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Monocyte CCL2 signaling possibly contributes to increased asthma susceptibility in type 2 diabetes

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In recent years, the respiratory system has been increasingly recognized as a key target organ in diabetes. Although observational studies have established significant clinical associations between type 2 diabetes (T2D), antidiabetic medication use, and asthma, the causal relationships and underlying molecular mechanisms remain unclear. This study employed a bidirectional two-sample Mendelian randomization (MR) approach combined with bioinformatics analysis to explore the causal relationships between T2D and asthma subtypes and complications, with a focus on immune-regulatory mechanisms. The MR analysis utilized inverse-variance weighted (IVW) and meta-analysis methods to evaluate overall effects, with sensitivity analyses confirming the robustness of the findings. Bioinformatics analysis focused on differential gene expression and pathway enrichment to identify potential molecular networks. The MR analysis showed that T2D has a significant positive causal effect on asthma ($P < 0.05$), with severe autoimmune T2D showing strong associations with specific asthma subtypes (eosinophilic and mixed asthma) and complications (e.g., acute respiratory infections and pneumonia) ($P < 0.05$). Bioinformatics analysis identified the monocyte-CCL2 signaling axis as a key mechanism linking T2D and asthma, where hyperglycemia-induced monocyte activation may promote asthma development. These findings reveal shared inflammatory pathways and deepen our understanding of the molecular mechanisms linking these two chronic diseases.

Keywords Mendelian randomization, Causal relationship, Type 2 diabetes, Asthma, Monocyte-CCL2 axis

Abbreviations

COPD	Chronic obstructive pulmonary disease
EAF	Effect allele frequency
GWAS	Genome-Wide Association Studies
IVs	Instrumental Variables
IVW	Inverse-variance weighted
LD	Linkage disequilibrium
MARD	Mild age-related type 2 diabetes
MORD	Mild obesity-related type 2 diabetes
MR	Mendelian randomization
SAID	Severe autoimmune type 2 diabetes
SIDD	Severe insulin-deficient type 2 diabetes
SIRD	Severe insulin-resistant type 2 diabetes
SNPs	Single nucleotide polymorphisms
STROBE-MR	Strengthening the Reporting of Mendelian Randomization Studies
T2D	Type 2 diabetes
Treg	Regulatory T cell

Type 2 diabetes (T2D) and asthma represent two of the most prevalent chronic diseases globally, each affecting millions of individuals[1,2]. T2D manifests as a metabolic disorder characterized by insulin resistance and pancreatic β-cell dysfunction, while asthma presents as a chronic respiratory condition marked by airway

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inflammation and hyperresponsiveness[3,4]. Both conditions significantly impact patient quality of life and pose substantial burdens on healthcare systems worldwide. Despite advances in treatment strategies, the complex interplay between these conditions remains poorly understood, particularly regarding their potential causal relationships and shared pathological mechanisms.

Recent advances in precision medicine have revolutionized our understanding of these diseases' heterogeneity[5]. T2D has been newly classified into five distinct subtypes[6]: severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MORD), and mild age-related diabetes (MARD). Notably, obesity emerges as a critical common risk factor, playing a central role in both T2D pathogenesis and the development of obesity-associated asthma phenotypes[7,8]. This shared risk factor suggests potential overlapping pathological pathways, particularly through chronic low-grade inflammation and metabolic dysregulation[9–11]. As a predominant metabolic disorder, T2D profoundly impacts immune cell function and regulation, potentially altering systemic immune responses[12,13]. This metabolic-immune interface, further modulated by obesity-induced inflammation, may significantly influence the susceptibility to immune-mediated diseases. Similarly, asthma manifests in various phenotypes and endotypes, including allergic, non-allergic, early-onset, and late-onset forms, with obesity-associated asthma emerging as a distinct phenotype characterized by unique inflammatory patterns[14–16]. These classifications, coupled with emerging evidence of shared inflammatory pathways and immune dysregulation between T2D and asthma, point to complex pathogenic mechanisms involving metabolic, immune, and obesity-related components. Notably, genetic factors appear to play crucial roles in orchestrating these metabolic-immune interactions, suggesting common genetic architectures underlying their comorbidity.

Mendelian randomization (MR) analysis has emerged as a effective tool for investigating causal relationships between diseases while minimizing confounding factors and reverse causality issues[17]. By leveraging genetic variants as instrumental variables (IVs), MR analysis can provide robust evidence for causal associations between complex traits[18]. The availability of large-scale Genome-Wide Association Studies (GWAS) data for both T2D subtypes and asthma presents an opportunity to systematically examine their genetic relationships and potential causal links, particularly in the context of immune system regulation and metabolic homeostasis.

This study aims to elucidate the causal relationships between T2D subtypes and asthma using MR analysis based on GWAS data. By investigating these genetic associations, we seek to uncover novel insights into how metabolic disturbances in T2D might influence immune system function and subsequent asthma risk. Understanding these relationships could reveal novel therapeutic targets and identify high-risk populations for targeted interventions. Moreover, this knowledge could inform personalized treatment strategies, potentially revolutionizing our approach to managing these complex chronic diseases through integrated metabolic and immune-based interventions.

Results

Overall levels

Bidirectional causal relationship between T2D and asthma

According to MR guidelines, we initially screened 118 SNPs closely related to the exposure variable (T2D) in the forward analysis, with detailed information provided in Table S2. For the reverse analysis, 122 SNPs related to asthma from the openGWAS database (ebi-a-GCST90038616, Table S3) and 18 SNPs from the FinnGen database (GWAS ID: finn-b-J10_ASTHMA, Table S4) were screened. Detailed information on these SNPs is provided in Tables S3 and S4. All SNPs had F-values greater than 10, indicating their rationality and validity as IVs in MR analysis (Fig. 1).

Using the IVW method, the forward analysis results (Fig. 2A, B) indicated a positive causal relationship between T2D and asthma obtained from the openGWAS database (Fig. 2A, $OR_{IVW} = 1.0038$, $P_{IVW} = 0.002$), while no significant causal effect was observed with asthma from the FinnGen database (Fig. 2B, $OR_{IVW} = 1.0224$, $P_{IVW} = 0.2565$). To assess the statistical difference in comprehensive effects, a meta-analysis was conducted by integrating MR results from different databases, confirming a statistically significant causal association between T2D and asthma at the overall level (Fig. 2C, $P_{meta} = 0.0063$, $OR_{meta} = 1.004$, $I^2 = 0\%$, $Q = 0.88$, $Tau^2 = 0$).

In the reverse analysis using the IVW method (Fig. 2D, F), no significant causal relationship was found between asthma from either the openGWAS (Fig. 2D) or FinnGen databases (Fig. 2E) and T2D ($P_{IVW} > 0.05$). Meta-analysis results integrating MR results from both databases did not show a statistically significant causal association between asthma and the risk of T2D (Fig. 2F, $P_{meta} > 0.05$, $I^2 = 10.68\%$, $Q = 1.12$, $Tau^2 = 0$). Detailed results of these analyses are provided in Table S5.

Meta-analysis of bidirectional MR results from different databases strengthened the evidence for a positive causal effect of T2D on asthma risk, though individual databases showed varying association strengths. This finding was further supported by consistent effect directions across different analytical methods, enhancing the robustness of our conclusions. Specifically, our analyses revealed that T2D might increase asthma susceptibility through immune-mediated pathways, particularly evident in the SAID subtype. These genetic associations lay the foundation for further mechanistic investigations into inflammatory pathways and immune responses shared between T2D and asthma, considering both genetic and environmental factors.

Sensitivity analysis between T2D and asthma

In both forward and reverse analyses, no significant pleiotropy or heterogeneity was observed (Table 1). Assessing the causal effect estimates of individual SNP related to diabetes on asthma revealed noticeable differences (Fig. S1). Subsequently, leave-one-out analysis was conducted, removing each SNP one by one. The results (Fig. S2) showed that excluding a particular SNP only affected the range of maximum and minimum causal effect estimates but had minimal impact on the overall causal effect estimate direction. This indicates that although

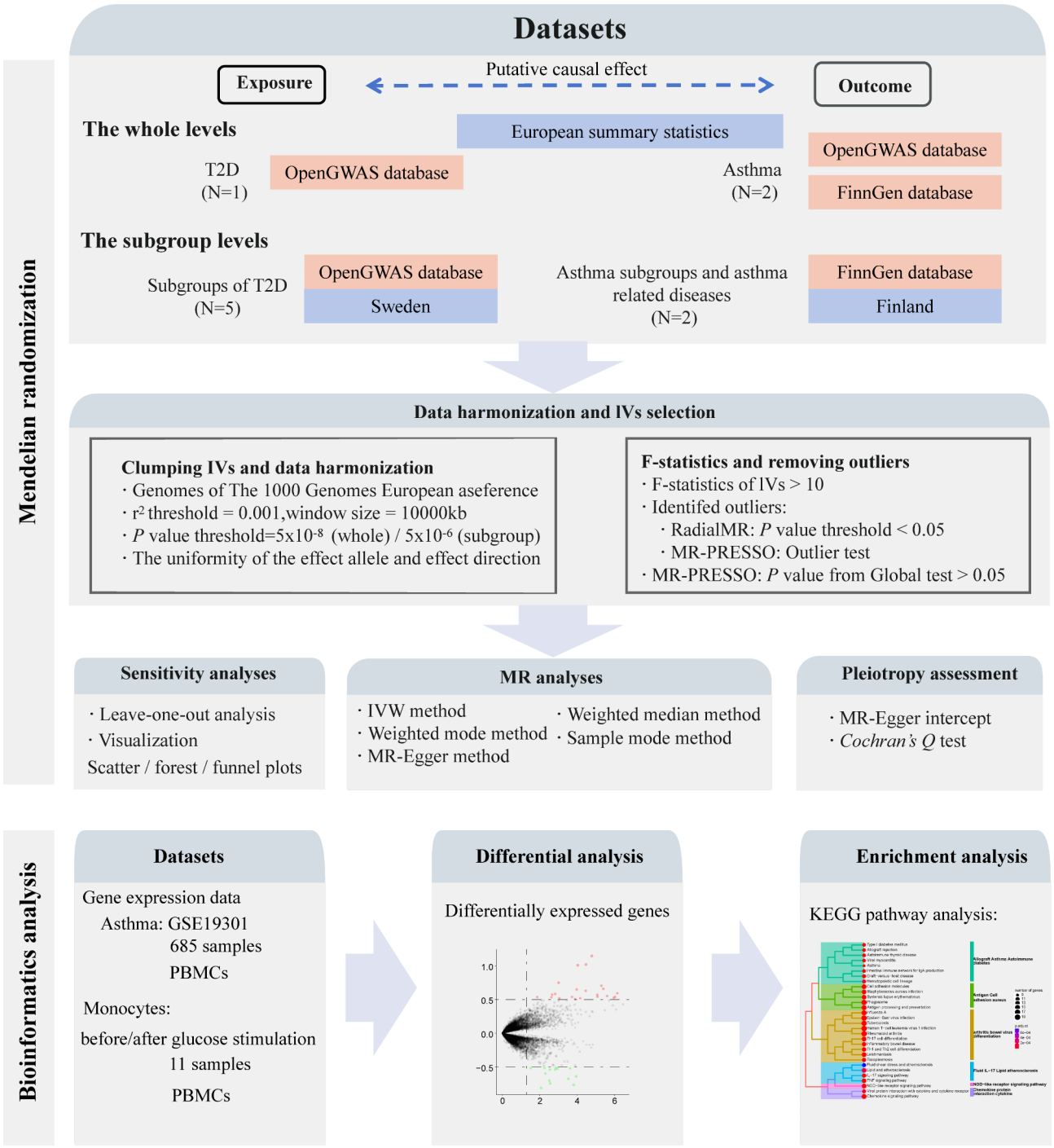

Fig. 1. The flowchart shows the study design and the details of instrumental variables (IVs) selection. Pink orange represents different public databases, while light blue represents different demographic structures.N represents the number of datasets related to the corresponding trait.

individual SNP show significant variability in different analysis directions, their causal effect estimates on the outcome variable are consistent from an overall perspective.

Scatter plots (Fig. 3A–D, with Fig. 3A, B for forward analysis and Fig. 3C, D for reverse analysis) displayed the effect values of SNPs included in the analysis on exposure and outcome variables, fitting potential linear trends. These plots affirmed the causal relationship between exposure and outcome variables in MR analysis. Additionally, funnel plots (Fig. 4A–D, with Fig. 4A, B for forward analysis and Fig. 4C, D for reverse analysis) showed symmetric distributions of SNPs in all analysis directions using the IVW method. This symmetric distribution further confirmed the robustness of the analysis, indicating no significant bias or invalidity of IVs in these MR analyses.

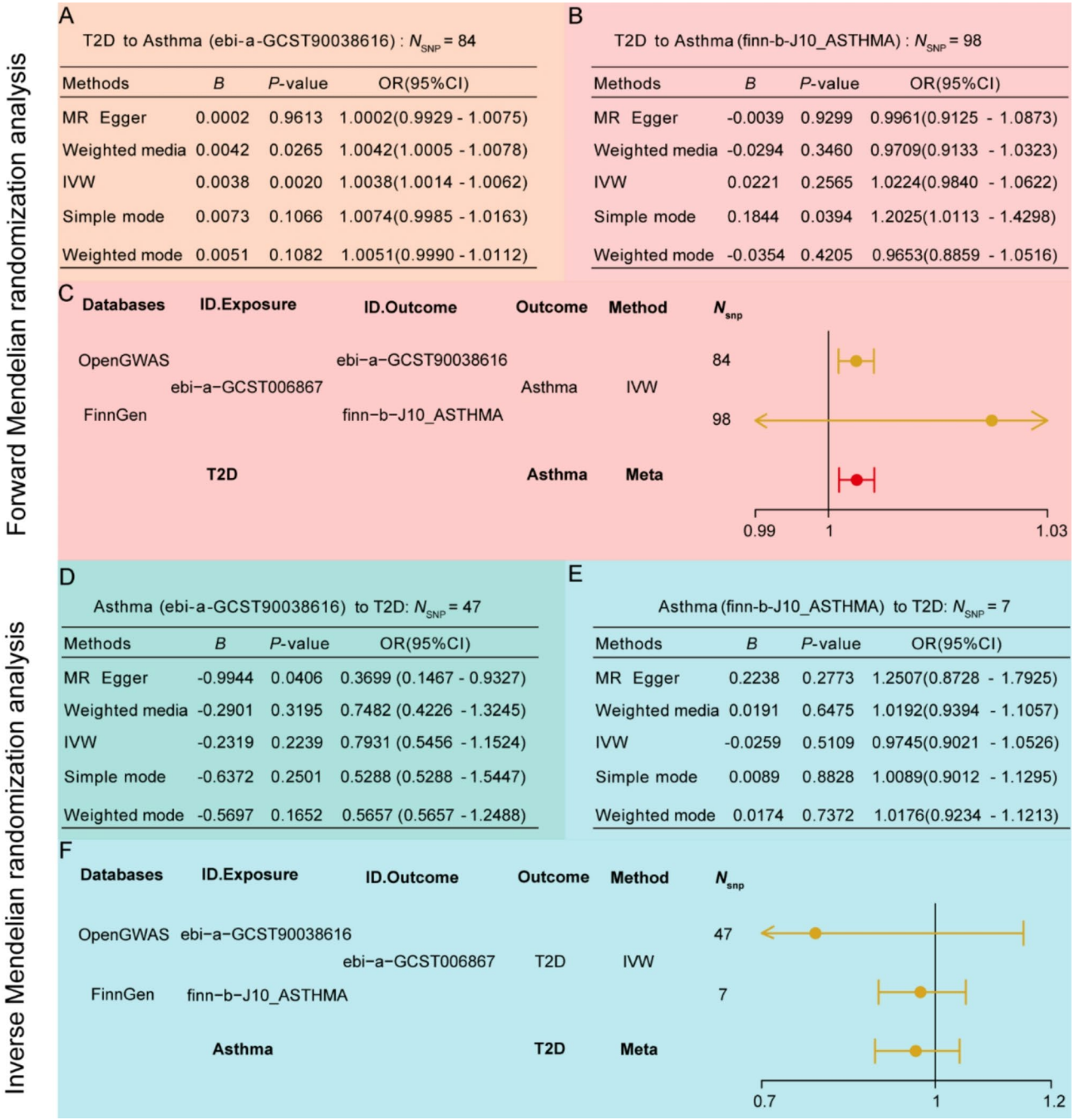

Fig. 2. Forest plots showing the bidirectional Mendelian randomization (MR) analysis results integrated through meta-analysis. (A–C) Forward analysis examining the causal effect of type 2 diabetes (T2D) on asthma: (A) MR results using OpenGWAS database, (B) MR results using FinnGen database, and (C) meta-analysis of A and B. (D–F) Reverse analysis examining the causal effect of asthma on T2D: (D) MR results using asthma data from OpenGWAS, (E) MR results using asthma data from FinnGen, and (F) meta-analysis of D and E. Significant meta-analysis results are shown in red, while non-significant results are shown in orange yellow. Points represent odds ratios (ORs) obtained from inverse-variance weighted (IVW) and meta-analysis methods. Nsnp: number of single nucleotide polymorphisms; B: causal effect estimate; OR: odds ratio; CI: confidence interval.

Subgroup levels

Causal relationship between diabetes subtypes and asthma

MR analysis was performed using 99 SNPs associated with five T2D subtypes (F-values > 10, detailed in Table S6). IVW analysis (Fig. 5) revealed a significant positive causal relationship between SAID and asthma in both openGWAS and FinnGen databases ($OR_{IVW} > 1$, $P_{IVW} < 0.05$). No significant causal associations were observed

Exposure	Outcome	Pleiotropy			Heterogeneity		
		Egger_intercept	SE	*P*-value	Q test	Q_df	P_{Q-test}
Forward analysis: T2D (ebi-a-GCST006867) to asthma							
T2D	Asthma (ebi-a-GCST90038616)	0.0003	0.0002	0.1552	87.5376	85	0.4037
T2D	Asthma (finn-b-J10_ASTHMA)	0.0021	0.0032	0.5182	102.294	97	0.3368
Inverse analysis: asthma to T2D (ebi-a-GCST006867)							
Asthma (ebi-a-GCST90038616)	T2D	0.0057	0.0032	0.0841	44.2662	46	0.5451
Asthma (finn-b-J10_ASTHMA)	T2D	− 0.0269	0.0194	0.2239	9.0534	6	0.1706

Table 1. The results of Pleiotropy and heterogeneity test in the bidirectional Mendelian randomization (MR) analysis between type 2 diabetes (T2D) and asthma. T2D, type 2 diabetes; SE, standard error; *Q test*, *Cochran's Q test*.

between other T2D subtypes (SIDD, SIRD, MORD, and MARD) and asthma ($P_{IVW} > 0.05$, Table S7). The distinct causal relationship of SAID with asthma, contrasting with other T2D subtypes, suggests subtype-specific pathogenic mechanisms. This heterogeneity likely reflects the different metabolic and immune characteristics of T2D subtypes, particularly the autoimmune features of SAID. The absence of causal associations for other subtypes may indicate either truly independent pathways or more complex interactions requiring further investigation. These findings highlight the importance of considering T2D heterogeneity in understanding diabetes-asthma relationships and developing subtype-specific treatment strategies.

Sensitivity analysis between diabetes subtypes and asthma

In the sensitivity analysis between diabetes subtypes and asthma, no significant pleiotropy or heterogeneity was observed, as shown in Table S8. Additionally, individual SNPs related to exposure showed some variability in causal effect estimates on asthma, as depicted in Fig. S3. In the leave-one-out analysis (Fig. S4), removing each SNP one by one resulted in only minor changes to the range of maximum and minimum causal effect estimates but had little impact on the overall causal effect estimate direction. This indicates that although individual SNPs show significant variability in different analysis directions, their causal effect estimates on the outcome variable are consistent from an overall perspective. For analysis directions showing significant results, scatter plots (Fig. 6A–J) illustrated the effect values of SNPs included in the analysis on exposure and outcome variables, successfully fitting potential linear trends, further affirming the causal relationship between exposure and outcome variables in MR analysis. Corresponding funnel plots (Fig. S5) also showed symmetric distributions of SNPs in each analysis direction using the IVW method as the main tool, enhancing the robustness and reliability of the analysis results.

Causal relationship between T2D subtypes and asthma subtypes

Using the IVW method, MR analysis of T2D as the exposure and 6 different asthma subtypes (allergic asthma, non-allergic asthma, mixed asthma, undefined asthma, eosinophilic asthma, and obesity-related asthma) as outcomes showed no significant results (Table S9, $P_{IVW}>0.05$). Detailed MR analysis results for each direction are provided in Table S9. MR analysis using the IVW method examined the causal relationship between 5 novel T2D subtypes as exposure and 6 different asthma subtypes as outcomes. The results indicated a positive causal effect between SAID and mixed asthma, and between SAID and eosinophilic asthma (Fig. 7, $OR_{IVW} > 1$, $P_{IVW} < 0.05$). Conversely, a negative causal relationship was observed between Mild Age-Related Diabetes and undefined asthma (Fig. 7, $OR_{IVW} < 1$, $P_{IVW}<0.05$). Detailed information on these MR analysis results is provided in Table S10. The specific association between SAID and eosinophilic asthma is particularly noteworthy, as both conditions share similar inflammatory characteristics including elevated eosinophil counts. These subtype-specific associations suggest that the relationship between T2D and asthma may be mediated through distinct immunological pathways, particularly in autoimmune diabetes where dysregulated immune responses might promote asthma development through enhanced inflammatory mediator production.

Causal relationship between T2D subtypes and asthma-related complications

MR analysis examining T2D effects on four asthma-related complications (acute respiratory infection, infection, pneumonia, and respiratory infection) showed no significant associations at the overall disease level (Table S9, $P_{IVW} > 0.05$). However, subtype-specific analysis revealed significant associations: SAID demonstrated positive causal relationships with all asthma-related complications (Fig. 8, $OR_{IVW} > 1$, $P_{IVW} < 0.05$), while MARD showed negative associations with acute respiratory infection and infection ($OR_{IVW} < 1$, $P_{IVW} < 0.05$). The association between MARD and asthma-related pneumonia, although significant in IVW analysis, was not supported by other MR methods and thus considered non-significant. Detailed results are provided in Table S10. The consistent associations between SAID and respiratory complications suggest shared pathogenic mechanisms, likely involving dysregulated immune responses. The positive associations with all respiratory complications highlight how autoimmune features of SAID might predispose patients to broader respiratory susceptibility, possibly through chronic immune system activation and enhanced inflammatory responses.

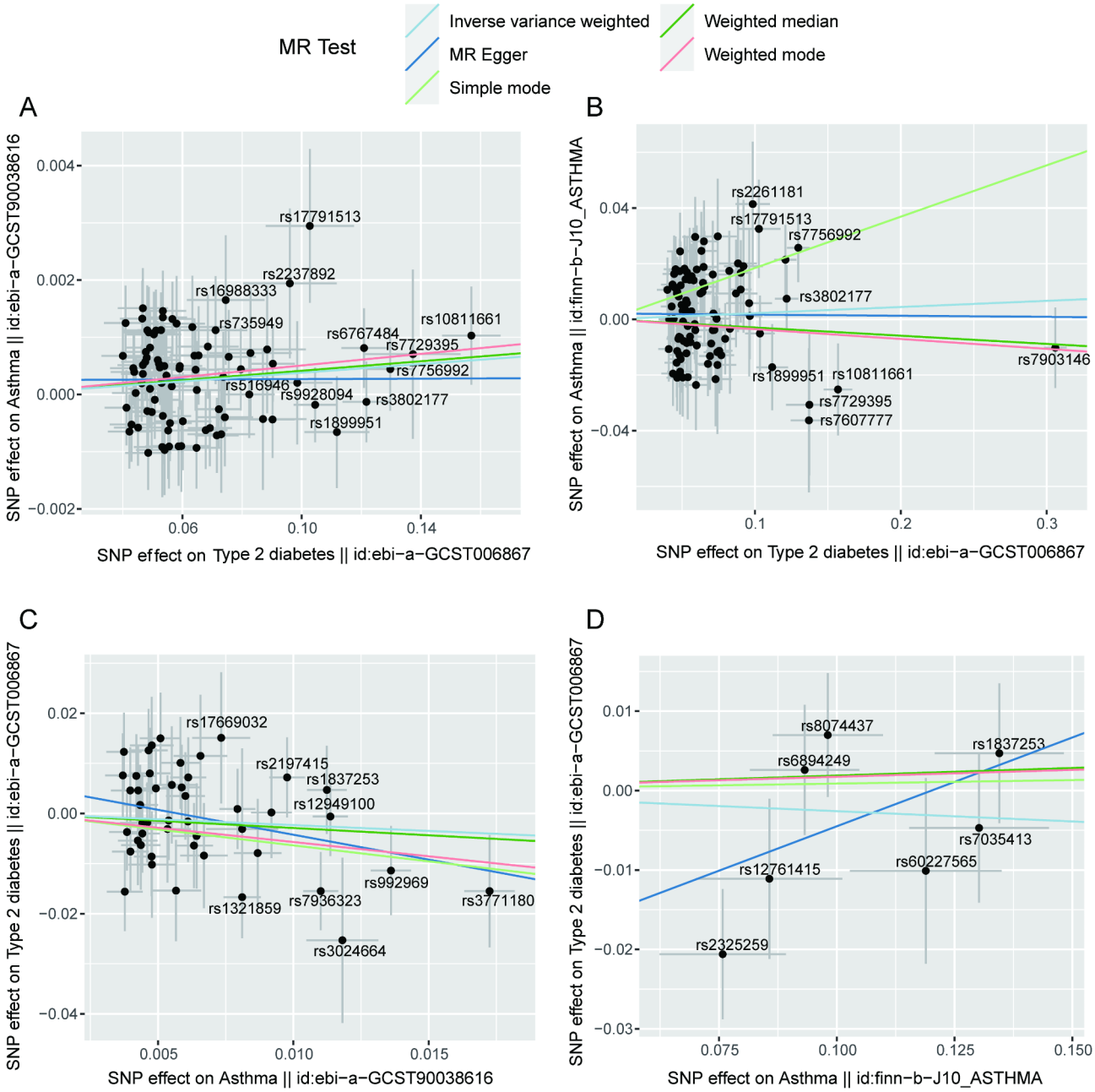

Fig. 3. Scatter plots depicting causal relationships between exposures and outcomes in bidirectional Mendelian randomization (MR) analyses. (A, B) Forward analysis examining T2D effects on asthma and (C, D) reverse analysis examining asthma effects on T2D. Lines represent fitted trends estimated by different MR methods (see legend). Each point represents a single nucleotide polymorphism (SNP), with outlier SNPs showing stronger effect estimates labeled by name. Different MR methods are indicated by distinct line types in the legend.

Sensitivity analysis in subgroup analyses

In the sensitivity analysis for diabetes (including subtypes) and asthma (including subtypes), no significant pleiotropy or heterogeneity was observed in each analysis direction, as shown in Table S11. Additionally, individual SNPs showed some variability in causal effect estimates on asthma, as depicted in Figure S6. In the leave-one-out analysis (Fig. 9), removing each SNP one by one resulted in only minor changes to the range of maximum and minimum causal effect estimates but had little impact on the overall causal effect estimate direction. This indicates that although individual SNPs show significant variability in different analysis directions, their causal effect estimates on the outcome variable are consistent from an overall perspective. For analysis directions with significant results, scatter plots (Fig. 10) illustrated the effect values of SNPs included in the analysis on exposure and outcome factors, successfully fitting potential linear trends, further affirming the causal relationship between exposure and outcome variables in MR analysis. Corresponding funnel plots (Figure

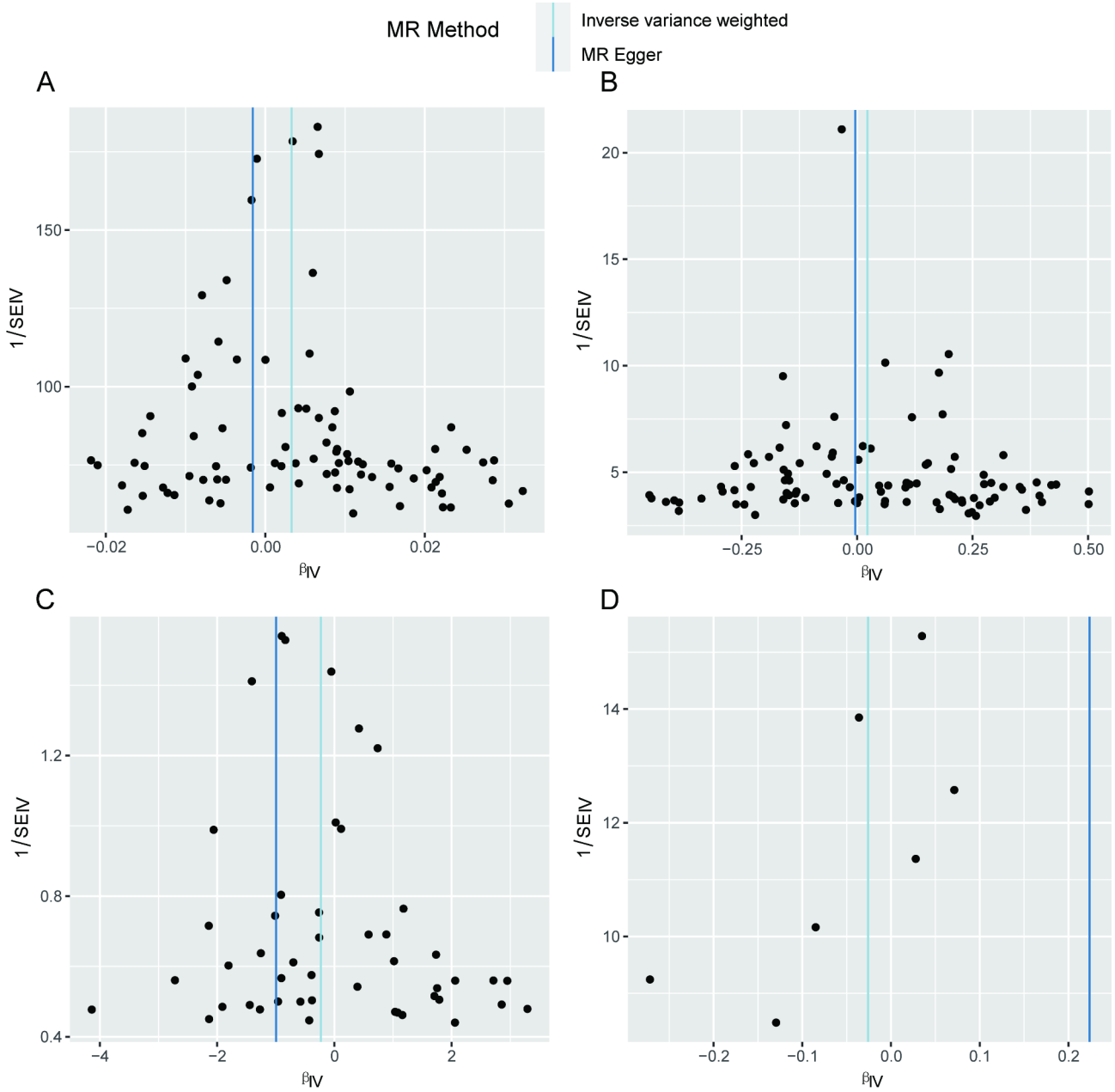

Fig. 4. Funnel plots demonstrating the distribution of instrumental variables in bidirectional Mendelian randomization (MR) analyses. (A, B) Forward analysis examining T2D effects on asthma and (C, D) reverse analysis examining asthma effects on T2D. Lines represent different MR methods (see legend). Each point represents a single nucleotide polymorphism (SNP) used as an instrumental variable (IV). β: causal effect estimate from inverse-variance weighted method; SE: standard error.

S7) also showed symmetric distributions of SNPs in each analysis direction using the IVW method as the main tool, enhancing the robustness and reliability of the analysis results.

MVMR analysis

At the overall level, after adjusting for smoking status, anxiety or panic attacks, body mass index, PM2.5 air pollution, and whole-body fat-free mass, MVMR analyses based on the OpenGWAS and FinnGen databases did not reveal any significant causal effect of diabetes on asthma (Table S12, $P > 0.05$). However, in the analysis using asthma as the outcome from the FinnGen database, we observed independent positive causal effects of smoking status ($B = 0.65$, $P = 0.008$), hypertension (Table S12, $B = 0.56$, $P = 0.02$), body mass index (Table S12, $B = 0.26$, $P < 0.001$), and PM2.5 air pollution (Table S12, $B = 0.59$, $P = 0.036$) on asthma. In the reverse MVMR analysis, we identified independent causal effects of hypertension (Table S12, to OpenGWAS data: $B = 1.84$, $P < 0.001$; to FinnGen data: $B = 1.84$, $P < 0.001$) and body mass index (Table S12, to OpenGWAS data: $B = 0.93$, $P < 0.001$;

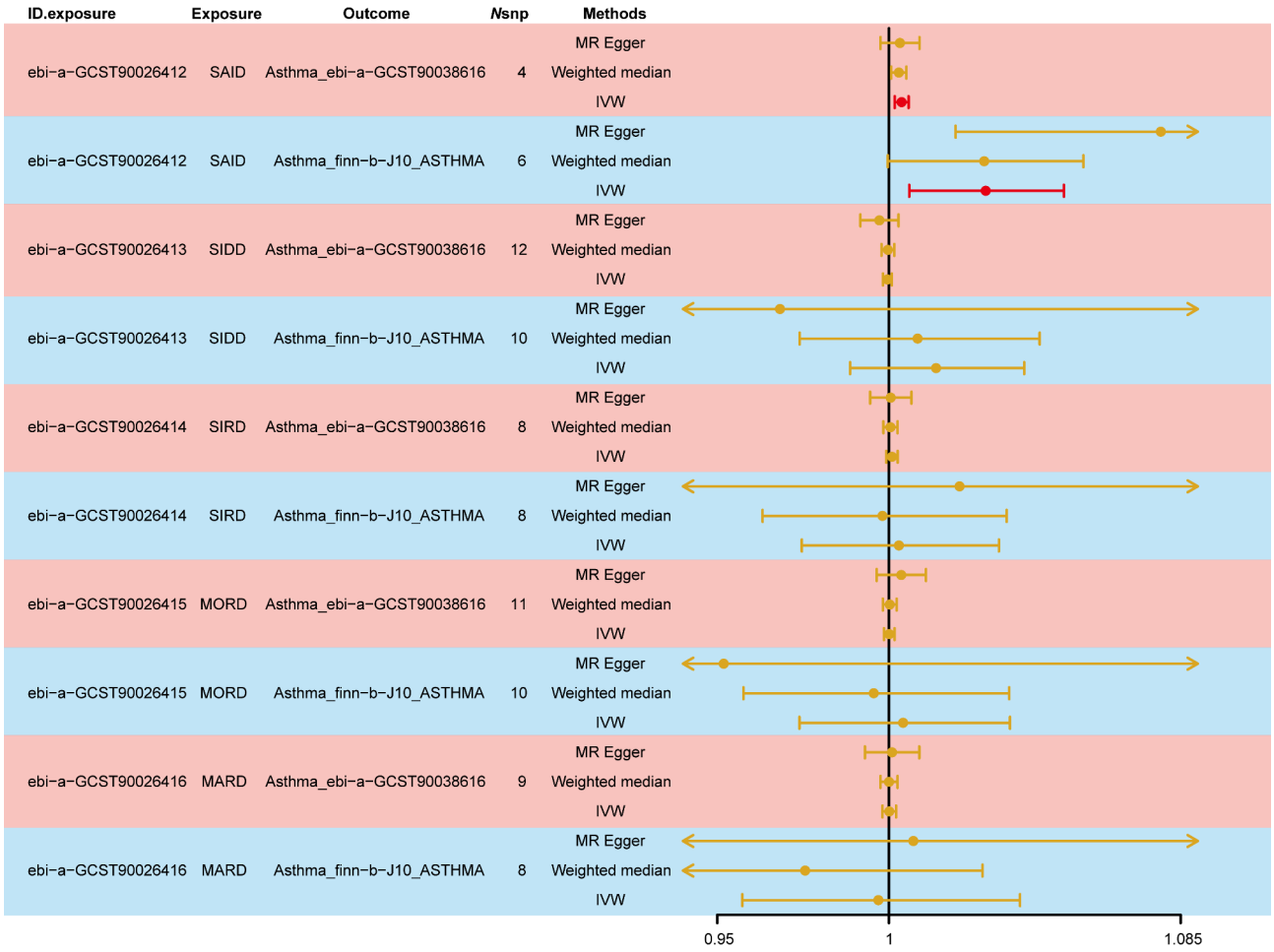

Fig. 5. Forest plots showing Mendelian randomization (MR) analysis results of T2D subtypes on asthma using different databases. Significant results are shown in red, while non-significant results are shown in orange yellow. Points represent odds ratios (ORs) obtained from inverse-variance weighted (IVW) and other MR methods. Nsnp: number of single nucleotide polymorphisms; SAID: severe autoimmune T2D; SIDD: severe insulin-deficient T2D; SIRD: severe insulin-resistant T2D; MORD: mild obesity-related T2D; MARD: mild age-related T2D.

to FinnGen data: $B = 0.93$, $P < 0.001$) on T2D. However, no significant causal effect of asthma on the risk of developing T2D was observed.

In the subgroup MVMR analyses, we confirmed an independent positive causal effect of severe autoimmune diabetes (SAID) on asthma (Table S12, to OpenGWAS data: $B = 0.005$, $P < 0.001$; to FinnGen data: $B = 0.038$, $P < 0.001$). Additionally, we identified a significant negative causal effect of severe insulin-deficient diabetes (SIDD) on asthma (Table S12, to OpenGWAS data: $B = -0.006$, $P = 0.002$; to FinnGen data: $B = -0.051$, $P = 0.016$). In the MVMR analyses of various diabetes subtypes and their risk factors on asthma, we found that after adjusting for smoking status, anxiety or panic attacks, body mass index, PM2.5 air pollution, and whole-body fat-free mass, none of the five diabetes subtypes showed a significant causal effect on asthma (Table S12, $P > 0.05$). However, within certain subtypes, we confirmed significant independent positive causal effects of smoking status, body mass index, and PM2.5 air pollution on asthma (Table S12, $B > 0$, $P < 0.05$). Detailed results are presented in Table S12.

Bioinformatics analysis

Analysis of immune cell composition across asthma progression stages revealed significantly elevated monocyte proportions within the peripheral blood lymphocyte population during exacerbation compared to follow-up and quiet phases ($P < 0.05$, Fig. 11A). Transcriptomic analysis was performed to explore the mechanistic role of monocytes in asthma exacerbation. Differential gene expression analysis comparing exacerbation versus follow-up phase (Fig. 11B) and exacerbation versus quiet phase (Fig. 11C) identified significant upregulation of CCL2 and multiple interferon-responsive genes (IFI44L and IFIT1) during exacerbation. The concurrent elevation of these inflammatory mediators suggests synergistic activation of chemokine and type I interferon pathways during acute asthma exacerbation. Notably, the upregulation of CCL2, a major monocyte-derived chemokine,

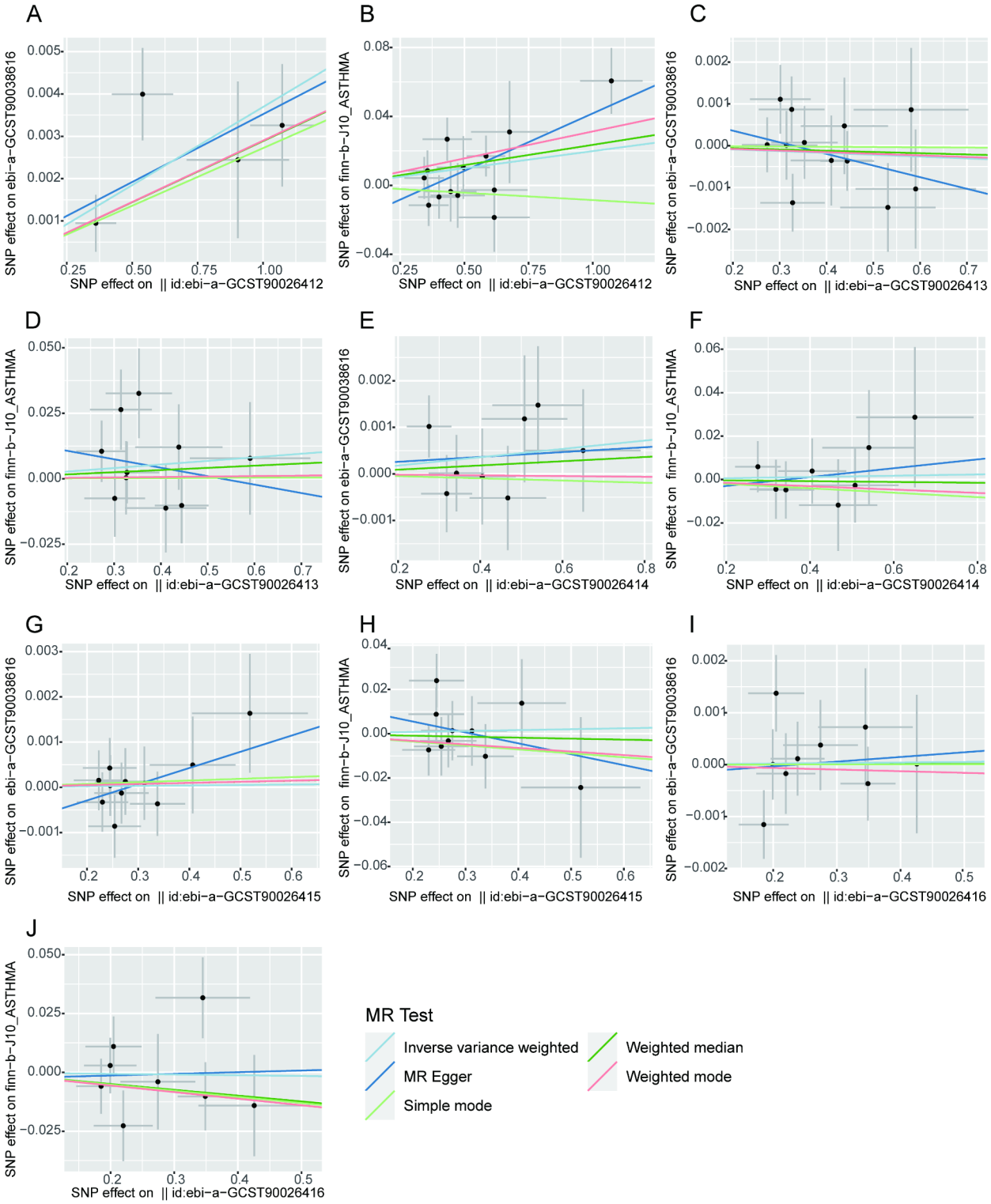

Fig. 6. Scatter plots show the causal effect between different type 2 diabetes subgroups and asthma in the different analysis directions. (A, B), the direction between severe autoimmune type 2 diabetes and asthma from OpenGWAS (A) and FinnGen (B) databases; (C, D), the direction between severe insulin-deficient type 2 diabetes and asthma from OpenGWAS (C) and FinnGen (D) databases; (E, F), the direction between severe insulin-resistant type 2 diabetes and asthma from OpenGWAS (E) and FinnGen (F) databases; (G, H), the direction between mild obesity-related type 2 diabetes and asthma from OpenGWAS (G) and FinnGen (H) databases; (I, J), the direction between mild age-related type 2 diabetes and asthma from OpenGWAS (I) and FinnGen (J) databases. Lines represent fitted trends estimated by different MR methods (see legend). Each point represents a single nucleotide polymorphism (SNP), with outlier SNPs showing stronger effect estimates labeled by name.

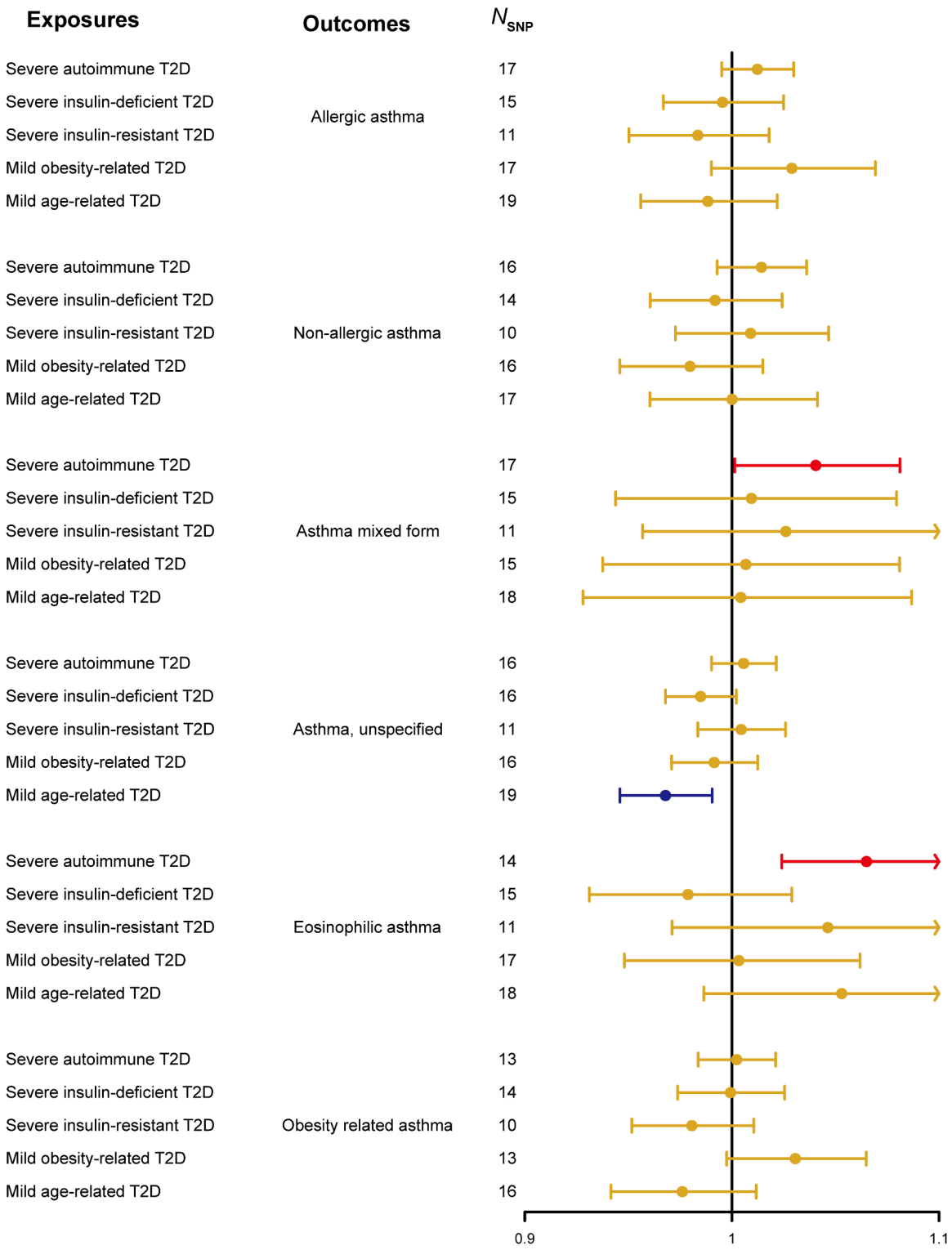

Fig. 7. Forest plots showing Mendelian randomization (MR) analysis results between type 2 diabetes (T2D) subtypes and asthma subtypes using inverse-variance weighted (IVW) method. Significant positive associations are shown in red, significant negative associations in blue, and non-significant results in orange yellow. Points represent odds ratios (ORs) from IVW analysis. Nsnp: number of single nucleotide polymorphisms.

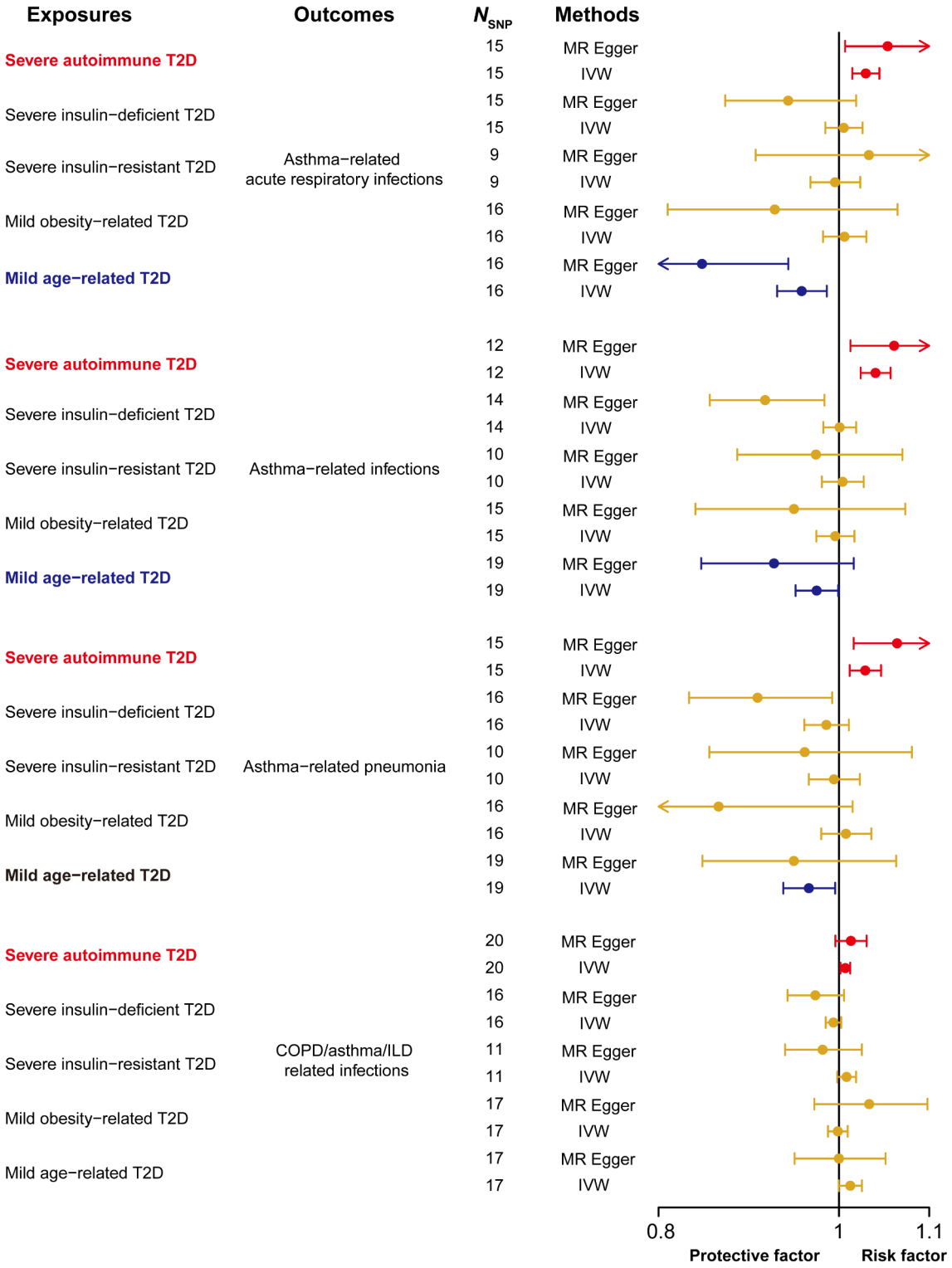

Fig. 8. Forest plots showing Mendelian randomization (MR) analysis results between type 2 diabetes (T2D) subtypes and asthma-related complications using inverse-variance weighted (IVW) and MR-Egger methods. Significant positive associations are shown in red, significant negative associations in blue, and non-significant results in orange yellow. Points represent odds ratios (ORs) from IVW analysis. Nsnp: number of single nucleotide polymorphisms.

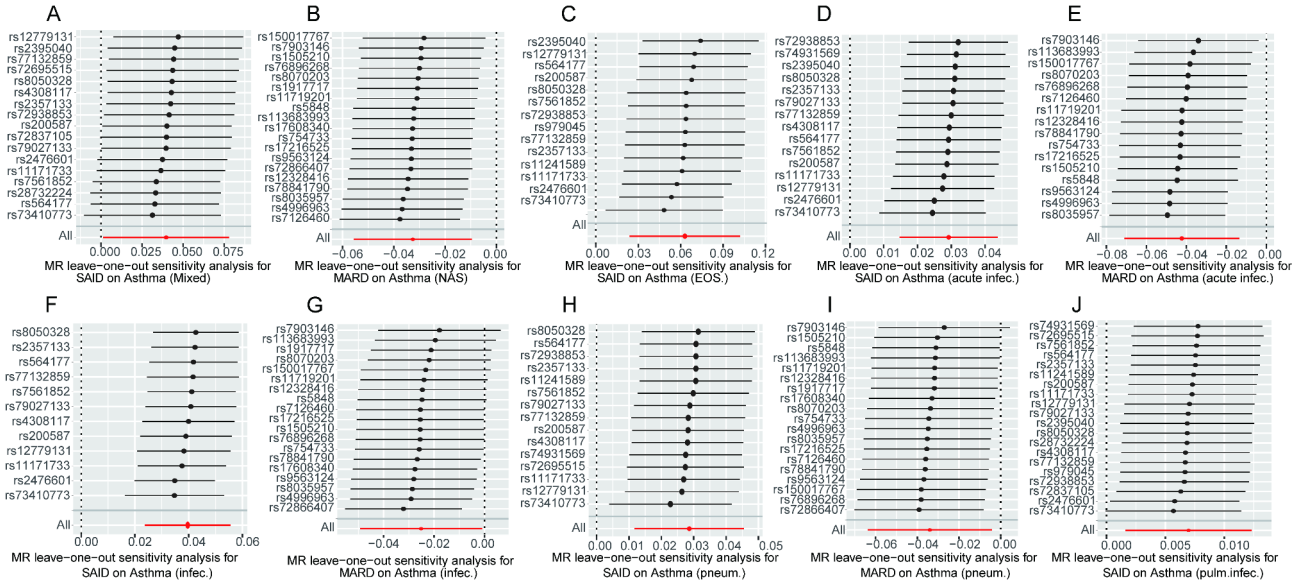

Fig. 9. Leave-one-out sensitivity analysis for significant Mendelian randomization results. (A–J) represent different analysis directions as indicated below each panel. Black dashed lines show the range of causal effect estimates after removing each single nucleotide polymorphism (SNP), with black dots indicating the specific effect size. Red dashed lines and dots represent the overall causal effect estimates. SAID, severe autoimmune type 2 diabetes; SIDD, severe insulin-deficient type 2 diabetes; SIRD, severe insulin-resistant type 2 diabetes; MORD, mild obesity-related type 2 diabetes; MARD, mild age-related type 2 diabetes. IVW, inverse-variable weighted method. Mixed, the subgroup of mixed asthma; NAS, unspecified asthma; EOS., eosinophilic asthma; acute infec., asthma-related acute respiratory infections; infec., asthma-related infections; pneum., asthma-related pneumonia; pulm. infec., COPD/asthma/ILD related infections.

together with increased monocyte proportions in clinical samples, establishes the monocyte-CCL2 axis as a central component in asthma exacerbation.

Comparison of gene expression profiles between glucose- and PBS-treated monocytes (Fig. 11D) revealed significant upregulation of CCL2, CXCL9, CXCL10, and antigen presentation-related genes (including HLA-DMB) under hyperglycemic conditions, indicating enhanced monocyte immune activity and antigen presentation capabilities. Parallel analysis of peripheral blood monocytes from T2D patients versus PBS-treated control monocytes (Fig. 11E) demonstrated significant upregulation of multiple immune regulatory genes (CCR7, CXCL5, and CCL2), mirroring the expression patterns observed in glucose-stimulated monocytes. These parallel findings establish glucose metabolic dysregulation as a potential mechanistic link between diabetes and asthma pathogenesis, particularly through enhanced monocyte activation and CCL2 secretion. KEGG pathway enrichment analysis of differentially expressed genes in glucose-stimulated monocytes (Fig. 11F) identified significant enrichment in multiple functional pathways. These included immune-related disease pathways (type 1 diabetes and asthma), antigen processing and presentation, cell adhesion, inflammatory cell activation and differentiation, lipid metabolism, and cytokine signal transduction. This comprehensive pathway analysis suggests that hyperglycemia may promote asthma development through three primary mechanisms: enhanced monocyte immune activation, metabolic dysfunction-induced immune cell perturbation, and increased pro-inflammatory cytokine production, collectively creating an immunological environment favorable for asthma pathogenesis.

Discussion

Our study revealed complex causal relationship between T2D and asthma through multi-level analyses. At the overall disease level, meta-analysis of MR results from two independent databases established a positive causal effect of T2D on asthma development. However, this association was attenuated after adjusting for multiple risk factors in MVMR analysis, including smoking status, hypertension, body mass index, and PM2.5 air pollution, suggesting the importance of environmental and metabolic factors in this relationship. Further subtype-specific analysis demonstrated that only SAID maintained a significant positive causal association with asthma after controlling for these confounders. Notably, SAID also exhibited consistent positive causal associations with specific asthma phenotypes, particularly mixed and eosinophilic types, as well as various asthma-related complications including respiratory infections. In contrast, MARD showed negative associations with undefined asthma and asthma-related infections. To elucidate potential biological mechanisms underlying these genetic associations, we performed transcriptomic analysis which revealed elevated monocyte proportions in peripheral blood during asthma exacerbation and identified CCL2 as a key molecular mediator in glucose-stimulated monocytes. These findings suggest that T2D, particularly its autoimmune subtype, may influence asthma susceptibility through immune cell modulation, notably via the monocyte-CCL2 axis.

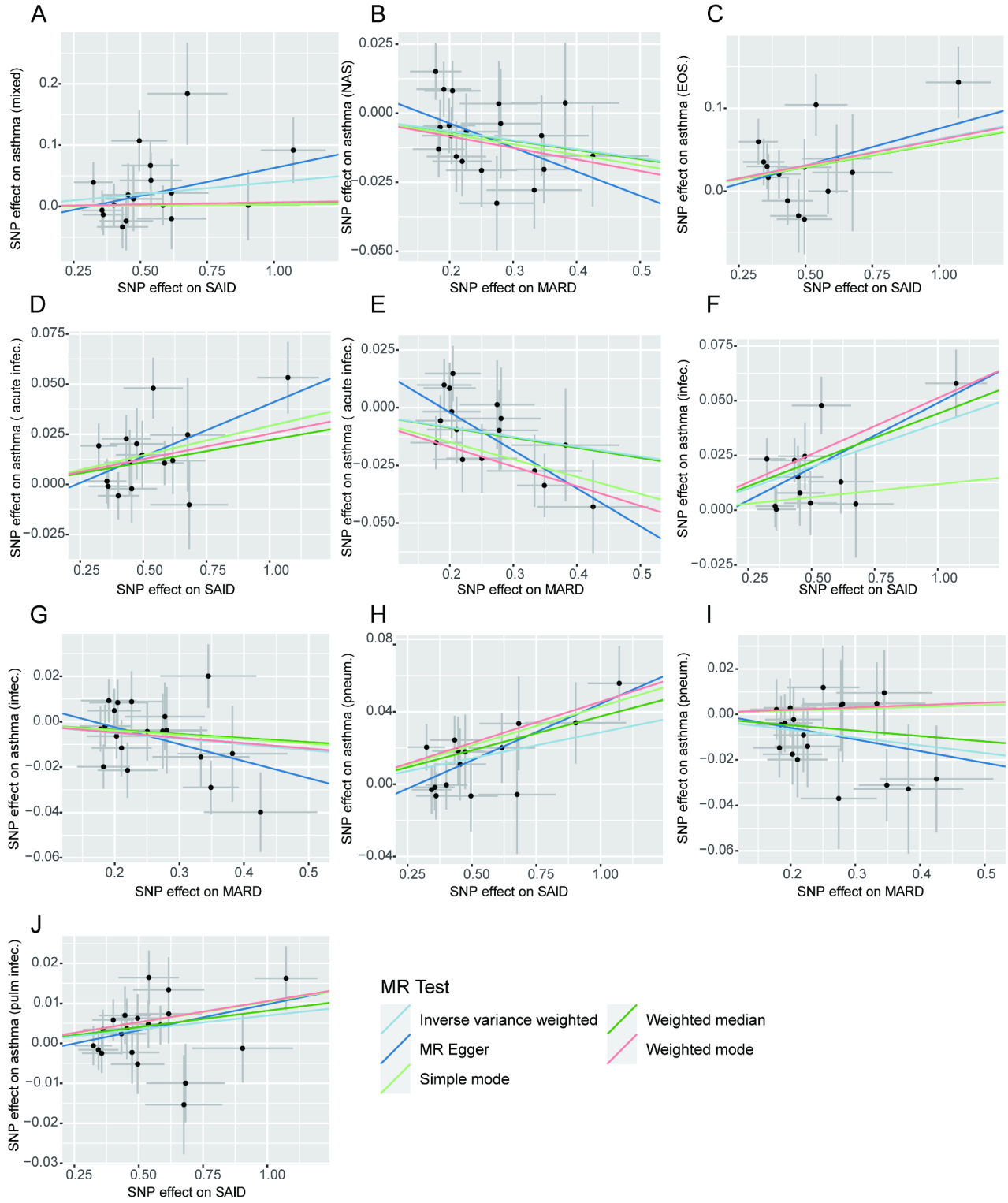

Fig. 10. Scatter plots depicting causal relationships between type 2 diabetes (T2D) subtypes and asthma phenotypes/complications using FinnGen database. (A) SAID and mixed asthma; (B) MARD and unspecified asthma; (C) SAID and eosinophilic asthma; (D) SAID and asthma-related acute respiratory infections; (E) MARD and asthma-related acute respiratory infections; (F) SAID and asthma-related infections; (G) MARD and asthma-related infections; (H) SAID and asthma-related pneumonia; (I) MARD and asthma-related pneumonia; (J) SAID and COPD/asthma/ILD related infections. Lines represent fitted trends estimated by different MR methods (see legend). Each point represents a single nucleotide polymorphism (SNP). SAID, severe autoimmune T2D; MARD, mild age-related T2D; COPD, chronic obstructive pulmonary disease; ILD. interstitial lung disease.

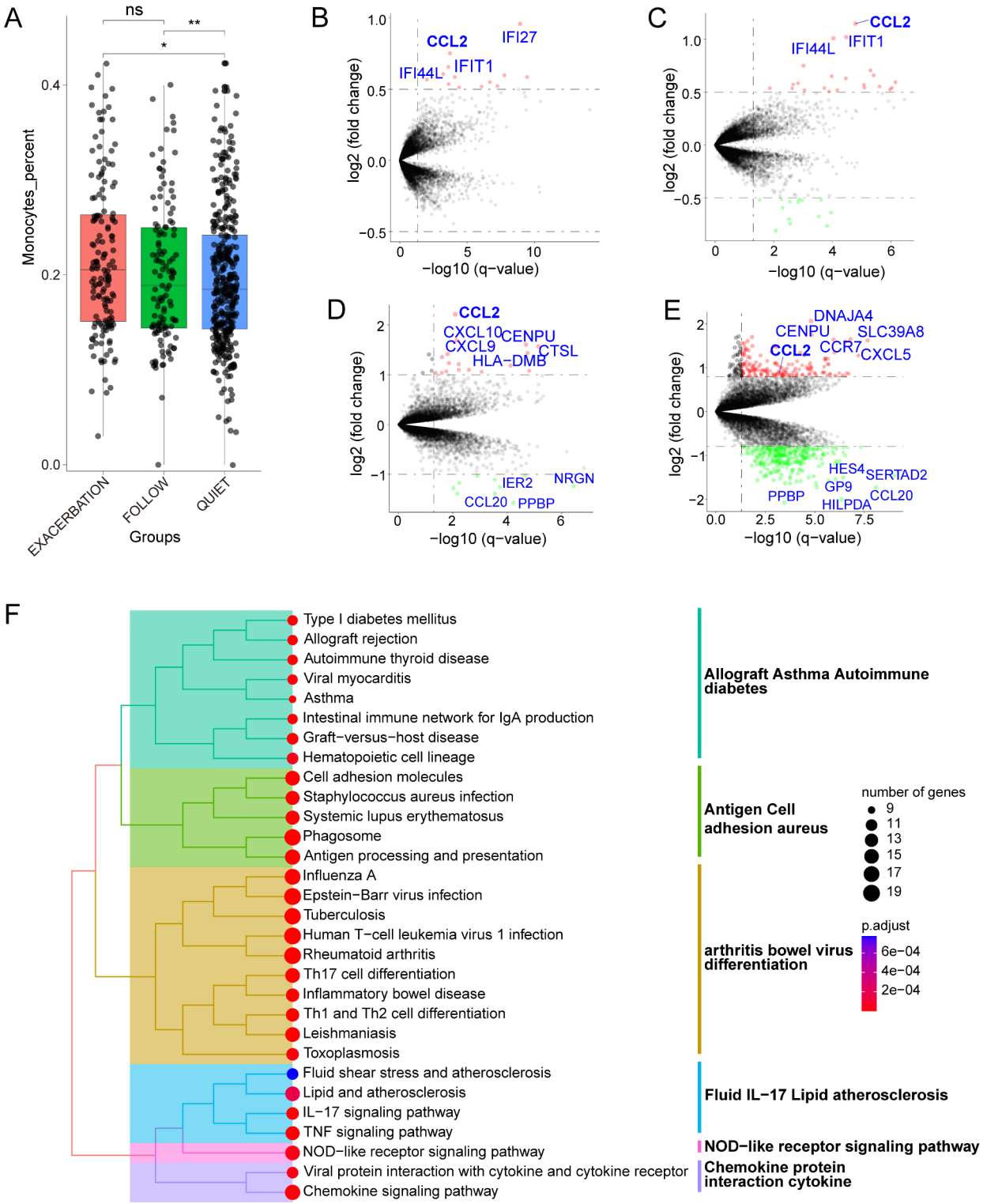

Fig. 11. Transcriptomic and pathway analysis reveals hyperglycemia-induced monocyte activation and CCL2 signaling as a key mechanism linking diabetes to asthma pathogenesis. (A) Comparison of monocyte proportions in peripheral blood across different asthma phases. (B, C) Differential gene expression analysis between asthma exacerbation versus follow-up (B) and quiet phases (C). (D) Gene expression changes in glucose-stimulated versus PBS-treated monocytes. (E) Transcriptomic comparison between T2D patient monocytes and PBS-treated controls. (F) KEGG pathway enrichment analysis of differentially expressed genes in glucose-stimulated monocytes.

These genetic findings both complement and extend previous epidemiological evidence. Earlier studies have consistently reported associations between T2D and increased asthma risk[19], with several cohort studies documenting elevated asthma incidence among diabetic patients compared to the general population[20–22]. While these observational findings suggested potential links through shared inflammatory pathways, they were unable to establish causality or distinguish between different disease subtypes. Our MR analyses extend these observations by providing genetic evidence for a causal relationship, particularly identifying SAID as the primary driver of asthma risk among T2D subtypes. Additionally, our findings help clarify the role of common risk factors. Previous studies have identified obesity as a shared risk factor for both conditions[23], but could not determine whether it acts as a mediator between T2D and asthma. Our MVMR analyses clarify this relationship by demonstrating that BMI independently influences both diseases rather than serving as a mediator of the T2D-asthma association. This is further supported by our finding that obesity-related diabetes subtypes show no significant causal relationship with obesity-related asthma. These results suggest that metabolic and immune pathways may contribute to disease development in parallel rather than sequential fashion, laying the foundation for exploring specific molecular mechanisms.

Our findings have several potential clinical implications. First, by identifying SAID as the primary driver of asthma risk among T2D subtypes, we highlight the importance of distinguishing diabetes subtypes in clinical practice. The strong association between SAID and specific asthma phenotypes (particularly eosinophilic and mixed asthma) as well as respiratory complications suggests that these patients may require more targeted monitoring of respiratory health. Second, our molecular findings, particularly the identification of the monocyte-CCL2 axis, point to potential biomarkers for risk stratification. While traditional risk factors such as smoking, BMI, and air pollution remain important as demonstrated by our MVMR analyses, the role of inflammatory markers may provide additional prognostic value. Third, the observed negative association between MARD and asthma-related infections represents an intriguing finding. This protective effect might be attributed to the distinct pathophysiological characteristics of MARD, which typically presents with milder metabolic perturbations and better preserved beta-cell function compared to other T2D subtypes[24,25]. The relatively stable glucose homeostasis in MARD patients may result in less immune system dysfunction, potentially explaining the lower susceptibility to asthma-related infections. However, it is important to note that the clinical utility of these findings, particularly the use of specific biomarkers such as monocyte ratios and CCL2 levels, requires validation through prospective clinical studies before implementation in routine practice.

To understand the molecular mechanism underlying the genetic associations, we focused on inflammatory pathways linking T2D and asthma. Our findings revealed a complex immune-inflammatory network, with the monocyte-CCL2 axis emerging as a central mechanistic link. In T2D patients, chronic low-grade inflammation, particularly in visceral adipose tissue[26,27], creates a systemic inflammatory environment that may predispose to asthma development[28]. This systemic inflammation is characterized by significant immune cell dysfunction, including altered monocyte/macrophage activity and impaired regulatory T cell function[29,30]. Specifically, diabetic patients exhibit macrophage overactivation and regulatory T cell (Treg) dysfunction, leading to persistent and nonspecific immune responses[31,32]. In asthma, this dysregulation manifests as airway hyperresponsiveness and sustained inflammatory activation[33], creating a mutually reinforcing immune environment that extends beyond local airways. Our transcriptomic analyses provided direct evidence for this immune dysregulation. We observed significantly elevated monocyte proportions in peripheral blood during asthma exacerbation, consistent with previous studies[34,35]. As monocytes are precursors to macrophages, which play crucial roles in asthma progression[36,37], these findings suggest that diabetes-induced abnormalities in monocyte lineage may contribute to asthma pathogenesis. More importantly, we identified a specific molecular signature: hyperglycemia-induced monocyte activation led to increased CCL2 secretion, potentially serving as a key inflammatory bridge between these conditions. This finding was further supported by the parallel upregulation of CCL2 in both asthma patients' peripheral blood monocytes and glucose-stimulated monocytes.

Additionally, we identified a broader inflammatory network involving multiple chemokines and cytokines. The concurrent upregulation of interferon-response genes (IFI44L and IFIT1) and chemokines (CXCL5, CXCL9, CXCL10) suggests a coordinated immune response. This network regulates the recruitment and activation of various inflammatory cells: CCL2 primarily recruits monocytes and macrophages, CXCL5 attracts neutrophils, and CXCL9/CXCL10 target T lymphocytes, particularly Th1 cells[38–40]. The synergistic effects of these molecules create a positive feedback loop that continuously amplifies the inflammatory response. Specifically, CCL2-mediated monocyte recruitment leads to increased local inflammation, while interferon-induced genes enhance both antiviral responses and inflammatory amplification. The elevated expression of CXCL5, CXCL9, and CXCL10 further expands this inflammatory cascade by recruiting additional immune cell populations. These molecular findings both align with and extend our genetic evidence. The strong causal association between SAID and asthma could be explained by enhanced immune system activation, with the monocyte-CCL2 axis serving as a key mediator. The importance of this axis is underscored by our observation that CCL2 is significantly upregulated in both asthma and diabetes contexts, suggesting its role as a central node in the inflammatory network linking these conditions. This mechanistic insight not only helps explain the epidemiological association between T2D and asthma but also identifies potential therapeutic targets. Conversely, the negative association between MARD and asthma-related infections might reflect better preserved immune homeostasis in this T2D subtype, highlighting how different diabetes subtypes may interact distinctly with immune pathways.

Recent experimental studies provide additional support for the role of hyperglycemia-induced monocyte activation in asthma pathogenesis. High glucose conditions can directly activate monocytes through enhanced glucose metabolism and oxidative stress, leading to epigenetic modifications that promote a pro-inflammatory phenotype[41–43]. These glucose-mediated changes result in increased production of inflammatory mediators, particularly CCL2 [44,45]. Animal models have demonstrated that CCL2-mediated monocyte recruitment significantly contributes to airway inflammation and hyperresponsiveness[46,47], while diabetic mouse models

show enhanced inflammatory responses through similar pathways[48–50]. The consistency between previous experimental findings and our transcriptomic analysis provides strong support for the mechanistic link between hyperglycemia, monocyte activation, and asthma development. Future studies utilizing combined diabetes-asthma models could further elucidate the detailed molecular interactions in this pathway.

Our study has several methodological strengths and limitations. Unlike traditional observational studies, MR analysis uses genetic variables as IVs to assess causal relationships, reducing the impact of confounding factors and reverse causality[51]. However, several limitations should be noted. First, our genetic instruments were primarily derived from European populations, potentially limiting the generalizability of our findings across different ethnic groups. Second, variations in disease classification criteria across databases might affect result interpretation. More importantly, while our bioinformatic analyses identified CCL2 as a key mediator in the T2D-asthma relationship, experimental validation is needed. CCL2 inhibitors have shown therapeutic potential in various inflammatory conditions, including asthma and diabetic complications[52,53], through mechanisms involving inflammatory cell recruitment inhibition and tissue damage reduction[54]. Building on this evidence, future studies should focus on several critical experimental validations. Animal studies comparing CCL2 expression and inflammatory responses in diabetic mice with and without asthma would help validate the proposed mechanism. Additionally, in vitro studies examining glucose-induced responses in primary monocytes from diabetic patients would provide direct mechanistic evidence. Furthermore, clinical validation studies measuring CCL2 levels and monocyte function in patients with both conditions would establish the clinical relevance of our findings. Intervention studies using CCL2 inhibitors could also assess the therapeutic potential of targeting this pathway, particularly given their demonstrated efficacy in managing chronic inflammation in metabolic disorders. These experimental validations would provide more concrete evidence for developing targeted therapeutic strategies, potentially leading to more effective treatments for patients with concurrent T2D and asthma.

Conclusion

Evidence from MR analysis confirms the positive causal relationship between T2D and asthma, with notably stronger associations observed between SAID and specific asthma subtypes. Through integrated bioinformatics analysis and transcriptomic profiling, we identified the monocyte-CCL2 axis as a crucial molecular mechanism underlying this relationship, where hyperglycemia-induced monocyte activation and subsequent CCL2 secretion may represent a central pathogenic link between these conditions. Furthermore, our analysis revealed a complex inflammatory network involving interferon-response genes (IFI44L and IFIT1) and chemokines (CXCL5, CXCL9, CXCL10), suggesting a broader immune dysregulation beyond monocyte activation. These findings not only elucidate the shared inflammatory and immune pathways between diabetes and asthma but also provide potential therapeutic targets, particularly highlighting CCL2 inhibition as a promising intervention strategy.

Materials and methods

Study design and data sources

This study employs an integrated analytical framework combining bidirectional two-sample MR analysis with bioinformatics analysis to explore the causal relationship between diabetes and asthma. The MR section, conforming to STROBE-MR (Strengthening the Reporting of MR Studies) guidelines[55], includes forward analysis—diabetes mellitus and its subtypes as exposures and asthma, its subtypes, and related complications as outcomes—and reverse analysis, evaluating causal influence of asthma on diabetes incidence, with detailed assessments at both disease-wide and subtype-specific levels (Fig. 1). Besides, bioinformatics analysis integrates peripheral blood mononuclear cell (PBMC) microarray sequencing data to identify shared immunological signatures, particularly monocyte-driven immune responses, between these conditions. This dual approach yields genetic and molecular insights into their potential causal relationships.

For the forward analysis, T2D exposure data were obtained from the largest dataset in the OpenGWAS database (GWAS ID: ebi-a-GCST006867)[56], comprising 655,666 samples, including 61,714 cases (Table S1). Outcome data were downloaded from two sources: the OpenGWAS database (GWAS ID: ebi-a-GCST90038616, Table S1) with 484,598 samples, including 56,087 cases[57], and the FinnGen database (https://r5.risteys.finngen.fi/phenocode/J10_ASTHMA, GWAS ID: finn-b-J10_ASTHMA) with 156,078 samples, including 20,629 cases (Table S1). For subtype-specific forward analysis, diabetes subtype data from a Swedish cohort (5 subtypes, Table S1) served as exposure variables[6]. To avoid potential influence from sample overlap, outcome variables were selected from asthma subtypes (6 diseases subtypes, Table S1) and asthma-related complications (4 different disease subtypes, Table S1) within the FinnGen database[58]. In both forward and reverse analyses, independent two-sample MR analyses were conducted for each direction. The overall design and framework of the study are illustrated in Fig. 1.

For the bioinformatics analysis, we focused on microarray data from PBMCs of asthma patients (GSE19301, samples = 685)[59] and monocyte transcriptome data (GSE105167) that included three experimental conditions: classical monocytes from PBMCs of T2D patients, and classical monocytes under phosphate buffered saline (PBS) or glucose stimulation, with a total of 11 samples across these three conditions[60]. All expression matrices and corresponding clinical information were obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds)[61]. Since this study utilized publicly available data from the GEO repository, institutional ethics review was not required.

Instrumental variables (IVs) selection

Exposure-related IVs

In this study, the R package "TwoSampleMR," specifically designed for two-sample MR analysis, was used to accurately identify single nucleotide polymorphisms (SNPs) closely related to exposure variables and use them as IVs[62]. Strict parameter standards were set for IV selection, including an overall *P*-value threshold of 5.0×10^{-8} and a subgroup *P*-value threshold of 5.0×10^{-6}, a linkage disequilibrium (LD) threshold of 0.001, and a window size of 10,000 base pairs[63]. The selected IVs had to meet the three core assumptions of MR analysis to ensure their validity[64]: the relevant assumption (strong genetic association between SNP and exposure), the independent assumption (SNP unrelated to any potential confounders), and the exclusive assumption (SNP affects the outcome only through the exposure). Comprehensive quality control was performed to ensure the validity of the IVs, ensuring complete data on sample size and effect allele frequency (EAF). Missing sample size data were supplemented from databases and missing EAF data were referenced from the "1000 Genomes Project"[65].

Exclusion of confounders

To effectively exclude potential confounding IVs, the LDtrait tool in the "LDlink" database (https://ldlink.nih.gov/?tab=ldtrait, accessed on June 20th, 2024) was utilized[66]. In the forward analysis, IVs associated with any type of asthma, asthma-related diseases, or allergic disease phenotypes were excluded. Similarly, in the reverse analysis, IVs related to diabetes, diabetes complications, or blood glucose level phenotypes were identified as confounding variables and excluded. After the screening process, the F-values for the remaining IVs were calculated ($F = beta^2/se^2$) to ensure that each IVs had an F-value greater than 10[67]. This threshold enhances the statistical power of the MR analysis and the robustness of the IVs. Additionally, IVs related to exposure and outcome were merged, with consistent effect and reference alleles. Two R packages, "RadialMR"[68] and "MR-PRESSO"[69], were used to identify and exclude outliers[70]. After these data cleaning procedures, a list of IVs for the final MR analysis was acquired.

MR analysis

MR analysis was primarily conducted with the "TwoSampleMR" R package[71]. The inverse-variance weighted (IVW) method[72] served as the primary analytical approach, complemented by MR Egger[73], weighted median[74], simple mode[75], and weighted mode[76] methods. Results were considered significant when meeting both criteria: for individual comparisons, results were considered significant at $P < 0.05$ from the IVW method; for multiple comparisons, Bonferroni-corrected thresholds were applied ($P < 0.025$ for overall analysis with 2 comparisons, and $P < 0.01$ for subgroup analysis with 5 comparisons); the effect estimates (β values) from all five methods were required to be directionally consistent (i.e., all positive or all negative)[77]. The "TwoSampleMR" R package was used to calculate the odds ratios (OR) and their 95% confidence intervals (CI) for each direction of analysis, assessing the magnitude and direction of causal effects. Additionally, via "metafor" R package[78], a meta-analysis was conducted to integrated causal effects from different data sources, providing combined effect estimates.

Sensitivity analysis

Sensitivity analysis was used to assess the horizontal pleiotropy and heterogeneity of IVs, ensuring the MR analysis's reliability[79]. In analyses involving more than two SNPs, the *Cochran's Q test* was used to assess the heterogeneity among IVs[80]. When the *P*-value of the *Q test* (marked as "P_{Q-test}") was less than 0.05, it pointed to significant heterogeneity among the IVs, prompting a re-assessment of MR analysis results using the random-effects-model IVW method to accommodate this heterogeneity. To evaluate horizontal pleiotropy, the MR Egger intercept method was employed[69], indicating whether IVs had effects beyond their influence on the outcome. Scatter and funnel plots were employed to visually depict the sensitivity analysis results, helping to illustrate data distribution and any potential biases. Furthermore, a leave-one-out analysis was executed, recalculating MR results by removing each IV one by one to determine the role and impact of each IV on the overall analysis findings.

Multivariable MR analysis

Multivariable Mendelian randomization (MVMR) analyses were performed to further explain the causal relationship between diabetes and asthma. First, we investigated the effect of diabetes on asthma at a general level using summary statistics from various databases, while controlling for five potential confounding variables: smoking status, anxiety or panic attacks, body mass index, PM2.5 air pollution, and whole-body fat-free mass. For the reverse MR analysis, with asthma as the exposure, adjustments included smoking status, hypertension, high cholesterol, body mass index, and PM2.5 air pollution. Furthermore, we conducted MVMR analyses to assess the causal relationship between five subtypes of type 2 diabetes (T2D) and asthma, as well as the causal risk of asthma associated with T2D subtypes and their respective risk factors. Given the stringent SNP selection criteria and reduced number of valid instrumental variables in the MVMR approach, which inherently provides a more conservative framework, a *P*-value threshold of < 0.05 was used to determine the significance of the results.

Bioinformatics analysis

Initially, we obtained gene expression matrices and clinical data from the GEO database[61], then performed data normalization and log2 transformation. In the GSE19301 dataset[59], there were 685 samples, all from asthma patients, including 166 with asthma exacerbation, 125 in the recovery phase (labeled as 'follow'), and 394 in the stable phase (labeled as 'quiet'). " We first analyzed the proportion of peripheral blood monocytes within the lymphocyte population across three asthma phases. Using the "limma" R package[81,82], we then

performed differential gene expression analysis to identify shared differentially expressed genes (DEGs) between exacerbation versus stable phase, and exacerbation versus recovery phase. DEGs were defined by |logFold Change (FC)| > 1 and $P < 0.05$ [82].

Using the GSE105167 dataset[60], we compared gene expression profiles between glucose- and phosphate buffered saline (PBS)-stimulated monocytes, as well as between PBS-stimulated classical monocytes and peripheral blood classical monocytes from T2D patients, to identify shared DEGs. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed on glucose- virus PBS-stimulated monocytes DEGs using the "clusterProfiler" R package[83], revealing molecular pathway potentially involved in hyperglycemia-induced monocyte dysfunction.

Data availability

The datasets generated and/or analysed during the current study are available in the ieu OpenGWAS (https://gwas.mrcieu.ac.uk/), FinnGen databases (https://www.finngen.fi/en), and GEO database (https://www.ncbi.nlm.nih.gov/gds).

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Author contributions

F.ZJ and L.YH contributed to conception and designed the project, L.T and G.WH performed the GWAS datasets and analyzed the data and edited graph, and wrote the draft. J.WT and D.WW validated the results and visualized them. All authors contributed to the article and approved the submitted version.

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Competing interests

The authors declare no competing interests.

Additional information

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