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Cholesterol paradox in the community-living old adults: is higher better?

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ABSTRACT

OBJECTIVE To evaluate the associations of lipid indicators and mortality in Beijing Elderly Comprehensive Health Cohort Study.

METHODS A prospective cohort was conducted based on Beijing Elderly Comprehensive Health Cohort Study with 4499 community older adults. After the baseline survey, the last follow-up was March 31, 2021 with an average 8.13 years of follow-up. Cox proportional hazard model was used to estimate the hazard ratios (HR) with 95% CI for cardiovascular disease (CVD) death and all-cause death in associations with baseline lipid indicators.

RESULTS A total of 4499 participants were recruited, and the mean levels of uric acid, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol (TC), triglyceride, and low-density lipoprotein cholesterol (LDL-C) showed an upward trend with the increasing remnant cholesterol (RC) quarters (P_{trend} < 0.05), while the downward trend was found in high-density lipoprotein cholesterol (HDL-C). During the total 36,596 person-years follow-up, the CVD mortality and all-cause mortality during an average 8.13 years of follow-up was 3.87% (95% CI: 3.30%–4.43%) and 14.83% (95% CI: 13.79%–15.86%) with 174 CVD death participants and 667 all-cause death participants. After adjusting for confounders, the higher level of TC (HR = 0.854, 95% CI: 0.730–0.997), LDL-C (HR = 0.817, 95% CI: 0.680–0.982) and HDL-C (HR = 0.443, 95% CI: 0.271–0.724) were associated with lower risk of CVD death, and the higher level of HDL-C (HR = 0.637, 95% CI: 0.501–0.810) were associated with lower risk of all-cause death. The higher level of RC (HR = 1.276, 95% CI: 1.010–1.613) increase the risk of CVD death. Compared with the normal lipid group, TC ≥ 6.20 mmol/L group and LDL-C ≥ 4.10 mmol/L group were no longer associated with lower risk of CVD death, while RC ≥ 0.80 mmol/L group was still associated with higher risk of CVD death. In normal lipid group, the higher levels of TC, LDL-C and HDL-C were related with lower CVD death.

CONCLUSIONS In community older adults, higher levels of TC and HDL-C were associated with lower CVD mortality in normal lipid reference range. Higher RC was associated with higher CVD mortality, which may be a better lipid indicator for estimating the CVD death risk in older adults.

Cardiovascular disease (CVD) death is the leading global mortality, increasing from 12.1 million in 1990 to 18.6 million in 2019.[1,2] Notably, CVD mortality in China ranks the first death cause and accounts for more than 40% of death, bringing heavy burden of disease.[3,4] Generally, higher levels of lipid and hyperlipidemia were generally acknowledged as the risk factor for CVD death.[5] However, in the older population, "cholesterol paradox" were reported by many observational studies that the higher cholesterol levels were not associated with incidence and mortality of CVD.[6–11] Systematic review about the exact association between low-density lipoprotein cholesterol (LDL-C) and all-cause death have identified high LDL-C was associated with lower mortality in most people over 60 years.[7] The inverse association was not only among the lipid with death, but in cognitive decline, disability and frailty in the oldest old, based on the Chinese Longitudinal Healthy Longevity Survey (CLHLS).[8]

Further, it is still unclear whether the "cholesterol paradox" existed among Chinese community older adults, and the extent to which the different lipid indicators affect CVD death, and screen the better lipid indicator for CVD mortality. Therefore, this study aims to examine whether the "cholesterol paradox" exist and vary in different lipid indicators among Beijing Elderly Comprehensive Health Cohort Study.

METHODS

Study Design and Participants

This study data comes from Beijing Elderly Comprehensive Health Cohort Study, which used multi-stage cluster sampling method to select community elderly people aged ≥ 60 years from Haidian urban district (2009) and Miyun rural county (2014) in Beijing as the research subjects. A total of 4499 community older adults were included in the study. After the baseline survey, follow-up was conducted every 2–3 years and the last follow-up was March 31, 2021. The detail of this cohort has been published previously.[12–14] This study has been approved by the Medical Ethics Committee of Chinese PLA General Hospital, Beijing, China (No.S2021-327-01) and registered at China Clinical Trial Registration Center (ChiCTR210049866).

During the Beijing Elderly Comprehensive Health Cohort Study baseline survey, face-to-face questionnaire surveys, physical examinations, and laboratory tests were conducted by uniformly trained medical staff. The questionnaire survey includes demographic characteristics, lifestyles (smoking, drinking, and exercise) and disease history. The venous blood (10 mL) from the participants after fasting for 10–12 h was used to detect blood lipids, uric acid and creatinine according to standardized methods.

Follow-up survey was carried out by telephone to obtain the survival or death information of the objects, and verified with the medical insurance system and the registered residence registration system of the public security department regularly to determine the time, place and cause of death.

Lipids

According to the "2023 Chinese guideline for lipid management",[15] total cholesterol (TC) ≥ 6.2 mmol/L and/or triglyceride ≥ 2.3 and/or LDL-C ≥ 4.1 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L is defined as dyslipidemia. Those who have at least one of the above conditions or have been diagnosed with dyslipidemia according to the patient's self-report are considered dyslipidemia. Non-high-density lipoprotein cholesterol (non-HDL-C) is calculated as follows: non-HDL-C = TC − HDL-C. Non-HDL-C ≥ 4.9 mmol/L was defined as dyslipidemia.[15] According to the European joint consensus statement from the European Atherosclerosis Society, fasting remnant cholesterol (RC) < 0.8 mmol/L was regarded as normal RC.[16] RC was divided into quarters for baseline characteristic description.

Definition

During the baseline survey questionnaire, the respondents were asked "Do you have hypertension", when respondents answered "No" and their systolic blood pressure ≥ 140 mmHg (1 mmHg = 0.133 kPa) or diastolic blood pressure ≥ 90 mmHg were still determined to suffering from hypertension. When the respondents were asked "Do you have diabetes mellitus?" to preliminarily determine their diabetes mellitus prevalence. If their answer were "No" but fasting blood glucose ≥ 7.0 mmol/L, they are still determined to suffering from diabetes mellitus. Based on the respondents' response to "Do you often participate in physical exercise?" to determine their exercise status, and "Do you currently

smoke/drink alcohol" and "Have you used to smoke/drink alcohol" to determine their smoking/drinking status.

Statistical Analysis

Differences among RC quarters were performed using analysis of variance for continuous variables and the Pearson's chi-squared test for categorical variables. Mortality and death density were calculated according to RC quarters. Cox proportional hazard model was used to estimate the hazard ratios (HR) with 95% CI for CVD death and all-cause death in associations with baseline lipid indicators. Schoenfeld residual trend test was used to test the proportional hazard assumption in the associations of lipids and CVD death and all-cause death, respectively. The results show that the independent variables (lipid indicators) and the two models meet the preconditions of proportional risk ($P > 0.05$). In multivariate analysis, adjusted variables were age, gender, body mass index, education, marital status, smoking, alcohol use, exercise, diabetes mellitus, and hypertension. Stratified analysis was performed by gender using multivariate Cox proportional hazards model. Statistical interpretation of data was performed by SPSS 24.0 (SPSS Inc., IBM, Armonk, NY, USA) and Excel, and the forest plot was by Rstudio (RStudio Inc., Boston, MA, USA). Two-sided P-value < 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 4499 participants (40.32% men and 59.68% women) were recruited, with an average age of 70.49 ± 6.77 years. Demographic and RC baseline characteristics were shown in Table 1. The mean levels of uric acid, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, TC, triglyceride, and LDL-C showed an upward trend with the increasing RC quarters ($P_{trend} < 0.05$), while the downward trend was found in HDL-C. It is substantial geographic variation that the downward trend of constituent ratio of subjects in rural and upward trend in urban with the increasing RC quarters were found ($P_{trend} < 0.05$). The sex difference that the downward trend of constituent ratio of male subject and upward trend in female subject with the increasing RC quarters was showed, and the prevalence of hypertension showed upward trend ($P_{trend} < 0.05$).

Follow-up Mortality

During the total 36,596 person-years follow-up, there are 174 CVD death participants and 667 all-cause death participants. The CVD mortality and all-cause mortality during an average 8.13 years of follow-up was 3.87% (95% CI: 3.30%–4.43%) and 14.83% (95% CI: 13.79%–15.86%), and the incidence density (per 100 person-years) was 0.48% (95% CI: 0.41%–0.55%) and 1.82% (95% CI: 1.69%–1.96%). The CVD mortality and mortality density showed an upward trend with the increasing RC quarters ($P_{trend} < 0.05$) (Table 2).

Contrary Associations of Lipid Level and CVD Death and All-cause Death

The values of HR with 95% CI of lipids level and mortality are shown in Table 3 and Table 4. After adjusting for confounders, the higher level of TC (HR = 0.854, 95% CI: 0.730–0.997), LDL-C (HR = 0.817, 95% CI: 0.680–0.982) and HDL-C (HR = 0.443, 95% CI: 0.271–0.724) were associated with lower risk of CVD death, and the higher level of HDL-C (HR = 0.637, 95% CI: 0.501–0.810) were associated with lower risk of all-cause death. The higher level of RC (HR = 1.276, 95% CI: 1.010–1.613) increase the risk of CVD death. Dyslipidemia specified by the respective normal reference value of the lipids was estimated its associations with mortality. High TC (≥ 6.20 mmol/L) (HR = 0.986, 95% CI: 0.630–1.542) and high LDL-C (≥ 4.10 mmol/L) (HR = 0.813, 95% CI: 0.491–1.347) were no longer associated with lower risk of CVD death, while low HDL-C (< 1.00 mmol/L) (HR = 1.287, 95% CI: 1.017–1.628) was associated with higher risk of all-cause death. Consistent with the association of continuous RC and CVD death, high RC (≥ 0.80 mmol/L) (HR = 1.422, 95% CI: 1.001–2.020) was still associated with higher risk of CVD death. The values of HR with 95% CI of lipids quarters and mortality are shown in Figure 1. Compared to the RC ≤ 0.28 mmol/L, the higher HDL-C quarters were related with lower risk of CVD mortality ($P_{trend} = 0.004$) and all-cause mortality ($P_{trend} = 0.001$), respectively. The correlation trend of decreasing mortality risk with increasing lipids quarter was not found in TC, triglyceride, LDL-C, non-HDL-C and RC.

Restricted cubic spline for associations with lipid indicators and CVD death are shown in Figure 1. There was a nonlinear association between TC, LDL-C, non-HDL-C and CVD mortality ($P_{nonlinear} < 0.05$) and a neg-

Table 1 Baseline remnant cholesterol characteristics of the community-living old adults.

Variables	Remnant cholesterol				*P*-value	P_{trend}-value
	≤ 0.28 mmol/L (*n* = 1242)	0.29–0.52 mmol/L (*n* = 1152)	0.53–0.76 mmol/L (*n* = 1082)	≥ 0.77 mmol/L (*n* = 1023)		
Age, yrs	70.02 ± 6.54	70.93 ± 6.74	70.71 ± 6.85	70.33 ± 6.95	0.005	0.331
Uric acid, μmol/L	286.41 ± 75.80	296.07 ± 82.19	303.69 ± 89.42	312.40 ± 88.85	< 0.001	< 0.001
Body mass index, kg/m^2	24.03 ± 3.34	24.31 ± 3.42	24.99 ± 3.42	25.08 ± 3.45	< 0.001	< 0.001
Systolic blood pressure, mmHg	131.86 ± 16.82	136.78 ± 18.08	138.55 ± 19.92	139.43 ± 20.54	< 0.001	< 0.001
Diastolic blood pressure, mmHg	78.49 ± 11.42	77.75 ± 10.48	78.50 ± 10.51	80.25 ± 11.77	< 0.001	< 0.001
Fasting plasma glucose, mmol/L	5.91 ± 1.52	5.87 ± 1.47	5.98 ± 1.71	6.33 ± 2.14	< 0.001	< 0.001
TC, mmol/L	4.45 ± 0.85	4.78 ± 0.86	5.15 ± 0.91	5.62 ± 1.15	< 0.001	< 0.001
Triglyceride, mmol/L	1.09 ± 0.44	1.24 ± 0.45	1.56 ± 0.59	2.42 ± 1.44	< 0.001	< 0.001
HDL-C, mmol/L	1.47 ± 0.36	1.48 ± 0.35	1.38 ± 0.33	1.28 ± 0.32	< 0.001	< 0.001
LDL-C, mmol/L	2.96 ± 0.84	2.90 ± 0.76	3.14 ± 0.84	3.16 ± 1.03	< 0.001	< 0.001
Creatinine, μmol/L	69.41 ± 18.48	72.34 ± 19.48	72.12 ± 20.73	70.63 ± 27.68	0.003	0.165
Area					< 0.001	< 0.001
Rural	1062 (85.51%)	405 (35.16%)	373 (34.47%)	557 (54.45%)		
Urban	180 (14.49%)	747 (64.84%)	709 (65.53%)	466 (45.55%)		
Gender					< 0.001	< 0.001
Male	597 (48.07%)	504 (43.75%)	405 (37.43%)	308 (30.11%)		
Female	645 (51.93%)	648 (56.25%)	677 (62.57%)	715 (69.89%)		
Ethnic					0.337	0.471
Han	1225 (98.63%)	1126 (97.74%)	1058 (97.78%)	1005 (98.24%)		
Minority nationality	17 (1.37%)	26 (2.26%)	24 (2.22%)	18 (1.76%)		
Educational level					< 0.001	< 0.001
Primary school and below	912 (73.43%)	551 (47.83%)	538 (49.72%)	621 (60.70%)		
Middle school and above	330 (26.57%)	601 (52.17%)	544 (50.28%)	402 (39.30%)		
Marital status					< 0.001	< 0.001
Married	153 (12.32%)	636 (55.21%)	603 (55.73%)	382 (37.34%)		
Widowed/Divorced/Single	1089 (87.68%)	516 (44.79%)	479 (44.27%)	641 (62.66%)		
Smoking					< 0.001	< 0.001
Never	790 (63.61%)	812 (70.49%)	764 (70.61%)	761 (74.39%)		
Ever	167 (13.45%)	165 (14.32%)	154 (14.23%)	108 (10.56%)		
Still	285 (22.95%)	175 (15.19%)	164 (15.16%)	154 (15.05%)		
Alcohol drinking					< 0.001	< 0.001
Never	619 (49.84%)	766 (66.49%)	738 (68.21%)	668 (65.30%)		
Ever	80 (6.44%)	67 (5.82%)	56 (5.18%)	47 (4.59%)		
Still	543 (43.72%)	319 (27.69%)	288 (26.62%)	308 (30.11%)		
Exercise					< 0.001	< 0.001
No	442 (35.59%)	222 (19.27%)	200 (18.48%)	269 (26.30%)		
Yes	800 (64.41%)	930 (80.73%)	882 (81.52%)	754 (73.70%)		
Hypertension					< 0.001	< 0.001
No	583 (46.94%)	407 (35.33%)	345 (31.89%)	309 (30.21%)		
Yes	659 (53.06%)	745 (64.67%)	737 (68.11%)	714 (69.79%)		

Data are presented as means ± SD or *n* (%). HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

Table 2 Mortality of baseline remnant cholesterol quarters.

Death	Remnant cholesterol				Total (n = 4499)
	≤ 0.28 mmol/L (n = 1242)	0.29–0.52 mmol/L (n = 1152)	0.53–0.76 mmol/L (n = 1082)	≥ 0.77 mmol/L (n = 1023)	
Cardiovascular disease death					
Number of death cases	36	45	45	48	174
Mortality, %	2.90 (1.96–3.83)	3.91 (2.79–5.03)	4.16 (2.97–5.35)	4.69 (3.39–5.99)	3.87 (3.30–4.43)
Total person-years	8489	10,281	9627	8199	36,596
Death density, per 100 person-years	0.42 (0.29–0.56)	0.44 (0.31–0.57)	0.47 (0.33–0.60)	0.59 (0.42–0.75)	0.48 (0.41–0.55)
All-cause death					
Number of death cases	166	174	172	155	667
Mortality, %	13.37 (11.47–15.26)	15.10 (13.03–17.18)	15.90 (13.71–18.08)	15.90 (13.71–18.08)	14.83 (13.79–15.86)
Total person-years	8489	10,281	9627	8199	36,596
Death density, per 100 person-years	1.96 (1.66–2.25)	1.69 (1.44–1.94)	1.79 (1.52–2.05)	1.89 (1.60–2.19)	1.82 (1.69–1.96)

Table 3 Associations of baseline lipid levels and CVD death and all-cause death among the community-living old adults.

	CVD death		All-cause death	
	Model 1	Model 2	Model 1	Model 2
TC, mmol/L	0.768 (0.659–0.897)	0.854 (0.730–0.997)	0.823 (0.761–0.889)	0.932 (0.861–1.009)
Triglyceride, mmol/L	0.998 (0.854–1.166)	1.066 (0.909–1.250)	0.899 (0.821–0.986)	1.005 (0.918–1.099)
LDL-C, mmol/L	0.729 (0.608–0.873)	0.817 (0.680–0.982)	0.833 (0.761–0.912)	0.962 (0.878–1.055)
HDL-C, mmol/L	0.415 (0.261–0.662)	0.443 (0.271–0.724)	0.648 (0.517–0.812)	0.637 (0.501–0.810)
Non-HDL-C, mmol/L	0.846 (0.724–0.989)	0.928 (0.793–1.086)	0.862 (0.796–0.932)	0.979 (0.904–1.061)
RC, mmol/L	1.227 (0.985–1.529)	1.276 (1.010–1.613)	0.952 (0.809–1.120)	1.032 (0.882–1.206)

Model 1: not adjusted. Model 2: adjusted for age, gender, body mass index, education, marital status, smoking, alcohol use, exercise, diabetes mellitus, and hypertension. CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RC: remnant cholesterol; TC: total cholesterol.

Table 4 Associations of baseline dyslipidemia and CVD death and all-cause death among the community-living old adults.

	CVD death		All-cause death	
	Model 1	Model 2	Model 1	Model 2
TC ≥ 6.20 mmol/L	0.876 (0.564–1.360)	0.986 (0.630–1.542)	0.798 (0.630–1.009)	0.939 (0.739–1.193)
Triglyceride ≥ 2.30 mmol/L	0.979 (0.650–1.477)	1.121 (0.731–1.721)	0.879 (0.706–1.095)	1.065 (0.847–1.338)
LDL-C ≥ 4.10 mmol/L	0.717 (0.434–1.183)	0.813 (0.491–1.347)	0.820 (0.642–1.048)	0.983 (0.767–1.259)
HDL-C < 1.00 mmol/L	1.539 (1.007–2.351)	1.362 (0.879–2.111)	1.359 (1.083–1.707)	1.287 (1.017–1.628)
Non-HDL-C ≥ 4.90 mmol/L	0.918 (0.569–1.480)	1.004 (0.618–1.630)	0.834 (0.646–1.078)	0.977 (0.753–1.268)
RC ≥ 0.80 mmol/L	1.378 (0.979–1.939)	1.422 (1.001–2.020)	1.042 (0.863–1.258)	1.104 (0.911–1.339)

Model 1: not adjusted. Model 2: adjusted for age, gender, body mass index, education, marital status, smoking, alcohol use, exercise, diabetes mellitus, and hypertension. CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RC: remnant cholesterol; TC: total cholesterol.

ative association between HDL-C and CVD mortality, and positive association between RC and CVD mortality after adjusting for the same confounders.

Associations of Lipids Level and CVD Death in Non-dyslipidemia and Dyslipidemia Groups

The HR with 95% CI of lipids level of normal, dyslipidemia group and mortality are shown in Table 5. In the non-dyslipidemia group, the higher level of TC (HR = 0.753, 95% CI: 0.586–0.967) and HDL-C (HR = 0.504, 95% CI: 0.265–0.957) were associated with lower risk of CVD death. However, in the dyslipidemia group, the higher level of LDL-C (HR = 0.781, 95% CI: 0.627–0.974) and HDL-C (HR = 0.445, 95% CI: 0.268–0.740) were associ-

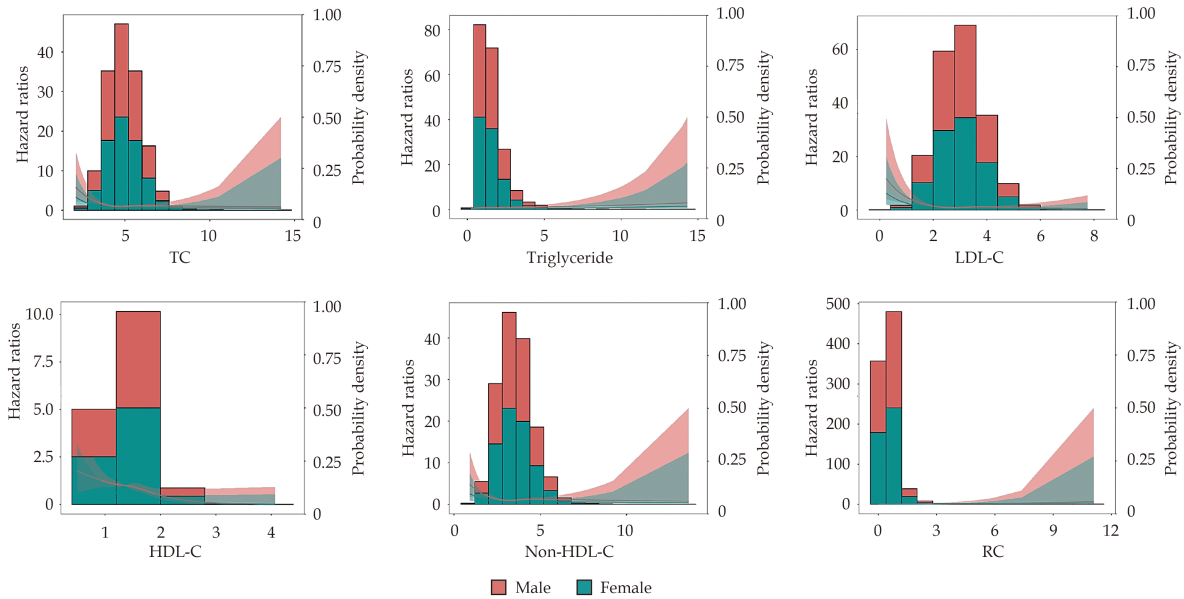

Figure 1 Restricted cubic spline for associations with lipid indicators and CVD death after adjusting for age, gender, body mass index, education, marital status, smoking, alcohol use, exercise, diabetes mellitus, and hypertension. The *P*-value for non-linear of TC, triglyceride, LDL-C, HDL-C, non-HDL-C and RC with CVD death were 0.011, 0.479, 0.001, 0.574, 0.015 and 0.857, which represent non-linear association between TC, LDL-C, non-HDL-C and CVD mortality. CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RC: remnant cholesterol; TC: total cholesterol.

Table 5 Associations of baseline lipid levels and CVD death in non-dyslipidemia and dyslipidemia groups based on the physiological reference values of indicators.

	Non-dyslipidemia group		Dyslipidemia group	
	HR	95% CI	HR	95% CI
TC	0.733	0.538–0.999	0.859	0.712–1.037
Triglyceride	1.359	0.796–2.321	1.009	0.828–1.231
LDL-C	0.847	0.597–1.202	0.781	0.627–0.974
HDL-C	0.504	0.265–0.957	0.445	0.268–0.740
Non-HDL-C	0.863	0.621–1.198	0.906	0.743–1.105
RC	0.815	0.283–2.346	1.309	1.006–1.703

The indicators in both non-dyslipidemia and dyslipidemia groups adjusted for age, gender, body mass index, education, marital status, smoking, alcohol use, exercise, diabetes mellitus, and hypertension. CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RC: remnant cholesterol; TC: total cholesterol.

ated with lower risk of CVD death, while the higher level of RC (HR = 1.309, 95% CI: 1.006–1.703) were associated with higher risk of CVD death.

DISCUSSION

In community older adults, higher levels of TC and HDL-C were associated with lower CVD mortality within normal lipid reference range and the associations were not significant in the dyslipidemia older population. Higher RC was associated with higher CVD mortality, which may be a better lipid indicator for estimating the CVD death risk in older adults. Higher HDL-C within normal lipid reference range was associated with lower CVD mortality and all-cause mortality, which may be a better lipid indicator for reducing the CVD death risk and all-cause death risk in older adults.

The "cholesterol paradox" in this study refers to those older adults within normal lipid reference range, while the older population with dyslipidemia is not applicable to the associations. Ravnskov, *et al.*[7] had reviewed the association between LDL-C and all-cause death among the population over 60 years, and conclude the none significant a positive or inverse association can be found. Moreover, the "cholesterol paradox" had been detailed descripted that the main challenge to uncover the true

face of "cholesterol paradox" need for longitudinal, even lifecycle follow-up to explain the cumulative impact of entire lifecycle lipid on the CVD death.[9] In this study, the results in older adults with normal lipid level seem to have verified "cholesterol paradox", which means choosing better indicators may help overturn this paradox.

This study has showed that RC, rather than traditional indicators, is the better lipid indicator for predicting the CVD death risk in older adults. RC is main triglyceride-rich lipoproteins characterized that triglycerides can be easier metabolized and the RC in triglyceride-rich lipoproteins might be more dangerous to health.[17] In an overweight and obese older population at high cardiovascular risk, RC rather than LDL-C was regarded as the better lipid biomarker for predicting the major adverse cardiovascular events.[18] From Atherosclerosis Risk in Communities (ARIC) study, RC was associated with coronary heart disease in older adults.[19] Moreover, RC might be the risk factor for atherogenic effect. A total of 1786 non-diabetic individuals were included that the RC could increase the risk of carotid intima-media thickness after three years follow-up.[20]

The high level of HDL-C in older adults is possible protective factors for CVD and all-cause death. The Cardiovascular Health in Ambulatory Care Research Team (CANHEART) study covering 631,762 individuals had been used to compare the association of HDL-C level with CVD and non-CVD mortality, which conclude the low and very high HDL-C was related with a higher cardiovascular and non-cardiovascular mortality and these associations between HDL-C and specific mortality cannot be clearly distinguished.[21] However, the association between HDL-C and mortality is more complicated. The very high HDL-C level may be harmful. The multiple center cohort study including 365,457 participants in South Korea, the very high HDL-C was associated with higher risk of all-cause death.[22] Sex difference between the association between HDL-C and mortality was significant. In healthy older men and women from the Aspirin in Reducing Events in the Elderly (ASPREE; n = 18,668) trial and UK Biobank (UKB; n = 62,849), higher HDL-C levels are related with increased mortality in old men and no significant association was found in women.[23]

LIMITATIONS

Some potential limitations should be noted. Firstly, the study only focus on the baseline lipid levels not the lipids changing trend. The results cannot reveal the impact of individual lipid changing caused by treatment and medication on CVD mortality. Secondly, this research result only represents the urban and rural in Beijing, and has only reference significance for the older population in other regions. Last but not least, complete and detailed information on the medication were lack, and some individuals with normal lipid levels may be the result of treatment, which may have certain impact on the mortality.

CONCLUSIONS

In Chinese community older population, higher levels of TC and HDL-C were associated with lower CVD mortality only in normal lipid reference range. Higher RC was associated with higher CVD mortality, which may be a better lipid indicator for estimating the CVD death risk in older adults.

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REFERENCES

[1] GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1736–1788.

[2] Roth GA, Mensah GA, Johnson CO, *et al*. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 Study. *J Am Coll Cardiol* 2020; 76: 2982–3021.

[3] Zhao D, Liu J, Wang M, *et al*. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol* 2019; 16: 203–212.

[4] Liu S, Li Y, Zeng X, *et al*. Burden of cardiovascular diseases in China, 1990–2016: findings from the 2016 Global Burden of Disease study. *JAMA Cardiol* 2019; 4: 342–352.

[5] Yusuf S, Joseph P, Rangarajan S, *et al*. Modifiable risk factors, cardiovascular disease, and mortality in 155,722 in-

dividuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020; 395: 795–808.
[6] Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017; 38: 2478–2486.
[7] Ravnskov U, Diamond DM, Hama R, *et al*. Lack of an association or an inverse association between low-density lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 2016; 6: e010401.
[8] Lv YB, Mao C, Gao X, *et al*. Triglycerides paradox among the oldest old: "the lower the better?". *J Am Geriatr Soc* 2019; 67: 741–748.
[9] Orkaby AR. The highs and lows of cholesterol: a paradox of healthy aging?. *J Am Geriatr Soc* 2020; 68: 236–237.
[10] Hamazaki T, Okuyama H, Ogushi Y, *et al*. Towards a paradigm shift in cholesterol treatment. A re-examination of the cholesterol issue in Japan. *Ann Nutr Metab* 2015; 66: 1–116.
[11] Lewington S, Whitlock G, Clarke R, *et al*. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007; 370: 1829–1839.
[12] He Y, Li XY, Yang HB, *et al*. [Beijing Elderly Comprehensive Health Cohort Study: study design and preliminary results]. *Chin J Prev Contr Chron Dis* 2022; 30: 938–943. [In Chinese].
[13] He Y, Lam TH, Jiang B, *et al*. Combined effects of tobacco smoke exposure and metabolic syndrome on cardiovascular risk in older residents of China. *J Am Coll Cardiol* 2009; 53: 363–371.
[14] He Y, Jiang B, Wang J, *et al*. Prevalence of the metabolic syndrome and its relation to cardiovascular disease in an elderly Chinese population. *J Am Coll Cardiol* 2006; 47: 1588–1594.
[15] Li JJ, Zhao SP, Zhao D, *et al*. 2023 Chinese guideline for lipid management. *Front Pharmacol* 2023; 14: 1190934.
[16] Nordestgaard BG, Langsted A, Mora S, *et al*. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J* 2016; 37: 1944–1958.
[17] Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014; 384: 626–635.
[18] Castañer O, Pintó X, Subirana I, *et al*. Remnant cholesterol, not LDL cholesterol, is associated with incident cardiovascular disease. *J Am Coll Cardiol* 2020; 76: 2712–2724.
[19] Hussain A, Sun C, Selvin E, *et al*. Triglyceride-rich lipoproteins, apolipoprotein C-III, angiopoietin-like protein 3, and cardiovascular events in older adults: Atherosclerosis Risk in Communities (ARIC) study. *Eur J Prev Cardiol* 2022; 29: e53–e64.
[20] Du X, Ding J, Ma X, *et al*. Remnant cholesterol has an important impact on increased carotid intima-media thickness in non-diabetic individuals. *Int J Cardiovasc Imaging* 2023.
[21] Ko DT, Alter DA, Guo H, *et al*. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. *J Am Coll Cardiol* 2016; 68: 2073–2083.
[22] Oh IH, Hur JK, Ryoo JH, *et al*. Very high high-density lipoprotein cholesterol is associated with increased all-cause mortality in South Koreans. *Atherosclerosis* 2019; 283: 43–51.
[23] Mørland JG, Magnus P, Vollset SE, *et al*. Associations between serum high-density lipoprotein cholesterol levels and cause-specific mortality in a general population of 345,000 men and women aged 20–79 years. *Int J Epidemiol* 2023; 52: 1257–1267.

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