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Longitudinal associations of high-density lipoprotein cholesterol or low-density lipoprotein cholesterol with metabolic syndrome in the Chinese population: a prospective cohort study

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ABSTRACT

Objective Currently, most studies only reveal the relationship between baseline high-density lipoprotein cholesterol (HDL-c) or low-density lipoprotein cholesterol (LDL-c) levels and metabolic syndrome (MetS). The relationship between dynamic changes in HDL-c or LDL-c and MetS remains unclear. We aimed to gain a deeper understanding of the relationship between the dynamic changes in HDL-c or LDL-c and MetS.

Design A prospective study.

Setting The Medical Centre of the Second Hospital affiliated with Dalian Medical University from 2010 to 2016.

Participants A total of 4542 individuals who were initially MetS-free and completed at least two follow-up examinations as part of the longitudinal population were included.

Methods The Joint Interim Statement criteria 2009 were used to define MetS. We used the Joint model to estimate the relative risks (RRs) of incident MetS.

Results The cumulative incidence of MetS was 17.81% and was 14.86% in men and 5.36% in women during the 7 years of follow-up. In the Joint models, the RRs of the longitudinal decrease in HDL-c and the longitudinal increase in LDL-c for the development of MetS were 18.8781-fold (95% CI 12.5156 to 28.4900) and 1.3929-fold (95% CI 1.2283 to 1.5795), respectively.

Conclusions The results highlight that the dynamic longitudinal decrement of HDL-c or the increment of LDL-c is associated with an elevated risk of MetS.

Strengths and limitations of this study

- This study is the first to investigate the relationship of dynamic changes in high-density lipoprotein cholesterol (HDL-c) or low-density lipoprotein cholesterol (LDL-c) with metabolic syndrome (MetS) in a Chinese population.
- The Joint model was used in this study to gain a deep understanding of the relationship between dynamic changes in HDL-c or LDL-c and the incidence of MetS.
- The main limitation of this study was the short follow-up period and the lack of waist circumference.

INTRODUCTION

Metabolic syndrome (MetS) is generally defined as a cluster of metabolically inter-related risk factors, including hypertension, high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-c) levels, abdominal obesity and high fasting plasma glucose (FPG).[1] MetS occurs commonly throughout the world and ranges in prevalence from 10% to 40%.[2] The prevalence of MetS has been reported as 33% in the USA,[3] and 28.9%[4] and 21.3%[5] in Korea and in China, respectively, as defined by the National Cholesterol Education Program Adult Treatment Panel III. MetS has been associated with increased risk of developing CVD, type 2 diabetes mellitus, stroke and chronic kidney disease.[6–9]

At present, it is known that insulin resistance (IR) is one of the underlying mechanisms of MetS.[10 11] Some studies[12–15] have indicated that MetS was associated with changes in HDL-c and low-density lipoprotein cholesterol (LDL-c) in the general population. A cross-sectional study indicated that HDL-c was strongly associated with IR and other MetS components in the Japanese population.[16] There are several cross-sectional studies on the associations between HDL-c or LDL-c and MetS.[17–21] Although there are some cohort studies on this relationship, they only revealed the associations between baseline HDL-c or LDL-c levels and the incidence of MetS during the follow-up period.[20 22 23] Nevertheless, individual HDL-c and LDL-c levels change over time, so these traditional methods ignore the effects of dynamic changes in these serum lipid parameters on

the incidence of MetS during the follow-up period. To fully understand the longitudinal associations between dynamic changes in HDL-c or LDL-c and MetS, longitudinal studies are required, especially research using repeated measures of the two indicators. Therefore, we conducted our analyses by the Joint Model based on health check-up data for 7 years.

MATERIALS AND METHODS

Design and subjects

Initially, 10 858 participants who visited the Medical Check-up Centre of the Second Hospital affiliated to Dalian Medical University for general health screening from March 2010 to April 2016 were included in the study. Among this group, 4786 patients were excluded because they had already been diagnosed with MetS (n=2409) at baseline (the initial examination), had a history of hypertension, diabetes, CVD, CHD, viral hepatitis, liver cirrhosis, autoimmune liver disease or renal tuberculosis (n=1676), or had missing baseline data of MetS components (n=701). There were then 6072 eligible participants remaining in the cohort study. Meanwhile, 1342 of the 6072 subjects had not attended any follow-up visit, thus, the follow-up rate was 77.9%. Of these individuals (n=4730), 188 subjects with only one completed MetS components data or LDL-c level in the follow-up period were excluded and regarded as censored cases when the statistical analysis was performed. Finally, 4542 individuals were included in our study (figure 1).

The first health check-up data were defined as the baseline data and the zeroth follow-up time, and so on. Once MetS occurred for a subject, his or her follow-up would terminate.

Anthropometric measurements and laboratory measurements

The general items of the health check-up included: name, gender, age, height, weight, blood pressure, medical history, family history and personal history. Laboratory measurements included routine blood and urine, liver and kidney function, FPG, total cholesterol (TC), TG, HDL-c, LDL-c, uric acid, and so on. The imageological examinations included liver, gall bladder, pancreas, spleen, kidneys, B-mode ultrasound, chest

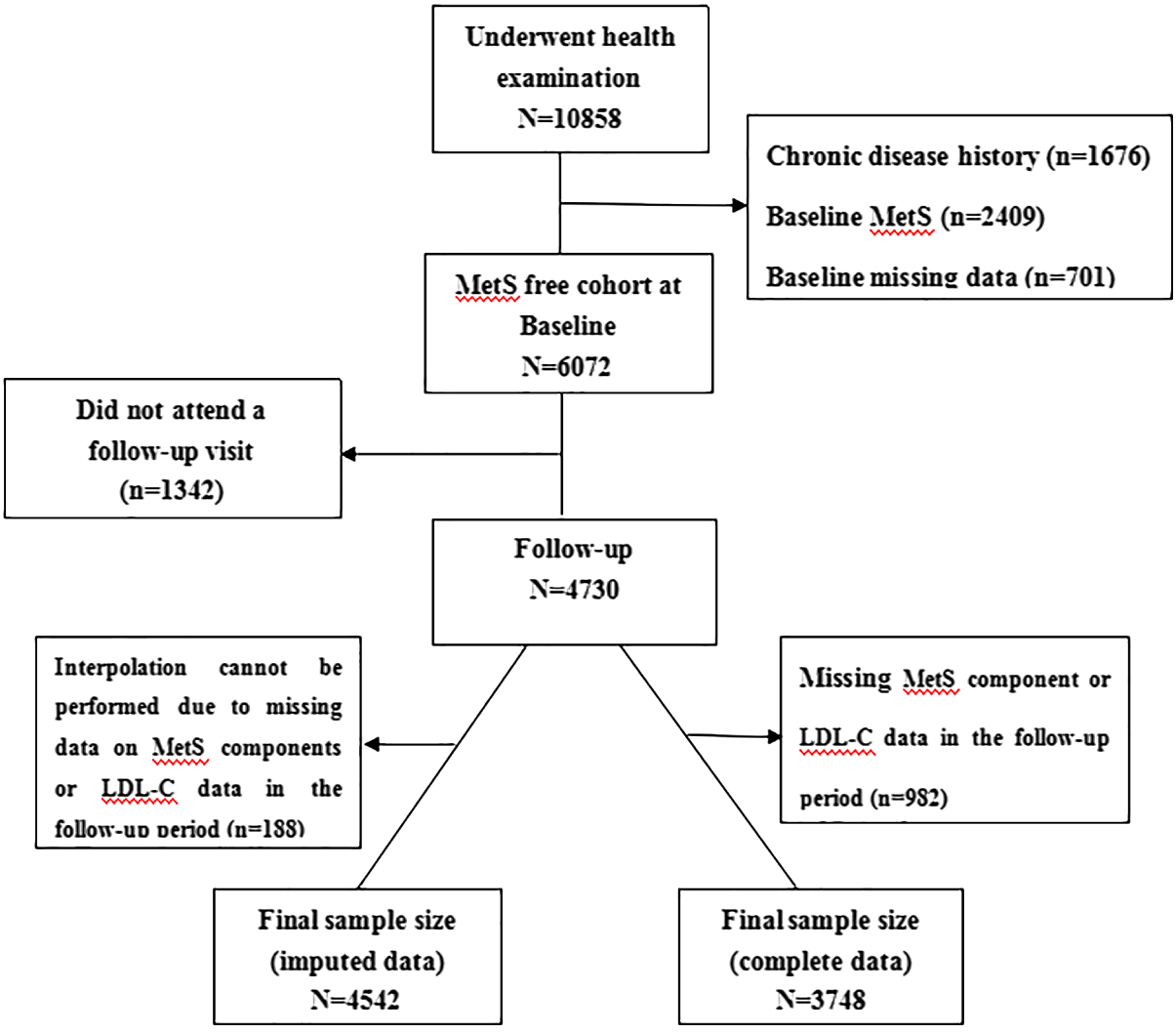

Figure 1 Selection of study participants. LDL-c, low-density lipoprotein cholesterol; MetS, metabolic syndrome.

X-ray, ECG, and so on. The subjects were required to refrain from smoking, alcohol and caffeine, before the health check-up. Body weight and height were measured by well-trained examiners in the vertical stand, with the participants wearing light, thin clothing and no shoes, to the nearest 1 kg and 1 cm, respectively. Body mass index (BMI) was calculated as weight (kg) divided by the square of height in metres (m^2) retaining two decimal places. Blood pressure was measured by an electronic sphygmomanometer with participants in a seated position after 5 min rest. The first measurement within normal range was recorded as the subject's blood pressure value; if this value was not within the normal range, the measurement was repeated after 20 min rest, and the minimum value of the two measurements was taken as the blood pressure value.

Biochemical blood samples were collected from an antecubital vein of participants in the early morning after a minimum of 12 hours overnight fasting. Then, the samples were analysed within 10~30 min. The serum levels of FPG, LDL-c, HDL-c, TG and TC were measured using De Ling Dimension Xpand Plus automatic biochemical analyser. The unit of measurement was mmol/L.

Definition of MetS

MetS was diagnosed if participants had three or more of the following risk determinants according to the Joint Interim Statement criteria of 2009.[24] However, in this study, we only measured height and weight and waist circumference (WC) was not measured in the health check-up ; BMI was taken, as a substitute for the component of obesity, which was strongly correlated with WC in patients with MetS.[25 26] The determinants were as follows: (1) Obesity: BMI≥25 kg/m^2. (2) Elevated TG (drug treatment for elevated TG is an alternate indicator): ≥150 mg/dL (1.7 mmol/L). (3) Reduced HDL-c (drug treatment for reduced HDL-c is an alternate indicator): <40 mg/dL (1.0 mmol/L) in men, <50 mg/dL (1.3 mmol/L) in women. (4) Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator): systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg. (5) Elevated FPG (drug treatment of elevated glucose is an alternate indicator): ≥100 mg/dL.

Missing data imputation

In our longitudinal study, there were some variables with missing values because certain physical examinations were missing. The imputed variables such as height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) had less than 8% missingness and others, such as FPG, TG, HDL-c and LDL-c had only less than 2% missingness and the results are presented in online supplementary table 1. If such records were entirely deleted for a certain participant, the information would be incomplete and the sample size will be insufficient; thus, the SEs from the analytical results may be increased. Therefore, linear regression was performed to impute the missing data using SPSS V.17.0.[27] The regression equation was established based on the complete data set, which can be used to predict the missing values.

Comparison of annual average changes in HDL-c and LDL-c

The average annual changes in HDL-c and LDL-c were compared in the MetS and the non-MetS groups by gender stratification.

$$k = (y_{\textit{the last follow-up}} - y_{\textit{the first follow-up}}) / \textit{years of follow-up} \quad (1)$$

In the formula, y stands for the measured value of HDL-c or LDL-c and k stands for the average annual change in HDL-c or LDL-c.

Model construction

We separately constructed the Cox model with $HDL\text{-}c_0$ ($LDL\text{-}c_0$) as one of the covariates to investigate the effects on the hazard for MetS by the 'stepwise' method in the R package JM. The optimal Cox model, containing only the significant (p<0.05) covariates, was determined by the Akaike information criterion (AIC).

The Joint model[28 29] typically combines a linear mixed-effects model for longitudinal measurement data and a relative risk (RR) survival model for the time to event via shared parameters, which can assess the impact of time-varying measurements on the personalised survival hazard function. The Joint model is specified as:

$$\begin{cases} y_{ij} = m_i(t) + \epsilon_{ij} = b_{00} + \mu_{0i} + (b_{10} + \mu_{1i})\, t_{ij} + \epsilon_{ij} \\ h_i\{t | M_i(t),\ x_i\} = h_0(t) \exp\{\sum \beta_i x_i + \alpha m_i(t)\} \end{cases} \quad (2)$$

Here, y_{ij} denotes the observed value of a specific variable for the i^{th} (i=1,2,…,n) subject at the j^{th}(j=0,1,…,t) follow-up time point; $m_i(t)$ denotes the true values of y_{ij}. In the longitudinal submodel, b_{00} denotes the fixed effects for the intercept and represents the average level of a specific variable for all subjects at baseline; b_{10} denotes the fixed effects for the slope term and represents the average rate of change of y_{ij} with follow-up time; μ_{0i} and μ_{1i} are the random effects of intercept and slope, and their standard deviations (σ) were used to describe them. ϵ_{ij} is the total error of the model with $(\epsilon_{ij}|\sigma) \sim N(0, \sigma x^2)$.

In the survival submodel, $h_i(t)$ denotes the hazard function for the i^{th} subject with covariates, and x_i, at time t. $M_i(t)$ represents the whole longitudinal history of the true marker levels up to time t; x_i denotes a certain time-independent covariate of $h_i(t)$; β_i denotes a vector of the regression coefficient of x_i; α stands for the association parameter assessing the relationship between the longitudinal measurement and the survival submodels.

First, we fitted a linear mixed-effects model with random intercept and random slope of time for HDL-c (or LDL-c), and the independent covariates, *time, age, and gender, time:age, time:gender*, and *age:gender* were all entered into the model. Then, based on the principle of backward stepwise regression, each covariate was tested one by one, and no significant covariate was excluded

Table 1 Comparison of baseline characteristics between excluded subjects and final study subjects

Variables	Excluded subjects (n=188)	Final study subjects (n=4542)	P values
Age (years)	32.00 (27.00 to 43.00)	37.00 (28.00 to 45.00)	0.000
Male (%)	21.28	33.36	0.000
SBP (mm Hg)	119.00 (110.00 to 127.00)	118.00 (110.00 to 127.00)	0.455
DBP (mm Hg)	72.00 (66.00 to 79.00)	72.00 (65.00 to 78.00)	0.772
BMI(kg/m^2)	22.28 (20.03 to 24.47)	22.32 (20.55 to 24.20)	0.654
FPG (mmol/L)	5.21 (4.86 to 5.49)	5.28 (5.01 to 5.54)	0.007
TG (mmol/L)	0.88 (0.65, 1.14)	0.87 (0.66 to 1.18)	0.692
HDL-c (mmol/L)	1.34 (1.22 to 1.53)	1.38 (1.19 to 1.59)	0.125
LDL-c (mmol/L)	2.56 (2.01 to 3.02)	2.60 (2.20 to 3.10)	0.103

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

from the model. The final model, containing only the significant (p<0.05) covariates, was determined by AIC. Second, we established the survival submodel for the Joint model by introducing time-independent covariates, such as $HDL\text{-}c_0$ (or $LDL\text{-}c_0$), *age, gender, age:gender*, and the linear mixed-effects model for HDL-c or LDL-c, which had been previously constructed via the association parameter α. Then, we followed the same steps in the process of fitting the linear mixed-effects model to exclude no significant time-independent covariates. The final Joint model met the minimum AIC only contained significant (p<0.05) covariates. Explanation of the variables used in the model fitting can be seen in online supplementary table 2.

Statistical analysis

Data are expressed as the mean±SD and for non-normally distributed variables, as median and IQR. Categorical data were described by proportion and compared by the χ^2 test. The Wilcoxon rank-sum test was used for variables that were non-normally distributed. Data were analysed using SPSS V.17.0, and p<0.05 was considered as statistically significant. The Joint model was conducted using the R package JM[30] to account for longitudinal correlations between HDL-c (LDL-c) and MetS.

RESULTS

Basic characteristics

Baseline characteristics of the subjects who were excluded due to missing data during the follow-up period and the final study subjects are shown in table 1. The final study subjects were significantly older than the excluded subjects. The proportion of male final study subjects was higher than the excluded subjects. However, the values of SBP, DBP, BMI, FPG, TG, HDL-c and LDL-c were similar in both groups. We also analysed the final study subjects (n=4542) and cohort subjects (n=6072), and the results are shown in online supplementary table 3. Basic characteristics of age, gender, MetS components and LDL-c were not significantly different, so our study subjects are representative of the cohort subjects.

This health check-up cohort enrolled a sample of 4542 subjects aged 19–80 years, with a median age of 37 years, including 1515 men (33.36%) and 3027 women (66.64%). The average follow-up time was 2.0 (1.0 to 4.0) years. During the 7-year follow-up period, 809 subjects developed MetS. The cumulative incidence of MetS was 17.81%; it was 14.86% in men and 5.36% in women.

As we can see from figure 2, the average level of HDL-c in the MetS group was generally lower than the non-MetS

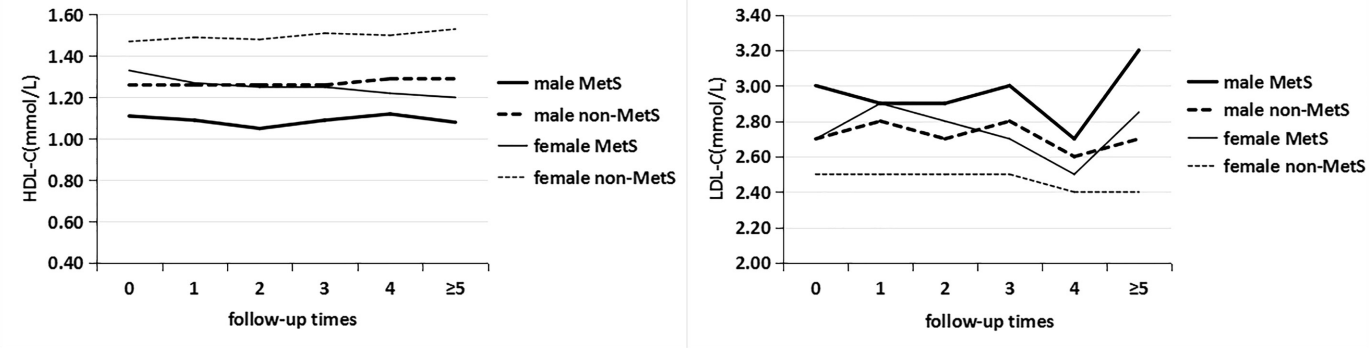

Figure 2 Changes in the trend of average level of high-density lipoprotein cholesterol (HDL-c) or high-density lipoprotein cholesterol (LDL-c) during follow-up in the metabolic syndrome (MetS) group and the non-MetS group.

Table 2 Comparison of the annual rate of change in high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) levels between metabolic syndrome (MetS) group and non-MetS group, (M(P_{25}, P_{75}))

	HDL-c			LDL-c		
	MetS	Non-MetS	P values*	MetS	Non-MetS	P values*
Male	−0.0300 (−0.1000 to 0.0300)	0.0000 (−0.0400 to 0.0600)	0.0000	−0.0115 (−0.2075 to 0.1700)	0.0000 (−0.1700 to 0.1000)	0.7290
Female	−0.0400 (−0.1375 to 0.0200)	0.0100 (−0.0400 to 0.0700)	0.0000	0.0300 (−0.1700 to 0.2700)	−0.0000 (−0.1000 to 0.1000)	0.0010

*p<0.05 is significant.

group regardless of gender, and the average level of LDL-c in the MetS group was generally higher than the non-MetS group regardless of gender. The average level of the two indicators in the non-MetS group remained more or less flat during the follow-up period but exhibited greater fluctuations in the MetS group. Table 2 shows that the average annual rate of change for HDL-c was decreased in the MetS group and remained almost unchanged in the non-MetS group regardless of gender. The average annual rate of change for LDL-c was increased in the MetS group and remained almost unchanged in the non-MetS group for women but not for men.

Joint model

By the previously mentioned method, two Joint models to investigate the effect of changes in HDL-c or LDL-c on the hazard for MetS were constructed separately. The results are shown in tables 3 and 4.

The longitudinal correlation between HDL-c and MetS is presented in the survival submodel results in table 3. We found a strong negative association between dynamic changes in HDL-c and risk of MetS, which implied a unit decrease in HDL-c represented as an 18.8781-fold (95% CI 12.5156 to 28.4900) increase in the RR of MetS.

The longitudinal correlation between LDL-c and MetS is presented in the survival submodel results in table 4. We found that a unit increase in LDL-c represented a 1.3929-fold (95% CI 1.2283 to 1.5795) increase in the RR of MetS.

We estimated the impact of different decrements of HDL-c and increments of LDL-c at specific HDL-c and LDL-c baseline values. Table 5 shows the estimated RR of MetS that corresponds with different longitudinal decreases in HDL-c and increases in LDL-c for different HDL-c and LDL-c baseline values. For instance, considering the estimated parameter $\hat{\alpha} = -2.9380$ in the survival submodel, decreases of 10% in HDL-c represent a 1.3415-fold, 1.7997-fold, 2.4143-fold or 3.2389-fold increase in the RR of MetS for baseline 'true HDL-c' values 1, 2, 3 or 4,

Table 3 Results of the Joint model for the association between longitudinal high-density lipoprotein cholesterol (HDL-c) values and metabolic syndrome (MetS)

Parameters	β	SE	z value	P value	RR (95% CI)
Longitudinal submodel					
Fixed effects					
Intercept	1.4902	0.0053	278.8231	0.0001	
Age	0.0018	0.0004	4.6674	0.0001	
Gender	−0.2372	0.0094	−25.1171	0.0001	
Time:age	0.0007	0.0002	4.6345	0.0001	
Time:gender	−0.0147	0.0040	−3.7158	0.0002	
Random effects					
σ_{b00}	0.2439				
σ_{b10}	0.0316				
ε	0.1636				
Survival submodel					
Age	0.0332	0.0045	7.3568	0.0001	1.0338 (1.0246 to 1.0429)
Gender	0.1732	0.0876	1.9778	0.0479	1.1891 (1.0016 to 1.4116)
Age:gender	−0.0125	0.0062	−2.0066	0.0448	0.9876 (0.9756 to 0.9997)
Assoct	−2.9380	0.2098	−14.0048	0.0001	0.0529 (0.0351 to 0.0799)

AIC, 4729.97.
RR, relative risk.

Table 4 Results of the Joint model for the association between longitudinal low-density lipoprotein cholesterol (LDL-c) values and metabolic syndrome (MetS)

Parameters	β	SE	z value	P value	RR (95% CI)
Longitudinal submodel					
Fixed effects					
Intercept	2.6618	0.0120	222.1383	0.0001	
Time	−0.0153	0.0041	−3.7243	0.0002	
Age	0.0167	0.0009	19.0607	0.0001	
Gender	0.1221	0.0218	5.5958	0.0001	
Time:gender	0.0218	0.0087	2.5096	0.0121	
Random effects					
σ_{b00}	0.5693				
σ_{b10}	0.0513				
ε	0.3965				
Survival submodel					
Age	0.0130	0.0032	4.1078	0.0001	1.0131 (1.0068 to 1.0965)
Gender	0.7610	0.0733	10.3833	0.0001	2.1404 (1.8540 to 2.4710)
Assoct	0.3314	0.0642	5.1647	0.0001	1.3929 (1.2283 to 1.5795)

AIC, 23321.03.
RR, relative risk.

respectively. Therefore, for a particular percent decrease of HDL-c, there is a larger impact on MetS risk at a higher baseline HDL-c level. However, for the same decreases in HDL-c, the RRs are the same across different baseline HDL-c values. Taken together, the greater decreases in HDL-c result in the greater occurrence of risk of MetS, regardless of the baseline HDL-c levels. Unlike HDL-c, the greater increases in LDL-c result in the greater occurrence of risk of MetS, regardless of the baseline LDL-c levels.

Sensitivity analysis

To test the robustness of our findings, we undertook sensitivity analyses. We established the Cox and Joint models based on the complete data according to the previous imputed data results. Results of the Cox model estimates are given in online supplementary table 4, and those for the Joint model are given in online supplementary tables 5, 6. The results in the tables show that the estimates obtained from the imputed data and complete data are not identical. This outcome is possibly because of the

Table 5 Estimated relative risk (RR) of metabolic syndrome (MetS) for different longitudinal decreases of high-density lipoprotein cholesterol (HDL-c) and increases of low-density lipoprotein cholesterol (LDL-c) at specific HDL-c and LDL-c baseline levels, under the Joint model

HDL-c, LDL-c baseline level (mmol/L)					
	1	2	3	4	5
RR for a decrease of HDL-c					
10%	1.3415	1.7997	2.4143	3.2389	4.3450
20%	1.7997	3.2389	5.8290	10.4904	18.8794
30%	2.4143	5.8290	14.0731	33.9770	82.0316
0.5 unit	4.3449	4.3449	4.3449	4.3449	4.3449
1 unit	18.8781	18.8781	18.8781	18.8781	18.8781
RR for an increase of LDL-c					
10%	1.0337	1.0685	1.1045	1.1417	1.1802
20%	1.0685	1.1417	1.2200	1.3036	1.3929
30%	1.1045	1.2200	1.3475	1.4884	1.6439
0.5 unit	1.1802	1.1802	1.1802	1.1802	1.1802
1 unit	1.3929	1.3929	1.3929	1.3929	1.3929

additional 794 cases that the imputations have allowed to be included in the analysis. However, the differences are not significant because the 95% CIs from the two approaches overlap. For the imputed data, the estimated SEs are generally less than for the complete data analysis and possibly reflect the effect of including the imputed data. Therefore, the results from the imputed data generally correspond to the results from the complete data.

DISCUSSION

In our study, the longitudinal associations between HDL-c or LDL-c and MetS were assessed by the association parameter (α) of the Joint model. It was suggested that longitudinal decreases in HDL-c or increases in LDL-c over time were associated with an increased risk of incident MetS. In table 5, similarly, as long as HDL-c absolutely decreased or LDL-c absolutely increased longitudinally, the risk of MetS would increase, regardless of HDL-c or LDL-c levels at baseline. It is acknowledged that the most critical pathophysiology of MetS is IR,[10 11] which is commonly believed to originate from central obesity.[31 32] A negative correlation was found between TG and HDL-c,[25] and the level of HDL-c was brought down with the level of elevated TG. The dyslipidaemia usually characterised by hypertriglyceridaemia decreased HDL-c and increased LDL-c.[33] Dyslipidaemia results in the accumulation of visceral fat, with the formation of central obesity inducing the occurrence of IR, which can promote the development of related MetS components that eventually lead to the occurrence of MetS.[34]

The results of the general Cox model in our study are shown in online supplementary table 7 and are in agreement with previous studies demonstrating that the baseline decrement of HDL-c or the increment of LDL-c is associated with an elevated risk of MetS. Leila Houti *et al* reported that low HDL-c was a risk factor for MetS in Algeria.[17]In a study in Iran with 10 years of follow-up, the adjusted OR for HDL-c in the development of MetS was 6.49 (95% CI 3.18 to 13.25).[22] A study on LDL-c and MetS conducted in a Japanese health screening population suggested that the ORs for the higher quartiles of LDL-c, compared with the lower quartiles, were 3.14 (95% CI 2.28 to 4.33) and 1.69 (95% CI 1.22 to 2.35), respectively, adjusted for smoking, drinking status and other confounding covariates.[20] These studies only focused on the effects of baseline HDL-c and LDL-c levels on MetS, which were not consistent with the actual changes in the index. The Joint model results showed that the baseline levels of HDL-c or LDL-c were not significant when considering the effects of dynamic changes in indicators on MetS and were excluded from the model. Our results indicated that the dynamic changes in HDL-c or LDL-c had greater effects on the hazard of time to the occurrence of MetS than the baseline level. From the individual point of view, the greater decrease in HDL-c or increase in LDL-c results in the greater occurrence risk of MetS, regardless of baseline HDL-c or LDL-c levels. This result is the most remarkable point of the present study and corresponds with our study aim. However, in most circumstances, dyslipidaemia has low rates of awareness and treatment. Changes of the dynamic longitudinal decrement in HDL-c or the increment in LDL-c should be a focal point for health checks in healthy individuals. When HDL-c or LDL-c levels present a certain dynamic trend of change, individuals should take corresponding measures, that is, caloric restriction, avoiding saturated fats, increasing physical activity, and so on, to ensure that levels remain stable. Our results showed that we should pay more attention to the long-term dynamic changes in HDL-c or LDL-c in a healthy population, rather than only to the level of HDL-c or LDL-c at one time; this helps to discover the signs of metabolic abnormalities earlier and also provides a basis to further develop a risk assessment model for predicting MetS using HDL-c or LDL-c levels. Our results can be applied to the healthy population, and not only for the Chinese population.

This study has a few limitations. First, 35.36% of the participants had three or more follow-up visits within 7 years of follow-up. The current short follow-up period was limited for accurately assessing the correlations between the changes in indexes and MetS over time. Second, there was the lack of WC, as an indicator for central obesity, however, BMI was used as a substitute. Third, the Joint model has some disadvantages, for example, it could not, at present, analyse two or more longitudinal variables simultaneously; therefore, we could not consider the other covariates that changed over time when we analysed the effects of longitudinal changes in HDL-c or LDL-c on MetS. Further, the assumption of the Joint model that the longitudinal trajectory feature of each subject is satisfied with a linear model is hardly ever achieved in reality.[35] Additionally, there was no discussion on the other factors that lead to the changes in HDL-c or LDL-c levels, except for age and gender. Hence, in further studies, we should provide a larger sample size with a relatively long follow-up period, use WC to diagnose central obesity, and discuss how to prevent and control these changes.

In conclusion, the dynamic longitudinal decrement of HDL-c or the increment of LDL-c for healthy adults indicates that the risk of MetS is increasing, even though their levels are within the reference limits. Furthermore, once adults find dynamic changes in HDL-c or LDL-c, they should take appropriate measures in time to keep HDL-c or LDL-c levels stable so as to prevent or delay the occurrence of MetS.

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Contributors QL and GS designed the study. YL contributed to the acquisition of the data. XW, ML, HS and YF screened and extracted the data and performed the statistical analysis under the supervision of QL and GS. XW reviewed the results, interpreted the data and wrote the manuscript. QL and GS critically revised the manuscript. All authors read and approved the final manuscript.

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Patient consent Not required.

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