

Serum triglycerides concentration in relation to total and cardiovascular mortality in an elderly Chinese population

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ABSTRACT

OBJECTIVE To investigate serum triglycerides in relation to all-cause, cardiovascular, and non-cardiovascular mortality in an elderly Chinese population.

METHODS The study participants ($n = 3565$) were elderly (≥ 60 years) community dwellers living in a suburban town of Shanghai. Hypertriglyceridemia was defined as a serum triglycerides concentration ≥ 2.30 mmol/L (definite) and ≥ 1.70 mmol/L (borderline), respectively.

RESULTS The prevalence of definite and borderline hypertriglyceridemia at baseline was 7.5% and 29.5%, respectively. It was higher in women ($n = 1982$, 9.0% and 33.8%, respectively) than men ($n = 1583$, 6.2% and 27.9%, respectively), in obese and overweight participants ($n = 1566$, 10.5% and 36.4%, respectively) than normal weight participants ($n = 1999$, 5.6% and 27.1%, respectively), and in diabetic participants ($n = 177$, 11.9% and 39.0%, respectively) than non-diabetic participants ($n = 3388$, 7.5% and 30.8%, respectively). During a median of 7.9 years follow-up, all-cause, cardiovascular and non-cardiovascular deaths occurred in 529, 216 and 313 participants, respectively. In analyses according to the quintile distributions of serum triglycerides concentration, the sex- and age-standardized mortality rate was lowest in the middle quintile for all-cause, cardiovascular and non-cardiovascular mortality (18.6, 7.8 and 11.9 per 1000 person-years, respectively, versus 21.5, 10.5 and 12.7 per 1000 person-years, respectively, in the two lower quintiles and 21.7, 9.5 and 14.0 per 1000 person-years, respectively, in the two higher quintiles). The fully adjusted hazard ratios (95% CI) for the middle quintile versus the combined two lower with two higher quintiles were 0.85 (95% CI: 0.67–1.07, $P = 0.17$), 0.81 (95% CI: 0.54–1.19, $P = 0.28$) and 0.87 (95% CI: 0.64–1.17, $P = 0.35$) for all-cause, cardiovascular and non-cardiovascular mortality, respectively.

CONCLUSIONS Our study showed high prevalence of hypertriglyceridemia, especially when defined as borderline and in obese and overweight participants, and mildly but non-significantly elevated risks of cardiovascular mortality relative to the middle level of serum triglycerides.

Serum triglycerides as a cardiovascular risk factor is revived, with the success of a recent trial on an efficacious triglycerides lowering agent, icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester.^[1] This fish oil product orally taken twice daily significantly reduced serum triglycerides concentration by 0.44 mmol/L and the risk of fatal and non-fatal ischaemic cardiovascular events by 25%.^[1] However, there is no consensus on the role of hypertriglyceridemia in the risk and pre-

vention of cardiovascular disease (CVD) and mortality, not only with regard to the fish oil intake,^[2] but also the use of fibrates.^[3] In fact, even observational studies produced conflicting results.^[4–8] Some,^[4,5] but not other,^[6–8] studies demonstrated significant association of serum triglycerides or hypertriglyceridemia with the risk of CVD.

With the recent changes in lifestyle in the Chinese population, the prevalence of dyslipidemia, especially hypertriglyceridemia, increased substantia-

lly.^[9,10] According to a series of China national surveys in 2002, 2012 and 2015, serum triglycerides concentration increased from 1.12 mmol/L to 1.41 mmol/L and to 1.47 mmol/L, respectively; and the prevalence of hypertriglyceridemia (serum triglycerides \geq 2.26 mmol/L) increased from 5.7% to 13.6% and to 15.0%, respectively.^[9] The health consequences of this emerging epidemic for the Chinese population, however, is uncertain.

We recently performed an elderly population-based study in a suburban town of Shanghai. In the present analysis, we investigated the association between serum triglycerides and all-cause, cardiovascular, and non-cardiovascular mortality in this elderly Chinese population sample.

METHODS

Study Population

Our study was conducted in the framework of the Chronic Disease Detection and Management in the Elderly (\geq 60 years of age) Program supported by the municipal government of Shanghai.^[11-14] In a newly urbanized suburban town 30 kilometers from the city centre, we invited all residents of at least 60 years of age to participate in comprehensive examinations of CVD and risk. The Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine approved the study protocol. All study participants provided written informed consent.

A total of 3830 subjects (participation rate: 90%) were enrolled in the period from 2006 to 2011 and followed up for vital status and cause of death till June 2015. Of them, 261 participants were excluded from the present analysis, because of extreme (\geq 10.0 mmol/L, $n = 17$) or missing values of serum triglycerides ($n = 248$), leaving 3565 participants in the analysis.

Serum Lipids and Other Biochemical Measurements and Definition of Dyslipidemia and Diabetes Mellitus

Venous blood samples were drawn after overnight fasting for the measurement of serum triglycerides, total cholesterol and plasma glucose. Serum lipids were measured using the enzymatic method. Dyslipidemia was defined according to the 2016

Chinese guideline for the management of dyslipidemia in adults.^[15] Hypertriglyceridemia was defined as a serum triglycerides concentration \geq 2.30 mmol/L (definite) and \geq 1.70 mmol/L (borderline), respectively; and hypercholesterolemia as a serum total cholesterol concentration \geq 6.20 mmol/L. Diabetes mellitus (DM) was defined as a plasma glucose level of at least 7.0 mmol/L, while fasting or 11.1 mmol/L at any time or use of antidiabetic agents.

Blood Pressure and Anthropometry

One experienced physician measured each participant's blood pressure (BP) three times consecutively using a validated Omron 7051 oscillometric BP monitor (Omron, Kyoto, Japan), after the subjects had rested for at least 5 min in the sitting position. These three BP readings were averaged for analysis. Hypertension was defined as a sitting BP of at least systolic BP with 140 mmHg or diastolic BP with 90 mmHg or use of antihypertensive drugs.

A trained technician performed anthropometric measurements, including body height and body weight. Body mass index (BMI) was calculated as the body weight in kilograms divided by the body height in meters squared. Obesity and overweight were defined as a BMI \geq 28 kg/m² and of 24–27.9 kg/m², respectively.^[16]

Follow-up

Information on vital status and the cause of death was obtained from the official death certificate, with further confirmation by the local Community Health Centre and family members of the deceased people. The International Classification of Diseases 10th Revision was used to classify the cause of death. Cardiovascular mortality included deaths attributable to stroke, myocardial infarction, and other CVDs. Deaths other than cardiovascular reasons were considered as non-cardiovascular mortality.

Statistical Analysis

Statistical analysis was performed using the SAS 9.4 (SAS Institute, Cary, NC, USA). Means and proportions were compared by the unpaired Student's *t*-test and the Pearson's chi-squared test, respectively. Continuous measurements with skewed distribution were expressed as median (interquartile range). Logistic regression analysis was performed to



analyze the associated factors of hypertriglyceridemia. The sex- and age-standardized mortality rate was calculated using the direct method. Multivariable Cox regression analysis was performed to compute adjusted hazard ratios (95% CI) for mortality according to the quintile distributions of serum triglycerides concentration. The cutoffs for the quintile distributions of serum triglyceride concentration were 1.15 mmol/L, 1.50 mmol/L, 1.65 mmol/L and 1.88 mmol/L, respectively.

RESULTS

Characteristics of the Study Participants

The study participants included 1583 men and 1982 women. Men and women significantly differed ($P \leq 0.05$) in most of the characteristics at baseline, except for systolic BP, the prevalence of hypertension and DM and serum creatinine. None of the study participants were treated for hypertriglyceridemia or with a statin ($P \geq 0.14$, Table 1).

Serum triglycerides concentration was significantly lower in men than women (1.56 mmol/L vs. 1.60

mmol/L, $P < 0.0001$). The prevalence of hypertriglyceridemia also significantly differed ($P \leq 0.002$) between men and women for both definite (6.2% vs. 9.0%) and borderline (27.9% vs. 33.8%). In addition, the prevalence of hypertriglyceridemia was higher with increasing BMI from the participants with a BMI < 20 kg/m², to 20–25 kg/m², to 25–30 kg/m² and to ≥ 30 kg/m² in men (19.4%, 25.8%, 32.5% and 56.7%, respectively; $P_{\text{trend}} < 0.0001$) as well as women (25.9%, 32.8%, 37.1% and 46.5%, respectively; $P_{\text{trend}} < 0.0001$; Figure 1).

Associated Factors of Serum Triglycerides Concentration

The multivariable stepwise logistic regression analyses identified gender, age, BMI, DM and alcohol intake as associated factors of definite hypertriglyceridemia ($P \leq 0.09$) and additionally the presence of hypertension as an associated factor of borderline hypertriglyceridemia ($P = 0.14$, Table 2). As the strongest determinant, BMI alone explained 2.2% of the variance for the prevalence of definite and borderline hypertriglyceridemia.

Table 1 Characteristics of the study population at baseline.

Characteristics	Men (n = 1583)	Women (n = 1982)	P-value
Age, yrs	68.2 ± 7.0	69.1 ± 7.4	0.0004
Body mass index, kg/m ²	23.5 ± 3.5	23.8 ± 3.7	0.053
Systolic blood pressure, mmHg	138.3 ± 19.6	139.0 ± 20.1	0.36
Diastolic blood pressure, mmHg	81.9 ± 10.8	80.5 ± 10.6	< 0.0001
Pulse rate, beat/min	74.7 ± 11.9	78.1 ± 11.5	< 0.0001
Hypertension	713 (45.0%)	921 (46.5%)	0.40
Use of antihypertensive drugs	600 (37.9%)	806 (40.7%)	0.052
Diabetes mellitus	69 (4.4%)	108 (5.5%)	0.14
Use of antidiabetic drugs	27 (1.7%)	26 (1.3%)	0.03
Current smoking	871 (55.0%)	48 (2.4%)	< 0.0001
Alcohol intake	579 (36.6%)	29 (1.5%)	< 0.0001
Preexisting cardiovascular disease	20 (1.3%)	14 (0.7%)	0.09
Blood biochemistry			
Plasma fasting glucose, mmol/L	5.1 (4.7–5.7)*	5.3 (4.8–5.8)*	< 0.0001
Serum total cholesterol, mmol/L	5.5 ± 1.4	5.7 ± 1.4	0.006
Serum triglycerides, mmol/L	1.56 (1.19–1.73)*	1.60 (1.31–1.80)*	< 0.0001
Serum creatinine, μmol/L	91.2 (79.0–105.8)*	91.5 (76.9–106.1)*	0.16
Serum uric acid, μmol/L	271 (221–340)*	259 (218–320)*	< 0.0001

Data are presented as means ± SD or n (%). *Presented as median (interquartile range). Preexisting cardiovascular disease included myocardial infarction, stroke and cardiac failure.



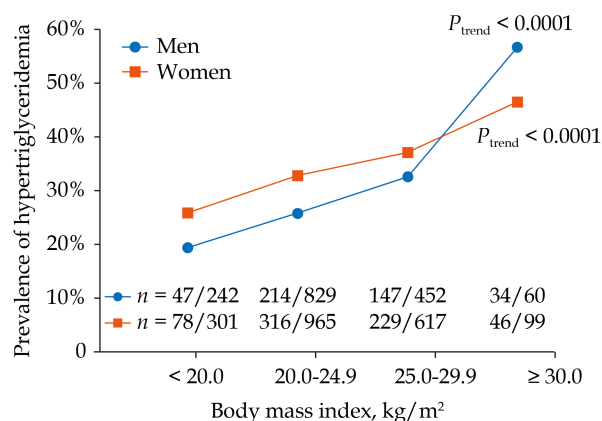


Figure 1 Prevalence of fasting hypertriglyceridemia (≥ 1.7 mmol/L) by sex and body mass index. The number of patients with hypertriglyceridemia/participants is given for each group at the top and for each body mass index subgroup at the bottom of the figure. The total number of participants and the *P*-value for trend are also given for men and women separately.

Associated Between Serum Triglycerides Concentration and Mortality

During a median follow-up of 7.9 years (interquartile range: 6.9–8.8 years), the cumulated number of person-years was 25,979, and all-cause, cardiovascular and non-cardiovascular deaths occurred in 529, 216 and 313 participants, respectively. The corresponding incidence rates were 20.4, 8.3 and 12.1 per 1000 person-years, respectively.

Analyses according to the quintile distributions of serum triglycerides concentration showed that the sex- and age-standardized mortality rate was lowest in the middle quintile for all-cause, cardiovascular and non-cardiovascular mortality (18.6, 7.8 and 11.9 per 1000 person-years, respectively, versus 21.5, 10.5 and 12.7 per 1000 person-years, respectively, in the two lower quintiles and 21.7, 9.5 and 14.0 per 1000 person-years, respectively, in the two higher quintiles; Figure 2).

After adjustment for the abovementioned identified associated factors and preexisting CVD, the adjusted hazard ratios (95% CI) for mortality with the middle quintile of serum triglycerides concentration at baseline as reference were not statistically significant for either the two lower or two higher quintiles ($P \geq 0.07$, Table 3). The adjusted hazard ratios (95% CI) for the middle quintile versus the combined two lower with two higher quintiles were 0.85 (95% CI: 0.67–1.07, $P = 0.17$), 0.81 (95% CI: 0.54–1.19, $P = 0.28$) and 0.87 (95% CI: 0.64–1.17, $P = 0.35$) for all-cause, cardiovascular and non-cardiovascular mortality, respectively.

DISCUSSION

Our study in elderly Chinese showed high prevalence of hypertriglyceridemia, especially defined as borderline and in those obese and overweight participants. Hypertriglyceridemia, in general, did not confer risk of mortality. However, middle levels of serum triglycerides concentration trended to be associated with a slightly but non-significantly lower risk of cardiovascular mortality than those with hyper- or hypotriglyceridemia.

The prevalence of definite hypertriglyceridemia in our elderly Chinese population is similar to that was reported in the third chronic non-communicable disease and risk factor surveillance in China in 2010.^[17] Indeed, among the surveillant population over 60 years of age ($n = 19,973$), the prevalence of hypertriglyceridemia (serum triglycerides ≥ 2.26 mmol/L) was 10.8%. It was higher ($P < 0.01$) in women ($n = 10,457$, 12.9%) than men ($n = 9,516$, 8.7%) and in urban ($n = 8,290$, 12.9%) than rural areas ($n = 11,683$, 10.1%).^[17] If the borderline hypertriglyceridemia is

Table 2 Logistic regression analysis on the associated factors of hypertriglyceridemia.

	Serum triglycerides ≥ 1.7 mmol/L		Serum triglycerides ≥ 2.3 mmol/L	
	Odds ratio (95% CI)	<i>P</i> -value	Odds ratio (95% CI)	<i>P</i> -value
Female	1.41 (1.19–1.66)	< 0.0001	1.61 (1.19–2.19)	0.002
Age, yrs	1.04 (0.92–1.16)	0.55	1.54 (1.28–1.85)	< 0.0001
Body mass index, kg/m ²	1.07 (1.05–1.09)	< 0.0001	1.13 (1.09–1.17)	< 0.0001
Diabetes mellitus	1.30 (0.94–1.78)	0.11	1.52 (0.94–2.47)	0.09
Alcohol intake	0.78 (0.63–0.97)	0.03	0.65 (0.44–0.96)	0.03
Hypertension	1.12 (0.96–1.30)	0.14	–	–

In a logistic regression model, we forced sex and age and considered body mass index, hypertension, diabetes mellitus, current smoking and alcohol intake for entry and stay at a significance of $P \leq 0.15$.



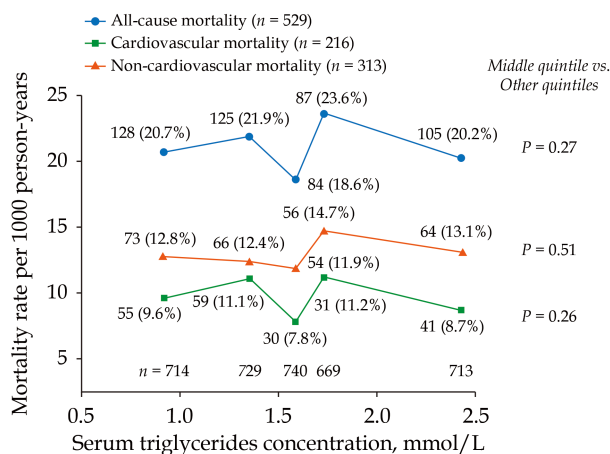


Figure 2 Sex- and age-standardized mortality rate according to the quintile distributions of fasting serum triglycerides concentration. The age and sex-standardized mortality rates were calculated for all-cause, cardiovascular, and non-cardiovascular mortality per 1000 person-years. The number of participants is given for each quintile at the bottom of the figure. The number of deaths (rate per 1000 person-years) is given for each quintile alongside the symbols. The *P*-value for the middle quintile versus all the other quintiles is also given.

compared between our study and studies in the Korean and American surveys in those over 60 years of age, the prevalence is also quite similar. In men ($n = 12,417$) and women ($n = 9091$) over 60 years of age, who were enrolled in the Korea National Health and Nutrition Examination Survey in 2013–2015, the prevalence of borderline hypertriglyceridemia was

31.5% and 27.0%, respectively.^[18] Similarly, in men ($n = 1509$) and women ($n = 1499$) over 60 years of age, who were enrolled in the National Health and Nutrition Examination Survey in 2009–2012, the prevalence of hypertriglyceridemia (triglycerides ≥ 1.7 mmol/L) was 24.8% and 30.9%, respectively.^[19]

Our observation on the association between hypertriglyceridemia and BMI suggests that calorie intake might have contributed to the increase in the prevalence of these two related metabolic disorders. Similar associations were observed in the recent chronic non-communicable disease and risk factor surveillance in China.^[20] The odds ratio for obese participants ($n = 6835$) versus normal weight participants ($n = 44,943$) was 1.97 (95% CI: 1.80–1.97, $P < 0.0001$) for any dyslipidemia in elderly Chinese.^[20] There is also evidence that dietary interventions for weight loss may reduce serum triglycerides concentration. Indeed, in a randomized controlled trial in 811 overweight participants, dietary weight loss interventions for two years reduced body weight by 4 kg and serum triglyceride concentration by 12%–17%.^[21]

Hypertriglyceridemia has never been properly established as a cardiovascular risk factor. In some,^[22,23] but not many other,^[24,25] studies, serum triglycerides concentration was associated with clinical outcomes. Nonetheless, there is some observational evidence that hypertriglyceridemia may be associated

Table 3 Adjusted hazard ratios (95% CI) for mortality according to quintile distributions of serum triglycerides concentration at baseline.

	Serum triglycerides concentration, mmol/L				
	Quintile 1 (0.09–1.15)	Quintile 2 (1.16–1.50)	Quintile 3 (1.51–1.65)	Quintile 4 (1.66–1.88)	Quintile 5 (1.89–9.98)
All-cause mortality					
All participants	1.14 (0.85–1.52)	1.20 (0.91–1.60)	Reference	1.22 (0.91–1.65)	1.16 (0.87–1.56)
Men	1.35 (0.90–2.02)	1.28 (0.85–1.91)	Reference	1.47 (0.97–2.22)	1.34 (0.88–2.03)
Women	0.92 (0.60–1.42)	1.11 (0.74–1.65)	Reference	0.97 (0.63–1.50)	0.96 (0.64–1.45)
Cardiovascular mortality					
All participants	1.13 (0.71–1.80)	1.44 (0.92–2.25)	Reference	1.37 (0.83–2.27)	1.22 (0.76–1.97)
Men	1.31 (0.69–2.49)	1.41 (0.74–2.67)	Reference	1.67 (0.85–3.28)	1.15 (0.58–2.30)
Women	0.91 (0.45–1.83)	1.42 (0.76–2.69)	Reference	1.04 (0.49–2.22)	1.13 (0.58–2.22)
Cardiovascular mortality					
All participants	1.18 (0.81–1.71)	1.10 (0.76–1.58)	Reference	1.22 (0.84–1.77)	1.16 (0.80–1.67)
Men	1.40 (0.83–2.35)	1.26 (0.75–2.12)	Reference	1.47 (0.87–2.48)	1.47 (0.87–2.48)
Women	0.92 (0.53–1.60)	0.90 (0.53–1.52)	Reference	0.97 (0.57–1.65)	0.88 (0.52–1.47)

Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, preexisting cardiovascular disease, current smoking and alcohol intake, and serum total cholesterol.



with higher risks of cardiovascular events in low risk populations,^[26] or in longer term follow-up studies.^[27] In an Italian low risk population followed up for 3.2 years, the odds ratios (95% CI) for serum triglycerides concentration of 150–500 mg/dL versus < 150 mg/dL was 1.49 (95% CI: 1.36–1.63, $P < 0.001$) for all-cause mortality and 1.61 (95% CI: 1.43–1.82, $P < 0.001$) for cardiovascular events.^[26] In a much longer term follow-up (mean: 19 years) study, initiated in the 1970s, the incidence of cardiovascular events increased from 4.09% in quartile 1 to 5.37%, 6.68% and 10.68% in quartiles 2, 3 and 4, respectively. The adjusted hazard ratio for quartile 4 versus quartile 1 was 1.40 (95% CI: 1.07–1.82, $P = 0.004$).^[27]

There is also some interventional evidence that serum triglycerides lowering may be beneficial in cardiovascular prevention. In diabetic patients in the Action to Control Cardiovascular Risk in Diabetes study, reducing serum triglycerides concentration with fenofibrate did not reduce the risk of non-fatal myocardial infarction and stroke and cardiovascular mortality. However, in patients with a serum triglycerides concentration ≥ 204 mg/dL and serum high-density lipoprotein cholesterol ≤ 34 mg/dL, fenofibrate reduced the incidence of cardiovascular events (12.4% vs. 17.3% on placebo, $P = 0.057$).^[28] In the recently published trial on serum triglycerides lowering with a highly purified eicosapentaenoic acid ethyl ester icosapent ethyl, serum triglycerides concentration was reduced by 0.44 mmol/L and the risk of fatal and non-fatal ischaemic cardiovascular events by 25%.^[1]

The lower risk of cardiovascular mortality in the middle quintile is incompletely understood. Our study was population-based, and did not apply any exclusion criteria. Those with lower serum triglycerides may have other unmeasured risk factors for CVD.

LIMITATIONS

Our study should be interpreted within the context of its limitations. Firstly, our study had a relatively small sample size, few measurements on serum lipids and limited information on socioeconomic status and lifestyle. Secondly, we collected sufficient information on fatal but not non-fatal cardiovascular events. We were unable to perform analysis ab-

out the association between serum triglycerides and the risk of fatal combined with non-fatal cardiovascular events. Last but not least, our study was conducted in an elderly Chinese population living in the suburban town of Shanghai. The results of our study probably cannot be extrapolated to younger populations, other ethnic groups, or even Chinese people with a different diet.

CONCLUSIONS

Our study showed high prevalence of hypertriglyceridemia in elderly Chinese, especially when defined as borderline and in those obese and overweight participants, and mildly but non-significantly elevated risks of cardiovascular mortality relative to the middle level of serum triglycerides. With the substantial increase in the prevalence of hypertriglyceridemia and in the availability of triglycerides lowering treatment, the health consequences of hypertriglyceridemia need to be further addressed in future observational and interventional studies.

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