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# Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: Analysis in a large Japanese population

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## ARTICLE INFO

## ABSTRACT

*Objectives:* To investigate the relationship between triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C) and chronic kidney disease (CKD).
*Methods:* We used data from 216,007 Japanese adults who participated in a nationwide health checkup program. Men ($n = 88,516$) and women ($n = 127,491$) were grouped into quartiles based on their TG/HDL-C levels ($<1.26$, $1.26-1.98$, $1.99-3.18$, and $>3.18$ in men; $<0.96$, $0.96-1.44$, $1.45-2.22$, and $>2.22$ in women). We cross-sectionally assessed the association of TG/HDL-C levels with CKD [defined as an estimated glomerular filtration rate (eGFR) of $<60$ mL/min/1.73 m$^2$ (low eGFR) and/or proteinuria (defined as urinary protein $\geq 1+$ on dipstick testing)], low eGFR, and proteinuria.
*Results:* The prevalence of CKD, low eGFR, and proteinuria increased significantly with elevating quartiles of TG/HDL-C in both genders (all *P* for trend $<0.001$). Participants in the highest quartile of TG/HDL-C had a significantly greater risk of CKD than those in the lowest quartile after adjustment for the relevant confounding factors (odds ratio: 1.57, 95% confidence interval: 1.49—1.65 in men; 1.41, 1.34—1.48 in women, respectively). Furthermore, there were significant associations with low eGFR and proteinuria. In stratified analysis, the risk of CKD increased linearly with greater TG/HDL-C levels in participants with and without hypertension, diabetes, and obesity. Moreover, higher TG/HDL-C levels were relevant for CKD, especially in participants with hypertension and diabetes (*P* for interaction $<0.001$, respectively).
*Conclusions:* An elevated TG/HDL-C is associated with the risk of CKD in the Japanese population.
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## 1. Introduction

Chronic kidney disease (CKD) is a global public health problem and a major risk factor for progressive kidney failure and cardio-vascular morbidity and mortality [1]. Identifying and managing the risk factors associated with mild CKD may well be the best strategy to prevent and delay advanced outcomes of CKD [1].

Abnormal lipoprotein metabolism has been identified as a possible cause of CKD [2,3], and moderate CKD is associated with

elevated levels of triglycerides (TG) and a decreased level of high-density lipoprotein cholesterol (HDL-C) [2–7].

Recent studies have shown that there is an association between TG/HDL-C and insulin resistance and that TG/HDL-C may be a better predictor of cardiovascular events than other lipid parameters, including TG, low-density lipoprotein-cholesterol (LDL-C), or the total cholesterol/HDL-C ratio [8–11]. In addition, TG/HDL-C has also been shown to predict the LDL particle size [12–14]. However, little is known about the association between TG/HDL-C and CKD. In the present study, we investigated the association between TG/HDL-C and CKD in a nationally representative group of Japanese adults.

## 2. Methods

### 2.1. Study population

This cross-sectional cohort study was conducted as a part of the prospective ongoing project entitled "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan", and it was based on data obtained from the Japanese Specific Health Check and Guidance System. This annual health check program was initiated in 2008 by the Japanese government and it promotes the early diagnosis of metabolic syndrome and intervention strategies for the prevention of this disease. In 2008 and 2009, data were collected from 676,905 individuals participated in the health checkups. Men ($n = 278,017$) and women ($n = 383,586$) involved were between 20 and 101 years of age. For our study, data from 216,007 of the participants (88,516 men and 127,491 women) aged between 20 and 88 years were used for statistical analyses. (We excluded 460,898 participants because essential data, including information on proteinuria and serum creatinine levels, were unavailable.) This study was conducted in accordance with the Private Information Protection Law and ethical guidelines for epidemiology research published by the Ministry of Health, Labour and Welfare in 2005.

### 2.2. Clinical evaluation and laboratory measurements

All participants completed a self-administered questionnaire that documented their medical history, current medications, smoking habits (current smoker or not), alcohol consumption (daily drinker or not), and regular exercise habits. A study physician physically examined every participant and checked the participants' reported medical history to ensure the accuracy of the information. The height and weight of participants were measured, and their body mass index (BMI) was calculated (kg/m$^2$). For these measurements, participants wore light clothing without shoes. Blood pressures were measured and blood as well as urine sampling was done at each participant's local medical institute, as stipulated by the health check program.

Blood samples were collected after participants fasted overnight and the blood was analyzed using an automated clinical chemical analyzer within 24 h of sampling. All blood analyses were conducted at a local, rather than a central, laboratory. Although the methods used for blood analyses were not calibrated between laboratories, the Japan Society of Clinical Chemistry-recommended methods for laboratory tests several years ago, and these recommendations have been widely adopted by laboratories across Japan. The enzymatic method was used to measure serum creatinine levels in fresh blood samples. Levels of LDL-C, HDL-C, and TG were determined enzymatically. Hemoglobin A1c (HbA1c) values were expressed as a National Glycohemoglobin Standardization Program equivalent value, which was calculated according to the following formula:

$$HbA1c(\%) = HbA1c\,(Japan\ Diabetes\ Society)\,(\%) + 0.4\%.$$

### 2.3. Definition of CKD, diabetes mellitus, obesity, hypertension, and TG/HDL-C

The estimated glomerular filtration rate (eGFR) was calculated using the following equation; eGFR (mL/min/1.73 m$^2$) = $194 \times$ serum creatinine (mg/dL)$^{-1.094} \times$ age (years)$^{-0287} \times 0.739$ (for women) [15]. Proteinuria was defined as urinary protein value of $\geq 1+$ with dipstick testing. CKD was defined as an eGFR <60 mL/min/1.73 m$^2$ (low eGFR) and/or the presence of proteinuria. Hypertension was defined as a systolic blood pressure (SBP) of $\geq 140$ mmHg, and/or a diastolic blood pressure (DBP) of $\geq 90$ mmHg, or self-reported use of antihypertensive drugs. Diabetes mellitus was defined in accordance with the guidelines of the American Diabetes Association [16]; fasting glucose concentration $\geq 126$ mg/dL, HbA1c concentration $\geq 6.5\%$, or self-reported use of antihyperglycemic drugs. TG/HDL-C was calculated as TG (mg/dL) divided by HDL-C (mg/dL). Male and female participants were separately grouped into quartiles based on their TG/HDL-C levels. TG/HDL-C levels for the quartile groups ($Q$) were as follows: $Q_1 < 1.26$, $Q_2$ 1.26–1.98, $Q_3$ 1.99–3.18, and $Q_4 > 3.18$ for men and $Q_1 < 0.96$, $Q_2$ 0.96–1.44, $Q_3$ 1.45–2.22, and $Q_4 > 2.22$ for women.

**Table 1**
Clinical features of all subjects.

| Variables | Men ($n = 88,516$) | Women ($n = 127,491$) | P value |
|---|---|---|---|
| Age, years | 63.8 ± 8.9 | 63.8 ± 8.5 | 0.77 |
| Body mass index, kg/m$^2$ | 23.7 ± 3.0 | 22.8 ± 3.5 | <0.001 |
| Waist circumference, cm | 85.3 ± 8.2 | 82.6 ± 9.8 | <0.001 |
| Systolic blood pressure, mmHg | 131 ± 17 | 128 ± 18 | <0.001 |
| Diastolic blood pressure, mmHg | 78 ± 11 | 75 ± 11 | <0.001 |
| Fasting blood glucose, g/dL | 102 ± 25 | 95 ± 18 | <0.001 |
| Hemoglobin A1c, % | 5.4 ± 0.8 | 5.3 ± 0.6 | <0.001 |
| LDL-C, mg/dL | 121 ± 30 | 130 ± 30 | <0.001 |
| HDL-C, mg/dL | 57 ± 15 | 66 ± 16 | <0.001 |
| TG, mg/dL | 133 ± 96 | 107 ± 61 | <0.001 |
| TG/HDL-C | 2.66 ± 2.59 | 1.83 ± 1.50 | <0.001 |
| Serum creatinine, mg/dL | 0.84 ± 0.27 | 0.63 ± 0.19 | <0.001 |
| Estimated GFR, mL/min/1.73 m$^2$ | 74.7 ± 16.6 | 76.1 ± 16.3 | <0.001 |
| Low eGFR, % | 17.7 | 11.4 | <0.001 |
| Proteinuria, % | 8.2 | 4.0 | <0.001 |
| Chronic kidney disease, % | 23.3 | 14.5 | <0.001 |
| Hypertension, % | 51.4 | 42.7 | <0.001 |
| Diabetes mellitus, % | 15.7 | 8.4 | <0.001 |
| Obesity, % | 31.0 | 23.0 | <0.001 |
| Current smoker, % | 25.3 | 5.9 | <0.001 |
| Daily drinker, % | 44.9 | 8.3 | <0.001 |
| Regular exercise, % | 47.6 | 39.8 | <0.001 |
| History of stroke, % | 5.3 | 2.8 | <0.001 |
| History of heart disease, % | 8.3 | 5.2 | <0.001 |
| Medication for hypertension, % | 34.2 | 29.0 | <0.001 |
| Medication for diabetes mellitus, % | 7.5 | 4.1 | <0.001 |
| Medication for dyslipidemia, % | 12.9 | 22.9 | <0.001 |

Low eGFR was defined as eGFR <60 mL/min/1.73 m$^2$. Proteinuria was defined as urinary protein of $\geq 1+$ on dipstick testing. Chronic kidney disease was defined as low eGFR and/or proteinuria. Hypertension was defined as a systolic blood pressure $\geq 140$ mmHg, diastolic blood pressure $\geq 90$ mmHg, or self-reported use of antihypertensive drugs. Diabetes was defined in accordance with American Diabetes Association guidelines as a fasting glucose concentration of $\geq 126$ mg/dL, hemoglobin A1c concentration of $\geq 6.5\%$, or self-reported use of antihyperglycemic drugs. TG/HDL-C was calculated as TG (mg/dL) divided by HDL-C (mg/dL).
Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; GFR, glomerular filtration rate; eGFR, estimated GFR.