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ORIGINAL ARTICLE

Myeloid Dendritic Cell Counts and Coronary Heart Disease: a Bidirectional Mendelian Randomization Study

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ABSTRACT

Background: **Coronary heart disease (CHD) remains a leading cause of morbidity and mortality worldwide, with immune and inflammatory mechanisms playing important roles in its pathogenesis. Dendritic cells (DCs) are key regulators of immune responses; however, the relationship between specific DC subsets and CHD risk remains incompletely understood.**
Methods: **This study conducted a bidirectional two-sample Mendelian randomization (MR) analysis using publicly available genome-wide association study (GWAS) summary statistics to investigate the potential associations between circulating dendritic cell traits and CHD. Genetic instruments for myeloid dendritic cells (Myeloid DCs) and plasmacytoid dendritic cells (Plasmacytoid DCs), including both absolute counts and relative proportions, were obtained from immune cell GWAS datasets. Summary statistics for CHD were derived from a large European-ancestry population. Multiple MR methods were applied, and sensitivity analyses were performed to assess the robustness of the findings and potential pleiotropic effects.**
Results: **Nominal associations between genetically predicted Myeloid DC counts and CHD risk were observed in the MR-Egger and weighted median analyses, whereas the inverse variance weighted analysis demonstrated no significant association. These nominal associations did not remain statistically significant after correction for multiple testing. No significant associations were observed for Plasmacytoid DC counts or for the relative proportions of either DC subset. Reverse MR analyses were inconclusive due to wide confidence intervals, precluding meaningful inference regarding a causal effect of CHD on DC-related traits. Sensitivity analyses revealed no substantial heterogeneity or horizontal pleiotropy.**
Conclusions: **This bidirectional MR study explored the potential relationships between circulating dendritic cell traits and CHD risk. Although nominal associations involving Myeloid DC counts were observed in secondary MR analyses, no robust evidence supporting an association remained after correction for multiple testing. Further studies using larger datasets and functional approaches are warranted to clarify the role of dendritic cells in CHD. (Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2026.260615)**

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KEYWORDS

coronary heart disease, dendritic cells, myeloid dendritic cells, Mendelian randomization, genome-wide association study

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LIST OF ABBREVIATIONS

CHD - Coronary heart disease
CI - Confidence interval
DCs - Dendritic cells
GWAS - Genome-wide association study
IV - Instrumental variable
IVW - Inverse variance weighted
LD - Linkage disequilibrium
MR - Mendelian randomization

INTRODUCTION

Coronary heart disease (CHD) is one of the leading causes of morbidity and mortality worldwide and remains a major public health concern despite substantial advances in prevention and treatment strategies [1-3]. The increasing prevalence of population aging, metabolic disorders, and unhealthy lifestyle factors has contributed to the persistent global burden of CHD [4-6]. In both Western and Asian populations, CHD continues to account for a substantial proportion of cardiovascular disease-related morbidity and mortality, resulting in considerable healthcare and socioeconomic costs [7,8]. Increasing evidence suggests that immune and inflammatory responses play pivotal roles in the initiation and progression of atherosclerosis and CHD [9-12]. Atherosclerosis is now recognized as a chronic inflammatory disease involving complex interactions among vascular cells, lipids, and immune cell populations. Among these immune cells, dendritic cells (DCs) are professional antigen-presenting cells that serve as key regulators of innate and adaptive immune responses [13-17]. Experimental and clinical studies have demonstrated that DCs participate in multiple processes associated with atherosclerotic lesion development, including antigen presentation, T-cell activation, and inflammatory regulation. Furthermore, hypercholesterolemia has been reported to impair DC migration from peripheral tissues to draining lymph nodes, whereas alterations in DC abundance may influence lipid metabolism and immune homeostasis [18].

DCs comprise several functionally distinct subsets, among which myeloid dendritic cells (Myeloid DCs) and plasmacytoid dendritic cells (Plasmacytoid DCs) are the most extensively studied. These subsets differ substantially in their biological functions and immunoregulatory properties, suggesting that they may contribute differently to cardiovascular disease pathogenesis. However, previous studies investigating the associations between DC-related traits and CHD have produced inconsistent findings, and the potential causal relationships between DC subset counts, their relative proportions, and CHD risk remain unclear.

Genetic factors also play an important role in CHD susceptibility [19-21]. Numerous single-nucleotide polymorphisms (SNPs) have been associated with CHD risk and related metabolic phenotypes, highlighting the contribution of inherited genetic variation to disease development [22-24]. Nevertheless, conventional observational studies are often limited by residual confounding and reverse causality, making it difficult to determine whether observed associations reflect true causal relationships.

Mendelian randomization (MR) is a genetic epidemiological approach that utilizes genetic variants as instrumental variables to infer causal relationships between exposures and outcomes. Because genetic variants are randomly allocated during meiosis and fixed before disease onset, MR analyses can reduce biases arising from confounding factors and reverse causation [25-27]. With the increasing availability of large-scale genome-wide association study (GWAS) data, MR has become a widely used tool for investigating potential causal mechanisms underlying complex diseases [28,29].

Therefore, in the present study, we performed a bidirectional two-sample MR analysis using publicly available GWAS summary statistics to systematically evaluate the potential associations between dendritic cell counts, dendritic cell proportions, and CHD risk. By exploring these relationships from a genetic perspective, we aimed to provide additional evidence regarding the involvement of DCs in CHD and to identify potential immune-related biomarkers relevant to cardiovascular risk assessment.

MATERIALS AND METHODS

Study Design and Data Sources

A bidirectional two-sample Mendelian randomization (MR) design was employed to investigate the potential causal relationships between dendritic cell (DC)-related traits and the risk of coronary heart disease (CHD). An overview of the study design is presented in Figure 1.

Summary-level GWAS data for CHD were obtained from the IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/) [30,31]. The dataset with GWAS ID "ukb-d-I9_CHD" was selected, comprising 361,194 individuals of European ancestry, including 10,157 CHD cases and 351,037 controls. A total of 13,295,130 single-nucleotide polymorphisms (SNPs) were available in this dataset (Table 1).

Genetic instruments for DC-related traits were derived from immune cell GWAS datasets generated by Orrù et al. in individuals of European ancestry [32] and accessed through the IEU Open GWAS Project. Four DC phenotypes were included in the present study: absolute counts of myeloid dendritic cells (Myeloid DCs; GWAS ID: ebi-a-GCST90001458), absolute counts of plasmacytoid dendritic cells (Plasmacytoid DCs; GWAS ID: ebi-a-GCST90001460), the proportion of Myeloid DCs (GWAS ID: ebi-a-GCST90001459), and the proportion of Plasmacytoid DCs (GWAS ID: ebi-a-GCST90001474) (Table 1). All GWAS datasets were restricted to participants of European ancestry to minimize potential bias arising from population stratification.

Table 1. GWAS Data Statistics.

GWAS ID	Trait	Population	Sample size	Case size	Control size	SNPs
ukb-d-I9_CHD	Major coronary heart disease event	European	361,194	10,157	351,037	13,295,130
ebi-a-GCST90001458	Myeloid Dendritic Cell Absolute Count	European	3,387	-	-	15,130,102
ebi-a-GCST90001460	Plasmacytoid Dendritic Cell Absolute Count	European	3,374	-	-	15,130,102
ebi-a-GCST90001459	Myeloid Dendritic Cell %Dendritic Cell	European	3,410	-	-	15,143,298
ebi-a-GCST90001474	Plasmacytoid Dendritic Cell %Dendritic Cell	European	3,410	-	-	15,143,298

Table 2. Characteristics of instrumental variables for dendritic cell traits.

Exposure	SNPs	Detected SNPs in outcome	Median R^2 [25th - 75th Percentile]	Median F [25th - 75th Percentile]
Myeloid Dendritic Cell Absolute Count	23	23 - > 22 (remove rs10763776)	0.0781 [0.0769 - 0.0815]	40.4700 [39.7400 - 41.0100]
Plasmacytoid Dendritic Cell Absolute Count	31	30 - > 29 (remove rs2545798)	0.0795 [0.0773 - 0.0830]	35.3400 [34.5100 - 35.7700]
Myeloid Dendritic Cell %Dendritic Cell	28	26	0.0790 [0.0776 - 0.0836]	37.5300 [36.3800 - 37.8800]
Plasmacytoid Dendritic Cell %Dendritic Cell	25	24	0.0790 [0.0770 - 0.0832]	39.7200 [38.6200 - 40.2900]
Major coronary heart disease event	12	9	0.0106 [0.0100 - 0.0127]	1,676.0000 [1,537.0000 - 1,720.00]

Instrumental variable selection and quality control

Single-nucleotide polymorphisms significantly associated with DC traits were selected as instrumental variables (IVs) from the corresponding GWAS datasets. Considering the relatively modest sample size of the available immune cell GWAS datasets, a significance threshold of $p < 1 \times 10^{-5}$ was adopted to obtain an adequate number of genetic instruments while maintaining statistical power [33]. Linkage disequilibrium (LD) clumping was performed using PLINK software (Version: 1.9.0, https://www.cog-genomics.org/plink2/) with a threshold of $r^2 < 0.001$ and a clumping window of 10,000 kb to ensure the independence of selected SNPs. The proportion of variance explained (R^2) and F statistics were calculated to evaluate instrument strength and reduce the risk of weak instrument bias. During harmonization of exposure and outcome datasets, palindromic SNPs with ambiguous allele frequencies were excluded. Alleles were aligned to ensure consistency in effect directions between exposure and outcome datasets.

Bidirectional Mendelian randomization analysis

MR analyses were conducted based on three core assumptions: 1) the selected SNPs are robustly associated with DC traits; 2) the SNPs are independent of potential confounding factors; and 3) the SNPs influence CHD risk exclusively through DC traits rather than through alternative biological pathways (Figure 1). Causal estimates were calculated using multiple complementary MR methods, including inverse variance weighted (IVW), MR-Egger regression, weighted median, simple mode, and MR-PRESSO. The IVW approach was considered the primary analytical method, whereas the remaining methods were used to assess the robustness of the findings under different model assumptions. To further evaluate the directionality of the observed associations, reverse MR analyses were performed with CHD as the exposure and DC-related traits as the outcomes. Genetic instruments for CHD were selected using the conventional genome-wide significance threshold ($p < 5 \times 10^{-8}$), followed by the same LD clumping and quality control procedures applied in the forward MR analyses.

Sensitivity analyses and assessment of pleiotropy

Heterogeneity among instrumental variables was evaluated using Cochran's Q statistics in both IVW and MR-Egger analyses. Horizontal pleiotropy was assessed

Table 3. Mendelian randomization analysis of dendritic cell indicators and coronary heart disease.

MR info							Cochran's Q			Horizontal pleiotropy		
Exposure	Snp(n)	Method	Beta	se	OR [95% CI]	p-val	Q	Q df	Q_p-val	Intercept	se	p
Myeloid Dendritic Cell Absolute Count	22	MR Egger	-0.0012	0.0005	0.9988 [0.9979 - 0.9997]	0.0209	18.2329	20	0.5721	0.0003	0.0002	0.1274
		IVW	-0.0007	0.0004	0.9993 [0.9986 - 1.000]	0.0524	20.7621	21	0.4736	-	-	-
		Weighted median	-0.0012	0.0006	0.9988 [0.9976 - 0.9999]	0.0401	-	-	-	-	-	-
		Simple mode	0.0003	0.0014	1.0003 [0.9976 - 1.003]	0.8158	-	-	-	-	-	-
		MR-PRESSO	-0.0006	0.0004	0.9994 [0.9986 - 1.0001]	0.0941	-	-	-	-	-	-
Plasmacytoid Dendritic Cell Absolute Count	29	MR Egger	0.0001	0.0004	1.0001 [0.9993 - 1.0009]	0.7799	27.2997	27	0.4477	0.0002	0.0002	0.3219
		IVW	0.0004	0.0003	1.0004 [0.9998 - 1.001]	0.2306	28.3291	28	0.4471	-	-	-
		Weighted median	0.0004	0.0004	1.0004 [0.9995 - 1.0012]	0.3977	-	-	-	-	-	-
		Simple mode	0.0006	0.0007	1.0006 [0.9991 - 1.0020]	0.4578	-	-	-	-	-	-
		MR-PRESSO	0.0004	0.0003	1.0004 [0.9998 - 1.0010]	0.2312	-	-	-	-	-	-
Myeloid Dendritic Cell %Dendritic Cell	26	MR Egger	4.02e-05	0.0008	1.0000 [0.9985 - 1.0016]	0.9595	19.7139	24	0.7129	-4.07e-05	0.0002	0.8386
		IVW	-8.79e-05	0.0005	0.9999 [0.9990 - 1.0008]	0.8532	19.7563	25	0.7595	-	-	-
		Weighted median	0.0003	0.0007	1.0003 [0.9990 - 1.0017]	0.6272	-	-	-	-	-	-
		Simple mode	-0.0012	0.0014	0.9988 [0.9962 - 1.0014]	0.3819	-	-	-	-	-	-
		MR-PRESSO	-8.79e-05	0.0004	0.9999 [0.9991 - 1.0007]	0.8368	-	-	-	-	-	-
Plasmacytoid Dendritic Cell %Dendritic Cell	24	MR Egger	0.0006	0.0005	1.0006 [0.9996 - 1.0016]	0.2803	17.4674	22	0.7371	-0.0001	0.0002	0.3566
		IVW	0.0002	0.0004	1.0002 [0.9995 - 1.0010]	0.5301	18.3541	23	0.7380	-	-	-
		Weighted median	0.0005	0.0006	1.0005 [0.9993 - 1.0016]	0.4258	-	-	-	-	-	-
		Simple mode	0.0011	0.0011	1.0011 [0.9990 - 1.0032]	0.3045	-	-	-	-	-	-
		MR-PRESSO	0.0002	0.0003	1.0002 [0.9996 - 1.0009]	0.4892	-	-	-	-	-	-

using the intercept obtained from MR-Egger regression. Leave-one-out sensitivity analyses were conducted by sequentially removing individual SNPs and re-estimating the causal effect to determine whether the observed associations were disproportionately influenced by any single instrument. In addition, the MR-PRESSO method was applied to detect potential outlier SNPs and perform correction analyses when appropriate. All statistical analyses were conducted using R software (version 4.3.2), primarily with the TwoSampleMR (version 0.5.8) and MRPRESSO (version 1.0) packages. Statistical significance was defined as a two-sided p-value < 0.05. To account for multiple testing across the four DC traits, we applied Bonferroni correction, with statistical significance defined as $p < 0.0125$ (0.05/4). After correction, none of the associations remained statistically significant.

Table 4. Reverse Mendelian randomization analysis of dendritic cell indicators and coronary heart disease.

MR info							Cochran's Q			Horizontal pleiotropy		
Outcome	Snp(n)	Method	Beta	se	OR [95% CI]	p-val	Q	Q df	Q p-val	Intercept	se	p
Myeloid Dendritic Cell Absolute Count	9	MR Egger	1.4196	6.1575	4.1355 [0.0000 - 720,885.5629]	0.8243	8.0520	7	0.3280	-0.0077	0.0247	0.7636
		IVW	-0.2846	2.7015	0.7523 [0.0038 - 149.9619]	0.9161	8.1645	8	0.4176	-	-	-
		Weighted median	-1.2616	3.7879	0.2832 [2e-04 - 474.6618]	0.7391	-	-	-	-	-	-
		Simple mode	-2.1106	6.1758	0.1212 [0.0000 - 21,895.2052]	0.7413	-	-	-	-	-	-
		MR-PRESSO	-0.2846	2.7015	0.7523 [0.0038 - 149.9619]	0.9187	-	-	-	-	-	-
Plasmacytoid Dendritic Cell Absolute Count	9	MR Egger	1.7636	5.4363	5.8336 [1e-04 - 247,400.217]	0.7551	7.0587	7	0.4228	-0.0075	0.0218	0.7426
		IVW	0.1197	2.5209	1.1272 [0.0081 - 157.7054]	0.9621	7.1765	8	0.5177	-	-	-
		Weighted median	0.7708	3.2074	2.1616 [0.0040 - 1,161.3851]	0.8101	-	-	-	-	-	-
		Simple mode	4.7873	4.6664	119.9746 [0.0128 - 1,125,200.1938]	0.3350	-	-	-	-	-	-
		MR-PRESSO	0.1197	2.3876	1.1272 [0.0105 - 121.4529]	0.9612	-	-	-	-	-	-
Myeloid Dendritic Cell %Dendritic Cell	9	MR Egger	1.2173	5.8009	3.3781 [0.0000 - 292,738.4926]	0.8398	4.9759	7	0.6629	-0.0033	0.0233	0.8928
		IVW	0.5005	2.7094	1.6496 [0.0081 - 333.9062]	0.8534	4.9955	8	0.7581	-	-	-
		Weighted median	-0.1725	3.7701	0.8415 [5e-04 - 1,362.1845]	0.9635	-	-	-	-	-	-
		Simple mode	3.8719	6.5285	48.0318 [1e-04 - 17,324,643.3308]	0.5695	-	-	-	-	-	-
		MR-PRESSO	0.5005	2.1410	1.6496 [0.0248 - 109.5974]	0.8210	-	-	-	-	-	-
Plasmacytoid Dendritic Cell %Dendritic Cell	9	MR Egger	-0.0424	5.6636	0.9585 [0.0000 - 63,461.2263]	0.9942	2.6969	7	0.9115	-0.0043	0.0228	0.8568
		IVW	-0.9802	2.6429	0.3752 [0.0021 - 66.6818]	0.7107	2.7320	8	0.9500	-	-	-
		Weighted median	-2.0465	3.3646	0.1292 [2e-04 - 94.4473]	0.5430	-	-	-	-	-	-
		Simple mode	-4.7348	5.2143	0.0088 [0.0000 - 241.0883]	0.3904	-	-	-	-	-	-
		MR-PRESSO	-0.9802	1.5445	0.3752 [0.0182 - 7.7443]	0.5434	-	-	-	-	-	-

Code availability

All analyses were performed using R software (version 4.3.2) with publicly available packages, including TwoSampleMR (version 0.5.8; https://github.com/MRCIEU/TwoSampleMR) and MRPRESSO (version 1.0). The significance threshold for instrument selection was adjusted as described in the section "Instrumental variable selection and quality control"

RESULTS

Characteristics of instrumental variables

After SNP selection and quality control of the GWAS datasets related to dendritic cell (DC) traits, independent sets of genetic instrumental variables were obtained for the Mendelian randomization analyses (Table 2).

For myeloid dendritic cell (Myeloid DC) absolute counts, a total of 23 SNPs were identified as instrumental variables. The proportion of variance explained (R^2)

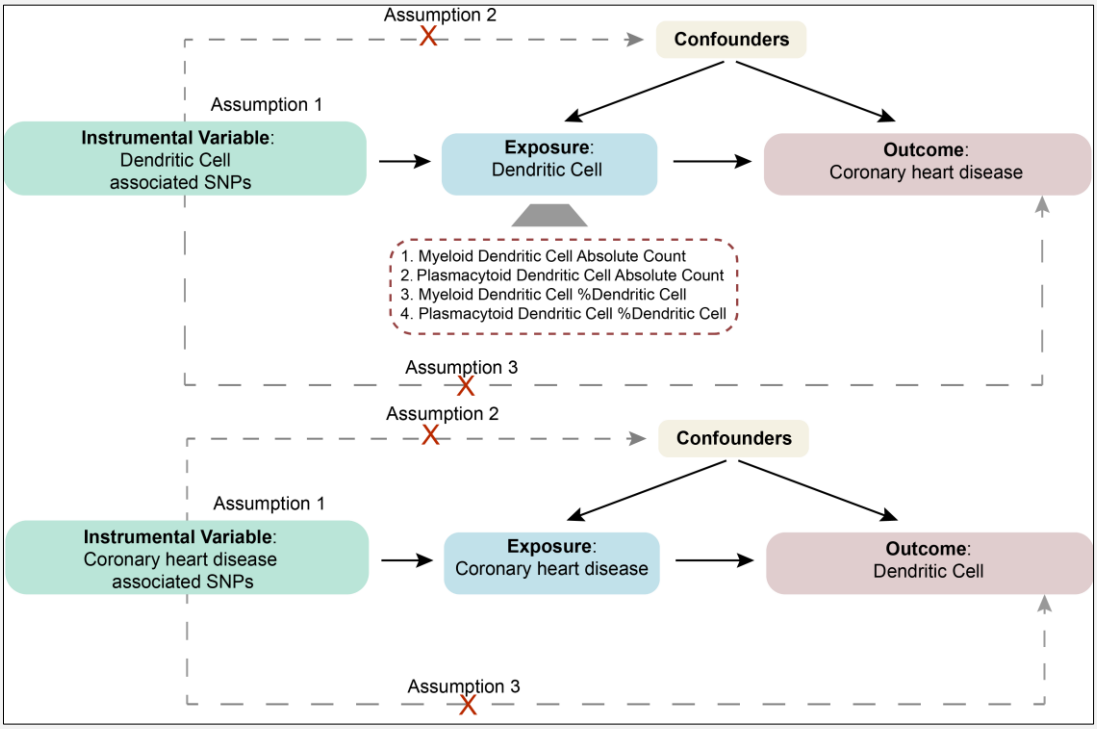

Figure 1. Three main hypotheses for the two-way Mendelian randomization analysis of dendritic cell indicators and the occurrence of coronary heart disease.

and F statistics were calculated for each SNP, and none of the instruments had an F statistic below 10, indicating no evidence of weak instrument bias. Similarly, 31 SNPs were selected for plasmacytoid dendritic cell (Plasmacytoid DC) absolute counts, while 28 and 25 SNPs were identified for the proportions of Myeloid DCs and Plasmacytoid DCs, respectively. All instrumental variables across the four DC traits exhibited F statistics greater than 10, supporting their suitability for MR analyses.

Mendelian randomization analyses of dendritic cell traits and CHD risk

For Myeloid DC absolute counts, 23 SNPs were initially selected as instrumental variables. After harmonization with the CHD outcome GWAS, one palindromic SNP with ambiguous allele frequency (rs10763776) was excluded during quality control, leaving 22 SNPs for downstream MR analyses. Using Myeloid DC absolute counts as the exposure and CHD as the outcome, two-sample MR analyses were performed.

The MR-Egger and weighted median methods indicated statistically significant associations between genetically predicted Myeloid DC counts and CHD risk, with p-values of 0.0209 and 0.0401, respectively. The corresponding effect estimates were OR = 0.9988 (95% CI: 0.9979 - 0.9997) for MR-Egger and OR = 0.9988 (95% CI: 0.9976 - 0.9999) for the weighted median method. In contrast, no significant associations were observed using the inverse variance weighted (IVW), simple mode, or MR-PRESSO methods (Table 3; Figure 2A, 3A). After Bonferroni correction for multiple testing across the five MR methods, none of the p-values remained statistically significant (adjusted p-values ranging from 0.0873 to 0.8158).

For Plasmacytoid DC absolute counts, 31 SNPs were initially selected as instrumental variables. After harmonization with the CHD outcome GWAS, one SNP (rs2545798) was excluded during quality control, leaving 29 SNPs for downstream MR analyses. None of the five MR methods demonstrated a statistically significant association between Plasmacytoid DC counts and CHD risk (all $p > 0.05$) (Table 3; Figure 2B, 3B).

For Myeloid DC proportion, 28 SNPs were initially selected as instrumental variables. After harmonization with the CHD outcome GWAS, two SNPs were not present in the outcome dataset, resulting in 26 SNPs retained for quality control; no additional SNPs were excluded during subsequent quality control steps. For Plasmacytoid DC proportion, 25 SNPs were initially se-

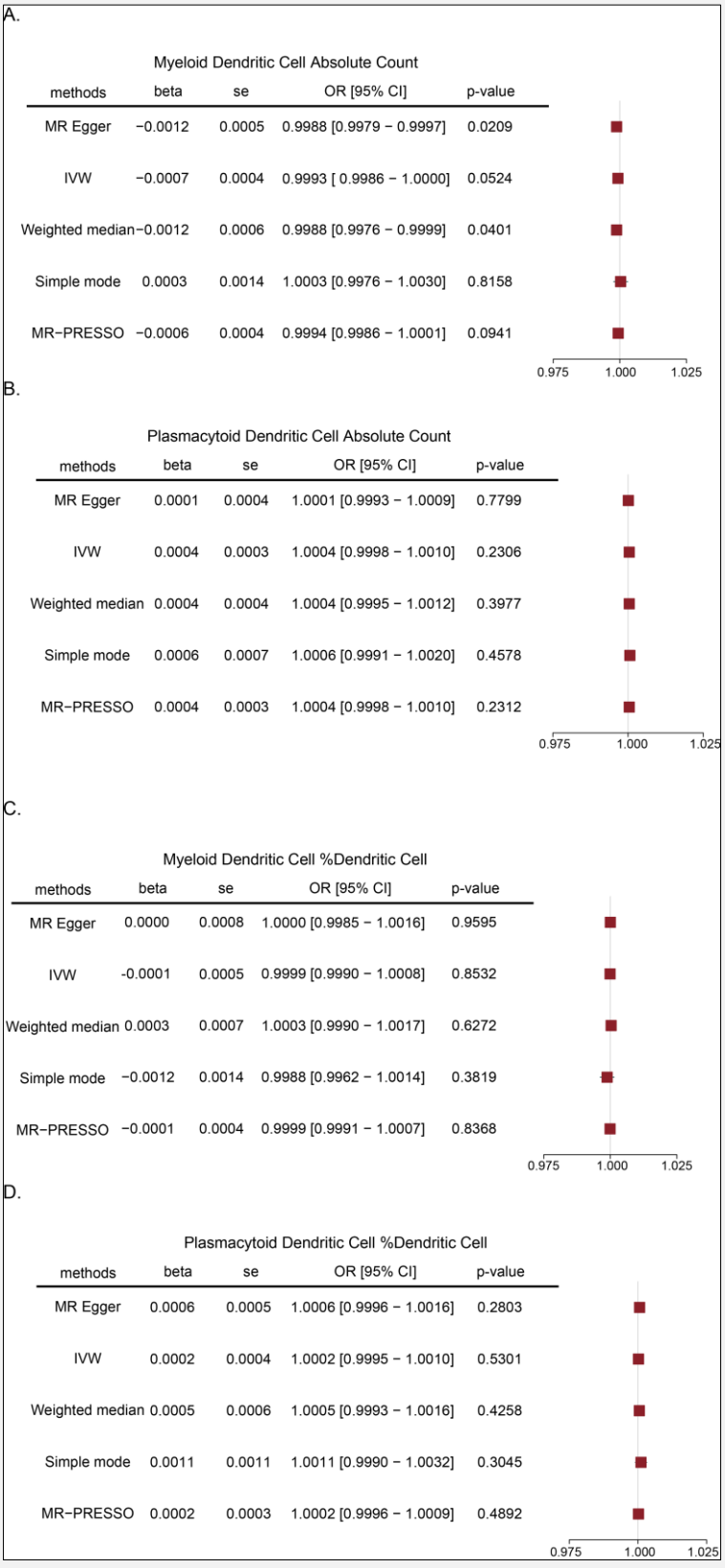

Figure 2. Results of Mendelian randomization analysis of dendritic cell indicators and coronary heart disease.

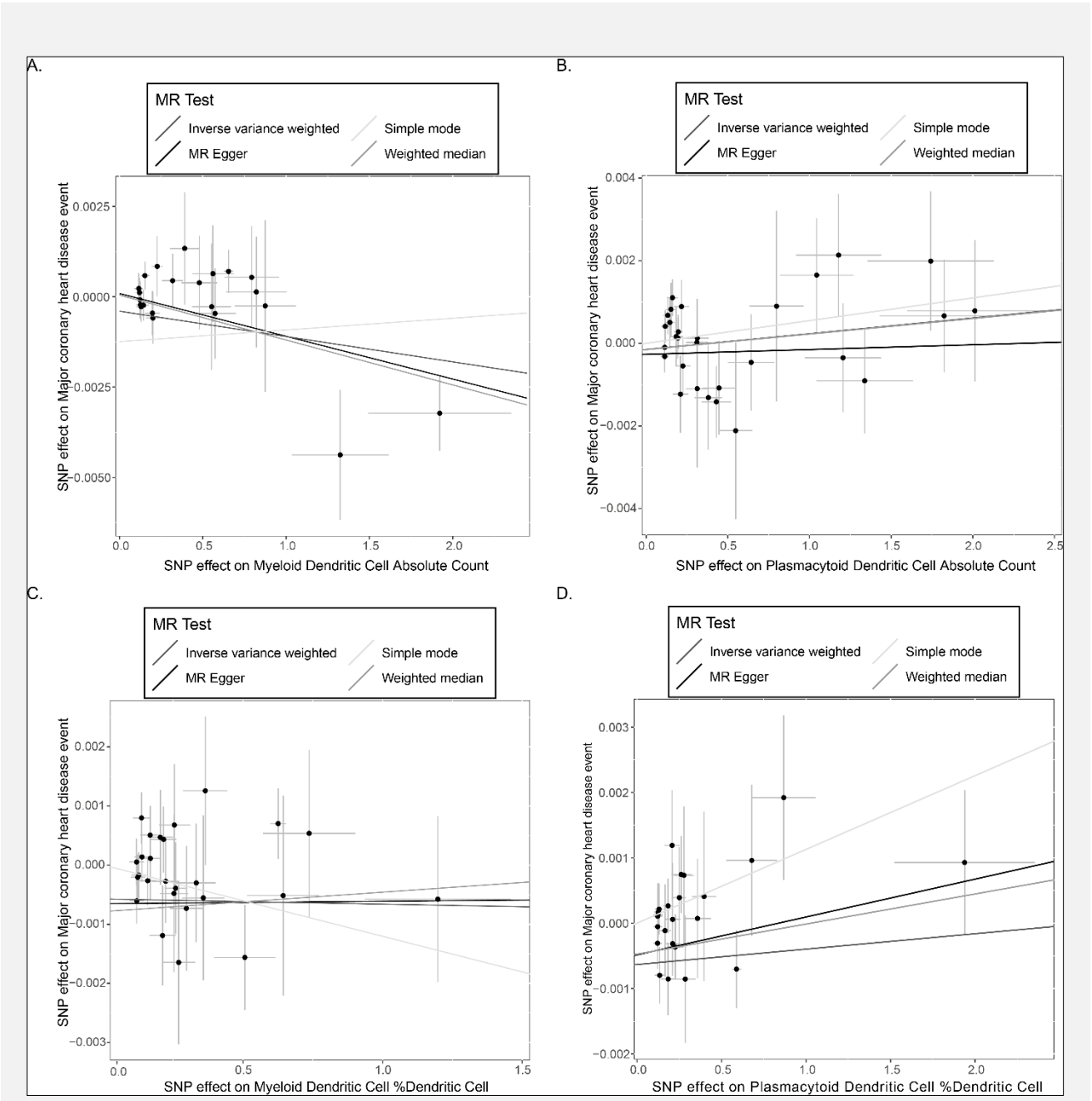

Figure 3. Sensitivity analysis of the causal association between myeloid dendritic cell counts and coronary heart disease using multiple Mendelian randomization methods.

lected; after harmonization, one SNP was not present in the outcome dataset, resulting in 24 SNPs retained for quality control; no additional SNPs were excluded during subsequent quality control steps. Subsequent MR analyses showed no evidence of significant causal effects of either Myeloid DC proportion or Plasmacytoid DC proportion on CHD risk across all five MR methods (Table 3; Figure 2C - D, 3C - D).

Reverse Mendelian randomization analyses

To assess the directionality of the observed associations, reverse MR analyses were conducted with CHD as the exposure and DC-related traits as the outcomes. Across analyses of Myeloid DC counts, Plasmacytoid DC counts, and the proportions of both DC subsets, none of the MR methods provided evidence supporting a statistically significant causal effect of CHD on DC

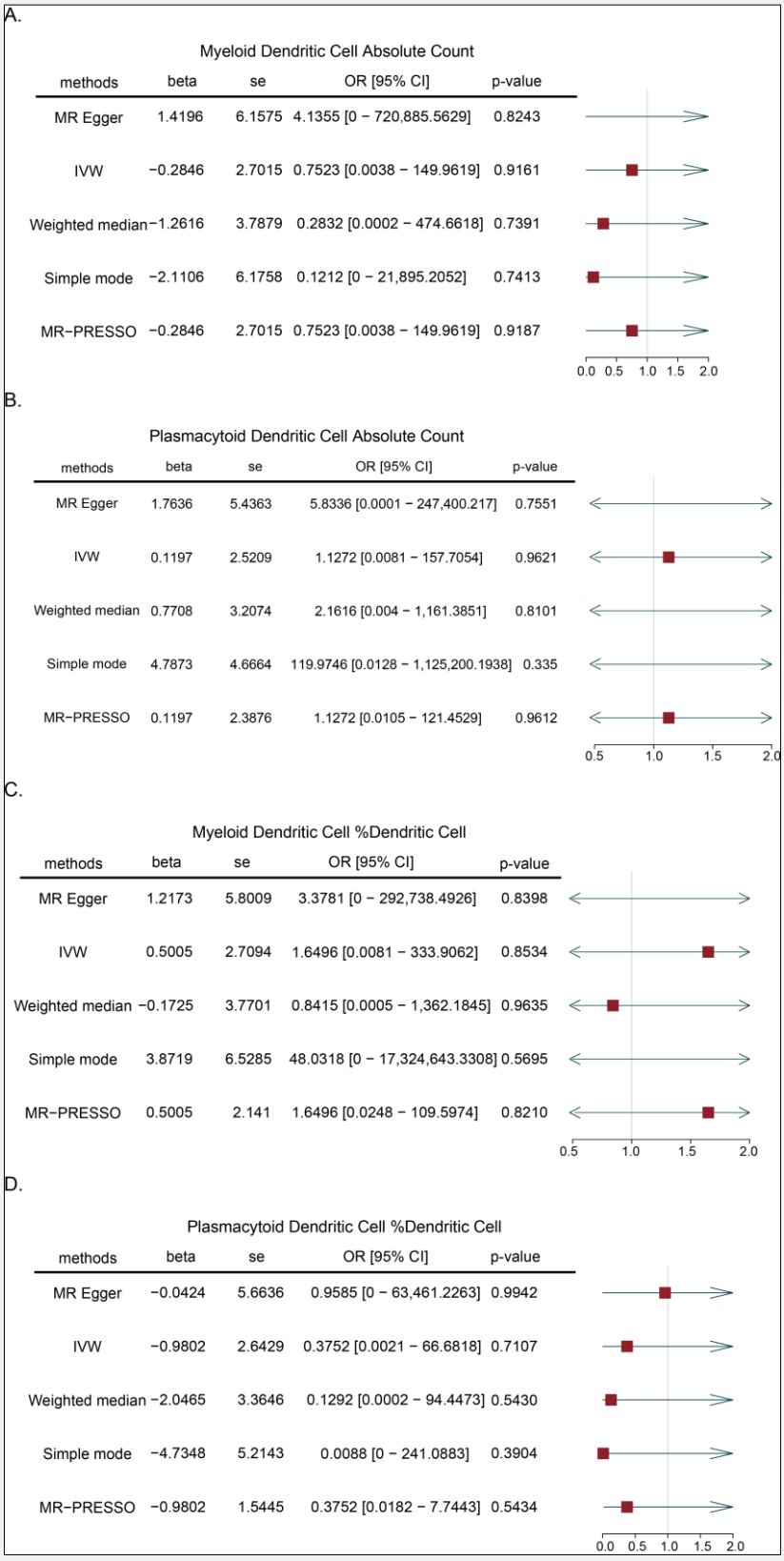

Figure 4. Results of Mendelian randomization analysis of coronary heart disease and dendritic cell indicators.

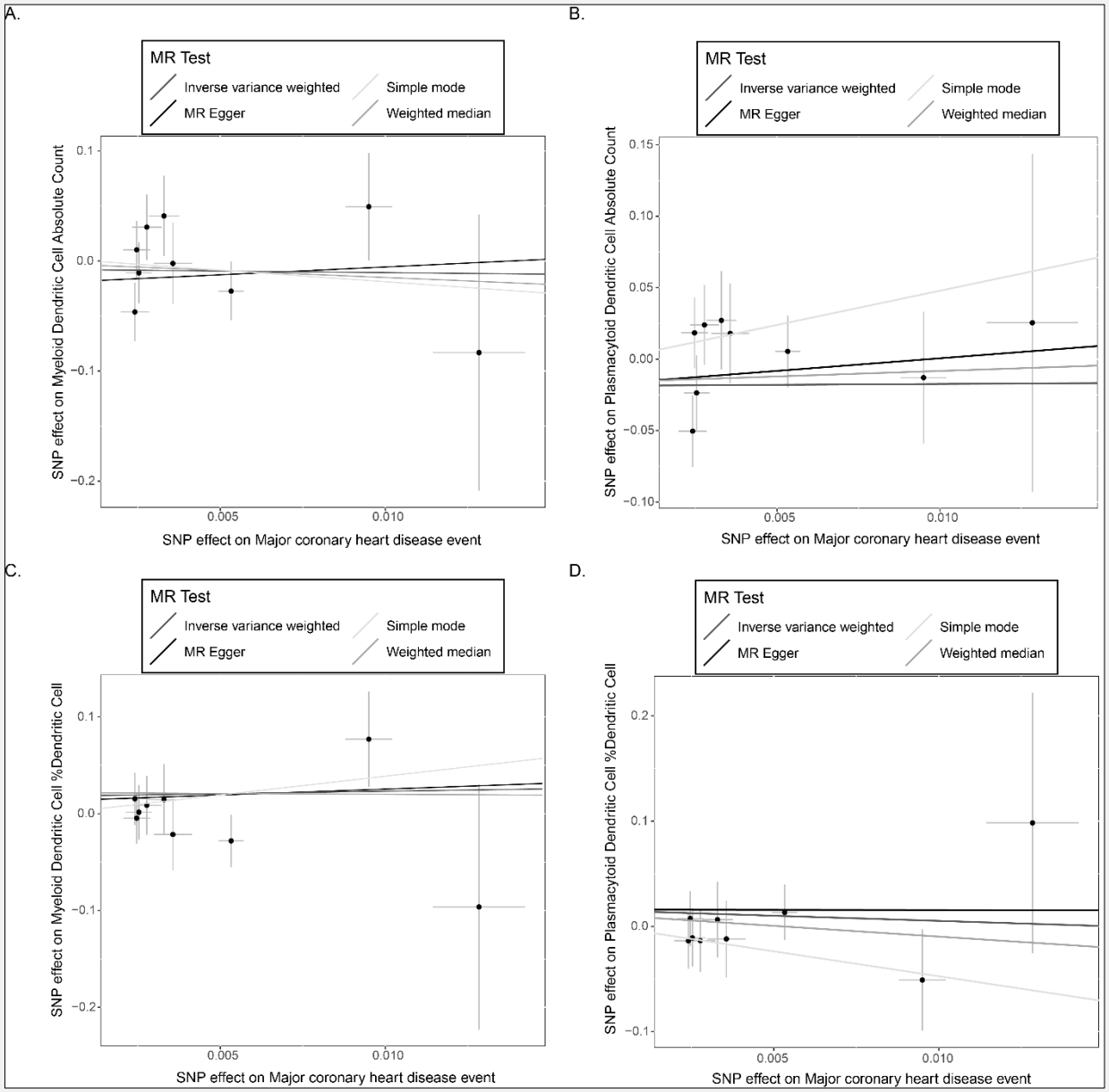

Figure 5. Sensitivity analysis of the causal effect of coronary heart disease on myeloid dendritic cell counts using multiple Mendelian randomization methods.

traits (Table 4; Figure 4, 5). However, the estimates were imprecise with wide confidence intervals, reflecting limited statistical power; thus, these results should not be interpreted as evidence against reverse causality.

Sensitivity analyses

Cochran's Q tests revealed no significant heterogeneity among the instrumental variables in either the IVW or MR-Egger analyses for any of the evaluated traits (all $p > 0.05$). The MR-Egger intercept tests did not indicate the presence of substantial horizontal pleiotropy (all $p > 0.05$).

Leave-one-out sensitivity analyses demonstrated that the overall causal estimates were not materially altered by the exclusion of any single SNP, indicating that the observed associations were not driven by individual instrumental variables and that the results were robust (Supplementary Figure S1 - 4).

DISCUSSION

In the present study, we employed a bidirectional two-sample MR approach using publicly available GWAS data to evaluate the relationships between DC-related traits and the risk of CHD. Our findings indicated that genetically predicted Myeloid DC counts were associated with CHD risk in multiple MR analyses, whereas no significant associations were observed for Myeloid DC proportions or for the counts and proportions of Plasmacytoid DCs. In addition, reverse MR analyses did not provide evidence supporting a causal effect of CHD on DC-related traits.

The association between Myeloid DC counts and CHD risk reached statistical significance in the MR-Egger and weighted median analyses, whereas the IVW analysis demonstrated no significant association. After Bonferroni correction for multiple testing, none of the MR estimates remained statistically significant. Differences among MR methods are not uncommon and may reflect variations in their underlying assumptions and sensitivity to horizontal pleiotropy and outlier SNPs. The IVW method assumes that all instrumental variables are valid, whereas MR-Egger and weighted median approaches can provide reliable estimates even when some instruments are invalid. Therefore, these complementary methods may offer additional robustness when evaluating complex immune-related traits. Nevertheless, given that the primary IVW analysis did not reach conventional statistical significance, the observed association should be interpreted with appropriate caution. Previous studies provide supporting biological evidence for a potential role of DCs in cardiovascular disease. Yilmaz et al. reported reduced circulating Myeloid DC precursors in patients with CHD, suggesting a possible association between impaired DC homeostasis and disease progression [34]. Zhang et al. demonstrated that DC-derived exosomes promoted CD4+ T-cell migration and improved cardiac functional recovery following myocardial infarction [35]. Moreover, Yetkin et al. observed impaired DC activation in patients with CHD, particularly among those with concomitant diabetes mellitus [36]. Collectively, these findings support the biological plausibility of a potential role for Myeloid DCs in CHD; however, such observational and mechanistic evidence does not by itself establish the causal direction or magnitude suggested by our MR analyses, which should be interpreted with caution.

No significant associations were identified for Plasmacytoid DC counts or for the relative proportions of either DC subset. These findings may suggest that absolute alterations in DC abundance are more closely related to CHD susceptibility than proportional changes within the DC compartment. Relative proportions may be influenced by concurrent fluctuations in other immune cell populations, thereby reducing their ability to reflect independent biological effects. In addition, functional differences between DC subsets may contribute to the heterogeneous findings observed in the present study. Myeloid DCs are primarily involved in antigen presentation and regulation of adaptive immune responses, whereas Plasmacytoid DCs are predominantly associated with antiviral immunity and type I interferon production. Such biological differences may partially explain the distinct patterns observed across DC subsets.

The reverse MR analyses yielded imprecise estimates with very wide confidence intervals, reflecting limited statistical power due to the small number of available instrumental variables. Therefore, these findings should not be interpreted as evidence against a reverse causal effect; rather, they are inconclusive and highlight the need for larger datasets to adequately assess the possibility of reverse causality.

Several limitations should be acknowledged. First, the GWAS datasets for DC-related traits were based on relatively modest sample sizes, necessitating the use of a less stringent SNP selection threshold to obtain an adequate number of instrumental variables. Although all selected instruments demonstrated sufficient strength and no evidence of substantial pleiotropy, residual bias cannot be completely excluded. Second, the primary IVW analysis did not reach conventional statistical significance, and the discordance between IVW and secondary MR methods may reflect directional pleiotropy or chance rather than a robust causal effect. Third, all analyses were restricted to individuals of European ancestry, which may limit the generalizability of the findings to other populations. Finally, the present study focused on quantitative DC traits and was unable to evaluate functional or activation-related DC phenotypes, which may provide additional insights into the underlying biological mechanisms.

CONCLUSION

In conclusion, this bidirectional MR study explored the relationships between circulating dendritic cell traits and CHD risk. Nominal associations involving Myeloid DC counts were observed in secondary MR analyses; however, the pre-specified primary IVW analysis did not reach conventional statistical significance, and these associations were not retained after correction for multiple testing. Reverse MR analyses were underpowered and inconclusive regarding reverse causality, and no associations were observed for Plasmacytoid DC-related traits. Therefore, the present findings should be interpreted with caution and regarded as hypothesis-generating. Further studies using larger independent datasets and functional investigations are required to clarify the potential role of dendritic cells in CHD.

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Declaration of Interest:
The authors declare no conflicts of interest.

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