Trajectories of Lipids Profile and Incident Cardiovascular Disease Risk: A Longitudinal Cohort Study

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Background—The association between low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides with cardiovascular disease (CVD) has been well studied. No previous studies considered trajectory of these lipids jointly. This study aims to characterize longitudinal trajectories of lipid profile jointly and examine its impact on incident CVD.

Methods and Results—A total of 9726 participants (6102 men), aged from 20 to 58 years who had lipids repeatedly measured 3 to 9 times, were included in the study. Three distinct trajectories were identified using the multivariate latent class growth mixture model: inverse U-shape (18.72%; n=1821), progressing (66.03%; n=6422), and U-shape (15.25%; n=1483). Compared with the U-shape class, the adjusted hazard ratio and 95% CI were 1.33 (1.05−1.68) and 1.49 (1.14−1.95) for the progressing and inverse U-shape class, respectively. The area under the curve was calculated using the integral of the model parameters. In the adjusted model, total and incremental area under the curve of lipid profile were significantly associated with CVD risk. Furthermore, the model-estimated levels and linear slopes of lipids were calculated at each age point according to the latent class growth mixture model model parameters and their first derivatives, respectively. After adjusting for covariates, standardized odds ratio of slope increases gradually from 1.11 (1.02, 1.21) to 1.21 (1.12, 1.31) at 20 to 40 years and then decreased to 1.02 (0.94, 1.11) until 60 years.

Conclusions—These results indicate that the lipids profile trajectory has a significant impact on CVD risk. Age between 20 and 42 years is a crucial period for incident CVD, which has implications for early lipids intervention. (*J Am Heart Assoc*. 2019;8: e013479. DOI: 10.1161/JAHA.119.013479.)

Key Words: cardiovascular disease • lipids • longitudinal cohort study • trajectory

Unfavorable lipid profile has been recognized as an important risk factor in the development and progression of cardiovascular disease (CVD).[1] Numerous epidemiological studies have shown that a high level of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) and lower levels of high-density lipoprotein cholesterol (HDL-C) are associated with increased risk of CVD.[1–4] In addition, age-related change in lipid and lipoprotein concentrations have been reported.[5,6] More precisely, TC, LDL-C, and TG levels increase up to middle age, then decrease.[7–12] Little is known about the dynamic trends in blood lipid profile over age.[7]

Most studies, however, focused on a single or limited measure of lipid profiles, ignoring its dynamic change over age. Few studies have reported the trajectory of lipids. Lee et al and Park et al reported 3 trajectory classes of lipids, whereas another study from Taiwan only reported 2 trajectory classes.[13–15] However, these studies considered the lipid trajectory separately, ignoring the correlation between lipids. The correlation between lipids have been studied, for example, increased TG concentration was related to reduced HDL-C concentration.[16] TC consists largely of the cholesterol in LDL-C and HDL-C. Another problem in these studies is that 1 individual may be classified into different risk latent groups for different lipids and give a conflicting result. Conducting separate analyses for each lipid does not account for the fact that these outcomes may measure the same underlying quantity. Exploring a common underlying quantity of different lipids may help us better understand the change of lipid profile over the life course. Recently, Proust–Lima et al

extended the group-based trajectory model to multiple correlated markers.[17,18] This method treats the multiple markers as reflecting a unique unobserved quantity following a latent process that shows distinct longitudinal patterns. The identified subpopulations have similar lipid profile patterns and therefore may share the same disease etiology. To the best of our knowledge, no previous study has been reported to jointly investigate the trajectory of lipid profiles and its implication in CVD.

By using repeated measurements of lipids during 2004–2015 in a longitudinal cohort from the Chinese population, the current study aimed to jointly explore common latent classes and patterns of lipid profiles based on multivariate trajectory analysis, examine the association of lipid trajectories with incident CVD, and determine the potentially critical period for the development of CVD related to rate of change in lipids.

Materials and Methods

The data supporting the findings of this study are available from the corresponding author upon request.

Study Cohort

The cohort data were collected from the population-based routine yearly health checkup at the Center of Health Management, affiliated with Jining Medical University Hospital, and this study started in May 2004. Individuals underwent health examinations from May 2004 until September 2015 and enrolled during this period. The health examination database was linked to databases from the Office for Medical Insurance in Shandong Province, hospital admissions, and vital statistics

from the Provincial Center for Disease Control, using a unique identification number for each participant. All CVD events reported by the end of 2017 were included. Individuals with age ranging from 20 to 60 years (given that a vast majority of people are retired at age ≤60 in China), no previous history of CVD, and at least 3 nonmissing lipid measurements available were included. For an individual with a reported CVD, all data until the date of the first CVD were included. In addition, participants with high lipids (TC≥7.76 mmol/L or LDL≥5.18 mmol/L or TG≥5.65 mmol/L) during any visit were excluded to remove potential treatment on lipid.[19]

Anonymous electronic records data set was acquired from Jining Medical University Hospital. The study protocol was approved on November 12, 2003, by the ethics committee of the School of Public Health, Shandong University (No. 20031112). Written informed consent was obtained from all participants.

Examinations

Height and weight were measured while the subjects were wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Systolic blood pressure (SBP) and diastolic blood pressure were recorded 3 times on the right upper arm using a mercury sphygmomanometer in a sitting position after a 5-minute rest. Information on smoking, alcohol use, and family history of CVD were obtained by means of a staff-administered standard questionnaire. Smoking and drinking were defined as having a history of smoking at least 1 cigarette per day and consuming alcohol every day, respectively. Family history of CVD was coded as yes/no.

Peripheral blood samples were collected in the morning after a 12-hour fast for the biochemical measurements and determined using a fully automatic blood analyzer (CELL-DYN 3700; Abbott, Abbott Park, IL), including fasting blood glucose, total cholesterol (coefficients of variation, 1.800%, SD, 0.077; bias, 0.034), TG (coefficients of variation, 1.656%; SD, 0.040; bias, 0.012), LDL-C (coefficients of variation, 2.922; SD, 0.066; bias, 0.058), and high-density lipoprotein cholesterol (coefficients of variation, 1.847; SD, 0.034; bias, 0.015). These biochemical measurements were assessed using the standard protocols at the clinical laboratory of the Jining Medical University Hospital. Diagnosis of diabetes mellitus was based on Chinese guidelines for prevention and treatment of diabetes mellitus (2013 edition), fasting plasma glucose≥7.0 mmol/L or glycated hemoglobin≥6.5%, or diagnosis by medical records.

Outcome

Medical histories of CVD were collected in the database, and the diagnosis date of CVD was defined as the earliest record

date. We used the *International Classification of Diseases, Tenth Revision* (ICD-10) clinical codes to identify cases. Subjects with the *ICD-10* codes from I00 to I99 were considered having CVD.[20]

Statistical Analysis

Unsupervised cluster analysis using a multivariate latent class growth mixed model was applied to explore the heterogeneity of lipids profile concentration. Given that TC was almost completely determined by HDL-C and LDL-C, we only included HDL-C, LDL-C, and TG in this study. Log transformation was applied for TG levels because of its positive skewness. For lower HDL-C considered as "bad," we used the reciprocal of HDL-C to make HDL-C the same direction as other lipids. Finally, the dependent variables for the model were 1/HDL-C, LDL-C, and log (TG). A series of polynomial specifications of lipids as a function of age with a class number ranging from 2 to 6 were assessed using the multlcmm function of the lcmm (version 1.7.9) package in R (version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria).[21] An outcome-specific random intercept was considered in the modeling process, and all the other options were set to its default. Age of participants was centered at the median age (40 years) of the population and divided by 10 to reduce the problems of too large value of ages in quadratic and cubic terms in the models. We considered 3 possible polynomial specification of the response of lipid profiles as a function of age: a linear, quadratic, and cubic to allow for nonlinear patterns of lipids profile. We included random intercept and random slope in all analysis. For each model, we considered sex and its interaction with the polynomial term of age for the fixed effect to address the pattern difference between sex. To avoid convergence toward local maxima, all models were rerun several times with different starting values and initial values obtained by grid searching (with a maximum of 15 iterations from 30 random vectors of values from the 1-class model). The final model was determined based on the smallest Bayesian information criterion.

The following criteria for the choice of a best fit model together with the study-specific requirements were used: (1) significant improvement of the model in Bayesian information criterion, a reduction of Bayesian information criterion of at least 10 points[22]; (2) a posterior probability above 0.7 for all latent classes; and (3) no less than 5% participants in any single trajectory class.

Characteristics across different groups were compared using ANOVA or Kruskal–Wallis tests for continuous variables and χ^2 statistics for categorical variables, and the log-rank test for time-to-event variables. Cox proportional hazard models with follow-up time as the time scale were used to investigate the association between trajectory classes and incident CVD, with unadjusted (model 1), adjusted for covariates (model 2), and model 3 further adjusting for baseline HDL, LDL, and TG. The adjusted covariates include age at baseline, sex, smoker, drinker, BMI, SBP, diabetes mellitus, and CVD family history.

The area under the curve (AUC) was calculated as a measure of long-term burden (total AUC) and trends (incremental AUC) of lipids. Total AUC was calculated as the integral of the model parameters during the follow-up for each individual; the method is reported elsewhere.[23] Because individuals had different follow-up periods, AUC values were divided by follow-up time. Incremental AUC was calculated by subtracting the estimated baseline AUC value of lipid from total AUC. Logistic regression analyses, adjusting for age and sex, were used to examine the association of total, baseline, and incremental AUC values with incident CVD. Before the logistic regression analyses, total, baseline, and incremental AUC values were adjusted for corresponding age and sex by regression analyses, and quantile of residuals of corresponding values were used in logistic regression to avoid collinearity.

The model-estimated levels and linear slopes of lipids were calculated at each age point in 1-year intervals according to the model parameters and their first derivatives, respectively. Logistic regression analyses were used to examine the association of model-estimated levels and linear slopes of lipids at each age point with incident CVD, adjusting for covariates mentioned above. Standardized odds ratios (ORs) of levels and level-adjusted slopes of lipids for incident CVD were estimated. The difference between slopes and levels of lipids for CVD at age points were tested using a 2-sample Z-test to determine the important long-lasting impact on CVD.

Results

A total of 9726 participants (6102 men) were included in the current study. Figure S1 and Table S1 present the flowchart of enrollment, and a summary of baseline characteristics of participants included and excluded respectively. The mean baseline age was 37.85 years (ranging from 20 to 58 years). On average, participants had 4.4 (range, 3–9) times of lipid profile measurements. The median follow-up year was 4.2 (range, 1.1–10.0). During the follow-up period, 739 incident cases were identified, with an incidence density of 16.86 per 1000 person-years. Log TG significantly correlated with 1/HDL-C and LDL-C, whereas no correlation was observed between 1/HDL-C and LDL-C (Figure S2).

Table S2 presents the latent class growth mixed model results of the fitting process. According to the criteria mentioned above, a model of quadratic parameters with 3 classes was chosen from all investigated models. Detailed parameter estimates of the best fitting 3-class quadratic

trajectory classes are shown in Table S3. Sex and its interaction with polynomial terms of age were significant, indicating that men and women had a different mean lipid profile trajectory over age.
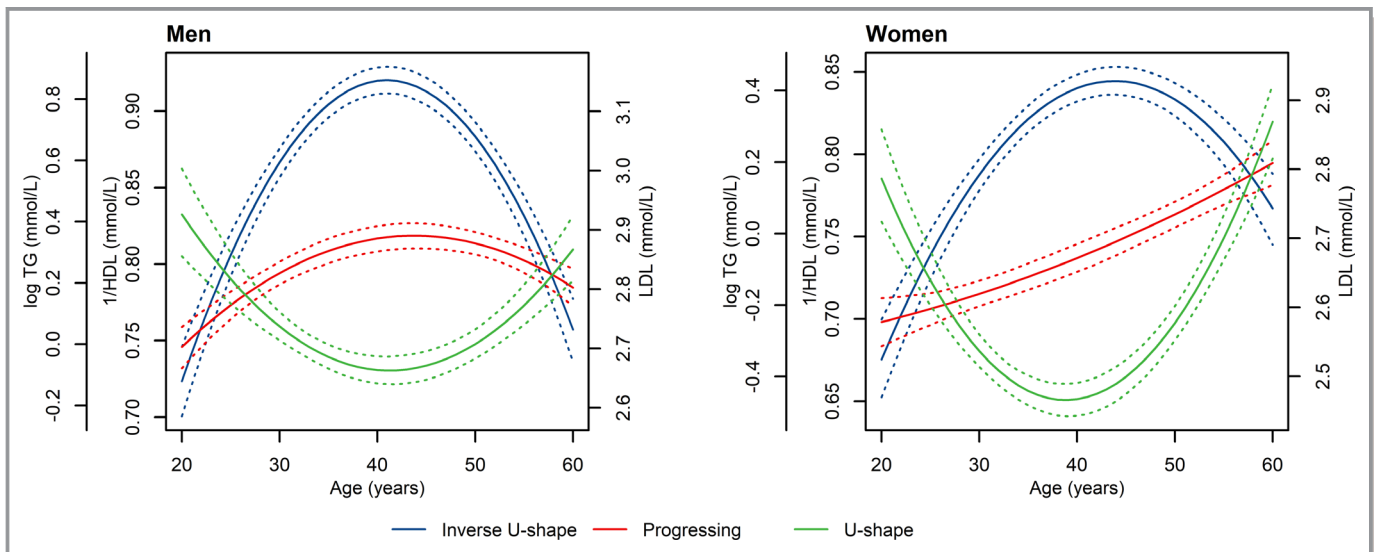
Figure 1 shows the predicted mean trajectory of lipid profile in men and women. Three trajectories were labeled as inverse U-shape (18.72%; n=1821), progressing (66.03%; n=6422), and U-shape (15.25%; n=1483). For all 3 predicted trajectories of lipid profile, men had a higher predicted concentration level of lipids. Predicted concentration level in the inverse U-shape class of lipids increase until age 40 years for men and age 45 for women. For progressing class, the predicted trajectory of lipid profile in women increases steadily over age, whereas men decrease around the age of 45. An increase of predicted lipid concentration level was observed around age >40 for men and <40 for women in the U-shape class. Figure S3 shows the estimated conditional mean and observed mean trajectory of lipid profile over age. The estimated means were close to the observed means, showing a good fit of the model.

Table 1 summarizes the baseline characteristics of the study population by lipid profile trajectory classes. Compared with other classes, the inverse U-shape class had higher values of BMI, SBP, diastolic blood pressure, LDL-C, TG, and TC and rates of diabetes mellitus, smoker, drinker, and CVD family history, whereas the U-shape class had higher HDL-C. The incidence density of CVD was significantly higher in the inverse U-shape class (20.49 per 1000 person-years) and progressing class (17.34 per 1000 person-years) than the U-shape class (10.91 per 1000 person-years). Table S4 shows the baseline characteristics grouped by sex and lipid profile trajectory classes.

Table 2 presents hazard ratios (HRs) and 95% CIs of lipid profile trajectory classes on incident CVD in the total, men, and women samples. Compared with the reference (U-shape) class, the unadjusted HRs (95% CI) were 1.69 (1.35, 2.12) and 2.05 (1.59, 2.64) for the progressing and inverse U-shape trajectory class, respectively. Adjusting for covariates of age at entry, sex, BMI, SBP, smoke, drink, diabetes mellitus, and CVD family history, the progressing and inverse U-shape classes had 1.33-fold (95% CI, 1.05–1.68) and 1.49-fold (95% CI, 1.14–1.95) risk of CVD compared with the U-shape class, respectively. In the unadjusted model, men showed similar results; HRs were 1.91 (1.46, 2.50) and 2.25 (1.67, 3.03) for the progressing class and inverse U-shape class, respectively. The progressing class and U-shape class remained significant after adjusting for potential confounders, with HRs 1.51 (1.14, 2.00) and 1.72 (1.25, 2.36). But only the inverse U-shape class was significant in the unadjusted model for women; no significant results were observed in the adjusted model. No noticeable change was observed in HR after further adjusting for baseline HDL, LDL, and TG.

Table 3 presents the odds ratio (OR) of AUC quantiles on incident CVD by logistic regression. The third and fourth quantile of total AUC (OR=1.48; 95% CI, 1.18, 1.86 and OR=1.65; 95% CI, 1.33, 2.06) and baseline AUC (OR=1.40; 95% CI, 1.12, 1.75 and OR=1.60; 95% CI 1.28, 1.99) were significant compared with the first quantile, whereas only the fourth quantile of incremental AUC was significant (OR=1.48; 95% CI, 1.19–1.85).

Figure 1. The predicted trajectory of 3 distinct lipid profile for men and women. Solid lines show class-specific mean predicted levels as a function of age estimated from the best fitting model (3-class quadratic latent class growth mixture modeling), dashed line indicates estimated 95% CIs. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table 1. Baseline Characteristics of the Study Population by Lipid Profile Trajectory Classes

Variables	Lipid Profile Trajectory Classes			P Value
	U-Shape	Progressing	Inverse U-Shape	
N	1483	6422	1821	
Age at entry, y	36.98 (6.50)	37.95 (8.90)*	38.19 (7.56)*	<0.001
Men, n (%)	976 (65.81)	3883 (60.46)*	1243 (68.26)	<0.001
BMI, kg/m^2	22.59 (3.03)	23.91 (3.39)*	25.81 (3.28)*	<0.001
SBP, mm Hg	120.38 (14.86)	123.50 (16.42)*	128.59 (16.59)*	<0.001
DBP, mm Hg	74.71 (11.04)	77.57 (12.27)*	81.98 (12.63)*	<0.001
TC, mmol/L	4.36 (0.74)	4.68 (0.83)*	5.08 (0.87)*	<0.001
HDL-C, mmol/L	1.42 (0.33)	1.34 (0.29)*	1.19 (0.27)*	<0.001
LDL-C, mmol/L	2.39 (0.59)	2.73 (0.67)*	2.98 (0.70)*	<0.001
TG, mmol/L	0.77 (0.43)	1.19 (0.59)*	2.33 (1.04)*	<0.001
Diabetes mellitus, n (%)	24 (1.62)	187 (2.91)*	103 (5.66)*	<0.001
Smoker, n (%)	218 (14.70)	1042 (16.23)	386 (21.20)*	<0.001
Drinker, n (%)	338 (22.79)	1410 (21.96)	535 (29.38)*	<0.001
CVD family history, n (%)	238 (16.05)	1141 (17.77)	376 (20.65)*	0.002
Age at CVD, y	46.55 (7.58)	47.40 (8.76)	45.79 (7.66)	0.091
Follow-up years, median (range)	4.88 (1.36, 9.68)	4.1 (1.12, 10.17)*	4.2 (1.14, 9.23)*	<0.001
CVD incidence density, per 1000 person-years	10.91	17.34*	20.49*	<0.001

Data are presented as mean (SD), median (range), or percentage. P values were calculated from the comparison between 3 identified trajectory classes. BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; TC, total cholesterol.
*Compared with the U-shape class: *P*<0.05.

Figure 2 presents OR and 95% CI of model-estimated levels and linear slopes of lipids for incident CVD, with adjusting for sex, BMI, SBP, smoke, drink, diabetes mellitus, and CVD family history. The standardized ORs of model-estimated lipid levels increased gradually from 0.83 (0.76, 0.90) to 1.21 (1.13, 1.30) during the age of 20 to 60, and no significant results were observed during the age of 28 to 43. Whereas standardized ORs of slope increased gradually from 1.11 (1.02, 1.21) to 1.21 (1.12, 1.31) between the age of 20 to 40 years, and then decreased to 1.02 (0.94, 1.11) until the age of 60, the results were significant before age 50. ORs of slopes were higher than those of levels before the age of 42 years and lower after the age of 53 years. No significant difference was observed between 43 and 52 years of age.

Discussion

In this longitudinal study, 3 distinct trajectory classes of lipid profiles were identified in a Chinese cohort. Compared with the U-shape class, individuals with the progressing and inverse U-shape trajectory had 1.33- to 1.49-fold risk of CVD. We also found a cumulative effect of lipid level with the risk of CVD. The observations of this study also emphasize that the change of lipid levels was a main risk compared with level

itself before the age of 42. Irrespective of the numerous evidence regarding the association of lipids with the risk of CVD, no previous studies have jointly explored the trajectory of lipids as a whole. The observations of this study provide new insights for the common evolution of lipid profile during the age of 20 to 60 years in relatively healthy adults.

The identified trajectories in this study extend the results from previous studies in this field that have examined the trajectory separately. Findings by Finns reported 2 U-shaped, 3 decreasing, and 2 increasing trajectories classes for LDL-C, HDL-C, and triglyceride, respectively.[13] Lee et al reported 3 trajectory class of HDL-C with a different pattern for men and women.[14] Furthermore, a Taiwan study described the U-shape and stable trajectory class for all 4 lipids.[15] Park et al reported the inverse U-shape and progressing trajectory of lipids according to cardiorespiratory fitness.[7] In the current study, we jointly analyzed 3 lipids as a whole, which overcame some spurious results from previous studies. A novel finding in our study was that lipids can be jointly characterized into 3 different trajectory classes over age, and sex difference was also observed.

We found that individuals in different classes showed a different risk of CVD. Observations from previous studies have confirmed that lipid level at baseline is an important risk

Table 2. HRs and 95% CI of Lipid Profile Trajectory Classes on Incident CVD in the Total, Men, and Women Samples

	Model 1*		Model 2†		Model 3‡	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Total						
U-shape	Reference		Reference		Reference	
Progressing	1.69 (1.35, 2.12)	<0.001	1.33 (1.05, 1.68)	0.017	1.33 (1.05, 1.69)	0.020
Inverse U-shape	2.05 (1.59, 2.64)	<0.001	1.49 (1.14, 1.95)	0.003	1.48 (1.07, 2.05)	0.018
Men						
U-shape	Reference		Reference		Reference	
Progressing	1.91 (1.46, 2.50)	<0.001	1.51 (1.14, 2.00)	0.004	1.48 (1.11, 1.97)	0.007
Inverse U-shape	2.25 (1.67, 3.03)	<0.001	1.72 (1.25, 2.36)	<0.001	1.62 (1.11, 2.38)	0.013
Women						
U-shape	Reference		Reference		Reference	
Progressing	1.33 (0.89, 1.99)	0.170	0.99 (0.65, 1.51)	0.969	1.02 (0.67, 1.56)	0.929
Inverse U-shape	1.66 (1.03, 2.67)	0.038	1.02 (0.61, 1.70)	0.940	1.17 (0.63, 2.20)	0.616

BMI indicates body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides.
*Unadjusted model.
†Adjusting for baseline age, sex (only for total), smoker, drinker, BMI, diabetes mellitus, SBP, and CVD family history.
‡Adjusted for variables in model 2 plus baseline HDL, LDL, and TG.

factor for developing an incident CVD.[1–4] The U-shape class had the lowest TC, LDL-C, TG, and highest HDL-C at baseline, whereas the levels of those lipids showed contrary results in an inverse U-shape class, which may partly explain the high risk of CVD for the progressing and inverse U-shape class. Sex difference in risk was observed in this study; the difference in lipid level at baseline value may partly explain this result. In addition, women in early age are less likely to develop an incidence of CVD.[24]

Risk difference between latent classes may indicate that the cumulative effect of lipid contributes risk to CVD. As observed in a recent trial that cumulative effect of achieving optimal lipid levels on the risk of cardiovascular events,[25] we also found the accumulative effect of lipids on the risk of CVD. In our study, we found that total AUC had higher OR compared with the baseline AUC, which confirmed the cumulative effect of lipid on the risk of CVD (Table 3). In addition, a significant incremental effect was only observed in the fourth quantile; no

strong dose-response effect was found between incremental effect and risk of CVD. Long-term cumulative burden and trends of lipids, measured as total AUC and incremental AUC, respectively, significantly predict later life incidence of CVD. A meta-analysis showed that statin therapy can reduce cardiovascular events irrespective of the initial lipid profile.[26] Admittedly, baseline lipid level predicts most of the risk of CVD, but the incremental effect cannot be ignored. These findings underscore the importance of assessing the lipid level at each visit and undertaking preventive strategies for CVD early in life by controlling lipid levels. More researches are needed to determine the minimum optimal lipid incremental level to achieve a clinical significance.

Although the current study does not address pathogenetic or treatment questions, the trajectory and risk of CVD identified in this article could inform future research on potential intervention and early prevention. In this study, the standardized OR of model-estimated lipid level increased

Table 3. OR of AUC Quantiles on CVD by Logistic Regression

Quantiles	Total AUC*		Baseline AUC*		Incremental AUC*	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Quantile 1	Reference		Reference		Reference	
Quantile 2	1.18 (0.93, 1.49)	0.168	1.17 (0.93, 1.48)	0.176	1.18 (0.94, 1.48)	0.156
Quantile 3	1.48 (1.18, 1.86)	<0.001	1.40 (1.12, 1.75)	0.004	1.11 (0.89, 1.39)	0.364
Quantile 4	1.65 (1.33, 2.06)	<0.001	1.60 (1.28, 1.99)	<0.001	1.48 (1.19, 1.85)	<0.001

*Residuals of linear regression adjusted for baseline age and sex. AUC indicates area under the curve; CVD, cardiovascular disease; OR, odds ratio.
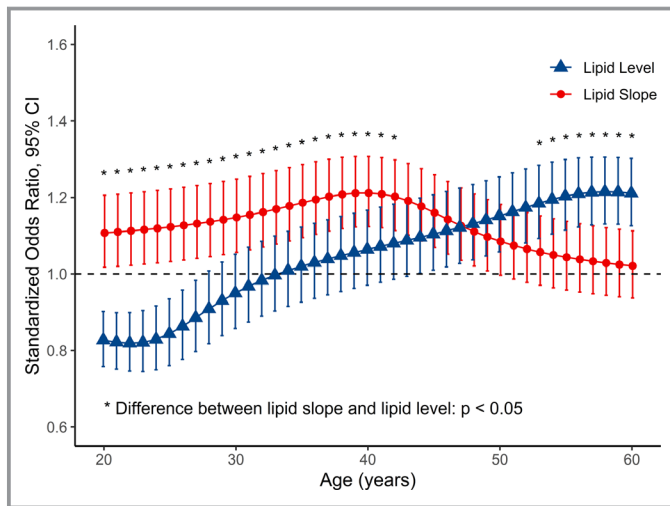
Figure 2. Standardized odds ratio (OR) and 95% CI of model-estimated levels and linear slopes of lipid profile during the age of 20 to 60 by age for incident CVD, adjusting for sex, smoker, drinker, BMI, diabetes mellitus, SBP, and CVD family history. BMI indicates body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure.

during the age of 20 to 60 years, whereas the standardized OR of slope decreased after the age of 40 years. Our association analyses showed that the linear slopes had higher ORs than model-estimated lipid levels before age 42 years. This phenomenon indicates that although lipid levels have been recognized as an important risk factor for CVD, lipid slope, which reflected the increasing velocity of lipids, is a better predictor before the age of 42, whereas lipid level is a better predictor after the age of 53. The results indicate that people whose lipid levels increase rapidly during the age of 20 to 42 years have a considerably higher risk of developing a CVD. Thus, during these periods, the control for lipid should be focused on the increasing rate rather than the level itself, whereas the elder adults should focus on the lipid level instead. The overlap in CI may suggest that both inverse U-shape and progressing trajectory classes may have a similar risk of CVD and disease etiology, given that both classes are increasing before around the age of 42. It should be noted that these results and previous incremental effect mutually testify as to their respective reasonability.

The strengths of our study are the large population cohort with the use of repeated measures of lipids over a substantial follow-up period. The method we applied, a multivariate latent class mixture model, accounts for the complex temporal relationship between biomarkers and is useful in data reduction and particularly helpful to describe the common pattern of multiple correlated biomarkers. This method helps us consider 3 lipids as a whole and identify distinct trajectory subgroups that are in a potential risk of developing CVD.

Further analysis of AUC provides evidence of the incremental effect of lipids, and model-estimated lipid slope parameters for each individual help to determine the critical age period. Our study had a few limitations. First, identification of CVD cases was based on medical records from the available database; some CVD cases may have been missed. Second, individuals were from routine health examinations from a relatively healthy population, which might reduce the generalizability of the results. Third, there was not enough lipid-lowering treatment information, which might affect the trajectory of lipids. Thus, we excluded those who had a high lipid level at any follow-up. Last, the median overall follow-up was 4.2 years; longer variation in the lipid pattern might be missed. We included participants who had ≥3 measures of lipids in this study to increase the sample size and the number of CVD events. However, the power of a smaller number of repeated measures for characterizing the lipid trajectories is limited.

Conclusions

In summary, we have identified 3 distinct trajectories of lipids and demonstrated such trajectories are associated with the development of CVD in a large relatively healthy population. We found the accumulative effect of lipids on the risk of CVD. The rate of changes in lipids has an important impact on the development of CVD in later life. Age between 20 and 42 years is a crucial period for the development of CVD. The observations from this study provide new insights into the understanding of CVD development and emphasize the importance of controlling the increasing velocity of lipids in young adulthood (ages from 20 to 42 years) to prevent CVD in later life. Public health intervention for lipid should emphasize control of the increasing velocity of lipids in younger adults.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of participants included and excluded (< 3 lipid profile measurements or complete missing of lipid profile).

Variable	Excluded (N=44986)	Included (N=9726)
Age at entry, years	35.93 (10.55)	37.85 (8.34)
Men	25770 (57.28)	6102 (62.74)
BMI, kg/m^2	24.22 (3.85)	24.07 (3.45)
SBP, mmHg	122.82 (16.17)	123.97 (16.41)
DBP, mmHg	75.97 (11.93)	77.96 (12.35)
HDL, mmol/L	1.36 (0.29)	1.32 (0.30)
LDL, mmol/L	2.79 (0.70)	2.72 (0.69)
TG, mmol/L	1.37 (0.89)	1.34 (0.84)
TC, mmol/L	4.77 (0.85)	4.71 (0.85)
Diabetes mellitus, n (%)	1732 (3.85)	314 (3.23)
Smoker, n (%)	4170 (9.27)	1646 (16.92)
Drinker, n (%)	4776 (10.62)	2283 (23.47)
CVD family history, n (%)	1193 (2.65)	1755 (18.04)

Data are presented as mean (SD), median (range) or percentage.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; CVD, cardiovascular disease

Table S2. Latent Class Growth Mixture models (LCGMM) results of the model fitting process.

No. of latent classes	Polynomial degree	Log-Lik	BIC	% Participants per class	Mean posterior probabilities
1	Linear	-26862.96	53882.03		
	Quadratic	-26725.56	53625.59		
	Cubic	-26714.78	53622.39		
2	Linear	-26801.55	53786.75	26.7/73.3	0.75/0.83
	Quadratic	-26526.3	53263.79	32.86/67.14	0.75/0.81
	Cubic	-26508.25	53255.24	33/67	0.75/0.81
3	Linear	-26796.81	53804.82	20.89/60.76/18.34	0.75/0.66/0.68
	Quadratic	**-26475.86**	**53199.66**	**18.72/66.03/15.25**	**0.76/0.71/0.73**
	Cubic	-26462.24	53209.14	28.27/67.15/4.58	0.7/0.72/0.62
4	Linear	-26776.15	53791.06	0.2/21.96/60.74/17.1	0.73/0.75/0.65/0.67
	Quadratic	-26448.17	53180.99	3.06/18.92/60.28/17.74	0.56/0.7/0.62/0.7
	Cubic	-26413.58	53157.74	20.83/5.94/67.97/5.25	0.7/0.58/0.66/0.62
5	Linear	-26773.63	53813.56	0.2/22.03/0.05/16.93/60.79	0.74/0.75/0.66/0.68/0.66
	Quadratic	-26424.16	53169.71	0.36/19.82/59.51/16.71/3.6	0.65/0.67/0.61/0.68/0.56
	Cubic	-26385.71	53147.91	7.79/12.49/66.9/5.61/7.2	0.54/0.6/0.63/0.62/0.54
6	Linear	-26772.34	53838.52	0.21/24.14/0.05/42.58/29.61/3.41	0.72/0.68/0.65/0.46/0.62/0.41
	Quadratic	-26417.93	53193.99	0.24/0.34/20.5/59.85/15.48/3.59	0.61/0.55/0.62/0.61/0.67/0.56
	Cubic	-26367.35	53157.1	7.8/15.7/14.12/2.91/54.61/4.86	0.6/0.52/0.51/0.61/0.53/0.58

Reported are: the number of latent class considered, the polynomial form of the model, the maximum Log-Likelihood (Log-Lik), the Bayesian Information Criterion (BIC), the posterior classification of subjects in each class (%), the mean of posterior probabilities in each latent class. The best fitting model is highlighted in bold characters.

Table S3. Parameter estimates for the best fitting 3-class quadratic latent class growth mixture model fitted to the lipid profile data.

Polynomial term	Class	Coefficient	Standard error	Wald	p-value
Intercept	Inverse U-shape *	0			
	Progressing	-2.89	0.15	-18.75	<0.001
	U-shape	-5.30	0.30	-17.48	<0.001
Age	Inverse U-shape	0.64	0.10	6.34	<0.001
	Progressing	0.68	0.06	11.55	<0.001
	U-shape	0.24	0.10	2.37	0.018
Age^2	Inverse U-shape	-0.83	0.08	-9.97	<0.001
	Progressing	0.07	0.06	1.20	0.231
	U-shape	1.06	0.10	11.12	<0.001
Sex		2.24	0.11	20.43	<0.001
*Sex*age*		-0.40	0.05	-8.24	<0.001
*Sex*age^2*		-0.43	0.04	-9.64	<0.001

* Not estimated, the mean intercept in the first class is constrained to 0.

Table S4. The baseline characteristics of the study population by lipid profile trajectory classes and sex.

Variables	Men			Women		
	U-shape (N = 976)	Progressing (N = 3883)	Inverse U-shape (N = 1243)	U-shape (N = 507)	Progressing (N = 2539)	Inverse U-shape (N = 578)
Age at entry, years	37.16 (6.66)	38.29 (9.20) *	38.28 (7.38) *	36.64 (6.19)	37.44 (8.38) *	37.98 (7.93) *
BMI, kg/m^2	23.29 (3.04)	25.05 (3.22) *	26.69 (2.92) *	21.24 (2.52)	22.17 (2.86) *	23.92 (3.22) *
SBP, mmHg	124.25 (14.59)	128.74 (15.45) *	132.68 (15.27) *	112.88 (12.30)	115.47 (14.50) *	119.76 (15.87) *
DBP, mmHg	77.25 (10.95)	81.24 (11.90) *	85.07 (12.05) *	69.81 (9.45)	71.93 (10.58) *	75.32 (11.22) *
HDL, mmol/L	1.36 (0.31)	1.27 (0.28) *	1.15 (0.26) *	1.54 (0.32)	1.44 (0.30) *	1.27 (0.28) *
LDL, mmol/L	2.44 (0.60)	2.84 (0.67) *	3.04 (0.71) *	2.27 (0.56)	2.55 (0.62) *	2.86 (0.67) *
TG, mmol/L	0.84 (0.39)	1.39 (0.62) *	2.64 (1.00) *	0.63 (0.46)	0.89 (0.38) *	1.68 (0.81) *
TC, mmol/L	4.37 (0.77)	4.76 (0.84) *	5.17 (0.88) *	4.34 (0.70)	4.56 (0.80) *	4.88 (0.82) *
Diabetes mellitus, n (%)	20 (2.05)	149 (3.84) *	85 (6.84) *	4 (0.79)	38 (1.50) *	18 (3.11) *
Smoker, n (%)	218 (22.34)	1042 (26.83) *	385 (30.97) *	0 (0.00)	0 (0.00)	1 (0.17) *
Drinker, n (%)	336 (34.43)	1399 (36.03)	534 (42.96) *	2 (0.39)	11 (0.43)	1 (0.17) *
CVD family history, n (%)	138 (14.14)	617 (15.89)	244 (19.63) *	100 (19.72)	524 (20.64)	132 (22.84) *
Age at CVD	20 (2.05)	149 (3.84)	85 (6.84)	47.00 (6.75)	47.01 (8.62)	46.26 (7.59)
Follow-up years, median (range)	5.01 (1.36, 9.68)	4.16 (1.12, 10.06) *	4.4 (1.14, 9.23) *	4.76 (1.52, 8.94)	4 (1.12, 10.17) *	4.06 (1.58, 9.13) *
CVD incidence density, per 1000 person-years	10.94	19.07 *	22.03 *	10.85	14.57 *	16.92 *

Data are presented as mean (SD), median (range) or percentage.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; CVD, cardiovascular disease

* Compared with U-shape class: P<0.05.

Figure S1. Flowchart showing numbers of patients excluded from the analysis.
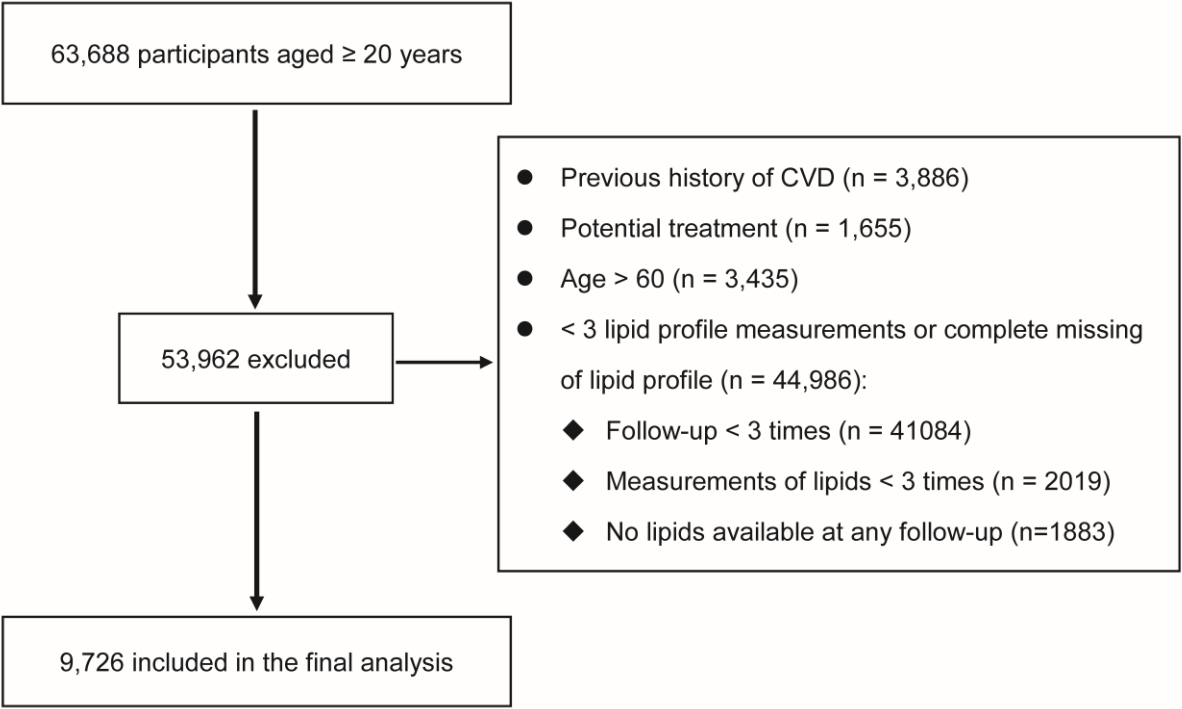
Figure S2. Correlation matrix of lipid profiles—reciprocal of high-density lipoprotein cholesterol (1/HDL-C), low-density lipoprotein cholesterol (LDL-C), and log-transformed triglyceride (log TG)—among the enrolled patients (n = 9,726).
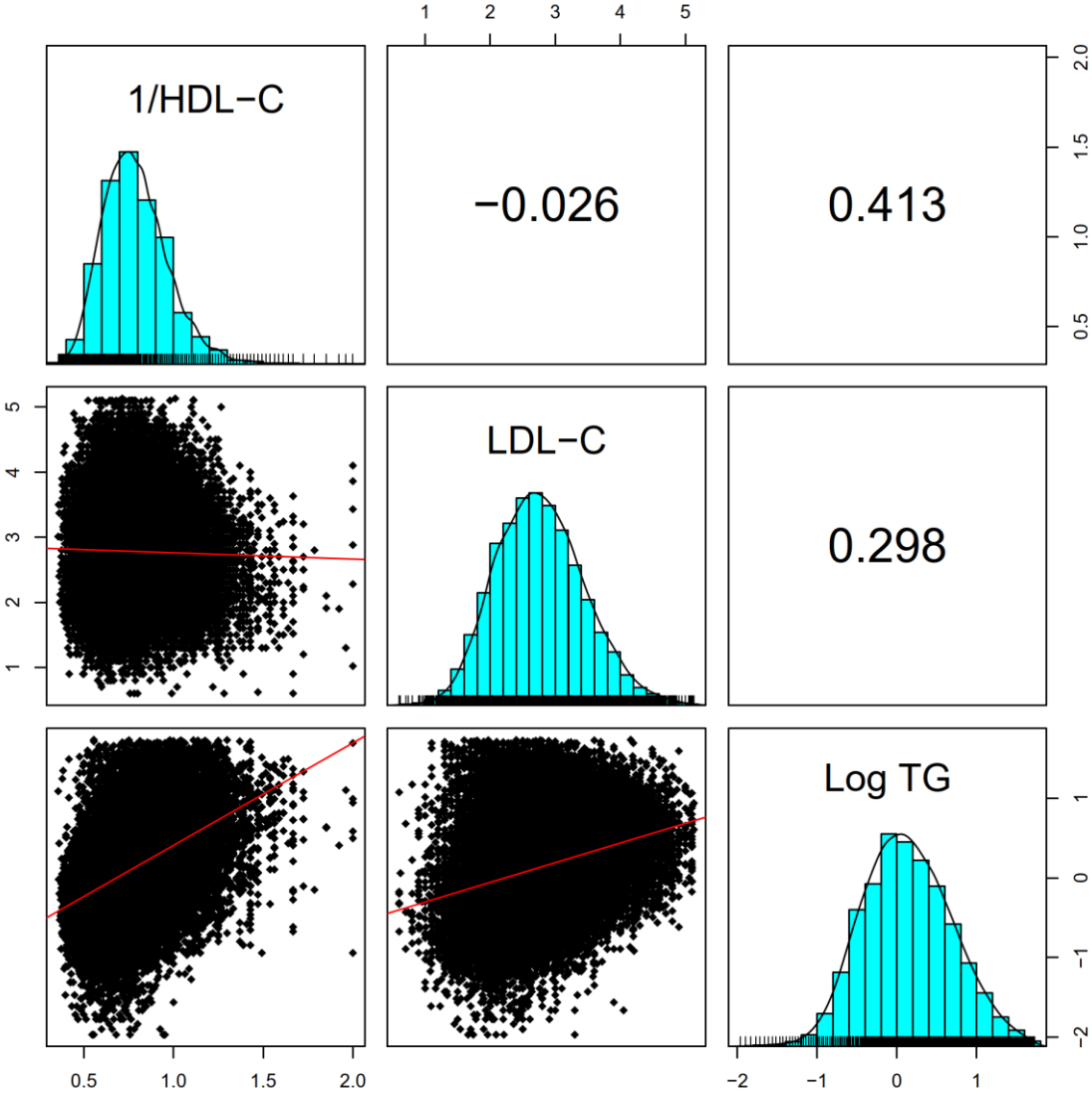
The diagonal panels (histogram) show the distribution of concentrations of three lipid components. The lower off-diagonal panels show scatterplots with linear fit (red) lines. The upper off-diagonal panels give pairwise Pearson's correlation coefficients.

Figure S3. Estimated and observed mean trajectory of lipid profiles over age (crosses = estimated subject-specific mean trajectory; dashed line with dots = observed mean trajectory; dashed line = 95% confidence interval of the observed mean).