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Triglycerides paradox among the oldest old: “the lower the better?”

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Abstract

OBJECTIVES: Currently most treatment guidelines suggest lowering hypertriglyceridemia of any severity, even in elderly. However associations of serum triglycerides (TG) with adverse health and mortality risk decrease with age, it remains unclear among the oldest old (80+). The study was to investigate the relationship of serum TG concentrations with cognitive function, activities of daily living (ADL), frailty, and mortality among oldest old in a prospective cohort study.

DESIGN: Longitudinal prospective cohort study

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Conflicts of Interest: None.

SETTING: Community-based setting in longevity areas in China

PARTICIPANTS: 930 (mean age 94.0 years) Chinese oldest old

MEASUREMENTS: The TG concentrations were measured at baseline survey in 2009.

Cognitive function, ADL, frailty and mortality were determined over 5 years of follow-up. Cox proportional hazards models and competing risk models were performed to explore the association, adjusting for potential confounders.

RESULTS: Each 1mmol/L increase in TG was associated with a nearly 20% lower risk of cognitive decline, ADL decline, and frailty aggravation during the 5 years of follow-up. Consistently, higher TG (each 1mmol/L) was associated with lower 5-year all-cause mortality after fully adjustment (hazard ratio (HR):0.79, 95% CI: 0.69–0.89). Non-elevated TG concentrations (<2.26 mmol/L) was associated with higher mortality risk (HR=1.72; 95%CI: 1.22–2.44), relative to TG 2.26 mmol/L. We observed similar results regarding TG concentrations and mortality in 1-year lag analysis and when excluding participants with identified chronic disease.

CONCLUSION: In the oldest old, a higher concentration of TG was associated with a lower risk of cognitive decline, ADL decline, frailty aggravation and mortality. This paradox suggests the clinical importance of revisiting the concept of “the lower the better” for the oldest old.

Keywords

triglycerides; mortality; cognitive function; activities of daily living; frailty

INTRODUCTION

Hypercholesterolaemia is an independent cardiovascular risk factor in populations younger than 65 years in whom there is a direct correlation of decreased cholesterolaemia with a reduced risk of cardiovascular mortality.^{1–3} However, there is no consensus regarding the impact of hypercholesterolaemia on disease, functional performance and mortality in the elderly, particularly in the oldest old (aged 80+). Studies have shown that cholesterol, such as higher concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) may be beneficial to functional performance and longevity.^{4–10} The findings that low cholesterol concentrations may be associated with increased mortality risk from cancer, respiratory disease and trauma in the oldest old,⁶ and benefits with statin therapy decreased considerably with advancing age,¹¹ have also engendered discussion. The term “risk factor paradox” has been coined to describe the fact that in contrast to middle aged and younger elderly, traditional risk factors for mortality (such as TC and LDL-C, higher body mass index (BMI),¹² higher blood pressures¹³ and abnormally high thyrotropin¹⁴) predict better survival in the oldest old.

Unlike other cholesterol measurements, the impact of triglycerides (TG) on functional performance and mortality in the oldest old has not garnered as much attention in recent years. The greater co-morbidity and functional impairment in the oldest old, and the cumulative effects of life-time exposure to TG, make it less clear whether a risk factor paradox exists for TG in those aged 80+.^{15–17} Lower TG (less than 1.7 mmol/L) is recommended as normal concentration in both Chinese guidelines and U.S. guidelines for

the general population, while whether the guidelines was appropriate for the oldest old needs further investigation. To better understand whether higher TG is deleterious to functional performance or survival, and should be treated or not, we explored the associations between TG and cognitive function, activities of daily living (ADL), frailty and mortality in a community-based prospective cohort of 930 oldest old.

METHODS

Participants and Study Design

The data were collected in the fifth wave of the Chinese longitudinal healthy longevity survey (CLHLS) in 7 longevity areas in 2009, and followed for a period of 5 years. All centenarians from the 7 longevity areas who agreed to participate in the study were interviewed. For each centenarian, one participant aged 40–64, 65–79, 80–89, 90–99 living nearby, with the predesignated age and sex were interviewed.¹⁸ In total, 2035 participants were included in 2009, after 911 participants aged 79 and younger and 194 participants with unavailable key variables were excluded, finally 930 participants aged 80 and older (mean age 94.0 years) met eligibility criteria for the study (Supplementary Figure S1). The baseline age (94.0 years V.S. 95.1 years), sex (30.5% V.S. 28.5% was men) and serum TG concentration (1.36 mmol/L V.S. 1.36 mmol/L) was not significantly different between 194 participants with missing data and 930 eligible participants. At baseline, a structured questionnaire, physiology assessment and laboratory analyses were used to collect information regarding socioeconomic and demographic characteristics, dietary behavior, lifestyle, cognitive function, ADL, frailty, anthropometry and biomarkers. All the participants signed informed consent and the study was approved by the Medical Ethics Committee of Peking University (Number-IRB00001052-13074) and the Ethics Committee of the National University of Singapore (Number: 12-260E).

Serum TG Determination and Classification

Serum TG concentrations were measured by an Automatic Biochemistry Analyzer (Hitachi 7180, Japan) using commercially available diagnostic kits (Roche Diagnostic, Mannheim, Germany) at Capital Medical University in Beijing. The coefficient of variation of TG was 68.2% (0.92/1.35). According to the Chinese guidelines on prevention and treatment of dyslipidemia, an elevated TG concentration was defined as ≥ 2.26 mmol/L.¹⁹ Four categories of TG concentrations were defined by the 1st, 2nd, 3rd and 4th quartiles corresponding to <0.84 mmol/L, $0.84 \leq \text{TG} < 1.04$ mmol/L, $1.04 \leq \text{TG} < 1.44$ mmol/L and ≥ 1.44 mmol/L, respectively.

Assessment of Cognitive Function, ADL and Frailty

Cognitive function was assessed by the Chinese version of the mini-mental state examination (MMSE);²⁰ participants whose MMSE scores were less than 18 were identified as cognitive impairment.²¹ ADL consisted of six tasks performed by each individual on a daily basis that are essential to independent living: dressing, eating, toileting, bathing, indoor activities and continence; disability was identified if the participant was not independent with one or more ADLs. Frailty was defined by the modified study of osteoporotic fractures (SOF) index using three components: (1) low body weight ($\text{BMI} < 18.5 \text{ kg/m}^2$); (2) inability

to rise from a chair without using one's arms; and (3) reduced energy concentration, as identified by a response of "yes" to the question, "For the last 6 months, were you limited in activities because of a health problem?". Frailty status was defined as robust (0 components), prefrail or frail (1–3 components positive).²²

At the follow-up surveys in 2012 and 2014, cognitive function and frailty were re-assessed for survivors, and ADL were re-assessed for survivors and decedents (answered by closest relatives). At follow-up, declines were defined as follows: cognitive decline was defined as a decrease of 3 points on the MMSE;²³ ADL decline was defined as a decrease of 1 point on the disability scores;²⁴ frailty aggravation was defined as a decrease of 1 point on the SOF index.²² A total of 320 participants were excluded from the analysis of cognitive decline on the basis of baseline MMSE<10. A total of 49 participants were excluded from the analysis of ADL decline due to a baseline lack of independence in all six tasks of ADL. A total of 25 participants were excluded from the analysis of frailty aggravation due to baseline abnormality in all 3 SOF criteria (Supplementary Figure S1).

Mortality

Survival status was ascertained during the follow-up survey in 2012 and 2014, including whether a subject died and the date of death, or survived or was lost-to-follow-up. The dates of death were acquired and confirmed by the participants' closest relatives or the village doctor. Survival time for participants was defined as the period from the date of the baseline visit to the date of death. A 'lost-to-follow-up' status was assigned to those who could not be found or contacted. Participants who were lost-to-follow-up in 2012 were censored at 3.0 years; those who survived or were lost to follow-up in 2014 were censored at 5.0 years. Additionally, data on cause of death were not collected because it was difficult to assess the cause of death in participants who were likely to suffer from various chronic diseases, especially among those who died at home rather than in hospital.⁸

Ethics

Informed consent was obtained from all participants and/or their relatives, and the study was approved by the Ethics Committee of Peking University and University of Singapore.

Statistical Analysis

Unadjusted Kaplan-Meier curves were constructed and survival probabilities were compared using log-rank test. To explore whether the associations of TG with mortality were linear or non-linear, Cox models with penalized splines have been further performed, which used penalized splines to fit Cox proportional hazards models for survival data by Akaike Information Criterion (AIC). Linear associations between TG and mortality were identified on the basis of AIC ($P<0.001$). Stepwise Cox proportional hazards models were used to identify the independent risk factors of mortality and the important confounders identified by previous studies. The models included age (year), sex (men or women), educational level (0 or 1 years formal education), marital status (married or not), self-reported quality of life (high or not), basic medical insurance (yes or no), often consumed meat (yes or no), often consumed egg (yes or no), often consumed fruit (yes or no), often consumed vegetables (yes or no), regular exercise (yes or no), central obesity (yes or no), BMI (kg/m^2), cognitive

impairment (yes or no), disability (yes or no), frailty (robust or not), cardiovascular and cerebrovascular disease (CVD) (yes or no), total lymphocyte count (TLC, $1.0 \times 10^9/L$), and chronic kidney disease (CKD, yes or no)^{25, 26}, diabetes (yes or no), anemia (yes or no) and hepatobiliary disease (yes or no). Age, BMI and TLC were modeled as continuous variables. The univariable and multivariable Cox proportional hazards models with adjustment of above-mentioned risk factors were done to estimate the hazard ratio (HR) and 95% confidential interval (CI) for different TG concentration. We also used Logistic regression models to explore the cross-sectional association of TG and cognitive impairment, disability and frailty, based on the baseline data. To address whether the associations between TG and mortality were stable, TG was analyzed as a continuous variable (in 1 mmol/L increments), a binary categorical variable (the non-elevated as reference) and in quartiles (the 1st quartile as reference) in logistic models and Cox models. In these time-to-event analyses, the occurrence of the event of cognitive decline, ADL decline and frailty aggravation was likely to be precluded by mortality. Competing risk models²⁷ were performed to explore the association of TG with cognitive decline, ADL decline and frailty aggravation, adjusting for the above-mentioned risk factors.

In an attempt to assess whether the paradox was distorted by reverse causality, survival bias, selection bias or confounding factors, sensitivity analyses were conducted as follows: 1) we removed participants who died during the first year of follow-up, thus potentially excluding participants with a co-morbidity whose low TG concentration was a marker of imminent death; 2) we evaluated the interactions of cognitive impairment, disability, frailty, CVD, CKD and co-morbidity with TG for mortality risk; 3) we restricted to participants with no identified chronic disease burden (without co-morbidity, including CVD, CKD and respiratory disease) to minimize disease-related TG decline; and 4) we conducted subgroup analyses, stratified by status of cognitive impairment, disability, frailty, CVD, and CKD, respectively; 5) we explored stratified analyses among participants in different nutrition status, such as BMI ($< 18.5 \text{ kg/m}^2$ or not), anemia (yes or not), and central obesity (yes or not).

Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA) and R, version 3.4.0 (R Core Team). 2-sided $p < 0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of these participants are presented in Table 1. The participants in the highest quartile of TG had the lowest prevalence of cognitive impairment, disability, and pre-frail or frail status (p -values were < 0.001 , < 0.001 and 0.008 respectively). Of the 930 participants, 571 participants died during the 5-year follow-up; the overall all-cause mortality probability was 63.4%.

Functional Performance

In the cross-sectional analyses based on the baseline data, 1 mmol/L increments of TG concentration was associated with lower odds of having cognitive impairment [odds ratio (OR)=0.82; 95% CI 0.69–0.99], disability (OR=0.73; 95% CI:0.55–0.97), and frailty

(OR=0.72; 95% CI:0.61–0.85). Compared to elevated TG, the ORs were 1.76(1.06–2.95), 1.83(0.86–3.90) and 2.45(1.53–3.94) for non-elevated TG for cognitive impairment, disability and frailty, respectively (Supplementary Table S1).

During 5 years of follow-up, we identified 29.2% (178/610) cognitive decline, 44.6% (393/881) ADL decline and 13.5% (122/905) frailty aggravation. Each 1mmol/L increase in TG corresponded to an approximately 20% decrease in risk of cognitive decline, ADL decline, and frailty aggravation during 5 years of follow-up, with unadjusted risk ratios (RR) of 0.85(0.73–0.98), 0.71(0.62–0.82), and 0.85 (0.70–1.02); and fully adjusted RR of 0.81(0.66–0.98), 0.81(0.69–0.94), and 0.83 (0.68–1.01), respectively (Figure 1).

Survival

The mortality probability was lower in: participants with elevated TG (36.6%) than non-elevated (67.1%) (p-value <0.001); and participants in the 4th (highest) quartile of TG (49.7%) compared with any other quartiles (68.9%, 65.6% and 71.2% for 1st, 2nd and 3rd quartiles, respectively) (p-value <0.001). High TG concentrations were associated with lower mortality risk (Figure 2). Adjusting for potential confounders, the mortality risk decreased with each 1 mmol/L increase in TG (HR, 0.79[0.69–0.89]) (Figure 2). Non-elevated TG (<2.26 mmol/L) was an independent predictor of mortality, with mortality-risk estimates of 1.72 (1.22–2.22), relative to TG ≥ 2.26 mmol/L. Participants with TG in the 1st and 3rd quartiles were approximately 1.5-fold as likely to die as those in the 4th quartile, the hazard ratios (HR) were 1.55 (1.21–1.99) and 1.53 (1.20–1.96), respectively (p-value for trend was 0.023) (Figure 2).

Sensitivity Analyses and Subgroup analyses

When sensitivity analyses were done, 1) we observed similar results after excluding the events that occurred during the first year of follow-up; 2) there were insignificant interactions of TG with cognitive impairment, disability, frailty, CKD, co-morbidity, BMI, anemia and central obesity for morbidity risk, and significant interactions of TG with CVD; 3) the inverse relationship between TG and mortality risk kept in participants with and without no identified chronic disease burden; 4) and sub-group analyses suggested that the inverse relationship persisted in participants in the following circumstances: with and without cognitive impairment; with and without disability; with pre-frailty or frailty; with and without CVD; with and without CKD; with different nutritional status, such as BMI (< 18.5 kg/m² or not), anemia (yes or not), and central obesity (yes or not) (Figure 3).

DISCUSSION

We found that for oldest old, a higher concentration of TG was associated with lower risk of cognitive decline, ADL decline, frailty aggravation and mortality. These results, in the individuals aged 80 and over, challenge the classic paradigm established in populations under 80 years old, that elevated TG is a risk factor for these age-related chronic disorders and mortality. The TG concentration (mean:1.35±0.92 mmol/L) was lower than the population in North America and Europe in our result, while it was basically consistent with the elderly aged 60 and older based on the results of China Chronic Disease Surveillance

Survey (mean: 1.23 ± 0.97 mmol/L)²⁸. The lower consumption of meat, egg and higher consumption of vegetables may contribute to the lower TG concentration for those Chinese oldest old^{29, 30}.

Association of TG with Functional Performance

Biological age is different from chronological age; it can be measured by functional performance, such as cognitive function, ADL and frailty, that play an extremely important role in longevity.³¹ This study demonstrated that a higher concentration of TG was associated with better functional performance and lower risk of decline in functional performance. Our current findings are consistent with our previous studies;^{11, 32} they are also supported by accumulating evidence^{33, 34} that the association between evaluated TG and cognitive impairment might not hold or even be inverted for the oldest old. Lower TG were negatively associated with ADL performance in women aged 95+;³⁵ predicted severe disability and higher all-cause mortality in patients with acute ischemic stroke;³⁶ additionally, TG has been shown to be a serological marker of frailty.³⁷ These results and ours challenged the classic reasoning established in individuals younger than 80 years, that evaluated TG is a risk factor for these disorders; suggested that TG may be a robust biomarker for biological age.

TG and Mortality

In this cohort of oldest old, we demonstrated a statistically significant relationship between higher serum TG and lower mortality. Several studies with limited numbers of oldest old (less than 320) found no significant association^{15–17} between TG and mortality risk. In contrast, a study with relatively large sample size reported that low TG was a robust predictor of mortality in the non-demented elderly aged 75+; the participants in the lowest TG quartile were approximately twice as likely to die as those in the highest quartile.³⁸ Other longitudinal studies, including the Honolulu and Framingham studies, observed increased all-cause mortality rates with lower total cholesterol concentrations in the elderly population,^{6, 39–41} including in elderly patients with severe acute or chronic pathological conditions such as infections,⁶ neoplasias⁴² and heart failure.⁴³ In this clinical context, the finding of higher cholesterol or TG concentrations may be considered to be a predictor of younger biological age and longevity among oldest old.^{44, 45}

TG paradox

It should be noted that whether the TG paradox was casual or spurious is still in question, even though we adjusted for a number of independent risk factors of mortality such as co-morbidities (CVD and CKD), and poor functional performance (cognitive impairment, disability and frailty). It is possible that malnutrition, cachexia or infectious disease were causally related to increased mortality by means of low concentrations of TG.^{6, 46} However, when some nutritional or immunological indices (e.g., BMI, anemia, central obesity and TLC) that were significantly and independently associated with mortality were adjusted, the inverse association between TG and mortality remained. We observed the same inverse association between TG and mortality in the 1-year lag analysis; importantly, this would have excluded participants with low TG concentrations due to cachexia just before death.

The paradox (inverse association of TG with functional performance and mortality) may have been distorted by survival bias⁴⁷ or selection bias.⁴⁸ For instance, TG could increase the risk of cardio-metabolic diseases that may cause early mortality that could have led to a loss of such individuals from the oldest old studied here. Interestingly, we did not observe a significant association between TG and CVD among those aged 80+, even though CVD was also an independent risk factor for mortality in this study. The inverse association remained for the analyses of the sub-group of participants without CVD, or without identified chronic disease burden. Taken together, these data suggest that the paradox cannot be totally attributed to malnutrition, cardiac cachexia, survival bias or selection bias. To gain a mechanistic understanding of the paradox, further study is warranted.

Strengths and Limitation

This is the first prospective observational study that specifically investigated the relationship of TG with cognitive function, ADL, frailty and mortality in a prospective cohort of elderly aged 80+. We investigated a wide range of predictors of all-cause mortality, thereby accounting for the relevant confounders or effect modifiers. However, information on lipid-lowering therapy was not available, although it was unlikely to reverse the association since only very few (3/930) participants with self-reported dyslipidemia were diagnosed by a doctor. In addition, the observational nature of the study prevents us from excluding residual confounding and drawing final conclusions on causality. Additionally, the present finding may not be appropriate for other ethnic population or other age group since we are investing a special population aged 80 and older with low TG concentration.

CONCLUSION

In the community-based oldest old, higher concentrations of TG were associated with lower risk of cognitive decline, ADL decline, frailty aggravation and mortality, suggesting that TG may be a robust biomarker for biological age and an independent predictor of longevity. These findings suggest the clinical importance of revisiting whether the concept of “the lower TG is better” generated from general population is appropriated for the oldest old. Taken together with other observational studies noting, after age 80, the limited prognostic value of a higher concentration of triglycerides for disease or mortality, cholesterol-lowering therapy in elderly aged 80+ with higher concentrations of triglycerides should be prescribed judiciously and may be without much or any benefit. We hold the same view as some specialists, that the decision to administer treatment to elderly patients with high or abnormally high serum triglycerides concentrations should be individualized and guided by chronological age and biological age. Definitive evidence of the beneficial or adverse effects of TG lowering in the oldest old can only come from a well-designed randomized placebo-controlled clinical trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. The association of TG (each 1 mmol/L) with cognitive decline, ADL decline, frailty aggravation and mortality during 5 years of follow-up.^a

Abbreviation: ADL= activities of daily living; RR=risk ratio; TG=triglycerides.

^aAdjusted for age, sex, educational level, marital status, self-reported quality of life, regular exercise, central obesity, BMI, cognitive impairment (was not adjusted in the analyses of cognitive decline), disability (was not adjusted in the analyses of ADL decline), frailty (was not adjusted in the analyses of frailty aggravation), CVD, TLC and CKD.

Figure 2. The 5-year all-cause mortality risk for different TG concentrations.^a

*p<0.05; **p<0.01; Abbreviation: TG= triglycerides; HR=hazard ratio.

^a Adjusted for age, sex, educational level, marital status, self-reported quality of life, regular exercise, central obesity, BMI, cognitive impairment, disability, frailty, CVD, TLC and CKD.

Figure 3. The association between TG and 5-year all-cause mortality risk in different subgroup.^a

Abbreviation: CKD= chronic kidney disease; CVD= cardiovascular and cerebrovascular disease; TG= triglycerides; HR=hazard ratio.

^a Adjusted for age, sex, educational level, marital status, self-reported quality of life, regular exercise, central obesity, BMI, cognitive impairment, disability, frailty, CVD, TLC and CKD.

Table 1.

Characteristics of 930 Chinese oldest old by quartiles of serum TG concentrations.

Variables	Q1	Q2	Q3	Q4	p-value
Survival status					
Died	165 (67.4)	143 (63.6)	150(67.3)	113(47.7)	<0.001
Censored	80(32.6)	82(36.4)	73(32.7)	124(52.3)	
Age (years)	93.7(8.0)	95.3(7.2)	94.3(7.4)	92.8(8.1)	0.005
Sex					
Men	102(41.6)	60(26.7)	54(24.3)	67(28.3)	<0.001
Women	143(58.4)	165(73.3)	169(75.8)	170(71.7)	
Marital status					
In marriage	56(22.9)	28(12.4)	28(12.6)	50(21.1)	0.002
Not in marriage	189(77.1)	197(87.6)	195(87.4)	187(78.9)	
Educational level					
Illiteracy	189(77.1)	190(84.4)	194(87.0)	184(77.0)	0.011
Literacy	56(22.9)	35(15.6)	29(13.0)	53(22.4)	
Self-reported high quality of life	113(46.1)	97(43.1)	94(41.3)	110(46.4)	0.631
Basic medical insurance	34 (13.9)	31 (13.8)	24 (10.8)	79 (33.3)	<0.001
Regular exercise	169(69.8)	154(69.1)	164(74.2)	175(74.8)	0.399
Often consumed meat	81 (33.1)	67 (29.8)	57 (25.6)	86 (36.3)	0.061
Often consumed egg	83 (33.9)	84 (37.3)	65 (29.1)	49 (20.7)	<0.001
Often consumed fruit	34 (13.9)	30 (13.3)	18 (8.1)	16 (6.8)	0.142
Often consumed vegetables	158 (64.5)	131 (58.2)	138 (61.9)	124 (52.3)	0.782
WC (cm)	76.4(8.9)	76.9(9.6)	76.6(9.1)	77.0(9.1)	0.924
Central obesity	65 (26.5)	73 (32.4)	68 (30.5)	74 (31.2)	0.526
BMI (kg/m ²)	17.4(3.0)	17.4(3.3)	17.7(3.9)	18.0(3.7)	0.148
Anemia	130 (53.1)	107 (47.6)	109 (48.9)	121 (51.1)	0.647
Cognitive impairment	112(45.7)	126(56.0)	118(52.9)	88(37.1)	<0.001
Disability	53(21.6)	71(31.6)	52(23.3)	37(15.6)	<0.001
Pre-frail or frail	200(81.6)	191(84.9)	174(78.0)	172(72.6)	0.008
Diabetes	22 (9.0)	12 (5.3)	24 (10.8)	31 (13.1)	0.043
Hepatobiliary disease	3 (1.2)	7 (3.1)	4 (1.8)	9 (3.8)	0.249
Self-reported dyslipidemia	0(0.0)	0(0.0)	0(0.0)	3(1.3)	<0.001
CVD	22(9.0)	19(8.4)	20(9.0)	23(9.7)	0.973
TLC (1.0×10 ⁹ /L)	1.43(0.55)	1.66(0.9)	1.62(0.85)	1.74(0.62)	<0.001
CKD	110(44.9)	101(44.9)	116(48.0)	115(48.5)	0.784

Data listed as n (%) for dichotomous variables, including survival status, sex, educational level, marital status, self-reported high quality of life, regular exercise, disability, CVD and CKD, were tested using chi-square test.

Data listed as mean (SD) for continuous variables, including age, WC, BMI and TLC, were tested for differences between the four groups using analysis of variance.

Abbreviations: WC=waist circumference; BMI=body mass index; CVD=cardiovascular disease; TLC= total lymphocyte count; CKD=chronic kidney disease.