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RESEARCH ARTICLE

Genetic variants linked to statin-associated Type 2 diabetes mellitus: Findings from the UK Biobank and the All of Us Research Program

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Background and Purpose: Statins are widely prescribed for the prevention of cardiovascular disease, yet recent studies suggest an increased risk of new-onset Type 2 diabetes mellitus. This study aimed to identify genetic variants associated with statin-associated new-onset Type 2 diabetes mellitus from the UK Biobank and All of Us.

Experimental Approach: Among statin users, cases were defined as those diagnosed with Type 2 diabetes mellitus after statin initiation and controls as those never having diabetes mellitus. A genome-wide association study (GWAS) was performed using logistic regression analysis with an additive model using the UK Biobank. We conducted a replication analysis in the All of Us cohort using the lead variants identified in the UK Biobank. Additionally, we tested interaction analyses between statin use and lead variants.

Key Results: The GWAS identified four significant lead variants. The most significant, *TCF7L2* rs7903146, increased risk of new-onset Type 2 diabetes mellitus by 1.3-fold. Similarly, *POU5F1* rs879882 was associated with a higher risk. By contrast, *CCND2* rs76895963 and *ADCY5* rs35841686 were associated with a lower risk. In the replication analysis of the All of Us cohort, *TCF7L2* rs7903146, *CCND2* rs76895963 and *POU5F1* rs879882 remained significant. In the interaction analyses, those three lead variants also exhibited additive interactions with statin use.

Conclusion and Implications: These findings provide insights that may support personalized statin therapy to mitigate diabetic risk.

KEYWORDS
diabetes mellitus, GWAS, pharmacogenomics, statin

Abbreviations: AP, attributable risk proportion; ATC, anatomical therapeutic chemical; CCND2, cyclin D2; CI, confidence interval; GEL, Genomics England; GWAS, genome-wide association study; HMG-CoA, hydroxymethylglutaryl-coenzyme A; ICD, International Classification of Diseases; INFO, imputation information metric; LD, linkage disequilibrium; MAF, minor allele frequency; OMOP, observational medical outcomes partnership; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin Type 9; QQ, quantile-quantile; RERI, relative excess risk due to the interaction; SI, synergy index; SNP, single nucleotide polymorphism.

Yoon-A Park and Da Hoon Lee contributed equally to this work.

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1 | INTRODUCTION

Inhibitors of **hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase**, commonly referred to as statins, are widely prescribed medications for preventing cardiovascular diseases. Their effectiveness in both primary and secondary prevention has been well-established, with a meta-analysis demonstrating a 10% reduction in all-cause mortality and a 30% decrease in cardiovascular events among high-risk patients (Adhyaru & Jacobson, 2018; Chou et al., 2022). Current guidelines recommend statin therapy for individuals with elevated atherosclerotic cardiovascular disease risk, particularly those with low-density lipoprotein (LDL) cholesterol levels of 190 mg·dl^{-1} or higher (Arnett et al., 2019).

However, new-onset **Type 2 diabetes mellitus** following the use of statins has emerged as a significant adverse effect, raising concerns regarding their use (Singh et al., 2022). Meta-analyses of clinical trials indicated that the risk of statin-associated new-onset Type 2 diabetes mellitus increases by approximately 9% to 13% (Casula et al., 2017). Several mechanisms have been proposed to explain how statins may contribute to new-onset Type 2 diabetes mellitus, including decreased insulin signalling via reduced G-protein-coupled receptors, impaired Ca^{2+} signalling in beta cells, decreased **GLUT4** transporter translocation, and oxidative stress leading to beta cell apoptosis (Galicia-Garcia et al., 2020; Paseban et al., 2019). Another mechanism suggests that reduced levels of **leptin** could alter glucose metabolism (Maeda & Horiuchi, 2009; Zhao & Wu, 2005).

While some studies have explored the relationship between genetic variants and Type 2 diabetes mellitus risk, these investigations predominantly focus on polymorphisms that mimic statin effects, particularly within the **HMGCR** gene (Swerdlow et al., 2015; Yang & Schooling, 2023). Therefore, more comprehensive research is needed to examine genetic variations across the genome and their influence on statin-associated new-onset Type 2 diabetes mellitus. Accordingly, our study aimed to investigate genetic polymorphisms associated with statin-associated new-onset Type 2 diabetes mellitus through a genome-wide association study (GWAS) in a Caucasian population utilizing UK Biobank data. We also conducted a replication analysis in a White population using All of Us Research Program. Additionally, we tested the interaction between genetic variants and statin use.

What is already known?

- Recent studies suggest a risk of new-onset Type 2 diabetes mellitus in statin users.
- Mechanisms underlying this adverse effect remain unclear, although genetic factors may affect the risk.

What does this study add?

- *TCF7L2* rs7903146, *CCND2* rs76895963 and *POU5F1* rs879882 were associated with statin-associated new-onset Type 2 diabetes.
- All three variants were associated with positive additive interactions with statin use.

What is the clinical significance?

- Our findings support personalized statin treatment by evaluating genetic risk for Type 2 diabetes.

2 | METHODS

2.1 | Discovery cohort

The UK Biobank is a large-scale biomedical data source with approximately 500,000 participants, aged between 40 and 69 years old, recruited from England, Wales, and Scotland since 2006 (Sudlow et al., 2015). It has collected extensive data from a touchscreen questionnaire, verbal interviews, health-related records and genomic data. The health-related records comprise electronically recorded primary care information, hospital inpatient data, death registers, cancer registers and the first occurrence dates of various diseases. This investigation was conducted using UK Biobank data release v18.1 under National Research Ethics Committee approval (16/NW/0274), adhering to established ethics and governance frameworks.

Among participants in the UK Biobank, statin users were identified from primary care records by interpreting read codes and drug names. Participants were excluded if they were non-Caucasian, prescribed **cerivastatin** (due to withdrawal from the market) or had pre-existing diabetes mellitus or prediabetes. Cases were defined as patients who developed new-onset Type 2 diabetes mellitus after initiating statin therapy, while controls were those who had never developed diabetes mellitus after statin initiation. Diagnoses were derived from primary care records, hospital inpatient data and first occurrence data using read codes and International Classification of Diseases (ICD) codes (Tables S1 and S2).

We also collected the following baseline data: age, sex, statin types, overweight status (body mass index [BMI] ≥ 25 kg·m^{-2}), comorbidities and concomitant medications. Comorbidities included hypertension, atrial fibrillation, dyslipidemia, ischemic stroke, myocardial infarction, peripheral vascular diseases, kidney diseases and liver diseases. Concomitant drugs were categorized into other lipid-lowering drugs (**ezetimibe**, fibrate, nicotinic acid derivatives and bile acid sequestrants) and antihypertensive drugs (angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, and calcium channel blockers). Additionally, statins are classified by intensity based on their ability to lower LDL cholesterol (National Clinical Guideline Centre [UK], 2014; Reiter-Brennan et al., 2020). High-intensity statins include **atorvastatin** 40–80 mg and **rosuvastatin** 20–40 mg. Moderate-intensity statins consist of atorvastatin 10–20 mg,

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fluvastatin 80 mg, pravastatin 40–80 mg, rosuvastatin 5–10 mg and simvastatin 20–40 mg. Low-intensity statins include fluvastatin at 20–40 mg, pravastatin at 10–20 mg and simvastatin at 10 mg.

2.2 | Replication cohort

The All of Us Research Program is a biomedical data source with a longitudinal cohort of participants aged 18 or older from across the United States of America since 2018 (All of Us Research Program I et al., 2019). It contains health questionnaires, electronic health records, physical measurements and genomic data. All participants provided informed consent either in-person or via an eConsent platform. The protocol was reviewed by the IRB of the All of Us Research Program, following the regulations and guidance of the NIH Office for Human Research Protections for all studies. For this study, we utilized the All of Us Controlled Tier Dataset v8 (C2024Q3R4; released February 2025), with follow-up data available up to 1 October 2023.

For the replication, we included White participants who were prescribed statins (excluding cerivastatin) and had no prior history of diabetes mellitus or prediabetes. Additionally, participants with missing or non-binary sex at birth were excluded. Following the same procedure applied to the discovery cohort, cases of new-onset Type 2 diabetes mellitus were determined if new-onset Type 2 diabetes mellitus developed after initiating statin therapy, whereas controls had never been diagnosed with diabetes mellitus after statin initiation. Diagnostic information was extracted using ICD9-CM and ICD10-CM (Table S3). Medication data were extracted using Anatomical Therapeutic Chemical (ATC) classification vocabularies from the Observational Medical Outcomes Partnership (OMOP) standard.

Demographic and clinical data were collected as follows: age, sex, statin types, overweight status, comorbidities (hypertension, atrial fibrillation, dyslipidemia, ischemic stroke, myocardial infarction, peripheral vascular diseases, kidney diseases and liver diseases) and concomitant drugs (other lipid-lowering drugs and antihypertensive drugs). Other lipid-lowering drugs included ezetimibe, fibrate, nicotinic acid derivatives, bile acid sequestrants, Proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitors, bempedoic acid, docosahexaenoate, policosanol and pyridoxal. Antihypertensive drugs consist of the same drugs included in the UK Biobank.

2.3 | Genotyping and GWAS

In the UK Biobank, genotyping was performed using either the UK Biobank Axiom Array (~450,000 participants) or UK BiLEVE Array (~50,000 participants). Data were phased and imputed using Eagle v2.4 and Minimac4 v1.0.2 with a Genomics England (GEL) reference panel as a reference. We performed the quality control via the following steps: retaining only single nucleotide polymorphisms (SNPs) in autosomes; a minor allele frequency (MAF) not less than 0.01; a Hardy–Weinberg equilibrium exact test P value for the variant not less than 0.00001; a genotyping call rate not less than 0.9; a call rate for samples not less than 0.9; imputation information metric (INFO) score not less than 0.8 (Southam et al., 2011; Zeng et al., 2015). Principal components provided by the UK Biobank were incorporated to account for population structure (Bycroft et al., 2018), and a principal component analysis plot was generated.

A GWAS was conducted using PLINK 2.0 (Chang et al., 2015). We used a logistic regression model with an additive model, adjusting for age, sex, overweight status (BMI ≥ 25 $kg{\cdot}m^{-2}$), dyslipidemia and 10 principal components. A $P < 5 \times 10^{-8}$ was used as the genome-wide significance threshold (Dudbridge & Gusnanto, 2008). Lead SNPs were identified as those exhibiting the lowest P values while maintaining independence from one another. Linkage disequilibrium (LD) clumping was performed using PLINK with an r^2 threshold of 0.1 and a window size of 250 kb (Purcell et al., 2007). Adjusted odds ratios (ORs) with 95% confidence interval (CI) were calculated. We created a Manhattan plot, a quantile-quantile (QQ) plot with the genomic inflation factor and a regional association plot via LocusZoom (Pruim et al., 2010).

2.4 | Replication analysis

For the All of Us, we utilized short-read whole genome sequencing data from the Allele Count/Allele Frequency threshold callset, which contains variants with allele frequency >1% or allele count >100 in any computed ancestry subpopulations. Lead SNPs previously identified in the UK Biobank GWAS were replicated using the same genetic model, with adjustments for age, sex, overweight status, dyslipidemia and the first 10 principal components.

2.5 | Stratified analyses

To address potential differences between the groups, we performed stratified analyses of the association between lead SNPs and new-onset Type 2 diabetes mellitus after statin treatment. Stratification factors included demographic and clinical characteristics, as well as statin type, intensity and duration. Logistic regression with an additive genetic model was applied within each subgroup.

2.6 | Gene-statin interaction analysis

We conducted interaction analyses to examine the joint effects of statin use and lead SNPs in the UK Biobank. In addition to statin users, as described in the discovery cohort, statin non-users were included together, who were identified as Caucasian individuals with no history of statin prescriptions, with the same exclusion criteria applied. Interaction effects were assessed on both additive and multiplicative scales. The relative excess risk due to the interaction (RERI), attributable risk proportion (AP) and synergy index (SI) were calculated to evaluate the additive interaction, while the multiplicative interaction was assessed using a multiplicative scale.

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2.7 | Statistical analyses

To compare the categorical variables between the case and control groups, we used the chi-squared test and Fisher's exact test. For continuous variables, the unpaired *t* test was used. A *P* value less than 0.05 was considered statistically significant. Due to the All of Us Research Program Data and Statistics Dissemination Policy, participant counts of 1 to 20 may not be published.

For the UK Biobank, analyses were performed in RStudio (version 2024.04.1 + 748) using R (version 4.4.0). For the All of Us Research Program, all analyses were conducted within the All of Us Researcher Workbench, using Python and R within cloud-based Jupyter notebooks.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Fabbro, Kelly, et al., 2023; Alexander, Fabbro, Kelly, et al., 2023; Alexander, Mathie, Peters, et al., 2023).

3 | RESULTS

3.1 | Discovery cohort and GWAS in the UK biobank

We identified 222,017 participants in the UK Biobank with primary care data on drug prescriptions. Among these, 78,159 participants were prescribed statins. We excluded 13,022 participants who were not Caucasian, 146 who were prescribed cerivastatin and 8962 with a previous history of diabetes mellitus or prediabetes. As a result, 56,029 patients were included in the GWAS, comprising 6524 in the case group and 49,505 in the control group (Figure 1). Out of 342,573,817 SNPs, 5,304,886 passed the quality control criteria. The QQ plot showed the genomic inflation factor was 1.01, indicating no population stratification (Figure S1). The principal component analysis plot showed that there was no difference in distribution between case and control groups (Figure S2).

Baseline characteristics are shown in Table 1. The mean age of the cohort was 61.9 years, which was higher in the case group than the control group. The percentage of male participants was also significantly higher in the case group compared with the control group. Simvastatin was the most prescribed statin, overall, followed by atorvastatin. Compared to the control group, simvastatin was less frequently prescribed, whereas atorvastatin was more frequently prescribed in the case group. High-intensity statins were more often prescribed in the case group compared to the control group. The mean duration of statin treatment was shorter in the case group than in the control group, due to censoring at the time of event occurrence in the case group. The case group were more overweight than those in the control group. Overall, 47.9% of participants had hypertension, and 37.6% had dyslipidemia. Other lipid-lowering drugs were more prescribed in the case group than the control group.

As shown in Figure 2 and Table 2, GWAS in the UK Biobank identified four significant loci for statin-associated new-onset Type 2 diabetes mellitus. We detected a total of 36 genome-wide significant variants ($P < 5 \times 10^{-8}$), comprising four lead SNPs and 32 SNPs in LD with these lead variants, as displayed in the regional association plots (Figure 3 and Table S4). As described in Table 2, the strongest association was observed for rs7903146 in the *TCF7L2* gene on chromosome 10, with the risk of new-onset Type 2 diabetes mellitus increasing by 1.3-fold per T allele. On chromosome 12, rs76895963 in the **CCND2** gene emerged as a significant protective variant, with each G allele reducing risk of new-onset Type 2 diabetes mellitus during statin therapy by approximately half. The analysis also identified rs879882 in

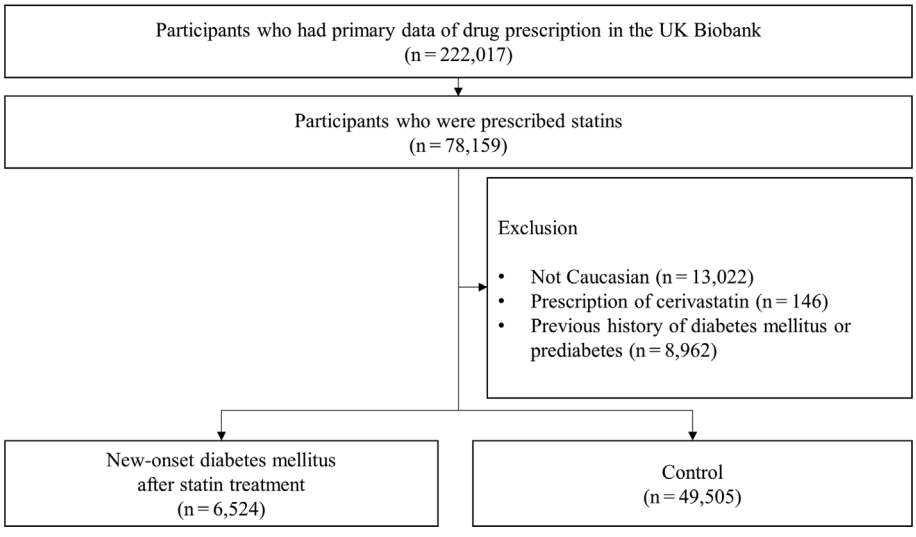


FIGURE 1 Flow chart of cohort selection in the UK Biobank.

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TABLE 1 Baseline characteristics of participants included in the UK Biobank cohort.

	Statin-associated new-onset diabetes (n = 6524)	Control (n = 49,505)	Total (n = 56,029)	*P*
Age (years)[a]	66.6 ± 8.0	61.3 ± 7.3	61.9 ± 7.5	<0.001
Sex				<0.001
Male	4091 (62.7)	27,724 (56.0)	31,815 (56.8)	
Female	2433 (37.3)	21,781 (44.0)	24,214 (43.2)	
Statin				<0.001
Atorvastatin	2564 (39.3)	12,122 (24.5)	14,686 (26.2)	
Fluvastatin	11 (0.2)	252 (0.5)	263 (0.5)	
Pravastatin	307 (4.7)	1106 (2.2)	1413 (2.5)	
Rosuvastatin	237 (3.6)	699 (1.4)	936 (1.7)	
Simvastatin	3405 (52.2)	35,326 (71.4)	38,731 (69.1)	
Statin intensity[b]				<0.001
Low	362 (5.5)	4433 (9.0)	4795 (8.6)	
Moderate	5048 (77.4)	42,235 (85.3)	47,283 (84.4)	
High	1114 (17.1)	2834 (5.7)	3948 (7.0)	
Duration (years)	4.1 ± 3.7	5.0 ± 4.1	4.9 ± 4.1	<0.001
Overweight status[c]	5873 (93.1)	37,368 (77.1)	43,241 (78.9)	<0.001
Comorbidities				
Hypertension	5006 (76.7)	21,832 (44.1)	26,838 (47.9)	<0.001
Atrial fibrillation	846 (13.0)	2170 (4.4)	3016 (5.4)	<0.001
Dyslipidemia	4138 (63.4)	16,903 (34.1)	21,041 (37.6)	<0.001
Ischemic stroke	246 (3.8)	954 (1.9)	1200 (2.1)	<0.001
Myocardial infarction	1009 (15.5)	3407 (6.9)	4416 (7.9)	<0.001
Peripheral vascular diseases	353 (5.4)	1165 (2.4)	1518 (2.7)	<0.001
Kidney diseases	914 (14.0)	1824 (3.7)	2738 (4.9)	<0.001
Liver diseases	472 (7.2)	767 (1.5)	1239 (2.2)	<0.001
Concomitant drugs				
Other lipid-lowering drugs[d]	259 (4.0)	441 (0.9)	700 (1.2)	<0.001
Antihypertensive drugs[e]	3061 (46.9)	23,820 (48.1)	26,881 (48.0)	0.069

[a]Values are presented as mean ± standard deviation. All other values are presented as number (percentage).
[b]Statins are classified by intensity based on their ability to lower low-density lipoprotein cholesterol: high intensity (atorvastatin 40–80 mg and rosuvastatin 20–40 mg), moderate intensity (atorvastatin 10–20 mg, fluvastatin 80 mg, pravastatin 40–80 mg, rosuvastatin 5–10 mg and simvastatin 20–40 mg) and low intensity (fluvastatin 20–40 mg, pravastatin 10–20 mg and simvastatin 10 mg).
[c]Body mass index ≥ 25 $kg \cdot m^{-2}$.
[d]Ezetimibe, fibrate, nicotinic acid derivatives and bile acid sequestrants were included.
[e]Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers and calcium channel blockers were included.

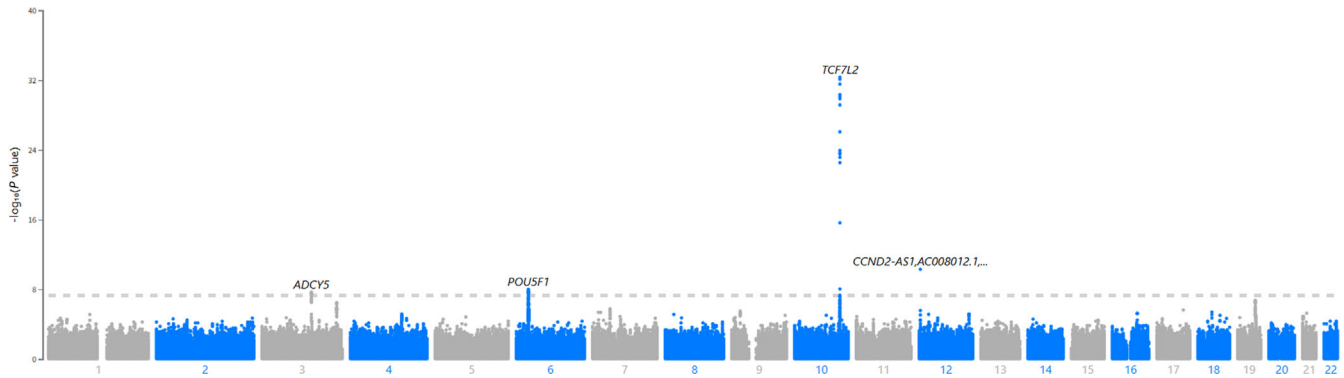


FIGURE 2 Manhattan plot of genome-wide association study on new-onset Type 2 diabetes mellitus among statin users in the UK Biobank cohort.

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TABLE 2 New lead SNPs associated with new-onset Type 2 diabetes mellitus after statin treatment in the UK Biobank cohort and replication analysis in the All of Us cohort.

			Discovery cohort from the UK Biobank		Replication cohort from the All of Us	
Chromosome	Gene	SNP	OR (95% CI)	*P*	OR (95% CI)	*P*
10	*TCF7L2*	rs7903146 (C > T)	1.30 (1.25–1.36)	4.57×10^{-33}	1.26 (1.21–1.30)	2.23×10^{-32}
12	*CCND2*	rs76895963 (T > G)	0.52 (0.43–0.63)	4.94×10^{-11}	0.66 (0.57–0.75)	2.22×10^{-9}
6	*POU5F1*	rs879882 (T > C)	1.13 (1.09–1.18)	1.02×10^{-8}	1.06 (1.02–1.10)	3.89×10^{-3}
3	*ADCY5*	rs35841686 (T > A)	0.88 (0.84–0.92)	2.03×10^{-8}	0.97 (0.94–1.01)	0.21

Abbreviation: SNP, single nucleotide polymorphism.

the **POU5F1**, with each C allele increasing the risk of statin-associated new-onset Type 2 diabetes mellitus by 1.1-fold. Additionally, rs35841686 in the ***ADCY5*** gene showed a significant protective effect, with each A allele decreasing the risk of new-onset Type 2 diabetes mellitus by 12% during statin therapy.

3.2 | Replication analysis in the All of Us

In the All of Us cohort, 109,617 participants were prescribed statins. We excluded 42,212 non-White participants, >614 with missing or unspecified information on sex at birth, <20 who were prescribed with cerivastatin and 12,126 with a previous history of diabetes mellitus or prediabetes. Participants who were prescribed cerivastatin were also excluded. A total of 54,645 participants were included in the replication analysis. Cases were 12,185, whereas controls were 42,460 (Figure S3). Baseline characteristics of the All of Us cohort are presented in Table S5. Atorvastatin was the most commonly used statin across the cohort (46.8%), followed by simvastatin (26.6%), which differs from the UK Biobank cohort. However, the case group exhibited a higher average age, a greater proportion of male sex, and a greater prevalence of all comorbidities compared to the control group, consistent with the findings from the UK Biobank cohort.

The replication analysis showed that *TCF7L2* rs7903146, *CCND2* rs76895963 and *POU5F1* rs879882 remained significant for statin-associated new-onset Type 2 diabetes mellitus among the four lead SNPs (Table 2). *TCF7L2* rs7903146 had a 1.3-fold increased risk of new-onset Type 2 diabetes mellitus per T allele. Participants with *CCND2* rs76895963 with each G allele were associated with a decreased risk of new-onset Type 2 diabetes mellitus. *POU5F1* rs879882 also remained significant. However, *ADCY5* rs35841686 did not show an association in the replication analysis.

3.3 | Stratified analyses

Stratified analyses are displayed in Figures S4–S6. Stratified analyses of demographic and clinical characteristics generally supported the significant association with all three lead SNPs, which showed significant associations in both the discovery and replication cohorts. However, statistical significance was not reached in certain subgroups with small sample sizes, such as those with ischemic stroke, peripheral vascular diseases and liver diseases. Regarding the stratification by statin type, intensity and duration, the associations remained significant across most subgroups, except for *POU5F1* rs879882 in the high-intensity statin group, which did not reach statistical significance; however, the direction and magnitude of the effect were consistent with the overall trend.

3.4 | Gene-statin interaction analysis in the UK Biobank

We further conducted gene-statin interaction analyses between statin use and risk alleles of the three lead SNPs, all of which showed significant associations in both the discovery and replication cohorts. As shown in Table 3, significant additive interactions were detected for all three variants. We observed the strongest additive interaction between statin use and each wild type allele (T allele) of *CCND2* rs76895693, with the highest RERI and AP. This indicates that 36% of risk of new-onset Type 2 diabetes mellitus in individuals exposed to both factors is attributable to their synergistic effect. The positive additive interactions with statin use were also observed in each T allele of *TCF7L2* rs7903146 and each C allele of *POU5F1*. All SIs significantly exceeded 1.0, confirming positive additive interactions. However, no significant multiplicative interactions were observed between statin use and these lead SNPs.

4 | DISCUSSION

Our discovery GWAS in the UK Biobank cohort revealed significant associations for variants in *TCF7L2*, *CCND2*, *POU5F1* and *ADCY5* genes. Notably, three of the lead SNPs (*TCF7L2* rs7903146, *CCND2* rs76895963 and *POU5F1* rs879882) were successfully replicated in the independent All of Us cohort, underscoring the robustness of our findings. The stratified analyses confirmed significant associations between statin-associated new-onset diabetes mellitus and the genetic variants across most subgroups. Also, our gene-statin interaction analyses further revealed significant additive interactions between statin use and these genetic variants.

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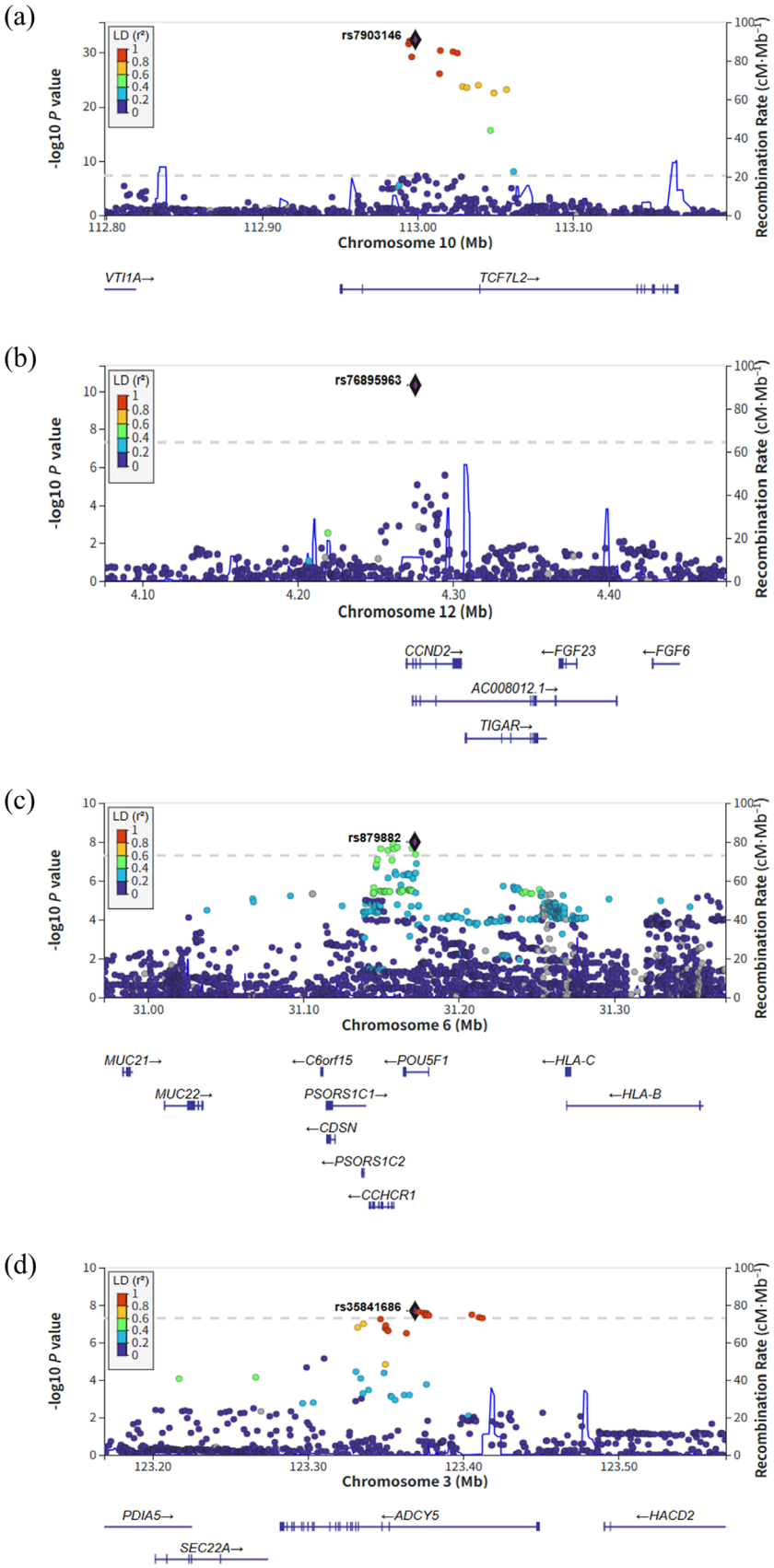


FIGURE 3 Regional association plot at significant loci of (a) Chromosome 10, (b) Chromosome 12, (c) Chromosome 6 and (d) Chromosome 3 in the GWAS of the UK Biobank.

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TABLE 3 Interactions between statin use and lead SNPs.

Subgroup	Multiplicative scale (95% CI)	RERI (95% CI)	AP (95% CI)	SI (95% CI)
Statin*_TCF7L2_ rs7903146	1.01 (0.94–1.07)	1.03 (0.82–1.24)†	0.17 (0.14–0.21)†	1.26 (1.20–1.32)†
Statin*_CCND2_ rs76895963[a]	1.00 (0.74–1.34)	3.17 (1.69–4.65)†	0.36 (0.28–0.44)†	1.69 (1.42–2.02)†
Statin*_POU5F1_ rs879882	1.04 (0.97–1.11)	0.36 (0.19–0.53)†	0.07 (0.04–0.11)†	1.10 (1.05–1.16)†

Abbreviations: AP, attributable proportion; RERI, relative excess risk due to interaction; SI, synergy index; SNP, single nucleotide polymorphism.
[a]Inverse value was used for interaction analysis when the odds ratio for the altered allele was less than 1.
†$P < 0.001$.

The rs7903146 variant in the *TCF7L2* gene was identified as the strongest association with new-onset Type 2 diabetes mellitus among the statin users. *TCF7L2* gene encodes a transcriptional factor of the **Wnt** signalling pathway that is critical for glucose homeostasis through regulation of insulin secretion and beta-cell function (Del Bosque-Plata et al., 2022). *TCF7L2* variants have been consistently identified as a strong genetic risk factor for Type 2 diabetes mellitus across diverse populations, especially rs7903146 (Cauchi et al., 2007; Del Bosque-Plata et al., 2022; Grant et al., 2006). Functional study demonstrated that the risk T allele of rs7903146 reduced insulin secretion by impairing incretin signalling and compromising beta-cell function (Lyssenko et al., 2007). In addition, *TCF7L2* regulates the auxiliary subunit of the **L-type voltage-gated calcium channels ($Ca_V1.x$ channels)**, which is critical for calcium influx triggering insulin exocytosis in pancreatic beta cells (Li et al., 2021; Ye et al., 2020). Several studies have reported that simvastatin inhibits the voltage-gated calcium channel, resulting in decreased insulin secretion (Curry et al., 2019; Yaluri et al., 2015), and it could be interpreted that statin treatment and *TCF7L2* interaction might have led to the occurrence of new-onset Type 2 diabetes mellitus.

The variant rs76895963 in the *CCND2* gene was associated with a lower risk of statin-associated new-onset Type 2 diabetes mellitus in our study. Consistently, it has been shown that rs76895963 reduces the risk of Type 2 diabetes mellitus, with increased *CCND2* expression (Steinthorsdottir et al., 2014; Yaghootkar et al., 2015). This may be attributable to cyclin D2 (CCND2) facilitating beta-cell proliferation and insulin secretion, with genetic variations potentially altering this process (Li et al., 2022). Regarding the relationship between statins and *CCND2*, one in vivo study demonstrated that statin treatment increased *CCND2* mRNA levels in the mouse heart, although the magnitude of this increase varied depending on the type of statin (Kumazaki et al., 2013). Liang et al. also found that simvastatin treatment lowered endothelial miR-652-3p expression, which is responsible for increasing CCND2 (Liang et al., 2020). These findings suggest that statins may influence *CCND2* mRNA expression, with the extent of the effect potentially modulated by the presence of the rs76895963 variant.

Our study indicated that *POU5F1* rs879882 was linked to statin-associated new-onset Type 2 diabetes mellitus. The *POU5F1* gene encodes the transcription factor protein Oct4, which is responsible for early embryonic development and stem cell pluripotency (Bakhmet & Tomilin, 2021). McGinnis et al. reported that rs879882 was associated with Type 1 diabetes mellitus, although the precise mechanism underlying the association remains unclear (McGinnis et al., 2009). Given the limited number of studies examining the link between statins and *POU5F1*, further clinical research is warranted to elucidate this relationship.

Although it failed to show significance in the All of Us cohort, *ADCY5* rs35841686 was linked to a reduced risk of new-onset Type 2 diabetes mellitus in the UK Biobank cohort. The *ADCY5* gene encodes adenylyl cyclase 5, which catalyses the conversion of **ATP** to **cyclic AMP (cAMP)**. cAMP is a key secondary messenger involved in glucose-stimulated insulin secretion in pancreatic beta cells (Hodson et al., 2014; Roman et al., 2017). A previous study showed that **lovastatin** decreased adenylyl cyclase activity in endocrine cells (Chiloeches et al., 1995). Taken together, altered gene expression of rs35841686 might modulate adenylyl cyclase activity and lower the risk of new-onset Type 2 diabetes mellitus, especially when combined with statin treatment.

In our study, significant differences were observed between the case and control groups for several known risk factors for Type 2 diabetes mellitus, including age, sex, overweight status, statin intensity and dyslipidemia (American Diabetes Association Professional Practice Committee, 2025; Kautzky-Willer et al., 2023; Cholesterol Treatment Trialists' (CTT) Collaboration, 2024). To address these differences, we further conducted stratified analyses of the association between statin-associated new-onset Type 2 diabetes mellitus and the lead SNPs. Our stratified analyses revealed that significant associations between the lead SNPs and new-onset Type 2 diabetes mellitus after statin treatment remained consistent regardless of risk factors, with a few exceptions in subgroups with limited sample sizes, possibly due to the reduced statistical power (Serdar et al., 2021), thereby supporting the robustness of our findings.

In an interaction analysis between statin use and the lead SNPs (*TCF7L2* rs7903146, *CCND2* rs76895963 and *POU5F1* rs879882), significant additive interactions were observed, suggesting a synergistic increase in the risk of new-onset Type 2 diabetes mellitus when both the genetic variant and statin exposure were present. However, multiplicative interactions were not statistically significant across all analyses. Given that the additive model is more suitable for examining biological interaction (Knol et al., 2011), the significance observed on the additive scale in this study may offer valuable insights into the genetic contribution to statin-associated new-onset Type 2 diabetes mellitus.

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Although we identified novel variants associated with statin-associated new-onset Type 2 diabetes mellitus, there were some limitations. First, we only included Caucasian groups. The results need to be validated in other racial groups. Second, we did not explore the underlying pharmacological mechanism of statin-associated new-onset Type 2 diabetes mellitus. Further mechanistic studies are warranted to elucidate the biological processes contributing to this association. Third, the new-onset Type 2 diabetes mellitus was identified based on diagnoses from electronic health records or self-reported medical conditions, which may introduce the risk of misclassification. Fourth, we did not assess lipid levels, which may have offered further insights into the potential mechanisms linking statin use to new-onset Type 2 diabetes mellitus. Lastly, the control group may appear healthier simply because they are younger and less overweight than the case group, and they might still develop Type 2 diabetes as they age.

Nonetheless, this is the first GWAS to examine statin-associated new-onset Type 2 diabetes mellitus using two independent large-scale cohorts, the UK Biobank and All of Us. Given that our results highlighted novel SNPs in various genes related to statin-associated new-onset Type 2 diabetes mellitus, this study may offer valuable genetic insights that could help advance statin therapy in clinical practice.

AUTHOR CONTRIBUTIONS

Yoon-A Park: Conceptualization (lead); formal analysis (lead); investigation (lead); methodology (lead); software (lead); writing—original draft (lead); writing—review and editing (lead). **Da Hoon Lee:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); writing—original draft (equal); writing—review and editing (equal). **Jung Sun Kim:** Conceptualization (supporting); formal analysis (supporting). **Jeong Yee:** Conceptualization (equal); investigation (equal); project administration (equal); supervision (equal); writing—review and editing (equal). **Hye Sun Gwak:** Conceptualization (equal); funding acquisition (lead); investigation (equal); project administration (lead); supervision (lead); writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available only to approved researchers in the UK Biobank and the All of Us.

DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the *BJP* guidelines for Design and Analysis and as recommended by funding agencies, publishers and other organizations engaged with supporting research.

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SUPPORTING INFORMATION

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