Genetically mimicked effects of evinacumab on psoriasis: a drug target Mendelian randomization study

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ABSTRACT

Background and Objectives: Dyslipidemia has been reported to contribute to the psoriasis pathogenesis. Thus, evinacumab, a novel lipid-lowering drug targeting angiopoietin-like 3, may have therapeutic potential to treat and/or manage psoriasis. **Methods and Study Design:** Summary statistics were obtained from genome-wide association studies addressing psoriasis (FinnGen Consortium; n=216,752) and serum lipid concentrations (United Kingdom Biobank; n=403,943–440,546). Two-sample Mendelian randomization analyses were conducted to evaluate the associations of serum lipid concentrations and genetically mimicked effects of evinacumab, respectively, with the risks of psoriasis and its subtypes. **Results:** Genetically determined per standard deviation increase in triglyceride concentrations was associated with increased risk of psoriasis (OR: 1.17, 95% CI: 1.03–1.32, *p*=0.018), whereas that in low-density lipoprotein-cholesterol (LDL-C) was associated with both psoriasis (OR: 1.22, 95% CI: 1.05–1.43, *p*=0.011) and its subtypes, including arthropathic psoriasis (OR: 1.30, 95% CI: 1.02–1.65, *p*=0.032), psoriasis vulgaris (OR: 1.87, 95% CI: 1.16–2.99, *p*=0.0095), and guttate psoriasis (OR: 2.19, 95% CI: 1.17–4.07, *p*=0.014). Moreover, genetically mimicked effects of evinacumab, via angiopoietin-like 3 inhibition, significantly reduced the risk of psoriasis (OR: 0.752 per standard deviation reduction in triglycerides, 95% CI: 0.577–0.982, *p*=0.036) and arthropathic psoriasis (OR: 0.266 per standard deviation reduction in LDL-C, 95% CI: 0.0886–0.799, *p*=0.018). **Conclusions:** The genetically mimicked effect of evinacumab has the potential to reduce the risk of psoriasis and arthropathic psoriasis by lowering circulating triglyceride and LDL-C concentrations, respectively. These findings suggest that evinacumab may help prevent psoriasis and psoriatic arthritis progression in clinical practice.

Key Words: psoriasis, angiopoietin-like 3, evinacumab, lipid metabolism, Mendelian randomization

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects 0.1–2.0% of the population worldwide.[1,2] Psoriasis presents with irritating skin symptoms and poor appearance. Furthermore, increasing evidence has revealed the association between psoriasis and various systematic medical conditions, including metabolic syndrome,[3] which further impairs the quality of life and increases the medical burden of the patients.[1, 3-7] Several meta-analyses have suggested an association between dyslipidemia and psoriasis,[8,9] and a Mendelian randomization (MR) study demonstrated the causal effects of genetic high-density

lipoprotein-cholesterol (HDL-C) deficiency and high triglyceride concentration on incident psoriasis,[10] thereby suggesting the potential of lipid-lowering drugs in the prevention and treatment of psoriasis.

Angiopoietin-like 3 (ANGPTL3) is a liver-synthesized angiopoietin-like protein that primarily inhibits lipoprotein lipase activity.[11] The pharmacological inactivation of ANGPTL3 with the monoclonal antibody evinacumab effectively reduces triglyceride and low-density lipoprotein-cholesterol (LDL-C) concentrations in patients with hypertriglyceridemia,[12] refractory hypercholesterolemia,[13] and homozygous familial hypercholesterolemia.[14] Since the causal effect of dyslipidemia in psoriasis has been demonstrated,10 evinacumab may be a promising adjuvant therapy for managing psoriasis via ANGPTL3 inhibition and should be carefully investigated.

Mendelian randomization is an analytical method that uses genetic variants (i.e., single-nucleotide polymorphisms (SNPs)) identified from genome-wide association studies (GWAS) as instrumental variables (IVs) to investigate relations between modifiable risk factors and disease.[15] Since genetic variants are randomly assigned before birth, fixed at conception, and unlikely to be related to confounders, the MR design is free from the common confounding biases that exist in observational studies.[16] Furthermore, whereas traditional MR employs identified SNPs from across the genome, the drug target MR utilizes those within or proximal to the gene encoding the drug-targeted protein as IVs.[17] Therefore, the drug target MR provides a proxy for the potential efficacy of lifelong genetic inhibition of the drug target on the outcome disease, thereby establishing it as a fundamental tool for pharmaceutical research and development.[18] Additionally, from a methodological standpoint, given that variants confined to a specific gene region are less likely to influence alternative disease pathways than those across the genome, the drug target MR is less susceptible to bias from horizontal pleiotropy compared to traditional MR.[19]

Therefore, we performed a two-sample drug-target MR analysis to examine the effect of genetically mimicked lifelong use of evinacumab on psoriasis and its subtypes, including arthropathic psoriasis, psoriasis vulgaris, and guttate psoriasis (Figure 1).

MATERIALS AND METHODS

Study design and data sources

First, we performed two MR analyses (Figure 1): 1) a univariable MR to examine the individual effect of three lipid traits on psoriasis and 2) a multivariable MR, with three lipid traits in the same model, to investigate the conditional effects of each lipid trait on psoriasis as

sensitivity analyses. Subsequently, we performed a drug-target MR in the primary analyses to investigate the genetically mimicked effects of lifelong evinacumab use, via ANGPTL3 inhibition, on psoriasis development, through three lipid metabolic pathways, including triglycerides, LDL-C, and HDL-C.

All analyses were performed using GWAS summary statistics, downloaded from the open-access genome-wide association study datasets (https://gwas.mrcieu.ac.uk/). No original data were collected for this study; thus, no ethical approval was required. Specifically, the GWAS summary statistics for psoriasis were obtained from the FinnGen Biobank Analysis Consortium 2021.[20] This database comprised 4,510 psoriasis cases diagnosed according to the International Classification of Diseases (ICD)-10 and 212,242 controls. Subtypes of psoriasis were also identified, including 1,637; 334; and 165 cases of arthropathic psoriasis, psoriasis vulgaris (including nummular and plaque psoriasis), and guttate psoriasis, respectively. All participants were of European descent. The GWAS summary statistics for lipid traits were obtained from the United Kingdom Biobank (UKB) 2020,[21] which was the most recent and largest GWAS of lipids. The GWAS of triglycerides, LDL-C, and HDL-C included 411,016; 440,546; and 403,943 participants of European descent, respectively. Additionally, the univariable MR analyses, including those examining the effect of lipid traits and genetic ANGPTL3 inhibition, respectively, on psoriasis, were replicated in sensitivity analyses, using lipid trait GWAS summary statistics from the Global Lipids Genetics Consortium (GLGC),[22] an independent lipid GWAS consortium from the UKB. The lipid data from GLGC included 177,861; 173,082; and 187,167 participants for triglycerides, LDL-C, and HDL-C, respectively.

Instrumental variable selection

To proxy the serum lipid concentrations, we selected the SNPs associated with serum lipids that were independent of genomic position as IVs, at a genome-wide significance level of $p<0.0001$ and with no linkage disequilibrium ($r^2<0.001$) in a 10,000kb window. In the primary analyses of univariable MR, which utilized UKB lipid data, 284, 158, and 326 SNPs were selected as IVs for triglyceride, LDL-C, and HDL-C concentrations, respectively (Table S1, see Supplementary Materials). In the sensitivity analyses of univariable MR, which utilized GLGC lipid data, 55, 78, and 86 SNPs were selected as IVs for triglyceride, LDL-C, and HDL-C concentrations, respectively (Supplementary Table 2). In the multivariable MR analyses, 384 SNPs identified in the UKB GWAS database as being associated with any of

the three lipid traits at the genome-wide significance level were pooled as IVs (Supplementary Table 3).

To emulate the expected effects of lifelong evinacumab administration, the genetic variants associated with serum lipid concentrations within or near the ANGPTL3 region (on chromosome 1, position 62813191–63321984) were selected as IVs at a significance level of $p<0.0001$.[23] SNPs with a strong linkage disequilibrium were pruned using a clumping procedure with a threshold of $r^2>0.30$ in a 250 kb window. Ultimately, in the primary analyses using the UKB database, 52, 16, and 3 SNPs associated with triglyceride, LDL-C, and HDL-C concentrations, respectively, were selected as IVs from the evinacumab-targeted ANGPTL3 region (Supplementary Table 4). Additionally, in the sensitivity analyses using the GLGC database, 10 and 6 SNPs in the ANGPTL3 region associated with triglyceride and LDL-C concentrations, respectively, were selected as IVs (Supplementary Table 5). No SNPs associated with HDL-C in the ANGPTL3 region were identified in the GLGC GWAS database.

F and conditional *F* statistics were calculated to evaluate the strength of the selected IVs with the exposure in the univariable and multivariable MR, respectively.[24] The possibility of weak instrumental variable bias was considered to be low when the *F* statistic was >10.

MR analyses

In the univariable MR analyses for lipid trait and drug target investigation, the inverse-variance-weighted (IVW) method was used in the primary MR analysis, whereas the weighted median method, weighted mode method, and MR-Egger regression were used for sensitivity analyses. The MR estimates in lipid trait investigation represented the effect of a one standard deviation (SD) increase in lipid-trait concentrations on the occurrence of psoriasis outcomes. In contrast, the drug target MR estimates represented the association between genetically mimicked effects of evinacumab, via ANGPTL3 inhibition, equivalent to per SD reduction in lipid-trait concentrations and the occurrence of psoriasis outcomes. Additionally, the MR-Egger intercept test was used to detect the significant directional horizontal pleiotropy driving the results, at a $p<0.05$.[25] Heterogeneity tests were performed using IVW and MR-Egger regression, with Cochran Q statistics used to quantify heterogeneity. A random-effect model in IVW was used when significant heterogeneity was detected at a $p<0.05$. Otherwise, a fixed-effect model was used by default. All of these univariable MR analyses were performed using lipid GWAS summary statistics from UKB in primary analyses and replicated using those from GLGC in sensitivity analyses.

For multivariable MR analyses, the multivariable IVW method was used in the primary MR analysis to estimate the genetically predicted effects of serum lipids on psoriasis, whereas the MR-Egger and MR-Lasso methods were used in the sensitivity analyses. Similarly, multivariable MR-Egger regression was used to detect pleiotropy and heterogeneity, and the multivariable IVW method was used to detect heterogeneity.

If a significant effect was detected between the genetically mimicked effects of lifelong evinacumab use and psoriasis, further investigation was conducted into the off-target effects of evinacumab on psoriasis, via genetically predicted ANGPTL3 inhibition. This was achieved by utilizing SNPs situated outside the ANGPTL3 region and associated with lipid traits as IVs. All statistical analyses were performed using R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) with statistical significance set at $p<0.05$.

RESULTS

Genetically predicted effects of serum lipids on psoriasis

In the univariable MR analyses using the lipid GWAS summary data from UKB, a genetically proxied one-SD increase in the serum LDL-C concentration was significantly associated with a higher risk of psoriasis (random-effect IVW: OR: 1.22, 95% CI: 1.05–1.43, p=0.011), as well as its subtypes, including arthropathic psoriasis (random-effect IVW: OR: 1.30, 95% CI: 1.02–1.65, p=0.032), psoriasis vulgaris (random-effect IVW: OR: 1.87, 95% CI: 1.16–2.99, p=0.0095), and guttate psoriasis (fixed-effect IVW: OR: 2.19, 95% CI: 1.17–4.07, p=0.014). Sensitivity analyses employing the weighted mode, weighted median, and MR-Egger regression methods all yielded results consistent with those of the primary analyses, namely a significant association between the elevated LDL-C concentration and an increased risk of psoriasis, including arthropathic psoriasis and psoriasis vulgaris. The sensitivity analyses also identified a directionally consistent association between the LDL-C concentration and the guttate psoriasis risk (Table 1). All these lend support to the robustness of primary findings. Additionally, a genetic predisposition to higher serum triglycerides was found to significantly increase the overall risk of psoriasis, as demonstrated by both IVW (random-effect IVW: OR: 1.17, 95% CI: 1.03–1.32, p=0.018) and other MR methods including weighted mode and weighted median (Table 1). In comparison, no significant correlation was observed between genetically predicted HDL-C concentration and psoriasis or its subtypes (Figure 2 and Table 1).

In the univariable MR sensitivity analyses using the GWAS summary data from GLGC, the genetically predicted elevated LDL-C concentration was also found to be significantly

associated with an increased risk of psoriasis (random-effect IVW: OR: 1.18, 95% CI: 1.04–1.33, *p*=0.010), arthropathic psoriasis (fixed-effect IVW: OR: 1.25, 95% CI: 1.05–1.48, *p*=0.012), and psoriasis vulgaris (fixed-effect IVW: OR: 1.74, 95% CI: 1.21–2.52, *p*=0.0031). The same significant associations were also derived from analyses by weighted mode, weighted median and MR-Egger regression methods (Supplementary Table 6). Although the effect of LDL-C on guttate psoriasis, and that of triglycerides on psoriasis became non-significant when using GLGC lipid data, the directions of both effects were consistent with those observed using UKB data. The remaining associations between lipid traits and psoriasis phenotypes remained non-significant when using GLGC lipid data (Supplementary Figure 1). All these results were consistent with those obtained using UKB lipid data, indicating a robust association between lipid traits and psoriasis phenotypes.

In the sensitivity analyses using the multivariable MR approach, the association between genetically predicted LDL-C concentration and psoriasis vulgaris was still significant after adjusting for concentrations of the other serum lipids (fixed-effect IVW: OR: 2.01 per SD increase in LDL-C, 95% CI: 1.19–3.40, *p*=0.009) (Supplementary Figure 2 and Supplementary Table 7). This indicated that increasing LDL-C concentration was an independent risk factor of psoriasis vulgaris. Furthermore, the effect of triglyceride concentration on psoriasis was indirect since the effect became non-significant (random-effect IVW: OR: 1.08, 95% CI: 0.917–1.28, *p*=0.34) when it was conditional on HDL-C and LDL-C. The MR-Egger intercept tests detected no horizontal pleiotropy in univariable and multivariable MR analyses (Table 1 and Supplementary Table 6 and 7).

Genetically mimicked effects of evinacumab, via ANGPTL3 inhibition, on psoriasis

In the primary analyses using the lipid GWAS summary data from UKB, genetically mimicked effects of evinacumab, equivalent to a one SD reduction in serum triglycerides, were significantly associated with a lower risk of psoriasis (fixed-effect IVW: OR: 0.752, 95% CI: 0.577–0.982, *p*=0.036) (Figure 3 and Table 2). The results were verified to be robust when using the weighted mode method (OR: 0.645, 95% CI: 0.445–0.934, *p*=0.024), weighted median method (OR: 0.670, 95% CI: 0.459–0.978, *p*=0.038), and MR-Egger regression (OR: 0.476, 95% CI: 0.246–0.922, *p*=0.032). Other triglyceride-associated SNPs outside the evinacumab-targeted ANGPTL3 region also demonstrated a significant association with psoriasis (random-effect IVW: OR: 0.858, 95% CI: 0.756–0.974, *p*=0.018) (Supplementary Table 8). These findings suggest that the genetically predicted lifelong protective effects of evinacumab on psoriasis, via ANGPTL3 inhibition, are dependent on triglyceride lowering and potentially other off-target effects.

The genetically mimicked effects of evinacumab, via ANGPTL3 inhibition, on the major subtypes of psoriasis were also investigated. A one-SD decrease in serum LDL-C, as predicted by genetic variants in both the evinacumab-targeted ANGPTL3 region and other regions across the genome, was found to be significantly associated with a lower occurrence of arthropathic psoriasis (ANGPTL3 region (fixed-effect IVW): OR: 0.266, 95% CI: 0.0886–0.799, p=0.018; other regions (random-effect IVW): OR: 0.770, 95% CI: 0.607–0.978, p=0.032, respectively) (Figure 3 and Supplementary Table 8). These findings indicate that the genetically mimicked effects of lifelong evinacumab administration on the reduction of arthropathic psoriasis occurrence are dependent on LDL-C lowering. In contrast, although the triglyceride- and HDL-C- associated SNPs within the ANGPTL3 gene were significantly associated with arthropathic psoriasis (fixed-effect IVW: OR: 0.477, 95% CI: 0.312–0.731, p<0.0001; and OR: 0.0165, 95% CI: 4.69×10-4–0.583, p=0.024, respectively), SNPs related to triglycerides and HDL-C that were located outside the ANGPTL3 coding region were not associated with arthropathic psoriasis (random-effect IVW: OR: 0.846 , 95% CI: 0.685–1.04, p=0.12; and fixed-effect IVW: OR: 1.11, 95% CI: 0.940–1.31, p=0.22, respectively) (Supplementary Table 8). This result suggest that the genetically predicted protective effects of lifelong evinacumab use, via ANGPTL3 inhibition, on arthropathic psoriasis are independent of triglyceride and HDL-C lowering (Figure 3). In addition, no significant association was observed between the genetically mimicked effects of evinacumab and psoriasis vulgaris or guttate psoriasis (Figure 3 and Table 2).

In the sensitivity analyses of the drug target MR, the MR-Egger intercept tests detected no significant horizontal pleiotropy (Table 2). In addition, neither the genetically mimicked effects of evinacumab via triglyceride-related ANGPTL3 inhibition on psoriasis nor that via LDL-C-related ANGPTL3 inhibition on arthropathic psoriasis remained significant when a Bonferroni correction for multiple testing was applied (p=0.050/3), indicating that the effects of evinacumab on psoriasis were not fully conclusive.

In the sensitivity analyses using the lipid GWAS summary statistics from GLGC, the genetically mimicked effect of evinacumab was only associated with a reduced risk of arthropathic psoriasis through triglyceride lowering (fixed-effect IVW: OR: 0.492, 95% CI: 0.246–0.981, p=0.044) (Supplementary Figure 3). However, the effect was no longer statistically significant when the weighted mode, weighted median, and MR-Egger regression methods were employed (Supplementary Table 9). This discrepancy may be attributed to the smaller sample size in GLGC relative to UKB, which resulted in a reduced number of SNPs selected as IVs. In accordance with the findings of the primary analysis, other triglyceride-

associated SNPs outside the evinacumab-targeted ANGPTL3 region were not found to be associated with the development of arthropathic psoriasis (Supplementary Table 10), supporting the former result that the potential effects of lifelong evinacumab use on arthropathic psoriasis are independent of triglyceride reduction.

DISCUSSION

In the present study, we employed a drug target MR approach to assess, for the first time, the genetically mimicked effects of evinacumab, via ANGPTL3 inhibition, on psoriasis. Our results suggest that the anticipated effects of lifelong evinacumab administration, as represented by genetic ANGPTL3 inhibition, may significantly diminish the risk of psoriasis and its arthropathic subtype, partially by lowering triglyceride and LDL-C concentrations, respectively. Although the results were not entirely conclusive, they offer valuable insights into the potential efficacy of evinacumab in the management of psoriasis and psoriatic arthritis (PsA) in patients with dyslipidemia, as well as the significance of lipid control in patients with psoriasis. These findings contribute to the exploration of novel therapeutic applications for the approved drug evinacumab, with the potential to expedite the development of treatments for unmet medical needs in psoriasis.

As most previous studies have focused on the association between lipids and the overall risk of psoriasis,[8-10,26] this study added the different subtypes of psoriasis, including arthropathic psoriasis, as outcomes. Most importantly, we investigated the effects of a novel drug target, ANGPTL3, on each subtype of psoriasis. The findings on the association between serum lipids and psoriasis were consistent with the results from previous meta-analyses of observational studies.[8,9] These studies reported an 80% higher risk of hypertriglyceridemia (OR: 1.80, 95% CI: 1.29–2.51),[8] and significantly higher means of serum triglycerides (mean difference (MD)=0.29 mmol/L; 95% CI: 0.23–0.35 mmol/L) and LDL-C (MD=0.29 mmol/L; 95% CI: 0.16–0.43 mmol/L) in patients with psoriasis than that in healthy controls.[9] MR studies further confirmed the causal effects of genetically predicted HDL-C deficiency and high triglyceride concentration on psoriasis incidence,[10,27] which were directionally consistent with our findings.

Additionally, our findings on the association between serum lipids and psoriasis subtypes are consistent with previous studies.28-30 Arthropathic psoriasis, also known as PsA, is the most recognized comorbidity of psoriasis.3 In meta-analysis studies, the prevalence of metabolic syndrome and hyperlipidemia in patients with PsA was 28.8% (95% CI: 14.0–46.2%) and 24.2% (95% CI: 17.4–31.8%), respectively,[28] and the risk of metabolic syndrome

in patients with PsA was 62% higher than that in patients with psoriasis without PsA (OR: 1.62, 95% CI: 1.50–1.74).[29] However, the results of these previous studies may be biased due to confounding variables and the causality cannot be determined in observational studies. In contrast, the findings of the present MR study provide genetic evidence, which was exempt from the above confounding factors, to support the important role of triglycerides in the overall pathogenesis of psoriasis and of LDL-C in the pathogenesis of psoriasis subtypes, including arthropathic psoriasis, psoriasis vulgaris, and guttate psoriasis.

The genetically proxied effects of higher serum triglycerides and LDL-C on psoriasis pathogenesis indicate the potential treatment effects of lipid-lowering drugs on psoriasis and PsA. Most studies have focused on the effects of statins (targeting β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase) and other drugs that primarily lower LDL-C, such as ezetimibe (targeting Niemann-Pick C1-Like 1 (NPC1L1)) and alirocumab (targeting Proprotein convertase subtilisin/kexin type 9 (PCSK9)) on psoriasis.[31,32] A meta-analysis of six clinical trials showed that treatment with oral statins for 8 weeks significantly improved psoriatic skin lesions.[31] A two-sample MR study, which included 12,116 psoriasis cases and 1.3 million individuals with LDL-C measurements, showed that genetically proxied PCSK9 inhibition was associated with a reduced risk of psoriasis (by 31%; OR: 0.69 per SD reduction in LDL-C, 95% CI: 0.55–0.88), whereas HMG-CoA reductase or NPC1L1 inhibition exhibited no significant effects on psoriasis.[32] These results indicate that, despite the similar effects on LDL-C lowering, the effect of drugs with different targets on psoriasis may vary significantly. Thus, research on lipid-lowering drugs with different drug targets is needed to develop novel treatment strategies for psoriasis management and comorbidity prevention.

As a novel drug with significant triglyceride and LDL-C lowering effects, the ANGPTL3 inhibitor evinacumab, is a potential adjuvant therapy for psoriasis. The herein genetically demonstrated protective effects of lifelong evinacumab administration on psoriasis pathogenesis, via ANGPTL3 inhibition, may be partly attributable to the inhibition of proinflammatory-cytokine release. In vitro experiments showed that human recombinant ANGPTL3 significantly promoted THP-1-derived macrophages expressing proinflammatory cytokines, including interleukin (IL)-1b, IL-6, and tumor necrosis factor (TNF)-α,[33] which are essential factors associated with psoriasis and PsA pathogenesis.[34-37] Furthermore, the three secreted cytokines stimulated the oxidized form of LDL-C,[38,39] enhanced the LDL-C receptor,[40] or inhibited HDL production,38 and the concentrations of IL-1b, IL-6, and TNF-α are significantly higher in patients with familial hypercholesterolemia.[41] Taken together, these findings confirm the possibility that ANGPTL3 inhibition may block psoriasis pathogenesis

by regulating lipid metabolism and inflammatory processes. Apart from lipid metabolism, ANGPTL3 binds integrin alpha-v/beta-3, which induces endothelial cell adhesion, migration, and angiogenesis.[42] These processes may participate in psoriasis pathogenesis by promoting microvascular formation in the dermis of the psoriatic skin.[43] Nonetheless, further laboratory studies are required to elucidate the detailed mechanisms of ANGPLT3 in psoriasis and PsA pathogenesis, and to further explore potential drug targets for psoriasis treatment. Moreover, to avoid confounded genetic estimates, further randomized controlled trials are needed to verify the drug-target MR estimates.[19] Real-world studies are also necessary to provide evidence for the use of evinacumab for the prevention and treatment of psoriasis and PsA in patients with dyslipidemia.

Our study adds to the existing literature in several ways. First, although an overall increased risk of psoriasis has been reported in patients with lipid metabolic disorders in both observational and MR studies, the present study further investigated the effects of dyslipidemia on the pathogenesis of different phenotypes of psoriasis, thereby providing more complete information on the role of lipid metabolism in psoriasis. Second, to the best of our knowledge, we are the first to predict the potential effects of evinacumab, an ANGPTL3 inhibitor, on psoriasis prevention prior to the commencement of clinical trials, utilizing a drug target MR approach. This provides a basis for repurposing the lipid-lowering drug, evinacumab, for a new indication in psoriasis, and potentially accelerates the development of systemic treatments for psoriasis. Third, the MR study design eliminates many biases inherent in observational studies, including confounding factors and reverse causality.

The present study has several limitations. First, the psoriasis outcomes in this study were binary; thus, the results only represent the preventive effect of evinacumab in patients without psoriasis or PsA, rather than the treatment effects against psoriatic lesions. Second, the MR-estimated effects of genetic ANGPTL3 inhibition on psoriasis prevention are analogous to the effects of lifelong administration of evinacumab, which, in an ideal scenario, would inhibit all the lipid-associated ANGPTL3 abnormal expression. This strategy exaggerates the effects of evinacumab, which vary with dosage and medication duration in a real-world setting. However, on a positive note, this offers insights into the long-term effects of targeting ANGPTL3, which is particularly beneficial for chronic diseases such as psoriasis, where long-term efficacy is a critical consideration. Third, the remarkable effects of genetically proxied ANGPTL3 inhibition by evinacumab on psoriasis prevention were not replicated when utilizing lipid GWAS data from GLGC, rendering the results inconclusive. This discrepancy may be attributed to the smaller sample size in GLGC relative to UKB, which resulted in a

reduced number of selected SNPs within/near the ANGPTL3 gene, thereby limiting the statistical power to achieve a significant result. Nevertheless, the results offer insights into the potential effects of modulating ANGPTL3, which is targeted by evinacumab. This information is valuable for further pharmaceutical research and development.

Conclusion

In conclusion, the genetically mimicked effects of evinacumab, via ANGPTL3 inhibition, may reduce the risks of psoriasis and its arthropathic comorbidity. Our findings underscore the potential therapeutic role of evinacumab in the prevention and treatment of psoriasis and PsA in patients with dyslipidemia, as well as the importance of lipid control in patients with psoriasis. Future research, including laboratory, clinical, and real-world studies, is warranted to gain insights into the efficacy of evinacumab in psoriasis and its underlying mechanism.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Univariable Mendelian randomization estimates of the association between lipid traits and different subtypes of psoriasis

Outcome and exposure	No. of SNP	Inverse variance weighting				Weighted mode		Weighted median	
		OR (95% CI)	*p* value	Cochran Q statistics (df)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Psoriasis									
TG	284	1.17 (1.03 to 1.32)	0.018	409 (283)	<0.0001	1.19 (1.01 to 1.41)	0.040	1.20 (1.01 to 1.43)	0.037
LDL-C	158	1.22 (1.05 to 1.43)	0.011	250 (157)	<0.0001	1.29 (1.09 to 1.52)	0.0030	1.33 (1.08 to 1.62)	0.0067
HDL-C	326	0.899 (0.805 to 1.00)	0.059	385 (325)	0.012	0.901 (0.766 to 1.06)	0.21	0.922 (0.769 to 1.11)	0.38
Arthropathic psoriasis									
TG	284	1.18 (0.958 to 1.46)	0.12	440 (283)	<0.0001	1.09 (0.851 to 1.41)	0.49	1.30 (0.980 to 1.71)	0.069
LDL-C	158	1.30 (1.02 to 1.65)	0.032	230 (157)	<0.0001	1.42 (1.08 to 1.86)	0.014	1.38 (1.01 to 1.89)	0.042
HDL-C	326	0.900 (0.762 to 1.06)	0.22	342 (325)	0.25	1.09 (0.826 to 1.43)	0.55	1.13 (0.857 to 1.49)	0.38
Psoriasis vulgaris									
TG	284	0.904 (0.628 to 1.30)	0.59	285 (283)	0.46	0.778 (0.441 to 1.37)	0.38	0.753 (0.410 to 1.38)	0.36
LDL-C	158	1.87 (1.16 to 2.99)	0.0095	193 (157)	0.025	3.09 (1.59 to 5.98)	0.0011	2.41 (1.14 to5.07)	0.021
HDL-C	326	0.968 (0.679 to 1.38)	0.86	332 (325)	0.39	1.25 (0.676 to 2.33)	0.47	1.31 (0.715 to 2.41)	0.38
Guttate psoriasis									
TG	284	0.999 (0.597 to 1.67)	0.998	291 (283)	0.36	0.969 (0.389 to 2.41)	0.95	1.08 (0.447 to 2.63)	0.86
LDL-C	158	2.19 (1.17 to 4.07)	0.014	171 (157)	0.21	2.06 (0.875 to 4.86)	0.10	2.20 (0.810 to 5.97)	0.12
HDL-C	326	0.844 (0.508 to 1.40)	0.51	347 (325)	0.20	0.781 (0.326 to 1.87)	0.58	0.646 (0.273 to 1.53)	0.32

Outcome and exposure	MR-Egger regression						*F* statistics
	OR (95%CI)	*p* value	Intercept (SE)	*p* value	Cochran Q statistics (df)	*p* value	
Psoriasis							
TG	1.09 (0.904 to 1.32)	0.37	0.0028 (0.0030)	0.35	408 (282)	<0.0001	138
LDL-C	1.34 (1.07 to 1.68)	0.013	-0.0043 (0.0042)	0.30	248 (156)	<0.0001	155
HDL-C	0.888 (0.751 to 1.05)	0.17	4.6E-4 (0.0026)	0.86	385 (324)	0.011	152
Arthropathic psoriasis							
TG	1.08 (0.793 to 1.48)	0.62	0.0037 (0.0049)	0.45	439 (282)	<0.0001	138
LDL-C	1.43 (1.01 to 2.04)	0.045	-0.0049 (0.0064)	0.45	229 (156)	<0.0001	155
HDL-C	0.950 (0.737 to 1.22)	0.69	-0.0021 (0.0039)	0.58	341 (324)	0.24	152
Psoriasis vulgaris							
TG	1.12 (0.656 to 1.93)	0.67	-0.0092 (0.0085)	0.28	284 (282)	0.46	138
LDL-C	2.43 (1.22 to 4.87)	0.013	-0.013 (0.013)	0.31	192 (156)	0.026	155
HDL-C	1.03 (0.602 to 1.77)	0.91	-0.0025 (0.0082)	0.76	332 (324)	0.38	152
Guttate psoriasis							
TG	1.23 (0.574 to 2.63)	0.60	-0.0087 (0.012)	0.47	290 (282)	0.36	138
LDL-C	2.87 (1.15 to 7.20)	0.026	-0.013 (0.017)	0.43	171 (156)	0.20	155
HDL-C	0.918 (0.424 to 1.99)	0.83	-0.0033 (0.012)	0.78	346 (324)	0.19	152

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval; SE, standard error; df, degree of freedom; SNP, single nucleotide polymorphisms; MR, Mendelian randomization; TG: triglycerides.

Table 2. Mendelian randomization estimates of the association between genetic ANGPTL3 variation in drug targets (Evinacumab) with different subtypes of psoriasis

Outcome and exposure	No. of SNP	Inverse variance weighting				Weighted mode		Weighted median	
		OR (95% CI)	*p* value	Cochran Q statistics (df)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Psoriasis									
TG	52	0.752 (0.577 to 0.982)	0.036	37.0 (51)	0.93	0.645 (0.445 to 0.934)	0.024	0.670 (0.459 to 0.978)	0.038
LDL-C	16	0.731 (0.367 to 1.45)	0.37	9.59 (15)	0.85	0.523 (0.169 to 1.61)	0.28	0.602 (0.230 to 1.58)	0.30
HDL-C	3	0.194 (0.0209 to 1.80)	0.15	0.101 (2)	0.95	0.262 (0.0171 to 4.02)	0.44	0.197 (0.0182 to 2.14)	0.18
Arthropathic psoriasis									
TG	52	0.477 (0.312 to 0.731)	<0.0001	26.3 (51)	0.998	0.425 (0.232 to 0.779)	<0.0001	0.426 (0.239 to 0.761)	<0.0001
LDL-C	16	0.266 (0.0886 to 0.799)	0.018	5.54 (15)	0.99	0.308 (0.0551 to 1.73)	0.20	0.297 (0.0643 to 1.38)	0.12
HDL-C	3	0.0165 (4.69E-4 to 0.583)	0.024	0.331 (2)	0.85	0.0217 (1.87E-4 to 2.52)	0.26	0.0200 (3.29E-4 to 1.22)	0.062
Psoriasis vulgaris									
TG	52	1.10 (0.438 to 2.74)	0.84	50.6 (51)	0.49	1.31 (0.304 to 5.61)	0.72	1.75 (0.438 to 7.01)	0.43
LDL-C	16	2.20 (0.140 to 34.5)	0.57	20.2 (15)	0.16	1.52 (0.0315 to 73.1)	0.84	3.22 (0.0958 to 108)	0.52
HDL-C	3	0.497 (2.31E-4 to 1.07E+3)	0.86	1.70 (2)	0.43	2.17 (1.03E-4 to 4.59E+4)	0.89	1.42 (1.90E-4 to 1.05E+4)	0.94
Guttate psoriasis									
TG	52	1.08 (0.299 to 3.92)	0.90	35.7 (51)	0.95	1.10 (0.197 to 6.16)	0.91	0.873 (0.131 to 5.83)	0.89
LDL-C	16	2.03 (0.0735 to 56.2)	0.68	6.99 (15)	0.96	0.453 (3.06E-3 to 67.2)	0.76	0.510 (6.08E-3 to 42.8)	0.77
HDL-C	3	0.203 (4.27E-6 to 9.65E+3)	0.77	0.0137 (2)	0.99	0.110 (9.06E-8 to 1.34E+5)	0.79	0.155 (1.65E-6 to 1.45E+4)	0.75

Outcome and exposure	MR-Egger regression						*F* statistics
	OR (95%CI)	*p* value	Intercept (SE)	*p* value	Cochran Q statistics (df)	*p* value	
Psoriasis							
TG	0.476 (0.246 to 0.922)	0.032	0.021 (0.014)	0.14	34.8 (50)	0.95	144
LDL-C	0.345 (0.0452 to 2.63)	0.32	0.018 (0.023)	0.45	8.99 (14)	0.83	67.4
HDL-C	0.0431 (8.06E-25 to 2.30E+21)	0.93	0.023 (0.41)	0.96	0.0979 (1)	0.75	45.6
Arthropathic psoriasis							
TG	0.314 (0.109 to 0.903)	0.036	0.019 (0.023)	0.40	25.6 (50)	0.998	144
LDL-C	0.287 (0.0112 to 7.36)	0.46	-0.0018 (0.037)	0.96	5.53 (14)	0.98	67.4
HDL-C	5.10E-13 (2.30E-4 to 1.13E+24)	0.63	0.37 (0.65)	0.67	0.00956 (1)	0.92	45.6
Psoriasis vulgaris							
TG	0.491 (0.0503 to 4.79)	0.54	0.037 (0.050)	0.45	50.0 (50)	0.47	144
LDL-C	0.597 (1.36E-4 to 2.62E+3)	0.91	0.031 (0.095)	0.75	20.1 (14)	0.13	67.4
HDL-C	2.27E-51(4.03E-129 to 1.28E+27)	0.42	1.8 (1.4)	0.43	0.0908 (1)	0.76	45.6
Guttate psoriasis							
TG	0.893 (0.0367 to 21.7)	0.94	0.0089 (0.069)	0.90	35.6 (50)	0.94	144
LDL-C	1.94 (1.07E-4 to 3.48E+4)	0.90	0.0012 (0.11)	0.99	6.99 (14)	0.94	67.4
HDL-C	338 (2.06E-108 to 5.54E+112)	0.97	-0.11 (2.0)	0.96	0.0104 (1)	0.92	45.6

ANGPTL3: angiopoietin-like 3; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval; SE, standard error; df, degree of freedom; SNP, single nucleotide polymorphisms; MR, Mendelian randomization; TG: triglycerides.

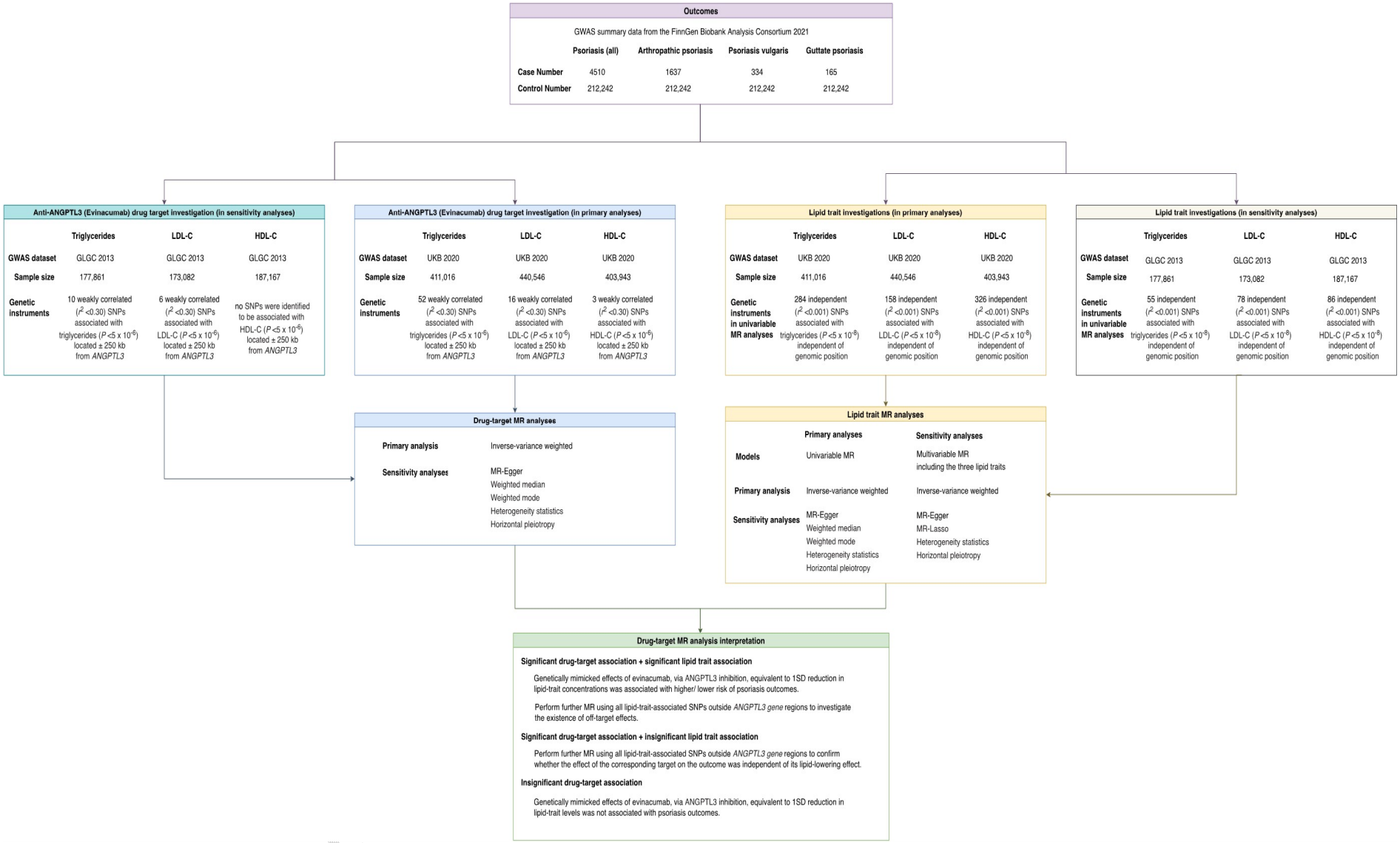

Figure 1. Overall study design

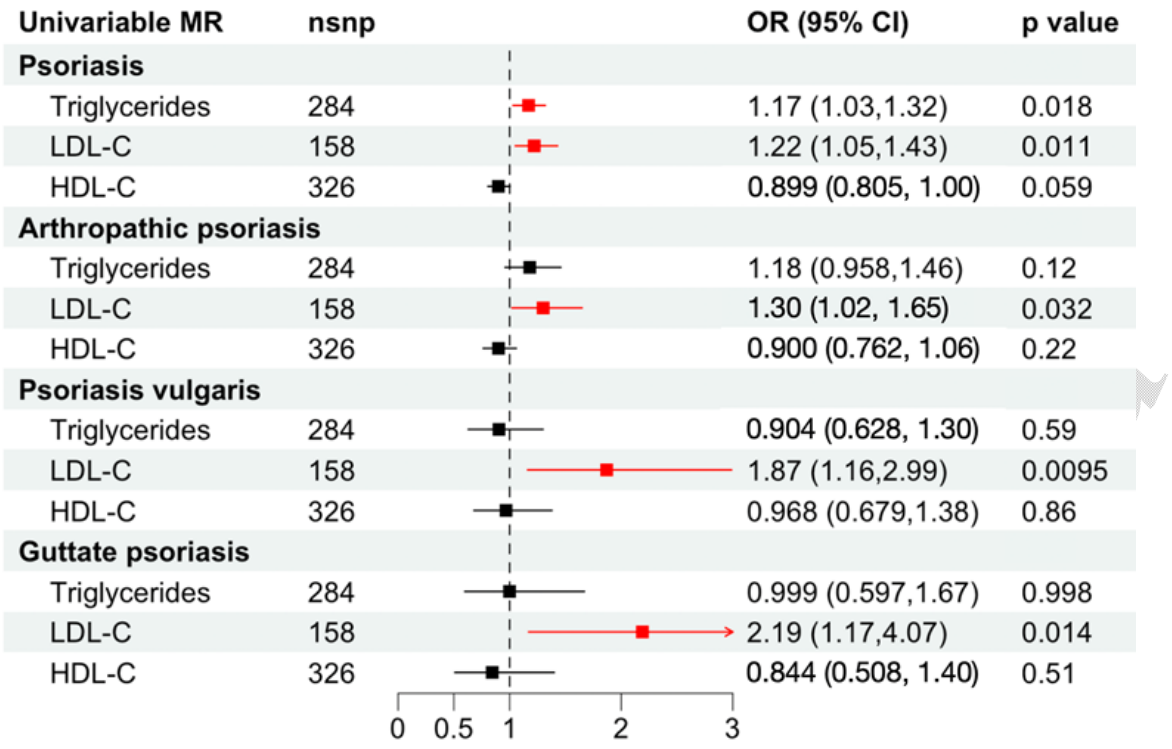

Figure 2. Univariable MR estimates of the association between circulating lipids and the risk of each phenotype of psoriasis. CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MR: Mendelian randomization; nsnp: number of single-nucleotide polymorphisms; OR: odds ratio

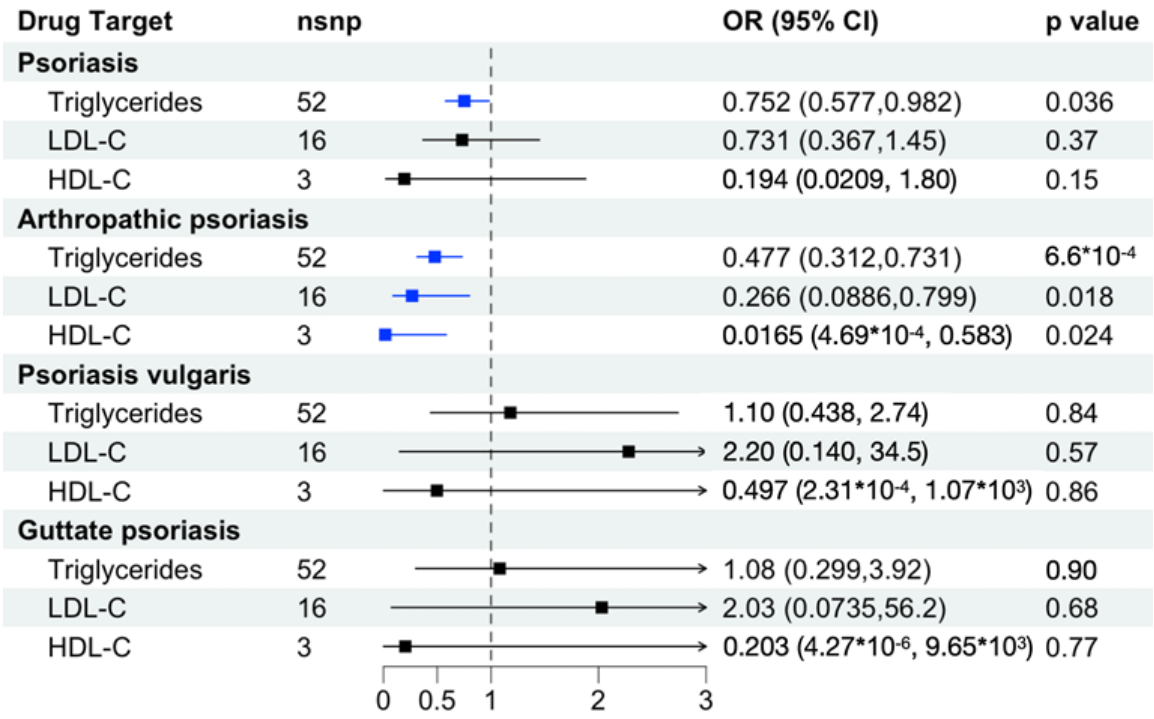

Figure 3. MR estimates of the association between genetically mimicked effects of evinacumab, via ANGPTL3 inhibition, equivalent to the lifelong one SD reduction in circulating lipids and the risk of each phenotype of psoriasis. *ANGPTL3*: angiopoietin-like 3; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MR: Mendelian randomization; nsnp: number of single-nucleotide polymorphisms; OR: odds ratio; SD: standard deviation

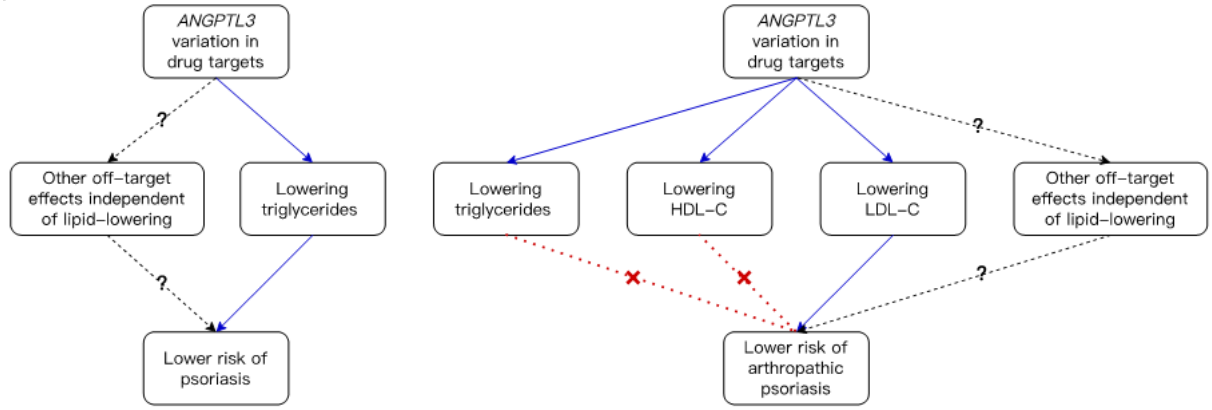

Figure 4. Major findings of the drug target MR. *ANGPTL3*: angiopoietin-like 3; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol