

# Serum Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is Independently Associated with Insulin Resistance, Triglycerides, Lipoprotein(a) Levels but not Low-Density Lipoprotein Cholesterol Levels in a General Population

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**Aim:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been identified as an important regulator of low-density lipoprotein (LDL) receptor processing. Evolocumab and alirocumab are PCSK9 inhibitors; however, little is known about the association between PCSK9 levels and lipid profiles in a general population. Because PCSK9 inhibitors have LDL-C lowering effects, we investigated whether there is a positive correlation between serum PCSK9 levels and LDL-C or lipoprotein(a) [Lp(a)].

**Methods:** In Uku town, 674 residents (mean age;  $69.2 \pm 8.3$  years) received health check-ups. The participants underwent a physical examination and blood tests, including PCSK9 and Lp(a). Serum PCSK9 and Lp(a) were measured by ELISA and Latex methods, respectively. HOMA-IR was calculated by fasting plasma glucose  $\times$  insulin levels/405.

**Results:** The mean (range) of PCSK9 and Lp(a) were 211.2 (49-601) ng/mL and 60 (1-107) mg/dL, respectively. Because of a skewed distribution, the log-transformed values were used. With univariate linear regression analysis, PCSK9 levels were associated with Lp(a) ( $p=0.028$ ), triglycerides ( $p<0.001$ ), and HOMA-IR ( $p<0.001$ ), but not with LDL-C ( $p=0.138$ ) levels. Multiple stepwise regression analysis revealed that serum PCSK9 levels were independently associated with triglycerides ( $p<0.001$ ), Lp(a) ( $p=0.033$ ) and HOMA-IR ( $p=0.041$ ).

**Conclusions:** PCSK-9 is independently associated with triglycerides, Lp(a) levels, and HOMA-IR, but not LDL-C, in a relatively large general population sample.

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**Key words:** Proprotein convertase subtilisin/kexin type 9 (PCSK9), Insulin resistance, Lipoprotein(a), Epidemiology

## Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the proprotein convertase family, is produced mainly by the liver and released directly into the circulation, playing a major role in regulating blood levels of low-density lipoprotein cholesterol (LDL-C). It binds with LDL-receptor (LDL-R) on hepatocytes, preventing their recycling and pro-

moting their degradation through the endosomal/lysosomal pathway<sup>1</sup>.

Data from clinical, *in vivo*, *in vitro*, and animal studies have associated PCSK9 with triglycerides<sup>2</sup>, triglycerides-rich lipoproteins<sup>3</sup>, high-density lipoprotein cholesterol (HDL-C)<sup>4</sup>, insulin, and insulin resistance<sup>5, 6</sup>. Studies on the relationship between PCSK9 and the components of metabolic syndrome have been reported; however, the results are inconsistent<sup>7, 8</sup>.

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Although evidence has been also presented in epidemiological studies<sup>2, 9</sup>), lipoprotein(a) [Lp(a)] has been highlighted as a novel risk factor for coronary artery disease (CAD) rather than PCSK9<sup>10</sup>). The positive association between PCSK9 and Lp(a) was reported in relatively small studies<sup>11, 12</sup>); however, these studies enrolled patients, but not the general population. Although PCSK9 inhibitors have been already approved as evolocumab and alirocumab<sup>13-17</sup>), little is known about the association between serum PCSK9 levels and lipid profiles, including Lp(a), in a general population. Therefore, in the present study, we examined the association between serum PCSK9 levels and lipid profiles, including Lp(a) levels and insulin resistance, in a general population.

## Methods

### Study Population

The present study enrolled 674 subjects (296 males and 378 females: aged over 40 years), who received a population-based health examination in Uku town, a fishing community in southwestern Japan, between 2017 and 2019. This town is an isolated island in Sasebo city, located in Nagasaki prefecture, and the total population is about 2,100. While the subjects' demographic backgrounds are similar to other Nagasaki prefecture residents, their diets and lifestyles differ slightly. Because this community is a typical island of fishermen, fish and shellfish are their main sources of protein. A detailed content of the recent survey in the same district was described previously<sup>18, 19</sup>).

### Data Collection

Medical histories, including the presence of heart diseases (angina pectoris, myocardial infarction, and arrhythmia), as well as other diseases, such as valvular diseases and stroke (cerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage), and medication data of lipid-lowering drugs were obtained. Height and weight were measured, and body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (square meters) as an index of the presence or absence of obesity. Waist circumference was measured at the level of the umbilicus in a standing position. Blood pressure (BP) was measured twice with the subjects in the sitting (first) and supine (second) position. The subjects were advised to avoid vigorous physical activity and smoking for at least 30 minutes before BP measurements. The second BP, with the fifth phase diastolic pressure, was used for analysis. Blood was drawn from the antecubital vein for lipid profiles (total cholesterol, LDL-C, HDL-C,

triglycerides, and lipoprotein(a) [Lp(a)]), liver functions (aspartate transaminase [AST], alanine transaminase [ALT], and  $\gamma$ -glutamyl transferase [ $\gamma$ -GTP]), creatinine, uric acid, fasting plasma glucose (FPG), insulin, and glycated hemoglobin A<sub>1c</sub> [HbA<sub>1c</sub> (NGSP)] in the morning after 12-hour fasting. Fasting blood samples were centrifuged within one hour of collection. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation, modified with a Japanese coefficient<sup>20</sup>. HOMA-IR was calculated from FPG and insulin levels [FPG (mg/dl)  $\times$  insulin ( $\mu$ U/ml)/405] as a marker of insulin resistance<sup>21</sup>), which was defined as HOMA  $\geq$  1.73, according to the diagnostic criteria used in Japan<sup>22-24</sup>). Serum Lp(a) was measured by latex immunoassay (LIA) method<sup>25</sup>). PCSK9 was measured by ELISA<sup>26</sup>). Intra- and inter-assay coefficients of variation of PCSK9 in the commercially available laboratory (SRL inc. Laboratory, Fukuoka, Japan) were 7.6% and 7.8%, respectively.

### Statistical Analysis

Because of skewed distributions, the natural logarithmic transformation was performed for Lp(a), insulin, HOMA index, and triglycerides. Mean values, and upper and lower 95% confidence limits, were exponentiated and presented as geometric mean  $\pm$  standard deviation (SD), where the SD was approximated as the difference of the exponentiated confidence limits divided by 3.92, the number of SD in a 95% confidence interval for normally distributed data. Chi-square tests were used to evaluate categorical parameters. Uni- and multiple linear regression analyses, adjusted for age and sex, were used. Using some significant factors from multivariate linear regression analysis, adjusted for age and sex, we performed the multiple stepwise regression analysis to determine the strength and independence of serum PCSK9 levels. We eventually re-analyzed data to examine the association between PCSK9 and parameters for participants, with or without medication for dyslipidemia, using multiple linear regression analysis.

*P*-values  $< 0.05$  were considered statistically significant. All statistical analyses were performed using the SAS system (Release 9.4, SAS Institute, Cary, NC, USA).

### Ethical Considerations

The mayor and the welfare section of Uku town and the Ethical Committee of Kurume University (No. 2284) approved this study. All participants gave informed consent.

**Table 1.** Demographics of study subjects

	Total (N=674)	Male (N=296)	Female (N=378)	p-value
Age, years	69.2 ± 8.3	69.5 ± 7.8	68.9 ± 8.8	0.334
Body mass index, kg/m <sup>2</sup>	23.7 ± 3.6	24.1 ± 3.3	23.4 ± 3.8	0.015
Waist circumference, cm	85.0 ± 9.8	86 ± 9.7	84.2 ± 9.9	0.015
Systolic blood pressure, mmHg	138.1 ± 18.8	138.2 ± 17.9	138 ± 19.5	0.862
Diastolic blood pressure, mmHg	76.4 ± 10.4	78.1 ± 10.7	75.2 ± 10.1	<0.001
Aspartate transaminase, U/L	24.9 ± 11.7	26.5 ± 15.3	23.7 ± 7.5	0.004
Alanine transaminase, U/L	20.2 ± 10.8	22.4 ± 12.4	18.5 ± 8.9	<0.001
γ-glutamyl transferase, U/L	37.6 ± 58.0	50.6 ± 79.7	27.4 ± 28	<0.001
Estimated GFR, ml/min/1.73 m <sup>2</sup>	70.2 ± 16.6	71.1 ± 16.7	69.5 ± 16.5	0.220
Triglycerides <sup>†</sup> , mg/dL (range)	85.7 (28-860)	91.3 (29-860)	81.6 (28-550)	0.003
Total cholesterol, mg/dL	197.1 ± 34.4	186.4 ± 31.5	205.6 ± 34.2	<0.001
HDL-cholesterol, mg/dL	65.9 ± 17.4	61.6 ± 18.6	69.4 ± 15.6	<0.001
LDL-cholesterol, mg/dL	112.2 ± 29.4	104.4 ± 26.4	118.4 ± 30.2	<0.001
Lipoprotein(a) <sup>†</sup> , mg/dl (range)	6.0 (1-107)	4.8 (1-75)	7.2 (1-107)	<0.001
PCSK9 <sup>†</sup> , ng/mL (range)	211.2 (49-601)	212 (96-601)	210.6 (49-520)	0.789
HOMA-IR <sup>†</sup> (range)	0.95 (0.19-19.01)	1.10 (0.19-19.01)	0.90 (0.2-5.77)	<0.001
Hemoglobin A <sub>1c</sub> , % (NGSP)	5.7 ± 0.4	5.7 ± 0.5	5.7 ± 0.4	0.217
Hs-CRP <sup>†</sup> , mg/dL (range)	0.04 (0-6.45)	0.06 (0-6.45)	0.04 (0-1.16)	<0.001
Alcohol intake, %yes	316 (46.9)	215 (72.6)	101 (26.7)	<0.001
Current smoking, %yes	63 (9.3)	58 (19.6)	5 (1.3)	<0.001
History of hypertension, %yes	422 (62.6)	201 (67.9)	221 (58.5)	0.012
History of diabetes, %yes	80 (11.9)	47 (15.9)	33 (8.7)	0.006
History of dyslipidemia, %yes	342 (50.6)	124 (41.9)	218 (57.7)	<0.001
Medication for dyslipidemia, %yes	251 (37.2)	99 (33.4)	152 (40.2)	0.076
History of heart disease, %yes	139 (20.6)	74 (25.0)	65 (17.2)	0.015
History of stroke, %yes	31 (4.6)	14 (4.7)	17 (4.5)	0.004

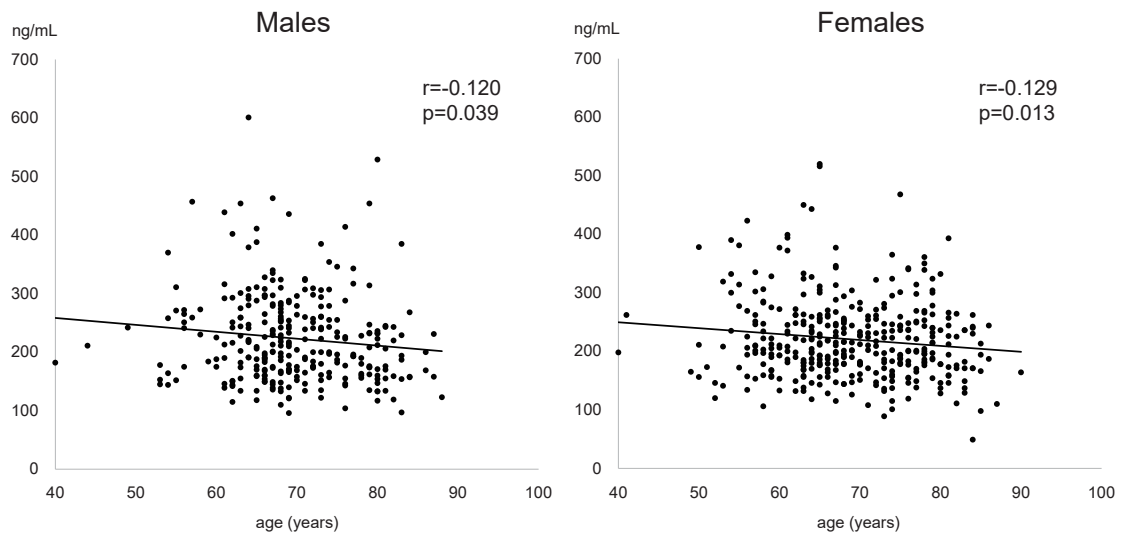
<sup>†</sup>: The variable was represented in the original scale after analysis using log (natural) transformed values.

## Results

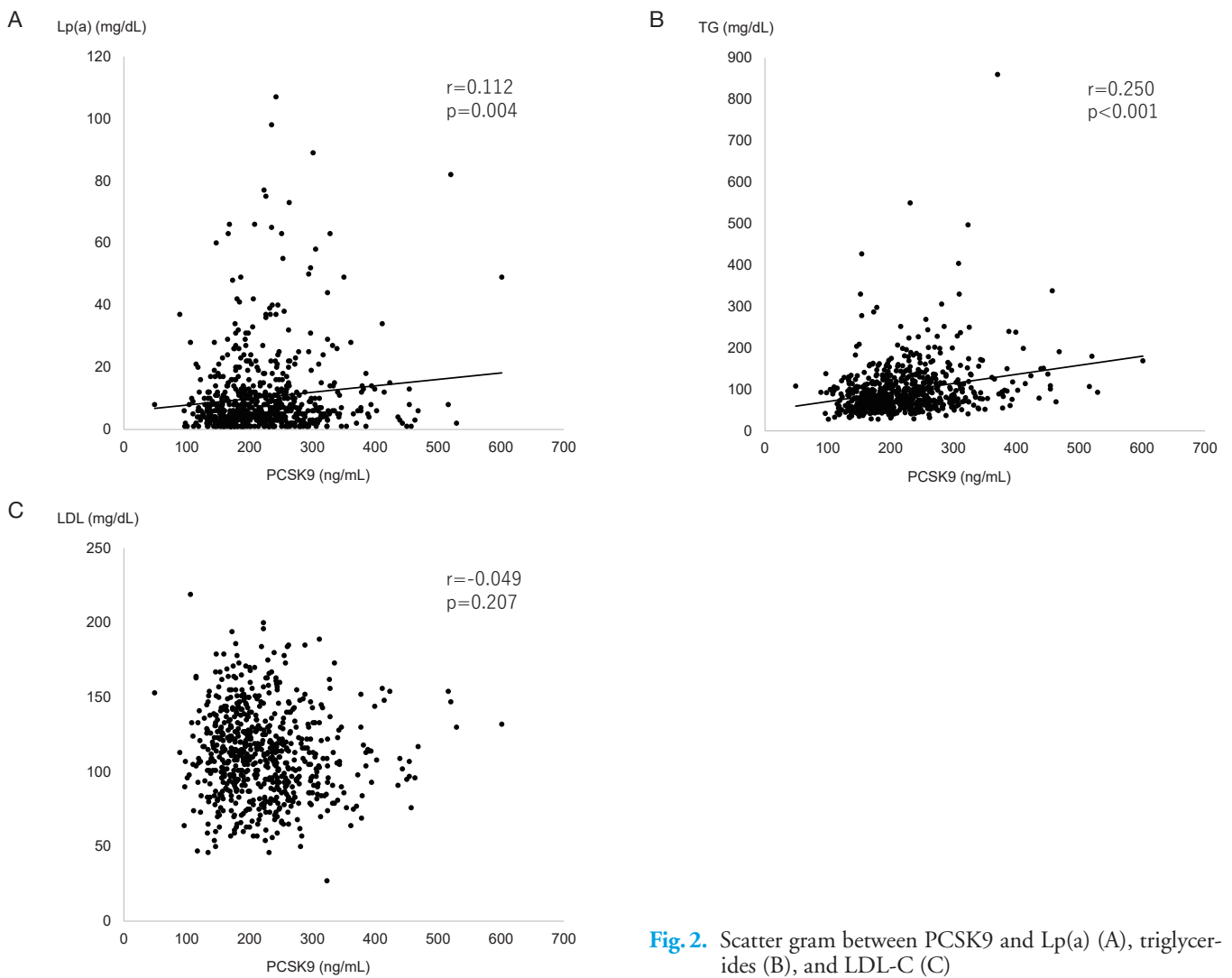
The 674 subjects' characteristics are presented in **Table 1**. There was no significant gender difference ( $p=0.789$ ) in serum PCSK9 levels. **Fig. 1** shows scatter gram of PCSK9 with age by gender. PCSK9 was significantly and inversely correlated with age in both genders. Also, a scatter gram of PCSK9 indicated significant correlation with Lp(a) (**Fig. 2A**) and triglycerides (**Fig. 2B**), but not with LDL-C (**Fig. 2C**). **Table 2** presents the results of uni- and multivariate analyses, adjusted for age and sex, for correlates of PCSK9 levels. With univariate linear regression analysis, PCSK9 levels were associated with BMI ( $p=0.004$ ), waist circumference ( $p=0.005$ ), systolic BP ( $p=0.013$ ), Lp(a) ( $p=0.028$ ), triglycerides ( $p<0.001$ ), HOMA-IR ( $p<0.001$ ), hemoglobin A<sub>1c</sub> ( $p<0.001$ ), hs-CRP ( $p=0.005$ ), and medication for dyslipidemia ( $p<0.001$ ), but not with LDL-C ( $p=0.138$ ). Multivariate linear regression analysis, after adjustment for age, sex, and medication for dyslipidemia, showed that the significances of these factors, except for BMI, remained.

Multiple stepwise regression analysis revealed that serum PCSK9 levels were independently associated with medication for dyslipidemia ( $p<0.001$ ), triglycerides ( $p<0.001$ ), age ( $p<0.001$ ; inversely), γ-GTP ( $p=0.003$ ), systolic BP ( $p=0.007$ ), Lp(a) ( $p=0.033$ ), hemoglobin A<sub>1c</sub> ( $p=0.033$ ), and HOMA-IR ( $p=0.041$ ) (**Table 3**).

We further analyzed the data to examine the association between PCSK9 and parameters for participants without medication for dyslipidemia using multiple linear regression analysis. **Supplementary Table 1** demonstrated univariable and multivariable linear regression analyses for correlates of serum PCSK9 level without lipid-lowering medication subjects ( $n=422$ ). With multivariate analysis adjusted for age and sex, PCSK9 levels were associated with systolic BP ( $p=0.006$ ), AST ( $p<0.001$ ), ALT ( $p<0.001$ ), γ-GTP ( $p<0.001$ ), triglycerides ( $p<0.001$ ), total cholesterol ( $p=0.003$ ), HOMA-IR ( $p=0.007$ ), and HbA<sub>1c</sub> ( $p=0.011$ ). **Supplementary Table 2** showed univariable and multivariable linear regression analyses for correlates of serum PCSK9 level with lipid-lower-



**Fig. 1.** Scatter gram of PCSK9 with age by gender



**Fig. 2.** Scatter gram between PCSK9 and Lp(a) (A), triglycerides (B), and LDL-C (C)

**Table 2.** Univariable and multivariable linear regression analyses for correlates of serum PCSK9 level

	Univariate			Adjusted for age, sex, and medication for dyslipidemia		
	$\beta$	SE	<i>p</i> -value	$\beta$	SE	<i>p</i> -value
Age	-0.005	0.001	<0.001			
Sex (Male=0, Female=1)	-0.007	0.024	0.789			
Body mass index	0.001	0.003	0.004	0.006	0.003	0.085
Waist circumference	0.003	0.001	0.005	0.002	0.001	0.042
Systolic blood pressure	0.002	0.001	0.013	0.002	0.001	0.001
Diastolic blood pressure	0.002	0.001	0.077			
Aspartate transaminase	0.003	0.001	0.004	0.003	0.001	0.002
Alanine transaminase	0.004	0.001	0.001	0.003	0.001	0.012
$\gamma$ -glutamyl transferase	0.001	0.0002	<0.001	0.001	0.001	<0.001
Estimated GFR	0.001	0.001	0.247			
Triglycerides <sup>†</sup>	0.180	0.024	<0.001	0.136	0.024	<0.001
Total cholesterol	-0.0001	0.0003	0.830			
HDL-cholesterol	0.0002	0.001	0.776			
LDL-cholesterol	-0.001	0.0004	0.138			
Lipoprotein(a) <sup>†</sup>	0.026	0.012	0.028	0.021	0.011	0.039
HOMA-IR <sup>†</sup>	0.095	0.017	<0.001	0.072	0.017	<0.001
Hemoglobin A <sub>1c</sub> (NGSP)	0.105	0.027	<0.001	0.081	0.026	0.002
Hs-CRP	0.027	0.010	0.005	0.024	0.009	0.008
Alcohol intake	0.043	0.024	0.077			
Current smoking	-0.006	0.041	0.891			
Medication for dyslipidemia	0.214	0.023	<0.001			

<sup>†</sup>: The variable was represented in the original scale after analysis using log (natural) transformed values.

**Table 3.** Multivariable stepwise linear regression analysis between serum PCSK9 level and parameters

	$\beta$	SE	<i>p</i> -value
Medication for dyslipidemia	0.170	0.023	<0.001
Triglycerides <sup>†</sup>	0.094	0.026	<0.001
Age	-0.005	0.001	<0.001
$\gamma$ -glutamyl transferase	0.001	0.001	0.003
Systolic blood pressure	0.002	0.001	0.007
Lipoprotein(a) <sup>†</sup>	0.023	0.011	0.033
Hemoglobin A <sub>1c</sub>	0.057	0.027	0.033
HOMA-IR <sup>†</sup>	0.037	0.018	0.041

R<sup>2</sup>=0.203

<sup>†</sup>: The variable was represented in the original scale after analysis using log (natural) transformed values.

ing medication subjects ( $n=252$ ). With multivariate analysis adjusted for age and sex, PCSK9 levels were associated with  $\gamma$ -GTP ( $p=0.002$ ), triglycerides ( $p=0.003$ ), HDL-C ( $p=0.043$ ), hs-CRP ( $p=0.028$ ), and alcohol intake ( $p=0.029$ ).

## Discussion

In the present study, we demonstrated that serum PCSK9 was independently associated with insulin

resistance, triglyceride, and Lp(a), but not with LDL-C, in a general population.

### 1. Associations between PCSK9 Levels and Triglycerides/Insulin Resistance

Several investigations previously revealed the relationship between serum PCSK9 and metabolic syndrome or insulin resistance<sup>1-3</sup>. Hasan H, *et al.*<sup>1</sup> correlated PCSK9 with some components of metabolic syndrome and central obesity. Baass A, *et al.*<sup>2</sup>

also associated PCSK9 with age, sex, and multiple metabolic markers, including HOMA-IR, both of which enrolled a small number of young females subjects<sup>1)</sup> and youth<sup>2)</sup>. In Japan, Furuhashi M, *et al.*<sup>9)</sup> reported that PCSK9 was independently correlated with metabolic factors, such as triglycerides and HOMA-IR, in 265 participants in a general population. Consistently, our data, obtained from a relatively large number of participants ( $n=674$ ), demonstrated that PCSK9 levels were independently associated with age, triglycerides, and HOMA-IR.

A strong positive association of PCSK9 with triglycerides was also observed in a previous study<sup>1)</sup>, suggesting that high PCSK9 levels regulate lipid profiles in a general population with normal nutritional status. This association may explain an increased risk of atherosclerosis development in such individuals, who seem to be normal but are “metabolically unhealthy.”

In a clinical study, the highest insulin resistance tertile, as evaluated by the HOMA-IR, presented significantly higher mean PCSK9 levels compared to the lowest tertile group<sup>27)</sup>, which demonstrated insulin's importance in PCSK9 regulation. Although the clinical study subjects were limited to postmenopausal obese women, our study, from the largest general population, consistently indicated that serum PCSK9 levels were positively and independently correlated with insulin resistance and triglycerides.

One of the mechanisms by which serum PCSK9 levels are correlated to triglycerides and HOMA-IR is that insulin upregulates LDL-R transcription in the liver, and LDL-R endocytosis is a major clearance pathway of plasma PCSK9. Thus, increased hepatocyte surface LDL-R would promote increased PCSK9 clearance<sup>27)</sup>.

## 2. Associations between PCSK9 and LDL-C

The present study was unable to demonstrate a significant association between PCSK9 and LDL-C, as consistently observed in the manuscript of Hasan H, *et al.*<sup>1)</sup> PCSK9's role in regulating LDL-C through LDL-R, and association of lower levels of PCSK9 with reduced CAD risk, have been well documented<sup>28)</sup>. No association between PCSK9 and LDL-C may be attributed, in part, to the presence of intra- and extracellular routes for PCSK9's interaction with LDL-R, which may influence PCSK9's secretion rate into the circulation<sup>29)</sup>. One more explanation may be the influence of dyslipidemia medication. Although a significant association between PCSK9 and LDL-C was not demonstrated, a weak tendency was found in the group with no lipid-lowering medication in the present study.

## 3. Associations between PCSK9 and Lp(a)

Serum Lp(a) has been highlighted as a novel risk factor for CAD<sup>10)</sup>. The positive association between PCSK9 and Lp(a) was reported in relatively small studies<sup>11, 12, 30)</sup>. Serum PCSK9 was associated with Lp(a) in type 2 diabetic patients in a study in Tunisia<sup>11)</sup>, and serum levels of PCSK9 were positively correlated to serum levels of Lp(a) in patients with CAD in Japan<sup>30)</sup>. However, a report from Han Chinese found no association between PCSK9 with Lp(a) levels in subjects with or without type 2 diabetes<sup>12)</sup>. The comparative analysis in different ethnic groups indicates marked inter-racial differences in the distribution of Lp(a) concentrations<sup>31, 32)</sup>. Therefore, the significant association between PCSK9 and Lp(a) remains controversial. Furthermore, statin treatment may increase Lp(a) levels in subjects with a low molecular weight Lp(a) phenotype<sup>33)</sup>. When we divided subjects into two groups (without and with lipid-lowering medication), Lp(a)'s significance disappeared, probably because the number of each group became smaller.

## 4. Associations between PCSK9 and systolic blood pressure/ $\gamma$ -glutamyl transferase

In the final multiple linear regression analysis, systolic BP and  $\gamma$ -GTP were also independently associated with PCSK9. Because previous studies investigated the relationship between PCSK9 polymorphism and alcohol consumption<sup>34, 35)</sup>, alcohol consumption may modify the PCSK9 E670G polymorphism's effects on serum total cholesterol and LDL-C levels<sup>34)</sup>. Of several single nucleotide polymorphisms (SNPs), the PCSK9 rs505151 genotype in drinkers was associated with higher BP levels rather than other genotypes. These findings indicate that several lipid-related SNPs may be associated with BP regulation and involved in hypertension development in the population study<sup>35)</sup>.

As for the association between PCSK9 and  $\gamma$ -GTP, Ruscica M, *et al.*<sup>36)</sup> suggested that circulating PCSK9 increases with hepatic fat accumulation and correlates with the severity of steatosis, independent of metabolic confounders and liver damage. Recently, Paquette M, *et al.*<sup>37)</sup> reported that circulating PCSK9 levels were strongly associated with all circulating liver biomarkers, as well as the presence of hepatic steatosis. These associations were independent of insulin resistance status, although the strength of the association between PCSK9 and hepatic steatosis decreased when corrected for HOMA-IR, BMI, and alcohol use. Since insulin resistance is a hallmark of metabolic syndrome, the association between PCSK9 and  $\gamma$ -GTP may reflect metabolic syndrome.

## 5. Strengths and Limitations

The strengths of the current study were the community-based cohort study design and its relatively large sample size. Our study results may be helpful for clinical studies<sup>38)</sup> in terms of PCSK9 distribution or association between PCSK9 and triglycerides, Lp(a), or statin use. It may be suggestive as an indicator of PCSK9 inhibitor use.

There are several limitations in our study. First, the study design was cross-sectional. Thus, nothing conclusive about the association of PCSK9 and Lp(a) can be stated. Second, we used only a single measurement to evaluate the PCSK9 and Lp(a). Third, it remains unclear whether the conclusions of a Japanese population-based study can be generalized to other ethnic populations with different genetic backgrounds.

## Conclusions

We demonstrated that PCSK9 levels were significantly and independently associated with triglycerides, Lp(a), and HOMA-IR, but not LDL-C, suggesting that the measuring serum PCSK9 levels may detect the early stage of atherosclerosis.

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**Supplementary Table 1.** Univariable and multivariable linear regression analyses for correlates of serum PCSK9 level without lipid-lowering medication subjects ( $n=422$ )

	Univariate			Adjusted for age and sex		
	$\beta$	SE	$p$ -value	$\beta$	SE	$p$ -value
Age	-0.006	0.002	<0.001			
Sex (Male=0, Female=1)	-0.051	0.027	0.065			
Body mass index	0.004	0.004	0.283			
Waist circumference	0.002	0.001	0.321			
Systolic blood pressure	0.002	0.001	0.040	0.002	0.001	0.006
Diastolic blood pressure	0.002	0.001	0.047	0.001	0.001	0.357
Aspartate transaminase	0.004	0.001	<0.001	0.004	0.001	<0.001
Alanine transaminase	0.005	0.001	<0.001	0.004	0.001	<0.001
$\gamma$ -glutamyl transferase	0.001	0.0002	<0.001	0.001	0.0002	<0.001
Estimated GFR	0.002	0.011	0.005	0.001	0.001	0.190
Triglycerides <sup>†</sup>	0.150	0.027	<0.001	0.143	0.027	<0.001
Total cholesterol	0.001	0.0004	0.014	0.001	0.0004	0.003
HDL-cholesterol	0.0002	0.001	0.807			
LDL-cholesterol	0.001	0.0004	0.117			
Lipoprotein(a) <sup>†</sup>	0.002	0.014	0.908			
HOMA-IR <sup>†</sup>	0.060	0.020	0.003	0.054	0.020	0.007
Hs-CRP <sup>†</sup>	0.017	0.010	0.094			
Hemoglobin A <sub>1c</sub> (NGSP)	0.071	0.031	0.021	0.076	0.030	0.011
Alcohol intake	0.055	0.027	0.043	0.022	0.031	0.475
Current smoking	0.052	0.044	0.234			

<sup>†</sup>: The variable was represented in the original scale after analysis using log (natural) transformed values

**Supplementary Table 2.** Univariable and multivariable linear regression analyses for correlates of serum PCSK9 level with lipid-lowering medication subjects ( $n=252$ )

	Univariate			Adjusted for age and sex		
	$\beta$	SE	$p$ -value	$\beta$	SE	$p$ -value
Age	-0.007	0.002	0.002			
Sex (Male=0, Female=1)	0.019	0.038	0.614			
Body mass index	0.006	0.005	0.270			
Waist circumference	0.001	0.002	0.724			
Systolic blood pressure	0.001	0.001	0.964			
Diastolic blood pressure	0.001	0.002	0.752			
Aspartate transaminase	-0.001	0.003	0.807			
Alanine transaminase	0.001	0.002	0.944			
$\gamma$ -glutamyl transferase	0.002	0.001	0.005	0.002	0.001	0.002
Estimated GFR	0.001	0.001	0.661			
Triglycerides <sup>†</sup>	0.119	0.041	0.004	0.123	0.041	0.003
Total cholesterol	0.001	0.001	0.082			
HDL-cholesterol	0.003	0.001	0.023	0.002	0.061	0.043
LDL-cholesterol	0.001	0.001	0.809			
Lipoprotein(a) <sup>†</sup>	0.018	0.018	0.307			
HOMA-IR <sup>†</sup>	0.049	0.027	0.074			
Hs-CRP <sup>†</sup>	0.034	0.016	0.040	0.037	0.017	0.028
Hemoglobin A <sub>1c</sub> (NGSP)	0.037	0.046	0.430			
Alcohol intake	0.082	0.037	0.028	0.090	0.041	0.029
Current smoking	-0.023	0.075	0.762			

<sup>†</sup>: The variable was represented in the original scale after analysis using log (natural) transformed values