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Plasma lipid concentrations and survival in geriatric population

A retrospective cohort study

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Abstract

Plasma lipids in mid-life are important predictors for cardiovascular events and deaths. However, the association between plasma lipid concentrations and mortality in late life is controversial. Recent studies showed that older people with extremely low total cholesterol (TC) have poor survival outcome, but this conclusion was drawn mostly from Western cohorts. Our study investigated association between plasma lipid concentrations and mortality in Taiwanese elderly population.

A retrospective cohort study was conducted among the 69,824 elderly people who participated in the Taipei City Geriatric Health Examination between 2006 and 2010, with a mean follow-up of 3.6 years. The measurements of TC, high density lipoprotein (HDL) and triglycerides were obtained from the records of the participants. Low density lipoprotein (LDL) was calculated using Friedewald formula in 69,088 participants. All lipid components were categorized into quartiles. Males and females were analyzed separately using multivariate Cox proportional hazards models.

The elderly with the lowest quartile of TC (<175 mg/dL), HDL cholesterol (<43 mg/dL) and LDL cholesterol (<100.4 mg/dL) were at higher risk of all-cause mortality. Older females with the lowest quartile of TC and LDL cholesterol had higher cardiovascular mortality. Older females with the lowest quartile of HDL had higher mortality from cardiovascular and cerebrovascular diseases.

We concluded that TC, mostly attributed to LDL cholesterol, was inversely related to all-cause mortality. HDL remained to be protective against both cardiovascular and stroke mortality in older females. The target levels of plasma lipids in people older than 65 years should be different from that in younger adults.

Abbreviations: ANOVA = analysis of variance, BMI = body mass index, HDL = high density lipoprotein, ICD-9/10 = International Classification of Diseases and Related Health Problems 9th revision/10th revision, LDL = low density lipoprotein, TC = total cholesterol, TG = triglycerides.

Keywords: all-cause mortality, cardiovascular mortality, high density lipoprotein, low density lipoprotein, stroke mortality, total cholesterol

1. Introduction

It is well known that higher total cholesterol (TC) in mid-life is associated with higher overall and cardiovascular mortality.[1,2] However, this positive relation attenuates with increasing age.[3,4] Studies have shown hypercholesterolemia is no longer a risk factor for cardiovascular mortality in people older than 70 years.[5,6] On the other hand, low TC may increase all-cause mortality in the oldest old.[7–12] Regarding to fractionated lipids, the results are inconsistent. High density lipoprotein (HDL) cholesterol remains to be protective against cardiovascular and all-cause mortality through to old age in some studies,[6,9] but not in others.[5,13,14] Low density lipoprotein (LDL) cholesterol is less associated with cardiovascular mortality as a person ages,[9] and inversely associated with all-cause mortality in the elderly.[11,13,15,16] Triglycerides (TG) are linearly related to both all-cause and cardiovascular mortality as shown in one meta-analysis,[17] but the relation weakens in older people.[13,18] Besides, the association between plasma lipid concentrations and death may be different by genders. Some studies showed older males with lower HDL cholesterol have higher all-cause mortality.[19,20] Others showed older males with higher TC have higher cardiovascular mortality,[21] but older females with lower TC or higher TG have higher all-cause mortality.[21,22]

There are several lipid guidelines released from Western countries, such as the National Cholesterol Education Program (NCEP) guideline,[23,24] the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline,[25] and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) dyslipidemia guideline,[26] but neither emphasizes the elderly population. Before sophisticated guidelines of plasma lipids targeting different combinations of age, gender, and race can be derived, more investigations of lipid concentrations and survival

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in these subgroups are warranted. The aim of this study is to use Cox regression to estimate the hazard ratios of all-cause and cardiovascular mortality in terms of 4 common lipid variables (TC, HDL cholesterol, TG, LDL cholesterol), in Taiwanese community-dwelling older males and females. We hypothesize that plasma lipid concentrations play a complex role in the survival of older people, and the differences between genders exist.

2. Methods

2.1. Study design and participants

We conducted a retrospective cohort study using the Taipei City Geriatric Health Examination Database between 2006 and 2010. All citizens aged 65 years and older were eligible for the annual health examination, which was sponsored by the city government, thus these participants were representative of healthy elders residing in the community. As an older person may take the examination more than once, only data from the first examination during the period of 2006 to 2010 were evaluated. Demographic and lifestyle information, including marital status, cigarette smoking, alcohol consumption, educational level, and physical activity, was collected through self-administered questionnaires. Measurements of height, body weight, blood pressure, and lipid profile were obtained from the records of the participants. The original cohort consisted of 92,688 individuals who were 65 years and older. After exclusion of missing data and outliers for the measurements, 76,381 participants with their initial visits were included. We further excluded those dying within one year after the health examination. Finally, the data of 69,824 participants were used for the analysis of TC, HDL cholesterol, and TG, and those of 69,088 participants for the analysis of LDL cholesterol (see below). The Taipei City Geriatric Health Examination Database had been described in several studies.[27–32] The current study was approved by Taipei City Hospital Institutional Review Board (THCIRB-1031005-W).

2.2. Measurements of lipid components

The laboratory measurements of fasting TC, HDL, and TG levels were obtained from all 69,824 participants. LDL cholesterol level was estimated using Friedewald formula after exclusion of those with TG over 400 mg/dL.[33] There were 69,088 participants left for the analysis of LDL cholesterol. Lipid variables were categorized into quartiles: <175, 175 to 197, 198 to 221, ≥222 mg/dL for TC; <43, 43to 50, 51 to 60, ≥61 mg/dL for HDL cholesterol; <78, 78 to 108, 109 to 153, ≥154 mg/dL for TG; <100.4, 100.4 to 119.9, 120.0 to 140.7, ≥140.8 mg/dL for estimated LDL cholesterol.

2.3. Measurements of confounders

The questionnaire consisted of age (in years), gender (male vs female), marital status (married or cohabited vs none), smoking (current vs non-current), drinking (current vs non-current), education level (≤6 years, 7–12 years, >12 years of formal schooling), and exercise habits (no exercise, 1–2 times a week, 3–5 times a week). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. BMI was categorized as underweight if <18.5 kg/m^2, normoweight if 18.5 to 23.9 kg/m^2, overweight if 24 to 26.9 kg/m^2, and obesity if ≥27 kg/m^2 according to the definition from the Ministry of Health and Welfare for Taiwanese adult population. The participant's blood pressure was classified into hypertensive if the systolic blood pressure ≥140 mmHg or the diastolic blood pressure ≥90 mmHg, and non-hypertensive otherwise, regardless of antihypertensive drug use. The fasting blood glucose was classified into hyperglycemic if ≥126 mg/dL, and non-hyperglycemic if <126 mg/dL.

2.4. Death ascertainment

We linked the database of death causes from the Ministry of Health and Welfare through December 31, 2010. The database depended on death certificates coded by the International Classification of Diseases and Related Health Problems 9th revision (ICD-9) or 10th revision (ICD-10). Cardiovascular diseases were classified as ICD-9 codes 390 to 459, and ICD-10 codes I00-I99. Coronary artery diseases were classified as ICD-9 codes 410 to 414, and ICD-10 codes I20-I25. Cerebrovascular diseases were classified as ICD-9 codes 430 to 438, and ICD-10 codes I60-I69.

2.5. Statistical analysis

The baseline characteristics were compared across different mortality status, using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Lipid variables were categorized into quartiles to account for nonlinear relation. The gender-specific hazard ratio (HR) and confidence interval (CI) of lipid components were estimated by the multivariate Cox proportional hazards model, adjusting for age, marital status, smoking, drinking, education level, exercise habits, BMI, blood pressure, and fasting blood glucose. The statistical analysis was implemented using SAS 9.3 software (SAS Institute, Cary, NC).

3. Results

Among the 69,824 participants, the mean age was 73.5 years and 48.1% were males. The mean follow-up time was 3.6 years. A total of 3220 (4.6%) participants died, and 702 (1.0%) were due to cardiovascular causes. Specifically, 172 (0.2%) were coronary artery diseases and 217 (0.3%) cerebrovascular diseases. After exclusion of those with TG > 400 mg/dL, the remaining 69,088 individuals were analyzed for the association between LDL cholesterol and mortality. Table 1 summarizes the comparison of baseline characteristics across mortality status. In general, those who survived longer were younger and female predominant, less hypertensive and hyperglycemic, but had higher BMI, TC, and HDL cholesterol. They tended to be married or cohabiting, well educated, and taking more exercise. Although the proportion of current smoking or drinking was not high, those who survived longer had even lower proportion of smoking, but a slightly higher proportion of drinking.

Figure 1 shows TC, HDL cholesterol, TG, and LDL cholesterol in relation to all-cause mortality. For males, the adjusted HR (95% CI) was 0.799 (0.719–0.887), 0.765 (0.681–0.859), and 0.705 (0.617–0.807) in the second, third, and fourth quartiles of TC, respectively. For females, the adjusted HR (95% CI) was 0.748 (0.630–0.888), 0.653 (0.549–0.777), and 0.560 (0.471–0.666) in the second, third, and fourth quartiles of TC, respectively. The relationship was similar for HDL cholesterol

Table 1

Baseline characteristics of 69,824 participants by mortality status, presented with mean ± standard deviation or number (percent).

Variables	Cardiovascular death (n = 702)	Non-cardiovascular death (n = 2518)	Alive (n = 66604)	*P* value*
Age (yr)	79.3 ± 6.7	79.0 ± 7.1	73.2 ± 6.4	<.0001
Male gender	439 (62.5)	1751 (69.5)	31388 (47.1)	<.0001
BMI				
<18.5 kg/m^2	63 (9.0)	229 (9.1)	2126 (3.2)	<.0001
24–26.9 kg/m^2	187 (26.6)	649 (25.8)	21560 (32.4)	
≥27.0 kg/m^2	103 (14.7)	389 (15.5)	12804 (19.2)	
Hypertension	347 (49.4)	1133 (45.0)	27856 (41.8)	<.0001
Hyperglycemia	95 (13.5)	429 (17.0)	8241 (12.4)	<.0001
TC (mg/dL)				
175-197	176 (25.1)	641 (25.5)	16495 (24.8)	<.0001
198-221	157 (22.4)	512 (20.3)	16929 (25.4)	
≥222	138 (19.7)	399 (15.9)	17408 (26.1)	
HDL-C (mg/dL)				
43-50	175 (24.9)	638 (25.3)	16559 (24.9)	<.0001
51-60	164 (23.4)	524 (20.8)	17581 (26.4)	
≥61	144 (20.5)	547 (21.7)	17754 (26.7)	
TG (mg/dL)				
78-108	184 (26.2)	614 (24.4)	17057 (25.6)	<.0001
109-153	162 (23.1)	576 (22.9)	16791 (25.2)	
≥154	165 (23.5)	571 (22.7)	16767 (25.2)	
Married/cohabiting	479 (68.2)	1746 (69.3)	50344 (75.6)	<.0001
Education (years)				
7-12	237 (33.8)	870 (34.6)	24019 (36.1)	.0069
>12	180 (25.6)	636 (25.3)	17923 (26.9)	
Smoking	78 (11.1)	345 (13.7)	5275 (7.9)	<.0001
Drinking	99 (14.1)	401 (15.9)	12196 (18.3)	.0002
Regular exercise				
1–2 times/wk	281 (40.0)	1012 (40.2)	24818 (37.3)	<.0001
≥3 times/wk	299 (42.6)	1031 (41.0)	34783 (52.2)	

BMI = body mass index, HDL-C = high density lipoprotein cholesterol, TC = total cholesterol, TG = Triglycerides.
* ANOVA for continuous variables and chi-squared tests for categorical variables.

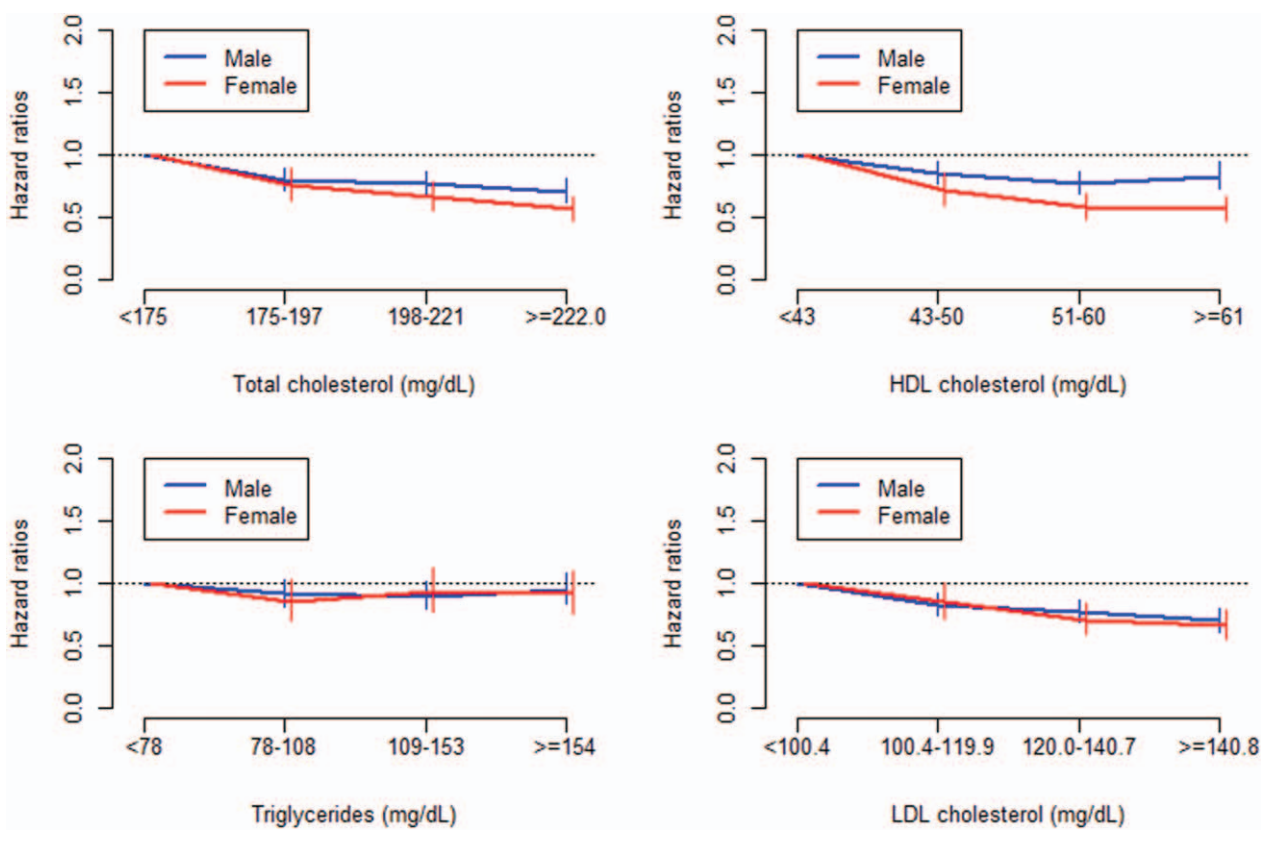

Figure 1. The relationship between all-cause mortality and plasma lipids. Hazard ratios in the second, third, and fourth quartiles compared with the first quartile of lipid levels.

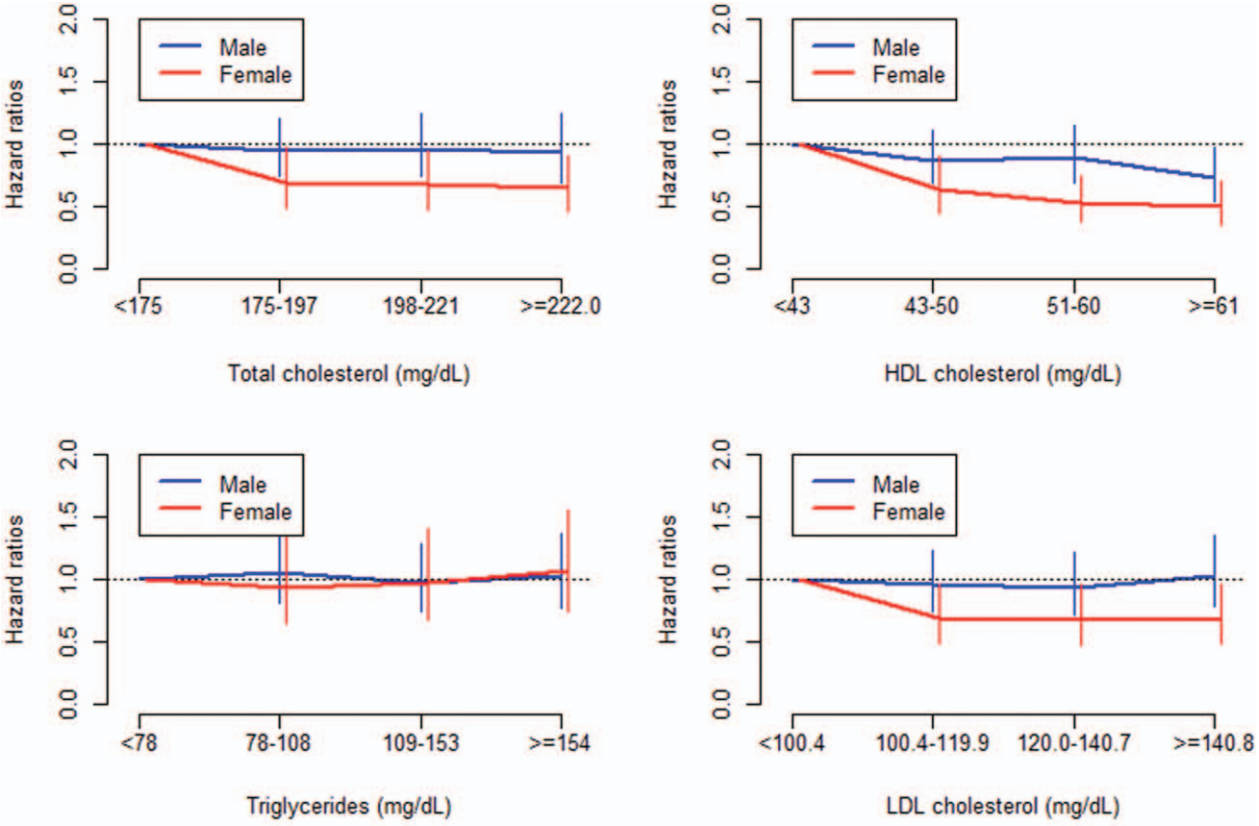

Figure 2. The relationship between cardiovascular mortality and plasma lipids. Hazard ratios in the second, third, and fourth quartiles compared with the first quartile of lipid levels.

and LDL cholesterol, except a slightly greater discrepancy between genders for HDL cholesterol. TG level was not significantly associated with all-cause mortality.

Figure 2 shows the relationship between lipids and cardiovascular mortality. Notably, low levels of TC, HDL cholesterol, and LDL cholesterol all increase cardiovascular mortality in females. The adjusted HR (95% CI) was 0.683 (0.481–0.970), 0.672 (0.475–0.949), and 0.646 (0.461–0.904) in the second, third, and fourth quartiles of TC, respectively. The relationship was similar for LDL cholesterol, but stronger for HDL cholesterol. The adjusted HR (95% CI) was 0.635 (0.445–0.928), 0.524 (0.369–0.746), and 0.494 (0.350–0.697) in the second, third, and fourth quartiles of HDL cholesterol, respectively. Being the fourth quartile of HDL was also protective in males, with borderline statistical significance.

We specified 2 common types of cardiovascular diseases: coronary artery diseases and cerebrovascular diseases. Deaths due to coronary artery diseases were not associated with all lipid components. Females with the first quartile of HDL cholesterol were at higher risk of stroke mortality; the adjusted HR (95% CI) was 0.411 (0.220–0.768), 0.480 (0.275–0.837), and 0.344 (0.194–0.612) in the second, third, and fourth quartiles of HDL cholesterol, respectively. We do not plot the details here. Figure 3 shows the relationship between lipids and non-cardiovascular mortality, which is close to that shown in Figure 1.

Consequently, our data showed TC and LDL cholesterol were inversely associated with all-cause mortality in older people, and even with cardiovascular mortality in older women. Apparent protective effects of HDL cholesterol against cardiovascular and stroke mortality were observed at a level of ≥43 mg/dL in older females. Gender matters in the relationships between lipid concentrations and survival in Taiwan geriatric population.

4. Discussion

Dyslipidemia is one of the most well-known cardiovascular risk factors, and thus related to deaths. However, the roles of plasma lipids are more complex in the survival of geriatric population. Our findings, in line with previous literature, have concluded an inverse relationship between TC and all-cause mortality in an elderly cohort. Furthermore, we have investigated fractionated lipid components in relation to cardiovascular cause-specific mortality, and analyzed separately in men and women. We have found a lower risk of cardiovascular mortality in older women with higher levels of TC and LDL cholesterol. Although HDL cholesterol has consistently been shown to protect from all-cause and cardiovascular deaths, the effect is more prominent in older women.

Though cardiovascular events contribute a large proportion of deaths in older population, literature with regard to plasma lipids and mortality has shown low cholesterol is a poor prognostic factor especially in the oldest old. Our findings confirmed the fact that the elders with the lowest quartile of TC and LDL cholesterol had the highest risk of death. The association patterns of all-cause and non-cardiovascular mortality were similar. Therefore, a possible explanation is that older people who are subjected to

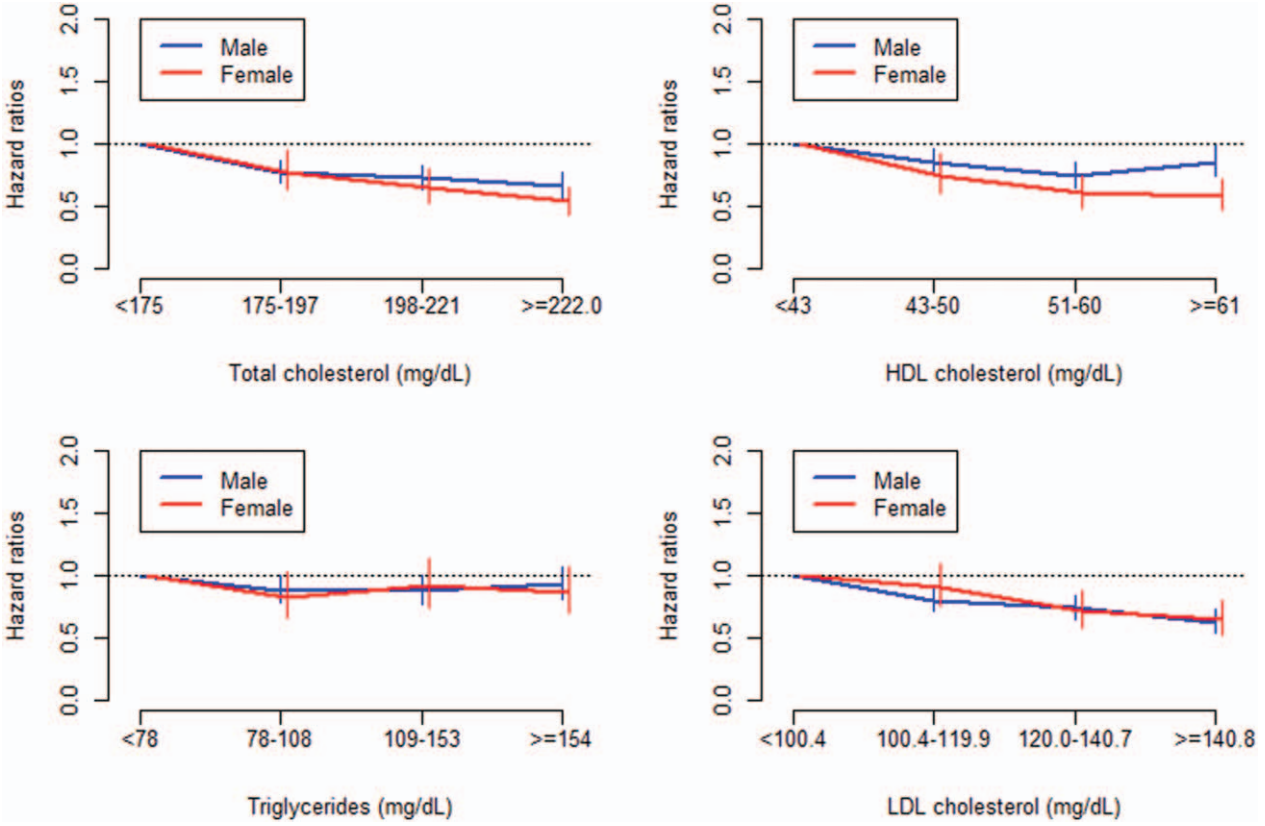

Figure 3. The relationship between non-cardiovascular mortality and plasma lipids. Hazard ratios in the second, third, and fourth quartiles compared with the first quartile of lipid levels.

comorbidity and frailty are at higher risk of non-cardiovascular mortality related with cancer, infection, and so on. Low TC and LDL cholesterol can be a marker of malnutrition or impaired biosynthesis in older people, predisposing to life-threatening non-cardiovascular diseases. Whereas our findings showed a negative association of TC and LDL cholesterol with cardiovascular mortality in older women, previous studies suggested a positive association between TC and cardiovascular mortality through old age,[6,21] but with attenuation.[4] Other studies showed there was no significant association between LDL cholesterol and cardiovascular mortality.[7,9] Though the controversial roles of LDL cholesterol in cardiovascular deaths are left unexplained, the understanding of "lower is better" is challenged not exclusively for the reason of non-cardiovascular deaths.

The cutoff values of HDL cholesterol for significant improvement on cardiovascular mortality in our results were 61 and 43 mg/dL for males and females, respectively. This was quite different from traditional recommendation, of which a higher cutoff level was set for females than males.[34] A negative relation between TC and stroke mortality in the elderly had been reported previously.[4] Our study showed older women with the lowest quartile of HDL cholesterol had a higher risk of fatal stroke, which was consistent with a previous study.[9] Other studies reported the relationship between lipids and stroke depended on stroke subtypes,[4,35] but our analysis did not further distinguish between hemorrhagic and ischemic stroke.

The discrepancies in genders can be partly explained by different age-specific distributions of lipid levels in males and females. It has been illustrated in a previous study that lipid levels varied substantially among populations.[36] TC and LDL cholesterol peak in mid-age and continue to decline in late-age, and women reach their peak levels of TC and LDL about 10 years later than men. Men have on average lower and less fluctuated HDL cholesterol than women, but a decline in HDL cholesterol in postmenopausal women has been reported in some regions. Women generally live longer than men, and developed heart diseases later than men. These facts contribute to the sex-difference in the association between lipid levels and survival in older persons. Another aspect to be addressed is sex-specific biological differences in the mechanisms of cardiovascular diseases, which is beyond the scope of this study.[37] Our conclusions suggest that current lipid-lowering strategy for adults may not be feasible for all elders, and sex-specific management and care would be necessary in clinical practice.

The strength of our study is the large database from government-sponsored health examinations for all citizens, representing the majority of community older population. Lipid variables were categorized into quartiles to account for nonlinear relation. We also considered gender as an effect modifier, which had not been extensively discussed. There are still some limitations. First, our conclusion that hypercholesterolemia "protects" from mortality in older people may be biased without assessing the confounding effects of nutrition and frailty status. People subjected to diseases that lead to death, for example, infection or cancer, tend to have lower cholesterol level. Though the elders dying within one year of follow-up were excluded, reverse causality may not be fully eliminated. Second, the information about the use of lipid-lowering agents was lacking,

thus residual confounding may mislead our inference. Furthermore, we were unable to differentiate intentional or unintentional decrease of cholesterol, whereas a previous study suggested an interaction between cholesterol level and statin use on mortality.[38] Besides, the definition of hypertension should be high blood pressure exceeding a cut-point, or currently taking antihypertensive medications. Since the information about medications was lacking, misclassification may exist. Third, there were substantial missing data and unreliable measurements, potentially affecting the results. We did not obtain laboratory measurements of LDL cholesterol level, instead, we applied Friedewald formula which excluded those with marked hypertriglyceridemia. Besides, we included only a lipid variable in each model. When we investigate the association between HDL cholesterol and mortality, we assume there is no confounding effect of LDL cholesterol or TG. As lipid fractions are highly correlated, one solution to this collinearity problem is to use ratios of two lipid variables.[39–42]

Our results in the Taiwanese community-dwelling elderly, to a great extent, agree with the conclusions drawn from Western countries. Future studies aimed at establishing causal models of hypercholesterolemia and death in geriatric population, taking into account the use of lipid lowering agents, are invited.

5. Conclusions

Low levels of TC (<175 mg/dL), HDL cholesterol (<43 mg/dL) and LDL cholesterol (<100.4 mg/dL) are related to high all-cause mortality in people older than 65 years. High HDL cholesterol (≥43 mg/dL) is related to low cardiovascular and stroke mortality in older females, while very high HDL cholesterol (≥61 mg/dL) is related to low cardiovascular mortality in older males. There is no association between TG and mortality in our Taiwanese older population.

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