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High circulating PCSK9 concentration is associated with increased and sex-specific risks of metabolic disease, diabetes mellitus, MASLD, and long-term mortality in a Taiwanese population

Kuan-Hung Yeh[1,2], Lung-An Hsu[3], Ngoc Yen Tran[1], Semon Wu[4] and Yu-Lin Ko[1,2,5*]

Abstract

Background Circulating PCSK9 concentrations have been linked to various metabolic disorders, with evidence suggesting sex-specific differences—stronger associations in women and inconsistent findings in men.

Methods This study enrolled 7,950 participants from the Taiwan Biobank. Associations of PCSK9 concentration with insulin resistance (IR), metabolic syndrome (MetS), diabetes mellitus (DM), and long-term outcomes were analyzed. Anthropometric, biochemical, and hematologic parameters were examined in a subgroup of 6,478 participants, and 4,185 participants underwent abdominal sonography for the assessment of metabolic dysfunction–associated steatotic liver disease (MASLD).

Results Increasing PCSK9 concentrations and quartiles were significantly associated with older age, female sex, adverse cardiometabolic traits, and several hematological parameters. Higher hematocrit count, higher triglyceride, low-density lipoprotein cholesterol, fasting plasma glucose, and gamma-glutamyl transferase concentrations, and lower total bilirubin concentrations were independently associated with high PCSK9 concentration, with these associations being more pronounced among female participants. Higher platelet count was independently associated with high PCSK9 concentration only in female participants. Odds ratios for IR, MetS, DM, and MASLD increased progressively across PCSK9 quartiles, with stronger associations in women. Kaplan–Meier survival and Cox regression analyses indicated associations of high PCSK9 concentration with higher all-cause, non-cardiovascular, and cancer mortalities, especially in women.

Conclusion High circulating PCSK9 concentration is independently associated with increased risks of IR, MetS, DM, MASLD, and all-cause and cancer mortality, indicating poor metabolic profiles and outcomes in the Taiwanese population. These associations are stronger in women, highlighting the importance of sex-specific risk evaluation in metabolic diseases and long-term outcomes.

*Correspondence:
Yu-Lin Ko
yulinkotw@gmail.com

Full list of author information is available at the end of the article

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Keywords PCSK9, MASLD, Insulin resistance, Metabolic syndrome, Diabetes mellitus

Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a multifaceted serine protease predominantly synthesized in the liver that regulates plasma low-density lipoprotein cholesterol (LDL-C) concentration through the endosomal and lysosomal degradation of low-density lipoprotein (LDL) receptors [1, 2]. PCSK9's role in cholesterol metabolism is well-established; nevertheless, accumulating evidence suggests that PCSK9 also participates in broader metabolic regulation, including glucose homeostasis, insulin sensitivity, hepatic lipid metabolism, and proatherothrombotic processes [1, 3, 4]. Clinical evidence has further associated high circulating PCSK9 concentration with key metabolic syndrome (MetS) components (i.e., obesity, hypertension, dyslipidemia, and hyperglycemia), indicating that PCSK9 has potential as a biomarker of metabolic risk [2, 5]. Hepatic steatosis is now recognized as the hepatic manifestation of MetS [6, 7]. The condition formerly named nonalcoholic fatty liver disease (NAFLD) was renamed to metabolic dysfunction–associated steatotic liver disease (MASLD) to emphasize its roots in metabolic problems, such as insulin resistance (IR) and MetS. Accordingly, researchers should study biomarkers that reflect metabolic dysfunction (e.g., PCSK9) when investigating this liver disease [8–10].

The relationships between PCSK9 and cardiometabolic traits have been observed to differ by ethnicity and gender, with these relationships being stronger in women than men [11–14]. However, the sex-specific differences in the association between PCSK9 levels and MASLD and long-term mortality outcomes remained unknown. Additionally, according to genetic and pharmacologic studies, variants and inhibitors of PCSK9 may influence risks of diabetes and hepatic steatosis [11–14]. In the Taiwanese population, prevalence rates of MetS, diabetes mellitus (DM), and fatty liver disease have increased substantially over recent decades, even when assessed using lower body mass index (BMI) thresholds than those used to assess these conditions in Western populations [15–17]. Results from genetic analyses have indicated that PCSK9 polymorphisms are associated with LDL-C concentrations and lipid metabolism, with suggestive evidence of causal and pleiotropic effects on glucose regulation [18, 19]. Nevertheless, population-level data on the associations between circulating PCSK9 and metabolic disorders and long-term outcomes remain limited. To address this gap, we analyzed Taiwan Biobank (TWB) data to investigate whether high circulating PCSK9 concentrations predict IR, MetS, DM, MASLD, and long-term mortality. We also explored whether PCSK9 has sex-specific effects. Our data revealed that high circulating PCSK9 concentrations are independently associated with increased risks of IR, MetS, DM, MASLD, and all-cause and cancer mortality and that these associations are stronger in women. Our findings highlight the importance of addressing the knowledge gap of sex-specific risk evaluation in metabolic diseases, which extend the results from existing studies on PCSK9, especially in Asian populations, particularly regarding the integration of MASLD and long-term mortality outcomes in the Taiwanese population.

Participants and methods

TWB population

This study enrolled 150,710 TWB participants who had no prior history of cancer. Data were collected using questionnaires at recruitment centers across Taiwan between 2008 and 2015, with all participants providing written informed consent. The participant selection process is illustrated in Fig. 1. From this cohort, 8,401 TWB participants who provided plasma samples were randomly selected. Of these participants, 451 were excluded because of third-degree relatedness (identity-by-descent > 0.187; $n = 162$), because they had fasted for < 6 h ($n = 208$), or because they had outlier concentrations of PCSK9 ($n = 81$). A total of 7,950 participants remained for screening by IR, MetS, and DM. Of these 7,950 participants, 1,472 were excluded because they had hypertension, hyperlipidemia, diabetes ($n = 1,414$), or chronic renal insufficiency (defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2; $n = 58$), leaving 6,478 participants for screening by metabolic traits and clinical, biochemical, and hematological parameters. Among the initially identified 7,950 participants, 4,185 underwent abdominal sonography between July 2011 and November 2021. The average follow-up duration was 4.2 ± 1.2 years. Among those who underwent abdominal sonography, 939 were excluded because of current alcohol consumption ($n = 309$), evidence of hepatitis B or C infection ($n = 550$), or other known causes of chronic liver disease ($n = 80$), leaving 3,246 participants for further analysis. Among these 3,246 participants, 1,375 had hepatic steatosis and were categorized into an NAFLD subgroup. Among these 1,375 participants, 1,272 had both hepatic steatosis and at least one metabolic dysfunction. These 1,272 participants were categorized into an MASLD subgroup (Supplementary Fig. 1). The study received approval from the Research Ethics Committee of Taipei Tzu Chi Hospital (08-XD-005) and the Ethics and Governance Council of the TWB (TWBR11011-02, TWBR11108-01 and TWBR11107-03). All procedures

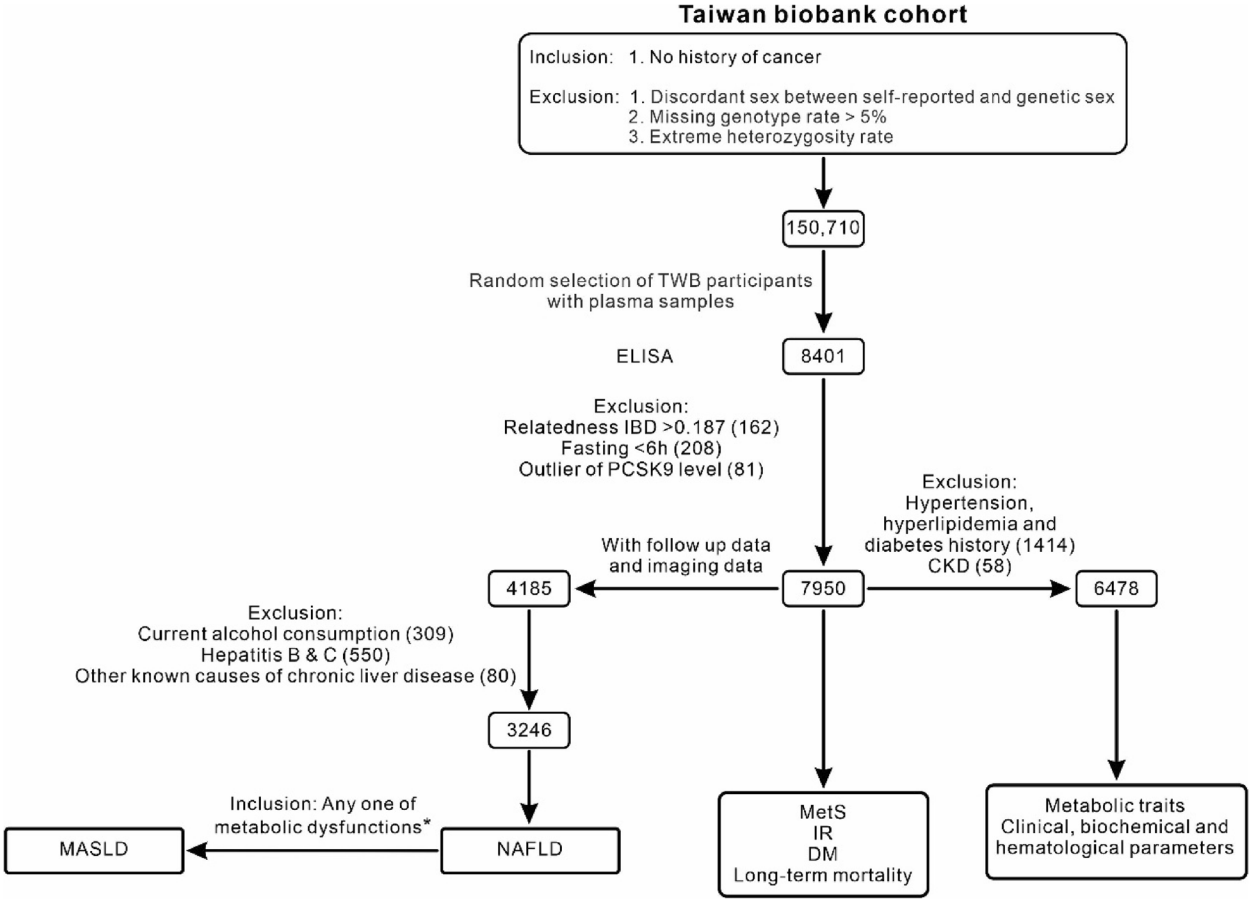

Fig. 1 Participant selection process. Participants were enrolled from the Taiwan Biobank (TWB). Abbreviations: ELISA: enzyme-linked immunosorbent assay; IBD, identity-by-descent; IR, insulin resistance; DM, diabetes mellitus; MetS, metabolic syndrome; CKD, chronic kidney disease; NAFLD, nonalcoholic fatty liver disease; MASLD, metabolic dysfunction–associated steatotic liver disease. *The definition of metabolic dysfunction was shown in Supplementary Fig. 1

were conducted in accordance with the Declaration of Helsinki.

Laboratory examinations

Biochemical and demographic data were extracted from the TWB. The demographic characteristics analyzed were age, gender, waist circumference (WC), waist: hip ratio, and BMI. The metabolic and biochemical parameters analyzed were systolic blood pressure, diastolic blood pressure, mean blood pressure and total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C, triglyceride, fasting plasma glucose, hemoglobin A1C (HbA1C), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γGT), albumin, and total bilirubin concentrations. Triglyceride glucose (TyG), TyG-BMI, and TyG-WC indices served as predictors of IR. These indices were calculated as follows: TyG index = Ln [triglyceride (mg/dL) × fasting plasma glucose (mg/dL) / 2]; TyG-BMI = TyG index × BMI; and TyG-WC = TyG index × WC [20]. Plasma PCSK9 concentrations were determined using a solid-phase sandwich enzyme-linked immunosorbent assay kit (Human Proprotein Convertase 9/PCSK9 Duo-Set ELISA kit; R&D Systems, Minneapolis, MN, USA).

Definitions of IR

The gold standard method for measuring insulin sensitivity is the hyperinsulinemic clamp technique. This technique is costly, complex, and invasive. The homeostatic model assessment of insulin resistance (HOMA-IR) is an alternative method that is widely used but not readily available in many laboratories. The TyG, TyG-BMI, and TyG-WC indices have been proposed as surrogate markers for evaluating IR because of their practical application and high sensitivity and specificity compared with the HOMA-IR and hyperinsulinemic clamp techniques [20, 21]. Participants in the highest quartile of TyG-related indices were defined as having IR [20].

Definitions of MetS, DM, and metabolic liver disease

Supplementary Method S1 present the definitions of various parameters, including MetS, DM, and metabolic liver disease, used in the present study [22–24].

Outcome analysis

Mortality data were obtained from the National Health Insurance Research Database. In total, 154 participants died between 2008 and 2023 [25]. Causes of death were classified as all-cause, cardiovascular-related, or cancer-related in accordance with the *International Classification of Diseases, 10th Revision* (Supplementary Method S1).

Statistical analysis

The clinical and biochemical characteristics of the participants are presented as mean ± standard deviation, except for highly skewed variables, which are presented as medians with interquartile ranges. Concentrations of PCSK9, total cholesterol, HDL-C, LDL-C, and triglycerides and TyG, TyG-BMI, and TyG-WC indices were logarithmically transformed prior to linear regression to meet the normality assumption. Chi-square tests were applied to assess differences in the distributions of categorical data between the sexes. Independent *t*-tests were used to compare PCSK9 concentrations across subgroups defined by atherosclerotic risk factors, and PCSK9 quartiles were evaluated using crosstab analyses. Pearson's correlation coefficients were used to assess associations between PCSK9 concentrations and clinical and biochemical parameters, stratified by sex. Variables significantly associated with PCSK9 were included in a stepwise multivariate linear regression model to determine independent predictors. Linear regression models were used to explore associations between PCSK9 concentrations and MetS, IR, DM, NAFLD, and MASLD, with adjustments for age, sex, BMI, and current smoking status. Logistic regression models were used to explore associations between the quartiles of PCSK9 and MetS, IR, DM, NAFLD, and MASLD, with the same covariate adjustments. We compared PCSK9–mortality relationships by plotting receiver operating characteristic curves. We then performed nonparametric comparisons of areas under the receiver operating characteristic curve. Kaplan–Meier survival curves were analyzed, and significance was examined adopting the log-rank method. $P < 0.05$ with Bonferroni correction was considered statistically significant. Statistical analyses were conducted in SPSS (version 22; IBM Corporation, Armonk, NY, USA). Missing data were handled by listwise deletion.

Sensitivity analysis

To assess robustness to measurement error, we performed a Monte Carlo simulation. A coefficient of variation (CV) of 10% was assumed for PCSK9. In each of 1,000 iterations, random error sampled from a normal distribution was applied to generate simulated PCSK9 values. Cox regression was repeated for each simulated dataset, and HRs, CIs, and *P* values were recorded. Data manipulation was conducted using dplyr (v1.1.4), simulation loops were facilitated with progress (v1.2.3), and visualization was performed with ggplot2 (v3.5.1). The sensitivity analyses were conducted in R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of male and female participants

A summary of the clinical, biochemical, and hematological parameters and anthropometric measurements of the 7,950 participants is provided in Supplementary Table 1. A distribution of PCSK9 concentrations by sex is shown in Supplementary Fig. 2. Several variables significantly differed between men and women. The results were similar when a smaller sample of 6,478 participants was enrolled in the analysis (Supplementary Table 2).

Associations of PCSK9 concentration with sex and atherosclerotic risk factors

Female participants had significantly higher PCSK9 concentrations than did male participants (Supplementary Fig. 2). Participants who had obesity, central obesity, hypertension, IR, MetS, or metabolic disease (i.e., NAFLD or MASLD) also had higher PCSK9 concentrations than did those without these atherosclerotic risk factors (Fig. 2, Supplementary Fig. 3, and Supplementary Table 3). In addition, the PCSK9 levels increased progressively from normal individuals to individuals with prediabetes and then to individuals with DM. We also conducted a stratified analysis using age 50 as a proxy cutoff, a commonly used surrogate in population-based studies to differentiate likely premenopausal and postmenopausal women (Supplementary Table 3). In these subgroup analyses, we found a larger difference (23 ng/mL) of higher PCSK9 levels in women aged ≥ 50 years when compared to women aged < 50 years. By contrast, the difference between men aged ≥ 50 years and men aged < 50 years was only 6 ng/mL. There was no significant difference between PCSK9 levels in women aged < 50 years when compared to men aged < 50 years (147.00 ± 40.68 vs. 148.03 ± 40.89, $P = 0.3792$), whereas significantly higher PCSK9 levels in women aged ≥ 50 years was noted when compared to men aged ≥ 50 years (170.23 ± 42.60 vs. 154.70 ± 42.45, $P = 2.21 \times 10^{-32}$). These results suggested that postmenopausal hormonal changes may play a role in the observed sex-specific differences. While this approach does not fully account for individual variation in menopausal timing, it offers preliminary insight into potential hormonal influences.

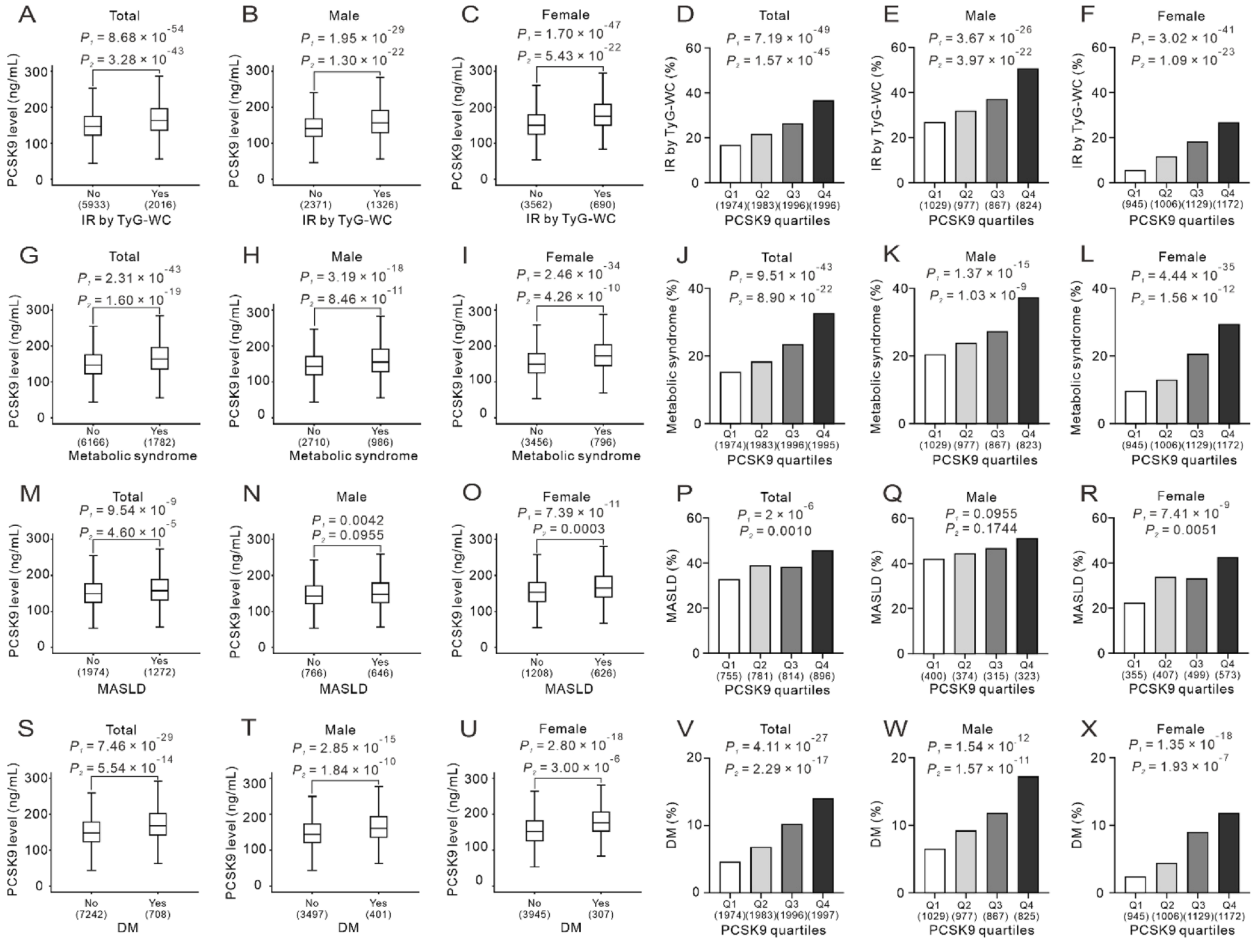

Fig. 2 PCSK9 concentrations in participants with IR by TyG-WC (**A**–**C**), MetS (**G**–**I**), DM (**M**–**O**), MASLD (**S**–**U**) and percentage of IR by TyG-WC (**D**–**F**), MetS (**J**–**L**), DM (**P**–**R**), and MASLD (**V**–**X**) across quartiles of PCSK9. P_1: unadjusted, P_2: adjusted for age, BMI, sex, and current smoking status. Abbreviations as in Fig. 1 and Table 1

Participant baseline characteristics, stratified into Circulating PCSK9 concentration quartiles and sex

The study variables were stratified by sex and PCSK9 concentration quartiles for the overall study population (Supplementary Table 4) and for male and female participants (Table 1). After adjustments for age, sex, BMI, and current smoking status with Bonferroni correction for the overall study population and for male and female participants, high PCSK9 concentration quartiles were found to be significantly associated with older age, high waist: hip ratios, high BMIs, adverse lipid profiles (i.e., high total cholesterol, LDL-C, and triglyceride concentrations), poor glucose metabolism parameters (i.e., high fasting plasma glucose and HbA1c concentrations), poor TyG, TyG-BMI, and TyG-WC indices, liver dysfunction biomarkers (high ALT and γGT concentrations), poor hematological parameters (high hemoglobin, hematocrit, and platelet counts), and low total bilirubin concentrations. By contrast, no significant associations were observed between PCSK9 concentration quartiles and systolic blood pressure and HDL-C, uric acid, serum creatinine, and serum albumin concentrations, eGFR, or leukocyte and red blood cell count in either sex. Furthermore, significant associations for WC and AST concentration were observed exclusively in female participants and for diastolic blood pressure and mean blood pressure exclusively in male participants.

Sex-stratified correlations between Circulating PCSK9 concentration and clinical, metabolic, biochemical, and hematological parameters

Sex-stratified pearson's correlation results on the associations of circulating PCSK9 concentration with clinical parameters, metabolic phenotypes, and biochemical and hematological measures are shown in Table 2. With Bonferroni correction, participants with high PCSK9 concentrations were older, had significantly higher BMI and WC values and waist: hip ratios, higher total cholesterol, LDL-C, triglyceride, fasting plasma glucose, and HbA1c concentrations, higher TyG-related indices, higher dysfunctional liver indices (i.e., ALT and γGT concentrations), higher hemoglobin and hematocrit counts, and

Table 1 Baseline characteristics of 6478 participants by Circulating PCSK9 concentration quartiles, stratified by sex

Clinical and biochemical parameters		Men						Women					
		Q1 (*N* = 856)	Q2 (*N* = 760)	Q3 (*N* = 661)	Q4 (*N* = 554)	*P*	Adjusted *P*	Q1 (*N* = 879)	Q2 (*N* = 906)	Q3 (*N* = 953)	Q4 (*N* = 909)	*P*	Adjusted *P*
Anthropology	Age (years)	46.23 ± 11.51	47.08 ± 11.06	47.86 ± 10.71	48.21 ± 10.93	2.70×10^{-5}	0.0008	43.73 ± 9.72	46.74 ± 10.43	49.49 ± 10.70	51.23 ± 10.13	1.14×10^{-56}	3.31×10^{-55}
	Waist circumference (cm)	85.76 ± 9.13	85.97 ± 8.56	86.87 ± 8.22	87.74 ± 8.70	0.0153	0.4437	77.32 ± 8.27	79.24 ± 9.76	79.84 ± 9.03	81.09 ± 9.11	9.00×10^{-6}	0.0003
	Waist hip ratio	0.88 ± 0.05	0.88 ± 0.05	0.89 ± 0.05	0.90 ± 0.05	0.0007	0.0203	0.82 ± 0.06	0.84 ± 0.07	0.84 ± 0.07	0.85 ± 0.07	2.00×10^{-6}	5.80×10^{-5}
	BMI (kg/m^2)	24.75 ± 3.45	24.68 ± 3.22	24.95 ± 3.18	25.33 ± 3.37	0.0002	0.0058	22.60 ± 3.27	23.04 ± 3.58	23.16 ± 3.35	23.52 ± 3.38	1.30×10^{-5}	0.0004
Blood Pressure	Systolic BP (mmHg)	117.28 ± 14.52	119.33 ± 15.54	118.81 ± 13.86	120.89 ± 15.20	0.0186	0.5394	107.67 ± 14.63	110.03 ± 15.56	111.38 ± 15.62	114.32 ± 17.15	0.2978	> 1
	Diastolic BP (mmHg)	74.66 ± 10.07	75.86 ± 10.07	76.15 ± 10.00	77.27 ± 10.46	0.0007	0.0203	66.79 ± 9.19	68.13 ± 9.75	68.54 ± 9.74	70.10 ± 10.00	0.0058	0.1682
	Mean BP (mmHg)	88.87 ± 10.76	90.35 ± 11.16	90.37 ± 10.61	91.81 ± 11.26	0.0015	0.0435	80.42 ± 10.30	82.10 ± 10.97	82.82 ± 10.99	84.84 ± 11.57	0.0305	0.8845
Lipid profiles	Total cholesterol (mg/dL)	185.64 ± 32.41	189.57 ± 31.99	197.63 ± 33.98	201.27 ± 41.46	2.55×10^{-18}	7.40×10^{-17}	181.32 ± 31.55	192.92 ± 32.72	197.49 ± 33.27	206.08 ± 36.64	5.68×10^{-24}	1.65×10^{-22}
	HDL-Cholesterol (mg/dL)	49.53 ± 10.97	48.69 ± 10.99	49.02 ± 10.63	49.19 ± 12.04	0.4869	> 1	59.26 ± 13.00	58.73 ± 12.48	59.02 ± 13.15	59.42 ± 13.94	0.3167	> 1
	LDL-Cholesterol (mg/dL)	114.55 ± 29.57	117.30 ± 29.53	123.02 ± 30.80	121.30 ± 31.49	7.00×10^{-6}	0.0002	106.96 ± 28.13	116.84 ± 29.02	119.06 ± 29.59	124.05 ± 33.03	1.33×10^{-10}	3.86×10^{-9}
	Triglyceride (mg/dL)	89.00 (64.00–131.75)	102.00 (71.00–145.75)	107.00 (76.00–149.50)	124.00 (87.00–182.50)	4.89×10^{-26}	1.42×10^{-24}	66.00 (50.00–88.00)	76.50 (56.00–106.00)	83.00 (61.50–116.00)	97.00 (68.00–136.00)	1.86×10^{-37}	5.39×10^{-36}
Glucose metabolism	Fasting plasma glucose (mg/dL)	93.56 ± 10.72	95.56 ± 14.82	96.03 ± 14.29	99.31 ± 23.94	7.22×10^{-8}	2.09×10^{-6}	87.81 ± 6.51	90.04 ± 9.62	91.81 ± 13.84	94.38 ± 17.16	1.59×10^{-13}	4.61×10^{-12}
	HbA1C (%)	5.56 ± 0.48	5.63 ± 0.63	5.66 ± 0.63	5.80 ± 0.97	1.22×10^{-7}	3.54×10^{-6}	5.42 ± 0.34	5.54 ± 0.47	5.61 ± 0.55	5.71 ± 0.63	7.59×10^{-11}	2.20×10^{-09}

Table 1 (continued)

Clinical and biochemical parameters		Men						Women					
		Q1 (*N* = 856)	Q2 (*N* = 760)	Q3 (*N* = 661)	Q4 (*N* = 554)	*P*	Adjusted *P*	Q1 (*N* = 879)	Q2 (*N* = 906)	Q3 (*N* = 953)	Q4 (*N* = 909)	*P*	Adjusted *P*
Insulin resistance surrogate markers	TyG index[a]	(5812.0–12207.0)	(6711.0–13866.0)	(6957.0–14427.0)	(8157.5–18272.8)	1.16×10^{-29}	3.36×10^{-28}	(4361.0–7776.0)	(4900.8–9617.0)	(5491.0–10821.5)	(6189.0–12706.0)	4.00×10^{-44}	1.16×10^{-42}
	TyG-BMI ($\times10^3$)[b]	(132.54–327.28)	(156.58–354.96)	(169.63–368.56)	(200.08–479.43)	1.86×10^{-27}	5.39×10^{-26}	(92.19–179.72)	(106.30–229.03)	(119.47–258.37)	(137.80–318.32)	5.20×10^{-42}	1.51×10^{-40}
	TyG-WC ($\times10^3$)[b]	(472.41–1105.42)	(557.51–1244.62)	(594.42–1272.11)	(697.69–1628.13)	1.30×10^{-21}	3.77×10^{-20}	(324.39–613.66)	(370.19–788.28)	(418.78–888.01)	(481.10–1068.72)	2.27×10^{-31}	6.58×10^{-30}
Uric acid*	Uric acid (mg/dL)	6.36 ± 1.21	6.26 ± 1.18	6.37 ± 1.23	6.37 ± 1.28	0.9565	> 1	4.70 ± 1.00	4.76 ± 1.01	4.79 ± 1.05	4.85 ± 1.07	0.4759	> 1
Renal function	Creatinine (mg/dL)	0.89 ± 0.13	0.87 ± 0.12	0.87 ± 0.13	0.87 ± 0.14	0.0611	> 1	0.60 ± 0.10	0.60 ± 0.11	0.60 ± 0.10	0.60 ± 0.10	0.0345	> 1
	eGFR (mL/min/1.73 m^2)	95.45 ± 16.82	97.04 ± 17.10	96.70 ± 17.53	96.84 ± 20.99	0.0297	0.8613	112.75 ± 23.55	111.49 ± 24.61	110.17 ± 23.99	109.68 ± 23.48	0.0366	> 1
Liver function	AST(GOT) (mkat/L)	23.00 (20.00–27.00)	23.00 (20.00–28.00)	24.00 (20.00–28.00)	24.00 (20.00–29.25)	0.0173	0.5017	20.00 (17.00–23.00)	21.00 (18.00–24.00)	22.00 (18.00–25.00)	22.00 (19.00–26.00)	1.00×10^{-6}	2.90×10^{-05}
	ALT(GPT) (mkat/L)	21.00 (17.00–30.00)	21.00 (17.00–30.00)	24.00 (18.00–34.00)	24.00 (18.00–33.25)	0.0001	0.0029	14.00 (11.00–19.00)	16.00 (12.00–20.00)	16.00 (13.00–22.00)	17.00 (13.00–23.00)	2.62×10^{-7}	7.60×10^{-06}
	γGT (mkat/L)	19.00 (15.00–30.00)	20.00 (15.00–31.00)	24.00 (17.00–35.00)	25.00 (18.00–39.00)	8.38×10^{-8}	2.43×10^{-6}	12.00 (9.00–16.00)	13.00 (10.00–19.00)	14.00 (11.00–21.00)	16.00 (12.00–24.00)	7.71×10^{-13}	2.24×10^{-11}
	Serum albumin (mg/dL)	4.65 ± 0.23	4.64 ± 0.23	4.64 ± 0.22	4.63 ± 0.25	0.5834	> 1	4.51 ± 0.22	4.51 ± 0.22	4.52 ± 0.21	4.50 ± 0.27	0.0845	> 1
	Total bilirubin (mg/dL)	0.81 ± 0.32	0.77 ± 0.31	0.72 ± 0.29	0.68 ± 0.28	7.71×10^{-16}	2.24×10^{-14}	0.67 ± 0.25	0.62 ± 0.22	0.61 ± 0.22	0.56 ± 0.22	6.06×10^{-25}	1.76×10^{-23}

Table 1 (continued)

Clinical and biochemical parameters		Men						Women					
		Q1 (*N* = 856)	Q2 (*N* = 760)	Q3 (*N* = 661)	Q4 (*N* = 554)	*P*	Adjusted *P*	Q1 (*N* = 879)	Q2 (*N* = 906)	Q3 (*N* = 953)	Q4 (*N* = 909)	*P*	Adjusted *P*
Hematological parameters	Leukocyte count ($\times 10^9$/L)	6.07 ± 1.52	6.19 ± 1.62	6.18 ± 1.48	6.30 ± 1.61	0.1377	> 1	5.88 ± 1.49	5.87 ± 1.55	5.79 ± 1.50	5.77 ± 1.58	0.6982	> 1
	Red blood cell (10^6/μL)	5.09 ± 0.50	5.07 ± 0.44	5.10 ± 0.41	5.10 ± 0.45	0.2256	> 1	4.51 ± 0.41	4.53 ± 0.41	4.53 ± 0.41	4.55 ± 0.40	0.0934	> 1
	Platelet count (10^3/μL)	222.86 ± 51.35	225.85 ± 49.34	228.04 ± 47.22	229.98 ± 51.15	0.0010	0.0290	248.99 ± 56.22	252.68 ± 60.66	247.37 ± 58.42	254.50 ± 58.23	1.20×10^{-5}	0.0003
	Hemoglobin (g/dL)	14.89 ± 1.15	15.06 ± 1.07	15.14 ± 1.10	15.20 ± 1.06	1.30×10^{-7}	3.77×10^{-6}	12.64 ± 1.29	12.88 ± 1.24	13.03 ± 1.19	13.18 ± 1.17	6.23×10^{-12}	1.81×10^{-10}
	Hematocrit (%)	46.03 ± 3.66	46.66 ± 3.43	46.98 ± 3.39	47.07 ± 3.33	1.08×10^{-9}	3.13×10^{-8}	39.99 ± 3.67	40.69 ± 3.67	41.33 ± 3.69	41.59 ± 3047	2.80×10^{-16}	8.12×10^{-15}

Participants were analyzed after the exclusion of those with a history of *gout; [a]Values of TyG index were presented prior to log-transformation, [b]Values of TyG-BMI and TyG-WC were presented prior to the log-transformation of TyG index

low total bilirubin concentrations. These findings were observed for the overall study population and for male and female subgroups. Higher AST concentrations were observed in the overall study population and in women, and higher platelet counts and lower serum albumin concentrations were observed in the overall study population. No significant associations were observed for HDL-C and uric acid concentrations, leukocyte and red blood cell counts, or eGFR in the overall study population or in the male and female subgroups.

Stepwise multivariate analysis of PCSK9 concentrations

A stepwise linear regression analysis was performed to identify the primary independent variables associated with PCSK9 concentration (Table 3). PCSK9 concentration was significantly associated with sex, age, LDL-C, triglyceride, fasting plasma glucose, ALT, γGT, and total bilirubin concentrations, and hematocrit and platelet counts (all $P \leq 0.05$; Table 3). The associations were then stratified by sex, revealing stronger associations for women than for men (all $P \leq 0.05$), with the exception of LDL-C concentration, for which a stronger association was found for men than for women.

Sex-stratified correlations between Circulating PCSK9 quartiles and cardiometabolic risk factors

PCSK9 concentrations in participants stratified by cardiometabolic risk factors across the four PCSK9 quartiles are illustrated in Fig. 2. PCSK9 quartiles were positively correlated with markers for several cardiometabolic risk factors, including IR, MetS, and DM and for metabolic liver diseases (Fig. 2 and Supplementary Fig. 3).

Sex-based differences in odds ratios for the association between PCSK9 quartiles and the risks of IR, metabolic syndrome, DM, and MASLD

We further tested whether the odds ratios of the association between PCSK9 quartiles and the risks of IR, MetS, DM, and MASLD differ by sex (Fig. 3). Our data revealed that the prevalence of IR, defined as the highest quartile of TyG-WC, increased progressively across quartiles of circulating PCSK9 concentrations (Fig. 3A). In sex-stratified analyses, the association remained significant in male participants, with an odds ratio (OR) of 2.82 (95% confidence interval [CI]: 2.19–3.62, $P = 7.17 \times 10^{-16}$). In female participants, the OR was 4.84 (95% CI: 3.25–7.23, $P = 1.14 \times 10^{-14}$). Notably, the analysis across quartiles revealed significant linear trends in both sexes (P for trend < 0.001), indicating a dose–response relationship between PCSK9 concentration and IR risk, with potential sex-specific differences in the strength of this association. The result was further supported by our finding of a significant interaction effect between sex and PCSK9 quartiles on the prevalence of IR (P for interaction = 0.0013).

Table 2 Correlation coefficients for PCSK9 concentration and clinical, metabolic, biochemical, and hematological correlates, stratified by sex

Clinical and biochemical parameters		All participants (*N* = 6478)			Men (*N* = 2831)			Women (*N* = 3647)		
		Correlation coefficient	*P*	Adjusted *P*	Correlation coefficient	*P*	Adjusted *P*	Correlation coefficient	*P*	Adjusted *P*
Anthropology	Age (years)	0.1778	3.77×10^{-47}	1.13×10^{-45}	0.0724	0.0001	0.0035	0.2597	2.73×10^{-57}	8.19×10^{-56}
	Waist circumference (cm)	0.0782	2.98×10^{-10}	8.94×10^{-9}	0.0755	5.80×10^{-5}	0.0017	0.1507	5.74×10^{-20}	1.72×10^{-18}
	Waist hip ratio	0.1035	6.87×10^{-17}	2.06×10^{-15}	0.0956	3.45×10^{-7}	1.04×10^{-5}	0.1801	5.62×10^{-28}	1.69×10^{-26}
	BMI (kg/m^2)	0.0599	1.00×10^{-6}	3.00×10^{-5}	0.0623	9.16×10^{-4}	0.0275	0.1033	4.04×10^{-10}	1.21×10^{-8}
Blood Pressure	Systolic BP (mmHg)	0.0941	3.28×10^{-14}	9.84×10^{-13}	0.0864	4.00×10^{-6}	0.0001	0.1445	1.82×10^{-18}	5.46×10^{-17}
	Diastolic BP (mmHg)	0.0697	1.96×10^{-8}	5.88×10^{-7}	0.0908	1.00×10^{-6}	3.00×10^{-5}	0.1208	2.49×10^{-13}	7.47×10^{-12}
	Mean BP (mmHg)	0.0851	6.80×10^{-12}	2.04×10^{-10}	0.0950	4.09×10^{-7}	1.23×10^{-5}	0.1401	1.91×10^{-17}	5.73×10^{-16}
Lipid profiles	Total cholesterol (mg/dL)	0.225	3.70×10^{-75}	1.11×10^{-73}	0.1858	2.13×10^{-23}	6.39×10^{-22}	0.2523	4.63×10^{-54}	1.39×10^{-52}
	HDL-Cholesterol (mg/dL)	0.0232	0.0619	>1	-0.0232	0.2163	>1	-0.0022	0.8960	>1
	LDL-Cholesterol (mg/dL)	0.1498	8.21×10^{-34}	2.46×10^{-32}	0.104	2.96×10^{-8}	8.88×10^{-7}	0.1912	2.37×10^{-31}	7.11×10^{-30}
	Triglyceride (mg/dL)	0.2258	1.07×10^{-75}	3.21×10^{-74}	0.228	1.09×10^{-34}	3.27×10^{-33}	0.2814	2.25×10^{-67}	6.75×10^{-66}
Glucose metabolism	Fasting plasma glucose (mg/dL)	0.1431	5.35×10^{-31}	1.61×10^{-29}	0.1263	1.55×10^{-11}	4.65×10^{-10}	0.1953	1.15×10^{-32}	3.45×10^{-31}
	HbA1C (%)	0.1524	5.92×10^{-35}	1.78×10^{-33}	0.1258	1.86×10^{-11}	5.58×10^{-10}	0.1948	1.67×10^{-32}	5.01×10^{-31}
Insulin resistance surrogate markers	TyG index	0.2421	4.83×10^{-87}	$1.45\times10–^{85}$	0.2431	2.35×10^{-39}	7.05×10^{-38}	0.3068	2.59×10^{-80}	7.77×10^{-79}
	TyG-BMI ($\times 10^3$)	0.1344	1.76×10^{-27}	5.28×10^{-26}	0.1445	1.12×10^{-14}	3.36×10^{-13}	0.1892	9.44×10^{-31}	2.83×10^{-29}
	TyG-WC ($\times 10^3$)	0.1592	4.91×10^{-38}	1.47×10^{-36}	0.1698	9.35×10^{-20}	2.81×10^{-18}	0.2415	1.46×10^{-49}	4.38×10^{-48}
Uric acid*	Uric acid (mg/dL)	-0.0307	0.0153	0.4590	-0.0007	0.9704	>1	0.0416	0.0121	0.3630
Renal function	Creatinine (mg/dL)	-0.0811	6.45×10^{-11}	1.94×10^{-9}	-0.0394	0.0363	>1	-0.0058	0.7271	>1
	eGFR (mL/min/1.73 m^2)	0.0096	0.4396	>1	0.0298	0.1131	>1	-0.048	0.0037	0.1110
Liver function	AST(GOT) (mkat/L)	0.0686	3.25×10^{-8}	9.75×10^{-7}	0.0491	0.009	0.2700	0.1411	1.15×10^{-17}	3.45×10^{-16}
	ALT(GPT) (mkat/L)	0.0694	2.25×10^{-8}	6.75×10^{-7}	0.0733	9.40×10^{-5}	0.0028	0.1343	3.89×10^{-16}	1.17×10^{-14}
	γGT (mkat/L)	0.0898	4.42×10^{-13}	1.33×10^{-11}	0.104	2.88×10^{-8}	8.64×10^{-7}	0.1479	2.74×10^{-19}	8.22×10^{-18}
	Serum albumin (mg/dL)	-0.0413	0.0009	0.0270	-0.0285	0.1298	>1	-0.0116	0.4848	>1
	Total bilirubin (mg/dL)	-0.1828	9.21×10^{-50}	2.76×10^{-48}	-0.1695	1.09×10^{-19}	3.27×10^{-18}	-0.167	3.23×10^{-24}	9.69×10^{-23}
Hematological parameters	Leukocyte count ($\times 10^9$/L)	0.0023	0.8548	>1	0.0575	0.0022	0.0660	-0.0236	0.1551	>1
	Red blood cell (10^6/μL)	-0.0267	0.0317	0.9510	0.0098	0.6025	>1	0.0374	0.0239	0.7170
	Platelet count (10^3/μL)	0.0538	1.50×10^{-5}	0.0005	0.0493	0.0088	0.2640	0.0271	0.1016	>1
	Hemoglobin (g/dL)	0.0435	0.0005	0.0150	0.0946	4.56×10^{-7}	1.37×10^{-5}	0.1658	7.01×10^{-24}	2.10×10^{-22}
	Hematocrit (%)	0.0631	3.76×10^{-7}	1.13×10^{-5}	0.1143	1.06×10^{-9}	3.18×10^{-8}	0.1757	1.14×10^{-26}	3.42×10^{-25}

Participants were analyzed after the exclusion of those with a history of *gout

Table 3 Stepwise multivariate analysis of PCSK9 concentrations in 6478 Taiwan biobank participants

	Total study population			Male participants			Female participants		
Variables	**beta**	**r^2**	***P***	**beta**	**r^2**	***P***	**beta**	**r^2**	***P***
Triglyceride (mg/dL)	0.0794	0.0510	5.25×10^{-31}	0.0799	0.0521	2.69×10^{-16}	0.0790	0.0793	3.14×10^{-16}
Total bilirubin (mg/dL)	-0.0694	0.0307	2.86×10^{-39}	-0.0583	0.0206	1.24×10^{-16}	-0.0876	0.0253	1.06×10^{-27}
Age (years)	0.0016	0.0242	6.20×10^{-30}	0.0008	0.0045	0.0001	0.0022	0.0376	3.01×10^{-29}
Sex (Male/Female)	0.0465	0.0086	3.24×10^{-37}	--	--	--	--	--	--
Hematocrit (%)	0.0039	0.0141	4.00×10^{-22}	0.0030	0.0053	3.00×10^{-6}	0.0044	0.0180	7.62×10^{-17}
Fasting plasma glucose	0.0006	0.0069	1.17×10^{-10}	0.0006	0.0069	4.00×10^{-5}	0.0008	0.0077	4.17×10^{-7}
LDL-C (mg/dL)	0.0752	0.0060	8.73×10^{-10}	0.0958	0.0109	1.09×10^{-7}	0.0436	0.0015	0.0098
γGT (mkat/L)	0.0001	0.0023	0.0022	0.0001	0.0026	0.0040	0.0004	0.0030	7.78×10^{-4}
Platelet count (10^3/μL)	9.02E-5	0.0015	0.0007	--	--	--	0.0001	0.0025	0.0025
ALT (GPT) (mkat/L)	0.0002	0.0005	0.0464	--	--	--	--	--	--
Waist hip ratio	--	--	--	--	--	--	--	--	--
Mean BP (mmHg)	--	--	--	--	--	--	--	--	--

Abbreviations: *LDL-C* Low-density lipoprotein cholesterol, *γGT* Gamma-glutamyl transferase, *ALT* Alanine aminotransferase, *BP* Blood pressure

The same findings were also noted for the risk of IR by TyG (Supplementary Fig. 4A) and IR by TyG-BMI (Supplementary Fig. 4B) with interaction $P=0.0016$ and 0.0014, respectively. Higher ORs of the association between PCSK9 quartiles and the risk of MetS (Fig. 3B) and DM (Fig. 3C) were observed in women than in men, although these were not significant (interaction $P=0.0582$ and 0.5922, respectively).

As for metabolic liver disease, a consistent and significant increase in MASLD risk with increasing PCSK9 quartiles was observed in the overall population (Q4 OR: 1.56; 95% CI: 1.24–1.96; $P=0.0001$). Stratification revealed stronger associations in female participants (Q2 OR: 1.65; $P=0.0063$ and Q4 OR: 1.81; $P=0.0007$), and no significant association was observed in male participants (Fig. 3D). Similar trends of associations were also noted for the risks of NAFLD (Supplementary Fig. 4C).

Outcome analysis

A mortality analysis was performed with an average follow-up of 9.25 ± 1.97 years and a total of 73,386 person-years. In total, 154 participants died (cancer mortality $n=69$; cardiovascular mortality $n=38$). This corresponds to annual incidence rates of 0.09 for cancer mortality and 0.05 for cardiovascular mortality per 100 person-years, respectively, indicating a relatively low risk in the population.

According to a receiver operating characteristic curve analysis and the Youden index, the best PCSK9 concentration prognostic cutoff was 176.1 ng/mL, with a sensitivity of 0.4286, specificity of 0.7178, and a Youden's Index of 0.1464. Kaplan–Meier survival analysis revealed that high PCSK9 concentration was a strong predictor of all-cause mortality ($P=0.0005$, 0.0236, and 0.0002 for the overall study population, for men, and for women, respectively), non-cardiovascular mortality ($P=0.0020$ and 0.0003 for the overall study population and for women, respectively), and cancer mortality ($P=0.0016$ for women; Fig. 4). Cox regression analysis, with adjustment for sex, age, BMI, and current smoking status, further revealed that high PCSK9 concentration was associated with (1) higher risks of all-cause and non-cardiovascular mortality in the overall study population (hazard ratio [HR]: 1.57, 95% CI: 1.14–2.18, $P=0.0063$ and HR: 1.59, 95% CI: 1.10–2.32, $P=0.0148$, respectively) and in women (HR: 2.19, 95% CI: 1.18–4.07, $P=0.0132$ and HR: 2.39, 95% CI: 1.19–4.77, $P=0.0138$, respectively) and (2) a higher risk of cancer mortality in women (HR: 2.74, 95% CI: 1.17–6.44, $P=0.0205$; Table 4). The results remained consistent after further adjustment of lipid profiles and TyG index (Model 2 of Table 4). Sensitivity analyses were further conducted to assess the impact of potential variability in PCSK9 levels on the reported associations (Supplementary Table 5). Sensitivity analyses simulating a potential 10% measurement error in PCSK9 showed that all outcomes show HR distribution remained positive in both original and simulated results, with minimal variation suggesting that our findings are robust to plausible measurement error.

Discussion

This investigation analyzed associations of PCSK9 concentration with several metabolic parameters and the risks of IR, MetS, DM, MASLD, and long-term mortality. Higher PCSK9 concentration was significantly associated with older age, female sex, general and central obesity, and adverse cardiometabolic traits, including lipid and glucose metabolism parameters, IR surrogate indices, and hematological parameters. Age and sex; triglyceride, LDL-C, fasting plasma glucose, γGT, and total bilirubin concentrations; and hematocrit and platelet counts were independently associated with PCSK9 concentrations in both male and female participants. These associations were mostly consistent across sexes but more

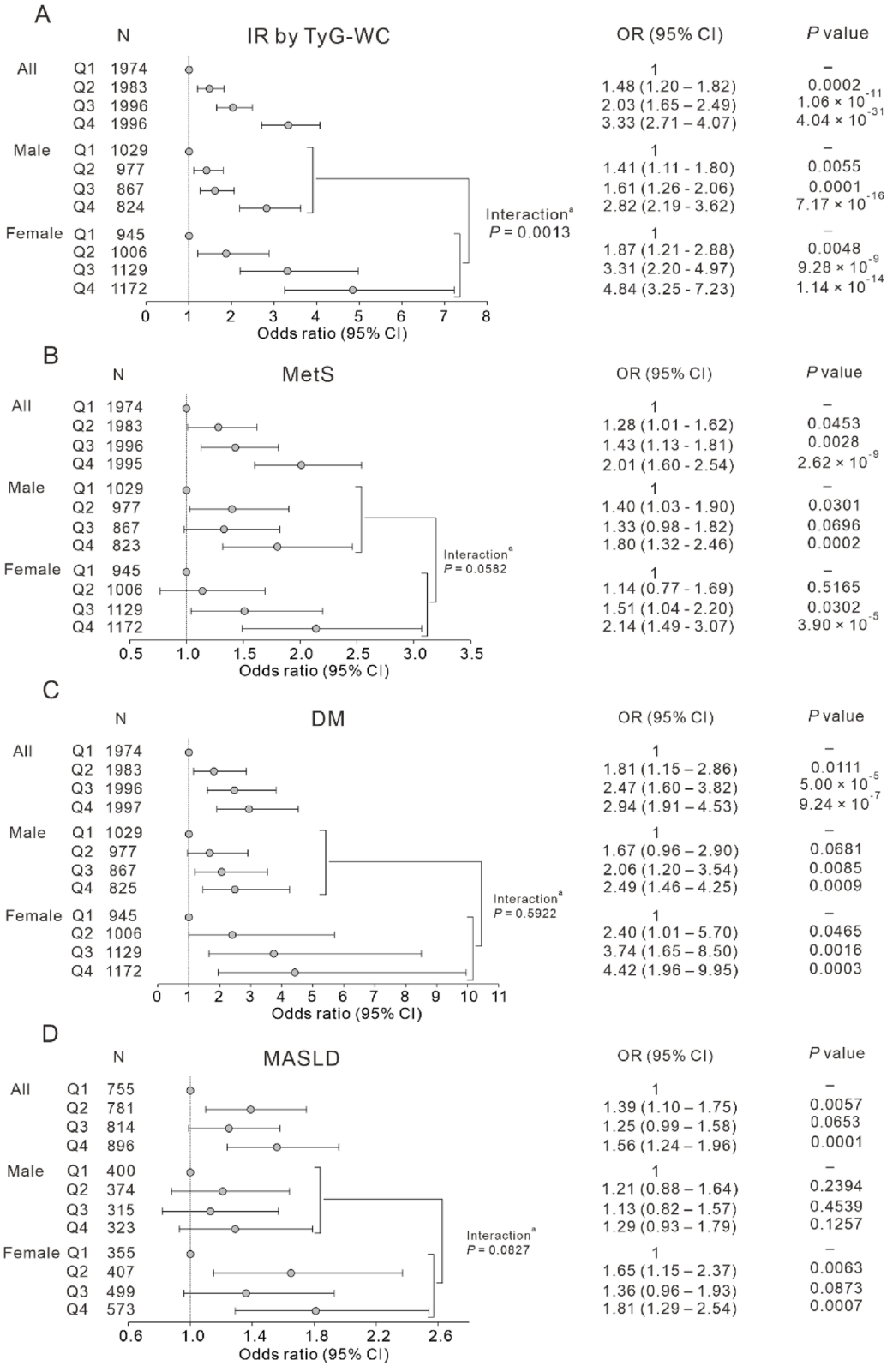

Fig. 3 ORs of the quartiles of PCSK9 in participants with IR by TyG-WC (**A**), MetS (**B**), DM (**C**), or MASLD (**D**), stratified by sex. Comparison of Q2, Q3, and Q4, with Q1 as the reference group. ORs of the quartiles of PCSK9 were estimated after adjusting for age, sex, BMI, and current smoking status for all participants and after adjusting for age, BMI, and current smoking status for male and female subgroups. [a]Effect of sex on the association between quartiles of PCSK9 and IR by TyG-WC, MetS, DM, or MASLD. Abbreviations as in Fig. 1 and Table 1

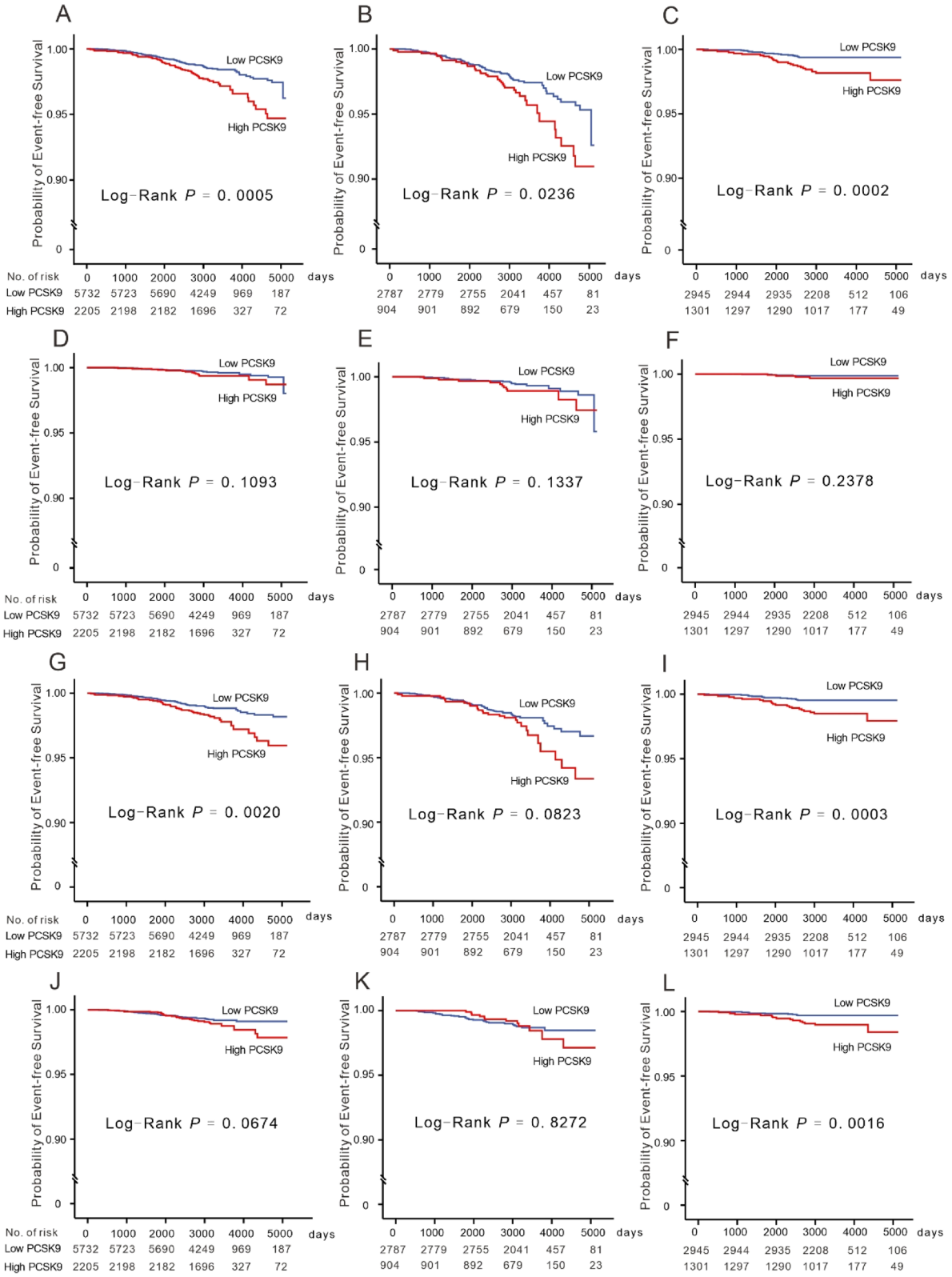

Fig. 4 Kaplan–Meier survival analysis of the effects of PCSK9 concentration on long-term outcomes, stratified by sex. Long-term outcomes were all-cause mortaliy (**A**–**C**), cardiovascular mortality (**D**–**F**), non-cardiovascular mortality (**G**–**I**), and cancer mortality (**J**–**L**) for the overall study population (A, D, G, J), for men (B, E, H, K), and for women (C, F, I, L)

Table 4 Cox regression analysis of all-cause, cardiovascular (CV), non-cardiovascular (non-CV), and cancer mortality, stratified by sex

	Total mortality		CV mortality		Non-CV mortality		Cancer mortality	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Model 1								
Total	1.57 (1.14–2.18)	0.0063	1.52 (0.79–2.92)	0.2148	1.59 (1.10–2.32)	0.0148	1.40 (0.85–2.29)	0.1835
Male	1.37 (0.93–2.03)	0.1126	1.51 (0.72–3.17)	0.2794	1.33 (0.84–2.11)	0.2262	0.97 (0.50–1.88)	0.9318
Female	2.19 (1.18–4.07)	0.0132	1.56 (0.38–6.33)	0.5347	2.39 (1.19–4.77)	0.0138	2.74 (1.17–6.44)	0.0205
Model 2								
Total	1.68 (1.16–2.42)	0.0059	1.73 (0.85–3.51)	0.1287	1.65 (1.07–2.53)	0.0230	1.58 (0.92–2.71)	0.0975
Male	1.40 (0.89–2.21)	0.1444	1.71 (0.75–3.88)	0.2023	1.29 (0.74–2.23)	0.3676	1.29 (0.74–2.23)	0.3676
Female	2.39 (1.23–4.63)	0.0099	1.72 (0.41–7.18)	0.4564	2.62 (1.24–5.54)	0.0119	2.62 (1.24–5.54)	0.0119

P value for model 1: adjusted for age, sex, BMI, and current smoking status for the overall study population and adjusted for age, BMI and current smoking status for male and female subgroups

P value for model 2: adjusted for age, sex, BMI, current smoking status, LDLC, HDLC, and TyG index for the overall study population and adjusted for age, BMI, current smoking status, LDLC, HDLC, and TyG index for male and female subgroups

pronounced in female participants, with higher platelet count independently associated with high PCSK9 concentration only in female participants. The ORs for IR, MetS, DM, and MASLD increased progressively across PCSK9 quartiles, with the associations stronger or only observed in women. Kaplan–Meier survival and Cox regression analyses also showed increased all-cause, non-cardiovascular, and cancer mortalities with elevated PCSK9 concentrations, especially in women. These results provide further evidence of the link between PCSK9 and metabolic disorders and related sex-specific differences.

Associations of PCSK9 concentration with anthropometric parameters and metabolic traits

Both age and sex affected PCSK9 associations in univariate and multivariate analyses, with elevated PCSK9 concentrations in older and female participants, aligning with results from other studies [11, 13, 14, 26, 27]. In the present study, high PCSK9 concentration was associated with high blood pressure and an increased risk of hypertension. Mean blood pressure was not independently associated with PCSK9 concentration in the overall study population or in sex subgroups. Inconsistent results regarding the association between PCSK9 concentration and blood pressure have also been observed in other studies [10, 13, 14, 28].

LDL-C concentration has typically been the metabolic parameter most consistently associated with PCSK9 concentration. Nevertheless, studies have demonstrated strong associations between triglyceride concentration and PCSK9 concentration [11, 13, 14, 26, 27]. In the present study, triglyceride concentration was the metabolic parameter most strongly associated with PCSK9 concentration. PCSK9 may be directly involved in triglyceride metabolism through an increase in apolipoprotein B synthesis and very-LDL production through the inhibition of intracellular apolipoprotein B degradation or through binding and degradation of very-LDL receptor [29]. We observed no association between PCSK9 concentration and HDL-C concentration in the overall study population and in both sex subgroups. This result is consistent with that of a Chinese study [14] but different from that of a study involving a Caucasian population and different from that of a study involving a Sub-Saharan population. Those studies have demonstrated that elevated PCSK9 concentration is associated with high HDL-C concentration [11, 13, 27, 30]. Whether ethnic heterogeneity affects the underlying mechanism remains unclear.

Association between PCSK9 concentration and MetS

High PCSK9 concentration is associated with a higher prevalence of MetS [14, 27]. Our data revealed a significant association between PCSK9 concentration and the risk of MetS in both sexes, with the risk being higher in female participants than in male participants. Shi J, et al. [14] demonstrated a significant association between PCSK9 concentration and the risk of MetS in women but not in men. Large, population-based studies or meta-analyses are warranted to elucidate the role of PCSK9 in MetS.

Association between PCSK9 concentrations and IR, DM and glucose metabolism parameters

High PCSK9 concentrations and quartiles were associated with higher fasting plasma glucose and HbA1c concentrations and higher risks of IR, DM, and DM, with a stronger association in female participants than in male participants. This is consistent with results of studies that have demonstrated involvement of PCSK9 in glucose homeostasis and IR [13, 14, 26, 30] and DM [31, 32] and in contrast to results of other studies that have demonstrated that PCSK9 concentration is positively correlated with LDL-C concentration and that LDL-C-lowering PCSK9 variants are associated with higher circulating fasting plasma glucose concentrations and increased risk of DM [18, 19]. PCSK9 inhibition does not increase the risk of new-onset diabetes nor worsen glycemia [33,

34]. Some animal and human studies have reported lower PCSK9 levels in diabetic subjects or suggested that low PCSK9 may impair insulin secretion [35, 36]. While PCSK9 was measured only at baseline, our findings demonstrate significant associations with long-term metabolic and mortality outcomes, consistent with prior literature. Future studies incorporating serial PCSK9 measurements would be valuable to evaluate intra-individual variability and strengthen causal inference regarding its prognostic utility. Further research is necessary to investigate the underlying mechanism of the association between PCSK9 and glucose homeostasis.

Association between PCSK9 concentrations and liver dysfunction biomarkers and the risk of MASLD

High PCSK9 concentrations and quartiles were significantly associated with an increased risk of MASLD and with lower bilirubin concentrations. High PCSK9 quartiles were associated with adverse liver enzyme profiles—including higher AST, ALT, and γGT concentrations—in the overall study population and in the female subgroup but not in the male subgroup. These findings align with those of other studies that have demonstrated a robust correlation between circulating PCSK9 and hepatic steatosis severity, independent of conventional metabolic confounders [37]. Notably, preclinical studies have shown that PCSK9 deficiency confers resistance to diet-induced hepatic steatosis in mice, suggesting a causal role in liver lipid accumulation. The relationship between PCSK9 and liver health is complex and context-dependent. PCSK9 was not associated with hepatic fat or histological severity in one study [38]. In another study, genetic PCSK9 loss-of-function mutations were not associated with increased NAFLD risk [39]. This mixed evidence underscores the possibility of ethnic, environmental, or methodological variability affecting the PCSK9–MASLD relationship.

Our results, together with those already published in the literature, suggest that elevated PCSK9 may serve both as a biomarker of hepatic steatosis—potentially through effects on very-LDL metabolism, cholesterol trafficking, or hepatic inflammation—and play a mechanistic role in disease progression. The emerging consensus reinforces MASLD as the hepatic manifestation of systemic metabolic dysfunction, with PCSK9 positioned at the intersection of lipid, glucose, and liver metabolism [8–10]. Given these complex associations, further longitudinal and mechanistic studies in diverse populations are warranted to determine whether PCSK9 inhibition could offer therapeutic benefit or prevention in MASLD, potentially augmenting current interventions targeting metabolic health and liver disease.

Association between PCSK9 concentration and hematological parameters

We observed increased hematocrit and platelet counts with elevated PSCK9 concentrations in univariate and multivariate analyses. In another study, PCSK9 concentration was positively associated with platelet count in patients with coronary artery disease (40). In yet another study, PCSK9 added to platelet-rich plasma samples significantly enhanced platelet aggregation induced by a subthreshold concentration of epinephrine (41). That study also observed reduced arterial thrombus formation and stability and platelet function in mice with a low PCSK9 concentration (41). These findings suggest that PCSK9 affects platelet aggregation behaviors. Platelet aggregation is relevant not only in thrombus formation but also in the onset and progression of atherothrombotic disease (42). The finding of an association between PCSK9 and red blood cell count is novel. The finding of an association between PCSK9 and leucocyte count is inconsistent with that of other studies (40, 43). Further research is warranted to confirm our findings.

Association between PCSK9 concentration and long-term outcomes

Associations between PCSK9 concentration and all-cause mortality are inconsistent in the literature (44–48). The present study provides new evidence that high circulating PCSK9 concentrations are significantly associated with increases all-cause mortality, a risk driven primarily by cancer-related deaths rather than cardiovascular mortality. Notably, this association was particularly pronounced in women. These findings challenge the conventional view of PCSK9 as solely a regulator of lipid metabolism and cardiovascular risk, highlighting its potential role in oncogenesis and disease progression. A growing body of preclinical evidence has been pointing to the multifunctional nature of PCSK9, which encompasses a wide range of cellular processes that directly influence cancer progression. PCSK9 modulates key oncogenic signaling pathways, such as PI3K/Akt, MAPK, and Wnt/β-catenin (49). By influencing these pathways, PCSK9 affects cellular proliferation, survival, apoptosis, and angiogenesis—all hallmarks of cancer (50). PCSK9 concentration may be a biomarker for the prognosis of several significant malignancies, including gastric, pancreatic, kidney, hepatocellular, and breast cancers (2, 3, 51). The clinical implications of these findings are substantial. First, they suggest that circulating PCSK9 could serve as a noninvasive prognostic biomarker in oncology, helping to stratify patients and predict outcomes. Second, they further indicate PCSK9's potential as a therapeutic target in cancer treatment. Targeting PCSK9, perhaps in conjunction with standard chemotherapy or immunotherapy, could

represent a novel strategy to inhibit tumor growth and metastasis.

The role of sex in the association between PCSK9 concentration and various phenotypes

Our findings underscore the significant influence of sex on the associations between circulating PCSK9 concentrations and a range of cardiometabolic and hematologic traits. Our findings on the influence of sex are consistent with those of several other studies (13, 14, 27). In the present study, female participants exhibited higher PCSK9 concentrations than did male participants, independent of age and other covariates. More importantly, sex-stratified analyses revealed stronger associations between PCSK9 concentrations and key metabolic phenotypes—including IR, MetS, DM, and triglyceride concentration—in female participants than in male participants. Age-stratified analyses also showed larger differences with PCSK9 levels in women than in men between different age subgroups (age ≥50 vs. age <50). These findings are in line with observations from other studies that have suggested that women may be more metabolically sensitive to variations in PCSK9, potentially because of differences in sex hormone regulation, lipid metabolism, or adipose tissue distribution (11, 26).

Sex-specific trends were particularly notable in associations of PCSK9 with biomarkers of IR, MetS, and DM, where elevated PCSK9 concentrations were significantly associated with increased odds of MetS in women but not in men, who had only slightly increased odds of MetS. Similarly, the risk of DM and high fasting glucose concentration across increasing PCSK9 quartiles was more pronounced among female participants, suggesting that PCSK9 may interact differently with glucose and lipid regulatory pathways by sex. Furthermore, in our study, long-term outcomes, namely all-cause mortality and cancer mortality, were also more robustly linked to PCSK9 concentrations in female participants. The biological basis for this finding remains to be clarified.

Collectively, these results highlight the necessity of considering sex as a biological variable in studies of PCSK9 and metabolic disease. They also point to the potential utility of sex-specific thresholds or interpretations of PCSK9 in clinical risk stratification. Future mechanistic studies are warranted to explore hormonal, genetic, and molecular mediators of these sex-dependent associations.

Study strengths and limitations

To the best of our knowledge, this is the largest population-based study to evaluate associations of circulating PCSK9 concentration with metabolic disorders and long-term mortality. The study enrolled 7,950 healthy Taiwanese participants. Multivariate stepwise linear regression analysis was performed to define the independent correlates of circulating PCSK9 concentration, adjusting for a broad range of confounding factors. A significant limitation of our study is the homogeneous ethnic composition of our cohort, which limits generalizability to other populations. While emerging evidence from European and African studies suggests that sex-specific PCSK9-metabolic associations may represent a universal biological phenomenon rather than an East Asian-specific finding, direct replication in diverse ethnic cohorts is needed. Future studies should specifically examine whether the magnitude of these associations varies across ethnicities, particularly given known genetic variations in PCSK9 function and expression across populations. The second limitation of this study is its low mortality rate, which made the significant level in the outcome studies became more difficult to achieve, especially in cardiovascular mortality. Extending the follow-up period may enhance the significance of the differences observed. The third limitation of this study is that it only enrolled adults between 30- and 70-years-old. The findings may not be generalizable to teenagers or older adults. The fourth limitation of this study is that we used TyG indices as IR markers instead of using the hyperinsulinemic clamp or HOMA-IR methods, which are considered the best methods for measuring IR. Further, in this study, we did not include Lp(a) for analysis. Given the established relationship between PCSK9 and lipoprotein(a), the absence of Lp(a) data limits the comprehensiveness of the metabolic risk assessment. We have recently reported a causal relationship between PCSK9 levels and Lp(a) concentrations through MR analysis. Including Lp(a) in future analyses would enhance the mechanistic insights [52]. In addition, information on pre-existing cardiovascular disease was based solely on self-reported data and not confirmed by clinical diagnosis. Therefore, we could not definitively exclude participants with baseline CVD, which may have contributed to residual confounding in mortality analyses. Although PCSK9 was measured only at baseline, our findings demonstrate significant associations with long-term metabolic and mortality outcomes, consistent with prior literature. Future studies incorporating serial PCSK9 measurements would be valuable for evaluating intra-individual variability and strengthening causal inference regarding its prognostic utility. The absence of data on inflammatory and specific cancer biomarkers prevented a more profound investigation into the drivers of the observed mortality risks. To validate PCSK9 as a clinically applicable biomarker, further studies should focus on optimizing cutoff values across diverse cohorts, evaluating predictive performance when combined with established metabolic and inflammatory markers, and conducting cost-effectiveness and feasibility analyses for routine screening. These steps will help

establish the generalizability and clinical utility of PCSK9 measurement and determine its integration into practice for risk prediction and disease prevention.

Conclusion

High circulating PCSK9 concentration is associated with progressively worse cardiometabolic risk profiles (i.e., increasing risks of IR, MetS, DM, and MASLD) and higher risks of all-cause and cancer mortality, predominantly in women. PCSK9 represents a promising therapeutic target for the prevention of metabolic disorders and for improving health outcomes in patients with high PCSK9 concentrations. Due to inflammation or lipid metabolism may be the potential mechanisms for the associations, future cohorts should be designed to concurrently measure circulating PCSK9, a comprehensive panel of metabolic and inflammatory markers, and detailed cancer risk profiles to untangle these complex relationships.

Supplementary Information

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Supplementary Material 1. Supplementary Figure 1. Definitions of NAFLD, MAFLD, and MASLD. Abbreviation: HBV: hepatic B virus; HCV: hepatic C virus; BMI: body mass index; WC: waist circumference; TG: triglycerides; HDL-C: high-density lipoprotein-cholesterol; HbA1c: glycosylated hemoglobin; hs-CRP: high sensitivity C-reactive protein; HOMA-IR, homeostatic model for assessment of insulin resistance; NAFLD: non-alcoholic fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease (Ko e al., 2025). Supplementary Figure 2. Frequency distribution of PCSK9 level in the study (N = 7950) (A), in male and female only (B) Supplementary Figure 3. Box plots of PCSK9 levels in 4064 participants with NAFLD (A-C) and percentage of NAFLD (D-F) across the quartiles of PCSK9. P1: unadjusted, P2: adjusted for age, BMI, sex and current smoking status. Supplementary Figure 4. ORs of the quartiles of PCSK9 in participants with IR by TyG (A), IR by TyG-BMI (B) or NAFLD (C), stratified by sex. Comparison of Q2, Q3 or Q4 with Q1 as the reference group. ORs of the quartiles of PCSK9 were estimated after adjusting for age, sex, BMI and current smoking status for all participants, adjusting for age, BMI and current smoking status for male or female participants. aEffect of sex on the association between quartiles of PCSK9 and IR by TyG, IR by TyG-BMI or NAFLD.

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Authors' contributions

Y.-L.K., and K.-H.Y. devised the main conceptual ideas of the study; L.-A.H., and S.W. designed and developed the methodology; S.W. validated the analytical data and software; K.-H.Y., and N.-Y.T performed the formal analysis; Y.L.K. resources; K.-H.Y., and N.-Y.T. wrote the original draft of the manuscript; Y.-L.K., and L.-A.H. wrote, reviewed and revised the manuscript; L.-A.H., and S.W. prepared visualization; Y.L.K. supervised the project; . Y.-L.K., and K.-H.Y. acquired funding. All authors have read and agreed to the published version of the manuscript.

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Data availability

Upon request, the corresponding author can provide access to the data presented in this study.

Declarations

Competing interests

The authors declare no competing interests.

Author details

[1]The Division of Cardiology, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan
[2]School of Medicine, Tzu Chi University, Hualien, Taiwan
[3]The First Cardiovascular Division, Department of Internal Medicine, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan
[4]Department of Life Science, Chinese Culture University, Taipei, Taiwan
[5]Department of Research, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan

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