ORIGINAL RESEARCH

Associations of Hypertriglyceridemia Onset Age With Cardiovascular Disease and All-Cause Mortality in Adults: A Cohort Study

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BACKGROUND: Limited studies have involved new-onset hypertriglyceridemia, and this study was to evaluate the associations of hypertriglyceridemia onset age with cardiovascular diseases (CVD) and all-cause mortality.

METHODS AND RESULTS: This population-based prospective study enrolled 98,779 participants free of hypertriglyceridemia and CVD at baseline in the Kailuan study initiated in June 2006. All participants underwent health checkups biennially until December 2017, and a total of 13,332 participants developed new hypertriglyceridemia. A 1:1 age- (±1 year) and sex-matched analysis was applied to select control subject of the same year for each new-onset case. There were 13,056 case-control pairs included. The total follow-up time was 179,409 person-years, with a median follow-up time of 7.0 years. Primary outcomes were CVD and all-cause mortality, and hazard ratios were estimated after adjustment for baseline characteristics. A total of 807 incident CVD events and 600 all-cause mortality events were documented. After multivariable adjustment, participants with hypertriglyceridemia onset age <45 years had the highest risk compared with matched controls, with hazard ratios of 2.61 (95% CI, 1.59–4.27) for CVD, 4.69 (95% CI, 2.34–9.40) for all-cause mortality, 2.23 (95% CI, 0.67–7.38) for myocardial infarction, and 2.68 (95% CI, 1.56–4.62) for stroke. The risk estimates gradually decreased with each decade increase in the onset age of hypertriglyceridemia.

CONCLUSIONS: Among Chinese adults, hypertriglyceridemia identified at an earlier onset age was associated with higher risks for CVD and all-cause mortality.

Key Words: cardiovascular disease risk • cohort study • hypertriglyceridemia onset age • mortality risk

Cardiovascular disease (CVD) remains the leading cause of mortality in adults worldwide,¹ and lipid metabolism disorders are significant risk factors for the development of CVD and all-cause mortality.² The onset trend for lipid metabolism disorders at a progressively younger age³⁻⁴ is consistent with increasing incidence among young individuals with CVD.⁵⁻⁶ Furthermore, lowering low-density lipoprotein cholesterol (LDL-C) levels in the middle-aged and older population is associated with a marked reduction in CVD and mortality risk.⁶⁻⁷ Previous studies have demonstrated that residual cardiovascular risk persists even though LDL-C is reduced to the recommended target, and this residual risk may be attributed to atherosclerotic dyslipidemia, including elevated triglycerides.⁸ Although Criqui et al⁹ and Angelantonio et al¹⁰ reported no independent association between plasma triglyceride levels and CVD and mortality, emerging studies have documented a positive relationship between elevated triglycerides and increased risk of CVD and mortality,¹¹⁻¹³ and the American Heart Association has embraced the view.⁸
The effect of risk factors on adverse events depends not only on the amount but also on the duration of exposure. Studies have noted that the association between risk factors and the development of diseases is age-dependent, and the risk of CVD related to new-onset hypertension or diabetes generally declines with onset aging. However, neither the Copenhagen City Heart Study nor the LRCFS nor the ERFC Study could determine the association between the age of onset of elevated triglycerides and incident CVD and mortality, which may lead to bias in risk estimates, causing an inconsistent relationship between hypertriglyceridemia, CVD, and mortality. To overcome the deficiency, we estimated the risks of incident CVD and all-cause mortality among subjects with new-onset hypertriglyceridemia versus age- and sex-matched controls across different age groups based on the data of the Kailuan population.

**CLINICAL PERSPECTIVE**

**What Is New?**
- New-onset hypertriglyceridemia was associated with increased risks for incident cardiovascular diseases (CVD) and all-cause mortality independent of traditional risk factors.
- Hypertriglyceridemia identified at an earlier onset age was associated with higher risks for CVD and all-cause mortality.
- The new-onset hypertriglyceridemia–related CVD risk was mainly driven by an increase in stroke incidence among Chinese adults.

**What Are the Clinical Implications?**
- Hypertriglyceridemia onset age was a vital determinant of CVD and all-cause mortality.
- Association in younger onset, although strong, earlier identification and prevention targeting hypertriglyceridemia would favorably influence CVD and all-cause mortality.

**METHODS**

**Research Design and Participants**

The Kailuan study, a prospective study among employees (including retired employees) of the Kailuan Group conducted in Tangshan, China, has been described in detail in previous studies. From June 2006 to December 2017, employees who underwent a biennial physical examination were enrolled as study subjects, with annual monitoring of adverse events, such as stroke, myocardial infraction, and death. Inclusion criteria consisted of those who participated in the physical examination twice or more from 2006 to 2017 and agreed to participate and sign informed consent forms. We excluded participants who had hypertriglyceridemia (triglyceride ≥2.3 mmol/L), a history of hyperlipidemia or lipid-lowering medication intake, and those with CVD before the diagnosis of hypertriglyceridemia. Moreover, participants with moderate-to-severe fatty liver disease at baseline and participants lacking essential variables, including age, sex, or triglyceride level, were also excluded from the analyses. In the end, 98,779 people were enrolled. The study followed the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the Kailuan Medical Group. The data that support the findings of this study are available from the corresponding author upon reasonable request.

A total of 13,832 participants developed new-onset hypertriglyceridemia during follow-up. For each subject with hypertriglyceridemia, one control matched by age (±1 year) and sex was randomly selected from the participants free of hypertriglyceridemia during follow-up in the examination of the same year as the case was identified. For instance, if a 40-year-old woman was first diagnosed with hypertriglyceridemia in 2012, she should be enrolled in the new-onset hypertriglyceridemia group. Then a woman, aged 39 to 41 years old, free of hypertriglyceridemia during follow-up and who attended the physical examination in 2012, would be randomly selected as a control (both initiated the follow-up at 2012). A total of 13,056 case-control pairs were successfully matched (Figure S1).

**Assessment of New-Onset Hypertriglyceridemia**

According to the 2016 Chinese guidelines for the management of dyslipidemia and the 2018 guidelines of the American College of Cardiology/American Heart Association, hypertriglyceridemia is defined as fasting plasma triglycerides of ≥2.3 mmol/L. Venous blood was collected in a fasting state (fasting for >8 hours) and assayed for the amount of triglyceride by automatic biochemical analyzers (Hitachi 7600, Tokyo, Japan) in the central Laboratory of Kailuan General Hospital.

**Follow-Up and Assessment of Outcomes**

The follow-up period began on the enrollment date of case-control pairs until the first occurrence of CVD consisting of stroke, MI, mortality, or follow-up until December 31, 2019, whichever came first. The primary outcomes of the present study were CVD and all-cause mortality, and detailed assessments have been described elsewhere. Briefly, potential CVD cases were identified according to International Classification of Diseases, Tenth Revision (ICD-10) codes (I60, I61, and I63 for stroke, I21 for MI). The database of CVD diagnosis was obtained from the Municipal Social
Insurance Institution and Hospital Discharge Register and was updated annually during the follow-up period. Confirmation of death was gathered from provincial vital statistics offices.

Assessment of Covariates
We also collected data on other related variables, such as sex, age, education background, smoking status, drinking status, physical exercise, medical history (hypertension, diabetes, fatty liver disease, and pancreatitis), and medication history (hypoglycemic, antihypertensive, and lipid-lowering medications), via a face-to-face questionnaire survey. Education background was classified as middle school or below, and high school or above. Smoking status was stratified into current smokers who had smoked ≥1 cigarette per day on average in the past year and those who had not. Similarly, the current drinkers were categorized as average alcohol consumption of ≥100 mL per day, and alcohol concentration of ≥50% v/v in a recent year. Regular physical exercise was classified as ≥3 times per week and ≥20 minutes per session, or none. Height, weight, and blood pressure (BP) were measured by trained physicians. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²), and delta BMI refers to the difference in BMI between baseline and last survey. Obesity was defined as a BMI cut-off point of ≥28 kg/m² for the Chinese population. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, any use of antihypertensive medications, or a self-reported history of hypertension. Diabetes was defined as fasting blood glucose levels ≥7.0 mmol/L, a self-reported history of diabetes, or any use of hypoglycemic medications. Metabolic syndrome was defined as central obesity plus any 2 of the following 4 factors: elevated triglyceride, reduced HDL-C, elevated blood pressure or diagnosed hypertension, elevated fasting blood glucose, or diagnosed diabetes. Fatty liver was diagnosed according to ultrasound examination, and pancreatitis was diagnosed based on abdominal computed tomography examination. Lipid-lowering medications refer to the self-reported use of lipid-lowering drugs, including statins, fibrates, and niacin. After fasting for 8 hours, venous blood was taken from the elbow on the morning of each physical examination for biochemical tests, including fasting blood glucose, triglyceride, HDL-C, and LDL-C. The above analyses were performed on Hitachi 7600 Auto Matic Analyzer.

Statistical Analysis
SAS 9.4 software (SAS Institute, Inc, Cary, NC) was used for statistical analyses. We presented the measurement data that were normally distributed as the mean (SD), skewness distribution as the median with interquartile range (25%–75%), and counting data as numbers or percentages. The new-onset participants with hypertriglyceridemia and the matched controls were divided into 4 groups according to the onset age of hypertriglyceridemia: <45 years old, 45 to 54 years old, 55 to 64 years old, and ≥65 years old. The incidence density rate of CVD and all-cause mortality were calculated by dividing incident events by total person-years of follow-up (per 1000 person-years). With adjustment for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, and LDL-C, we calculated the hazard ratios (HRs) and 95% CIs for incident CVD and all-cause mortality related to new-onset hypertriglyceridemia by the Cox regression model, as well as the HRs for subtypes of CVD, including stroke, hemorrhagic stroke, ischemic stroke, and MI. The fully conditional specification method was adopted for multiple imputations of missing covariables.

We further performed stratified analyses of sex among participants with new-onset hypertriglyceridemia versus controls across age groups. Several sensitivity analyses were performed to verify the robustness of our results, which included: (1) the adjustment for BMI in last survey, (2) the adjustment for delta BMI, (3) the adjustment with no medication history in model, (4) the adjustment for lipid-lowering medications, (5) the adjustment for the presence of metabolic syndrome, (6) the exclusion of participants with pancreatitis, (7) the exclusion of diabetes at baseline, (8) the exclusion of the events of incident CVD or all-cause mortality occurring within the first 2 years of follow-up, and (9) the use of the Fine-Gray method to consider the competing risk of non-cardiovascular death on cardiovascular outcome.

RESULTS
A total of 13,056 participants with new-onset hypertriglyceridemia and 13,056 matched controls were included in the present analyses with a mean onset age of 48.4±12.2, and 82.2% of them were men. The sample sizes of subjects with new-onset hypertriglyceridemia or in the control group by age group were as follows: 5004 at <45 years, 4208 at 45 to 54 years, 2780 at 55 to 64 years, and 1064 at ≥65 years, respectively (Tables 1 and 2). Participants with younger-onset hypertriglyceridemia were more likely to smoke, drink, be physically inactive, be obese, have higher triglyceride levels, and have lower use of hypoglycemic medications, antihypertensive medications, and lipid-lowering medications (Table 2).

During a median follow-up of 7.0 (interquartile range, 4.3 to 9.4) years, 807 incident CVD events including...
668 strokes (of which 601 were ischemic strokes, 71 were hemorrhagic strokes, and 4 concurrent ischemic strokes and hemorrhagic strokes), 148 MIs, and 9 concurrent strokes and MIs, and 600 all-cause mortality events were documented. However, we found that participants with new-onset hypertriglyceridemia had higher risks of incident CVD and all-cause mortality than their controls across age groups, and the risk estimates gradually increased with each decade decline in the age of hypertriglyceridemia onset after multivariable adjustment. Participants with hypertriglyceridemia onset <45 years old had the highest adjusted HR for study outcomes with HRs (95% CI) of 2.61 (1.59–4.27) for CVD and 4.69 (2.34–9.40) for all-cause mortality. Furthermore, the HRs (95% CI) for new-onset hypertriglyceridemia–related CVD in 45 to 54, 55 to 64 and ≥65 years old were 1.41 (1.11–1.77), 1.30 (1.01–1.69), and 1.24 (0.87–1.75), respectively, whereas the HRs (95% CI) for all-cause mortality were 3.74 (2.53–5.54), 3.34 (2.22–5.05), and 3.17 (2.31–4.35), respectively (Figure 1).

In terms of specific CVD risk, the analyses based on individual CVD outcomes (ie, MI and stroke) revealed that hypertriglyceridemia–related CVD risk was mainly confined to an increase of stroke risk, both for ischemic and hemorrhagic stroke, but not for MI (Figures 2 and 3). We next evaluated sex differences in hypertriglyceridemia-onset–related CVD and all-cause mortality risk. The analyses based on male participants yielded consistent findings with the main analyses. Because few CVD and death cases were found in young female participants, we, therefore, used binary categories of age groups (ie, <55 years and ≥55 years) instead of 4 categories used for main analyses and male participant-based analyses. The results showed that hypertriglyceridemia was associated with an increased risk for all-cause mortality in women for both age groups, and the magnitude of this association was stronger at a younger age (<55 years) as compared with elderly women (≥55 years). Notably, hypertriglyceridemia identified in either age group was not associated with an increased CVD risk in female participants (Table S1 through S10).

In the sensitivity analyses, adjusting for BMI in the last survey, delta BMI, no medication history in model, the use of lipid-lowering medications, metabolic syndrome, restricting the study population to participants without a history of pancreatitis at baseline (n=26,030), diabetes at baseline (n=22,596), or outcome events occurring within the first 2 years of follow-up (Tables S2 through S9) gave essentially the same associations as the primary analyses did. Finally, the results remained robust after a competing risk model was performed to assess the relationship between onset age of hypertriglyceridemia and CVD (Table S10).

Table 1. Baseline Characteristics of Controls

| Variables                        | Total controls, n (%) | Control subjects, n (%) |
|----------------------------------|----------------------|-------------------------|
|                                  | <45y                 | 45–54y                  | 55–64y                  | ≥65y                  |
| Participants, n                  | 13,056               | 5,004                   | 4,208                   | 2,780                 |
| Age, mean (SD), y                | 48.4±12.2            | 36.0±6.1                | 50.1±2.9                | 59.4±2.8              |
| Men                              | 10,730 (82.2)        | 4,390 (87.7)            | 3,316 (78.8)            | 2,153 (77.4)          |
| BMI at baseline, mean (SD), kg/m² | 24.0±3.0             | 23.8±3.1                | 24.1±2.9                | 24.4±3.0              |
| BMI in last survey, mean (SD), kg/m² | 24.6±3.2             | 24.8±3.4                | 24.5±3.1                | 24.4±3.1              |
| Delta BMI, median (IQR), kg/m²    | 1.2 (0.5–2.3)        | 1.4 (0.5–2.4)           | 1.2 (0.5–2.3)           | 1.0 (0.4–2.1)         |
| Triglyceride, median (IQR), mmol/L | 1.0 (0.8–1.4)       | 1.0 (0.8–1.4)           | 1.1 (0.8–1.4)           | 1.0 (0.8–1.3)         |
| HDL-C, median (IQR), mmol/L      | 1.4 (1.2–1.7)        | 1.4 (1.2–1.6)           | 1.5 (1.3–1.8)           | 1.5 (1.3–1.8)         |
| LDL-C, median (IQR), mmol/L      | 2.6 (2.1–3.1)        | 2.5 (2.1–3.0)           | 2.6 (2.1–3.0)           | 2.7 (2.2–3.2)         |
| Smoking                          | 3978 (30.5)          | 2485 (49.7)             | 956 (22.7)              | 368 (13.2)            |
| High school or above             | 3697 (28.3)          | 1509 (30.2)             | 1377 (22.7)             | 620 (22.3)            |
| Drinking                         | 4142 (31.7)          | 1808 (36.1)             | 1478 (35.1)             | 647 (23.3)            |
| Obesity                          | 1176 (9.0)           | 434 (8.7)               | 337 (8.0)               | 305 (11.6)            |
| Diabetes                         | 621 (4.8)            | 89 (1.8)                | 232 (5.5)               | 214 (7.7)             |
| Hypertension                     | 4917 (37.7)          | 932 (18.6)              | 1763 (41.9)             | 1489 (33.6)           |
| Metabolic syndrome              | 519 (4.0)            | 90 (1.8)                | 168 (4.0)               | 184 (6.6)             |
| Hypoglycemic medications        | 246 (1.9)            | 24 (0.5)                | 81 (1.9)                | 92 (3.3)              |
| Antihypertensive medications    | 952 (7.3)            | 97 (1.9)                | 296 (7.0)               | 333 (12.0)            |
| Lipid-lowering medications      | 422 (3.4)            | 35 (0.7)                | 138 (3.4)               | 161 (6.3)             |

BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.
Zhou et al: Hypertriglyceridemia Onset Age Modified the CVD and Mortality Risk

DISCUSSION

In a large cohort in the Chinese population, the current study found that new-onset hypertriglyceridemia was associated with increased risks for incident CVD and all-cause mortality independent of traditional risk factors. The risk estimates between new-onset hypertriglyceridemia and incident CVD and all-cause mortality increased with each decade decline in hypertriglyceridemia onset age, but the result of CVD in female participants should be further verified. Notably, the new-onset hypertriglyceridemia–related CVD risk was mainly driven by an increase in stroke incidence. The findings from the present study, therefore, highlight the potential benefit of implementing preventive and therapeutic strategies targeting early-onset hypertriglyceridemia to reduce the risks for CVD and all-cause mortality.

The Copenhagen City Heart Study reported that elevated triglyceride levels (2 to 2.99 mmol/L) only increased the risk of CVD in individuals aged <55 years and were associated with a 4.2-fold increased risk of CVD in comparison with triglycerides <1 mmol/L, but this association was null in the ≥55 years age group. In our analyses, participants with new-onset hypertriglyceridemia (triglyceride ≥2.3 mmol/L) displayed a 2.61-fold, 1.41-fold, and 1.30-fold increased risk of CVD versus the matched controls (triglyceride <2.3 mmol/L) at age <45 years, 45 to 54 years, and 55 to 64 years, respectively. For the ≥65 years age group, participants diagnosed with hypertriglyceridemia had no difference in CVD risk relative to their regular counterparts, which was consistent with the result of the Copenhagen City Heart Study. However, the estimated relative risk of CVD in young Copenhagen individuals was substantially higher than that found in ours, and the overestimation is more likely because of the inability to determine the exposure duration of elevated triglycerides. Although no similar study has been found, recent studies focused on new-onset hypertension or diabetes have revealed that the relative risks of CVD gradually decrease as the onset age increases each decade, which indirectly supports our findings. In addition, the epidemiological characteristics of CVD in Chinese populations differ significantly from those in the West. From the project of Sino Monitoring Trends and Determinants in Cardiovascular Disease, one significant feature of the CVD occurrence in China has been the higher age-standardized incidence of stroke and lower age-standardized incidence of coronary heart disease, more than 3-fold in difference. Although a recent review showed the transition, stroke occurrence is still much higher than ischemic heart disease.

Our findings that new-onset hypertriglyceridemia significantly increased the risk of all-cause mortality

Table 2. Baseline Characteristics of New-Onset Hypertriglyceridemia Participants

| Variables                        | Total cases, n (%) | Subjects with new-onset hypertriglyceridemia, n (%) |
|----------------------------------|--------------------|----------------------------------------------------|
|                                  | <45y | 45–54y | 55–64y | ≥65y |
| Participants, n                  | 13 056 | 5 004 | 4 208 | 2 780 | 1 064 |
| Age, mean (SD), y                | 48.4±12.2 | 36.0±6.1 | 50.1±2.9 | 59.4±2.8 | 71.1±5.0 |
| Men                              | 10 730 (82.2) | 4 390 (87.7) | 3 316 (78.8) | 2 153 (77.4) | 871 (81.9) |
| BMI at baseline, mean (SD), kg/m² | 25.2±2.9 | 25.3±3.0 | 25.0±2.8 | 25.2±2.8 | 25.1±2.8 |
| BMI in last survey, mean (SD), kg/m² | 25.6±3.2 | 26.0±3.3 | 25.3±3.0 | 25.3±3.2 | 25.3±3.1 |
| Delta BMI, median (IQR), kg/m²   | 1.1 (0.4–2.2) | 1.2 (0.4–2.3) | 1.1 (0.4–2.2) | 1.1 (0.4–2.1) | 1.1 (0.4–2.4) |
| Triglyceride, median (IQR), mmol/L | 2.9 (2.5–3.7) | 2.9 (2.6–3.8) | 2.9 (2.5–3.8) | 2.7 (2.5–3.3) | 2.7 (2.5–3.3) |
| HDL-C, median (IQR), mmol/L      | 1.3 (1.1–1.8) | 1.3 (1.1–1.5) | 1.4 (1.1–1.6) | 1.3 (1.1–1.5) | 1.3 (1.1–1.6) |
| LDL-C, median (IQR), mmol/L      | 2.6 (2.0–3.2) | 2.6 (2.0–3.1) | 2.6 (2.0–3.2) | 2.7 (2.1–3.3) | 2.7 (2.1–3.3) |
| High school or above             | 4 038 (30.9) | 2 542 (50.8) | 929 (22.1) | 412 (14.8) | 155 (14.6) |
| Smoking                          | 4 237 (32.5) | 1 791 (35.8) | 1 577 (37.5) | 707 (25.4) | 162 (15.2) |
| Drinking                         | 4 724 (36.2) | 2 103 (42.0) | 1 737 (41.3) | 725 (26.1) | 159 (14.9) |
| Physical exercise                | 3 273 (25.1) | 1 193 (23.8) | 921 (21.7) | 818 (29.4) | 350 (32.9) |
| Obesity                          | 1 973 (15.1) | 853 (17.0) | 559 (13.3) | 407 (14.6) | 154 (14.5) |
| Diabetes                         | 1 210 (9.3) | 204 (4.1) | 434 (10.3) | 362 (13.0) | 210 (19.7) |
| Hypertension                     | 5 477 (42.0) | 1 258 (25.1) | 2 005 (47.6) | 1 565 (56.3) | 649 (61.0) |
| Metabolic syndrome               | 3 367 (25.8) | 716 (14.3) | 1 183 (28.1) | 1 044 (37.6) | 424 (39.8) |
| Hypoglycemic medications         | 327 (2.5) | 24 (0.5) | 106 (2.5) | 111 (4.0) | 86 (8.1) |
| Antihypertensive medications     | 1 467 (11.2) | 154 (3.1) | 514 (12.2) | 515 (18.5) | 284 (26.7) |
| Lipid-lowering medications       | 594 (4.9) | 91 (1.9) | 218 (5.5) | 199 (8.1) | 86 (10.0) |

BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.
Zhou et al. Hypertriglyceridemia Onset Age Modified the CVD and Mortality Risk

echoed the results from previous studies, but it remains unclear whether age affects the risk of all-cause mortality associated with hypertriglyceridemia. The National Health and Nutrition Examination Surveys study found no association of elevated triglycerides with all-cause mortality after age-stratified analyses, and the Copenhagen City Heart Study showed that the positive correlation between elevated triglycerides and all-cause mortality disappeared in participants aged ≥55 years. Unlike previous studies, we observed that the risks of all-cause mortality were significantly higher in the new-onset hypertriglyceridemia population across the age range, with a stronger association among younger onset. Hypertriglyceridemia increases the risk of CVD events and the incidence of other chronic non-communicable diseases such as kidney disease and tumor, and these non-CVD deaths increase the relative risk of all-cause mortality.

It is challenging to clarify the mechanisms for the association between new-onset hypertriglyceridemia and the risk of CVD and all-cause mortality demonstrated in our observational study, but according to other studies, some potential explanations are as follows. First, triglyceride is transported in atherogenic lipoproteins containing apoB particles which cause damage to the arterial wall immediately, and the Mendelian randomization studies have identified genetic variants, including APOA5, TRIB1, and APOC3, that are associated with both plasma triglycerides and clinical CVD.

Second, primary hypertriglyceridemia has been diagnosed at an earlier age because of the increased prevalence of risk factors for hypertriglyceridemia in young adults, such as smoking, obesity, and lack of physical exercise, which also contribute to the development of CVD and all-cause mortality. Third, hypertriglyceridemia takes part in the development and progression of atherosclerosis, the main cause of incident CVD, by stimulating inflammation, regulating various cytokines, and promoting endothelial dysfunction. The age ranging from 20 to 42 years, during which lipid levels increase rapidly, is a critical age window for lipid control to reduce incident CVD. In addition, the risk of CVD and all-cause mortality increased because of much lower dyslipidemia awareness, treatment, and control rates in the younger generation.

The current findings suggest that the relative risk of CVD and all-cause mortality in participants with new-onset hypertriglyceridemia were higher at a younger

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**Figure 1.** Hazard ratios for incident cardiovascular disease and all-cause mortality among participants with new-onset hypertriglyceridemia versus control subjects across age groups.

All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, anti-hypertensive medications, body mass index, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. *P* for interaction was between age groups and new-onset hypertriglyceridemia groups.
onset age. Available guidelines for lipid management overlook hypertriglyceridemia and focus on decreasing LDL-C levels to reduce CVD risks among the middle-aged and older population.\textsuperscript{7,42} However, our study provides evidence for triglyceride as the optional intervention target for lipid management, especially among young individuals. As reported, the increasing incidence of hypertriglyceridemia was associated with increased work pressure, changes in marital status and dietary structure, and intensive lifestyle intervention could meaningfully reduce triglyceride levels.\textsuperscript{43} Although the risks of CVD and all-cause mortality were decreased by 13% and 12% per 1-mmol/L decrease in triglyceride level,\textsuperscript{27} dyslipidemia initiates irreversible damages to the blood vessels,\textsuperscript{39} and the risk of CVD cannot be wholly eliminated even after lowering triglyceride to the target levels.\textsuperscript{44} Therefore, early screening and identification of hypertriglyceridemia may entail greater benefits for young individuals. Moreover, the result of our study does not mean that we can entirely ignore the effect of new-onset hypertriglyceridemia in the elderly population. Hence, reducing the incidence of adverse events in an elderly population should also be noted.

Our study has several strengths. First, we found that the association of new-onset hypertriglyceridemia with CVD and all-cause mortality decreased with onset age based on a large prospective study of repeatable measures data for the first time. Second, the controls we matched were with normal triglyceride levels from the enrollment date to the end point of follow-up. Third, biennial physical examinations and medical information registers covering the entire study population enabled us to track outcomes from diagnosis and to include age- and sex-matched controls. Furthermore, the outcome events (CVD and death) in our study, confirmed by medical record review, were accurate and reliable. However, some potential limitations also have to be acknowledged in the interpretation of our findings. First, the onset age of hypertriglyceridemia was defined as the date of the first diagnosis during physical examination minus the date of birth, which may slightly differ from the actual onset age, but the confusion of onset age was weakened in our age- and sex-matched process. Second, the study participants were selected from active or retired workers in the Kailuan Group, a coal-mining company, and men accounted for a large proportion, but our previous findings have been well

### Table

| Hypertriglyceridemia onset age | Controls case/total | New-onset Hypertriglyceridemia case/total | Hazard ratio (95% CI) |
|-------------------------------|--------------------|------------------------------------------|-----------------------|
| Myocardial infarction (P for interaction=0.313) |
| <45 y                         | 4/5004             | 10/5004                                  | 2.23 (0.67–7.38)      |
| 45–54 y                       | 19/4208            | 25/4208                                  | 1.09 (0.58–2.01)      |
| 55–64 y                       | 28/2780            | 30/2780                                  | 1.05 (0.62–1.79)      |
| ≥65 y                         | 16/1064            | 16/1064                                  | 0.80 (0.37–1.70)      |
| Stroke (P for interaction=0.109) |
| <45 y                         | 18/5004            | 55/5004                                  | 2.68 (1.56–4.62)      |
| 45–54 y                       | 106/4208           | 175/4208                                 | 1.42 (1.11–1.82)      |
| 55–64 y                       | 81/2780            | 113/2780                                 | 1.37 (1.02–1.84)      |
| ≥65 y                         | 53/1064            | 67/1064                                  | 1.36 (0.92–2.01)      |

**Figure 2.** Hazard ratios for subtypes of cardiovascular disease among participants with new-onset hypertriglyceridemia versus control subjects across age groups.

All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, body mass index, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. P for interaction was between age groups and new-onset hypertriglyceridemia groups.
verified. Third, assessing the specific causes of death was difficult because of the lack of detailed information on death classification and all-cause mortality. Fourth, during a short median follow-up of 7.0 years, some outcome events of participants were not wholly observed before the end of the follow-up. Fifth, the medical and medication history might be subject to recall bias because the information was collected from questionnaire surveys. Finally, our data sets included the Chinese ethnicity of study subjects, which limited the applicability of results for other ethnicities.

CONCLUSIONS

Our study showed that onset age appears to be a vital determinant of CVD and all-cause mortality and that a younger age of hypertriglyceridemia onset was more strongly associated with an increased risk of CVD and all-cause mortality, especially in men. More aggressive efforts to identify hypertriglyceridemia earlier in life, as well as efforts to develop appropriate preventive and therapeutic strategies, are warranted to reduce hypertriglyceridemia-related CVD and mortality risk.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S10

Figure S1
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### Table S1. HRs for the stratified analyses of sex among participants with new-onset HTG versus control subjects across age groups

| HTG onset age | Control subjects | Subjects with new-onset HTG | HR (95%CI) |
|---------------|------------------|-----------------------------|------------|
|               | Event/Total      | Event/Total                 |            |
| Men (N=21,460) |                  |                             |            |
| CVD           |                  |                             |            |
| < 45Y         | 22/4,390         | 64/4,390                    | 2.66(1.62-4.38) |
| 45-54Y        | 112/3,316        | 176/3,316                   | 1.46(1.14-1.86) |
| 55-64Y        | 96/2,153         | 132/2,153                   | 1.39(1.06-1.83) |
| ≥ 65Y         | 61/871           | 66/871                      | 1.14(0.78-1.67) |
| All-cause mortality |          |                             |            |
| < 45 Y        | 9/4,390          | 45/4,390                    | 4.72(2.27-9.82) |
| ≥ 55Y         | 32/3,316         | 120/3,316                   | 3.73(2.50-5.56) |
| ≥ 55Y         | 26/2,153         | 97/2,153                    | 3.66(2.34-5.71) |
| ≥ 65Y         | 45/871           | 156/871                     | 3.39(2.39-4.83) |
| Women* (N=4,652) |                  |                             |            |
| CVD           |                  |                             |            |
| < 55Y         | 10/1,506         | 25/1,506                    | 1.35(0.61-2.98) |
| ≥ 55Y         | 18/820           | 25/820                      | 1.13(0.59-2.17) |
| All-cause mortality |          |                             |            |
| < 55 Y        | 2/1,506          | 12/1,506                    | 6.43(1.39-29.70) |
| ≥ 55Y         | 17/820           | 39/820                      | 2.04(1.11-3.75) |

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HR=hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, LDL-C, and fatty liver disease. *Due to the small sample size of participants with < 45 Y and ≥ 65Y groups in women, we combined and divided women into two groups according to HTG onset age: participants with less HTG onset age (< 55 Y) or more HTG onset age (≥ 55Y).
Table S2. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis adjusted BMI in the last survey

| HTG onset age | CVD Event/ Total | HR (95%CI) | All-cause mortality Event/ Total | HR (95%CI) |
|---------------|------------------|------------|---------------------------------|------------|
| < 45Y         | 87/10,008        | 2.72(1.66-4.46) | 60/10,008 | 5.08(2.54-10.15) |
| 45-54Y        | 322/8,416        | 1.39(1.10-1.75) | 160/8,416 | 3.75(2.53-5.55) |
| 55-64Y        | 248/5,560        | 1.25(0.96-1.62) | 141/5,560 | 3.02(2.00-4.56) |
| ≥ 65Y         | 150/2,128        | 1.18(0.83-1.68) | 239/2,128 | 2.73(1.99-3.75) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI in the last survey, HDL-C, and LDL-C.
Table S3. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis adjusted delta BMI

| HTG onset age | CVD               | All-cause mortality |
|--------------|-------------------|---------------------|
|              | Event/ Total      | HR (95%CI)          | Event/ Total | HR (95%CI) |
| < 45Y        | 87/10,008         | 2.73(1.67-4.46)     | 60/10,008    | 4.71(2.37-9.37) |
| 45-54Y       | 322/8,416         | 1.42(1.13-1.78)     | 160/8,416    | 3.54(2.40-5.22) |
| 55-64Y       | 248/5,560         | 1.32(1.02-1.71)     | 141/5,560    | 3.34(2.22-5.04) |
| ≥ 65Y        | 150/2,128         | 1.21(0.86-1.71)     | 239/2,128    | 3.05(2.23-4.16) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, delta BMI, HDL-C, and LDL-C.
Table S4. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis with no medication history in model

| HTG onset age | CVD Event/Total | HR (95%CI) | All-cause mortality Event/Total | HR (95%CI) |
|---------------|-----------------|------------|---------------------------------|------------|
| < 45Y         | 87/10,008       | 2.60(1.59-4.27) | 60/10,008 | 4.73(2.36-9.47) |
| 45-54Y        | 322/8,416       | 1.46(1.16-1.84) | 160/8,416 | 3.92(2.65-5.80) |
| 55-64Y        | 248/5,560       | 1.32(1.02-1.72) | 141/5,560 | 3.41(2.26-5.13) |
| ≥ 65Y         | 150/2,128       | 1.27(0.89-1.79) | 239/2,128 | 3.28(2.40-4.50) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, BMI, HDL-C, and LDL-C.
Table S5. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis adjusted lipid-lowering medications

| HTG onset age | CVD |  | All-cause mortality |  |
|--------------|-----|---|---------------------|---|
| Event/ Total | HR (95%CI) | Event/ Total | HR (95%CI) |
| < 45Y        | 87/10,008 | 2.39(1.45-3.94) | 60/10,008 | 4.57(2.28-9.18) |
| 45-54Y       | 322/8,416 | 1.38(1.09-1.74) | 160/8,416 | 3.73(2.52-5.52) |
| 55-64Y       | 248/5,560 | 1.35(1.04-1.75) | 141/5,560 | 3.34(2.21-5.05) |
| ≥ 65Y        | 150/2,128 | 1.27(0.89-1.80) | 239/2,128 | 3.14(2.29-4.30) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, LDL-C, and lipid-lowering medications.
### Table S6. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis adjusted metabolic syndrome

| HTG onset age | CVD | All-cause mortality |
|--------------|-----|---------------------|
|              | Event/ Total | HR (95%CI) | Event/ Total | HR (95%CI) |
| < 45Y        | 87/10,008 | 2.45(1.47-4.09) | 60/10,008 | 4.65(2.31-9.37) |
| 45-54Y       | 322/8,416 | 1.44(1.13-1.84) | 160/8,416 | 3.95(2.66-5.89) |
| 55-64Y       | 248/5,560 | 1.43(1.09-1.89) | 141/5,560 | 3.37(2.21-5.15) |
| ≥ 65Y        | 150/2,128 | 1.25(0.86-1.82) | 239/2,128 | 3.21(2.31-4.46) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, LDL-C, and metabolic syndrome.
Table S7. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis excluding participants who were diagnosed with pancreatitis at baseline (n=26,030)

| HTG onset age | CVD Event/ Total | HR (95%CI) | All-cause mortality Event/ Total | HR (95%CI) |
|---------------|------------------|------------|---------------------------------|------------|
| < 45Y         | 87/9,988         | 2.61(1.59-4.28) | 60/9,988             | 4.69(2.34-9.40) |
| 45-54Y        | 321/8,386        | 1.42(1.12-1.79)  | 160/8,386             | 3.73(2.52-5.53) |
| 55-64Y        | 246/5,536        | 1.33(1.03-1.73)  | 139/5,536             | 3.28(2.17-4.95) |
| ≥ 65Y         | 149/2,120        | 1.23(0.87-1.74)  | 236/2,120             | 3.20(2.33-4.40) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, and LDL-C.
Table S8. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis excluding participants with diabetes at baseline (n=22,596)

| HTG onset age | CVD          | All-cause mortality |
|---------------|--------------|---------------------|
|               | Event/ Total | HR (95%CI)          | Event/ Total | HR (95%CI) |
| < 45Y         | 79/9,436     | 2.52(1.51-4.19)     | 52/9,436     | 5.36(2.49-11.56) |
| 45-54Y        | 239/7,132    | 1.47(1.12-1.92)     | 128/7,132    | 3.57(2.32-5.48)  |
| 55-64Y        | 186/4,462    | 1.26(0.93-1.69)     | 102/4,462    | 3.56(2.20-5.75)  |
| ≥ 65Y         | 97/1,566     | 1.34(0.88-2.03)     | 168/1,566    | 2.49(1.75-3.54)  |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, hypertension, antihypertensive medications, BMI, HDL-C, and LDL-C.
### Table S9. HRs for incident cardiovascular disease and all-cause mortality among patients with HTG versus controls, across age groups: Sensitivity analysis excluding outcome events within first two years of follow-up

| HTG onset age | CVD Event/ Total | HR (95%CI) | All-cause mortality Event/ Total | HR (95%CI) |
|---------------|------------------|------------|-------------------------------|------------|
| < 45Y         | 82/9,984         | 2.89 (1.71-4.89) | 53/9,994 | 4.81 (2.31-10.02) |
| 45-54Y        | 293/8,344        | 1.37 (1.08-1.75) | 149/8,396 | 3.52 (2.36-5.26) |
| 55-64Y        | 211/5,474        | 1.33 (1.00-1.76) | 129/5,536 | 3.20 (2.08-4.90) |
| ≥ 65Y         | 129/2,050        | 1.37 (0.94-2.00) | 217/2,088 | 3.32 (2.38-4.64) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, and LDL-C.
Table S10. Competing risk analyses of CVD among patients with new-onset HTG versus controls across age groups

| HTG onset age | Control subjects Event/Total | Subjects with new-onset HTG Event/Total | HR (95%CI) |
|---------------|------------------------------|-----------------------------------------|------------|
| < 45Y         | 22/5,004                     | 65/5,004                                | 2.61(1.59-4.27) |
| 45-54Y        | 122/4,208                    | 200/4,208                               | 1.41(1.11-1.77) |
| 55-64Y        | 107/2,780                    | 141/2,780                               | 1.30(1.01-1.69) |
| ≥ 65Y         | 68/1,064                     | 82/1,064                                | 1.24(0.87-1.75) |

Abbreviations: CI= confidence interval; CVD= cardiovascular disease; HTG= hypertriglyceridemia; HR= hazard ratio. All models were adjusted for education background, smoking status, drinking status, physical exercise, diabetes, hypertension, hypoglycemic medications, antihypertensive medications, BMI, HDL-C, and LDL-C.
Figure S1. Study Flowchart

98,779 employees of the Kailuan Group met the inclusion criteria during 2006 - 2017

13,832 participants with hypertriglyceridemia during the follow-up

A 1-to-1 age (±1 year) and sex matched cohort without hypertriglyceridemia of the same year

Median follow-up duration 7.0 years

13,056 controls and 13,056 participants with new-onset hypertriglyceridemia included for analyses