Association between the Triglyceride-Glucose Index and Incident Cardiometabolic Multimorbidity in the Elderly: A Prospective Cohort Study Postprint

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Abstract

Background Existing studies have extensively investigated the association between the triglyceride-glucose index (TyG) and cardiometabolic disease (CMD), but have overlooked the correlation between TyG and cardiometabolic multimorbidity (CMM) in the elderly population.

Objective This study aims to investigate the association between TyG and new-onset CMM in the elderly population.

Methods A prospective cohort study was conducted using the Cheeloo Longitudinal Electronic Health Research Database (Cheeloo LEAD), selecting elderly individuals aged $ 60 $years in 2016. $With 2016 as the baseline, the study endpoint events were incidence of CMM or death $ up ending on December 31, 2022. $Based on quartiles of baseline TyG, participants were divided into four groups : $Q1 (5.88 \ TyG < 8.22), Q2 (8.22 \ TyG < 8.53), Q3 (8.53 \ TyG < 8.90), and Q4 (8.90 $TyG<11.33). Kaplan-Meier survival curves were plotted, Cox proportional hazards models were used to evaluate the effect of TyG on new-onset CMM risk, and subgroup and sensitivity analyses were performed. Restricted cubic spline (RCS) curves were used to explore the relationship between the two.

Results A total of 15,258 participants were included in the analysis, including 3,875 in Q1, 3,776 in Q2, 3,840 in Q3, and 3,767 in Q4. The mean follow-up time was 5.63 years, with a total follow-up of 85,862.48 person-years. There were 1,328 (8.70%) new-onset CMM cases. The cumulative incidence of new-onset CMM in Q1-Q4 was 5.81%, 7.65%, 9.27%, and 12.16%, respectively, with a statistically significant difference among the four groups (2=104.300, P<0.001). Fully adjusted Cox proportional hazards model results showed that compared with Q1, the risk of new-onset CMM in Q2, Q3, and Q4 increased by 25.4%

(HR=1.254, 95%CI=1.052-1.494, P<0.05), 42.0% (HR=1.420, 95%CI=1.196-1.686, P<0.001), and 83.6% (HR=1.836, 95%CI=1.535-2.195, P<0.001), respectively. Trend tests showed a dose-dependent relationship between TyG and new-onset CMM risk, and this association persisted in subgroup analyses by sex and BMI and in sensitivity analyses (P<0.05). RCS showed a dose-response relationship between TyG and new-onset CMM risk (P<0.001, P for nonlinearity=0.175).

Conclusion TyG is an independent risk factor for new-onset CMM in the elderly population, and there exists a dose-response relationship between them. As TyG levels increase, the risk of new-onset CMM increases progressively. High TyG levels significantly increase the risk of CMM in the elderly population, particularly among males and individuals with higher body mass index. Control of TyG levels is important for disease prevention in the elderly population.

Full Text

Association between Triglyceride-Glucose Index and Incident Cardiometabolic Multimorbidity in the Elderly: A Prospective Cohort Study

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Abstract

Background: Existing studies have extensively explored the association between the triglyceride-glucose index (TyG) and individual cardiometabolic diseases (CMD), while the relationship between TyG and the development of cardiometabolic multimorbidity (CMM) in elderly populations has been largely overlooked.

Objective: This study aims to investigate the association between TyG and incident CMM among elderly individuals.

Methods: We conducted a prospective cohort study using the Cheeloo Lifetime Electronic Health Database (Cheeloo LEAD), selecting elderly individuals aged

$ $60 years in 2016. Using 2016 as the baseline, the study endpoints were defined as the occurrence of CMM or death, with follow-up continuing until December 31, 2022. Participants were divided into four groups based on baseline TyG quartiles: Q1 ($5.88 \leq$ TyG < 8.22), Q2 ($8.22 \leq$ TyG < 8.53), Q3 ($8.53 \leq$ TyG < 8.90), and Q4 ($8.90 \leq$ TyG < 11.33). Kaplan-Meier survival curves were plotted, and Cox proportional hazards models were used to assess the impact of TyG on incident CMM risk, with subgroup and sensitivity analyses performed. Restricted cubic splines (RCS) were applied to explore the dose-response relationship between TyG and CMM.

Results: A total of 15,258 participants were included in the analysis, with 3,875 in Q1, 3,776 in Q2, 3,840 in Q3, and 3,767 in Q4. The average follow-up duration was 5.63 years, totaling 85,862.48 person-years. There were 1,328 new cases of CMM (8.70%). The cumulative incidence rates of incident CMM in the Q1–Q4 groups were 5.81%, 7.65%, 9.27%, and 12.16%, respectively, with statistically significant differences among the four groups (^{2} = 104.300, P < 0.001). The fully adjusted Cox proportional hazards model showed that compared with Q1, the risk of incident CMM increased by 25.4% (HR = 1.254, 95%CI = 1.052–1.494, P < 0.05), 42.0% (HR = 1.420, 95%CI = 1.196–1.686, P < 0.001), and 83.6% (HR = 1.836, 95%CI = 1.535–2.195, P < 0.001) in Q2, Q3, and Q4, respectively. Trend tests indicated a dose-response relationship between TyG and incident CMM risk, which persisted in subgroup analyses by sex and BMI as well as in sensitivity analyses (P < 0.05). RCS analysis revealed a dose-response relationship between TyG and incident CMM risk (P < 0.001, P_{non}-linearity = 0.175).

Conclusion: TyG is an independent risk factor for incident CMM in the elderly population, with a clear dose-response relationship. As TyG levels increase, the risk of incident CMM rises progressively, with high TyG levels significantly elevating CMM risk, particularly among males and individuals with higher BMI. Controlling TyG levels plays an important role in disease prevention among elderly populations.

Keywords: Cardiometabolic multimorbidity; Metabolic cardiovascular syndrome; Triglyceride-glucose index; Aged; Shandong province; Cohort studies; Prospective studies; Survival analysis

Background

Multimorbidity refers to the coexistence of at least two chronic diseases in an individual. Compared with those with a single chronic condition, multimorbid patients face heavier economic burdens and higher mortality risks. Cardiometabolic multimorbidity (CMM) is defined as having at least two cardiometabolic diseases (CMD), such as diabetes, ischemic heart disease, and stroke. CMM is becoming increasingly prevalent with population aging. A longitudinal cohort study including one million Chinese adults showed that the

prevalence of CMM is growing rapidly, more than doubling within five years. Compared with patients with a single CMD, CMM patients have shorter life expectancy and higher mortality risk. Multimorbidity also accelerates cognitive decline synergistically, with a dose-dependent increase in dementia risk associated with the number of diseases present.

Insulin resistance (IR) refers to the diminished regulatory effect of insulin on target organs due to reduced responsiveness. IR is a major risk factor for type 2 diabetes and promotes the development of cardiovascular diseases, being closely associated with the progression of CMD including diabetes, stroke, and ischemic heart disease. The hyperinsulinemic-euglycemic clamp (HEC) is the gold standard for assessing IR, but its complexity, time consumption, and labor intensity limit widespread application. Consequently, many surrogate indices for IR have been developed, among which the triglyceride-glucose index (TyG) is an effective and economical assessment tool. While numerous studies have examined the association between TyG and individual CMD such as diabetes, ischemic heart disease, and stroke, the relationship between TyG and CMM remains incompletely understood, particularly in elderly populations.

Therefore, this study aims to explore the potential association between TyG and CMM risk in the elderly population, conducting a large-scale prospective cohort study based on elderly individuals ($ $60 years) with long-term follow-up and collection of health examination data.

Methods

1.1 Study Population This prospective cohort study utilized data from the Cheeloo Lifetime Electronic Health Research Data-library (Cheeloo LEAD). This database includes five million individuals selected through cluster random sampling from Shandong Province, comprising comprehensive information on residents' health records throughout their lifespan, basic public health services, electronic medical records, health examinations, disease surveillance, and mortality monitoring.

Using 2016 as the baseline from Cheeloo LEAD, we initially identified 195,544 participants. Exclusion criteria were: (1) age <60 years at baseline or abnormal gender data; (2) pre-existing diagnosis of diabetes (E10–E14), ischemic heart disease (I20–I25), stroke (I60, I61, I63, I64), or malignant tumors (C00–C97); (3) history of insulin, metformin, statin, or aspirin use; (4) missing diagnostic records at baseline or during follow-up; (5) abnormal or missing values for triglycerides (TG) or fasting blood glucose (FBG); (6) abnormal TyG values; (7) fewer than three valid examinations after removing records with abnormal or missing values for these three variables; and (8) any missing values for other variables.

The final study included 15,258 participants, who were divided into four groups

based on TyG quartiles: Q1 ($5.88 \leq$ TyG < 8.22), Q2 ($8.22 \leq$ TyG < 8.53), Q3 ($8.53 \leq$ TyG < 8.90), and Q4 ($8.90 \leq$ TyG < 11.33). The participant selection flowchart is shown in Figure 1 [Figure 1: see original paper].

1.2 Variables and Follow-up **1.2.1 TyG Calculation:** The TyG index was calculated using the formula: TyG = ln[TG (mg/dL) × FBG (mg/dL) / 2]. Baseline TyG was calculated using TG and FBG values from the 2016 health examination, while average TyG was calculated as the mean of TyG values from examinations between 2016 and 2020.

1.2.2 Follow-up and Outcomes: The follow-up period extended from 2016 until death or December 31, 2022. The study outcome was incident CMM, defined as the development of at least two diseases among diabetes, ischemic heart disease, and stroke. Outcome data were derived from clinical diagnostic records, with ICD-10 codes used to identify type 2 diabetes (E11, E14), ischemic heart disease (I20–I25), and stroke (I60, I61, I63, I64). Other types of diabetes (E10, E12, E13) were excluded.

1.2.3 Covariates: Professional healthcare personnel collected clinical examination data and health records using standardized procedures, with personal ID serving as the identifier to match health records, examination data, medical records, and mortality data. Based on literature review, we identified covariates including sociodemographic characteristics, lifestyle factors, physiological indicators, and health status. Sociodemographic variables comprised age, sex, and education level (categorized as high school, below high school, or above high school). Lifestyle variables included smoking (current vs. non-smoker), alcohol consumption (current drinker vs. non-drinker), and dietary habits (assessed based on daily recommended maximum intake of salt and oil according to the Chinese Dietary Guidelines, categorized as preference for salty/oily foods or not). Physiological indicators included BMI. Health status variables comprised hypertension (defined as systolic blood pressure $ $140 mmHg or diastolic blood pressure $ $90 mmHg, or use of antihypertensive medication, or existing hypertension diagnosis) and dyslipidemia (defined as LDL cholesterol $ $4.1 mmol/L, HDL cholesterol <1.0 mmol/L, total cholesterol $ $6.2 mmol/L, or TG $ $2.3 mmol/L, or use of lipid-lowering medication, or existing dyslipidemia diagnosis).

1.3 Statistical Analysis The Kolmogorov-Smirnov test was used to assess normality of continuous variables. Normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median (P25, P75). Categorical variables were expressed as frequencies and percentages. Participants were divided into Q1–Q4 groups based on baseline TyG quartiles. Between-group comparisons were performed using one-way ANOVA for normally distributed variables, Kruskal-Wallis H test for non-normally distributed variables, and ^{2} test for categorical variables.

Kaplan-Meier survival curves were plotted with Log-rank tests. Cox proportional hazards regression models were used to examine the effect of TyG on

incident CMM risk, with results expressed as hazard ratios (HR) and 95% confidence intervals (95%CI). Three Cox models were constructed: Model 1 (crude model without covariate adjustment), Model 2 (adjusted for sociodemographic characteristics), and Model 3 (additionally adjusted for lifestyle factors, physiological indicators, and health status). All covariates had variance inflation factors (VIF) <10, and proportional hazards assumptions were tested using Schoenfeld residuals. Restricted cubic spline (RCS) curves were plotted to assess the dose-response relationship between TyG and CMM risk.

Subgroup analyses were conducted by sex (male and female) and BMI (<24 and $ 24kg/m^{2}$). Sensitivity analyses were performed using both baseline TyG and average TyG as continuous variables. In the Cox models, the following variables were included: TyG (independent variable), age, sex (male = 0, female = 1), education level (high school = 0, below high school = 1, above high school = 2), smoking (non-smoker = 0, current smoker = 1), alcohol consumption (non-drinker = 0, current drinker = 1), dietary habits (no preference for salty/oily foods = 0, preference for salty or oily foods = 1), BMI (continuous), hypertension (no = 0, yes = 1), and dyslipidemia (no = 0, yes = 1). Statistical analyses were performed using R software (version 4.4.1), with two-sided tests and $P < 0.05$ considered statistically significant.

Results

2.1 Baseline Characteristics and CMM Incidence A total of 15,258 participants were included, with 728 deaths (4.77%) occurring during follow-up through December 31, 2022. Participants had a median age of 69 (66, 74) years, and the overall mean baseline TyG level was 8.57 ± 0.55. The cohort comprised 6,224 males (40.79%) and 9,034 females (59.21%), with 14,538 participants (95.28%) having below high school education.

Baseline characteristics differed significantly across TyG quartile groups in terms of TyG levels, age, sex distribution, education level, BMI, smoking status, alcohol consumption, preference for salty/oily foods, hypertension, dyslipidemia, and incidence of individual CMD components (all $P < 0.05$). Detailed baseline characteristics are presented in Table 1 .

2.2 Kaplan-Meier Survival Curves The mean follow-up duration was 5.63 years, totaling 85,862.48 person-years. During follow-up, 1,328 participants (8.70%) developed incident CMM. The cumulative incidence rates in Q1–Q4 groups were 5.81%, 7.65%, 9.27%, and 12.16%, respectively. Kaplan-Meier analysis showed statistically significant differences in CMM incidence among the four groups ($^{2} = 101.281$, $P < 0.001$), as illustrated in Figure 2 [Figure 2: see original paper].

2.3 Cox Proportional Hazards Models Using incident CMM as the outcome variable and follow-up time (in years) as the time metric, Cox proportional hazards models revealed a progressive increase in CMM risk with higher TyG quartiles. In Model 1 (crude model), compared with Q1, the HRs (95%CIs) for Q2-Q4 were 1.324 (1.112-1.576), 1.610 (1.362-1.902), and 2.139 (1.824-2.510), respectively ($P < 0.05$). Model 2, adjusted for age, sex, and education level, showed similar results: HRs (95%CIs) were 1.334 (1.120-1.589), 1.609 (1.359-1.904), and 2.159 (1.836-2.537) for Q2-Q4, respectively ($P < 0.05$). Model 3, fully adjusted for all covariates, demonstrated that compared with Q1, the risk of incident CMM increased by 25.4% in Q2 (HR = 1.254, 95%CI = 1.052-1.494, $P < 0.05$), 42.0% in Q3 (HR = 1.420, 95%CI = 1.196-1.686, $P < 0.001$), and 83.6% in Q4 (HR = 1.836, 95%CI = 1.535-2.195, $P < 0.001$). Trend tests confirmed a dose-response relationship ($P < 0.001$). Detailed results are presented in Table 2 .

2.4 Restricted Cubic Spline Curves In Model 3, RCS analysis revealed a dose-response relationship between TyG and incident CMM risk ($P < 0.001$, P_{non}-linearity = 0.175). The HR became significantly greater than 1 when TyG exceeded 8.74, as shown in Figure 3 [Figure 3: see original paper].

2.5 Subgroup Analysis Subgroup analyses of the fully adjusted Model 3 by sex and BMI showed consistent associations. In males, compared with Q1, Q2-Q4 had significantly increased CMM risk: HRs (95%CIs) were 1.298 (1.005-1.677), 1.482 (1.145-1.917), and 1.985 (1.512-2.605), respectively ($P < 0.05$). In females, only Q3 and Q4 showed significantly increased risk: HRs (95%CIs) were 1.355 (1.074-1.710) and 1.739 (1.368-2.211), respectively ($P < 0.05$).

Among participants with BMI <24 kg/m^2, Q2-Q4 had significantly increased risk compared with Q1: HRs (95%CIs) were 1.349 (1.051-1.732), 1.364 (1.046-1.780), and 1.823 (1.369-2.426), respectively ($P < 0.05$). In those with BMI $ 24kg/m^{2}$, only Q3 and Q4 showed significantly increased risk: HRs (95%CIs) were 1.485 (1.178-1.873) and 1.927 (1.523-2.439), respectively ($P < 0.001$). Interaction analyses showed no statistically significant effect modification by sex or BMI (P_{interaction} > 0.05). Results are detailed in Table 3 .

2.6 Sensitivity Analysis Sensitivity analysis using baseline TyG as a continuous variable yielded an HR (95%CI) of 1.490 (1.330-1.670), indicating a significant association with incident CMM ($P < 0.001$). Analysis using average TyG as a continuous variable produced similar results: HR (95%CI) = 1.631 (1.418-1.877, $P < 0.001$). Both sensitivity analyses confirmed that elevated TyG is associated with increased CMM risk.

Discussion

Insulin resistance impairs insulin' s regulatory function and obstructs glucose uptake and utilization, representing a risk factor for cardiovascular disease and diabetes. CMD includes cardiovascular and metabolic diseases, while CMM represents a more complex condition involving multiple CMDs. IR is associated with the development and progression of CMM. Given the complexity of the gold-standard HEC method, lipid indices such as TyG have been developed as surrogate markers for IR, with TyG considered a reliable indicator.

This large-scale prospective cohort study of elderly individuals followed for a mean of 5.63 years demonstrated that baseline TyG quartiles were associated with incident CMM risk. As TyG increased, the risk of incident CMM rose significantly in Q2, Q3, and Q4 groups. In the fully adjusted model, Q4 participants had an 83.6% higher risk compared with Q1 (HR = 1.836, 95%CI = 1.535-2.195). Trend tests confirmed a dose-response relationship. Subgroup and sensitivity analyses validated the robustness of these findings, though no significant interactions were observed with sex or BMI. These results indicate that TyG has important value for predicting incident CMM risk in elderly populations.

Previous research has primarily focused on associations between TyG and individual CMDs. Meta-analyses have shown that the highest TyG quartile is associated with a 27% increased stroke risk (RR = 1.27, 95%CI = 1.24-1.29), establishing high TyG as an independent risk factor for stroke, particularly ischemic stroke. Another meta-analysis demonstrated that high TyG is associated with higher recurrence risk and mortality in ischemic stroke patients. Cohort studies have linked high TyG to new-onset diabetes in middle-aged and elderly populations, with one study reporting a linear positive association (HR = 1.75, 95%CI = 1.56-1.97). Meta-analyses have also associated high TyG with increased coronary heart disease risk and severity. While these studies thoroughly examined TyG' s relationship with individual CMD events, our study extends this evidence by evaluating TyG in relation to CMM.

CMM patients face higher mortality risk and reduced life expectancy compared with CMD patients. Previous studies have examined associations between overweight/obesity, household air pollution, and CMM risk, emphasizing the importance of BMI control and indoor air pollution prevention. Another study investigated the differential impact of high-risk lifestyle factors across transitions from healthy status to CMD, then to CMM, and finally to death, highlighting the significance of lifestyle interventions. Our study further demonstrates that high TyG is an independent risk factor for CMM. This may be because TyG, as a reliable IR indicator, reflects individual insulin resistance status, a key pathological mechanism in CMM development. The physiological link between IR and CMM may involve ectopic and visceral fat accumulation, which releases pro-inflammatory factors triggering chronic inflammation. Fat accumulation in muscle and liver interferes with insulin signaling, induces insulin resistance, and exacerbates glucose metabolism disorders and dyslipidemia. These changes pro-

mote metabolic syndrome, the core manifestation of IR, which further drives the progression of cardiovascular disease and diabetes, ultimately facilitating CMM development. Additionally, ectopic fat accumulation is associated with mitochondrial dysfunction, particularly in elderly populations, further promoting IR and metabolic disturbances.

This large-scale prospective cohort study of elderly individuals enriches the literature on TyG and CMM. The conduct of sex- and BMI-stratified subgroup analyses and sensitivity analyses provides comprehensive evaluation of the TyG-CMM relationship in elderly populations. However, several limitations should be noted. First, as an observational study, residual confounding cannot be completely eliminated, and causality cannot be directly established. Second, the study population was limited to elderly individuals, restricting generalizability. Future intervention studies are needed to verify causal relationships, and expanding the age range to include middle-aged populations would enhance generalizability.

In conclusion, high TyG is an independent risk factor for incident CMM in elderly populations, with a clear dose-response relationship. Maintaining lower TyG levels is important for health management and CMM prevention in elderly individuals.

Author Contributions

CHEN Qiaoqiao conceptualized the study, designed the research, implemented the study, wrote the manuscript, screened and organized data, performed statistical analyses, and created figures and tables. SU Ping, ZHAO Yingying, PANG Jinhong, SHI Jie, WANG Yaqian, LI Qiuchun, HE Ruiyan, WANG Yue, CHEN Xueyu, and QIAO Junpeng reviewed the manuscript and provided revision suggestions. CHI Weiwei supervised the study and ensured the quality of the article.

Conflict of Interest: The authors declare no conflict of interest.

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