Effect of serum lipid levels on depressive symptoms during adolescence and early adulthood

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A Dissertation
Submitted to the Department of Public Health
and the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy of Public Health

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June 2018

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ABSTRACT

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INTRODUCTION:

Increasing evidence suggests that serum lipids are associated with depressive symptoms. However, these associations are inconsistent according to age, sex and

race. Thus, we aimed to investigate the association between baseline serum lipids and changes in serum lipids during adolescence on depressive symptoms in early adulthood in Korean young population.

METHODS:

This prospective cohort study included participants aged 20-26 years from the JS High School study (JSHS), a cohort study of Korean adolescents, with an average follow-up of 6 years. Participants were free of depression and major cardiovascular disease at baseline. A generalized linear model was used to estimate the association between serum lipids and depressive symptoms. Age, follow-up period, health behaviors, socioeconomic status, body mass index (BMI), and depressive symptoms at baseline were considered as covariates.

RESULTS:

After adjusting for age, follow-up period, health behaviors, socioeconomic status, BMI, and depressive symptoms at baseline, participants with increased levels of total cholesterol and triglycerides during follow-up experienced a significant increase in depressive symptoms (for males, $\beta = 4.02$, $p = 0.013$; for females, $\beta = 3.82$, $p = 0.008$). Only male participants with consistently high levels of total cholesterol and triglycerides reported higher depressive symptoms ($\beta = 4.51$, $p = 0.014$) than stable individuals. In addition, we found a U-shaped association in which males in the lowest and highest tertiles of total cholesterol reported higher depressive symptoms than males in the intermediate tertile.

CONCLUSION:

These findings suggest that both low and high cholesterol levels were associated with depressive symptoms in males and a large increase in total cholesterol was associated with depressive symptoms in both sexes. In addition, persistently high total cholesterol during adolescence predicts an increased risk of depressive symptoms in early adulthood in males. These findings suggest that different strategies to manage lipid risk factors by age and sex should be developed.

Keywords: serum lipids, depressive symptoms, adolescence, early adulthood

I. INTRODUCTION

1. Background

Many studies have shown that rates of depressive symptoms increase in early adolescence[1-4]. In addition, studies show that these symptoms are persistent and are a risk factor for future depressive disorder or suicide attempts[5-7]. Suicide is a serious public health problem in the worldwide. Among all the countries comprising the Organisation for Economic Co-operation and Development (OECD), South Korea has the highest suicide rate (28.7 out of 100,000 people according to date from 2013). Particularly in young age groups of people aged 10-39 years, suicide is the first leading cause of death. According to reports from the National Police Agency, suicide motives include mental and psychological problems. It is easy to see that early adulthood is a special developmental stage connecting adolescence and adulthood. In this crucial period, adolescents and young adults experience not only emotional and financial independence from their parents, but also intense changes in their emotions, which can put a lot of pressure and stress on social relationships and the transition to adult life[8].

Recently, many previous studies have reported that serum lipid concentrations have been shown to be associated with depression, and serum lipids have been investigated as potential markers for suicidal behavior[9-12]. Other studies have reported positive associations between cholesterol and completed suicide in sample populations[13-15]. Thus, there is considerable controversy regarding the association between serum lipid levels and depression or suicidality, with this association seeming to be age-dependent insofar as there has been no positive association between depression and low cholesterol in young men[16]. Furthermore, current knowledge about the association between lipid profile and mental health problems has been derived mainly from studies conducted in middle-aged or elderly populations[17-19]. It is unclear to what extent these findings apply to adolescents without a history of depression. Although most research on mental health focuses on intensive clinical endeavors to care for children and adults already suffering from mental illness, the study of prevention requires the investigation of general populations of various ages.

2. Objectives

There is a need for further investigation using longitudinal data in order to demonstrate consistency over time regarding any associations between lipid profiles and depressive symptoms. In addition, because the association between serum lipid levels and depression may differ by age, it is necessary to investigate this association during adolescence and early adulthood.

This study aimed to (1) examine whether serum lipid profile in adolescence may lead to later depressive symptoms in early adulthood and (2) evaluate the longitudinal association between the two-year change in lipid profile during adolescence and depressive symptoms in early adulthood.

II. MATERIALS AND METHOD

1. Study population

Our study was based on data collected for the JS High School study (JSHS), a prospective cohort study of an adolescent population in Korea. The target population of this study was freshman at a high school located in a rural area of South Korea. The study design has been described in detail elsewhere[20].

The 1,071 individuals who participated from 2007 through 2012 were recruited and enrolled in the JSHS at a baseline visit (phase 1). We retained 884 (82.2% males and 82.9% females) participants who had successfully completed the first follow-up study (phase 2), over a follow-up period of 24–30 months. Six hundred two individuals participated in the second follow-up study (phase 3) between 2016 and 2018. The maximum follow-up for this analysis was 9 years, and average follow-up was 6.3 years. We excluded participants who were diagnosed with depression (n = 3) and those with missing key variables (n = 213) from analysis. The total number of participants for the final analysis was 386 (149 males and 237 females). All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of Severance Hospital at Yonsei University College of Medicine.

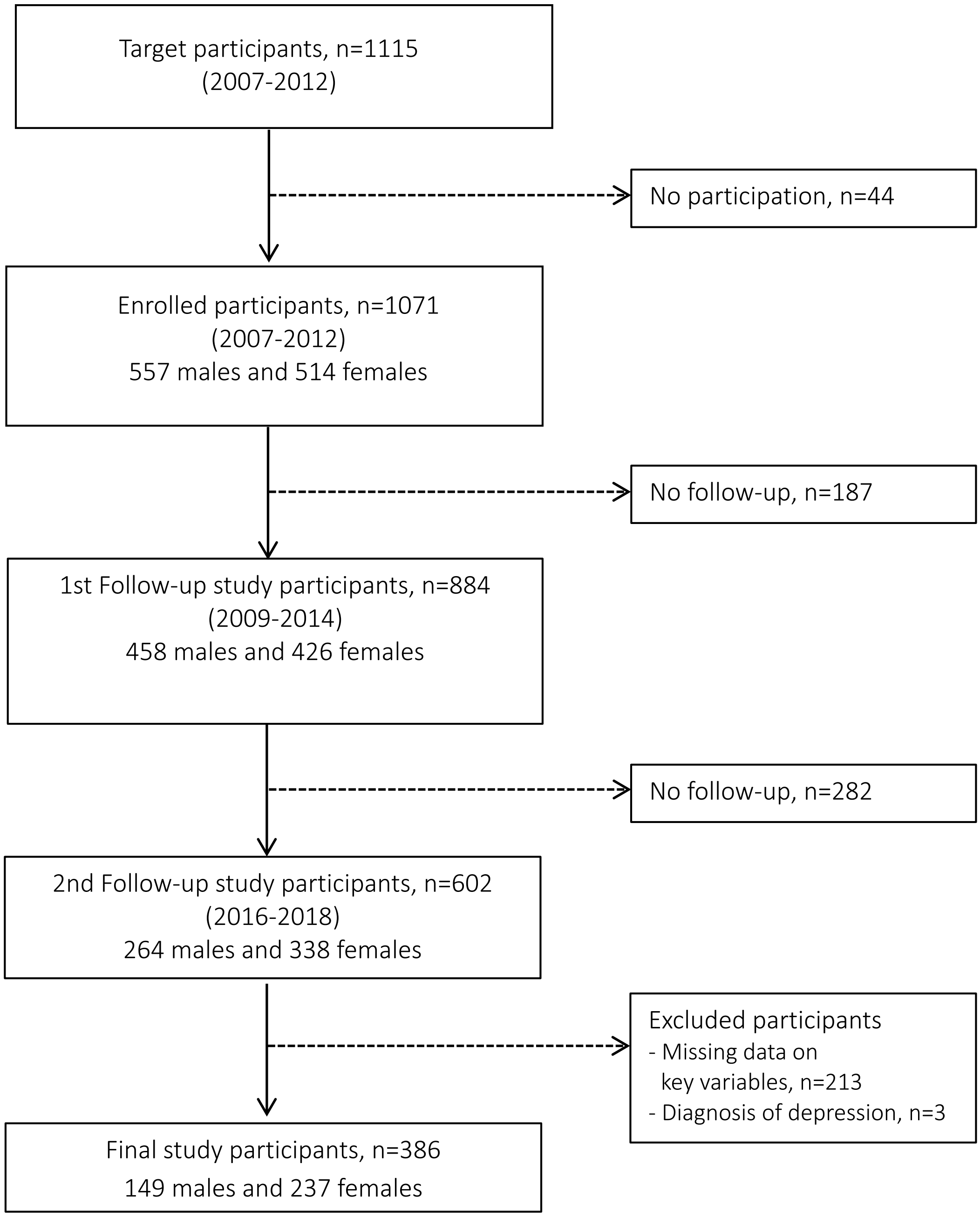

Figure 1. Flowchart of the numbers of participants of JSHS study

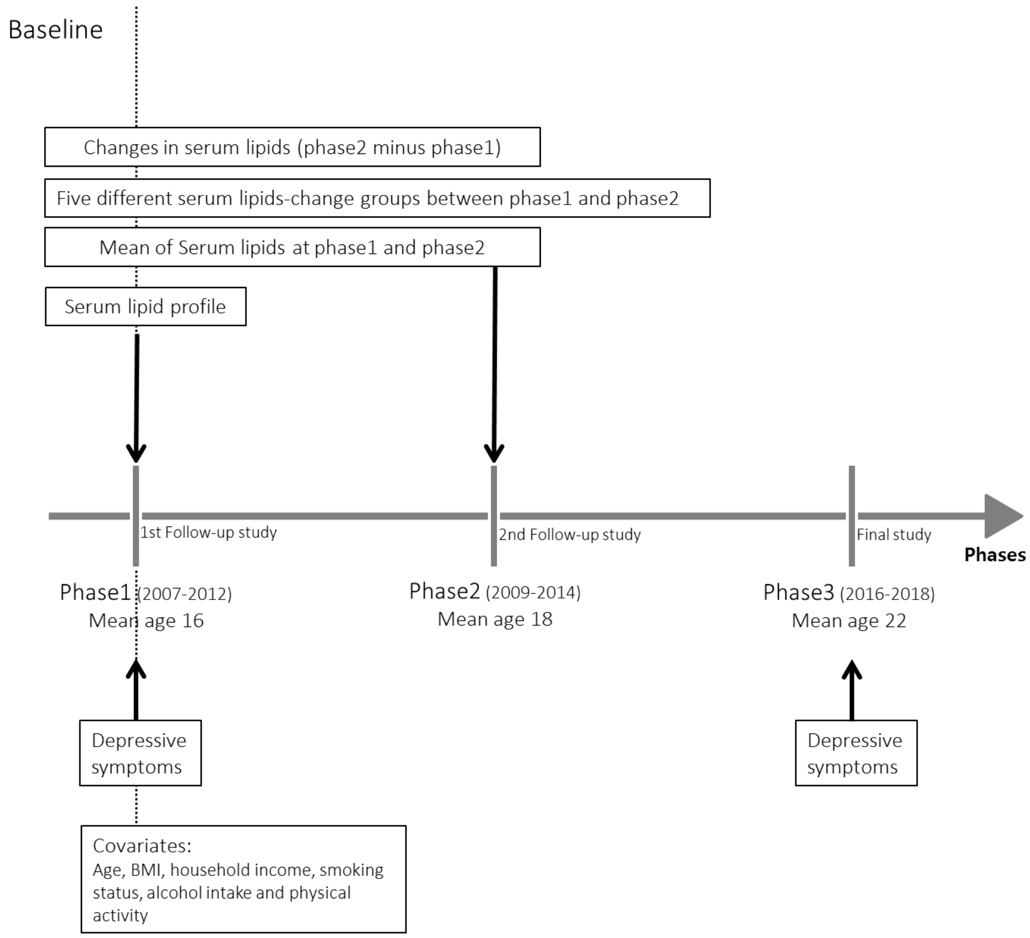

Figure 2. Study design

2. Measurements

A. Questionnaire

Depressive symptoms were assessed in participants at phases 1, 2, and 3 using the Beck Depression Inventory (BDI) questionnaire. The BDI[21] is a 21-item self-administered instrument designed to assess the severity of depression symptoms over the preceding week. Each item is assigned a score of 0–3, with 3 indicating the most severe symptoms. A cumulative score is determined by adding the scores of the individual items. The total score can range from 0 to 63. The revised version of the Beck, the BDI-II[22], represents a significant improvement over the original instrument across all aspects of the instrument including content, psychometric validity, and external validity. The BDI was used in phases 1 and 2 of the study. The revised BDI-II was used in phase 3. The validated Korean version of the BDI has good psychometric properties (Cronbach's $\alpha = 0.93$)[23]. The presence of depressive symptoms was defined as a BDI score of 10 or more.

B. Physical examination

Height was measured to the nearest 0.1 cm using a stadiometer. Body weight was measured to the nearest 0.1 kg on a digital scale, with the subject wearing his/her school uniform. Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference was measured between the lower borders of the rib cage and the iliac crest with a measuring tape.

C. Laboratory test

The lipid and lipoprotein determinations were performed at phases 1 and 2. Blood samples were collected from the antecubital vein after fasting for at least 8 hours. All blood samples were sent to independent research laboratory center for analysis. Serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using the enzymatic method with an automatic analyzer (ADVIA 1800, Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA).

D. Statistical analysis

Data are presented as mean values (with standard deviations) or percentages. For variables with a skewed distribution, data are presented as median values (with interquartile ranges) and were log-transformed prior to analysis. Characteristics of study participants by sex were compared using t-test for continuous variables with normal distribution or chi-square test for categorical variables. Because there were no well-validated clinical cutoff points, all psychological variables were analyzed as continuous variables. Triglycerides were log-transformed for parametric testing due to right-skewed distribution.

To estimate the cross-sectional associations between serum lipids and depressive symptoms at baseline (phase 1) , we used multivariable linear regression model, model 1 was adjusted for age and BMI; model 2 was additionally adjusted for household income, smoking status, alcohol intake, physical activity; model 3 was additionally adjusted for study year. To estimate the associations between serum lipids at phase 1 and depressive symptoms at phases 3, we used multivariable linear regression model, model 1 was adjusted for age, BMI, depressive symptoms in phase 1 and follow-up period; model 2 was additionally adjusted for household income, smoking status, alcohol intake, physical activity; model 3 was additionally adjusted for study year.

Each lipid value was categorized based on the sex-specific distribution of this cohort because levels varied significantly by sex. Total cholesterol, HDL cholesterol, and triglycerides were divided into tertiles so that individuals with the highest and intermediate lipid levels could be compared with individuals with the lowest levels.

We also chose to investigate not only the baseline, but also the impact of changes over time. Changes in serum lipids were assessed in two ways: first, changes in serum lipids were calculated simply by subtracting the value at phase 1 from the value at phase 2, and then participants were categorized using tertile distribution according to the magnitude of serum lipid changes. Second, after assigning all participants to categories based on serum lipids at phase 1 and phase 2 determinations, the changes that occurred between phase 1 and phase 2 were grouped (Table 1). This approach facilitates the study of individuals whose lipid values dropped to the lower tertile or rose to the upper tertile, as well as those who remained at either the highest or lowest levels throughout the period of analysis. The consistently low group was comprised of participants that consistently maintained lipid levels in the lower tertile. The consistently high group was comprised of those whose phase 1 and phase 2 lipid levels remained in the upper tertile. The decrease group of participants consisted of those with lipid levels that dropped to the lower tertile over the study period, the stable group had phase 2 values in the middle tertile, and the increase group consisted of participants with lipid levels that rose to the upper tertile over the study period. To estimate the associations between changes in serum lipids (between phase 1 and phase 2) and depressive symptoms at phase 3, we used multivariable linear regression models. Model 1 was adjusted for age, BMI, and depressive symptoms in phase 1 and the follow-up period; model 2 was additionally adjusted for household income, smoking status, alcohol intake, and level of physical activity among participants; model 3 was additionally adjusted for study year; and model 4 was additionally adjusted for lipid concentrations in phase 1 (only an analysis for absolute changes in serum lipids). All statistical analyses were performed using SAS software (version 9.4, SAS; NC, USA) and R, version 3.2.4. Statistical significance was defined as a two-sided *p*-value of less than 0.05.

Table 1. Five different serum lipids-change groups between phase1 and phase2

Change groups	Phase 1	Phase 2
Consistently low	Lower tertile	Lower tertile
Decrease	Middle or upper tertile	Lower tertile
	Upper tertile	Middle tertile
Stable	Middle tertile	Middle tertile
Increase	Lower or middle tertile	Upper tertile
	Lower tertile	Middle tertile
Consistently high	Upper tertile	Upper tertile

III. RESULTS

1. Baseline characteristics of the study participants

Table 2 presents the baseline characteristics of the study participants. The depressive symptoms score at baseline in males was significantly lower than that in females (7.6 versus 8.5, $p = 0.014$). The mean serum total and HDL cholesterol in males was significantly lower than that in females (total cholesterol 148.7 versus 162.5 mg/dl, $p < 0.001$; HDL cholesterol, 44.2 versus 49.9 mg/dl, $p < 0.001$). The median serum triglycerides in males were higher than that in females (77 versus 75 mg/dl, $p = 0.066$). Current cigarette smoking, alcohol drinking and regular exercise were more frequent in males than in females.

Table 2. Baseline characteristics of participants of the JSHS study

Variables	Males (N = 557)			Females (N = 514)			*p*-value
Age, years	15.9	±	0.4	15.9	±	0.4	0.501
Depressive symptom, score	7.6	±	5.6	8.5	±	6.1	0.014
Normal (0 to 9)	392	(70.4)		343	(66.7)		0.288
Mild (10 to 16)	125	(22.4)		122	(23.7)		
Moderate to severe (17 to 63)	40	(72.0)		49	(9.5)		
Metabolic factors							
BMI, kg/m^2	22.2	±	3.2	21.3	±	2.6	<.001
Waist circumference, cm	73.6	±	8.1	68.6	±	6.7	<.001
Total cholesterol, mg/dl	148.7	±	24.6	162.5	±	26.2	<.001
HDL cholesterol, mg/dl	44.2	±	10.0	49.9	±	10.9	<.001
Triglycerides, mg/dl	77	[59-96]		75	[59-91]		0.066
Monthly household income, won							
Do not wish to answer	161	(28.9)		139	(27.0)		0.392
< 3.0 million	91	(16.3)		74	(14.4)		
3.0-<5.0 million	156	(28.0)		168	(32.7)		
≥ 5.0 million	149	(26.8)		133	(25.9)		
Health behaviors							
Current cigarette smoking	45	(8.1)		3	(0.6)		<.001
Current alcohol drinking	60	(10.8)		26	(5.1)		0.001
Regular exercise	473	(84.9)		363	(70.6)		<.001

Data are expressed as means ± standard deviation, median [25%-75%] and Number (%).
BMI, Body mass index; HDL, high-density lipoprotein.

2. Characteristics according to depressive symptoms at phase 1

Table 3 shows the baseline characteristics of the study participants according to depressive symptoms at phase 1 (at baseline). Males having depressive symptoms were with significantly higher total cholesterol (p = 0.005), as well as higher frequencies of current alcohol drinking (p = 0.009), than normal group. There was no statistically significant difference between females having depressive symptoms and those with normal people, except for current smoking. Females having depressive symptoms were higher frequencies of current cigarette smoking than normal group (p = 0.010).

Table 3. Characteristics of participants in phase 1 of the JSHS study by depressive symptoms

Variables	Males (N = 557)			Females (N = 514)		
	Normal	Having depressive symptoms	*p*-value	Normal	Having depressive symptoms	*p*-value
No of participants	392 (70.3)	165 (29.6)	<.001	343 (66.7)	171 (33.3)	<.001
Age, years	15.9 ± 0.4	15.9 ± 0.4	0.060	15.9 ± 0.4	15.9 ± 0.4	0.079
Metabolic factors						
BMI, kg/m^2	22.2 ± 3.3	22.1 ± 3.2	0.941	21.3 ± 2.6	21.2 ± 2.7	0.925
<18.5	47 (78.3)	13 (21.7)	0.363	38 (60.3)	25 (39.7)	0.638
18.5-<23	215 (68.7)	98 (31.3)		231 (68.3)	107 (31.7)	
23-<25	62 (67.4)	30 (32.6)		42 (64.6)	23 (35.4)	
≥ 25	68 (73.9)	24 (26.1)		32 (66.7)	16 (33.3)	
Waist circumference, cm	73.9 ± 8.2	73.1 ± 8.0	0.298	68.4 ± 6.7	69.1 ± 6.8	0.219
< 90th percentile	352 (70.3)	149 (29.7)	0.978	312 (67.5)	150 (32.5)	0.321
≥ 90th percentile	40 (71.4)	16 (28.6)		31 (59.6)	21 (40.4)	
Total cholesterol, mg/dl	146.6 ± 22.3	153.8 ± 28.8	0.005	162.9 ± 26.4	161.8 ± 25.8	0.659
HDL cholesterol, mg/dl	44.0 ± 9.8	44.4 ± 10.5	0.659	50.0 ± 10.8	49.8 ± 11.2	0.881
Log triglycerides, mg/dl	4.3 ± 0.4	4.4 ± 0.3	0.094	4.3 ± 0.3	4.3 ± 0.4	0.915
Monthly household income, won						
Do not wish to answer	111 (68.9)	50 (31.1)	0.098	95 (68.4)	44 (31.7)	0.347
< 3.0 million	56 (61.5)	35 (38.5)		43 (58.1)	31 (41.9)	
3.0-<5.0 million	111 (71.2)	45 (28.9)		117 (69.6)	51 (30.4)	
≥ 5.0 million	114 (76.5)	35 (23.5)		88 (66.2)	45 (33.8)	
Health behaviors						
Current cigarette smoking	31 (68.9)	14 (31.1)	0.954	0 (0.0)	3 (100.0)	0.010
Current alcohol drinking	33 (55.0)	27 (45.0)	0.009	16 (61.5)	10 (38.5)	0.568
Regular exercise	382 (70.4)	161 (29.7)	0.930	343 (67.0)	169 (33.0)	0.210

Data are expressed as means ± standard deviation, median [25%-75%] and Number (%). BMI, Body mass index; HDL, high-density lipoprotein.

3. Cross-sectional association between lipid concentrations and depression symptoms

Table 4 and 5 outlines the cross-sectional associations between lipid concentrations and depressive symptoms for males and females. After adjusting for age, BMI, household income, smoking status, alcohol intake and physical activity, the highest tertile group for total cholesterol had significantly higher depressive symptoms compared to the lowest tertile only in males (β = 0.49, *p* = 0.040). A significant association between one standard deviation (SD) increase in higher total cholesterol and depression symptoms was only observed for males. HDL cholesterol was not associated with depression symptoms before adjusting for study year, after adjusting for study year, one SD increase in higher HDL cholesterol was associated with depressive symptoms only in males (β = 0.65, *p* = 0.010). In females, serum lipids were not associated with depressive symptoms before and after adjusting for covariates.

Table 4. Cross-sectional association between lipid concentrations and depressive symptoms at phase 1 in males (n = 548)

Serum lipids	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (<137)	177	Ref			Ref			Ref		
T2 (137-<156)	184	0.35	0.58	0.548	0.39	0.57	0.498	0.45	0.57	0.429
T3 (≥ 156)	187	1.02	0.58	0.079	1.23	0.57	0.031	1.28	0.57	0.025
Continuous, per SD		0.49	0.24	0.040	0.58	0.23	0.013	0.60	0.23	0.010
HDL cholesterol, mg/dl										
T1 (<39)	178	Ref			Ref			Ref		
T2 (39-<48)	175	0.30	0.59	0.616	0.45	0.58	0.437	0.69	0.59	0.243
T3 (≥ 48)	195	0.54	0.61	0.380	0.55	0.60	0.362	1.05	0.64	0.098
Continuous, per SD		0.32	0.26	0.218	0.34	0.25	0.185	0.65	0.28	0.020
Log triglycerides, mg/dl										
T1 (<4.19)	182	Ref			Ref			Ref		
T2 (4.19-<4.49)	183	0.12	0.58	0.842	0.16	0.57	0.786	0.20	0.57	0.725
T3 (≥ 4.49)	183	-0.01	0.60	0.991	-0.12	0.60	0.840	-0.14	0.60	0.809
Continuous, per SD		0.11	0.25	0.654	0.07	0.25	0.780	0.08	0.25	0.758

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age and body mass index
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Table 5. Cross-sectional association between lipid concentrations and depressive symptoms at phase 1 in females (n = 498)

Serum lipids	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (< 151)	170	Ref			Ref			Ref		
T2 (151 -< 171)	156	-0.28	0.67	0.676	-0.28	0.67	0.671	-0.09	0.67	0.893
T3 (≥ 171)	172	-0.04	0.67	0.957	-0.12	0.67	0.861	0.03	0.66	0.962
Continuous, per SD		-0.15	0.28	0.600	-0.18	0.27	0.502	-0.09	0.28	0.741
HDL cholesterol, mg/dl										
T1 (< 44)	154	Ref			Ref			Ref		
T2 (44 -< 54)	180	0.48	0.68	0.475	0.52	0.69	0.450	0.68	0.68	0.321
T3 (≥ 54)	173	-0.21	0.58	0.764	-0.20	0.70	0.781	0.43	0.72	0.548
Continuous, per SD		-0.16	0.28	0.570	-0.22	0.28	0.439	0.15	0.30	0.622
Log triglycerides, mg/dl										
T1 (< 4.15)	179	Ref			Ref			Ref		
T2 (4.15 -< 4.44)	160	-0.16	0.66	0.810	-0.23	0.66	0.728	-0.22	0.66	0.733
T3 (≥ 4.44)	168	0.39	0.66	0.551	0.31	0.66	0.644	0.51	0.66	0.438
Continuous, per SD		0.10	0.28	0.726	0.06	0.28	0.819	0.15	0.28	0.597

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age and body mass index
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

4. Characteristics according to baseline serum lipids in tertiles

Table 6, 7 and 8 shows the baseline characteristics of study population according to the categories of baseline total cholesterol in tertiles. Males with higher level of total cholesterol had significantly higher BMI, waist circumference, levels of HDL cholesterol and triglycerides at baseline. On the other hand, females who had a higher level of total cholesterol had significantly older ages and higher levels of HDL cholesterol and triglycerides. Table 6 shows the baseline characteristics of study population according to the categories of baseline serum HDL cholesterol in tertiles. Both males and females with higher level of HDL cholesterol had significantly lower BMI, waist circumference and levels of triglycerides and higher levels of total cholesterol at baseline. Females with higher level of HDL cholesterol had significantly higher monthly household income. Table 7 shows the baseline characteristics of study population according to the categories of baseline triglycerides in tertiles. Both males and females with higher level of triglycerides had significantly higher BMI, waist circumference and levels of total cholesterol and lower levels of HDL cholesterol at baseline. Males with higher level of triglycerides had significantly higher frequencies of current alcohol drinking than other groups. In both males and females, there was no difference in serum lipids and depressive symptoms.

Table 6. Characteristics of study participants according to baseline total cholesterol

Variables	Males (N = 547)				Females (N = 505)			
	Tertile 1 (<137 mg/dl)	Tertile 2 (137-<156 mg/dl)	Tertile 3 (≥156 mg/dl)	*p*-value	Tertile 1 (<151 mg/dl)	Tertile 2 (151-<171 mg/dl)	Tertile 3 (≥171 mg/dl)	*p*-value
Age, years	15.9±0.4	15.9±0.4	16.0±0.4	0.280	15.8± 0.4	15.9±0.4	16.0±0.4	0.004
Depressive symptom, score	7.2±5.2	7.4±5.7	8.1±5.5	0.249	8.7± 5.4	8.3±6.8	8.5±6.2	0.837
Normal (0 to 9)	130 (73.5)	134 (73.2)	119 (63.6)		110 (64.7)	115 (69.7)	110 (64.7)	
Mild (10 to 16)	35 (19.8)	38 (20.8)	52 (27.8)	0.229	46 (27.1)	33 (20.0)	43 (25.3)	0.605
Moderate to severe (17 to 63)	12 (6.8)	11 (6.0)	16 (8.6)		14 (8.2)	17 (10.3)	17 (10.0)	
Metabolic factors								
BMI, kg/m^2	22.0± 3.0	21.8±3.2	22.6±3.4	0.052	20.9± 2.6	21.6±2.7	21.3±2.5	0.093
Waist circumference, cm	73.1± 7.6	72.9±7.7	74.9±8.9	0.031	68.9± 7.1	68.4±6.7	68.4±6.5	0.738
Total cholesterol, mg/dl	124.2± 9.7	145.4±5.4	175.4±19.3	<.001	135.1± 11.1	160.8±5.3	191.2±18.0	<.001
HDL cholesterol, mg/dl	39.6± 8.6	45.3±10.1	47.5±9.6	<.001	45.2± 8.8	50.2±9.7	54.7±11.9	<.001
Log triglycerides, mg/dl	4.2± 0.3	4.3±0.3	4.5±0.3	<.001	4.2± 0.3	4.3±0.4	4.4±0.3	<.001
Monthly household income, won								
Do not wish to answer	49 (27.7)	62 (33.9)	44 (23.5)		45 (26.5)	43 (26.1)	49 (28.8)	
< 3.0 million	27 (15.3)	33 (18.0)	31 (16.6)	0.317	29 (17.1)	21 (12.7)	22 (12.9)	0.845
3.0 -< 5.0 million	53 (29.9)	42 (23.0)	59 (31.6)		56 (32.9)	57 (34.6)	52 (30.6)	
≥ 5.0 million	48 (27.1)	46 (25.1)	53 (28.3)		40 (23.5)	44 (26.7)	47 (27.7)	
Health behaviors								
Current cigarette smoking	16 (9.0)	10 (5.5)	19 (10.2)	0.231	0 (0)	1 (0.6)	2 (1.2)	0.369
Current alcohol drinking	24 (13.6)	15 (8.2)	21 (11.2)	0.263	6 (3.5)	9 (5.5)	11 (6.5)	0.460
Regular exercise	173 (97.7)	181 (98.9)	179 (95.7)	0.145	170 (100)	165 (100.0)	168 (98.8)	0.138

Data are expressed as means ± standard deviation, median [25%-75%] and Number (%).
BMI, Body mass index; HDL, high-density lipoprotein.

Table 7. Characteristics of study participants according to baseline HDL cholesterol

Variables	Males (N = 547)				Females (N = 505)			
	Tertile 1 (< 39 mg/dl)	Tertile 2 (39 -< 48 mg/dl)	Tertile 3 (≥ 48 mg/dl)	*p*-value	Tertile 1 (< 44 mg/dl)	Tertile 2 (44 -< 54 mg/dl)	Tertile 3 (≥ 54 mg/dl)	*p*-value
Age, years	15.8± 0.4	15.9 ± 0.3	16.1±0.4	<.001	15.8±0.3	15.9±0.4	16.0 ± 0.4	<.001
Depressive symptom, score	7.5± 5.2	7.7 ± 6.3	7.5±5.0	0.954	8.5± 5.3	8.8±6.3	8.1 ± 6.5	0.528
Normal (0 to 9)	122 (68.5)	124 (70.9)	137 (70.6)		97 (63.0)	119 (66.9)	119 (68.8)	
Mild (10 to 16)	44 (24.7)	38 (21.7)	43 (22.2)	0.968	45 (29.2)	41 (23)	36 (20.8)	0.456
Moderate to severe (17 to 63)	12 (6.7)	13 (7.4)	14 (7.2)		12 (7.8)	18 (10.1)	18 (10.4)	
Metabolic factors								
BMI, kg/m^2	23.1± 3.8	22.4± 3.0	21.1±2.6	<.001	21.8±3.0	21.0±2.4	21.0 ± 2.4	0.004
Waist circumference, cm	76.3± 9.4	74.1± 7.7	70.9±6.3	<.001	71.1±7.6	68.2±6.0	66.6 ± 5.9	<.001
Total cholesterol, mg/dl	140.4± 26.5	148.5± 20.8	156.8±23.7	<.001	150.5±22.8	161.7±25.4	174.2 ± 24.9	<.001
HDL cholesterol, mg/dl	33.6± 3.4	43.0± 2.5	55.1±6.4	<.001	38.4±3.8	48.3±2.8	61.9 ± 8.0	<.001
Log triglycerides, mg/dl	4.5± 0.4	4.3± 0.3	4.2±0.3	<.001	4.4±0.4	4.3±0.3	4.3 ± 0.4	<.001
Monthly household income, won								
Do not wish to answer	49 (27.5)	44 (25.1)	62 (32.0)		48 (31.2)	42 (23.6)	47 (27.2)	
< 3.0 million	30 (16.9)	29 (16.6)	32 (16.5)	0.620	26 (16.9)	25 (14.0)	21 (12.1)	0.034
3.0-< 5.0 million	48 (27.0)	58 (33.1)	48 (24.7)		53 (34.4)	65 (36.5)	47 (27.2)	
≥ 5.0 million	51 (28.7)	44 (25.1)	52 (26.8)		27 (17.5)	46 (25.8)	58 (33.5)	
Health behaviors								
Current cigarette smoking	7 (3.9)	19 (10.9)	19 (9.8)	0.037	0 (0.0)	1 (0.6)	2 (1.2)	0.397
Current alcohol drinking	24 (13.5)	16 (9.1)	20 (10.3)	0.399	5 (3.3)	9 (5.1)	12 (6.9)	0.321
Regular exercise	175 (98.3)	170 (97.1)	188 (96.9)	0.661	154 (100.0)	177 (99.4)	172 (99.4)	0.644

Data are expressed as means ± standard deviation, median [25%-75%] and Number (%).
BMI, Body mass index; HDL, high-density lipoprotein.

Table 8. Characteristics of study participants according to baseline triglycerides

Variables	Males (N = 547)				Females (N = 505)			
	Tertile 1 (< 4.2 mg/dl)	Tertile 2 (4.2 -< 4.5 mg/dl)	Tertile 3 (≥ 4.5 mg/dl)	*p*-value	Tertile 1 (< 4.2 mg/dl)	Tertile 2 (4.2-< 4.5 mg/dl)	Tertile 3 (≥ 4.5 mg/dl)	*p*-value
Age, years	16.0± 0.4	15.9 ± 0.4	15.9±0.4	0.131	15.9±0.4	15.9±0.4	15.9 ± 0.4	0.957
Depressive symptom, score	7.5± 5.1	7.6 ± 6.1	7.6±5.3	0.977	8.4±6.2	8.2±6.2	8.8 ± 5.9	0.690
Normal (0 to 9)	133 (73.1)	125 (68.7)	125 (68.3)		116 (64.8)	113 (71.5)	106 (63.1)	
Mild (10 to 16)	37 (20.3)	43 (23.6)	45 (24.6)	0.859	48 (26.8)	31 (19.6)	43 (25.6)	0.425
Moderate to severe (17 to 63)	12 (6.6)	14 (7.7)	13 (7.1)		15 (8.4)	14 (8.9)	19 (11.3)	
Metabolic factors								
BMI, kg/m^2	21.1± 2.4	22.1 ± 3.0	23.3±3.8	<.001	21.0±2.4	20.9±2.5	21.8 ± 2.9	0.002
Waist circumference, cm	70.8± 5.9	73.3 ± 7.1	76.9±9.8	<.001	68.5±6.3	67.8±6.2	69.3 ± 7.5	0.111
Total cholesterol, mg/dl	140.4± 23.0	147.7 ± 22.0	158.3±25.7	<.001	156.9±24.4	158.8±22.2	172.3 ± 28.9	<.001
HDL cholesterol, mg/dl	47.7± 10.5	44.1 ± 9.1	40.9±9.2	<.001	52.9±10.7	49.2±10.2	48.0 ± 11.3	<.001
Log triglycerides, mg/dl	3.9± 0.2	4.3 ± 0.1	4.7±0.2	<.001	3.9±0.2	4.3±0.1	4.7 ± 0.2	<.001
Monthly household income, won								
Do not wish to answer	51 (28.0)	48 (26.4)	56 (30.6)		40 (22.4)	51 (32.3)	46 (27.4)	
< 3.0 million	31 (17.0)	25 (13.7)	35 (19.1)	0.564	25 (14.0)	19 (12.0)	28 (16.7)	0.203
3.0-< 5.0 million	52 (28.6)	59 (32.4)	43 (23.5)		57 (31.8)	50 (31.7)	58 (34.5)	
≥ 5.0 million	48 (26.4)	50 (27.5)	49 (26.8)		57 (31.8)	38 (24.1)	36 (21.4)	
Health behaviors								
Current cigarette smoking	14 (7.7)	16 (8.8)	15 (8.2)	0.930	0 (0.0)	1 (0.6)	2 (1.2)	0.397
Current alcohol drinking	13 (7.1)	17 (9.3)	30 (16.4)	0.013	12 (6.7)	6 (3.8)	8 (4.8)	0.466
Regular exercise	180 (98.9)	178 (97.8)	175 (95.6)	0.131	179 (100.0)	157 (99.4)	167 (99.4)	0.575

Data are expressed as means ± standard deviation, median [25%-75%] and Number (%).
BMI, Body mass index; HDL, high-density lipoprotein.

5. Association between lipid concentrations at phase 1 and depression symptoms at phase 3

Table 9 shows associations between lipid concentrations at phase 1 and depressive symptoms at phase 3 for males and females. In males, the highest tertile group for total cholesterol had significantly higher depressive symptoms in comparison to the intermediate tertile after adjusting for age, BMI, depressive symptoms in phase 1, follow-up period, household income, smoking status, alcohol intake, physical activity, and study year (β = 4.07, p = 0.005). The lowest tertile group for total cholesterol, although not significantly, had higher depression symptoms in comparison to the intermediate tertile in males (β = 2.65, p= 0.065). A significant association between one SD increase in higher total cholesterol at phase 1 and depressive symptoms at phase 3 was only observed for males. In females, one SD increase in higher triglycerides at phase 1 was associated with depressive symptoms at phase 3 after adjusting for age, BMI, depressive symptoms in phase 1, follow-up period household income, smoking status, alcohol intake, physical activity and study year (β = 1.20, p = 0.028). All results were similar following the exclusion of participants with depressive symptoms (BDI score ≥ 10) at baseline (Appendix Table 1 and 2).

Table 9. Association between lipid concentrations at phase 1 and depressive symptoms at phase 3

Serum lipids at phase 1	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Males (n = 158)										
Total cholesterol, mg/dl										
T1 (< 136)	52	2.68	1.44	0.062	2.88	1.41	0.041	2.65	1.44	0.065
T2 (136 -< 154)	53	Ref			Ref			Ref		
T3 (≥ 154)	53	4.26	1.43	0.003	4.28	1.40	0.002	4.07	1.43	0.005
Continuous, per SD		1.12	0.62	0.071	1.11	0.61	0.070	1.10	0.61	0.073
HDL cholesterol, mg/dl										
T1 (< 39)	51	Ref			Ref			Ref		
T2 (39 -< 48)	53	0.86	1.16	0.569	0.65	1.50	0.665	0.57	1.49	0.700
T3 (≥ 48)	54	1.23	1.58	0.436	1.11	1.56	0.478	1.34	1.56	0.389
Continuous, per SD		0.28	0.57	0.672	0.13	0.68	0.854	0.28	0.67	0.672
Log triglycerides, mg/dl										
T1 (< 4.20)	54	Ref			Ref			Ref		
T2 (4.20 -< 4.42)	52	1.29	1.45	0.376	1.33	1.42	0.350	1.35	1.42	0.340
T3 (≥ 4.42)	52	1.75	1.50	0.243	1.86	1.48	0.209	1.83	1.47	0.213
Continuous, per SD		0.75	0.63	0.236	0.73	0.63	0.245	0.71	0.63	0.261
Females (n = 245)										
Total cholesterol, mg/dl										
T1 (< 153)	83	0.966	1.26	0.444	0.77	1.26	0.538	0.84	1.25	0.503
T2 (153 -< 172)	80	Ref			Ref			Ref		
T3 (≥ 172)	83	0.86	1.24	0.489	0.79	1.24	0.523	0.73	1.23	0.554
Continuous, per SD		0.663	0.52	0.203	0.69	0.52	0.192	0.65	0.52	0.219
HDL cholesterol, mg/dl										
T1 (< 45)	74	Ref			Ref			Ref		
T2 (45 -< 55)	90	-1.67	1.28	0.194	-1.56	1.29	0.224	-1.52	1.28	0.237
T3 (≥ 55)	82	-1.02	1.35	0.450	-0.91	1.36	0.501	-1.27	1.38	0.359
Continuous, per SD		0.02	0.55	0.967	0.10	0.55	0.853	-0.08	0.57	0.888
Log triglycerides, mg/dl										
T1 (< 4.17)	86	Ref			Ref			Ref		
T2 (4.17 -< 4.47)	83	1.07	1.25	0.393	1.05	1.22	0.390	1.47	1.24	0.236
T3 (≥ 4.47)	77	1.93	1.32	0.144	1.40	1.29	0.277	1.64	1.29	0.204
Continuous, per SD		1.17	0.53	0.029	1.06	0.54	0.049	1.20	0.54	0.028

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index and depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

6. Characteristics of the study participants at baseline and 2 years later

Table 10 shows changes in the characteristics of the participants over two years. All variables except for triglycerides and depressive symptoms significantly increased within two years in males and females. On the other hand, triglycerides was decreased by 6.5 mg/dL for males and 4.8 mg/dL for females, and depression scores decreased by 2.2 point for males and 3 point for females. Changes in serum lipid concentrations during two years varied according to the study year. The reason for this is that the study was conducted in winter only in 2012. According to previous studies [24, 25], the blood lipid concentration tended to increase in winter, and the difference between phase 1 and phase 2 was actually smaller than in other years (Appendix Table 3 and 4). For this reason, the analysis of the association between changes in serum lipids and depressive symptoms was excluded from the study participants in 2012. Figure 3 shows the distribution of depressive symptoms scores for phases 1, 2, and 3, respectively. The depressive symptoms score decreased in phase 2 immediately after the college entrance examination, but it increased again in the early adulthood at phase 3 among males and females.

Table 10. Characteristics at baseline and 2 years later

Variables	Phase 1 (baseline)	Phase 2 (1st follow up)	Mean change	*p*-value
Males				
No of participants	548	451		
Age, year	15.9 ± 0.4	18.3 ± 0.3	2.4 ± 0.2	<.001
Height, cm	171.4 ± 5.2	172.9 ± 5.1	1.5 ± 1.6	<.001
Weight, kg	64.8 ± 10.1	68.1 ± 10.3	3.2 ± 4.6	<.001
Body mass index, kg/ m^2	22.0 ± 3.1	22.7 ± 3.0	0.7 ± 1.5	<.001
Waist circumference, cm	73.4 ± 7.9	75.7 ± 8.1	2.3 ± 5.0	<.001
Total cholesterol, mg/dl	149.0 ± 25.4	158.8 ± 28.8	10.1 ± 18.2	<.001
Triglycerides, mg/dl	76[59, 97]	68[52, 89]	-6.5 ± 34.1	<.001
HDL cholesterol, mg/dl	44.6 ± 10.3	52.1 ± 10.4	7.6 ± 8.8	<.001
Depressive symptom, score	7.6 ± 5.6	5.4 ± 6.0	-2.2 ± 6.2	<.001
Females				
No of participants	498	409		
Age, year	15.9 ± 0.4	18.3 ± 0.3	2.4 ± 0.2	<.001
Height, cm	159.9 ± 5.0	160.5 ± 5.1	0.6 ± 0.8	<.001
Weight, kg	54.2 ± 7.4	56.0 ± 8.2	1.8 ± 3.8	<.001
Body mass index, kg/ m^2	21.2 ± 2.6	21.7 ± 2.9	0.6 ± 1.5	<.001
Waist circumference, cm	68.6 ± 6.7	69.7 ± 8.3	1.1 ± 7.4	0.002
Total cholesterol, mg/dl	162.1 ± 26.6	164.9 ± 25.6	3.7 ± 20.6	<.001
Triglycerides, mg/dl	75[56, 65]	66[52, 84]	-4.8 ± 35.6	0.009
HDL cholesterol, mg/dl	50.2 ± 11.0	56.9 ± 11.4	7.3 ± 9.6	<.001
Depressive symptom, score	8.5 ± 6.1	5.6 ± 5.5	-3.0 ± 6.3	<.001

Data are expressed as means ± standard deviation, median [25%-75%] and Number (%).

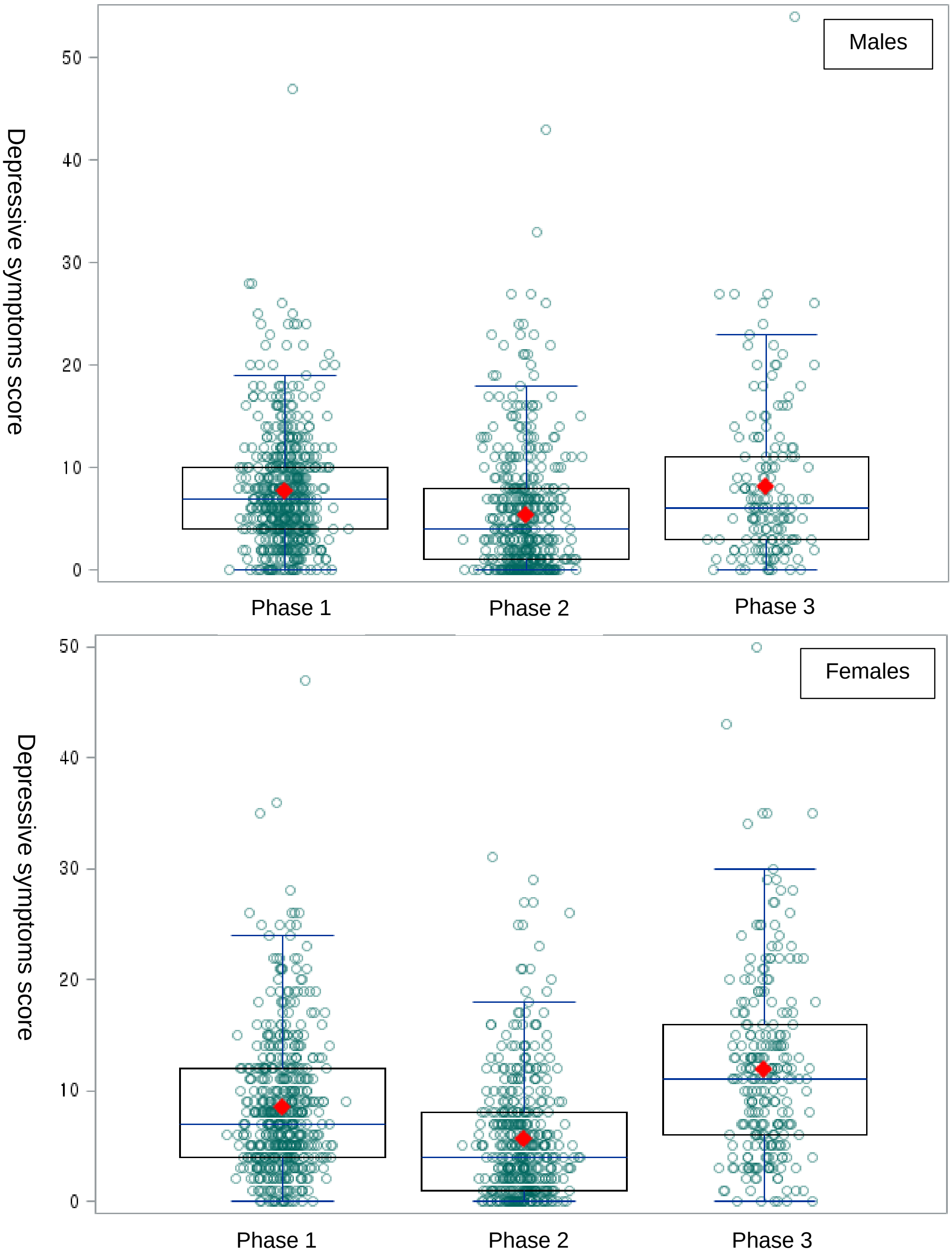

Figure 3. Distribution of depression scores by phases

7. Association between changes in lipid concentrations at phase 1 and 2 and depression symptoms at phase 3

Table 11 and 12 shows associations between the changes in lipid concentrations measured during phase 1 and 2 and depressive symptoms at phase 3 for males and females. In both males and females, the highest tertile for total cholesterol had significantly higher depressive symptoms in comparison to the lowest tertile after adjusting for age, BMI, depressive symptoms in phase 1, follow-up period, household income, smoking status, alcohol intake, physical activity, study year and total cholesterol in phase 1 (β = 4.02, p = 0.013 for males; β = 3.82, p = 0.008 for females). All results were similar following the exclusion of participants with depressive symptoms (BDI score $\geq$ 10) at baseline (Appendix Table 5 and 6).

Table 11. Association between changes in lipid concentrations at phase 1 and 2 and depression symptoms score at phase 3 in males (n = 126)

Δ Serum lipids	N (%)	Model 1			Model 2			Model 3			Model 4		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl													
T1 (< 4)	48 (38.1)	Ref			Ref			Ref			Ref		
T2 (4 -< 17)	39 (31.0)	0.63	1.64	0.700	0.24	1.62	0.881	0.20	1.61	0.904	0.52	1.59	0.742
T3 (≥ 17)	39 (31.0)	3.51	1.67	0.036	3.55	1.65	0.031	3.54	1.64	0.030	4.02	1.62	0.013
HDL cholesterol, mg/dl													
T1 (< 6)	44 (34.9)	Ref			Ref			Ref			Ref		
T2 (6 -< 12)	39 (31.0)	3.12	1.75	0.074	3.08	1.73	0.076	3.34	1.72	0.053	3.46	1.73	0.046
T3 (≥ 12)	43 (34.1)	2.02	1.83	0.270	2.21	1.82	0.226	2.36	1.81	0.193	2.35	1.81	0.193
Log Triglycerides, mg/dl													
T1 (< -0.26)	47 (37.3)	Ref			Ref			Ref			Ref		
T2 (-0.26 -< 0.05)	39 (31.0)	2.67	1.64	0.104	1.93	1.74	0.267	2.00	1.73	0.246	2.36	1.74	0.176
T3 (≥ 0.05)	40 (31.8)	0.90	1.63	0.582	0.63	1.64	0.703	0.74	1.63	0.652	1.34	1.70	0.433

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus lipid concentrations in phase 1

Table 12. Association between changes in lipid concentrations at phase 1 and 2 and depression symptoms score at phase 3 in females (n = 195)

Δ Serum lipids	N (%)	Model 1			Model 2			Model 3			Model 4		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl													
T1 (< -7)	80 (41.0)	Ref			Ref			Ref			Ref		
T2 (-7 -< 10)	55 (28.2)	0.35	1.41	0.805	0.19	1.41	0.894	0.42	1.41	0.767	0.94	1.42	0.510
T3 (≥ 10)	60 (30.8)	2.54	1.36	0.062	2.59	1.35	0.054	2.94	1.35	0.030	3.82	1.43	0.008
HDL cholesterol, mg/dl													
T1 (< 4)	58 (29.7)	Ref			Ref			Ref			Ref		
T2 (4 -< 13)	64 (32.8)	0.34	1.43	0.812	0.31	1.42	0.830	0.61	1.43	0.669	0.71	1.46	0.623
T3 (≥ 13)	73 (37.4)	0.73	1.47	0.619	0.60	1.48	0.685	0.93	1.49	0.532	1.06	1.53	0.491
Log triglycerides, mg/dl													
T1 (< -0.33)	78 (40.0)	Ref			Ref			Ref			Ref		
T2 (-0.33 -< 0)	58 (29.7)	0.82	1.39	0.554	0.84	1.38	0.541	0.75	1.37	0.584	1.04	1.37	0.449
T3 (≥ 0)	59 (30.3)	-1.34	1.47	0.360	-1.28	1.45	0.378	-2.03	1.50	0.174	-1.19	1.57	0.448

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus lipid concentrations in phase 1

8. Association between serum lipids-change groups at phase1 and 2 and depression symptoms at phase 3

Table 13 and 14 shows associations between the lipids change groups that were measured during phase 1 and 2 and depressive symptoms at phase 3 for males and females. In males, participants with consistently high levels of total cholesterol and triglycerides reported higher depressive symptoms than stable individuals ($\beta = 6.00$, $p = 0.010$ for total cholesterol; $\beta = 5.37$, $p = 0.028$ for triglycerides): a U-shaped association was identified for males (Figure 4 and 6). In females, the lipid change groups were not associated with depressive symptoms at phase 3 before and after adjusting for covariates (Table 14 and Figure 4-6). All results were similar following the exclusion of participants with depressive symptoms (BDI score $\geq$ 10) at baseline (Appendix Table 7 and 8).

Table 13. Association between serum lipids-change groups at phase1 and 2 and depressive symptoms at phase 3 in males (n = 126)

Lipid change groups	N (%)	BDI score	Model 1			Model 2			Model 3		
		Mean ± SD	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol											
Consistently low	29 (25.2)	8.7 ± 6.6	4.08	2.28	0.074	4.65	2.34	0.047	4.33	2.40	0.071
Decrease	30 (26.1)	7.1 ± 5.5	2.41	2.27	0.289	3.22	2.33	0.167	2.99	2.36	0.204
Stable	17 (14.8)	4.7 ± 3.8	Ref			Ref			Ref		
Increase	9 (7.8)	8.9 ± 6.6	4.47	3.08	0.147	5.58	3.11	0.073	5.30	3.15	0.092
Consistently high	30 (26.1)	10.7 ± 11.7	5.85	2.26	0.010	6.39	2.24	0.004	6.00	2.34	0.010
HDL cholesterol											
Consistently low	34 (29.8)	6.9 ± 5.9	-3.75	2.27	0.100	-3.70	2.22	0.097	-3.61	2.20	0.101
Decrease	23 (20.2)	8.5 ± 6.4	-1.72	2.49	0.490	-1.79	2.46	0.467	-1.97	2.44	0.418
Stable	18 (15.8)	10.4 ± 12.1	Ref			Ref			Ref		
Increase	17 (14.9)	7.9 ± 7.3	-2.23	2.57	0.386	-2.36	2.55	0.354	-2.09	2.53	0.409
Consistently high	22 (19.3)	8.1 ± 8.3	-1.84	2.41	0.445	-1.80	2.40	0.454	-1.63	2.38	0.493
Log triglycerides											
Consistently low	22 (19.6)	7.9 ± 7.2	1.17	2.32	0.615	1.20	2.31	0.603	1.14	2.29	0.619
Decrease	36 (32.1)	7.2 ± 6.9	0.44	2.10	0.835	0.68	2.12	0.747	0.77	2.11	0.715
Stable	22 (17.9)	7.1 ± 4.6	Ref			Ref			Ref		
Increase	16 (14.3)	8.2 ± 5.6	2.01	2.54	0.429	1.47	2.60	0.571	1.22	2.59	0.639
Consistently high	18 (16.1)	12.1 ± 13.0	5.07	2.47	0.041	5.34	2.46	0.030	5.37	2.44	0.028

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Table 14. Association between serum lipids-change groups at phase1 and 2 and depressive symptoms at phase 3 in females (n = 195)

Lipid change groups	N (%)	BDI score	Model 1			Model 2			Model 3		
		Mean ± SD	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol											
Consistently low	49 (26.6)	12.5 ± 8.1	-0.05	2.01	0.980	-0.40	1.99	0.842	-0.50	1.98	0.803
Decrease	51 (27.7)	11.5 ± 8.7	-0.91	1.99	0.649	-0.93	1.97	0.638	-1.04	1.97	0.598
Stable	23 (12.5)	12.1 ± 7.2	Ref			Ref			Ref		
Increase	24 (13.0)	10.4 ± 5.2	-1.91	2.29	0.405	-1.58	2.26	0.484	-1.17	2.28	0.610
Consistently high	37 (20.1)	12.3 ± 9.7	0.46	2.09	0.825	0.77	2.07	0.710	0.82	2.07	0.690
HDL cholesterol											
Consistently low	40 (22.4)	14.3 ± 11.0	0.28	1.91	0.883	-0.22	1.92	0.910	-0.24	1.92	0.900
Decrease	49 (27.4)	10.9 ± 7.0	-2.82	1.81	0.120	-3.08	1.82	0.091	-3.05	1.82	0.093
Stable	32 (17.3)	12.5 ± 7.3	Ref			Ref			Ref		
Increase	20 (11.2)	10.5 ± 8.5	-3.27	2.27	0.149	-3.89	2.28	0.088	-3.70	2.29	0.106
Consistently high	39 (21.8)	11.5 ± 7.1	-1.43	1.87	0.444	-1.75	1.85	0.347	-1.60	1.86	0.389
Log triglycerides											
Consistently low	36 (20.0)	11.5 ± 7.6	-0.91	2.26	0.689	-0.56	2.25	0.802	-1.21	2.28	0.598
Decrease	62 (34.4)	11.9 ± 8.0	-0.73	2.13	0.732	-0.64	2.11	0.762	-0.66	2.10	0.754
Stable	19 (10.6)	12.4 ± 8.0	Ref			Ref			Ref		
Increase	33 (18.3)	11.4 ± 8.5	-1.31	2.36	0.578	-1.04	2.34	0.656	-1.84	2.39	0.443
Consistently high	30 (16.7)	13.5 ± 9.6	0.42	2.35	0.858	0.32	2.35	0.891	-0.11	2.36	0.962

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

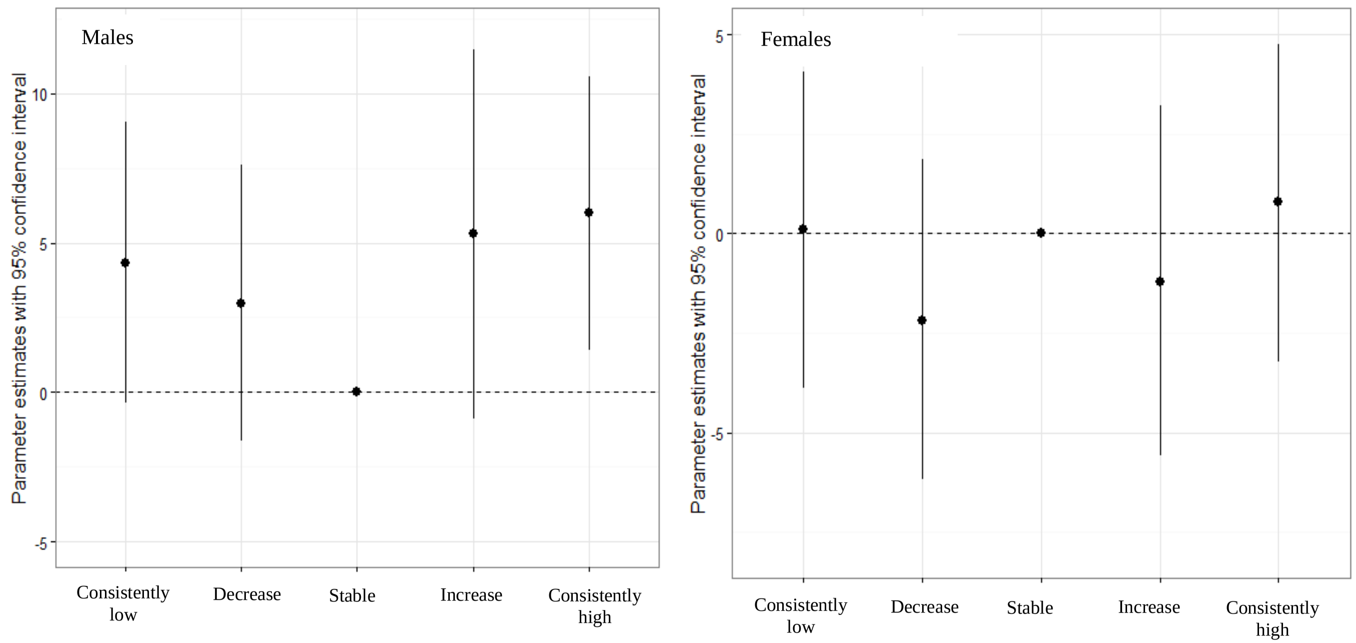

Figure 4. Association between total cholesterol change groups at phase1 and 2 and depressive symptoms at phase 3

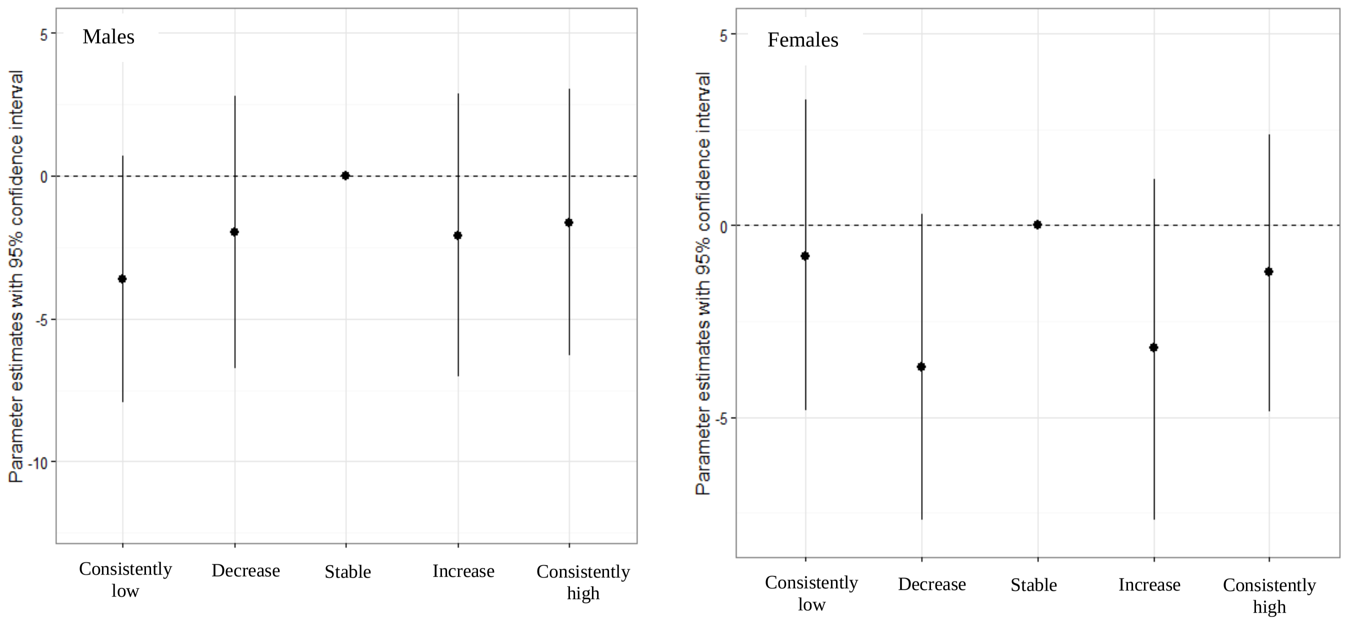

Figure 5. Association between HDL cholesterol change groups at phase1 and 2 and depressive symptoms at phase 3

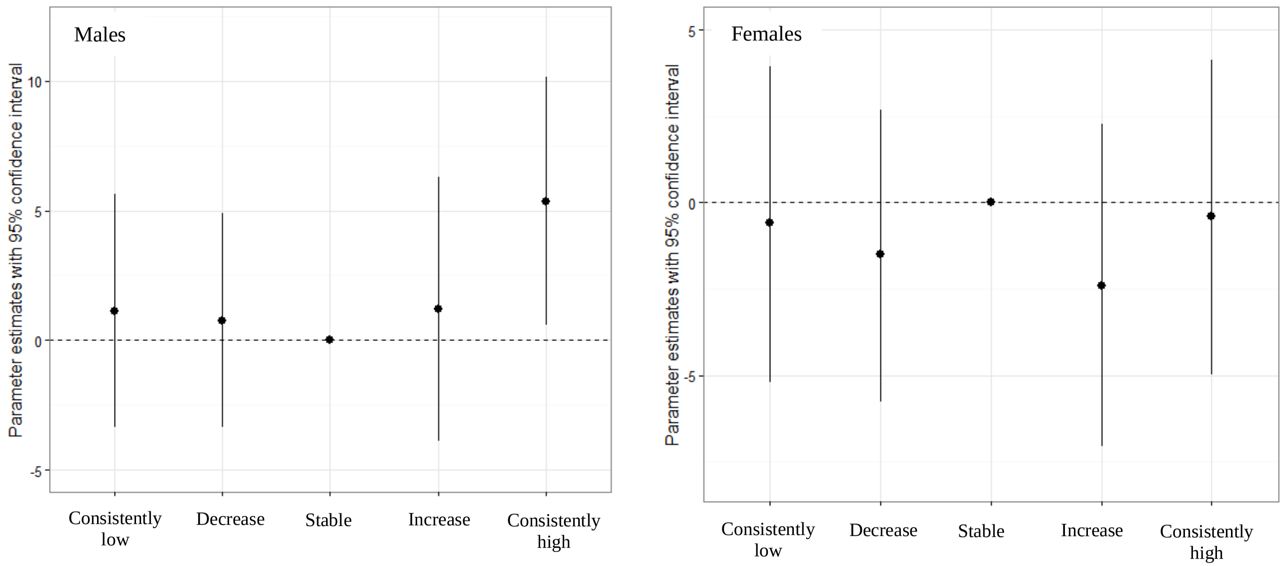

Figure 6. Association between triglycerides change groups at phase1 and 2 and depressive symptoms at phase 3

9. Association between mean of lipid concentrations during phase 1 and 2 and depression symptoms at phase 3

Table 15 and 16 shows associations between the mean of lipid concentrations that were measured during phase 1 and 2 and depressive symptoms at phase 3 for males and females. In males, the highest tertile for total cholesterol and triglycerides had significantly higher depressive symptoms at phase3 compared to the intermediate tertile after adjusting for age, BMI, depressive symptoms in phase 1, follow-up period, household income, smoking status, alcohol intake, physical activity and study year (β = 3.07, p = 0.042 for total cholesterol; β = 3.49, p = 0.018 for triglycerides). A one SD increase in total cholesterol and triglycerides was associated with depressive symptoms at phase3 (β = 1.58, p = 0.022 for total cholesterol; β = 1.33, p = 0.050 for triglycerides). In females, the mean of lipid concentrations were not associated with depressive symptoms at phase 3 before and after adjusting for covariates. All results were similar after excluding participants with having depressive symptoms (BDI score $\geq$ 10) at baseline (Appendix Table 7).

Table 15. Association between mean of lipid concentrations during adolescence and depressive symptoms score at phase 3 in males (n = 141)

Serum lipids	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (< 141)	47	0.73	1.42	0.606	1.01	1.46	0.491	0.75	1.48	0.612
T2 (141 -< 157)	46	Ref			Ref			Ref		
T3 (≥ 157)	48	3.38	1.50	0.024	3.35	1.49	0.025	3.07	1.51	0.042
Continuous, per SD		1.54	0.69	0.026	1.64	0.68	0.018	1.58	0.68	0.022
HDL cholesterol, mg/dl										
T1 (< 44)	45	Ref			Ref			Ref		
T2 (44 -< 52)	47	1.63	1.46	0.263	1.76	1.42	0.216	1.74	1.42	0.219
T3 (≥ 52)	49	1.33	1.54	0.385	1.12	1.54	0.469	1.31	1.54	0.393
Continuous, per SD		0.05	0.71	0.949	0.01	0.72	0.989	0.03	0.72	0.963
Log triglycerides, mg/dl										
T1 (< 4.11)	47	0.85	1.44	0.555	1.20	1.43	0.401	1.31	1.42	0.357
T2 (4.11 -< 4.38)	46	Ref			Ref			Ref		
T3 (≥ 4.38)	48	3.44	1.50	0.022	3.43	1.49	0.022	3.49	1.48	0.018
Continuous, per SD		1.40	0.67	0.038	1.36	0.67	0.046	1.33	0.67	0.050

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Table 16. Association between mean of lipid concentrations during adolescence and depressive symptoms score at phase 3 in females (n = 208)

Serum lipids	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (< 152)	68	1.74	1.23	0.158	1.55	1.24	0.211	1.38	1.24	0.265
T2 (152 -< 172)	67	Ref			Ref			Ref		
T3 (≥ 172)	73	1.50	1.34	0.261	1.31	1.34	0.326	1.33	1.33	0.319
Continuous, per SD		0.702	0.56	0.210	0.76	0.57	0.185	0.80	0.57	0.164
HDL cholesterol, mg/dl										
T1 (< 50)	69	Ref			Ref			Ref		
T2 (50 -< 58)	70	-1.83	1.22	0.133	-1.75	1.21	0.148	-1.62	1.21	0.182
T3 (≥ 58)	69	-0.41	1.27	0.745	-0.36	1.27	0.778	-0.33	1.26	0.792
Continuous, per SD		0.23	0.60	0.702	0.28	0.62	0.653	0.23	0.61	0.712
Log triglycerides, mg/dl										
T1 (< 4.11)	73	Ref			Ref			Ref		
T2 (4.11 -< 4.36)	68	0.21	1.22	0.863	-0.01	1.22	0.994	0.17	1.22	0.887
T3 (≥ 4.36)	67	1.11	1.23	0.366	0.80	1.24	0.517	0.88	1.23	0.477
Continuous, per SD		0.57	0.56	0.308	0.48	0.57	0.396	0.53	0.57	0.348

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

IV. DISCUSSION

1. Summary of Findings

The principal findings of this longitudinal study are that serum lipids in adolescence were associated with depressive symptoms in early adulthood. In males, high level of total cholesterol in 16-year-old adolescents was associated with elevated depressive symptoms in early adulthood. In addition, we found a U-shape association in which males in the lowest and highest tertiles of total cholesterol reported higher depressive symptoms than those in the intermediate tertile. According to results of absolute changes in serum lipids between males aged 16 and 18 years, the group with the highest increase in total cholesterol had higher depressive symptoms in early adulthood than the lowest group. In addition, participants with consistently high levels of total cholesterol and triglycerides reported higher depressive symptoms than stable individuals. According to results of mean serum lipid concentrations between males aged 16 and 18 years, high levels of total cholesterol and triglycerides were associated with elevated depressive symptoms in adulthood. In females, high level of triglycerides in 16-year-old adolescents was associated with elevated depressive symptoms in early adulthood. According to results of absolute changes in serum lipids between females aged 16 and 18 years, the group with the highest increase in total cholesterol had higher depressive symptoms in early adulthood than the lowest group. All results were similar following the exclusion of participants with depressive symptoms (BDI score $\geq$ 10) at baseline.

2. Comparison with previous studies

Several previous studies have confirmed that biological markers might be linked to depression and suicidality, among which serum lipid levels might play an important role. Indeed, experimental evidence indicates that lipid fluidity markedly modulates the binding of serotonin in mouse brain membranes. Therefore, with low cholesterol levels, cellular membrane fluidity increases and serotonin receptors are less exposed to serotonin in the synaptic cleft[26]. Evidence also exists of an association between reduced serotonin activity and suicide[27]. Nevertheless, there has been considerable controversy about the association between serum lipid levels and mental health in observational studies. Some previous studies show that suicide attempters demonstrated lower cholesterol levels[28-30], while others report positive associations between cholesterol and completed suicide[15, 31, 32]. Still other studies indicate that there was no evidence for an association between serum cholesterol and suicidality[33, 34]. These discrepancies in findings may be due to different sample sizes and different ages of participants, as well as various methods of measuring depression used by researchers, together with the background psychiatric illness of study participants.

Finding from previous studies based on the general population indicated that serum lipid is significantly associated with depression or suicidal ideation. A previous cross-sectional study[9] suggested that the level of HDL cholesterol was significantly higher in men with depression, and in women, high level of triglyceride was associated with depression. Higher level of triglyceride was an only factor that predicted suicidality age under 65. Another cross-sectional study[10] found that lower triglycerides level were significantly associated with a decreased risk of suicidal ideation only among men. However, no significant associations were found with other lipid profiles, such as a total cholesterol, LDL cholesterol, or HDL cholesterol among either men or women. Consistent with these studies, we found that both higher total and HDL cholesterol concentrations were significantly associated with an increased risk of depressive symptoms during adolescence only among males.

In addition, we suggest that lipid profiles in adolescence are significantly associated with depressive symptoms in early adulthood. To the best of our knowledge, however, there are only two studies examining the association between serum cholesterol concentrations and mental health. One study[35] was conducted in adolescent psychiatric in-patients aged 12 to 21 years, suggesting that serum cholesterol levels were significantly higher in adolescent patients who were currently suicidal than in non-suicidal adolescents. The other study[36] was conducted in young adults aged 17 to 39 years, suggesting that low level of serum HDL cholesterol was significantly associated with suicide attempts, but not with suicide ideation, in young women. In that study, serum cholesterol was shown to be unrelated to either suicide ideation or suicide attempts in young men. The results of these previous studies are not comparable to our results because no cohort studies have been conducted in adolescents without depression, and most studies on adolescent depression have focused on psychiatric in-patients. Thus, we compared our results with the findings of prospective studies of participants in middle and older adulthood. A longitudinal study[11] from the Canadian Mortality Database suggests that serum total cholesterol concentrations in the lowest quartile of a sample population showed that subjects in the group had a greater than six-fold increased risk of committing suicide in comparison to subjects in the highest quartile. Findings of an inverse association between serum total cholesterol level and suicide have also been noted elsewhere[12, 37, 38]. Consistent with the findings of these studies, we found that males in the lowest tertile of total cholesterol in adolescence reported higher depressive symptoms in early adulthood than males in the intermediate tertile. However, we also found that high and low levels of total cholesterol at age 16 were significantly associated with higher depressive symptoms in early adulthood. Moreover, participants with consistently high level of total cholesterol reported higher depressive symptoms than stable individuals. Additionally, high level of mean total cholesterol between subjects aged 16 and 18 years was associated with higher depressive symptoms in early adulthood. The findings from our study are supported by the findings of several previous studies[32, 39]. The results of a longitudinal study[39] with two years of follow-up in a Korean elderly population are similar to our results. Kim et al. suggested that both higher and lower total and LDL cholesterol levels at baseline together with a decline in total cholesterol level over the follow-up period predicted an increased incidence of suicidal ideation at follow-up. A large Japanese general population cohort study[32] with an average follow-up of 20 years suggests that high total cholesterol level was associated with an almost two-fold increase in risk of suicide in women.

We also found that the level of triglycerides in adolescence were significantly associated with depressive symptoms in early adulthood. In previous cross-sectional study[40] in the Japanese population, elevated depressive symptoms were associated with hypertriglyceridemia in Japanese male workers. In previous cross-sectional study[31] in the Germany population, triglycerides showed a positive association with attempted suicide and ‘‘thinking a lot about death’’ in subjects with depressive symptoms during the past 12 months versus subjects with major depression without suicide attempts. Consistent with these studies, we found that participants with consistently high level of triglycerides reported higher depressive symptoms than stable individuals and high level of mean triglycerides between 16 and 18 years old was associated with higher depressive symptoms in early adulthood among males. In females, high level of triglycerides at age 16 significantly associated with higher depressive symptoms in early adulthood.

3. Possible mechanisms

The role of lipids in neuronal function in the brain is increasingly recognized[41]. The lipid composition of the brain substantially influences subjective perception, mood, and emotional behavior[42]. A previous study proposes a hypothesis regarding an association between low cholesterol and depression[12]. According to this hypothesis, cholesterol is distributed in the phospholipid layer in biological membranes, where it is loosely bound and thus able to freely exchange with serum cholesterol[43]. Accordingly, any reduction in serum cholesterol may decrease brain-cell membrane cholesterol, lower lipid microviscosity, and decrease serotonin concentration or receptors. These processes will reduce the amount of serotonin in the brain, hence causing depression. The fact that low serum cholesterol concentration in subjects with depression was shown to rise significantly following clinical recovery points to the need for further research in this area.

This study supports an association between higher levels of triglycerides as well as total cholesterol level and an increased risk of depression from adolescence to early adulthood. These results differ from the results of most studies in adult populations that report an association between low cholesterol and mental health. One possible explanation for the variance in findings is that the increase in triglycerides and total cholesterol levels following psychological distress could result from direct sympathetic activation[44-47]. Furthermore, dietary differences in target populations should be considered. Decreased appetite, one of the symptoms of major depression and a symptom that may cause low cholesterol, is relatively infrequent in adolescents[48]. Moreover, adolescents with depressive symptoms have been shown to have higher scores on an unhealthy diet scale and to exhibit more unhealthy changes in diet over the follow-up period[49, 50]. Our results do not show any association between BMI and depression, people who frequently eat unhealthy foods, such as refined sugars and saturated fats, tend to have a lower intake of omega-3 polyunsaturated fatty acids (ω-3 PUFAs). It is well established that ω-3 PUFAs lower serum cholesterol and triglycerides[51-54]. The mechanism for these lipid-lowering effects seems to involve activation of peroxisome proliferator-activated receptors (PPARs)[55]. Although fatty acids (FA) are classically observed as an energy substrate, they are also endogenous ligands for PPARs and regulate the expression of genes encoding key proteins controlling fatty acid uptake and metabolism and the formation of very-low-density lipoproteins carrying triglycerides in the liver[55, 56]. Although the exact transcriptional mechanism by which fish oils improve lipid levels is not completely understood, ω-3 PUFAs do reduce hepatic synthesis of triglycerides and increase hepatic fatty acid beta-oxidation[57]. The lipid composition of the brain can be altered with long-term changes in diet. This effect may have direct consequences on mood and emotional behavior. Several lines of evidence indicate that an association exists between ω-3 PUFAs and depression. This relationship is confirmed in both observational and experimental research and is consistent across study designs, study groups, and populations. In case-control studies, serum lipid analyses have revealed lower concentration of ω-3 PUFAs in cases of depressed subjects in comparison to non-depressed controls[58-61]. Additionally, in two cohort studies, females with postpartum depression had lower concentration of ω-3 PUFAs in comparison to non-depressed female participants[62, 63]. Brain membranes contain a high proportion of PUFAs, with n-3 FA being the most prevalent in the brain's gray matter [64, 65]. n-3 PUFAs cannot be synthetized de novo by mammals but must be obtained from the diet. The incorporation of these FA into the brain occurs most efficiently during the infancy and requires more time during adulthood [66, 67]. The effects of n-3 FA deprivation on brain content and behavior can be accumulated over the course of the diet and over several generations[68-70]. Cortex, hippocampus, striatum and recently also the cerebellum are brain areas serving a multitude of different functions in behavioral organization and performance, and dysfunction of them was associated with depression[71, 72]. The mechanism between serum lipids and mental health has not yet been precisely identified.

4. Limitations

The present study has several limitations. First, we measured depressive symptoms using a self-reported questionnaire. There is a possibility of misclassification bias in measuring depressive symptoms. Second, depressive symptoms at phase 2 were assessed immediately after college entrance examination during follow-up. Changes in serum lipid profiles may cause depression, but changes in diet or activity related to depression may likewise cause changes in serum lipid profiles. We tried to identify the bidirectional relationship between serum lipids and depressive symptoms, but BDI score decreased overall for participants at phase 2 (Figure 3) and did not yield meaningful results (Appendix Table 11-13). Third, it is well known that serum lipids are mainly affected by nutrition and nutritional status is related to depression. The current study, however, did not control for nutritional effects because there is no nutrition information for participants herein. Fourth, although we considered a wide range of potential confounders, it is possible that imprecision in measurement could lead to residual confounding, and there remains the possibility of confounders by other unconsidered factors. Lastly, because our study population was limited to students from a single rural area, our findings may not be generalizable.

V. CONCLUSIONS

This study showed that both low and high cholesterol levels were associated with depressive symptoms in males and a large increase in total cholesterol was associated with depressive symptoms in both sexes. In addition, persistently high total cholesterol during adolescence predicts an increased risk of depressive symptoms in early adulthood in males. These findings suggest that different strategies to manage lipid risk factors by age and sex should be developed. Further studies are necessary to examine age and sex differences in the relationship between lipid levels and depression and to investigate the biological and behavioral mechanisms involved.

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APPENDIX

Appendix Table 1. Association between lipid concentrations at phase 1 and depressive symptoms score at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in males (n = 113)

Serum lipids at phase 1	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (<136)	39	2.50	1.67	0.134	2.76	1.57	0.079	2.46	1.63	0.132
T2 (136-<154)	34	Ref			Ref			Ref		
T3 (≥ 154)	40	4.68	1.67	0.005	3.98	1.57	0.011	3.70	1.62	0.022
Continuous, per SD		2.10	0.79	0.009	1.92	0.80	0.018	2.05	0.80	0.012
HDL cholesterol, mg/dl										
T1 (<39)	42	Ref			Ref			Ref		
T2 (39-<48)	38	1.50	1.77	0.396	0.82	1.75	0.642	0.79	1.74	0.650
T3 (≥ 48)	33	1.71	1.80	0.345	1.00	1.86	0.592	1.47	1.87	0.432
Continuous, per SD		0.77	0.81	0.347	0.37	0.85	0.664	0.65	0.87	0.460
Log triglycerides, mg/dl										
T1 (<4.20)	38	Ref			Ref			Ref		
T2 (4.20-<4.42)	39	1.72	1.76	0.327	1.40	1.72	0.415	1.45	1.71	0.397
T3 (≥ 4.42)	36	2.61	1.70	0.125	2.43	1.67	0.147	2.38	1.66	0.151
Continuous, per SD		1.08	0.73	0.144	0.97	0.73	0.187	1.00	0.73	0.174

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Appendix Table 2. Association between lipid concentrations at phase 1 and depressive symptoms score at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in females (n = 162)

Serum lipids at phase 1	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (<153)	56	1.23	1.49	0.410	1.17	1.49	0.429	1.17	1.48	0.431
T2 (153-<172)	58	Ref			Ref			Ref		
T3 (≥ 172)	57	1.70	1.46	0.246	1.63	1.46	0.429	1.59	1.46	0.277
Continuous, per SD		1.18	0.60	0.053	1.16	0.61	0.059	1.15	0.61	0.062
HDL cholesterol, mg/dl										
T1 (<45)	50	Ref			Ref			Ref		
T2 (45-<55)	63	-1.75	1.54	0.257	-1.67	1.54	0.278	-1.58	1.56	0.309
T3 (≥ 55)	58	-1.01	1.62	0.534	-0.95	1.64	0.562	-1.04	1.65	0.528
Continuous, per SD		-0.14	0.68	0.834	-0.09	0.69	0.893	-0.19	0.71	0.789
Log triglycerides, mg/dl										
T1 (<4.17)	59	Ref			Ref			Ref		
T2 (4.17-<4.47)	54	2.08	1.40	0.138	1.95	1.41	0.166	2.25	1.44	0.118
T3 (≥ 4.47)	58	2.08	1.60	0.192	1.98	1.60	0.216	2.14	1.60	0.182
Continuous, per SD		1.63	0.63	0.011	1.57	0.64	0.016	1.67	0.65	0.011

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Appendix Table 3. Baseline and follow-up (phase 2) characteristics according to study year in males

Variables	2007 (n = 140)	2010 (n = 140)	2011 (n = 136)	2012 (n = 133)	*p*-value
Age, years	15.68 ± 0.4	15.86 ± 0.3	15.9 ± 0.3	16.3 ± 0.3	
Depressive symptom, score	9.5 ± 5.7	7.2 ± 6.0	6.5 ± 5.0	7.3 ± 5.0	<.001
Normal (0 to 9)	88 (60.3)	102 (71.8)	108 (79.4)	94 (70.7)	
Mild (10 to 16)	37 (25.3)	33 (23.2)	23 (16.9)	32 (24.1)	0.002
Moderate to severe (17 to 63)	21 (14.4)	7 (4.9)	5 (3.7)	7 (5.3)	
Metabolic factors					
BMI, kg/m^2	21.9 ± 3.4	22.4 ± 3.3	22.2 ± 3.2	22.1 ± 3.1	0.548
Waist circumference, cm	73.6 ± 8.6	73.9 ± 7.5	75.3 ± 8.6	71.7 ± 7.4	0.004
Total cholesterol, mg/dl	148.9 ± 28.1	145.0 ± 21.4	150.0 ± 26.5	151.2 ± 21.1	0.184
HDL cholesterol, mg/dl	39.7 ± 9.2	41.4 ± 7.9	43.0 ± 7.7	53.2 ± 9.3	<.001
Triglycerides, mg/dl	83 [58-104]	74 [62-86]	83 [65-99]	73 [54-89]	0.093
Monthly household income, won					
Do not wish to answer	40 (27.4)	33 (23.2)	37 (27.2)	51 (38.4)	
< 3.0 million	33 (22.6)	21 (14.8)	18 (13.2)	19 (14.3)	0.003
3.0-<5.0 million	40 (27.4)	54 (38.0)	40 (29.4)	22 (16.5)	
≥ 5.0 million	33 (22.6)	34 (23.9)	41 (30.2)	41 (30.8)	
Health behaviors					
Current cigarette smoking	4 (2.7)	12 (8.5)	12 (8.8)	17 (12.8)	0.021
Current alcohol drinking	32 (21.9)	9 (6.3)	10 (7.4)	9 (6.8)	<.001
Regular exercise	142 (97.3)	136 (95.8)	135 (99.3)	130 (97.7)	0.318

Data are expressed as means ± standard deviation.
BMI, Body mass index; HDL, high-density lipoprotein.

Appendix Table 4. Baseline and follow-up (phase 2) characteristics according to study year in females

Variables	2007 (n = 133)	2010 (n = 135)	2011 (n = 131)	2012 (n = 108)	*p*-value
Age, years	15.7 ± 0.3	15.8 ± 0.3	15.9 ± 0.3	16.3 ± 0.3	
Depressive symptom, score	9.9 ± 6.8	8.7 ± 6.1	8.0 ± 5.9	7.1 ± 5.1	<.001
Normal (0 to 9)	76 (27.4)	92 (23.2)	89 (27.2)	79 (38.4)	
Mild (10 to 16)	40 (22.6)	30 (14.8)	29 (13.2)	23 (14.3)	0.201
Moderate to severe (17 to 63)	17 (27.4)	13 (38.0)	13 (29.4)	6 (16.5)	
Metabolic factors					
BMI, kg/m^2	21.0 ± 2.7	21.2 ± 2.6	21.3 ± 2.5	21.6 ± 2.6	0.251
Waist circumference, cm	72.9 ± 6.6	65.9 ± 5.8	68.8 ± 6.0	66.3 ± 6.0	<.001
Total cholesterol, mg/dl	158.7 ± 24.9	159.5 ± 24.4	164.8 ± 26.1	168.4 ± 28.9	0.018
HDL cholesterol, mg/dl	46.1 ± 9.7	47.7 ± 8.7	48.2 ± 9.1	59.6 ± 11.5	<.001
Triglycerides, mg/dl	65 [52-83]	81 [81-97]	74 [59-94]	75 [56-93]	<.001
Monthly household income, won					
Do not wish to answer	26 (27.4)	39 (23.2)	43 (27.2)	29 (38.4)	
< 3.0 million	35 (22.6)	11 (14.8)	12 (13.2)	14 (14.3)	0.001
3.0-<5.0 million	45 (27.4)	49 (38.0)	39 (29.4)	33 (16.5)	
≥ 5.0 million	27 (22.6)	36 (23.9)	37 (30.2)	32 (30.8)	
Health behaviors					
Current cigarette smoking	1 (0.8)	1 (0.7)	1 (0.8)	0 (0.0)	0.845
Current alcohol drinking	5 (3.8)	8 (5.9)	6 (4.6)	7 (6.5)	0.759
Regular exercise	132 (99.3)	135 (100.0)	131 (99.2)	108 (100.0)	0.605

Data are expressed as means ± standard deviation.
BMI, Body mass index; HDL, high-density lipoprotein.

Appendix Table 5. Association between changes in lipid concentrations and depression symptoms score at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in males (n = 113)

Δ Serum lipids	N	Model 1			Model 2			Model 3			Model 4		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl													
T1 (<4)	40	Ref			Ref			Ref			Ref		
T2 (4-<17)	37	1.69	1.65	0.307	1.96	1.60	0.219	1.66	1.61	0.302	1.75	1.56	0.262
T3 (≥ 17)	36	4.55	1.73	0.008	5.17	1.71	0.003	4.96	1.71	0.004	5.08	1.65	0.002
HDL cholesterol, mg/dl													
T1 (<6)	37	Ref			Ref			Ref			Ref		
T2 (6-<12)	31	0.00	1.84	0.999	0.66	1.80	0.713	0.44	1.81	0.808	0.83	1.85	0.653
T3 (≥ 12)	45	1.90	1.71	0.266	2.42	1.70	0.154	2.00	1.74	0.251	2.23	1.75	0.203
Log Triglycerides, mg/dl													
T1 (<-0.26)	45	Ref			Ref			Ref			Ref		
T2 (-0.26-<0.05)	33	0.86	1.74	0.622	0.24	1.75	0.889	0.38	1.74	0.825	1.32	1.79	0.460
T3 (≥ 0.05)	35	1.53	1.69	0.368	1.22	1.68	0.469	1.36	1.67	0.415	2.43	1.75	0.165

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus lipid concentrations in phase 1

Appendix Table 6. Association between changes in lipid concentrations and depression symptoms score at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in females (n = 162)

Δ Serum lipids	N	Model 1			Model 2			Model 3			Model 4		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl													
T1 (<-7)	68	Ref			Ref			Ref			Ref		
T2 (-7-<10)	50	-0.50	1.46	0.734	-0.62	1.48	0.675	-0.42	1.50	0.781	0.35	1.50	0.816
T3 (≥ 10)	44	1.20	1.50	0.425	1.24	1.51	0.413	1.47	1.54	0.340	2.81	1.60	0.079
HDL cholesterol, mg/dl													
T1 (<4)	68	Ref			Ref			Ref			Ref		
T2 (4-<13)	50	0.65	1.43	0.649	0.48	1.43	0.735	0.67	1.48	0.651	0.75	1.51	0.621
T3 (≥ 13)	44	-0.54	1.46	0.710	-0.67	1.47	0.648	-0.33	1.63	0.840	-0.23	1.68	0.893
Log triglycerides, mg/dl													
T1 (<-0.33)	75	Ref			Ref			Ref			Ref		
T2 (-0.33-<0)	42	0.10	1.48	0.945	0.07	1.48	0.963	0.22	1.48	0.885	0.41	1.46	0.777
T3 (≥ 0)	45	-2.02	1.53	0.187	-2.01	1.53	0.187	-2.18	1.53	0.156	-0.75	1.63	0.645

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus lipid concentrations in phase 1

Appendix Table 7. Association between serum lipids-change groups at phase1 and 2 and depressive symptoms at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in males (n=83)

Lipid change groups	N (%)	BDI score	Model 1			Model 2			Model 3		
		Mean ± SD	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol											
Consistently low	21 (25)	7.9 ± 5.7	3.80	2.58	0.142	4.66	2.61	0.075	4.55	2.77	0.101
Decrease	19 (22.6)	5.0 ± 4.1	1.48	2.67	0.580	2.42	2.74	0.377	2.35	2.81	0.404
Stable	14 (16.7)	4.5 ± 3.8	Ref			Ref			Ref		
Increase	8 (9.5)	8.5 ± 7.0	4.51	3.32	0.174	6.36	3.39	0.061	6.28	3.46	0.070
Consistently high	22 (26.2)	11.1 ± 12.6	6.85	2.58	0.008	7.10	2.51	0.005	6.99	2.67	0.009
HDL cholesterol											
Consistently low	23 (27.7)	5.3 ± 4.1	-5.86	2.73	0.032	-5.43	2.69	0.043	-5.61	2.66	0.035
Decrease	15 (18.1)	7.6 ± 5.4	-3.30	3.01	0.273	-4.19	3.03	0.167	-4.74	3.02	0.116
Stable	13 (15.7)	11.0 ± 14.2	Ref			Ref			Ref		
Increase	15 (18.1)	8.3 ± 7.7	-2.36	2.85	0.408	-2.46	2.82	0.384	-2.37	2.79	0.396
Consistently high	17 (20.5)	7.5 ± 7.5	-3.33	2.76	0.229	-3.95	2.82	0.161	-3.82	2.79	0.171
Log triglycerides											
Consistently low	17 (20.0)	7.6 ± 6.4	0.85	2.70	0.753	0.92	2.70	0.734	0.80	2.68	0.766
Decrease	27 (31.8)	6.3 ± 7.1	-0.40	2.45	0.870	-0.18	2.47	0.942	-0.13	2.45	0.958
Stable	15 (17.7)	6.8 ± 4.9	Ref			Ref			Ref		
Increase	11 (12.9)	7.9 ± 6.4	2.59	3.14	0.410	2.17	3.18	0.496	1.92	3.17	0.545
Consistently high	15 (17.7)	11.8 ± 13.6	5.03	2.81	0.073	5.30	2.79	0.058	5.36	2.77	0.053

BDI, Beck Depression Inventory; HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Appendix Table 8. Association between serum lipids-change groups at phase1 and 2 and depressive symptoms at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in females (n=124)

Lipid change groups	N (%)	BDI score	Model 1			Model 2			Model 3		
		Mean ± SD	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol											
Consistently low	33 (26.6)	11.1 ± 7.6	0.93	2.38	0.696	0.76	2.36	0.746	0.91	2.39	0.705
Decrease	32 (25.8)	9.59 ± 8.6	0.21	2.39	0.931	-0.03	2.38	0.990	-0.03	2.38	0.990
Stable	17 (13.7)	9.94 ± 6.3	Ref			Ref			Ref		
Increase	17 (13.7)	9.41 ± 4.4	-0.37	2.71	0.893	-0.01	2.70	0.999	-0.18	2.74	0.947
Consistently high	25 (20.2)	11.8 ± 10.5	2.80	2.52	0.266	2.90	2.50	0.245	2.95	2.50	0.238
HDL cholesterol											
Consistently low	24 (19.8)	13.3 ± 11.0	0.86	2.22	0.698	0.63	2.24	0.779	0.90	2.26	0.691
Decrease	33 (27.3)	9.42 ± 6.6	-2.59	2.05	0.207	-2.77	2.05	0.176	-2.87	2.05	0.161
Stable	25 (20.7)	11.9 ± 7.3	Ref			Ref			Ref		
Increase	11 (9.1)	7.45 ± 5.1	-4.03	2.80	0.150	-4.14	2.79	0.138	-4.36	2.80	0.120
Consistently high	28 (23.1)	10.2 ± 7.0	-1.34	2.13	0.530	-1.41	2.12	0.508	-1.61	2.13	0.452
Log triglycerides											
Consistently low	25 (20.8)	10.6 ± 7.5	0.84	2.73	0.758	0.86	2.74	0.753	0.63	2.80	0.821
Decrease	41 (34.2)	11.1 ± 7.4	1.66	2.60	0.522	1.59	2.59	0.539	1.56	2.59	0.546
Stable	14 (11.7)	10.3 ± 6.7	Ref			Ref			Ref		
Increase	24 (20.0)	9.92 ± 9.2	0.19	2.82	0.946	0.12	2.83	0.966	-0.06	2.86	0.982
Consistently high	16 (13.3)	12.2 ± 11.0	2.43	3.09	0.432	2.18	3.09	0.481	2.05	3.11	0.509

BDI, Beck Depression Inventory; HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Appendix Table 9. Association between mean of lipid concentrations during adolescence and depressive symptoms score at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in males (n = 104)

Serum lipids	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (<141)	34	1.78	1.76	0.313	2.42	1.80	0.178	2.11	1.85	0.253
T2 (141-<158)	36	Ref			Ref			Ref		
T3 (≥ 158)	34	5.13	1.77	0.004	4.90	1.76	0.005	4.63	1.80	0.010
Continuous, per SD		2.74	0.84	0.002	2.69	0.85	0.002	2.68	0.84	0.002
HDL cholesterol, mg/dl										
T1 (<44)	34	Ref			Ref			Ref		
T2 (44-<52)	32	2.34	1.92	0.222	2.38	1.87	0.203	2.17	1.86	0.245
T3 (≥ 52)	38	2.83	1.90	0.138	2.42	1.95	0.216	2.60	1.95	0.181
Continuous, per SD		0.79	0.82	0.339	0.65	0.87	0.454	0.68	0.86	0.435
Log triglycerides, mg/dl										
T1 (<4.11)	35	1.52	1.82	0.406	1.88	1.81	0.298	2.13	1.80	0.235
T2 (4.11-<4.39)	34	Ref			Ref			Ref		
T3 (≥ 4.39)	35	4.43	1.78	0.013	4.23	1.77	0.017	4.51	1.76	0.010
Continuous, per SD		1.82	0.76	0.019	1.69	0.77	0.030	1.75	0.76	0.024

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Appendix Table 10. Association between mean of lipid concentrations during adolescence and depressive symptoms score at phase 3 after excluding participants with having depressive symptoms (BDI score≥10) at phase 1 in females (n = 137)

Serum lipids	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Total cholesterol, mg/dl										
T1 (<151)	49	2.86	1.57	0.068	2.93	1.60	0.067	2.83	1.63	0.082
T2 (151-<171)	43	Ref			Ref			Ref		
T3 (≥ 171)	45	2.64	1.61	0.100	2.68	1.62	0.098	2.67	1.62	0.098
Continuous, per SD		1.29	0.65	0.049	1.29	0.66	0.052	1.32	0.66	0.049
HDL cholesterol, mg/dl										
T1 (<50)	38	Ref			Ref			Ref		
T2 (50-<58)	50	-2.46	1.65	0.135	-2.45	1.66	0.139	-2.38	1.66	0.151
T3 (≥ 58)	49	-0.88	1.72	0.609	-0.82	1.75	0.640	-0.78	1.76	0.658
Continuous, per SD		0.13	0.76	0.869	0.12	0.78	0.874	0.12	0.78	0.879
Log triglycerides, mg/dl										
T1 (<4.11)	52	2.04	1.55	0.189	2.07	1.56	0.185	2.00	1.57	0.202
T2 (4.11-<4.36)	44	Ref			Ref			Ref		
T3 (≥ 4.36)	41	2.72	1.66	0.102	2.72	1.66	0.102	2.68	1.66	0.107
Continuous, per SD		0.53	0.69	0.444	0.54	0.70	0.440	0.58	0.71	0.412

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index, depressive symptoms in phase 1 and follow-up period
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year

Appendix Table 11. Association between BDI score at phase 1 and total cholesterol at phase 2

Depressive symptoms score	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Males (n=336)										
T1 (<4)	75	Ref			Ref			Ref		
T2 (4-<8)	121	0.82	2.49	0.744	1.01	2.48	0.682	1.22	2.48	0.623
T3 (≥ 8)	140	0.75	2.44	0.760	1.06	2.42	0.661	1.59	2.46	0.517
Continuous, per SD		-0.41	0.95	0.665	-0.19	0.96	0.844	-0.02	0.97	0.984
Females (n=337)										
T1 (<5)	80	Ref			Ref			Ref		
T2 (5-<10)	134	-0.38	2.59	0.882	-0.24	2.56	0.926	-1.41	2.56	0.581
T3 (≥ 10)	123	1.09	2.64	0.679	0.83	2.63	0.752	-0.60	2.64	0.819
Continuous, per SD		-0.06	0.97	0.947	0.09	1.00	0.926	-0.35	0.99	0.724

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index and depressive symptoms in phase 1
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus total cholesterol level in phase 1

Appendix Table 12. Association between BDI score at phase 1 and HDL cholesterol at phase 2

Depressive symptoms score	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Males (n=336)										
T1 (<4)	75	Ref			Ref			Ref		
T2 (4-<8)	121	-2.02	1.11	0.069	-1.93	1.11	0.082	-1.10	0.95	0.247
T3 (≥ 8)	140	-3.26	1.08	0.003	-3.08	1.09	0.005	-1.16	0.94	0.217
Continuous, per SD		-1.34	0.42	0.002	-1.25	0.43	0.004	-0.58	0.37	0.123
Females (n=337)										
T1 (<5)	80	Ref			Ref			Ref		
T2 (5-<10)	134	-2.93	1.21	0.015	-2.91	1.20	0.016	-1.23	1.06	0.247
T3 (≥ 10)	123	-3.00	1.23	0.015	-3.19	1.23	0.010	-1.13	1.09	0.299
Continuous, per SD		-1.06	0.46	0.020	-1.18	0.47	0.012	-0.54	0.41	0.190

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index and depressive symptoms in phase 1
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus HDL cholesterol level in phase 1

Appendix Table 13. Association between BDI score at phase 1 and triglycerides at phase 2

Depressive symptoms score	N	Model 1			Model 2			Model 3		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Males (n=336)										
T1 (<4)	75	Ref			Ref			Ref		
T2 (4-<8)	121	-0.07	0.05	0.174	-0.07	0.05	0.150	-0.08	0.05	0.106
T3 (≥ 8)	140	0.01	0.05	0.788	0.01	0.05	0.806	-0.01	0.05	0.837
Continuous, per SD		0.03	0.02	0.075	0.03	0.02	0.077	0.03	0.02	0.168
Females (n=337)										
T1 (<5)	80	Ref			Ref			Ref		
T2 (5-<10)	134	-0.05	0.05	0.369	-0.05	0.05	0.344	-0.08	0.05	0.129
T3 (≥ 10)	123	0.03	0.05	0.612	0.03	0.05	0.549	-0.002	0.05	0.968
Continuous, per SD		0.02	0.02	0.300	0.03	0.02	0.172	0.02	0.02	0.371

HDL, high-density lipoprotein; SD, Standard deviation; SE, Standard error
Model 1: adjusted for age, body mass index and depressive symptoms in phase 1
Model 2: adjusted for variables in Model 1 plus household income, smoking status, alcohol intake and physical activity
Model 3: adjusted for variables in Model 2 plus study year
Model 4: adjusted for variables in Model 3 plus triglycerides level in phase 1

ABSTRACT (KOREAN)

청소년기의 혈중 지질 농도와 초기 성인기 우울과의 관련성

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배경 및 목적

우리나라 10-30대 사망원인 중 1위는 자살이며, 자살 사망자 중 대다수는 정신과적 질환이 동반되어 있다. 정신과적 질환 중 자살과 연관이 가장 높은 것은 우울증으로 알려져 있는데, 최근 혈중 지질 농도와 우울 및 자살과의 관련성에 대한 연구들이 주목되고 있다. 혈중 지질 농도가 정신건강과 관련이 있다는 연구 결과들이 있으나 이와 상반되는 결과 혹은 관련이 없다는 결과를 보이는 연구들도 있

다. 또한 대부분의 연구들은 이미 정신질환 병력이 있는 환자를 대상으로 하거나 일반 인구 집단을 대상으로 하더라도 중년 또는 노년을 대상으로 한 연구가 대부분이다. 따라서, 본 연구는 한국의 초기 성인을 대상으로 청소년기의 혈중 지질 농도와 우울증상과의 독립적인 관련성을 평가하고자 하였다.

연구 방법

본 연구는 일개 고등학교 재학생을 대상으로 한 전향적 코호트 연구인 JS High School study (JSHS)의 일부로, 고등학교 1학년 재학 기간의 기반 조사, 고등학교 3학년 재학 기간의 1차 추적 조사, 및 초기 성인기의 2차 추적 조사에 참여한 20-26세 사이의 성인을 대상으로 하였다. 추적 관찰 기간은 평균 6년이었다. 혈액검사는 기반 조사와 1차 추적조사에서 두 차례 공복에 시행되었고, 초기 성인기의 우울증상은 자기보고형 척도로 사용되고 있는 한국판 Beck 우울 척도를 이용하였다. 척도의 절단점은 국내에서 표준화되지 않았으므로 본 연구에서는 원점수를 사용하여 총점을 연속형 척도로 사용하였다. 혈중 지질 농도에 따른 우울증상의 관련성을 평가하기 위해서 청소년기의 연령, 체질량지수, 우울 점수, 추적조사기간, 사회경제적 수준, 건강행태, 연구 시점을 보정한 이후에 일반화 된 선형 모형 방식을 이용하였다.

연구 결과

고등학교 1학년에서 3학년 사이의 청소년기 동안 총 콜레스테롤과 중성지방의 농도의 변화 수준이 상위 삼분위수에 속하는 대상자들은 하위 분위수에 비해 초기 성인기의 우울 점수가 남자에서는 4.02점 ($p = 0.013$), 여자에서는 3.82점 ($p = 0.008$)으로 유의하게 높았으며, 남자에서만 지속적으로 높은 총 콜레스테롤과 중

성지방 수치를 보인 그룹에서 안정된 그룹에 비해 우울 점수가 4.51 점 높았다 ($p = 0.014$). 또한, 남자에서 총 콜레스테롤 및 중성지방의 농도와 우울 증상과의 연관성에서 선형이 아닌 U-형의 연관성을 보였다.

결론 및 고찰

본 연구에서는 기존의 연구에서와 마찬가지로 낮은 혈중 콜레스테롤이 우울증상과 연관성이 있었지만, 청소년기 동안 총 콜레스테롤 및 중성지방의 농도가 많이 증가하거나 지속적으로 높은 경우에도 우울 증상의 위험과 연관성이 있었다. 따라서 혈중 지질 농도와 우울증상과의 연관성에서 연령에 따른 생물학적 및 행동적 기전의 차이에 대한 추가적인 연구가 필요한 것으로 생각된다.

중심 단어: 혈중 지질 농도, 우울 증상, 청소년기, 초기 성인기