

Association Between Chronic Kidney Disease and New-Onset Dyslipidemia: The Japan Specific Health Checkups (J-SHC) Study

Takaaki Kosugi ^a, Masahiro Eriguchi ^a, Hisako Yoshida ^b, Hikari Tasaki ^a, Fumihiro Fukata ^a, Masatoshi Nishimoto ^a, Masaru Matsui ^a, Ken-ichi Samejima ^a, Kunitoshi Iseki ^c, Shouichi Fujimoto ^c, Tsuneo Konta ^c, Toshiki Moriyama ^c, Kunihiro Yamagata ^c, Ichiei Narita ^c, Masato Kasahara ^c, Yugo Shibagaki ^c, Masahide Kondo ^c, Koichi Asahi ^c, Tsuyoshi Watanabe ^c, Kazuhiko Tsuruya ^{a,c}, The Japan Specific Health Checkups (J-SHC) Study

^a Department of Nephrology, Nara Medical University, Kashihara, Nara, Japan

^b Department of Medical Statistics, Osaka City University Graduate School of Medicine, Osaka, Osaka, Japan

^c Steering Committee of The Japan Specific Health Checkups (J-SHC) Study, Fukushima, Japan

Corresponding author: Masahiro Eriguchi, MD, PhD

Department of Nephrology, Nara Medical University

840 Shijo-cho, Kashihara, Nara 634-8521, Japan

Phone: +81-744-29-8865; Fax: +81-744-23-9913

E-mail: meriguci@gmail.com

Supplemental Table S1. Baseline characteristics of participants according to eGFR criteria.

	G1–2	G3a	G3b	G4–5	p-value	Avg.SMD
N	252,313	33,906	2,778	465		
Age	63 [57, 68]	67 [62, 70]	68 [64, 71]	68 [62, 71]	<0.001	0.384
Male, n (%)	110,032 (43.6)	18,591 (54.8)	1,638 (59.0)	252 (54.2)	<0.001	0.157
Body mass index (kg/m ²)	22.8 [20.8, 24.9]	23.4 [21.5, 25.5]	23.7 [21.7, 26.1]	23.7 [21.1, 25.9]	<0.001	0.159
Waist circumference (cm)	83.0 [77.0, 89.0]	85.0 [79.0, 90.0]	86.0 [80.0, 92.0]	85.5 [79.0, 91.5]	<0.001	0.164
Systolic blood pressure (mmHg)	127 [116, 138]	130 [119, 140]	130 [120, 142]	130 [121, 142]	<0.001	0.147
Diastolic blood pressure (mmHg)	76 [70, 82]	78 [70, 84]	78 [70, 84]	76 [70, 84]	<0.001	0.073
AST (U/L)	22 [19, 26]	23 [19, 27]	22 [19, 27]	20 [16, 24]	<0.001	0.146
ALT (U/L)	18 [14, 25]	18 [15, 24]	18 [14, 23]	15 [11, 21]	<0.001	0.163
Fasting blood glucose (mg/dL) [°]	93 [87, 101]	94 [88, 102]	95 [88, 104]	95 [88, 106]	<0.001	0.109
HbA1c (%)	5.2 [5.0, 5.5]	5.2 [5.0, 5.5]	5.2 [5.0, 5.6]	5.3 [5.0, 5.7]	<0.001	0.111
TG (mg/dL) [°]	96 [69, 138]	105 [76, 146]	114 [83, 162]	113 [85, 157]	<0.001	0.133
HDL-C (mg/dL) [°]	61 [51, 72]	58 [48, 69]	54 [45, 65]	52 [42, 65]	<0.001	0.267
LDL-C (mg/dL) [°]	123 [104, 142]	125 [107, 144]	122 [103, 140]	114 [94, 137]	<0.001	0.17
Creatinine (mg/dL) [°]	0.7 [0.6, 0.8]	1.0 [0.8, 1.0]	1.3 [1.1, 1.4]	2.3 [1.9, 3.6]	<0.001	1.913
eGFR (ml/min/1.73m ²)	76.1 [68.9, 87.7]	55.3 [52.8, 57.6]	42.0 [38.1, 43.2]	21.3 [12.0, 27.0]	<0.001	3.996
Urine protein excretion					<0.001	0.819
(-) or (±)	242,147 (96.0)	31,303 (92.3)	2,100 (75.6)	187 (40.2)		
(1+)	7,734 (3.1)	1,744 (5.1)	335 (12.1)	91 (19.6)		
(2+)	1,984 (0.8)	688 (2.0)	245 (8.8)	115 (24.7)		
(3+)	448 (0.2)	171 (0.5)	98 (3.5)	72 (15.5)		

Current smoker, n (%)	38,979 (15.5)	3,610 (10.6)	319 (11.5)	56 (12.1)	<0.001	0.075
Alcohol consumption, n (%)					<0.001	0.103
Daily drinker	62,097 (26.0)	8,100 (25.3)	596 (22.6)	85 (20.1)		
Social drinker	55,540 (23.2)	7,271 (22.7)	539 (20.4)	90 (21.3)		
Non-drinker	121,375 (50.8)	16,614 (51.9)	1,506 (57.0)	247 (58.5)		
Medication for hypertension, n (%)	54,874 (21.8)	10,811 (31.9)	1,510 (54.4)	310 (66.8)	<0.001	0.572
Medication for diabetes, n (%)	7,800 (3.1)	1,296 (3.8)	237 (8.5)	63 (13.6)	<0.001	0.228
History of stroke, n (%)	5,920 (2.5)	1,294 (4.1)	206 (8.1)	35 (8.5)	<0.001	0.162
History of heart disease, n (%)	9,438 (4.0)	2,026 (6.5)	270 (10.6)	49 (12.0)	<0.001	0.175
Exercise habits, n (%)	85,737 (41.0)	14,024 (52.0)	1,075 (49.9)	128 (35.2)	<0.001	0.201
Daily walking, n (%)	105,170 (50.6)	14,487 (54.5)	1,133 (53.8)	177 (49.2)	<0.001	0.064

^a Exercise habits, exercise habit of more than 30 minutes at least 2 days a week

^b Daily walking, daily walking for more than 1 hour.

^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 umol/L.

Abbreviations: 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;

Avg.SMD, average standardized mean difference.

Supplemental Table S2. Baseline characteristics of participants according to proteinuria status.

	Proteinuria (-)	Proteinuria (+)	<i>p</i> -value	SMD
N	275,737	13,725		
Age	64 [58, 68]	65 [58, 69]	<0.001	0.101
Male, n (%)	121,871 (44.2)	8,642 (63.0)	<0.001	0.383
Body mass index (kg/m ²)	22.8 [20.8, 24.9]	24.1 [21.8, 26.6]	<0.001	0.368
Waist circumference (cm)	83.2 [77.3, 89.0]	86.5 [80.2, 93.0]	<0.001	0.35
Systolic blood pressure (mmHg)	127 [116, 138]	134 [122, 146]	<0.001	0.416
Diastolic blood pressure (mmHg)	76 [70, 82]	80 [70, 87]	<0.001	0.34
AST (U/L)	22 [19, 26]	23 [19, 29]	<0.001	0.203
ALT (U/L)	18 [14, 24]	20 [15, 29]	<0.001	0.223
Fasting blood glucose (mg/dL) ^c	93 [87, 100]	97 [90, 111]	<0.001	0.403
HbA1c (%)	5.2 [5.0, 5.5]	5.3 [5.0, 5.7]	<0.001	0.333
TG (mg/dL) ^c	97 [70, 138]	110 [77, 162]	<0.001	0.225
HDL-C (mg/dL) ^c	60 [51, 72]	56 [47, 68]	<0.001	0.212
LDL-C (mg/dL) ^c	123 [104, 142]	122 [102, 142]	0.001	0.027
Creatinine (mg/dL) ^c	0.7 [0.6, 0.8]	0.8 [0.6, 0.9]	<0.001	0.345
eGFR (ml/min/1.73m ²)	75.0 [65.1, 85.9]	72.6 [59.4, 83.6]	<0.001	0.286
Urine protein excretion			<0.001	1.783
(-) or (±)	275,737 (100.0)	0 (0.0)		
(1+)	0 (0.0)	9,904 (72.2)		
(2+)	0 (0.0)	3,032 (22.1)		
(3+)	0 (0.0)	789 (5.7)		
Current smoker, n (%)	40,058 (14.5)	2,906 (21.2)	<0.001	0.174
Alcohol consumption, n (%)			<0.001	0.141
Daily drinker	66,912 (25.6)	3,966 (31.2)		
Social drinker	60,386 (23.1)	3,054 (24.0)		
Non-drinker	134,032 (51.3)	5,710 (44.9)		
Medication for hypertension, n (%)	61,813 (22.4)	5,692 (41.5)	<0.001	0.417
Medication for diabetes, n (%)	8,166 (3.0)	1,230 (9.0)	<0.001	0.255
History of stroke, n (%)	6,861 (2.6)	594 (4.7)	<0.001	0.109
History of heart disease, n (%)	10,947 (4.2)	836 (6.6)	<0.001	0.106
Exercise habits, n (%) ^a	96,271 (42.3)	4,693 (42.0)	0.542	0.006
Daily walking, n (%) ^b	115,427 (51.1)	5,540 (49.9)	0.013	0.024

^a Exercise habits, exercise habit of more than 30 minutes at least 2 days a week

^b Daily walking, daily walking for more than 1 hour.

^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 umol/L.

Abbreviations: 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.

Supplemental Table S3. HRs for new-onset of composite dyslipidemia (both TG \geq 200 mg/dL and HDL-C $<$ 35 mg/dL).

Model	HR (95% CI)		<i>p</i> -value
	Non-CKD	CKD	
1 ^a	1 (Ref)	1.93 (1.77–2.11)	$<$ 0.001
2 ^b	1 (Ref)	1.67 (1.53–1.82)	$<$ 0.001
3 ^c	1 (Ref)	1.53 (1.39–1.68)	$<$ 0.001
4 ^d	1 (Ref)	1.19 (1.06–1.33)	0.004
5 ^e	1 (Ref)	1.20 (1.06–1.36)	0.005

^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.

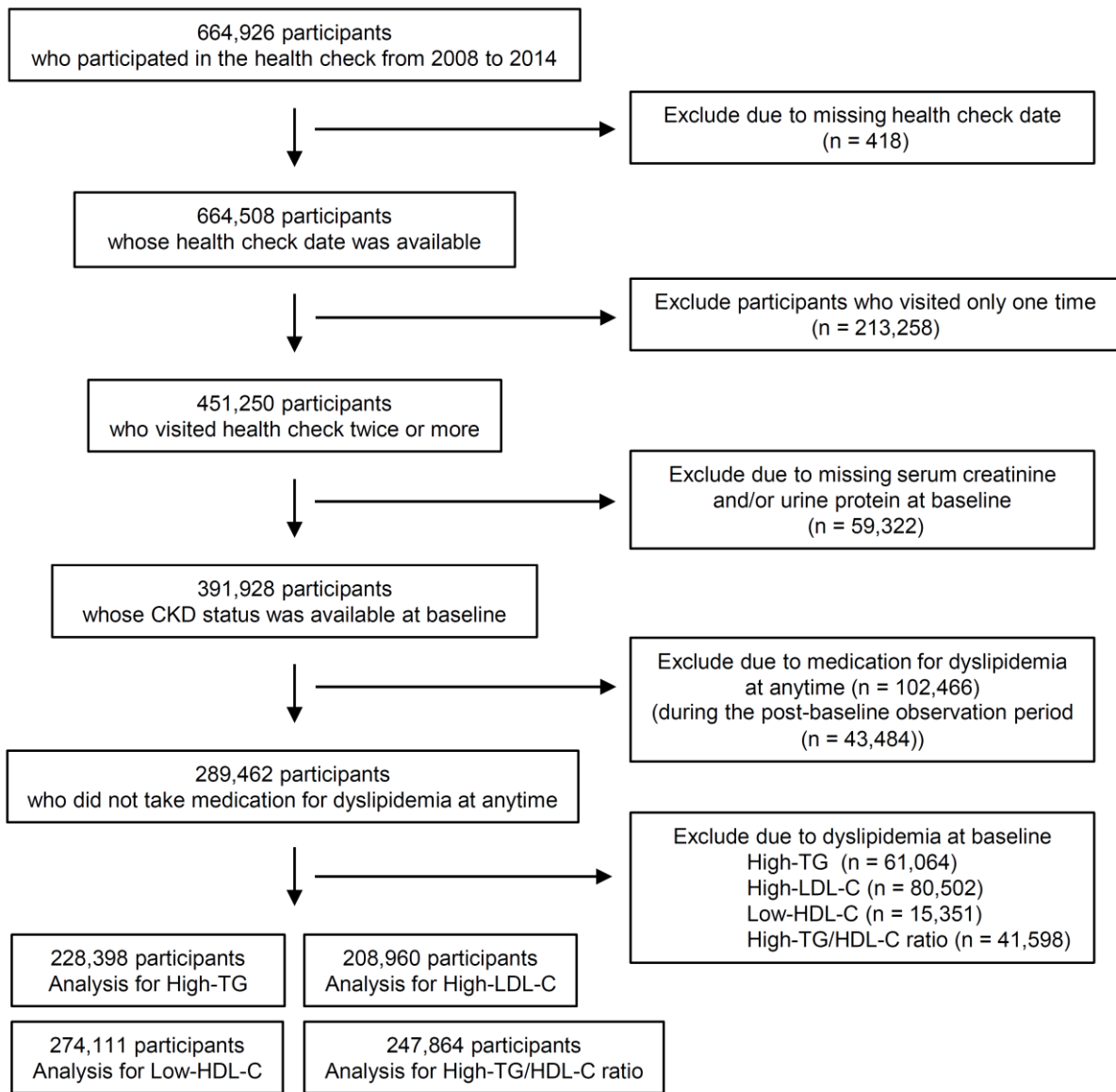
^e Model 5, Model 4 + exercise habit of more than 30 minutes at least 2 days a week and daily walking for more than 1 hour.

Abbreviations: 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.

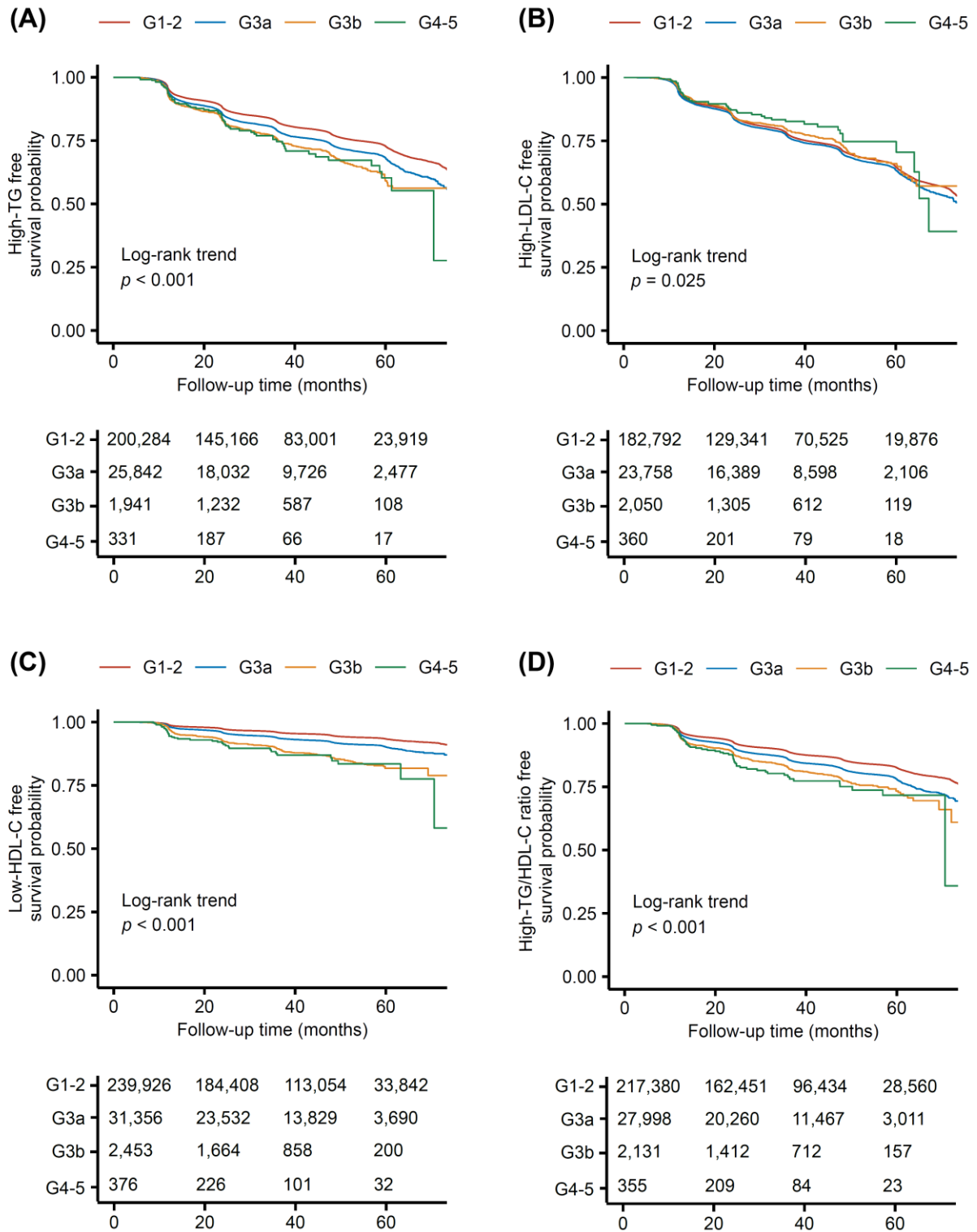
supplemental figures

Supplemental Fig. 1. Flowchart of study participants.



Abbreviations: High-TG, hypertriglyceridemia; High-LDL-C, hyper-low-density lipoprotein cholesterolemia; Low-HDL-C, hypo-high-density lipoprotein cholesterolemia.

Supplemental Fig. 2. Kaplan–Meier survival curves for each dyslipidemia onset among patients stratified by eGFR stage.

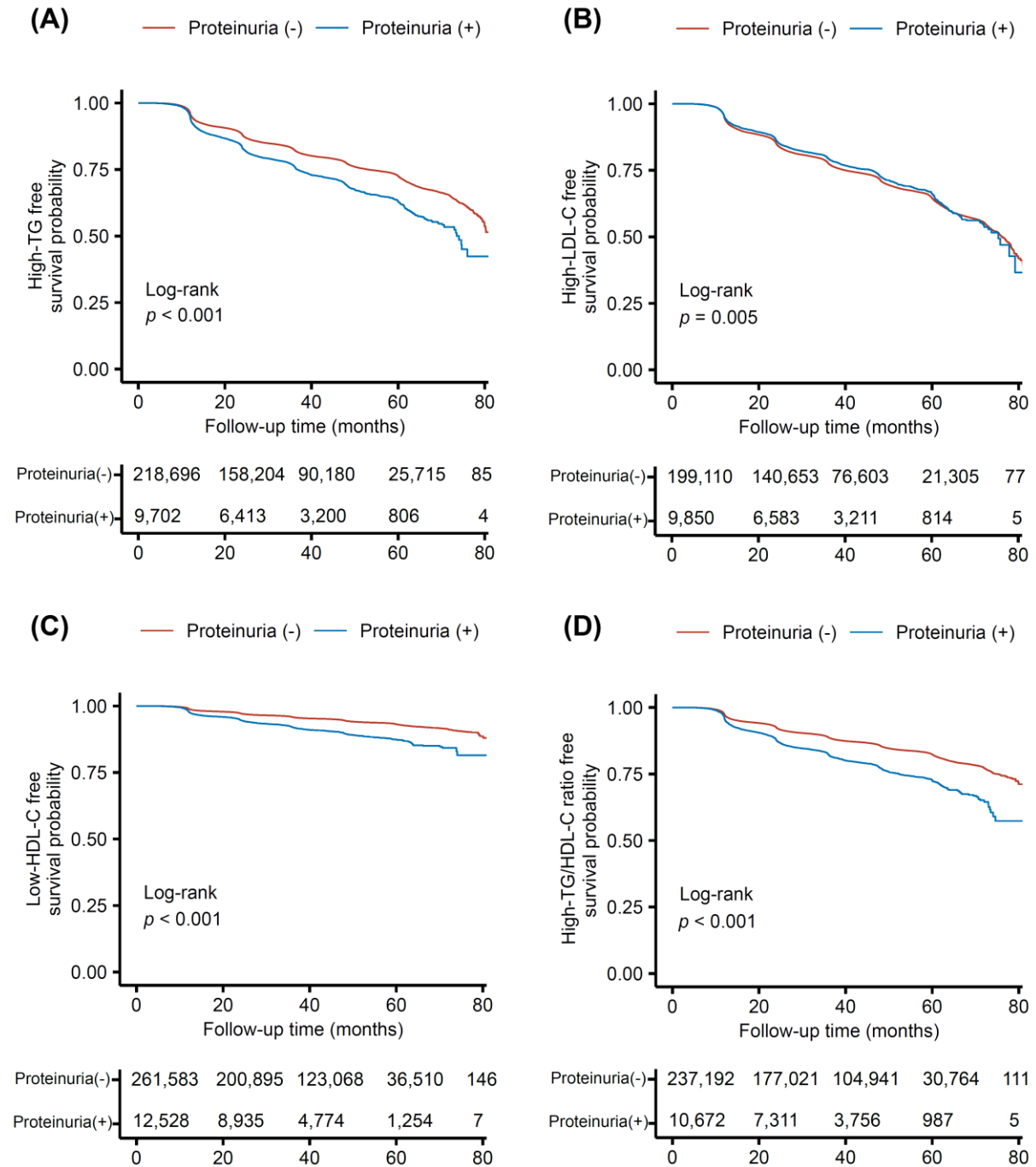


A figure shows the survival curves for new onset of (A) High-TG, (B) High-LDL-C, (C)

Low-HDL-C, (D) High-TG/HDL-C ratio. eGFR stages were defined as “G1–2”: ≥ 60 , “G3a”:
45–59, “G3b”: 30–44 and “G4–5”: < 30 .

Abbreviations: eGFR, estimated glomerular filtration rate; High-TG, hypertriglyceridemia;
High-LDL-C, hyper-low-density lipoprotein cholesterolemia; Low-HDL-C, hypo-high-
density lipoprotein cholesterolemia.

Supplemental Fig. 3. Kaplan–Meier survival curves for each dyslipidemia onset between patients with and without proteinuria.



A figure shows the survival curves for new onset of (A) High-TG, (B) High-LDL-C, (C) Low-HDL-C, (D) High-TG/HDL-C ratio.

Abbreviations: High-TG, hypertriglyceridemia; High-LDL-C, hyper-low-density lipoprotein cholesterolemia; Low-HDL-C, hypo-high-density lipoprotein cholesterolemia.