Association between hyperlipidemia and chronic kidney disease in a Japanese population; a cross-sectional study

Yuko AGO SHIRAISHI (agoyuko818@jichi.ac.jp)

Jichi Medical University School of Medicine Graduate School of Medicine: Jichi Ika Daigaku Igakubu Daigakuin Igaku Kenkyuka https://orcid.org/0000-0002-6087-0855

Yukiko ISHIKAWA

Jichi Medical University: Jichi Ika Daigaku

Joji ISHIKAWA

Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology: Tokyo-to Kenko Choju Iryo Center

Masami MATSUMURA

Jichi Medical University: Jichi Ika Daigaku

Shizukiyo ISHIKAWA

Jichi Medical University: Jichi Ika Daigaku

Research

Keywords: chronic kidney disease, prevalence, hyperlipidemia, hypertriglyceridemia

Posted Date: January 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-151545/v1

Abstract

Background

Strategies to prevent the development and progression of chronic kidney disease (CKD) are now an important theme in clinical practice due to increased life expectancy. The present study investigated the prevalence of CKD as well as lipid profiles affecting CKD.

Methods

In total, 5,169 subjects were eligible for a cross-sectional analysis of baseline data from the Jichi Medical School Cohort Study. We examined CKD subjects with an estimated glomerular filtration rate (eGFR) of 59 (mL/min/1.73m^2) or lower and independent factors associated with reductions in eGFR.

Results

The prevalence of CKD was 17.7%. Age, systolic blood pressure, and hyperlipidemia were defined as related factors for CKD. The lowest, second, third, and highest quartile ranges of total cholesterol (TC) and triglycerides (TG) were 0-166, 167–188, 189–212, and 213 mg/dL or higher and 0–71, 72–100, 101–148, and 149 mg/dL or higher, respectively. The odds ratio (OR) of Q2 to Q4 of TC relative to that of Q1 for CKD increased linearly [OR (95%CI): Q2, 1.3 (1.0-1.7); Q3, 1.38 (1.1–1.8); Q4, 1.5 (1.4–2.4)]. The ORs of Q2 and Q3 of TG for CKD did not increase, whereas that of Q4 did [OR (95% CI): Q2, 0.95 (0.7–1.2); Q3, 0.98 (0.8–1.2); Q4, 1.21 (1.0-1.5)].

Conclusion

TC and TG elevations were both independently associated with CKD. The relationship with CKD became stronger as TC increased, and TG was considered to have a threshold of 149 mg/dL. Prospective studies are expected in the future.

Background

Chronic kidney disease (CKD) is a global topic in clinical practice due to increases in life expectancy. In 2005, 13% of Japanese adults who participated in the annual health check program were reported to have CKD. [1] Another cohort study in Japan showed that the prevalence of CKD was increasing. [2] The progression of CKD ultimately results in end-stage renal disease and dialysis. In Japan, 339,841 patients were receiving dialysis in 2018 and this number is increasing by approximately 5,000 patients annually. [3] Care for end-stage renal disease is one of the burdens on medical economics.

The relationship between dyslipidemia and CKD currently remains unclear. [4] Metabolic syndrome (MetS) consists of at least three of the following five disorders: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), hypertension, and hyperglycemia. A systematic review identified MetS as a predictor of the development of CKD. [5] Schaeffner et al. demonstrated in a prospective study that renal dysfunction was more common in men with total cholesterol (TC) greater than 240 mg/dL. [6] However, the threshold level of triglycerides (TG) that affects the development of CKD has not yet been established. Limited information is currently available on the relationship between TG levels and CKD. In a Chinese cross-sectional study, increases in TG levels were linearly associated with mild declines in renal function in subjects with an estimated glomerular filtration rate (eGFR) of between 60 and 90 mL/min/1.73m^2. [7] Another cross-sectional study in Taiwan reported that TG levels higher than 200 mg/dL were associated with the development of CKD in subjects recruited from a medical screening program. [8]

Therefore, we herein investigated lipid profiles related to CKD in a cross-sectional study of Japanese community-based residents.

Methods

The aim of this study is to investigate the frequency of CKD and the association of CKD-related factors, especially lipids and CKD. We conducted a cross-sectional analysis of baseline data from the Jichi Medical School (JMS) Cohort Study.

Subjects

The objective of the JMS Cohort Study was to evaluate the relationship between risk factors and cardiovascular diseases (CVD) in a general Japanese population. Details on the JMS cohort have been described previously. [9] Subjects were recruited from mass screening examinations for CVD by the Health and Medical Service Law for the Aged conducted by 11 communities between April 1992 and July 1995. The baseline data of this cohort were used in this cross-sectional study. The total number of subjects in the cohort was 12,490 (4,913 men and 7,577 women) and they were aged between 19 and 93 years. After the exclusion of subjects whose serum creatinine (SCr) value was not obtained, 5,169 subjects (1,870 men and 3,299 women) remained eligible for the CKD study.

Variables

Baseline information on age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), blood sugar (BS), TC, and TG was collected. Information on the smoking and drinking status as well as previous medical histories was obtained from questionnaires. Diabetes was defined as fasting BS (FBS) ≥126 mg/dL and/or casual BS ≥200 mg/dL and receiving medication for diabetes. Hyperlipidemia was defined as TC ≥220 mg/dL and/or TG ≥150 mg/dL and receiving medication for hyperlipidemia. We calculated eGFR according to the modification of diet in renal disease eGFR (MDRD-eGFR) for Japanese using the following equations: eGFR in men = $194 \times SCr^{-1.094} \times Age^{-0.287}$, while eGFR

in women = 194 × $SCr^{-1.094}$ × $Age^{-0.287}$ × 0.739. [10] Subjects were classified into CKD stages based on the definition of the Kidney Disease Outcomes Quality Initiative by eGFR. [11] In the present study, subjects with eGFR less than 60 (mL/min/1.73m^2) were defined as the CKD group.

Statistical analysis

Continuous variables are expressed as means and standard deviations (SD). Categorical variables are expressed as percentages (%). Differences in mean values between CKD and non-CKD were calculated using the *t*-test, while differences in percentages were calculated using the χ^2 test. We performed a multiple linear regression analysis to assess the relationships between various factors and reductions in eGFR adjusted for age, sex, BMI, SBP, hyperlipidemia, diabetes, and current smoking and alcohol habits. β, standard errors (SE), and P values were calculated using this model. We performed a logistic regression analysis to evaluate related factors for the CKD group, and calculated odds ratios (OR), 95% confidence intervals (95% CI), and P values adjusted for age, sex, BMI, SBP, the category of hyperlipidemia, diabetes, and current smoking and alcohol habits. To assess lipid profile risks, we used TG ≥150 mg/dL, TC ≥220 mg/dL, and both TC ≥220 mg/dL and TG ≥150 mg/dL as independent variables as a category of hyperlipidemia. We then examined the OR of the quartiles of TC and TG for CKD adjusted for age, sex, BMI, SBP, diabetes, and current smoking and alcohol habits by a logistic regression analysis.

Statistical analyses were performed using SPSS ver.21 (IBM SPSS Statistics 21.0).

Results

The total number of subjects was 5,169 and 36.2% were men. The mean age of subjects was 53.9 (standard deviation [SD] 11.2) years, 53.6 (11.4) years for men, 54.1 (11.0) years for women. The prevalence of CKD was 17.7% (15.7% in men, 18.9% in women). The numbers of subjects with eGFR of 90 mL/min/1.73m^2 or higher, 60–89 mL/min/1.73m^2, 30–59 mL/min/1.73m^2, and ≤ 30 mL/min/1.73m^2 were 1,194 (23.1%), 3,058 (59.2%), 913 (17.7%), and 4 (0.08%) respectively. The prevalence of CKD in each age group of 30–39, 40–49, 50–59, and ≥ 60 years were 0.8, 7.6, 11.5, and 27.3% in men and 0.4, 5.8, 23.1, and 27.9% in women, respectively (Fig. 1).

Table 1 shows the general characteristics of CKD and non-CKD subjects. Age, the percentage of men, BMI, SBP, DBP, TC, TG, hyperlipidemia, and BS were higher in the CKD group than in the non-CKD group. No significant differences were observed in the prevalence of diabetes between the two groups. The percentage of subjects with current smoking and alcohol habits was lower in the CKD group than in the non-CKD group.

Table 2 shows that age ($p < 0.001$), sex ($p < 0.05$), SBP ($p < 0.001$), and hyperlipidemia ($p < 0.001$) were associated with reductions in eGFR in a multiple linear regression analysis model.

Table 3 shows the OR for the CKD group adjusted for multiple variables. Age [OR (95%CI): 1.07, (1.06–1.09)], SBP [1.01, (1.00-1.01)], TG ≥ 150 mg/dL alone [1.34, (1.07–1.66)], TC ≥ 220 mg/dL alone [1.55,

(1.23–1.94)], and high TC and TG [1.94, (1.48–2.54)] correlated with CKD. An additive effect of TC and TG on CKD was observed (data not shown). The synergistic effect of TG and TC on CKD was also noted in this regression model in another evaluation.

Figure 2 shows the OR of TC and TG in quartiles for CKD adjusted by multiple variables. The lowest, second, third, and highest quartile ranges of total TC and TG were 0-166, 167–188, 189–212, and 213 mg/dL or higher and 0–71, 72–100, 101–148, and 149 mg/dL or higher, respectively. The OR of Q2 to Q4 of TC relative to Q1 for CKD increased linearly [OR (95%CI): Q2, 1.3 (1.0-1.7); Q3, 1.38 (1.1–1.8); Q4, 1.5 (1.4–2.4)]. Although the OR of Q2 and Q3 of TG for CKD did not increase, the OR of Q4 of TG for CKD was significantly higher than that for Q1 [OR (95% CI): Q2, 0.95 (0.7–1.2); Q3, 0.98 (0.8–1.2); Q4, 1.21 (1.0-1.5)]. The OR by TG elevations significantly increased only in the highest quartile valued as 149 mg/dL or higher. The OR of Q4 with a TG level of 149 mg/dL or more was higher than that of Q1 to Q3 [OR (95% CI): 1.24 (1.0-1.5)].

Discussion

The prevalence of CKD in the present study was 17.7%. This value is considered to be close to the prevalence of CKD in general populations in Japan. Another study conducted in 2005 reported that the prevalence of CKD was 13%, which was lower than that in the present study and may be due to our subjects being recruited from mass screening examinations and theirs volunteering to participate in the program. [1, 12] The prevalence of CKD in the present study may also have been higher because 63.8% of our subjects were women, among whom those in their 50s or higher had a high prevalence of CKD.

In the present study, significant differences were observed in age, BMI, SBP, DBP, TC, TG, and hyperlipidemia between the CKD and non-CKD groups. Our multiple linear regression analysis showed that age, sex, SBP, and hyperlipidemia were associated with reductions in eGFR. Our logistic regression analysis revealed that age, SBP, TG ≥ 150 mg/dL alone, TC ≥ 220 mg/dL alone, and high TC and TG were associated with CKD after adjustments for other risk factors. The OR of TC in quartiles for CKD increased linearly, whereas similar changes were not observed for elevations in TG. The risk of developing CKD appeared only at the highest TG quartile (≥ 149 mg/dL). Elevations greater than 149 mg/dL, even without increases in TC, may be a risk factor for CKD in this population.

Although the relationship between TC and CKD progression has been extensively examined, few studies have investigated that between TG and CKD using different lipid profiles and outcomes. [5, 6] Tsuruya et al. reported that the TG/HDL-C ratio was linearly related to CKD. [13] Muntner et al. also indicated that hypertriglyceridemia and low HDL were markers of elevated SCr. [14] Shimizu et al. identified intima-media thickening and hypertriglyceridemia as risk factors for CKD. [15] A Taiwan study conducted in 2009 reported a relationship between the TG threshold and CKD; the adjusted OR of CKD in subjects with TG ≥ 200 mg/dL was significantly higher than those with TG < 200 mg/dL [OR (95%CI): 1.901, (1.07–3.36)]. [8] The TG threshold may differ between countries or regions depending on lifestyles, such as

eating habits and physical activities. The TG threshold may be used to stratify the risk of developing CKD in each background.

Hyperlipidemia has been identified as one of the strongest risk factors for CVD. CKD is also an established risk factor for the development of CVD. Therefore, common factors such as arterial inflammation caused by hyperlipidemia may contribute to the progression of vascular damage in the heart and kidney. [16] On the other hand, lipid abnormalities secondarily caused by glomerulosclerosis have been proposed based on the hypothesis of lipid nephrotoxicity. [17–19] This vicious lipid cycle is considered to accelerate the progression of CKD, and its mechanism is related to inhibition of the cascade of very-low-density lipoprotein (VLDL) degradation by apoproteins. Altered lipoprotein effects have been reported as one of the main factors affecting nephrotoxicity in hypertriglyceridemia. [20] Recent studies have focused on changes in the n-3 polyunsaturated fatty acid profile and cholesterol metabolism that cannot be evaluated by lipoprotein levels. [21, 22] The management of hyperlipidemia may be important for preventing the progression of CKD and reducing total mortality rates.

Interventional studies on statins recently reported reductions in CVD events and possible renal protection. [4] A meta-analysis by Sandhu et al. revealed that statins suppressed impairments in renal function, increases in urinary proteins, and the onset and recurrence of CVD events. [23] On the other hand, in a meta-analysis by Ting et al., fibrates were shown to reduce CVD events and suppress declines in renal function in subjects with type 2 diabetes and renal impairment. [24]

Limited information is currently available to support the beneficial effects of reductions in TG on the prognosis of CKD. Therefore, further interventional trials are expected.

Although diabetes is one of the conventional risk factors for CKD, it was not associated with CKD or reductions in eGFR in the present study. As the underlying mechanism, glomerular hyperfiltration has been suggested to increase eGFR in patients with diabetes. [25, 26] Smoking is one of the risk factors for CKD; however, it showed a negative relationship with CKD in the present study. The lower BMI in subjects who smoke may have affected the results obtained.

The present study had the following limitation. As a measurement bias, TG data included pre- and post-prandial levels. However, the impact of this bias was not large because the subjects in the present study were recruited from a large, multicenter general population. [9]

Conclusions

In conclusion, TC and TG elevations were both independently associated with CKD in a general Japanese population. The relationship with CKD became stronger as TC increased. A TG level of 149 mg/dL or higher may be the threshold for a relationship with CKD. Since only a few interventional studies have been conducted on TG in the clinical field of CKD, the relationship between TG levels and the development of CKD warrants further research. Interventional studies are expected because the management of TG may prevent the development and progression of CKD.

Abbreviations

CKD: Chronic kidney disease

eGFR: estimated glomerular filtration rate

TC: total cholesterol

TG: triglyceride

OR: odds ratio

Mets: metabolic syndrome

HDL-C: high-density lipoprotein cholesterol

JMS: Jichi Medical School

CVD: cardiovascular disease

SCr: serum creatinine

BMI: body mass index

SBP: systolic blood pressure

DBP: diastolic blood pressure

BS: blood sugar

FBS: fasting blood sugar

MDRD-eGFR: modification of diet in renal disease estimated glomerular filtration rate

SD: standard deviation

SE: standard errors

VLDL: very low-density lipoprotein

Declarations

Acknowledgements

We thank all the participants and staff who helped us during this study's process.

Authors' Contributions

Author contributions were as follows: SI was responsible for data collection. YS and YI performed data analyses. JI and SI planned the analysis and interpretation of data. YS, YI, and MM designed the research, contributed to data interpretation, and prepared the draft of the manuscript. All authors read and approved the final version of the manuscript.

Corresponding author: Correspondence to yuko AGO SHIRAISHI

Funding

This study was funded by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan; grants from the Foundation for Community Development, Tochigi, Japan; a grant-in-aid from the Ministry of Health, Labor and Welfare of Japan; and Health and Labor Sciences Research Grants (Research on Health Services:

H26-Junkankitou [Seisakuk]-Ippan-001; H29-Junkankitou-Ippan-003 and

20FA1002).

Ethics declarations

Ethics approval and consent to participate

We obtained informed consent individually in writing and all subjects agreed to participate in the present study.

Each community government and the Institutional Review Board of Jichi Medical University has approved this study design and methods (Epidemiology 06-11).

Consent for publication

All authors have read and approved the content, and they agree to submit it for consideration for publication in the journal.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author information

Affiliations

1. Division of General Medicine, Center for Community Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan

Yuko Ago SHIRAISHI, Yukiko ISHIKAWA & Masami MATSUMURA

2. Department of Cardiology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2, Sakae, Itabashi, Tokyo, 173-0015, Japan

Joji ISHIKAWA

3. Division of Public Health, Center for Community Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan

Shizukiyo ISHIKAWA

Authors

1. Yuko AGO SHIRAISHI
2. Yukiko ISHIKAWA
3. Joji ISHIKAWA
4. Masami MATSUMURA
5. Shizukiyo ISHIKAWA

References

1. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009;13(6):621-30.
2. Yamagata K, Yagisawa T, Nakai S, Nakayama M, Imai E, Hattori M, et al. Prevalence and incidence of chronic kidney disease stage G5 in Japan. Clin Exp Nephrol. 2015;19(1):54-64.
3. Medicine JSfD Dialysis Medicine Statistics Survey Report 2018. https://docs.jsdt.or.jp/overview/; 2018, Accessed 07.Jul. 2020
4. Cases A, Coll E. Dyslipidemia and the progression of renal disease in chronic renal failure patients. Kidney Int Suppl. 2005(99):S87-93.
5. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2011;6(10):2364-73.
6. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol. 2003;14(8):2084-91.
7. Hou X, Wang C, Zhang X, Zhao X, Wang Y, Li C, et al. Triglyceride levels are closely associated with mild declines in estimated glomerular filtration rates in middle-aged and elderly Chinese with normal serum lipid levels. PLoS One. 2014;9(9):e106778.

8. Lee PH, Chang HY, Tung CW, Hsu YC, Lei CC, Chang HH, et al. Hypertriglyceridemia: an independent risk factor of chronic kidney disease in Taiwanese adults. Am J Med Sci. 2009;338(3):185-9.
9. Ishikawa S, Gotoh T, Nago N, Kayaba K, Jichi Medical School Cohort Study G. The Jichi Medical School (JMS) Cohort Study: design, baseline data and standardized mortality ratios. J Epidemiol. 2002;12(6):408-17.
10. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982-92.
11. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713-35.
12. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11(2):156-63.
13. Tsuruya K, Yoshida H, Nagata M, Kitazono T, Hirakata H, Iseki K, et al. Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. Atherosclerosis. 2014;233(1):260-7.
14. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int. 2000;58(1):293-301.
15. Shimizu M, Furusyo N, Mitsumoto F, Takayama K, Ura K, Hiramine S, et al. Subclinical carotid atherosclerosis and triglycerides predict the incidence of chronic kidney disease in the Japanese general population: results from the Kyushu and Okinawa Population Study (KOPS). Atherosclerosis. 2015;238(2):207-12.
16. Mathur S, Devaraj S, Jialal I. Accelerated atherosclerosis, dyslipidemia, and oxidative stress in end-stage renal disease. Curr Opin Nephrol Hypertens. 2002;11(2):141-7.
17. Moorhead JF, Chan MK, El-Nahas M, Varghese Z. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet. 1982;2(8311):1309-11.
18. Heine GH, Eller K, Stadler JT, Rogacev KS, Marsche G. Lipid-modifying therapy in chronic kidney disease: Pathophysiological and clinical considerations. Pharmacol Ther. 2020;207:107459.
19. Ruan XZ, Varghese Z, Moorhead JF. An update on the lipid nephrotoxicity hypothesis. Nat Rev Nephrol. 2009;5(12):713-21.
20. Vaziri ND, Moradi H. Mechanisms of dyslipidemia of chronic renal failure. Hemodial Int. 2006;10(1):1-7.
21. Shoji T, Kakiya R, Hayashi T, Tsujimoto Y, Sonoda M, Shima H, et al. Serum n-3 and n-6 polyunsaturated fatty acid profile as an independent predictor of cardiovascular events in hemodialysis patients. Am J Kidney Dis. 2013;62(3):568-76.
22. Sonoda M, Shoji T, Kimoto E, Okute Y, Shima H, Naganuma T, et al. Kidney function, cholesterol absorption and remnant lipoprotein accumulation in patients with diabetes mellitus. J Atheroscler Thromb. 2014;21(4):346-54.

23. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006;17(7):2006-16.
24. Ting RD, Keech AC, Drury PL, Donoghoe MW, Hedley J, Jenkins AJ, et al. Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD Study. Diabetes Care. 2012;35(2):218-25.
25. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-45.
26. Fu WJ, Li BL, Wang SB, Chen ML, Deng RT, Ye CQ, et al. Changes of the tubular markers in type 2 diabetes mellitus with glomerular hyperfiltration. Diabetes Res Clin Pract. 2012;95(1):105-9.

Tables

Due to technical limitations, table 1, 2, 3 is only available as a download in the Supplemental Files section.

Figures

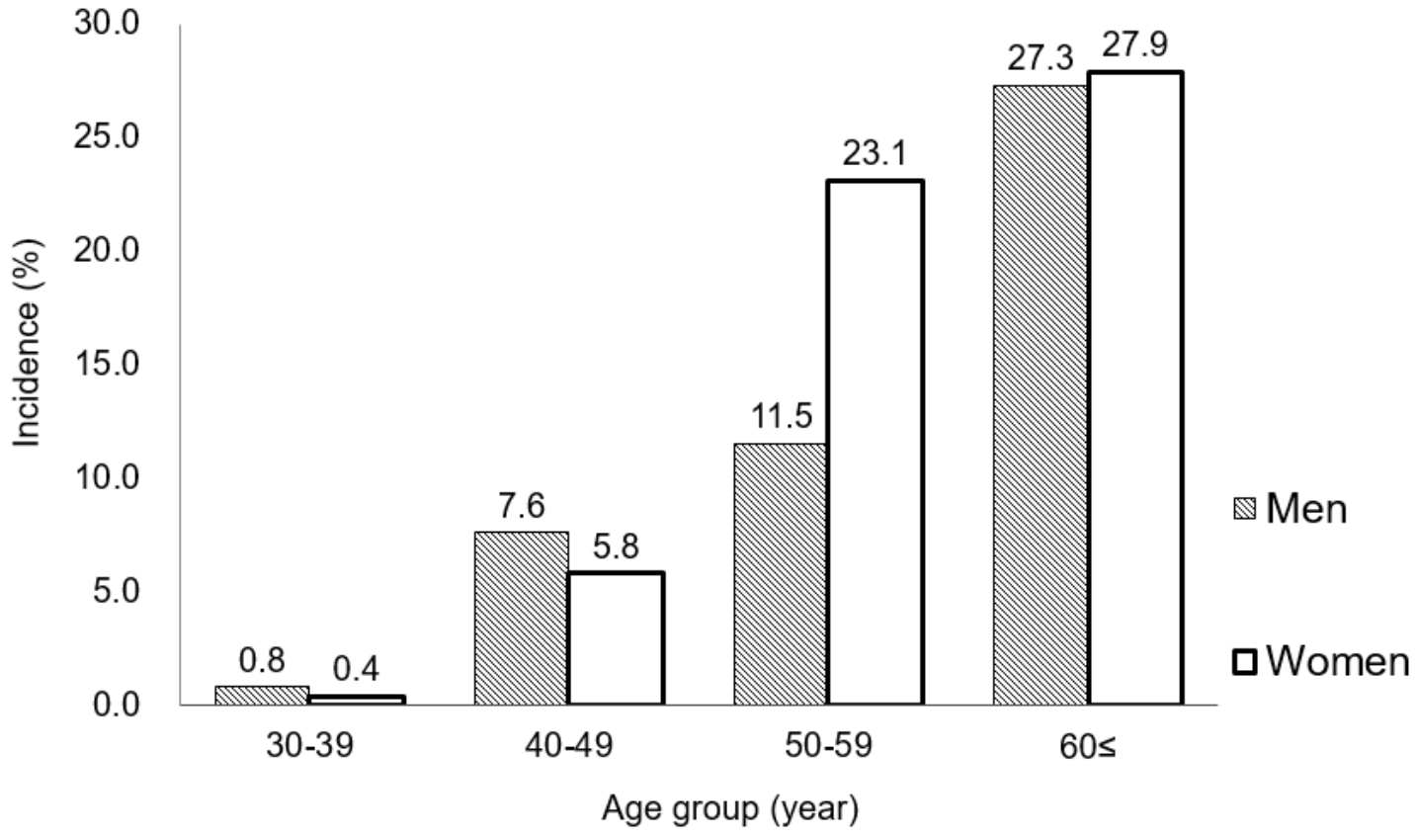

Figure 1

Prevalence of chronic kidney disease by age and sex The prevalence of CKD by age and sex was shown as percentages in each age group of 30-39, 40-49, 50-59, and ≥60 years. CKD, chronic kidney disease.

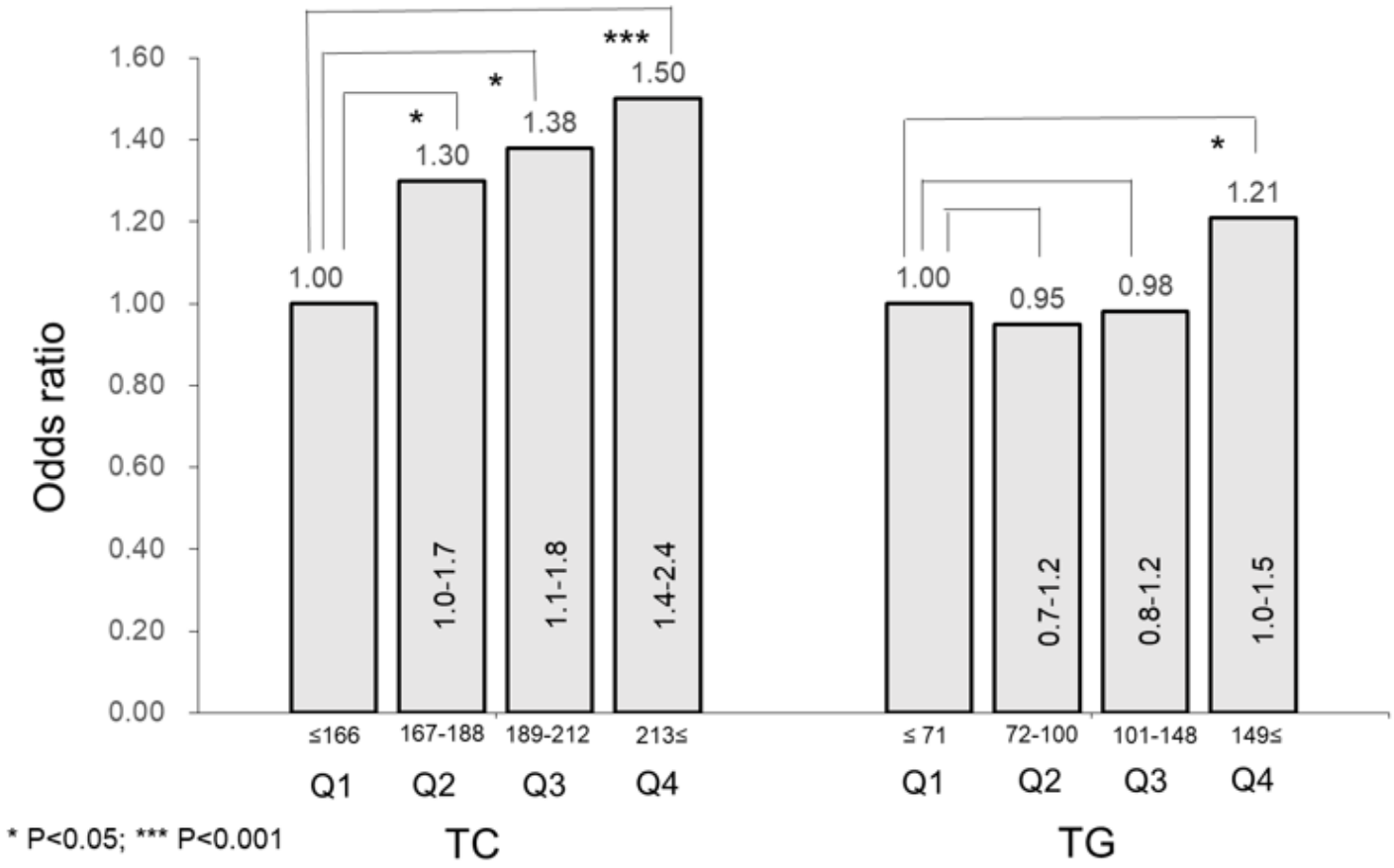

Figure 2

Odds ratios of quartiles of total cholesterol and triglycerides for chronic kidney disease The odds ratio of quartiles of TC and TG for CKD and 95% confidence intervals were calculated with adjustments for age, sex, body mass index, systolic blood pressure, diabetes, and current smoking and drinking habits by a logistic regression analysis. TC, total cholesterol; TG, triglycerides; CKD, chronic kidney disease.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables1218.xlsx