Lipids in Health and Disease

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Causal relationship between drug target genes of LDL-cholesterol and coronary artery disease: drug target Mendelian randomization study

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Abstract

Background High LDL-cholesterol (LDL-C) is a well-known risk factor for coronary artery disease (CAD). *PCSK9*, *HMGCR*, *NPC1L1*, *ACLY*, and *LDLR* gene have been reported as lipid lowering drug genes related to LDL-C lowering. However relevant Asian studies were rare.

Methods We examined the causality between LDL-c drug target genes and CAD using Korean and Japanese data using the two sample Mendelian Randomization (MR) method. We conducted two-sample MR analysis of LDL-c lowering drug target genes (7 Single-nucleotide polymorphisms (SNP) in *PCSK9*, 6 SNPs in *HMGCR*, 5 SNPs in *NPC1L1*, 9 SNPs in *ACLY*, 3 SNPs in *LDLR*) and CAD. We used summary statistics data from the Korean Genome Epidemiology Study (KOGES) for LDL-C data, and Biobank of Japan (BBJ) for CAD data.

Results For every 10 mg/dl decrease in LDL-C determined by four significant SNPs in the *PCSK9* gene, the risk of CAD decreased by approximately 20% (OR = 0.80, 95% CI: 0.75–0.86). The risk of CAD decreased by 10% for every 10 mg/dl decrease in LDL-C due to the six significant SNPs in the *HMGCR* gene (OR = 0.90, 95% CI: 0.86–0.94). Due to the two significant SNPs in the gene *LDLR*, the risk of CAD decreased by approximately 26% for every 10 mg/dl decrease in LDL-C (OR = 0.74, 95% CI: 0.66–0.82). The combined effect on CAD showed the largest effect size for the PCSK9 gene and LDLR gene, and the reduced CAD risk induced by these two genes together was OR = 0.78 (95%CI, 0.74–0.83). Finally, the combined effect of all three genes (PCSK9, HMGCR, and LDLR) was OR = 0.85 (95%CI, 0.79–0.91).

Conclusion LDL-C reduction estimated by SNPs in LDL-C lowering drug target genes significantly reduced the risk of CAD. We found the potential of using of proxy research design for clinical trials using LDL-C lowering drugs.

Keywords LDL-cholesterol, Coronary artery disease, Mendelian randomization, Durg target gene

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Introduction

Atherosclerosis is well known as the underlying pathophysiology of coronary artery disease (CAD). An increase in LDL-cholesterol (LDL-C) leads to CAD through low-grade inflammation, lipid accumulation, and plaque formation within the intima of the vessel wall. Therefore, high LDL-C is a well-known risk factor for the development of CAD and has been a target of treatment [1].

PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9), HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase), NPC1L1 (NPC1L1, ACLY and LDLR), ACLY (ATP Citrate Lyase) and *LDLR (Low-Density Lipoprotein Receptor)* genes have been indentified as targets of lipid lowering drugs associated with LDL-c reduction. At the moment, the association between these drugs and the risk of CAD has been largely investigated through observational studies [2, 3] or clinical trials [4, 5]. In the case of observational studies, conclusions regarding causality between drugs and CAD were limited due to limitations such as confounding variables, reverse causation, and measurement error. Clinical trials are currently considered the most robust method for establishing causality. However, clinical trials require a huge budget, and there are some aspects that cannot be easily conducted due to reporting of side effects from drug administration to patients, ethical aspects, etc.

Recently, the Mendelian randomization (MR) method using genetic factors has been reported as a method to complement part of clinical trials [6–10]. It has been reported as a way to solve the three limitations that have been problematic in observational studies by taking advantage of the fact that genes used as instrumental variables in MR research are randomly assigned at the time of conception [11, 12]. In fact, recently, attempts have been made to use scores estimated based on genes related to LDL-C for Western people as scores that mimic drugs [6, 7, 13]. Studies using gene-based mimic drug reported results consistent with the effect observed in clinical trials.

In fact, Ference et al. [6] calculated a genetic score that mimics the effects of statins or an ATP citrate lyase inhibitor through single necleotide polymorphisms (SNPs) included in genes related to LDL-C and estimated the clinical effect of whether this actually reduces the risk of developing CAD. If this research is successfully conducted and replicated from many races and countries, it is expected that it can be used as a way to predict the effects of actual clinical trials on drugs in advance. However, there is still a lack of research on LDL-C lowering drug genes in Asian populations, highlighting the need for further studyies.

We estimated LDL-C determined by drug target genes based on LDL-C lowering genes reported through existing literature [6, 13], using data from Koreans and Japanese biobank, and conducted a two-sample MR method to determine whether a decrease in genetically determined LDL-C level reduces the risk of CAD. For this purpose, our study was conducted in three steps. The first step was to determine whether the SNPs (G) reported in the genes for each LDL-C lowering drug target genes had a sufficient association with LDL-C (X) in Korean biobank data. The second step was to determine whether the SNPs (G) reported in the genes for each drug were associated with the risk of CAD (Y) using Japanese Biobank. In the third step, the ultimate goal is to determine the extent to which LDL-C lowering drugs, alone or in combination, reduce the risk of CAD by gene.

This study aims to test two hypotheses

The first hypothesis is that SNPs associated with lipid lowering, which have been identified in Western populations, will also be relevant in East Asians.

The second hypothesis is that a combination of two or more lipid-lowering drug target genes will lead to a greater reduction in LDL-C levels.

Materials and methods

Data source

Genetic instruments regarding drug targets on LDL-C were extracted from the summary level GWAS (Genome Wide Association Study) data from the Korean Genome Epidemiology Study (KoGES) ($n = 72,299$) [14]. For CAD outcomes, GWAS summary statistics were obtained from Biobank of Japan (BBJ) ($n = 178,726$) [15]. The data usage and study design of our study were approved by the Institutional Review Board of Ewha Womans University Seoul Hospital (2021-08-026).

Mendelian randomization

We conducted two-sample MR aiming to determine whether the reduction of LDL-C caused by genetic variants from the gene encoding the drug target protein reduced the risk of CAD (Fig. 1).

In the primary drug target MR analysis, effect estimates for genetically proxied inhibition of lipid lowering drug target genes were derived using the random-effects inverse-variance weighted (IVW) model [16]. Wald ratio was calculated to estimate the association between genetically proxied expression and CAD. Herein, using the Wald ratio method, we calculated the beta values and standard errors (SEs) for the association with CAD by leveraging the effect estimates from the exposure GWAS (GX) and the outcome GWAS (GY) for each individual SNP within respective genes. In this study, we analyzed the effect of individual drug targets on CAD in the primary analysis and the combination of drug targets on CAD in the secondary analysis separately. These values were then meta-analyzed per gene, yielding integrated

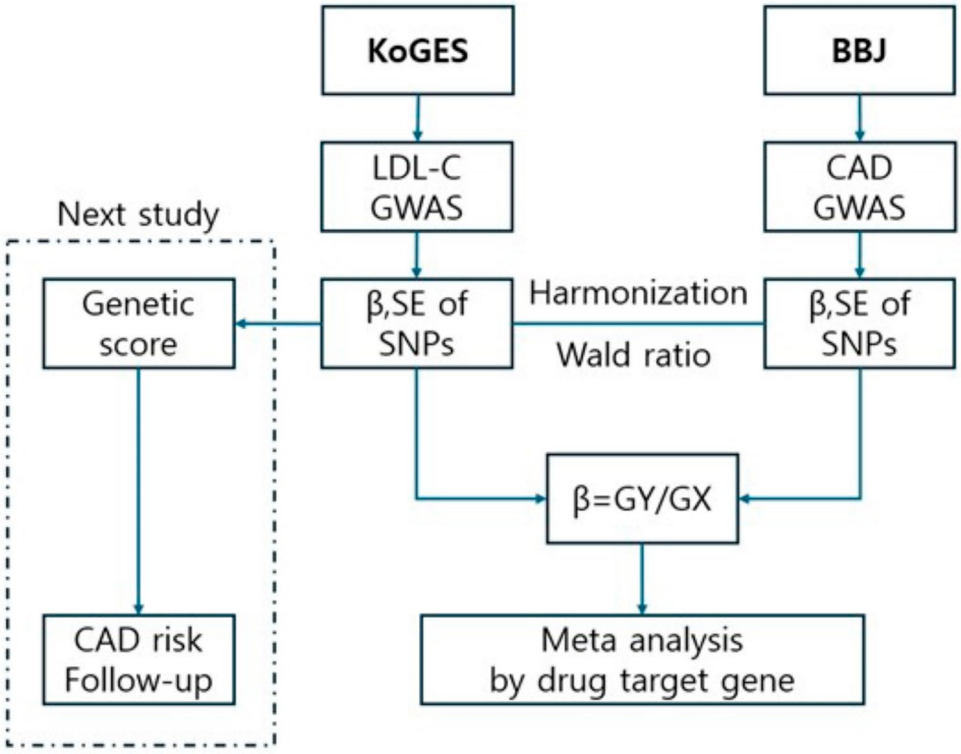

Fig. 1 Overview of the Mendelian randomization study design

outcomes. To improve the robustness and accuracy of causal effect estimates, we conducted an additional analysis incorporating the prediction interval (PI), which accounts for both the estimated effect size and the variability among studies (heterogeneity).

Instrumental variables

The instrumental variables in this study were selected from SNPs located in lipid lowering drug target genes, as reported by Ference et al. in Western populations. Regarding allele harmonization, we checked the genotype direction and minor allele frequency (MAF) in both datasets to ensure consistency.

Statistical analysis

Two-sample MR was conducted to investigate the associations of genetically proxied inhibition of lipid-lowering drug targets and LDL-C on the risk of CAD. *TwoSampleMR* R package (v0.5.6, https://github.com/mrcieu/TwoSampleMR) was used for performing our analysis.

For each genetic variant, we first assessed its association with serum LDL-cholesterol (LDL-C) levels in the Korean Genome and Epidemiology Study (KoGES) dataset and estimated its effect size. We then examined the association of these variants with CAD risk using summary statistics from the Biobank Japan (BBJ) dataset. The Wald ratio method was applied to estimate causal effects for single instrumental variables, while for multiple instrumental variables, we used the inverse-variance weighted (IVW) method as the primary MR analysis. To facilitate comparison across different genetic variants and drug target genes, we scaled each effect-size estimate to reflect the change in CAD risk per standard decrement of 10 mg/dL in LDL-C levels. This standardization ensures comparability with previous lipid-lowering drug target MR studies.

Table 1 Baseline characteristics of the study cohort participants

	KoGES	Biobank Japan
Baseline year	2004–2013	2003–2013
Individual data	79,916	NA
Summary data	72,299	178,726
Age, year	54.2	62.1
Female (%)	63.1	46.9
LDL-cholesterol, mg/dL	119.1	122.8
Coronary artery disease event	NA	32,512

KoGES: Korean Genome Epidemiology Study; NA: not available

The baseline characteristics are based on summary statistics from the KoGES and Biobank Japan datasets

Results

Table 1 shows the summary level characteristics of the data sources used in our study. We analyzed the summary level data of 79,916 participants from KoGES data and 178,726 participants were involved in BBJ. In KOGES, where personal data was available, the mean age of the

subjects was 54.2 years- old and the average LDL-C was 119.1 mg/dl. In BBJ used as outcome data, the number of participants with coronary artery events was 32,512. The mean age of the subjects was 62.1 years-old and the average LDL-C was 122.8 mg/dl.

In this study, among the five genes that lower LDL, two genes (NPC1L1, ACLY) were excluded because they had no SNPs showing significant association or had many missing SNPs in the Asian data (Supplementary Table 1).

Table 2 described the estimated effects of genetic variant (G) in lipid lowering drug targets on LDL-C (X) derived from KoGES summary level data (G-X association). The gene *PCSK9* exhibited significant reductions in LDL-C with four out of seven SNPs, while all six SNPs of *HMGCR* and one out of five SNPs of *NPC1L1* showed significant reductions in LDL-C. For the gene *ACLY*, although nine SNPs were reported, only two were present in the KOGES dataset, neither of which demonstrated significant associations with LDL-C. Table 2 also provides a summary of the effect of SNPs (G) related to LDL-C lowering drugs on CAD (Y) (G-Y association), based on summary statistics obtained from the BBJ dataset. Among the five SNPs of the gene *PCSK9*, one SNP (rs2479394) showed significant association with CAD, while among the six SNPs of *HMGCR*, three SNP (rs12916, rs17238484, rs10066707) showed significant association, and among the three SNPs of *LDLR*, two SNPs (rs1122608, rs688) exhibited significant association with CAD.

Figure 2 shows the causal relationship between the three genes (*PCSK9*, *HMGCR* and *LDLR*) and CAD. The random effect of four SNPs on *PCSK9* was OR = 0.80 (95%CI, 0.76–0.86). Among them, the one with the largest effect size was rs2479394 (OR = 0.71) (Fig. 2A). The HMGCR gene contained the most 6 SNPs, and the random effect of these SNPs on CAD was OR = 0.90 (95%CI, 0.86–0.94) (Fig. 2B). Among the three genes, *LDL-R* gene has the greatest effect on reducing CAD risk. Two SNPs (rs1122608, rs688) belonging to the *LDL-R* gene showed negative effects and were significant, and the random effect on CAD risk was OR = 0.74 (Fig. 2C).

Figure 3 shows the combined effect of two or three combinations of the three genes (*PCSK9*, *HMGCR*, and *LDLR*) and CAD. The combined effect of *PCSK9* and *HMGCR* (Fig. 3A) and the combined effect of *HMGCR* and *LDLR* (Fig. 3C) showed the same effect size (OR = 0.87). The combined effect on CAD showed the largest effect size for the *PCSK9* gene and *LDLR* gene (Fig. 3B). The common reduction in CAD risk induced by these two genes was OR = 0.78 (95%CI, 0.74–0.83). Finally, the combined effect of all three genes (*PCSK9*, *HMGCR*, and *LDLR*) was OR = 0.85 (95%CI, 0.79–0.91) (Fig. 3D).

Discussion

Our study evaluated whether the reduction in LDL-C determined by SNPs within genes related to lipid-lowering drug targets decreases the risk of coronary artery disease (CAD). Among the five lipid-lowering genes reported by Ference et al., [6, 13] evaluation was feasible in KoGES and BBJ datasets for the final three genes: *PCSK9*, *HMGCR*, and *LDLR*. Meta-analysis of the effects of SNPs existing within these three genes yielded integrated outcomes. The estimated effect of a mimicked

Table 2 Estimated effects of genetic variations in lipid Lowering drug targets on LDL-cholesterol

Target gene, Chr	Instrument(s)	Ference et al.		Korean Genome Epidemiology Study (KoGES)				Biobank Japan (BBJ)			
		EA	EAF	EA/OA	EAF	beta (SE)*	*P* value	EA/OA	EAF	beta (SE)*	*P* value
PCSK9, 1	rs11206510	C	0.154	C/T	0.054	-1.622 (0.379)	1.945E-05	C/T	0.054	-0.018 (0.022)	0.4121
	rs2479409	A	0.667	A/G	0.356	-0.233 (0.179)	0.1951	A/G	0.378	-0.005 (0.001)	0.6022
	rs2149041	C	0.839	C/G	0.314	-1.547 (0.184)	5.757E-17			NA	
	rs2479394	A	0.715	A/G	0.354	-1.012 (0.179)	1.580E-08	A/G	0.329	-0.034 (0.010)	0.0009
	rs10888897	T	0.394	T/C	0.210	-1.413 (0.2111)	2.229E-11	C/T*	0.831	0.024 (0.013)	0.0648
	rs7552841	C	0.635			NA				NA	
	rs562556	G	0.194	G/A	0.020	0.617 (0.618)	0.3181	A/G	0.969	0.008 (0.028)	0.7837
HMGRC, 5	rs12916	T	0.569	T/C	0.475	-2.527 (0.172)	4.722E-49	C/T	0.526	-0.028 (0.009)	0.0035
	rs17238484	G	0.747	T/G*	0.320	-2.364 (0.184)	1.445E-37	T/G*	0.340	-0.034 (0.010)	0.00088
	rs5909	G	0.898	A/G*	0.015	-1.932 (0.715)	0.0069	A/G*	0.013	-0.032 (0.042)	0.4439
	rs2303152	G	0.880	A/G	0.112	-1.567 (0.274)	1.075E-08	A/G*	0.073	0.022 (0.019)	0.2264
	rs10066707	G	0.583	G/A	0.482	-1.041 (0.172)	1.086E-09	A/G*	0.512	-0.020 (0.010)	0.0498
	rs2006760	C	0.814	G/C*	0.287	-1.045 (0.190)	3.787E-08	G/C*	0.247	0.013 (0.012)	0.2835
LDLR, 19	rs6511720	T	0.109			NA		T/G	0.0009	0.283 (0.156)	0.0692
	rs1122608	T	0.227	T/G	0.099	-0.692 (0.287)	0.0159	T/G	0.120	-0.035 (0.015)	0.0194
	rs688	C	0.559	T/C*	0.187	-2.371 (0.248)	1.443E-21	T/C*	0.123	-0.068 (0.014)	4.275E-06

EA/OA: Effect allele/Other allele; EAF: effect allele frequency; NA: not available

* The sign of the regression coefficient was changed to match the genotype in the study by Ference et al. (2019)

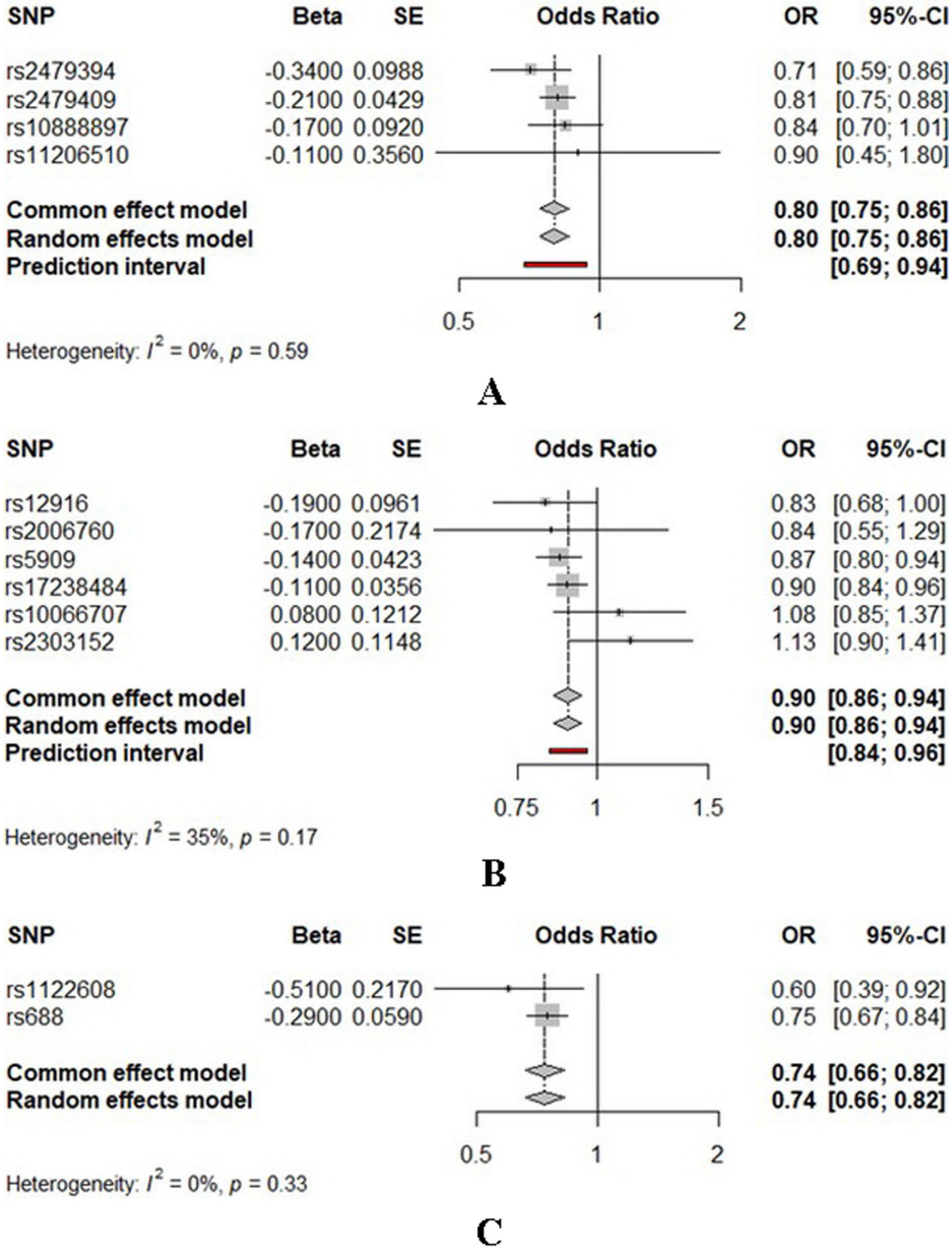

Fig. 2 Meta-analysis results of the effect on CAD per 10 mg/dl reduction in LDL-C by the LDL-C drug target gene. (**A**) PCSK9 gene. (**B**). SNPs in HMGCR gene. (**C**). SNPs in LDLR gene

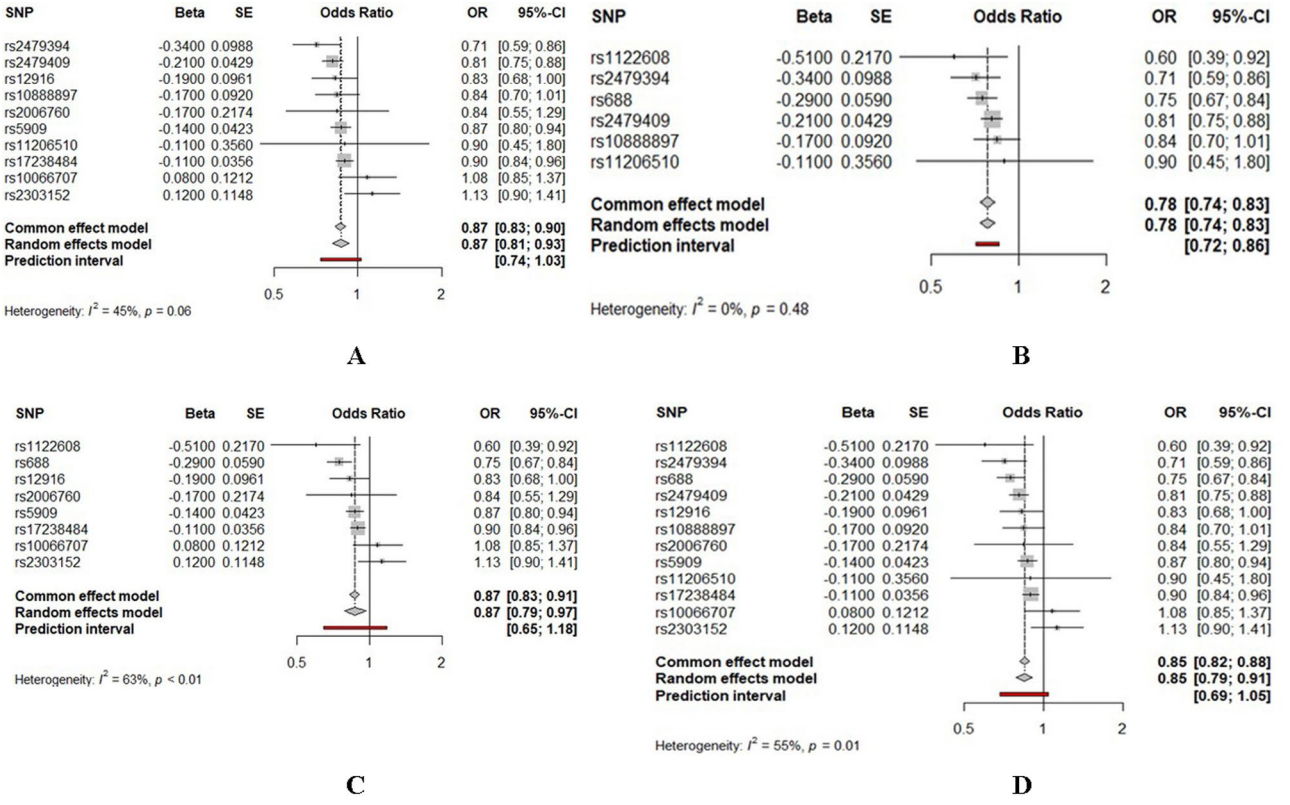

Fig. 3 Meta-analysis results of the effect on CAD per 10 mg/dl reduction in LDL-C by the combined LDL-C drug target gene. (**A**). SNPs in PCSK9 gene plus HMGCR gene. (**B**). SNPs in PCSK9 gene plus LDLR gene. (**C**). SNPs in HMGCR gene plus LDLR gene. (**D**). SNPs in PCSK9 gene plus HMGCR gene plus LDLR gene

drug attributed to *LDLR* on CAD was found to be the most significant. Specifically, for each 10 mg/dl reduction in LDL-C attributed to the mimicked drug estimated by LDLR, the risk of CAD decreased by approximately 26% (OR = 0.74, 95% CI: 0.66–0.82), which was significantly higher than the effect estimated by *HMGCR* (OR = 0.80, 95% CI: 0.86–0.94). That is, the 95% CIs of the odds ratios of *LDLR* and *HMGCR* did not overlap.

The *PCSK9* gene is well known for its effect on cholesterol levels in the bloodstream. In the study by Ference et al. [6, 13], conducted in a Western population, the odds ratio for CAD per 10 mg/dL reduction in LDL-C due to the PCSK9 gene was 0.83 (95% CI, 0.83–0.87). In contrast, our study found a similar odds ratio of 0.80 (95% CI, 0.75–0.86). Among the *PCSK9* gene variants reported by Ference et al. [6, 13], evaluation of six out of seven selected SNPs revealed significant reductions in LDL-C based on the KoGES dataset, a repository of Korean biospecimens. Notably, within these three SNPs, rs11206510 (b=-1.622), rs2149041 (b=-1.547), and rs10888897 (b=-1.413) demonstrated similar LDL-C reductions. Conversely, comparisons using data from the Global Lipids Genetics Consortium (GLGC) showed higher effects for rs11206510 (b=-2.6592), rs2149041 (b=-2.0352), and rs10888897 (b=-1.6224) compared to KoGES, as reported by Ference et al. in 2019 [13]. Furthermore, the genetic frequencies of these SNPs exhibited a similar pattern.

Loss-of-function mutations in the *HMGCR* gene may lead to reduced cholesterol levels. In this study, six SNPs within the *HMGCR* gene, known to lower LDL-C, were selected and applied to the KoGES dataset, comprising biospecimens from Korean individuals. All six SNPs significantly lowered LDL-C levels. Among these, rs12916 exhibited a greater reduction in LDL-C as the number of T alleles increased, with a decrease of 2.527 mg/dl (b=-2.527, SE = 0.172, p value = 4.722E-49) compared to individuals with only the C allele (Table 2). This effect was slightly larger than the − 2.3456 mg/dl (SE = 0.1216, p value = 7.79E-78) reported in the GLGC dataset, which primarily consists of individuals of Western descent. The KoGES dataset included 72,299 participants, while the GLGC dataset comprised 1,654,860 individuals from 201 studies. Comparing the frequency of the rs12916 SNP, the T allele frequency in Koreans (0.475) was lower than that in the British population (0.5686). The second most influential SNP within the *HMGCR* gene was rs17238484, where each additional G allele, compared to the T allele, resulted in a decrease of 2.364 mg/dl in LDL-C (b=-2.364, SE = 0.184, P value = 1.445E-37). Similarly, the effect observed in KoGES for the G allele (-2.0064 mg/dl,

SE = 0.1984, p value = 7.79E-21) exceeded that reported in the GLGC dataset. The frequency of SNPs associated with the *HMGCR* gene in Koreans appears to be high and similar to that in Western populations, suggesting a comparable genetic architecture. Therefore, comparing the clinical effects attributable to this similarity seems meaningful. Recent research has highlighted that loss-of-function mutations in the *HMGCR* gene may result in reduced cholesterol levels similar to those achieved with statin therapy. Analyzing genetic information from 402,000 individuals using data from the UK Biobank [17] found that for each 38.7 mg/dL reduction in LDL cholesterol due to *HMGCR* gene mutations, the risk of cataracts increased by 14%, and the likelihood of undergoing cataract surgery increased by 25%. This underscores the importance of investigating this topic among the East Asian population.

The *LDLR* gene encodes receptors that bind to LDL cholesterol, a major cause of dyslipidemia, and higher levels of *LDLR* correspond to lower levels of LDL cholesterol. In this study, three SNPs within the LDLR gene, known to lower LDL-C, were selected and applied to the KoGES dataset, comprising biospecimens from Korean individuals, resulting in a significant reduction in LDL-C. Among these, rs688 exhibited a greater reduction in LDL-C as the number of C alleles increased, with a decrease of 2.371 mg/dl (b=-2.371, SE = 0.248, p value = 1.443E-21) compared to individuals with only the T allele (Table 2). This effect was larger than the − 1.728 mg/dl (SE = 0.1184, p value = 3.034E-48) reported in the GLGC dataset [18], primarily composed of individuals of Western descent, as reported by Ference et al. in 2019. The frequency of the C allele of rs688 in KoGES was 0.187, lower than the 0.5586 in the GLGC dataset. Furthermore, SNP rs6511720, reported by Ference et al. [13] was not present in the KoGES dataset and therefore could not be evaluated in this study. *LDLR* facilitates the uptake of LDL particles from circulation, reducing plasma LDL-C levels. Loss-of-function mutations in *LDLR* lead to hypercholesterolemia and increased CAD risk. *PCSK9* promotes *LDLR* degradation, reducing its ability to clear LDL-C, thereby increasing CAD risk [19, 20]. Inhibiting *PCSK9* enhances *LDLR* recycling and lowers LDL-C, reducing CAD incidence. To our knowledge, this study is the first to evaluate the impact of LDL-C-lowering drug target genes on LDL-C levels and CAD risk specifically in East Asians. Our findings highlight significant differences not only in the frequencies of SNPs within LDL-C-lowering genes between East Asians and Western populations but also in their effects on LDL-C and CAD risk, underscoring the importance of population-specific genetic investigations. Such findings suggest the potential utility of these studies as preliminary investigations for clinical trials aimed at assessing CAD occurrence related to LDL-C. Ultimately, these studies are expected to serve as foundational data for treating and preventing complications of heart disease.

A limitation of this study is that it did not analyze the impact of lipid-lowering drug target genes using data from actual cohort studies, limiting the ability to assess longitudinal effects. Additionally, potential confounding factors and sample diversity were not fully accounted for. Future research using data from the National Health Insurance Service of Korea could help validate our findings and address these limitations.

Conclusion

In conclusion, LDL-C reduction estimated by SNPs in LDL-C lowering drug target genes significantly reduced the risk of CAD. We found the potential of using of proxy research design for clinical trials using LDL-C lowering drugs.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02502-z.

Supplementary Material 1

Author contributions

Y.J. conceived the study. Y.J., J.W.S. and M.R. designed the project. Y.J. analyzed the data. T.J.S. supervised the work. Y.J. and J.W.S. wrote the manuscript. All authors have read and agreed to the publication of this manuscript.

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Data availability

The summary statistics data used in this study are publicly available from two sources. The LDL-C data were obtained from the Korean Genome Epidemiology Study (KOGES), while the CAD data were sourced from the Biobank of Japan (BBJ). The datasets can be accessed through their respective databases: KOGES data: [URL or Accession number for KOGES]BBJ data: [URL or Accession number for BBJ]No new data were generated specifically for this study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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