictability of adult dyslipidemia were evaluated. The Kanghwa study has lasted over 23 years and such long follow-up period makes it possible to investigate this issue.

II. METHODS

1. Study participants

The Kangwha study was a community-based prospective cohort study, which was started in 1986 with 484 children at Kangwha area in Korea. The participants of Kangwha study were first-grade students of elementary school, and most of them were 6-years old. The follow-up study was conducted for the Kangwha study participants, and at the same time, several expansions that targeted same-grade students of original Kangwha study participants were done during 1987-1997. For all Kangwha study participants, four adults follow-up study have been made (wave 1: 1999-2001, wave 2: 2005, wave 3: 2010-11, wave 4: 2014-15). In 1992, 1994, and 1996, lipid profile measurements were done. I chose 875 participants who had measured lipid profile at least once during this period. Among the 875 participants, 400 participants who measured lipid profiles at adult (at least once during wave 2-4) enrolled in this study (Figure 1). Informed consent was obtained from all participants of this study, and study protocol was approved by Institutional Review Board, Yonsei University Graduate School of Public Health (4 2-1040939-AB-N-01-2016-164).

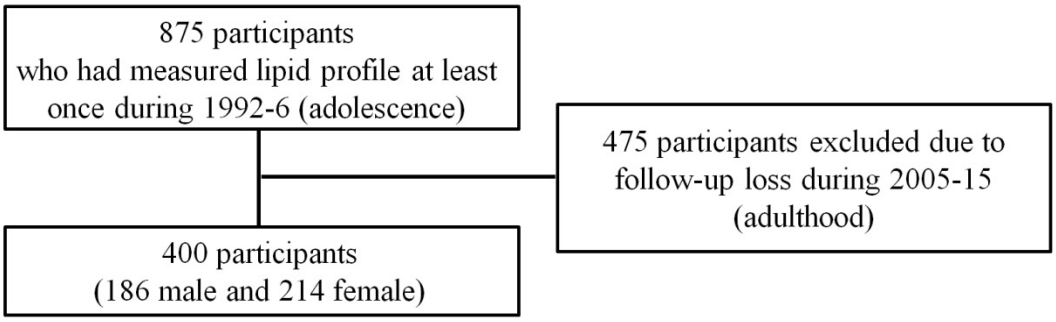


Figure 1. Flowchart of the selection of study participants

2. Measurements

The participant's age was calculated by subtracting birthdate from examination date. During 1992-1996, I could not confirm the exact date of individual examination. However, since the examination was conducted from late August to early September each year, I assumed all examinations to be done at September 1. Accordingly, the participant's age was obtained by subtracting his/her birthdate from September 1. Standing height and weight of each study participant was measured down to 0.1 cm and 0.1 kg. During 1992-1996, weight was measured in pounds (ib), so I converted it to kilograms by multiplying 0.453592. I calculated body mass index (BMI) by dividing the weight (kg) by the square of the height (m^2). Waist circumstance was measured down to 0.1 cm at umbilical level during 1992-1996, at iliac crest in wave 2, and at between the inferior margin of the last rib and the iliac crest since wave 3 in a horizontal line.

Disease history and family history of CVD were examined at adult follow-up study only. Hypertension was determined when systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or when a participant has self-reported history based on physician's diagnosis. Dyslipidemia was determined when total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/dL, HDL cholesterol ≤ 40 mg/dL, triglyceride ≥ 200 mg/dL, or when a participant has self-

reported history based on physician's diagnosis. Smoking and alcohol drinking status was evaluated by interview using standardized questionnaire.

Lipid profile measurements were performed using blood samples after overnight fasting state. Total cholesterol, triglyceride, and HDL cholesterol were measured by enzymatic methods (Hitachi-747, Japan during 1992-1996, Hitachi-7150, Japan at wave 2, ADVIA 1650, USA at 2010 (wave 3), and ADVIA 1800, USA since 2011 (wave 3, 4). LDL cholesterol was calculated using Friedewald formula when blood triglyceride < 400 mg/dL (Friedewald et al., 1972).

3. Statistical analysis

General characteristics of study participants at enrollment and last follow-up were represented by mean and standard deviation (SD) or number and proportion. Because study participants did not participate in all measurements, I used lipid profile levels at enrollment as adolescence lipid profile level for this analysis. Among 400 participants, 78% of them was come from measurement information at 1992, 3% of them was used from measurement information at 1994, and 19% of them was from measurement information at 1996. For adult follow-up examination, I used data at the time of dyslipidemia diagnosis. For those who

were not diagnosed participants, data at the last follow-up period were used. Overall, 34% of participants' information was come from data at wave 2, 43% of participants' information was come from data at wave 3, and 23% of participants' information was come from data at wave 4. Age, sex, BMI, SBP at adolescence, adult current smoking, adult BMI, and family history of CVD were used as covariates. A total of 2 participants showed covariate vacancy. In this case, I used data from next measurements. Then, I compared the difference of lipid profile and other characteristics of participants according to conducting adult follow-up examination. T-test and chi-square were used for this purpose.

The tracking patterns were evaluated by three methods. First, the tracking pattern visualized in several figures which track the change of median value of baseline group with time. For this purpose, each lipid profile value at 16-years old (measurement year=1996) was divided into four groups, according to quartile value of lipid profile, since the number of participants was greater than other measurement years (n=376). Then, the median values of each baseline groups at each follow-up examination were presented. Second, the correlation between two measurements each year was presented by Spearman and Pearson correlation coefficients. From 16-years old to 35-years old of study participants, each correlation coefficient between all measurements was presented. Third, since these coefficients could manage only two measurements, I calculated the tracking

coefficients using Generalized Estimating Equation in order to evaluate the overall correlation. The formula to calculate the tracking coefficient is as follows:

$$Y_{it} = \beta_0 + \beta_1 Y_{it1} + \beta_2 t + \sum_{j=1}^{J} \beta_{3j} X_{ijt} + \varepsilon_{it}$$

In the above formula, Y_{it} is the observations for subject i at time t, and Y_{it1} is the first observation for subject i. X_{ijt} is the j-th covariate for subject i at time t (the number of total covariates = J), and ε_{it} indicates the error term. Detailed information on the formula was introduced in(Twisk, 2003). Among regression coefficients β, the standardized β_1 is the tracking coefficient. To obtain the standardized β_1, I multiply the SD of Y_{it1} to β_1, divided by the SD of Y_{it}. Correlations between the initial measurement and all other remaining measurements are integrated into a single tracking coefficient, β. The tracking coefficient has competitive strength when unbalanced data sets are used because it can handle missing values and data with unequal time interval. Besides, other strength of the tracking coefficient is that it allows the adjustment of possible confounders. For calculating the tracking coefficient of lipid profile, I analyzed 1,000 measurements for 400 participants based on lipid profile levels at 16-years old. The tracking coefficients for male, female, and both of participants were

calculated, and I analyzed the adjusted tracking coefficient by adjusting sex, age, body mass index, waist circumstance, SBP, and DBP for each measurement. For confirmation of the value of tracking coefficients, tracking coefficients were compared to those using Linear Mixed Model. To solve the problem of multiple comparisons, the Bonferroni correction was used. The study participants took part in up to four measurements, so p-values < 0.013 were considered to be statistically significant for this comparison.

In order to evaluate the association and predictability of lipid profile level at adolescence for adult dyslipidemia, the odds ratio (OR) and the area under curve (AUC) from receiver operating characteristic (ROC) curve were used for multiple logistic regressions. The Goodness-of-fit of was evaluated by Hosmer-Lemeshow test. The analysis to find out the association between lipid profile level at adolescence and adult dyslipidemia was conducted, including all study participants (n=400). Sex-separated analyses were conducted, too. The AUCs of the model including lipid profile level and that of the model without lipid profile level were compared. For evaluating whether repeated measurement during adolescence enhanced the predictability of adult dyslipidemia, the study participants who had available lipid profile levels both at 14-years old (measurement year = 1994) and 16-years old (measurement year = 1996). The AUCs of the model using lipid profile levels at age 14, age 16, and using average

lipid profile level were compared. Unless otherwise noted, p-values <0.05 were considered to be statistically significant, and all analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

III. RESULTS

1. General characteristics of study participants

Table 1 shows the general characteristics of total study participants where the increase of SBP, waist circumstance, BMI, total cholesterol, and HDL cholesterol are illustrated. Otherwise, DBP and triglyceride were decreased at last follow-up. The SD difference of the general characteristics between enrollment period and last follow-up period does not show notable increase or decrease when compared to the SD of the general characteristics at enrollment or last follow-up period. The mean age at enrollment is 13.8 years-old, and the mean age at last follow-up is 30.1 years-old. The 46.5% of total participants are male. The prevalence of adult dyslipidemia is observed to be 26.3 %. Family history of CVD, hypertension, dyslipidemia, smoking, and drinking was evaluated only adulthood follow-up periods, so the information at last follow-up was presented.

Table 2 shows the difference of the general characteristics between respondents and non-respondents to adult follow-up examination. Except for triglyceride, all characteristics do not show significant difference.

Table 1. General characteristics of total study participants at adolescence and adulthood

Characteristics	At enrollment (n=400)	At last follow-up (n=400)	Difference
Age, years	13.8 ± 1.6	30.1 ± 3.7	16.3 ± 3.8
Systolic blood pressure, mmHg	112.3 ± 10.6	117.0 ± 14.3	4.8 ± 15.5
Diastolic blood pressure, mmHg	72.2 ± 8.7	70.9 ± 9.1	-1.3 ± 11.2
Weight circumstance, cm	65.7 ± 7.1	79.4 ± 8.6	13.7 ± 8.9
Body mass index, kg/m^2	19.4 ± 3.1	22.7 ± 3.3	3.3 ± 3.3
Total cholesterol, mg/dL	159.5 ± 26.8	177.7 ± 33.6	17.8 ± 32.1
Triglyceride, mg/dL	101.9 ± 41.4	101.1 ± 68.5	-0.8 ± 70.7
HDL cholesterol, mg/dL	46.7 ± 8.8	54.1 ± 13.3	7.5 ± 12.6
LDL cholesterol, mg/dL*	93.9 ± 22.0	103.0 ± 29.1	8.4 ± 28.8
Sex (male)	186 (46.5)	186 (46.5)	
Family history of CVD	Not examined	42 (10.5)	
Hypertension	Not examined	33 (8.3)	
Dyslipidemia	Not examined	105 (26.3)	
Current smoking	Not examined	123 (30.8)	
Current drinking	Not examined	234 (58.5)	

Data is expressed as mean ± SD or number (%). Abbreviation: HDL, high density lipoprotein, LDL, low density lipoprotein. CVD, cardiovascular disease *The number of participants was 324 at enrollment, 397 at last f/u, and 321 for difference due to missing.

Table 2. Comparison of baseline characteristics between respondents and non-respondents to adult follow-up examination

Characteristic at enrollment	Respondents to adult f/u (n=400)	Non-respondents to adult f/u (n=475)	p value
Age, years	13.8 ± 1.1	13.65 ± 1.5	0.25
Systolic blood pressure, mmHg	112.3 ± 10.6	112.2 ± 10.5	0.85
Diastolic blood pressure, mmHg	72.2 ± 8.7	72.9 ± 8.4	0.24
Weight circumstance, cm	65.7 ± 7.1	65.6 ± 7.8	0.93
Body mass index, kg/m^2	19.4 ± 3.1	19.3 ± 3.2	0.80
Total cholesterol, mg/dL	159.5 ± 26.8	160.4 ± 26.1	0.62
Triglyceride, mg/dL	101.9 ± 41.5	109.3 ± 61.0	0.03
HDL cholesterol, mg/dL	46.7 ± 8.8	46.6 ± 10.7	0.93
LDL cholesterol, mg/dL*	93.9 ± 22.0	93.1 ± 22.7	0.63
Sex (male)	186 (46.5)	210 (44.2)	0.54

Data is expressed as mean ± SD or number (%). p value was calculated by T-test for continuous variables and chi-square test for categorical variables. Abbreviation: HDL, high density lipoprotein, LDL, low density lipoprotein. *The number of study participants was 324, that of participants lost to follow-up was 410 for difference due to missing

2. Tracking patterns of lipid profile levels in study participants

Figure 2-4 show the tracking patterns of lipid profile of study participants from age 16 to age 35 according to the median value of quartile group at age 16. Figure 2 shows tracking patterns of lipid profile or study participants. The smallest quartile group of HDL cholesterol at age 16 shows the smallest median value at adulthood, and the biggest quartile group of HDL cholesterol at age 16 shows the biggest median value at adulthood. Total cholesterol shows similar trend, but the difference of median value between 25-50p and 50-75p group was disappeared at age 35. Triglyceride shows the worst tracking pattern. Overall, total cholesterol level has increased over time, and triglyceride level shows U-shape pattern over time. In addition, the data form baseline measurement age at 25 shows especially high HDL cholesterol level.

Figure 3 shows the tracking patterns of male's lipid profile. Although a crossing point was shown in male, total cholesterol and HDL cholesterol show visual tracking trend. Figure 4 shows the tracking patterns of female's lipid profile. There was no obvious different trend pattern, compared to those of tracking patterns of male.

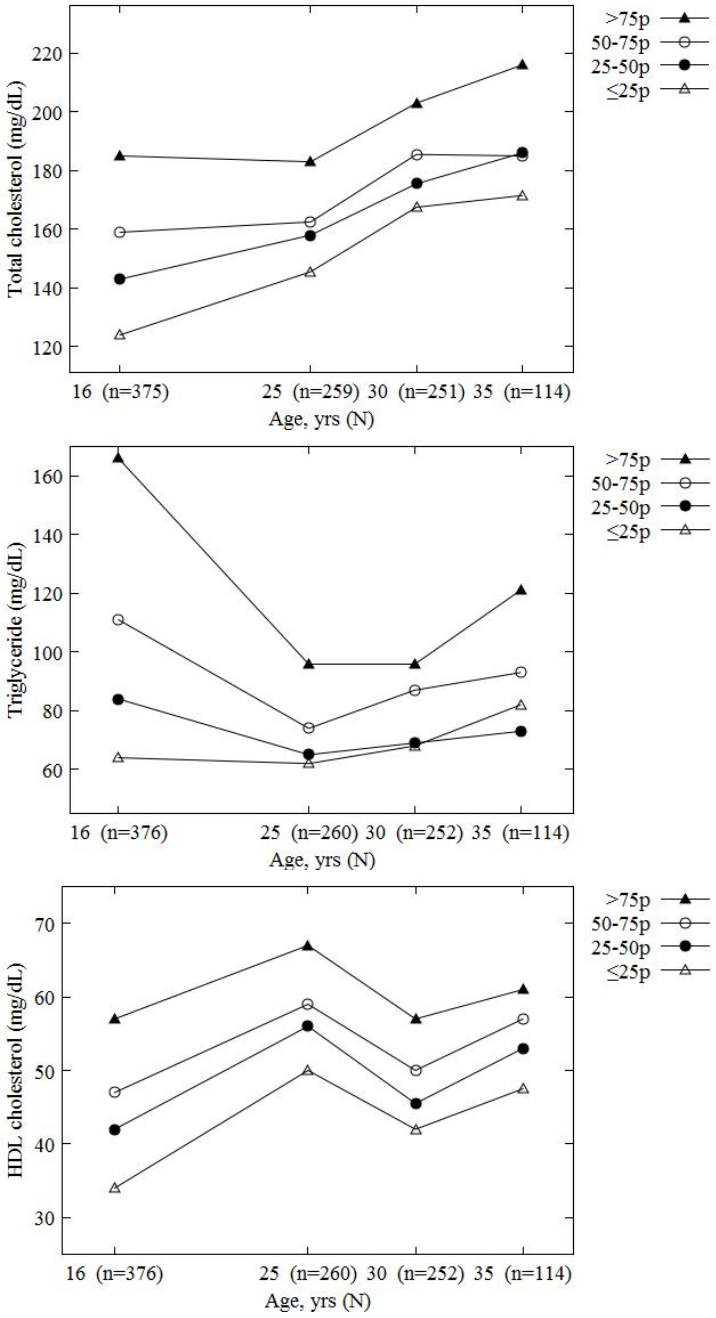


Figure 2. Tracking patterns of lipids levels of total study participants

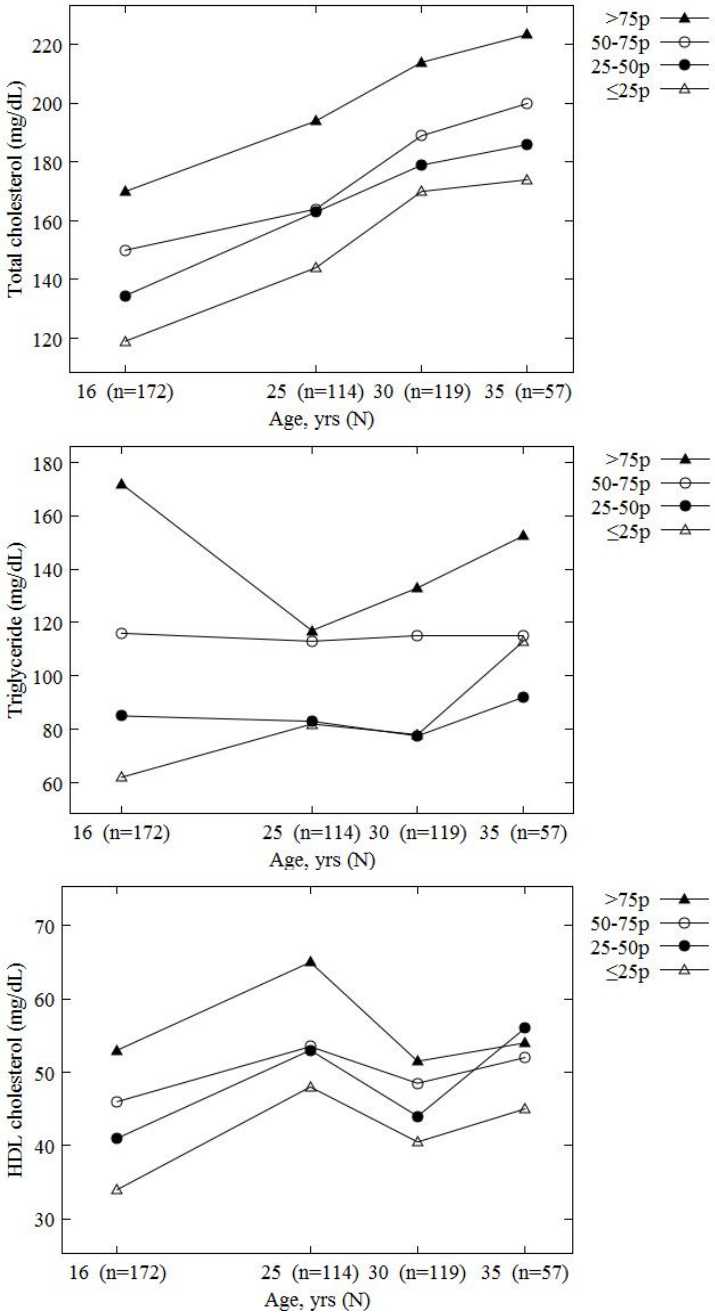


Figure 3. Tracking patterns of lipids levels of male study participants

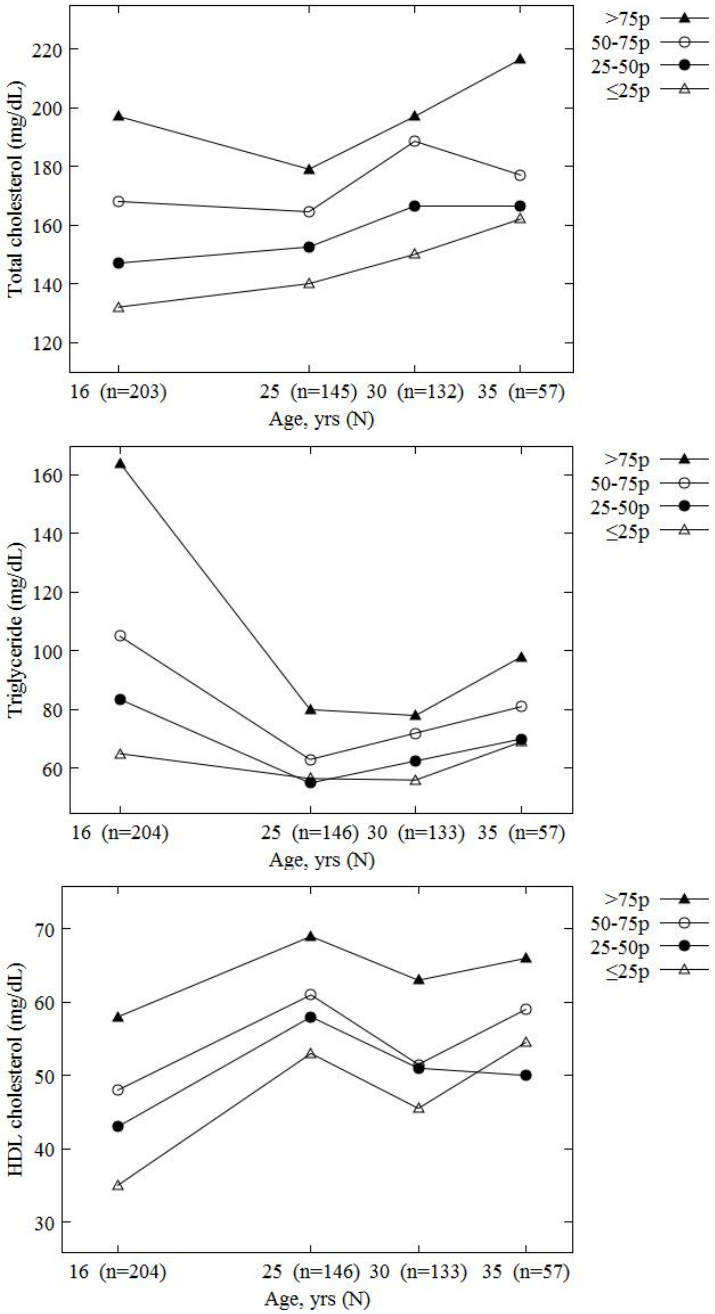


Figure 4. Tracking patterns of lipids levels of female study participants

3. Tracking coefficients of serum lipid profile level

To evaluate statistical significant tracking patterns, correlation coefficients and tracking coefficients were calculated (Table 3 and 4). Table 3 shows the correlation coefficients between two lipid profile measurements. All correlation coefficients were significant. Correlation coefficients range from 0.22 to 0.71, and the average value of them is 0.53. As the time interval is longer, the correlation coefficients tend to decrease. Especially, the correlation coefficients of triglyceride are lower than those of other lipid profiles. When calculating tracking coefficients (Table 4), the adjustment does not change significance. It is 0.64 (95% confidence interval [CI], 0.59-0.68) for total cholesterol, 0.54 (0.43-0.65) for triglyceride, 0.58 (0.54-0.63) for HDL cholesterol. In sex-separated analysis, the tracking coefficient of HDL cholesterol was highest among male, and that of total cholesterol was highest in female.

Table 3. Correlation coefficients between lipids levels according to different measurement interval

Correlation of lipids measurement by different interval	Pearson coefficient	Spearman coefficient
Total cholesterol		
19-year correlation (age 16 to 35)	0.42	0.43
14-year correlation (age 16 to 30)	0.48	0.46
10-year correlation (age 25 to 35)	0.59	0.57
9-year correlation (age 16 to 25)	0.53	0.50
5-year correlation (age 25 to 30)	0.68	0.69
5-year correlation (age 30 to 35)	0.60	0.58
Triglyceride		
19-year correlation (age 16 to 35)	0.22	0.32
14-year correlation (age 16 to 30)	0.39	0.31
10-year correlation (age 25 to 35)	0.71	0.63
9-year correlation (age 16 to 25)	0.38	0.38
5-year correlation (age 25 to 30)	0.59	0.58
5-year correlation (age 30 to 35)	0.67	0.64
HDL cholesterol		
19-year correlation (age 16 to 35)	0.43	0.40
14-year correlation (age 16 to 30)	0.51	0.51
10-year correlation (age 25 to 35)	0.62	0.63
9-year correlation (age 16 to 25)	0.59	0.54
5-year correlation (age 25 to 30)	0.69	0.69
5-year correlation (age 30 to 35)	0.65	0.63

All p values of correlation coefficients were below 0.05. Abbreviation: HDL, high density lipoprotein.

Table 4. Tracking coefficients for lipids of study participants from adolescence to adulthood

Lipids	The number of participants	Average number of measurements per person	Tracking coefficient (95% CI)	
			Unadjusted	Adjusted*
Total participants				
Total cholesterol	376	2.65	0.60 (0.55-0.64)	0.64 (0.59-0.68)
Triglyceride	376	2.66	0.59 (0.48-0.70)	0.54 (0.43-0.65)
HDL cholesterol	376	2.66	0.61 (0.56-0.67)	0.58 (0.54-0.63)
Male participants				
Total cholesterol	172	2.67	0.58 (0.52-0.63)	0.55 (0.49-0.61)
Triglyceride	172	2.67	0.61 (0.49-0.73)	0.55 (0.41-0.69)
HDL cholesterol	172	2.67	0.60 (0.53-0.67)	0.64 (0.57-0.70)
Female participants				
Total cholesterol	204	2.63	0.69 (0.63-0.75)	0.68 (0.62-0.74)
Triglyceride	204	2.65	0.58 (0.48-0.68)	0.56 (0.47-0.66)
HDL cholesterol	204	2.65	0.59 (0.53-0.66)	0.57 (0.50-0.63)

p values of all tracking coefficients' were below 0.013. Abbreviation: No, number, HDL, high density lipoprotein, CI, confidence interval. *Adjusted for sex, measurement year, body mass index, waist circumstance, systolic blood pressure, and diastolic blood pressure at each measurements

4. The association between adolescence lipid profile and adult dyslipidemia

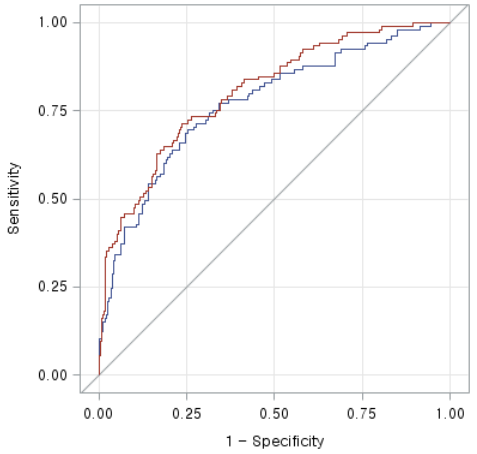
Table 5 shows the association of adolescence lipid profile level and adult dyslipidemia. In adjusted model, total cholesterol and HDL-cholesterol are associated with adult dyslipidemia. The OR was presented by 1 SD unit scale, according to each lipid profile. The OR for adult dyslipidemia of HDL-cholesterol is 0.54 (0.37-0.77), and OR for adult dyslipidemia of total cholesterol is 1.47 (1.05-2.05). In sex-separated analysis, total cholesterol is associated with adult dyslipidemia in female (OR, 1.81; 95% CI, 1.07-3.06), and HDL cholesterol is associated with adult dyslipidemia in male (OR 0.45; 95% CI, 0.27-0.75). The p values of Hosmer-Lemeshow test of goodness-of-fit for final prediction models were higher than 0.05. OR for other covariates in these prediction model is shown at Appendix table 1.

Table 5. The association between adolescence lipids levels and adult dyslipidemia

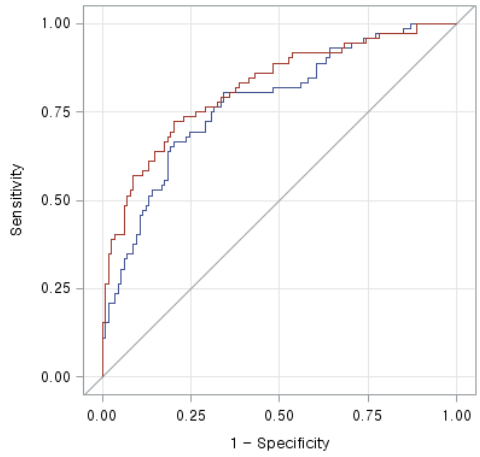
Variables (per 1 SD unit increase)	OR (95% CI) for adult dyslipidemia		
	Model 1	**Model 2**	**Model 3**
Total (n=400)			
Total cholesterol	1.18 (0.89-1.55)	1.29 (0.95-1.76)	**1.47 (1.05-2.05)**
Triglyceride	1.18 (0.92-1.50)	1.22 (0.94-1.60)	1.22 (0.92-1.62)
HDL cholesterol	**0.61 (0.45-0.83)**	**0.64 (0.46-0.90)**	**0.54 (0.37-0.77)**
The Hosmer-Lemeshow test of goodness-of-fit	0.536	0.024	0.255
Male (n=186)			
Total cholesterol	1.08 (0.74-1.58)	1.14 (0.77-1.69)	1.32 (0.84-2.08)
Triglyceride	1.20 (0.83-1.73)	1.11 (0.75-1.63)	1.13 (0.74-1.74)
HDL cholesterol	**0.60 (0.39-0.92)**	**0.63 (0.40-0.98)**	**0.45 (0.27-0.75)**
The Hosmer-Lemeshow test of goodness-of-fit	0.284	0.453	0.764
Female (n=214)			
Total cholesterol	**1.91 (1.21-3.00)**	1.60 (0.99-2.59)	**1.81 (1.07-3.06)**
Triglyceride	1.31 (0.91-1.87)	1.40 (0.96-2.04)	1.40 (0.94-2.08)
HDL cholesterol	**0.53 (0.32-0.88)**	0.64 (0.37-1.11)	0.56 (0.31-1.02)
The Hosmer-Lemeshow test of goodness-of-fit	0.179	0.212	0.767

Abbreviation: SD, standard deviation, OR, odds ratio, HDL, high density lipoprotein, CI, confidence interval, AUC, Area under curve. Model 1: include total cholesterol, triglyceride, HDL cholesterol; Model 2: model 1 + sex, age, body mass index, systolic blood pressure (at adolescence); Model 3: model 2 + age, body mass index, current smoking (at adulthood), and family history of cardiovascular disease.

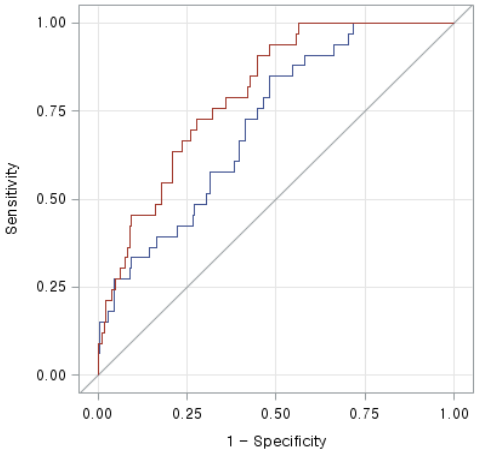
In figure 5, the predictability of adult dyslipidemia was evaluated by AUC comparison in ROC curve. The results of total, male, and female study participants were presented. The model using adult dyslipidemia prediction model included total cholesterol, triglyceride, HDL cholesterol, sex, age, body mass index, systolic blood pressure (at adolescence), age, body mass index, current smoking (at adulthood), and family history of cardiovascular disease. All the AUC value is greater than 0.8, and adding lipid profile level in my prediction model shows significant enhancement of AUC, compared to the model without lipid profile ($p=0.015$ for total participants, $p=0.030$ for male, and $p=0.014$ for female).



Total participants (n=400)	AUC (95% CI)
Without lipid profile	0.77 (0.72-0.83)
With lipid profile	0.80 (0.75-0.85)
p for AUC comparison	0.015



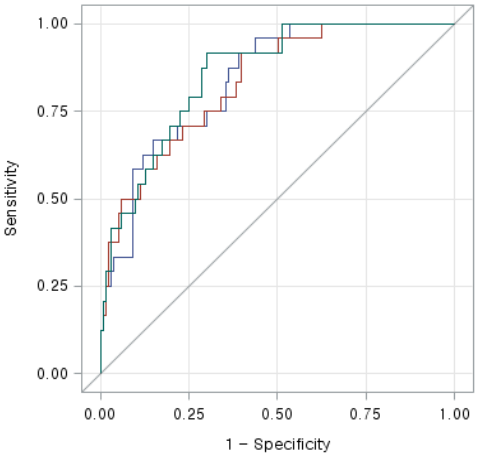
Male participants (n=186)	AUC (95% CI)
Without lipid profile	0.78 (0.71-0.84)
With lipid profile	0.82 (0.76-0.88)
p for AUC comparison	0.030



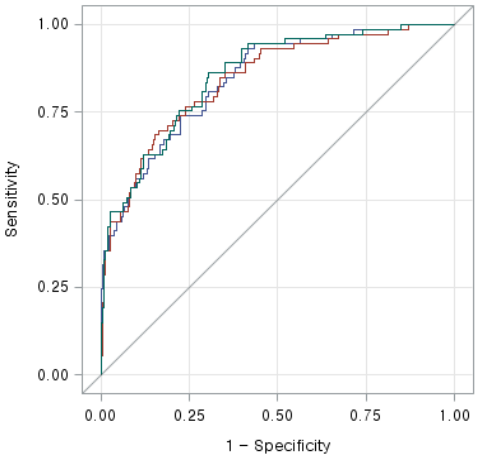
Female participants (n=214)	AUC (95% CI)
Without lipid profile	0.71 (0.63-0.80)
With lipid profile	0.80 (0.73-0.87)
p for AUC comparison	0.014

Figure 5. ROC curve of adult dyslipidemia prediction model according to the addition of lipid profile

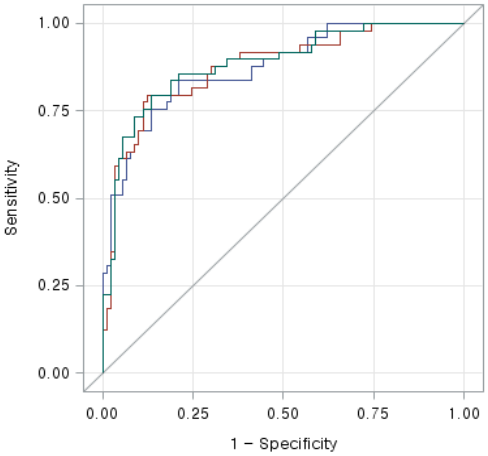
Figure 6 shows the enhancement of predictability of adult dyslipidemia when using repeated measurement lipid profile value. The results of total, male, and female study participants were presented, too. The adult dyslipidemia prediction model at Figure 6 includes total cholesterol, triglyceride, HDL cholesterol, sex, age, body mass index, systolic blood pressure (at adolescence), age, body mass index, current smoking (at adulthood), and family history of cardiovascular disease. The AUC values between model using lipid profile level at age 14 (A) and model using repeated lipid profile level at age 14 and 16 (C) were compared by ROC curve. The AUC values between model using lipid profile level at age 16 (B) and model using repeated lipid profile level at age 14 and 16 were compared, too. The AUC of the model using average lipid profile levels at 14 and 16-years old was higher than the model using single lipid profile levels at 14 or 16-years old. But p values for AUC comparison were not significant ($p>0.05$). In these models, the p values of Hosmer-Lemeshow test of goodness-of-fit for all models were higher than 0.05.



Total participants (n=296)	AUC (95% CI)
A Measurement at age 14	0.84 (0.79-0.89)
B Measurement at age 16	0.84 (0.79-0.90)
C Repeated measurement at age 14 and 16	0.85 (0.81-0.90)
p for AUC comparison (between A and C)	0.303
p for AUC comparison (between B and C)	0.260



Male participants (n=139)	AUC (95% CI)
A Measurement at age 14	0.87 (0.81-0.93)
B Measurement at age 16	0.88 (0.82-0.94)
C Repeated measurement at age 14 and 16	0.89 (0.83-0.94)
p for AUC comparison (between A and C)	0.422
p for AUC comparison (between B and C)	0.416



Female participants (n=157)	AUC (95% CI)
A Measurement at age 14	0.84 (0.76-0.91)
B Measurement at age 16	0.83 (0.75-0.91)
C Repeated measurement at age 14 and 16	0.86 (0.79-0.93)
p for AUC comparison (between A and C)	0.387
p for AUC comparison (between B and C)	0.225

Figure 6. ROC curve of adult dyslipidemia prediction model according to the repeated measurements of lipid profile

IV. DISCUSSION

The study results showed longitudinal tracking pattern of serum lipid profile measurements in general Korean population. There was no gold standard for evaluating tracking patterns among multiple measurements, several methods were used to show tracking patterns in this study. Visually, tracking patterns of total cholesterol and HDL cholesterol were stronger than that of triglyceride (Figure 2-10). Correlation coefficients of triglyceride were generally lower than those of other lipid profiles, and correlation coefficients of HDL cholesterol and total cholesterol were generally higher than those of other lipid profiles (Table 6). The tracking coefficients show similar trend, but more specifically, tracking coefficients of total cholesterol was the most remarkable in female, and that of HDL cholesterol was the most remarkable in male (Table 7).

There have been a few researches that address the tracking of serum lipids change from adolescence to adulthood. The results of Busselton study showed correlation coefficients of cholesterol for tracking that range from 0.35 to 0.55, and showed that with shorter time periods between measurements, there were strong correlation (Adams et al., 2005). The results of Muscatine Study reported 0.61 of correlation coefficients between six years (Clarke et al., 1978). The results

of the Child and Adolescent Trial for Cardiovascular Health showed 5-year correlation coefficients of 0.67–0.72 for serum lipid Kendall concordance coefficient, and they reported only small difference according to sex and ethnic (Kelder et al., 2002). Recently, the Pune Children's Study showed 13-year correlation coefficients of 0.21-0.53, The Cardiovascular Risk in Young Finns Study showed correlation coefficients of 0.34-0.64 between childhood and adulthood measurements (Nuotio et al., 2015). And previous study in Kangwha cohort showed 4-year correlation coefficients of 0.36-0.73 between adolescence measurements (Lee et al., 1997). My study results for correlation coefficients were consistent when comparing above results, although evaluating methods were somewhat different. In addition, the lowest correlation coefficient of triglyceride might be affected the inappropriate fasting status of study population at adolescence examination.

For assessing the value of tracking coefficients, I followed the suggestion as below: low for ≤0.30, moderate for 0.30-0.59, moderately high for 0.60-0.89, and high for ≥0.9 (Ulmer et al., 2003). The study results show that there was a significant correlation on lipid profile measurements and tracking coefficients were 0.53-0.68. In total and female participants, tracking confidents of total cholesterol, non-HDL cholesterol, and LDL cholesterol show moderately high correlation. But, in male participants, tracking coefficient of HDL cholesterol

shows moderately high correlation. Other tracking coefficients show moderate correlation, according to the above criteria. One research that presented tracking coefficients showed 0.62-0.66 of tracking coefficients for serum lipid in male, and 0.63-0.69 in female (Ulmer et al., 2003). Another study showed tracking coefficients of 0.43-0.77 of tracking coefficients for serum lipid in male, and 0.39-0.64 in female, and tracking coefficients for triglyceride was the lowest (Wilsgaard et al., 2001). Other study that targeted adulthood and evaluated until adulthood showed 0.51 of tracking coefficient for serum HDL cholesterol in male, and 0.65 in female (Twisk et al., 1997). My study results for tracking coefficients were consistent with the above studies. In order to confirm stability of the tracking coefficients, the value using Generalized Estimating Equation was compared to that using Linear mixed model, and there was no remarkable difference (Appendix Table 2).

This study also evaluated the association and predictability of lipid profile at adolescence for adult dyslipidemia. In addition to the studies that dealt with the tracking pattern of lipid profile (Juhola et al., 2011, Adams et al., 2005, Wilsgaard et al., 2001, Tan et al., 2000, Lee et al., 1997), there were some studies regard the effect of abnormal lipid profile at childhood on adult dyslipidemia. One study evaluated the usefulness of childhood non-HDL cholesterol level (Srinivasan et al., 2006), another study evaluated the usefulness of multiple lipid measurements in

childhood (Nuotio et al., 2015). My study regarded the lipid profile during adolescence, and the study results suggest high total cholesterol and low HDL cholesterol are associated with adult dyslipidemia. In addition, including the lipid profile enhanced the predictability of adult dyslipidemia (Figure 11-13), but repeated measurements of lipid profile during adolescence did not enhance the predictability of adult dyslipidemia (Figure 14-16).

Current guideline for dyslipidemia recommends that universal screening tests need to be done twice, at 9-11 years and 17-21 years old (National Heart Lung and Blood Institute, 2012), and one study showed the benefit of repeat measurements of lipid profile (Nuotio et al., 2015). In my study, although the lack of lipid profile measurements at childhood and late adolescence in my study might affect the results, the results suggest that universal screening of lipid profile at 12-16 years old could help the prediction of adult dyslipidemia.

Since my study has relatively small number of participants, and could not represent the whole Korean, comparison with other studies was necessary. Large representative cross-section studies in Korea showed reference value of serum lipid profile measurements (Ha et al., 2015, Yang et al., 2012). In these studies, median values of total cholesterol level for male was 161 mg/dL during 10-12 years old, 148 mg/dL during 13-15 years old, 147 mg/dL during 16-18 year old, and 189 mg/dL for adult. The median values of total cholesterol level of female in

these studies were higher than that of male. It was 162 mg/dL during 10-12 years old, 160 mg/dL during 13-15 years old, 161 mg/dL during 16-18 years old, and 192 mg/dL for adult. Such sex difference of serum lipid profile levels and change pattern believed to be due to effect of sex hormone (Laskarzewski et al., 1983, Ford et al., 2009). Sex hormone might affect difference of association between lipid profile during adolescence and adult dyslipidemia according to sex, in my study results. High tracking patterns of HDL cholesterol in male, and that of total cholesterol in female might affect the difference of the association, too.

Small number of participants affects the stability of the logistic model between lipid profile during adolescence and adult dyslipidemia. The selection of covariate was done based on AUC and The Hosmer-Lemeshow test of goodness-of-fit. Since family history of CVD, current smoking, BMI, and blood pressure at adolescence are well-known risk factor of dyslipidemia, those was selected by covariates (National Heart Lung and Blood Institute, 2012). Current smoking at adult was used as covariate because it is not examined at adolescence, and adult BMI was used as covariate because BMI was significantly associated in my study. Although study participants had similar birthdate, their enrollment year of this study was somewhat different, so age was selected by covariate, too.

The strength of this study is summarized as follows. First, this study is the first, to this knowledge, which deals with tracking pattern of lipid profile from

adolescence to adulthood in Korea. The long follow-up period, that is over 23 years, is also a strong point of this study. Second, the study participants had similar age and residence at adolescence, and thus the potential compounding effect of participants' age or residence might be minimized. Third, I derive an integrated tracking coefficient using the method that can handle missing values, reflect unequal time intervals, and adjust other potential confounders such BMI and SBP. Fourth, I tried to compare the results to up-to-date guideline for dyslipidemia in childhood.

Meanwhile, there are some limitations in this research. Above all, the study participants did not represent the whole Korean population. Thus, the study results should be applied carefully to other populations. Next, the small number of the study participants might not be sufficient to elicit significant results, especially for separated analyses. Third, low follow-up rate was one of limitations, although I conducted comparison analysis about baseline characteristics according follow-up status, and confirmed that most variables did not show significant difference. Fourth, the lack of lipid profile measurements at childhood was another limitation, too. In the future, researches which regarded the whole human life were needed. Fifths, risk factors in adolescents of adult dyslipidemia were not sufficiently examined. Finally, I could not get reliable data for medication of study participants that might affect tracking coefficients. However, it is known that

lipid-lowering drug stabilized lipid profile of participants who have abnormal lipid profile level, so it might not cause overestimation in our results.

V. CONCLUSION

It is known that various risk factors of cardiovascular disease show tracking pattern, which means that early detection of them is crucial to prevent cardiovascular disease. A lot of work has been done to examine the tracking pattern of serum lipid profile level during long follow-up periods in Western countries. However, to our knowledge, there are few in East Asia. In this study, the evaluation for tracking pattern of serum lipid profile level was done from adolescence to adulthood in Korea and also the effect of lipid profile level at adolescence was evaluated on the incidence of adult dyslipidemia.

Based on the study, serum lipid profile showed moderate high tracking pattern from adolescence to adulthood in Korea. Total cholesterol and HDL cholesterol measurement during adolescence could predict adult dyslipidemia, but repeated measurement did not add benefit on dyslipidemia prediction. I hope that the study findings support the need of universal screening of lipid profile for Korean adolescents.

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Appendix Table 1. The association between adolescence lipids levels and adult dyslipidemia (for all covariates)

Variables	Total (n=400) OR (95% CI)	Male (n=186) OR (95% CI)	Female (n=214) OR (95% CI)
Total cholesterol (per 1 SD unit)	1.47 (1.05-2.05)	1.32 (0.84-2.08)	1.81 (1.07-3.06)
Triglyceride (per 1 SD unit)	1.22 (0.92-1.62)	1.13 (0.74-1.74)	1.40 (0.94-2.08)
HDL cholesterol (per 1 SD unit)	0.54 (0.37-0.77)	0.45 (0.27-0.75)	0.56 (0.31-1.02)
Age at adolescence	1.25 (1.05-1.49)	1.48 (1.12-1.95)	1.07 (0.82-1.38)
SBP at adolescence	0.98 (0.96-1.01)	0.99 (0.96-1.04)	0.94 (0.90-0.99)
BMI at adolescence	0.95 (0.85-1.07)	0.85 (0.70-1.02)	1.04 (0.89-1.20)
Age at adulthood	0.92 (0.85-1.00)	0.84 (0.75-0.94)	1.05 (0.92-1.19)
BMI at adulthood	1.33 (1.20-1.47)	1.55 (1.30-1.84)	1.22 (1.06-1.41)
Current smoking at adulthood	1.55 (0.87-2.78)	1.75 (0.85-3.59)	1.13 (0.31-4.15)
Family history of CVD	1.67 (0.74-3.76)	4.05 (1.31-12.55)	0.33 (0.05-2.06)
Sex (male)	2.20 (1.16-4.18)	-	-

Abbreviation: SD, standard deviation, OR, odds ratio, HDL, high density lipoprotein, CI, confidence interval, SBP, systolic blood pressure, BMI, body mass index, CVD, cardiovascular disease. Model 1: adjusted for sex, age, BMI, SBP (at adolescence), age, BMI, current smoking (at adulthood), and family history of CVD.

Appendix Table 2. The comparison of tracking coefficients, between GEE and LMM

Lipid profile	Adjusted* tracking coefficient (95% CI), using GEE	Adjusted* tracking coefficient (95% CI), using LMM
Total participants		
Total cholesterol	0.637 (0.590-0.684)	0.637 (0.590-0.684)
Triglyceride	0.538 (0.427-0.650)	0.539 (0.486-0.592)
HDL cholesterol	0.580 (0.535-0.626)	0.580 (0.532-0.627)
Male participants		
Total cholesterol	0.550 (0.490-0.609)	0.550 (0.489-0.612)
Triglyceride	0.551 (0.412-0.689)	0.551 (0.472-0.630)
HDL cholesterol	0.636 (0.571-0.700)	0.635 (0.563-0.707)
Female participants		
Total cholesterol	0.681 (0.619-0.744)	0.681 (0.619-0.743)
Triglyceride	0.561 (0.467-0.655)	0.561 (0.494-0.627)
HDL cholesterol	0.568 (0.503-0.633)	0.568 (0.502-0.634)

Because of missing, the number of total measurements was somewhat different according to lipid profile. P values of all tracking coefficients' were below 0.013. Abbreviation: GEE, generalized estimating equation, LMM, linear mixed model, HDL, high density lipoprotein, LDL, low density lipoprotein, CI, confidence interval. *Adjusted for sex, measurement year, body mass index, waist circumstance, systolic blood pressure, and diastolic blood pressure at each measurements

ABSTRACT (KOREAN)

청소년기에서 성인기까지 혈청 지질의 변화와 지속성에 대한 23 년간 추적 연구: 강화 스터디

지도교수 김현창

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이정현

연구배경 및 목적:

성인기 심뇌혈관질환의 많은 위험요인들은 아동기에서부터 유래된다고 알려져 있다. 이러한 지속성 때문에 위험요인의 조기 발견은 심뇌혈관 질환 예방에 매우 중요하다. 혈중 지질 농도는 잘 알려진 심뇌혈관질환의 위험요인으로, 서구에서는 몇몇 연구를 통해 혈중 지질의 장기간 지속성을 분석한 바 있지만, 아시아 지역에서는 많은 연구가 이루어지지 못하였다. 이 연구의 목적은 한국 사람을 대상으로 청소년기부터 성인기에 걸친 혈청 지질 농도의 지속성을 탐구하는 것이다. 또한 청소년기의 지질 농도와 성인기의 이상지질혈증의 연관관계에 대해서도 탐구할 것이다.

연구 방법:

400 명의 청소년이 이 연구에 참여하였다 (남자 186 명, 여자 214 명). 1992-1996 년 동안 모든 연구참여자의 총 콜레스테롤, 중성지방, HDL 콜레스테롤이 1 회 이상 측정되었으며, 이는 2005-2015 년 동안 적어도

1 회 이상 반복 측정되었다. 체질량지수, 허리둘레, 수축기 혈압, 이완기 혈압을 측정하였으며, 심뇌혈관질환 가족력, 흡연력, 성인기 이상지질혈증의 유무를 확인하였다. 혈중 지질 수치에 대한 Tracking coefficient 는 Generalized Estimating Equation 방법을 통하여 계산되었다. 다중 로지스틱 회귀분석 및 area under curve (AUC) 값을 이용하여 청소년기의 혈중 지질 수치와 성인기 이상지질혈증 발생 사이의 연관성 및 예측력을 평가하였다. 이 시기 동안 반복적인 지질 수치 측정이 성인기 이상지질혈증 예측력을 향상시킬 수 있느냐를 확인하기 위한 추가 분석도 시행하였다.

연구 결과:

이 연구에서, 성인기 이상지질혈증의 유병률은 26.3%였다. 연령, 체질량지수, 허리둘레, 수축기혈압, 이완기 혈압을 보정하였을 때 혈중 총 콜레스테롤 수치에 대한 Tracking coefficient 는 0.64 였으며, 혈중 트리글리세라이드에 대해서는 0.54, 고밀도지단백 콜레스테롤에 대해서는 0.58 이었다. 연령, 체질량지수, 수축기 혈압, 심뇌혈관질환의 가족력, 흡연력을 보정하였을 때, 청소년기의 혈중 총 콜레스테롤 농도 증가는 성인기 이상지질혈증과 관련이 있었으며 (오즈비, 1.47, 95% 신뢰구간, 1.05−2.05, 1 표준편차 증가당), 청소년기의 고밀도지단백 콜레스테롤 농도 감소는 성인기 이상지질혈증과 관련이 있었다. (오즈비, 0.54, 95% 신뢰구간, 0.37−0.77, 1 표준편차 감소당). 모형에 혈중 지질 수치를 추가하면 area under curve (AUC) 값은 통계적으로 유의하게 향상되었다 (전체 연구 참여자에서 $p=0.02$, 남자에서 $p=0.03$, 여자에서 $p=0.01$). 하지만, 반복 측정시의 평균 지질 수치를 사용하였을 때에는 그러한 향상은 없었다 (전체 연구 참여자에서 $p\geq0.26$, 남자에서 $p\geq0.42$, 여자에서 $p\geq0.23$).

결론:

혈중 지질 농도에 대해서는 중등도 지속성이 있었다. 청소년기의 혈중 지질 농도 측정은 성인기 이상지질혈증의 예측력을 높였으며, 청소년기의 혈중 총 콜레스테롤의 증가와 고밀도지단백 콜레스테롤의 감소는 성인기 이상지질혈증과 관련 있었다. 이 연구를 통해서 심뇌혈관질환 예방을 위한 청소년기의 혈중 지질 농도 검사의 중요성을 확인하였다.

핵심 단어: 혈중지질 농도, 이상지질혈증, tracking coefficients, 예측력