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Association between chronic kidney disease and new-onset dyslipidemia: The Japan Specific Health Checkups (J-SHC) study

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ABSTRACT

Background and aims: Dyslipidemias are common among patients with chronic kidney disease (CKD) and are a major risk factor for cardiovascular disease. This study aimed to investigate the association between early-stage CKD and new-onset dyslipidemia for each lipid profile.

Methods: This nationwide longitudinal study included data from the Japan Specific Health Checkups (J-SHC) Study. New-onset dyslipidemia was indicated by hypertriglyceridemia (High-TG; ≥150 mg/dL), hyper-LDL cholesterolemia (High-LDL-C; ≥140 mg/dL), or hypo-HDL chelesterolemia (Low-HDL-C; <40 mg/dL) levels according to the guideline of Japan Atherosclerosis Society, or High-TG/HDL-C ratio (≥3.5) which was a good predictor of atherosclerosis. The incidence of new-onset dyslipidemia was compared between participants with and without CKD. Survival curves were used to analyze the incidence of each dyslipidemia.

Results: Of 289,462 participants with a median follow-up period of 3 years, the incidence of High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratios were 64.4/1000 person-years, 83.1/1000 person-years, 14.5/1000 person-years, and 39.6/1000 person-years, respectively. The adjusted hazard ratios (95% confidence intervals) for High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio were 1.09 (1.05–1.13), 0.99 (0.95–1.04), 1.12 (1.05–1.18), and 1.14 (1.09–1.18), respectively, in CKD participants as compared to non-CKD participants. Decreased eGFR and presence of proteinuria were independently associated with higher risks for new-onset of High-TG, Low-HDL-C, and High-TG/HDL-C ratios.

Conclusions: CKD was associated with a higher risk of new-onset High-TG, Low-HDL-C, and High-TG/HDL-C ratios, but not High-LDL-C, in the general population. These CKD-specific lipid abnormalities may explain the residual risk for CKD-related cardiovascular disease.

1. Introduction

It is well known that chronic kidney disease (CKD) is a global public health problem and a major risk factor for cardiovascular disease (CVD) [1]. It has been reported that CKD patients have a 20–30% higher prevalence of atheromatous plaques than matched controls with normal renal function, and this prevalence increases as CKD progresses [2,3]. CVD is a significant cause of mortality for patients with CKD before the development of end-stage kidney disease [4]. Therefore, cardiovascular risk management for patients with CKD is as important as treatment for the progression of CKD.

Among various CKD-related CVD risk factors [5,6], dyslipidemia remains one of the most important and classical risk factors. Low-density lipoprotein cholesterol (LDL-C) is one of the major causes of atherosclerosis, and statins are the standard treatment for dyslipidemia. However, even after adequately lowering LDL-C levels with statins, CVD

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events continue to occur with unacceptable frequency among CKD patients [7]. The effectiveness of statins to lower LDL-C in CKD patients with moderate to severe renal dysfunction is yet to be established, though statins have failed to show a significant effect on the prevention of CVD events in hemodialysis patients [8,9].

CKD influences lipoprotein metabolism, and CKD patients have unique lipid profile abnormalities [10]. It is well known that CKD patients frequently have hypertriglyceridemia (High-TG) and decreased high-density lipoprotein cholesterol (HDL-C) levels [11,12], and that heavy proteinuria is associated with increased LDL-C levels [13]. Patients with CKD have more progressive atherosclerosis than that seen in matched controls, despite the absence of hyper-LDL cholesterolemia (High-LDL-C) [14]. The residual risk remains extremely high [15], and careful management of residual risks associated with the CKD-specific lipid profile, such as High-TG and hypo-HDL cholesterolemia (Low-HDL-C), is required in this population. These residual lipid abnormalities are associated with increased small dense LDL and oxidized LDL [16,17], which may be atherogenic. An increased TG to HDL-C (High-TG/HDL-C) ratio was also reported to be a good predictor of increased small dense LDL, insulin resistance [18,19], and cardiovascular mortality [20,21]. Understanding CKD-specific dyslipidemia is important for the development of management protocols for CKD patients.

Few studies have investigated new-onset CKD-specific dyslipidemias in early CKD patients compared to the general population. We hypothesized that CKD patients were more likely to develop High-TG and Low-HDL-C or High-TG/HDL-C ratios, and these lipid abnormalities were associated with atherosclerosis and responsible for the residual risk for CVD in CKD patients. In this longitudinal study, we aimed to investigate the association between CKD and new-onset atherogenic dyslipidemia in Japanese patients.

2. Materials and methods

2.1. Study population

This longitudinal study utilized data from the Japanese Specific Health Check and Guidance System (J-SHC Study). All participants were between the ages of 40 and 74 years and voluntarily participated an annual health checkup between 2008 and 2014. This study was conducted in accordance with the Private Information Protection Law and ethical guidelines for epidemiology research published by the Japanese Ministry of Health, Labor and Welfare in 2008. The details of the health check-up system have been previously reported [22].

The exclusion criteria were as follows: missing data (such as health check-up date or baseline creatinine or proteinuria), only one health check during the study period, dyslipidemia at baseline, and the use of medication for dyslipidemia during the observational period. Dyslipidemias were defined as triglycerides (TG) ≥150 mg/dL, LDL-C ≥140 mg/dL, and/or HDL-C <40 mg/dL, according to the Japan Atherosclerosis Society guidelines [23]. We compared the rates of new-onset dyslipidemia between participants with and without CKD. In addition to investigating abnormalities in individual dyslipidemia components, we also evaluated the incidence of composite lipid abnormalities, including a High-TG/HDL-C ratio of equal to 3.5 or higher, which was based on a previous report by McLaughlin et al. [18].

CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or the presence of proteinuria evaluated via the dipstick test at baseline. The eGFR was calculated using the following equation:

$$\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{serum creatinine (mg/dL)}^{-1.094} \times \text{age (years)}^{-0.287} \times 0.739 \text{ (for women)}$$ [24].

The urinary protein excretion dipstick test included 5 categories: (−), (±), (1+), (2+), and (3+). Proteinuria was defined as (1+) or higher.

2.2. Measurements

During follow-up period (2008–2014), visits to the annual medical check-up program were completely voluntary. As such, each participant had different visit frequencies and intervals. All participants completed a self-administered questionnaire to document their medical history, current medications, smoking habit (smoker or non-smoker), alcohol consumption (daily drinker, social drinker, or non-drinker), regular exercise habits (more than 30 min at least two days a week or not), and daily walking habit (more than 1 h every day or not). The height and weight of the participants were measured, and their body mass index (BMI) was calculated. Blood pressure measurements and blood and urine sampling were performed at each participant's local medical institute after overnight fasting for more than 10 h, according to the health check program. In terms of lipid measurements, TG, HDL-C, and LDL-C were measured, but total cholesterol levels were not available in this study.

2.3. Statistical analysis

Continuous and categorical variables are presented as median and interquartile range and as total number and percentage, respectively. The Mann-Whitney *U* test was used to determine the differences between the CKD and non-CKD groups for continuous variables, and the Chi squared test was used for categorical variables. Standardized mean differences (SMD) were also calculated to evaluate differences between the groups.

The association between new-onset dyslipidemia (High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio) and baseline CKD status was analyzed using the Kaplan–Meier method (log-rank test) and Cox regression analyses. To compare the incidence rates between the groups, rate ratios (RRs) and 95% confidence intervals (95% CIs) were also calculated using Poisson regression analyses. For supported analysis, we also compared the risk of new-onset composite dyslipidemia (both TG ≥ 200 mg/dL and HDL-C <35 mg/dL) between participants with and without CKD. Based on the results of some studies, this subset is considered to be at high risk of CVD and would benefit from additional drug therapies other than statins [25,26]. Model results were estimated using four progressive sets of potential confounders: age and sex (Model 2); model 2 plus BMI, current smoking status, and alcohol consumption (Model 3); model 3 plus baseline TG, LDL-C, HDL-C, aspartate aminotransferase, alanine transaminase, fasting plasma glucose, and hemoglobin A1c (HbA1c) levels (Model 4); and model 4 plus exercise and daily walking habits (Model 5). To examine potential effect of each CKD definition component (decreased eGFR or the presence of proteinuria) on new-onset dyslipidemia, we analyzed the effects of each subcategory on the primary analysis. According to CKD guideline [27], eGFR stages were defined as "G1–2": ≥60, "G3a": 45–59, "G3b": 30–44 and "G4–5": <30. The association between new-onset dyslipidemia (High-TG, High-LDL-C, Low-HDL-C and High-TG/HDL-C ratio) and baseline eGFR stage or proteinuria status (presence or absence) was analyzed using the Kaplan–Meier method (log-rank trend test) and Cox regression analyses. In addition to clinically relevant confounders, alternative CKD definition components, eGFR stage, and proteinuria status were adjusted for Cox regression analyses of each CKD definition subcategory models.

Furthermore, we performed subgroup analyses to explore the consistency of the association between CKD and new onset of dyslipidemia for sex, age, BMI, HbA1c, alcohol consumption, exercise habits, and daily walking habits.

We also performed sensitivity analyses. Because HDL-C levels are reportedly affected by sex, we performed additional analysis defining Low-HDL-C as HDL-C <40 mg/dL for men and HDL-C <50 mg/dL for women. In addition to the main analyses, we examined hazard ratios for new-onset dyslipidemias, including participants who received lipid-lowering therapies during the observational period. Furthermore, because new onset of diabetes during the study period can influence on

Table 1
Baseline characteristics of participants according to CKD status.

	Non-CKD	CKD	*p*-value	SMD
N	242,147	47,315		
Age	63 [57, 68]	66 [61, 70]	<0.001	0.422
Male, n(%)	103,844 (42.9)	26,669 (56.4)	<0.001	0.272
Body mass index (kg/m^2)	22.7 [20.7, 24.9]	23.6 [21.5, 25.7]	<0.001	0.239
Waist circumference (cm)	83.0 [77.0, 89.0]	85.0 [79.5, 91.0]	<0.001	0.228
Systolic blood pressure (mmHg)	127 [116, 138]	130.00 [120, 140]	<0.001	0.217
Diastolic blood pressure (mmHg)	76 [70, 82]	78 [70, 84]	<0.001	0.179
AST (U/L)	22 [19,26]	23 [19,27]	<0.001	0.096
ALT (U/L)	18 [14,24]	19 [15,25]	<0.001	0.055
Fasting blood glucose (mg/dL) [c]	93 [87, 100]	95 [88, 103]	<0.001	0.163
HbA1c (%)	5.2 [5.0, 5.5]	5.2 [5.0, 5.5]	<0.001	0.129
TG (mg/dL) [c]	96 [69, 137]	106 [77, 150]	<0.001	0.135
HDL-C (mg/dL) [c]	61 [51, 72]	57 [48, 69]	<0.001	0.204
LDL-C (mg/dL) [c]	123 [104, 142]	124 [105, 143]	<0.001	0.046
Creatinine (mg/dL) [c]	0.7 [0.6, 0.8]	0.9 [0.8, 1.0]	<0.001	0.944
eGFR (ml/min/1.73m^2)	76.1 [68.9, 87.7]	56.6 [52.8, 59.4]	<0.001	1.458
Urine protein excretion			<0.001	0.904
(−) or (±)	242,147 (100.0)	33,590 (71.0)		
(1+)	0 (0.0)	9904 (20.9)		
(2+)	0 (0.0)	3032 (6.4)		
(3+)	0 (0.0)	789 (1.7)		
Current smoker, n(%)	36,647 (15.1)	6317 (13.4)	<0.001	0.051
Alcohol consumption, n(%)			<0.001	0.021
Daily drinker	59,025 (25.7)	11,853 (26.6)		
Social drinker	53,273 (23.2)	10,167 (22.8)		
Non drinker	117,251 (51.1)	22,491 (50.5)		
Medication for hypertension, n(%)	51,188 (21.1)	16,317 (34.5)	<0.001	0.301
Medication for diabetes, n(%)	6989 (2.9)	2407 (5.1)	<0.001	0.113
History of stroke, n(%)	5574 (2.4)	1881 (4.3)	<0.001	0.104
History of heart disease, n(%)	8928 (3.9)	2855 (6.6)	<0.001	0.119
Exercise habits, n(%) [a]	82,350 (41.0)	18,614 (49.1)	<0.001	0.163
Daily walking, n(%) [b]	101,050 (50.7)	19,917 (53.2)	<0.001	0.051

ALT, alanine aminotransferase; AST, aspartate transaminase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; SMD, standardized mean difference.

[a] Exercise habits, exercise habit of more than 30 min at least 2 days a week.

[b] Daily walking, daily walking for more than 1 h.

[c] Conversion factors to SI unit are as follows: fasting blood glucose x0.05551 mmol/L, TG x 0.01129 mmol/L, HDL-C x0.02586 mmol/L, LDL-C x0.02586 mmol/L, Creatinine x88.4 μmol/L.

lipid abnormalities, we also analyzed the incidence of dyslipidemias, excluding the participants who developed diabetes during the study period.

Statistical significance was defined as $p < 0.05$. In terms of interaction analyses, statistical significance was defined as $p < 0.1$. All statistical analyses were performed using R software version 3.6.1 (R Foundation, Vienna, Austria).

2.4. Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Fukushima Medical University; IRB Approval Number #1485, #2771) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was conducted according also to the Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted by the Ministry of Health, Labour and Welfare of Japan [http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000069410.pdf].

3. Results

3.1. Study participants

Of the 664,926 participants, 272,998 were excluded due to only having one observation or lacking data with regards to the CKD criteria (Supplemental Fig. 1). After excluding participants on lipid-lowering therapies or who received lipid-lowering therapies during the observational period, the remaining 289,462 participants were considered for analyses. Of the 102,466 participants excluded due to taking medication for dyslipidemia, 43,484 participants were excluded from the study due to the use of medication for dyslipidemia during the post-baseline observation period: 8955 participants with CKD (12.9%) and 34,529 participants without CKD (10.7%) ($p < 0.001$ for Chi-square test, SMD = 0.070). For the final analyses, 228,398, 208,960, 274,111, and 247,864, who did not have dyslipidemia at baseline, were included for new-onset High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio analysis, respectively. For the supported analysis to examine new-onset composite dyslipidemia (both TG ≥ 200 mg/dL and HDL-C <35 mg/dL), 287,326 participants were included.

3.2. Baseline differences between CKD and non-CKD participants

The mean number of visits to the check-up program was 3.6 and 3.7 times for participants with and without CKD, respectively. Forty-five percent of the study participants were males. The medians (interquartile ranges) of demographic and laboratory parameters were as follows: age, 64 (58–68) years; BMI, 22.8 (20.8–25.0) kg/m^2; eGFR, 74.7 (64.9–85.8) mL/min/1.73 m^2; TG, 97 (70–139) mg/dL; LDL-C, 123 (104–142) mg/dL; and HDL-C, 60 (50–72) mg/dL. The urinary protein dipstick test was (1+) in 3.4% of the participants, (2+) in 1.0%, and (3+) in 0.3%. The participants' baseline characteristics are shown in Table 1. The differences of each variable between the CKD and the non-CKD groups were all statistically significant due to the large sample size, but most of these differences did not appear to be clinically relevant. According to the SMD (>0.2), participants with CKD were more likely to be older, male, have a higher BMI, greater waist circumference, higher

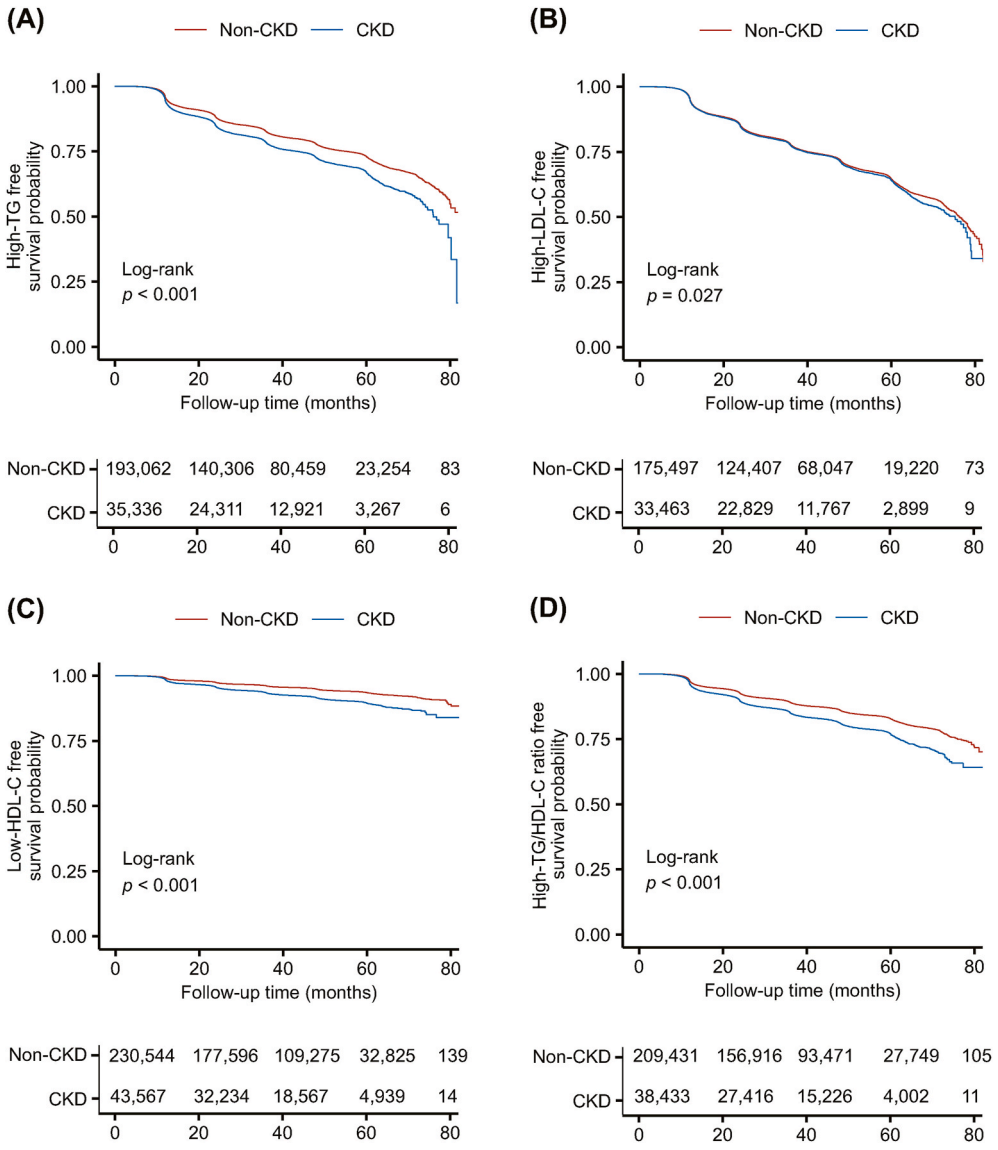

Fig. 1. Kaplan–Meier survival curves for each dyslipidemia onset between patients with and without CKD.
Survival curves for new onset of (A) High-TG, (B) High-LDL-C, (C) Low-HDL-C, and (D) High-TG/HDL-C ratio. CKD, chronic kidney disease; High-TG, hypertriglyceridemia; High-LDL-C, hyper-low-density lipoprotein cholesterolemia; Low-HDL-C, hypo-high-density lipoprotein cholesterolemia.

systolic blood pressure, lower HDL-C, and use hypertension medications compared to participants without CKD. The participants' baseline characteristics according to eGFR stage (G1-2, G3a, G3b, and G4-5) and proteinuria status (presence or absence of proteinuria) are shown in Supplemental Tables S1 and S2.

3.3. Incidence of dyslipidemias between CKD and non-CKD participants

During the median follow-up period of roughly 3 years, the incidence of a new-onset High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio was 64.4/1000 person-years, 83.1/1000 person-years, 14.5/1000 person-years, and 39.6/1000 person-years, respectively. The incidence of the composite dyslipidemia (TG $\geq$ 200 mg/dL and HDL-C <35 mg/dL) was only 2.9/1000 person-years. The incidence RRs (95% CIs) for High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio calculated by Poisson regression analysis were 1.27 (1.24–1.30), 1.02 (0.99–1.04), 1.67 (1.60–1.74) and 1.39 (1.35–1.43), respectively, in CKD participants as compared to non-CKD participants.

As shown in Fig. 1, the cumulative incidences of High-TG, Low-HDL-C, and High-TG/HDL-C ratio in participants with CKD were 29% (95% CI: 25–32%, $p < 0.001$; Figs. 1A), 68% (95% CI: 61–75%, $p < 0.001$; Fig. 1C), and 40% (95% CI: 36–44%, $p < 0.001$; Fig. 1D), higher than those without CKD. Although the cumulative incidence of new-onset High-LDL-C in participants with CKD was also significantly higher than those without CKD, the absolute difference was only 2% (95% CI 0–5%, $p = 0.027$; Fig. 1B), implying that the difference is not clinically relevant. Moreover, this small difference was not statistically significant in the fully adjusted Cox regression analysis (Table 2B). In contrast, the hazard ratios (HRs) of a new-onset High-TG, Low-HDL-C, and High-TG/HDL-C ratio in participants with CKD compared to those without CKD remained statistically significant even after adjustment for all confounders (HR 1.09, 95% CI 1.05–1.13 for High-TG; HR 1.12, 95% CI 1.05–1.18 for Low-HDL-C; HR 1.14, 95% CI 1.09–1.18 for High-TG/HDL-C ratio shown in Table 2A, C and D, respectively). In the supported analysis, the risks of new-onset the composite dyslipidemia of hypertriglyceridemia and hypo-HDL cholesterolemia (both TG $\geq$ 200 mg/dL and HDL-C <35 mg/dL) was significantly higher in participants with CKD than those without CKD (HR 1.20, 95% CI 1.06–1.36), after fully adjusting for relevant confounders (Supplemental Table S3).

Table 2
HRs and 95% CIs for incident (A) High-TG by CKD status and (B) High-LDL-C by CKD status, (C) Low-HDL-C by CKD status and (D) High-TG/HDL-C ratio (≥3.5) by CKD status.

(A)			
Model	HR (95% CI)		*p*-value
	Non-CKD	CKD	
1[a]	1 (Ref)	1.29 (1.25–1.32)	<0.001
2[b]	1 (Ref)	1.21 (1.18–1.24)	<0.001
3[c]	1 (Ref)	1.16 (1.13–1.19)	<0.001
4[d]	1 (Ref)	1.09 (1.06–1.13)	<0.001
5[e]	1 (Ref)	1.09 (1.05–1.13)	<0.001
(B)			
Model	HR (95% CI)		*p*-value
	Non-CKD	CKD	
1[a]	1 (Ref)	1.03 (1.00–1.05)	0.027
2[b]	1 (Ref)	1.05 (1.03–1.08)	<0.001
3[c]	1 (Ref)	1.03 (1.00–1.05)	<0.001
4[d]	1 (Ref)	0.98 (0.95–1.01)	0.16
5[e]	1 (Ref)	0.99 (0.96–1.02)	0.56
(C)			
Model	HR (95% CI)		*p*-value
	Non-CKD	CKD	
1[a]	1 (Ref)	1.68 (1.61–1.75)	<0.001
2[b]	1 (Ref)	1.42 (1.36–1.48)	<0.001
3[c]	1 (Ref)	1.31 (1.25–1.37)	<0.001
4[d]	1 (Ref)	1.13 (1.07–1.19)	<0.001
5[e]	1 (Ref)	1.12 (1.05–1.18)	<0.001
(D)			
Model	HR (95% CI)		*p*-value
	Non-CKD	CKD	
1[a]	1 (Ref)	1.40 (1.36–1.44)	<0.001
2[b]	1 (Ref)	1.29 (1.25–1.33)	<0.001
3[c]	1 (Ref)	1.23 (1.20–1.27)	<0.001
4[d]	1 (Ref)	1.15 (1.11–1.19)	<0.001
5[e]	1 (Ref)	1.14 (1.09–1.18)	<0.001

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; High-LDL-C, hyper-low-density lipoprotein cholesterol; High-TG, hypertriglyceridemia; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Low-HDL-C, hypo-high-density lipoprotein cholesterol; TG, triglycerides.

[a] Model 1, unadjusted model.

[b] Model 2, Model 1 + adjusted for age and sex.

[c] Model 3, Model 2 + adjusted for BMI, current smoking status and alcohol consumption.

[d] Model 4, Model 3 + adjusted for baseline TG, LDL-C, HDL-C, AST, ALT, fasting plasma glucose and HbA1c.

[e] Model 5, Model 4 + exercise habit of more than 30 min at least 2 days a week and daily walking for more than 1 h.

3.4. Subgroup analyses

In subgroup analyses, daily walking for more than an hour was found to decrease the risk of new-onset High-TG in participants with CKD (p for interaction = 0.07) (Fig. 2[A]). Age ≥64 years significantly increased the risk of new-onset Low-HDL-C in participants with CKD (p for interaction <0.01) (Fig. 2B). In addition, women were found to have an increased risk of a new-onset High-TG/HDL-C ratio in participants with CKD (p for interaction = 0.004), drinking habit (p for interaction = 0.009), and daily walking for more than an hour (p for interaction = 0.014) were found to decrease the risk of a new-onset High-TG/HDL-C ratio in participants with CKD (Fig. 2C).

To examine the impact of each CKD definition component (decreased GFR and presence of proteinuria) on new-onset dyslipidemias, we separately examined the incidence of new-onset dyslipidemias in participants with decreased GFR-dominant CKD and proteinuria-dominant CKD. The Kaplan-Meier survival curves show that higher category of eGFR stage (lower eGFR) was incrementally associated with greater risk of new-onset High-TG (log-rank trend $p < 0.001$), Low-HDL-C (log-rank trend $p < 0.001$), and High-TG/HDL-C ratio (log-rank trend $p < 0.001$), but there was weak association between eGFR stages and new-onset High-LDL-C (log-rank trend $p = 0.025$) (Supplemental Fig. 2). The presence of proteinuria was also associated with new-onset High-TG (log rank $p < 0.001$; Supplemental Fig. 3A), Low-HDL-C (log rank $p < 0.001$; Supplemental Fig. 3C), and High-TG/HDL-C ratio (log rank $p < 0.001$; Supplemental Fig. 3D). The difference in cumulative incidence of new-onset High-LDL-C between participants with and without CKD was also significant (log rank $p = 0.005$). However, this difference was small (−6.1%, 95% CI −10.2% to −1.9%) and was not clinically relevant (Supplemental Fig. 3B). These associations between CKD stages/proteinuria status and new-onset High-TG, Low-HDL-C, and High-TG/HDL-C ratio were mostly remained significant even after adjusting for alternative CKD definition component in fully adjusted cox model, suggesting decreased GFR and proteinuria were independently associated with these new-onset lipid abnormalities. The HRs for new-onset dyslipidemias associated with each CKD definition component (eGFR stages and proteinuria status) is shown in Table 3 (A-D). In terms of eGFR stage category, higher category of eGFR stage was incrementally associated with greater risk of new-onset Low-HDL. HR of CKD stage G4-5 (*vs.* G1-2) for new-onset Low-HDL-C was 2.20 (95% CI, 1.42–3.39) (Table 3C). However, the association between the highest CKD stage categories (G4-5) and new-onset High-TG or High-TG/HDL-C ratio appeared to be weaker (HRs *vs.* G1-2; 0.89, 95% CI; 0.62–1.28: HRs *vs.* G1-2; 1.13, 95% CI; 0.76–1.68, respectively) (Table 3A and D). In terms of proteinuria category, proteinuric participants had a significantly higher risk of a new-onset High-TG, Low-HDL, and High-TG/HDL ratio compared to non-proteinuric participants after adjusting for all relevant confounders. However, this association was not observed for new-onset High-LDL-C. HRs (95% CI) of proteinuria for new-onset High-TG, Low-HDL-C, and High-TG/HDL-C ratio were 1.15 (1.09–1.17), 1.14 (1.04–1.24), and 1.27 (1.19–1.35), respectively.

3.5. Sensitivity analysis

We performed additional analysis defining Low-HDL-C as HDL-C <40 mg/dL for men and HDL-C <50 mg/dL for women. The incidence of Low-HDL-C was 27.0/1000 person-years and rate ratio (95% CI) was 1.31 (1.26–1.35) in participants with CKD as compared to those without CKD. In Cox regression analyses, HRs (95% CIs) for Low-HDL-C were 1.32 (1.27–1.36); Model 1, 1.32 (1.27–1.36); Model 2, 1.24 (1.19–1.28); Model 3, 1.11 (1.06–1.16); Model 4, 1.10 (1.05–1.16); and Model 5 (fully adjusted model).

We also performed the sensitivity analyses, including participants who received lipid-lowering therapies during the observational period, and we obtained similar results. The fully adjusted HRs (95% CIs) of CKD vs non-CKD participants for High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio were 1.08 (1.05–1.11), 0.98 (0.95–1.01), 1.13 (1.08–1.19), and 1.11 (1.07–1.15), respectively.

In addition, the number of participants who developed diabetes during the study period in the analyses for High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio were 5236 (900 participants with CKD (2.5%) and 4336 participants without CKD (2.2%); $p < 0.001$ for Chi-square test; SMD = 0.031), 5156 (927 participants with CKD (2.8%) and 4229 participants without CKD (2.4%); $p < 0.001$ for Chi-square test; SMD = 0.040), 6587 (1176 participants with CKD (2.7%) and 5411 participants without CKD (2.3%); $p < 0.001$ for Chi-square test; SMD = 0.035), and 5722 (993 participants with CKD (2.6%) and 4729 participants without CKD (2.3%); $p < 0.001$ for Chi-square test; SMD = 0.032), respectively. When performing Cox regression analyses excluding the participants with new-onset diabetes during the

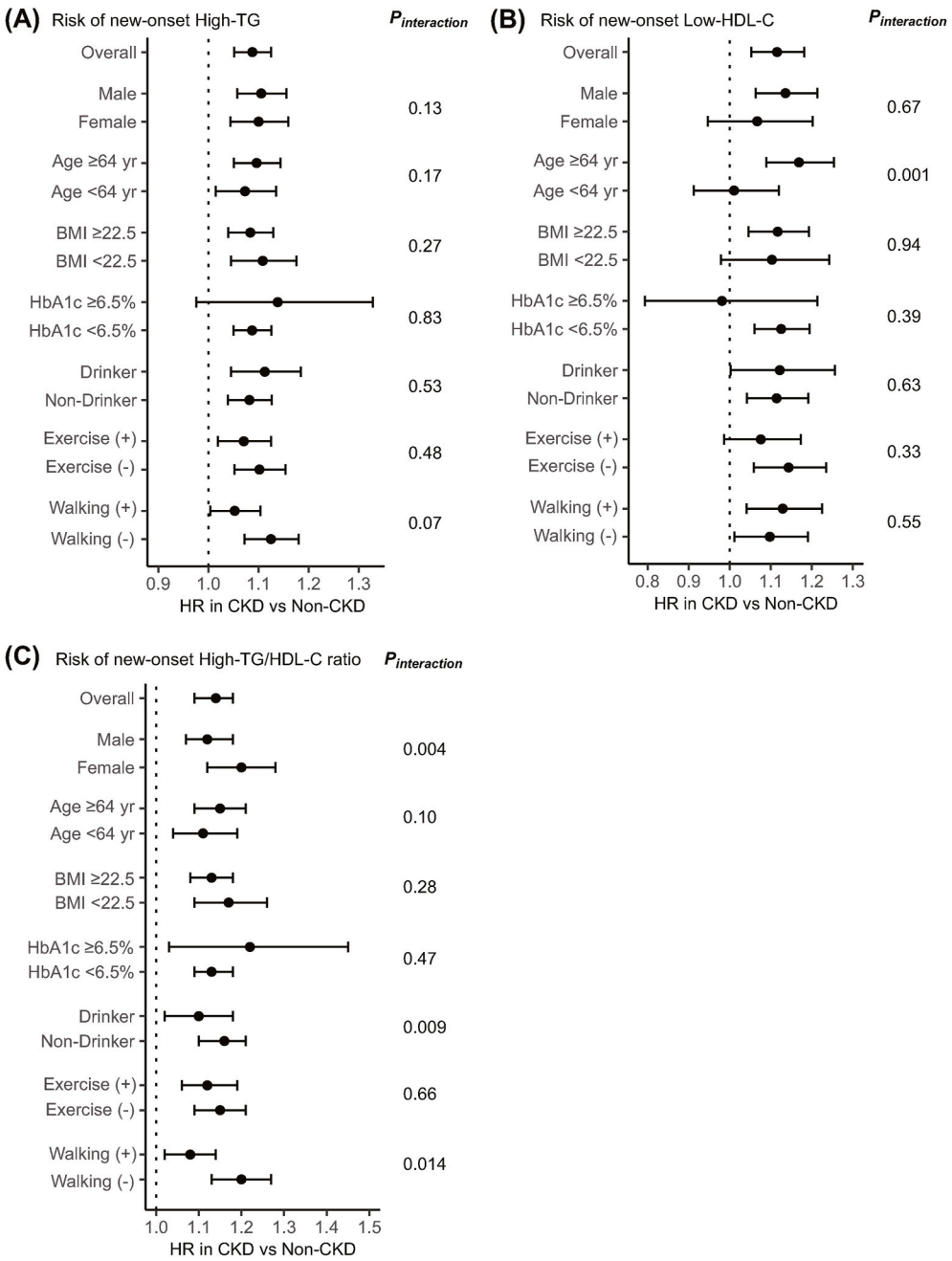

Fig. 2. Forest plot of the association between CKD and new onset of each dyslipidemia in relevant subpopulations.
Forest plot for (A) High-TG, (B) Low-HDL-C, and (C) High-TG/HDL-C ratio. Age and BMI were dichotomized based on the cohort median. Drinker represents participants who drank alcohol every day. Exercise represents an exercise habit of more than 30 min at least two days a week. Walking represents daily walking for more than 1 h. BMI, body mass index; CKD, chronic kidney disease; High-TG, hypertriglyceridemia; High-LDL-C, hyper-low-density lipoprotein cholesterolemia; HR, hazard ratio; Low-HDL-C, hypo-high-density lipoprotein cholesterolemia.

observational period, the fully adjusted HRs (95% CIs) of CKD vs non-CKD participants for High-TG, High-LDL-C, Low-HDL-C, and High-TG/HDL-C ratio were 1.09 (1.05–1.13), 0.99 (0.96–1.02), 1.11 (1.05–1.18), and 1.14 (1.09–1.19), respectively.

4. Discussion

In this large, community-based, longitudinal study, CKD was found to be associated with new-onset High-TG and Low-HDL-C, but not High-LDL-C. In addition, the risks of a new-onset High-TG/HDL-C ratio or composite dyslipidemia of hypertriglyceridemia and hypo-HDL cholesterolemia were higher in participants with CKD than those without CKD. To our knowledge, this is the first large cohort study investigating new-onset dyslipidemia in participants with early-stage CKD among general population. We also found that decreased eGFR (uremic toxin-driven dyslipidemia) and proteinuria (protein-driven dyslipidemia) were ~~equally~~ independently associated with a higher risk of new-onset lipid abnormalities.

It is well known that CKD patients frequently have metabolic dysregulation of lipoproteins, and this dysregulation is associated with CKD-specific dyslipidemia. Various mechanisms have been proposed for CKD-specific dyslipidemias, including an increase in apolipoprotein C-III in CKD patients and inhibition of the activity of lipoprotein lipase (LPL) [28,29]. Insulin resistance decreases LPL activity in patients with diabetic nephropathy [30]. As a result, the catabolism of chylomicrons and very-low-density lipoproteins are inhibited, and patients with CKD, especially those with diabetic nephropathy, are more likely to develop High-TG.

CKD is associated with various abnormalities in HDL metabolism which lead to low plasma HDL-C concentrations and dysregulation of HDL function, including reverse cholesterol transport [31]. In CKD patients, apolipoprotein (apo) A-I, which is a component of HDL capable of

Table 3
HRs and 95% CIs for incident (A) High-TG by status of eGFR and proteinuria, (B) High-LDL-C by status of eGFR and proteinuria, (C) Low-HDL-C by status of eGFR and proteinuria and (D) High-TG/HDL-C ratio (≥3.5) by status of eGFR and proteinuria.

(A)

Model	HR (95% CI)				HR (95% CI)	
	G1–2	G3a	G3b	G4–5	Proteinuria (−)	Proteinuria (+)
1[a]	1 (Ref)	1.21 (1.18–1.24)	1.39 (1.27–1.53)	1.28 (1.01–1.62)	1 (Ref)	1.39 (1.33–1.45)
2[b]	1 (Ref)	1.15 (1.11–1.18)	1.32 (1.20–1.45)	1.26 (0.99–1.60)	1 (Ref)	1.28 (1.23–1.34)
3[c]	1 (Ref)	1.13 (1.10–1.17)	1.29 (1.17–1.42)	1.26 (0.98–1.62)	1 (Ref)	1.17 (1.12–1.22)
4[d]	1 (Ref)	1.05 (1.01–1.09)	1.20 (1.06–1.36)	0.86 (0.61–1.22)	1 (Ref)	1.15 (1.09–1.22)
5[e]	1 (Ref)	1.04 (1.00–1.08)	1.21 (1.06–1.38)	0.89 (0.62–1.28)	1 (Ref)	1.15 (1.09–1.17)

(B)

Model	HR (95% CI)				HR (95% CI)	
	G1–2	G3a	G3b	G4–5	Proteinuria (−)	Proteinuria (+)
1[a]	1 (Ref)	1.06 (1.03–1.09)	0.96 (0.87–1.06)	0.83 (0.63–1.10)	1 (Ref)	0.94 (0.90–0.98)
2[b]	1 (Ref)	1.07 (1.04–1.10)	0.97 (0.87–1.07)	0.81 (0.61–1.06)	1 (Ref)	1.00 (0.96–1.05)
3[c]	1 (Ref)	1.04 (1.01–1.07)	0.92 (0.83–1.02)	0.82 (0.62–1.09)	1 (Ref)	0.98 (0.94–1.03)
4[d]	1 (Ref)	0.97 (0.93–1.00)	0.90 (0.79–1.02)	0.65 (0.41–1.02)	1 (Ref)	0.99 (0.94–1.05)
5[e]	1 (Ref)	0.98 (0.94–1.01)	0.97 (0.85–1.11)	0.61 (0.37–1.02)	1 (Ref)	0.99 (0.94–1.05)

(C)

Model	HR (95% CI)				HR (95% CI)	
	G1–2	G3a	G3b	G4–5	Proteinuria (−)	Proteinuria (+)
1[a]	1 (Ref)	1.49 (1.42–1.57)	2.41 (2.12–2.75)	2.37 (1.73–3.25)	1 (Ref)	1.77 (1.65–1.89)
2[b]	1 (Ref)	1.29 (1.23–1.35)	2.01 (1.81–2.35)	2.36 (1.72–3.24)	1 (Ref)	1.47 (1.37–1.57)
3[c]	1 (Ref)	1.21 (1.15–1.28)	1.82 (1.59–2.08)	2.39 (1.72–3.32)	1 (Ref)	1.32 (1.23–1.41)
4[d]	1 (Ref)	1.09 (1.02–1.16)	1.30 (1.09–1.55)	2.01 (1.35–2.99)	1 (Ref)	1.17 (1.08–1.27)
5[e]	1 (Ref)	1.08 (1.01–1.15)	1.28 (1.05–1.55)	2.20 (1.42–3.39)	1 (Ref)	1.14 (1.04–1.24)

(D)

Model	HR (95% CI)				HR (95% CI)	
	G1–2	G3a	G3b	G4–5	Proteinuria (−)	Proteinuria (+)
1[a]	1 (Ref)	1.27 (1.23–1.32)	1.47 (1.32–1.64)	1.47 (1.13–1.90)	1 (Ref)	1.58 (1.51–1.66)
2[b]	1 (Ref)	1.20 (1.16–1.24)	1.39 (1.25–1.55)	1.47 (1.13–1.90)	1 (Ref)	1.40 (1.33–1.47)
3[c]	1 (Ref)	1.18 (1.14–1.22)	1.34 (1.20–1.49)	1.56 (1.19–2.04)	1 (Ref)	1.26 (1.20–1.32)
4[d]	1 (Ref)	1.08 (1.03–1.13)	1.08 (0.94–1.25)	1.08 (0.75–1.56)	1 (Ref)	1.26 (1.19–1.34)
5[e]	1 (Ref)	1.06 (1.01–1.11)	1.07 (0.92–1.25)	1.13 (0.76–1.68)	1 (Ref)	1.27 (1.19–1.35)

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; High-LDL-C, hyper-low-density lipoprotein cholesterol; High-TG, hypertriglyceridemia; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Low-HDL-C, hypo-high-density lipoprotein cholesterol; TG, triglycerides.

[a] Model 1, alternative CKD definition component; eGFR stage or presence of proteinuria.

[b] Model 2, Model 1 + adjusted for age and sex.

[c] Model 3, Model 2 + adjusted for BMI, current smoking status and alcohol consumption.

[d] Model 4, Model 3 + adjusted for baseline TG, LDL-C, HDL-C, AST, ALT, fasting plasma glucose and HbA1c.

[e] Model 5, Model 4 + exercise habit of more than 30 min at least 2 days a week and daily walking for more than 1 h.

taking up the transported cholesterol and phospholipid from peripheral cells, is decreased due to impaired synthesis in the liver [32]. Decreased HDL-C levels in CKD patients are associated with low lecithin cholesterol acyltransferase (LCAT) activity [33,34]. LCAT is an enzyme that converts free cholesterol into cholesteryl ester and plays an important role in HDL maturation [35].

Although participants' lipid profile data were not available in our study, the high incidences of High-TG, Low-HDL-C, and High-TG/HDL-C ratio in patients with CKD in our study are compatible with previous reports. In additional analysis, composite dyslipidemia of TG ≥ 200 mg/dL and HDL-C <35 mg/dL was more likely to occur in CKD participants compared to non-CKD participants. It is well known that these lipid abnormalities are associated with diabetes (insulin resistance), increased small dense LDL, and a high risk for CVD [18,36,37]. Although the incidence of new-onset High-LDL-C was not increased in CKD participants compared to non-CKD participants in this study, the tendency for patients with CKD to have small dense LDL-C may explain the atherogenicity, and residual CVD risk in CKD patients and High-TG and Low-HDL-C should also be recognized as a potent CKD-related atherogenic factor. Although the management for these lipid abnormalities in CKD patients is a future issue, patients with both High-TG and Low-HDL-C were reported to benefit from additional drug therapies other than statins [25,26].

For CKD status, which includes decreased GFR and/or the presence of proteinuria, we separately examined the incidence of new-onset dyslipidemia in participants with decreased GFR-dominant CKD and proteinuria-dominant CKD. Typically, predominant lipoprotein phenotypes are type IV and III in reduced GFR-dominant CKD, and are type IIa, IIb, and IV in proteinuria-dominant CKD [10]. In our study, the presence of proteinuria was associated with a new-onset High-TG, Low-HDL-C, and increased TG/HDL-C ratio ≥3.5, even after adjustment for eGFR stage. In terms of reduced GFR, a lower GFR was incrementally associated with higher risk of new-onset Low-HDL-C even after adjustment for proteinuria. In contrast, the association between the highest CKD stage categories (G4-5) and a new-onset High-TG or High-TG/HDL-C ratio appeared to be weaker in the fully adjusted model, although we lacked substantial evidence to conclude this fact, especially considering the small number of advanced CKD stage population and multiple comparisons. The results may differ in participants with more advanced kidney disease, and further study is needed to confirm the relationship between advanced renal dysfunction and these new-onset dyslipidemias.

We also performed subgroup analyses to explore the associations between CKD and new-onset High-TG, Low-HDL-C, and High-TG/HDL-C ratio. We found that walking for more than 1 h each day may reduce the risk of new-onset High-TG associated with CKD, and elder age (≥64 years) may increase the risk of new-onset Low-HDL-C associated with CKD. We also found that male sex, drinking habit, and walking for more than 1 h each day were associated with a lower risk of a new-onset High-TG/HDL-C ratio in CKD participants compared to non-CKD participants. Several studies have reported that exercise is a potent stimulator of LPL activity [38,39], and brisk walking has also been shown to increase LPL activity and decrease plasma TG concentration [40]. Decreased LPL activity in CKD participants may be modified by daily walking. Although exercise habits did not significantly affect the incidence of new-onset dyslipidemia in this study, daily walking should be recommended to CKD patients to prevent the onset of High-TG. On the other hand, plasma HDL-C levels in adults have been reported to decrease with age in both men and women, and a major determinant of plasma HDL-C levels is reverse cholesterol transport [41]. Reverse cholesterol transport is influenced by age-sensitive factors, such as insulin resistance [41,42], inflammation [41,43], and reduced sex hormones [41]. Furthermore, alcohol consumption is reported to increase blood HDL-C levels via increased LPL activity and increased the transport rate of apo A-I and A-II [44,45]. Although the factors underpinning the interaction between age, sex, and alcohol consumption and CKD status are undetermined in this study, impairment of the reverse cholesterol transport of HDL, increased LPL activity, and/or increased apo A-I and A-II may play a role.

Our study is not without limitations. First, this is an observational study, and some potential confounders, including inflammatory diseases, metabolic disorders, and drugs associated with the development of dyslipidemia, may have been overlooked. In particular diabetes is associated with High-TG and Low-HDL-C, and new onset diabetes during the study period could be a confounder. Therefore, we added sensitivity analysis excluding participants who developed diabetes during the study period. We found that the differences in the proportions of participants with new-onset diabetes between the CKD group and the non-CKD group were statistically significant but not clinically relevant according to SMD, and we obtained the similar results as main ones. Second, we excluded participants who used medications for dyslipidemia at baseline and/or during the observation, as data regarding specific drug classes (for example, TG-lowering drugs or LDL-C-lowering drugs) were not available. This may be a source of selective bias because CKD status is generally indicative of statin treatment. In fact, 8955 participants with CKD (12.9%) and 34,529 participants without CKD (10.7%) were excluded from the analyses due to the use of medication for dyslipidemia during the post-baseline observation period ($p < 0.001$ for Chi-square test). However, participants in our study were basically general population, and most participants may not go to a hospital regularly for CKD treatment. We also performed the sensitivity analyses, including the participants who received lipid-lowering therapies during observational period, and we obtained the consistent results. Finally, we used the cutoff points of each dyslipidemia according to the Japanese guideline [23]. There are different cutoffs for the definition of lipid abnormalities or therapeutic target levels depending on community, society, and disease status, including that of CKD [46–49]. Differences regarding definitions and the treatment theories may affect our results and conclusions. However, participants in this study were from the general population who participated a nation-wide health check program and as such, the majority of them generally had normal renal function. Unlike studies from the regular outpatients (recruited participants from hospitals), most participants with CKD in this study did not go to hospitals regularly and did not receive lipid lowering therapies. In fact, the frequency of receiving lipid-lowering drugs at baseline or during the observational period between CKD and non-CKD participants was statistically different due to the exceptionally large sample size of this study. However, the SMD was small (0.135) and as such, the difference would not be clinically relevant. Considering sex differences in blood HDL-C levels, we performed the sensitivity analysis defining different cut-off of Low-HDL-C depending on sex (HDL-C <40 mg/dL for men and HDL-C <50 mg/dL for women), and we confirmed the consistent results.

In conclusion, CKD was associated with a higher risk of a new-onset High-TG, Low-HDL-C, and High-TG/HDL-C ratio but not High-LDL-C in the Japanese health check-up population. These CKD-specific abnormalities in lipid metabolism can explain the residual risk for CKD-related CVD, which is associated with more progressive and more prevalent atherosclerosis than CVD in the general population, despite the normalization of LDL-C levels using medications.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

Takaaki Kosugi: Research idea and study design, data acquisition, data Formal analysis/interpretation, statistical Formal analysis, Supervision, mentorship. **Masahiro Eriguchi:** Research idea and study design, data Formal analysis/interpretation, Supervision, mentorship. **Hisako Yoshida:** data acquisition. **Hikari Tasaki:** Research idea and study design. **Fumihiro Fukata:** Research idea and study design. **Masatoshi Nishimoto:** Research idea and study design. **Masaru Matsui:** Research idea and study design. **Ken-ichi Samejima:** Research idea and study design. **Kunitoshi Iseki:** data acquisition. **Shouichi Fujimoto:** data acquisition. **Tsuneo Konta:** data acquisition. **Toshiki Moriyama:** data acquisition. **Kunihiro Yamagata:** data acquisition. **Ichiei Narita:** data acquisition. **Masato Kasahara:** data acquisition. **Yugo Shibagaki:** data acquisition. **Masahide Kondo:** data acquisition. **Koichi Asahi:** data acquisition. **Tsuyoshi Watanabe:** data acquisition. **Kazuhiko Tsuruya:** data acquisition, data Formal analysis/interpretation, Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Appendix A. Supplementary data

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