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The causal relationship between immune cells and knee osteoarthritis: Mendelian randomization study

Chenghao Gao[1†], Hongxu Pu[1†], Yifan Zeng[1] and Jun Xiao[1*]

Abstract

Knee osteoarthritis (OA) is a common degenerative joint disease that affects millions of people worldwide. Inflammation is one of the key pathogenic factors of knee OA. However, the causal relationship between immune cells and knee OA development remains unclear. Herein, we used Mendelian randomization (MR) analysis to evaluate causal relationship between 731 immune cells and knee OA. Several methods were applied to ensure the robustness of our results, including inverse-variance weighted (IVW), simple mode, weighted median, weighted mode, and MR-Egger. We found that 23 immune cell phenotypes were causally associated with knee OA ($P < 0.05$), including various subpopulations of B cells, T cells, TBNK (T cells, B cells, Natural Killer cells) and monocytes, which was confirmed by heterogeneity, sensitivity, and pleiotropy tests. B cells had dominant effects on OA development, and specifically, our findings suggest that BAFF-R in IgD + CD38- unswitched memory B cells may have a protective role, whereas CD25 in IgD + CD24 + B cells appears to be associated with increased risk, pending further validation. Moreover, a higher population of regulatory T (Treg) cells indicated a higher risk of OA and reversely, OA could induce Treg differentiation. Collectively, our study identified several immune cells that were closely related to OA development, which provided novel insights into the pathogenesis of OA and therapeutic targets for OA treatment.

Keywords Osteoarthritis, Immune cell, Mendelian randomization, Causal inference

Introduction

It is estimated that osteoarthritis (OA) affects over 300 million people globally [1]. OA manifests with cartilage damage and osteophyte formation, leading to joint pain and functional impairment [2]. As the life span extends, more and more OA patients will suffer from protracted periods of pain and disability. While OA can affect any joints of the body, knee joint is the most commonly affected site [3]. Currently, knee OA is understood as a systemic ailment affecting the entire joint.

Various evidence suggest that mechanical injury is not the only driving factor of OA. Inflammation, particularly chronic inflammation, highly contributes to the development and progression of OA [4]. Studies have indicated that low-grade inflammation is involved in the occurrence of cartilage diseases [5, 6], where cytokines including IL-6, IL-15, IL-17, IL-18, IL-21, and IL-8 potentially induce chronic inflammation that promotes cartilage disease [7]. Cytokines secreted by synovium and cartilage cells, such as IL-1β and TNF-α, are also involved in the inflammatory processes of OA [8]. Meanwhile, immune cells such as activated macrophages are associated with the severity of osteophyte formation in OA [9]. Reprogramming or depleting macrophages could inhibit the

†Chenghao Gao and Hongxu Pu contribute equally to this work.

*Correspondence:
Jun Xiao
jun_xiao@hust.edu.cn
[1] Department of Orthopedic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, People's Republic of China

inflammation [10]. Moreover, Th1 cell population can promote the progression of local inflammation at joints [11, 12]. One study has shown that in mouse models of OA, neutrophils and B cells are significant sources of metalloproteinases [13]. Moreover, T cells in peripheral blood and synovial fluid exhibit a strong response to autologous chondrocyte and fibroblast membrane preparations [14]. Additionally, infiltrating B cells in OA synovium display features of antigen activation [15]. The role of autoantibodies targeting cartilage components in OA progression further underscores their involvement and cytotoxic effects on cartilage. Subgroup analyses have revealed that an imbalance between Th and Treg cells in OA can lead to inflammatory responses and joint damage [16]. The activation of these immune cells may be mediated by the recognition of damage-associated molecular patterns produced by the impaired extracellular matrix of cartilage, thereby triggering sterile inflammation. In addition, chondrocytes can synthesize complement components, which remains in a prolonged activated state during OA progression. Since immune responses play a critical role in OA, the causal relationship between specific immune cells and OA development remains unclear. Uncovering molecular mechanisms underlying OA pathogenesis will provide novel targets for developing drugs.

Mendelian randomization (MR) analysis emerges as a potent methodology designed to discern causality between a specific factor (exposure) and a particular ailment (outcome). By leveraging genetic markers in the form of single nucleotide polymorphisms (SNPs) as instrumental variables (IVs), MR analysis deftly circumvents confounding factors that are often encountered in observational studies. MR analysis relies on three premises: IVs had robust association with the exposure, IVs had no independent association with the outcome, and IVs affected the outcome through affecting the exposure. In this study, a comprehensive two-sample MR analysis was performed to determine the causal association between immune cells and knee OA.

Materials and methods

Genome-wide association study (GWAS) data of knee OA and immune cells

The exposure and outcome data used in this Mendelian randomization study were obtained from publicly available GWAS datasets that had already undergone rigorous quality control procedures. Descriptive statistics for the underlying phenotypes are reported in the original GWAS publications. Both GWASs were conducted in independent European cohorts with no known sample overlap, used genome-wide genotyping arrays with imputation to reference panels, and applied standard association testing procedures.

The SardiNIA project is a longitudinal study that includes 6,602 individuals from the general population, comprising 57% females and 43% males, aged 18 to 102 years. These participants are from the central eastern region of Sardinia, Italy. Of these, 3,757 individuals have undergone both genetic analysis and immune profiling. GWAS data of 731 immune cells from 3,757 European individuals were retrieved from GWAS database (GCST0001391 to GCST0002121) [17], including absolute cell (AC) counts, median fluorescence intensity (MFI), morphological parameters (MP) and relative cell (RC) counts. T cells, B cells, natural killer (NK) cells, Treg cells, and other immune cells were labeled by these one or more features.

GWAS data of 24,955 OA cases and 378,169 controls were obtained from the IEU openGWAS project (https://gwas.mrcieu.ac.uk/datasets) with the GWAS ID (GCST007090) which included approximately 29 million SNPs [18]. The source data was obtained from the UK Biobank, a cohort study that includes 500,000 participants aged 40 to 69 years, recruited between 2006 and 2010 across 22 assessment centers throughout the United Kingdom.

Selection of instrumental variables

We identified SNPs associated with immune cells at a genome-wide significance threshold ($P < 1 \times 10^{-5}$). These SNPs were subsequently employed as IVs. To diminish potential biases in MR analysis [19], we selected independent SNPs devoid of substantial linkage disequilibrium ($R^2 < 0.001$ in a kb < 10000 window) using the "clump_data" function of R package "TwoSampleMR" [20]. Palindromic SNPs with intermediate allele frequencies were excluded due to their propensity to reverse causality relationships.

Statistical analysis

All analyses were performed in R 3.5.3 software (http://www.Rproject.org) along with dplyr and ggplot2 for data manipulation and visualization.The main analytical method of MR analysis was inverse variance weighted (IVW) because of its potent ability in rendering causal inferences. Meanwhile, supplementary analytical methods including MR Egger, weighted median method, simple mode method and weighted mode method were adopted to test the robustness of results. Using diverse methods could accommodate varied tenets of MR assumptions, especially for those pertaining to pleiotropy. The odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to indicate the causal associations. The heterogeneity was estimated by Cochrane's Q

value while MR-Egger intercept test was used to estimate the horizontal pleiotropy. We also performed the leave-one-out analysis to test the robustness of the results. The $P < 0.05$ was regarded as statistical significance. Individual SNP-level associations were not included in this analysis, given that the MR analysis was based on publicly available summary-level data.

Code availability

The code used in this study can be found in the supplementary file.

Results

The causal effect of knee OA on immune cells

Only one immunophenotype was detected to be causally affected by knee OA. The two-sample MR analysis was performed mainly on the IVW method at the significance of 0.05. We found that *CD4 on activated Treg* (OR = 1.553, 95% CI = 1.067 ~ 2.261, $P = 0.02$, Fig. 1) increased upon the OA onset. This was insistent with the simple mode method at the significance of 0.1 (OR = 2.487, 95% CI = 1.047 ~ 5.904, $P = 0.08$, Fig. 1). However, the results of other three methods did not support this finding (Fig. 1). The horizontal pleiotropy was excluded according to the intercept of MR-Egger (Supplement Table 1). The robustness of association was confirmed by the heterogeneity (Supplement Table 2) and sensitivity analysis of leave-one-out method (Fig. 2A). Scatter plots and funnel plots also indicated the stability of the results (Fig. 2B and C).

Exploration of the causal effect of immune cells on knee OA

We identified 23 immune cell phenotypes to be causally associated with OA (Supplement Table 3), of which 9 were in the B cell panel, 4 in the Treg and Maturation stages of T cell panel, 1 in the cDC panel,1 in myeloid cell, 1 in monocyte and 7 in the TBNK panel.

By using the IVW method, there are three B cell subpopulations indicating protective effect on OA: BAFF − R on IgD + CD38 − unswitched memory (unsw mem) (OR = 0.984, 95% CI = 0.969 ~ 0.999, $P = 0.038$, Fig. 3), BAFF − R on IgD + CD38 dim (OR = 0.984, 95% CI = 0.969 ~ 0.999, $P = 0.038$, Fig. 3), and CD24 on IgD + CD24 + (OR = 0.983, 95% CI = 0.967 ~ 0.999, $P = 0.042$, Fig. 3). The increased risk of OA was detected in the other 6 B cell populations(Fig. 3): IgD + %Lymphocyte (OR = 1.026, 95% CI = 1.005 ~ 1.047, $P = 0.013$), Sw mem %lymphocyte (OR = 1.038, 95% CI = 1.004 ~ 1.072, $P = 0.027$), CD25 on IgD + CD24 + (OR = 1.017, 95% CI = 1.000 ~ 1.033, $P = 0.045$), CD25 on IgD − CD38 dim (OR = 1.025, 95% CI = 1.002 ~ 1.049, $P = 0.037$), CD27 on CD20 − (OR = 1.027, 95% CI = 1.001 ~ 1.055, $P = 0.044$), CD27 on CD24 + CD27 + (OR = 1.018, 95% CI = 1.001 ~ 1.036, $P = 0.041$).

Similarly, not all T cell subpopulations increased the risk of OA causally. Treg (Activated & resting Treg %CD4 + (OR = 1.029, 95% CI = 1.012 ~ 1.046, $P = 0.001$) increased the risk of OA while CD4 on EM CD4 + (Maturation stages of T cell) (OR = 0.984, 95% CI = 0.969 ~ 0.999, $P = 0.040$), Treg(CD4 on activated Treg (OR = 0.985, 95% CI = 0.971 ~ 0.998, $P = 0.028$), and CD45RA on TD CD8br (Maturation stages of T cell (OR = 0.958, 95% CI = 0.924 ~ 0.994, $P = 0.022$) exhibited protective effect against OA (Fig. 4).

Myeloid cells, cDC and monocyte identified in this study all increased the risk of OA (Fig. 5): CD14 + CD16 + monocyte %monocyte (OR = 1.037, 95% CI = 1.004 ~ 1.071, $P = 0.029$), CD86 on CD62L + myeloid DC (OR = 1.026, 95% CI = 1.001 ~ 1.052, $P = 0.038$), CD45 on CD33br HLA DR + (Myeloid cell) (OR = 1.018, 95% CI = 1.001 ~ 1.036, $P = 0.041$).

As for TBNK panel, HLA DR expression on T cells, B cells, and NK cells showed a protective causal association with OA. The increasing of HLA DR + + monocyte %monocyte (OR = 0.973, 95% CI = 0.949 ~ 0.998, P = 0.031), HLA DR + T cell%lymphocyte (OR = 0.982, 95% CI = 0.966 ~ 0.998, P = 0.024), and HLA DR + CD4 + %T cell (OR = 0.969, 95% CI = 0.940 ~ 0.998, P = 0.039) all indicated a protect effect on OA (Fig. 6). In contrast, the

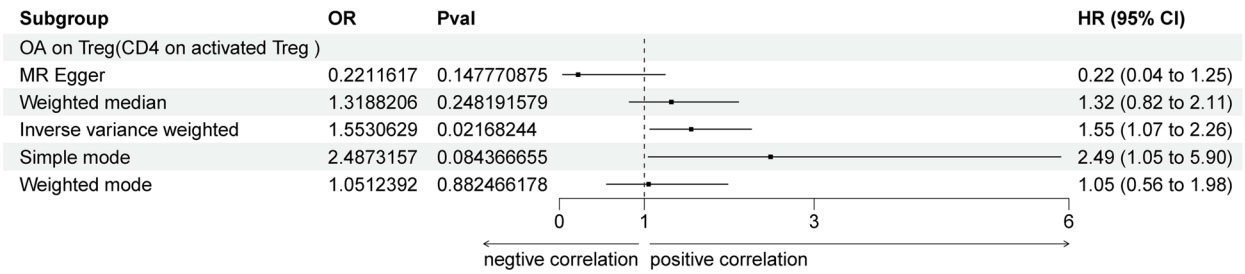

Fig. 1 Forest plots of the causal relationship between OA and CD4 on activated Treg by different MR methods. OR: odds ratios, CI: confidence interval

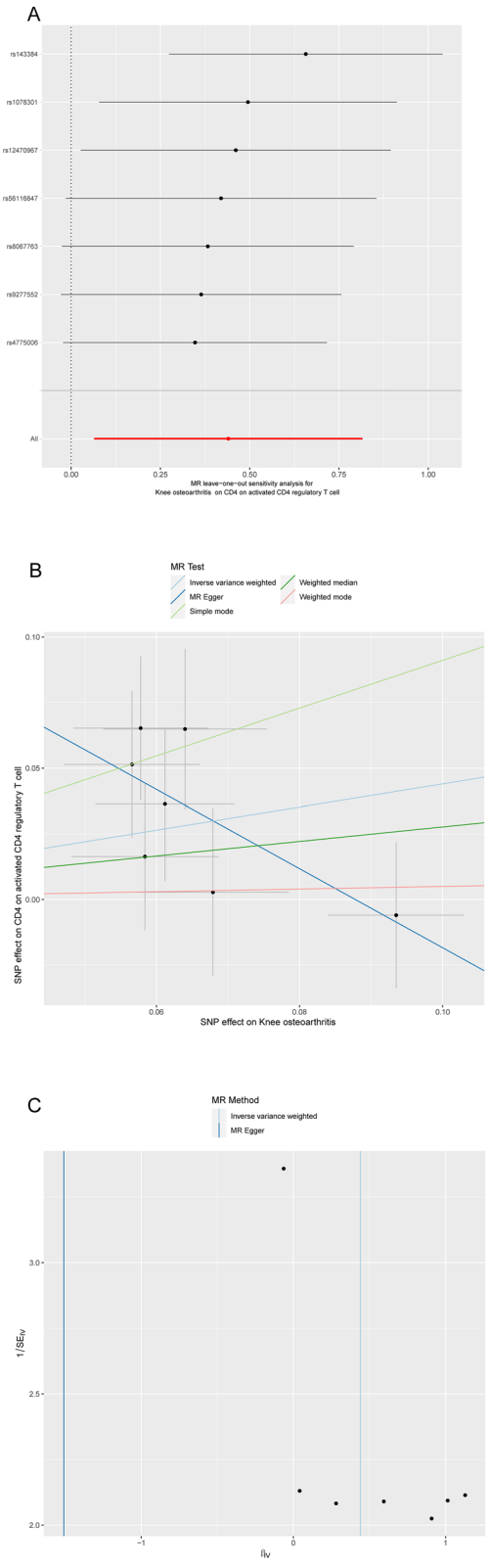

Fig. 2 The leave one out analysis of OA on CD4 on activated Treg (**A**), scatter plot of OA on CD4 on activated Treg (**B**) and funnel plot of OA on CD4 on activated Treg (**C**)

increasing TCRgd expression suggested a higher risk of OA: TCRgd AC (OR = 1.029, 95% CI = 1.000 ~ 1.058, P = 0.050), TCRgd %lymphocyte (OR = 1.019, 95% CI = 1.000 ~ 1.038, *P* = 0.049) (Fig. 6). In addition, CD45 on T cell (OR = 1.025, 95% CI = 1.005 ~ 1.046, *P* = 0.013) showed a potential risk on OA while SSC − A on lymphocyte (OR = 0.965, 95% CI = 0.935 ~ 0.996, *P* = 0.027) tend to play a protective role in OA (Fig. 6).

The robustness of association of each immune cell on knee OA was confirmed by the heterogeneity (Supplement Table 4) and sensitivity analysis of leave-one-out method (Supplement Fig. 1-4). The horizontal pleiotropy of each immune cell was excluded according to the intercept of MR-Egger (Supplement Table 5). Scatter plots and funnel plots also indicated the stability of the results (Supplement Fig. 1-4).

Heterogeneity among instrumental variables was assessed using Cochran's Q test. Cochran's Q test revealed no significant heterogeneity for most immune cell phenotypes, indicating consistent causal effect estimates across the SNPs. However, SNPs associated with CD14 + CD16 + monocytes showed significant heterogeneity, with Q p-values of 0.01 for both MR-Egger and Inverse Variance Weighted methods. This suggests variability in the causal effect estimates for this phenotype, reflecting the complex and potentially multifactorial roles of CD14 + CD16 + monocytes in OA pathogenesis.

In our analysis, the Egger intercept p-values for all tested phenotypes were greater than 0.05, indicating no significant evidence of horizontal pleiotropy. This suggests that the genetic instruments used in our study influence the outcome primarily through the exposure of interest, supporting the validity of our causal estimates.

Discussion

Although OA has traditionally been considered a non-inflammatory degenerative disease, emerging evidence highlights the role of immune-related factors in its pathogenesis. Specially, the suppressed anti-inflammatory factors and the enhanced of pro-inflammatory factors can trigger the inflammation cascade, thereby contributing to the progression of OA.

Changes in T and B cell expression have been associated with OA progression, suggesting that the adaptive immune system may play a significant role in OA advancement [21, 22]. However, there is little research on the correlation between specific cell subsets and the development of OA. In our study, we observed that BAFF − R and CD24 in IgD + B cells were associated with protective effects against OA though further validation in independent studies is required. BAFF is critical for regulating B cell function [23] and the inhibition of BAFF-mediated activation of B cells can alleviate the

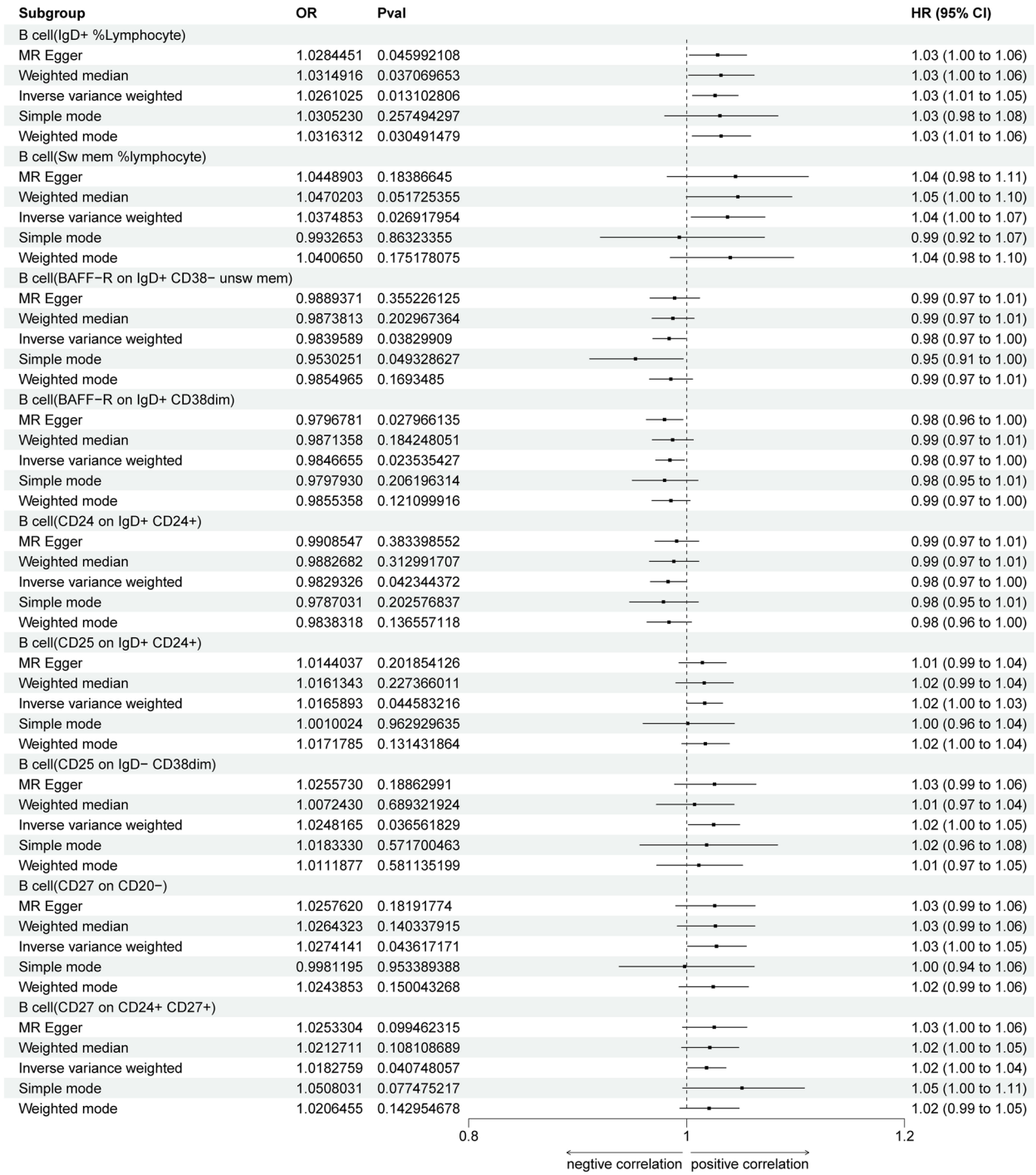

Fig. 3 Forest plots of the causal relationship between B cells and OA by different MR methods. OR: odds ratios, CI: confidence interval

arthritis symptoms of collagen-induced arthritis (CIA) mice. This seems to contradict our conclusion. However, since previous studies did not distinguish specific B cell subpopulations, we speculated that BAFF − R on IgD + CD38 − unsw mem and IgD + CD38 dim B cells exerted protective effects, and only when these cells were lost will they manifest as a pro-inflammatory state [24]. IgD + %Lymphocyte, Sw mem %lymphocyte, CD25 on IgD + CD24 +, CD25 on IgD − CD38 dim, CD27 on CD20 −, and CD27 on CD24 + CD27 + showed a causal

Subgroup	OR	Pval	HR (95% CI)
Treg (Activated & resting Treg %CD4+)			
MR Egger	1.0164552	0.184742575	1.02 (0.99 to 1.04)
Weighted median	1.0172920	0.173629942	1.02 (0.99 to 1.04)
Inverse variance weighted	1.0285994	0.000919252	1.03 (1.01 to 1.05)
Simple mode	1.0059667	0.76549535	1.01 (0.97 to 1.05)
Weighted mode	1.0151759	0.243631338	1.02 (0.99 to 1.04)
Maturation stages of T cell (CD4 on EM CD4+)			
MR Egger	0.9927067	0.484919291	0.99 (0.97 to 1.01)
Weighted median	0.9896490	0.308401916	0.99 (0.97 to 1.01)
Inverse variance weighted	0.9837835	0.040033746	0.98 (0.97 to 1.00)
Simple mode	0.9936167	0.787310774	0.99 (0.95 to 1.04)
Weighted mode	0.9892205	0.248151792	0.99 (0.97 to 1.01)
Treg(CD4 on activated Treg)			
MR Egger	0.9876512	0.18285216	0.99 (0.97 to 1.01)
Weighted median	0.9856430	0.144852516	0.99 (0.97 to 1.00)
Inverse variance weighted	0.9845873	0.028073936	0.98 (0.97 to 1.00)
Simple mode	0.9708781	0.098854317	0.97 (0.94 to 1.00)
Weighted mode	0.9860176	0.132014507	0.99 (0.97 to 1.00)
Maturation stages of T cell(CD45RA on TD CD8br)			
MR Egger	0.9524081	0.221005357	0.95 (0.88 to 1.03)
Weighted median	0.9573832	0.10011751	0.96 (0.91 to 1.01)
Inverse variance weighted	0.9582796	0.02169177	0.96 (0.92 to 0.99)
Simple mode	0.9557861	0.271296574	0.96 (0.88 to 1.03)
Weighted mode	0.9549309	0.187275435	0.95 (0.89 to 1.02)

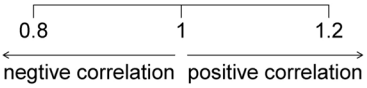

Fig. 4 Forest plots of the causal relationship between T cells and OA by different MR methods. OR: odds ratios, CI: confidence interval

Subgroup	OR	Pval	HR (95% CI)
Myeloid cell(CD45 on CD33br HLA DR+)			
MR Egger	1.012660	0.252902259	1.01 (0.99 to 1.03)
Weighted median	1.011466	0.311111155	1.01 (0.99 to 1.03)
Inverse variance weighted	1.019127	0.018797315	1.02 (1.00 to 1.04)
Simple mode	1.028636	0.151001399	1.03 (0.99 to 1.07)
Weighted mode	1.011423	0.257296207	1.01 (0.99 to 1.03)
cDC(CD86 on CD62L+ myeloid DC)			
MR Egger	1.039309	0.062319058	1.04 (1.00 to 1.08)
Weighted median	1.012681	0.509294175	1.01 (0.98 to 1.05)
Inverse variance weighted	1.026457	0.037966098	1.03 (1.00 to 1.05)
Simple mode	1.000670	0.987654409	1.00 (0.92 to 1.09)
Weighted mode	1.007034	0.878932207	1.01 (0.92 to 1.10)
Monocyte(CD14+ CD16+ monocyte %monocyte)			
MR Egger	1.019968	0.509801443	1.02 (0.96 to 1.08)
Weighted median	1.015684	0.379176107	1.02 (0.98 to 1.05)
Inverse variance weighted	1.036831	0.028720747	1.04 (1.00 to 1.07)
Simple mode	1.045305	0.241732028	1.05 (0.97 to 1.12)
Weighted mode	1.019808	0.286818651	1.02 (0.98 to 1.06)

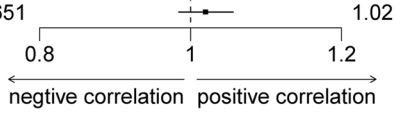

Fig. 5 Forest plots of the causal relationship between myeloid cells, DC and monocyte and OA by different MR methods. OR: odds ratios, CI: confidence interval

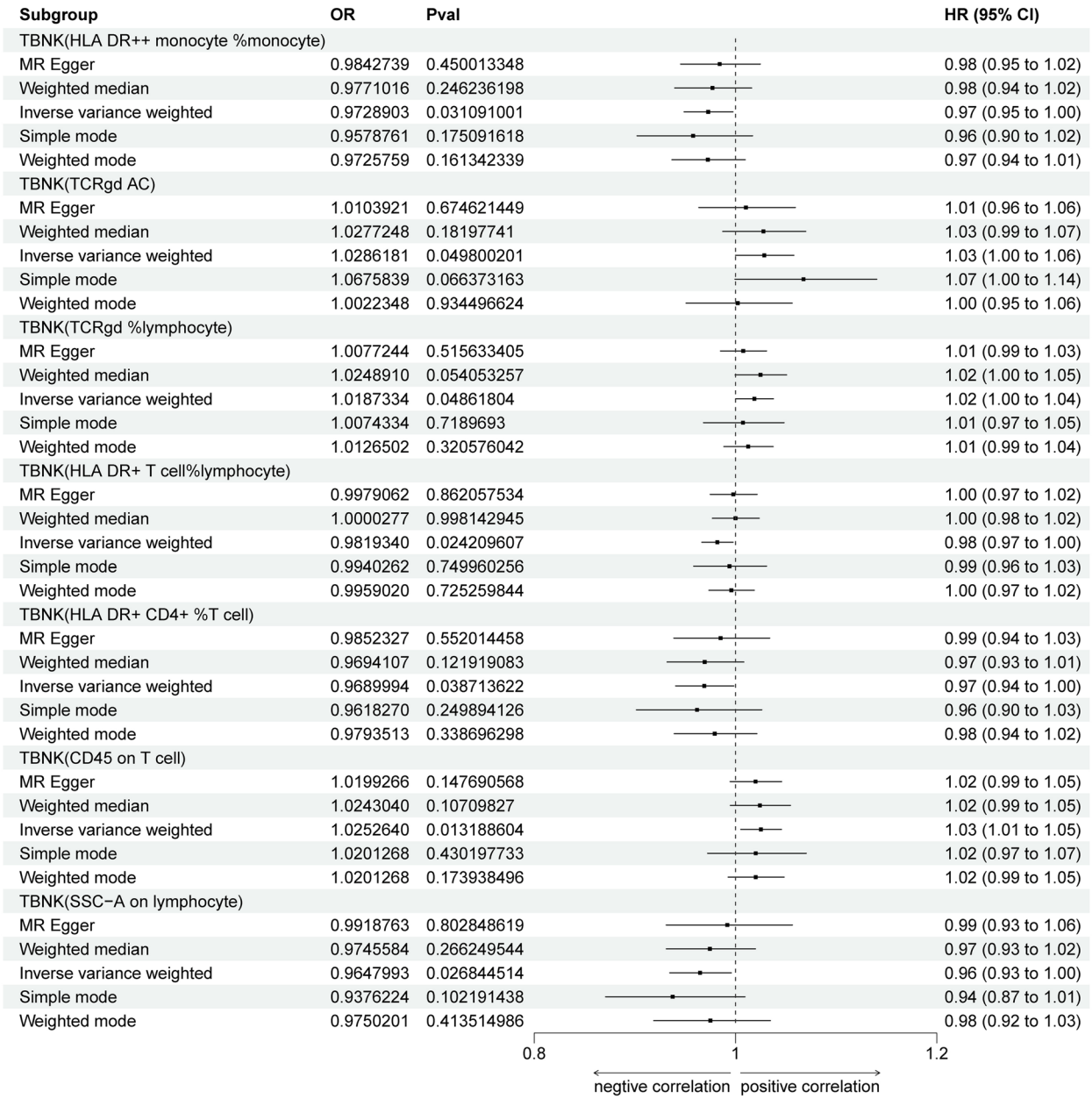

Fig. 6 Forest plots of the causal relationship between TBNK and OA by different MR methods. OR: odds ratios, CI: confidence interval

association that promotes OA. Notably, the expression of CD25 and CD27 on B cells seems to be a common factor for the causal risk factors of OA. This is consistent with the study related to rheumatoid arthritis, which showed the frequency of CD25 increased in rheumatoid arthritis patients [25]. The CD25 expression in B cell indicates the memory phenotype, which marked by CD27 and is functionally characterized by an increased IL-10 secretion. These cells exhibit a more mature phenotype, with significantly higher levels of surface immunoglobulin expression, and display antigen-presenting function. Blocking the expression of CD25 on B cells almost completely eliminates the corresponding T cell proliferation, indicating that CD25-expressing B cells drive the activation of T cell. Therefore, they are considered as important targets for graft-versus-host disease [25–27].

Myeloid cell is a heterogeneous group of myeloid progenitor cells and immature myeloid cells that have been widely described as having strong immunosuppressive activities. It is suggested that myeloid cells are associated

with the progression of OA, however, few studies have clarified their relationships and underlying mechanisms. Studies have suggested the critical role of monocytes in the occurrence and development of OA, which is related to their accumulation at the lesion suite and functions of producing pro-inflammatory factors. CD14 + CD16 + monocyte is considered as inflammatory subtype with enhanced abilities of secreting pro-inflammatory cytokines, which may be related to the increased expression of CCR2 [28–30]. Moreover, CD62L + DC was indicated to promote OA progression. The mechanism may be due to the accumulation of activation signals released by inflammation, which drives DC to acquire immunogenicity and present antigen, thereby triggering immune responses [31, 32]. Nevertheless, additional studies are needed to validate the causal effects of myeloid cells in OA progression.

Myeloid cells, a heterogeneous group of myeloid progenitor cells and immature myeloid cells that have been widely described as having strong immunosuppressive activity, have been suggested to be associated with the progression of OA in previous reports, and their possible mechanism is subchondral bone remodeling.

Treg cells are considered a class of immune cells with anti-inflammatory effects, characterized by the secretion of anti-inflammatory factor IL10. Little is known about the role of Treg cells in the pathogenesis of OA. Our results showed that activated or resting Treg cells tended to be a risk factor for OA, while maturated T cell (CD4 on EM CD4 +), CD4 on activated Treg, and CD45RA on maturated CD8br T cell showed a protective effect against OA, which was similar to their roles in rheumatoid arthritis. The expansion of effector memory Tregs can contribute to the control of intra-tissue inflammation/regeneration [33]. The bidirectional causal effect of knee OA on activated Treg cells may reflect a compensatory mechanism to limit the joint inflammation or promote joint degeneration, which requires further investigation.

HLA-DR is a human class II major histocompatibility complex (MHC), constitutively expressed on the surface of B cells, monocytes, and macrophages, and is involved in the antigen presentation to CD4 + T cells. Our results indicated that HLA-DR expression on T cells, B cells, and NK cells showed a protective causal effect on OA. However, HLA-DR only expressed in the late stage of activated T cell activation and the reasons of HLA-DR upregulation in T cell have not been fully studied. Monocytes are highly plastic cells that can either trigger inflammation or exert anti-inflammatory effects. HLD-DR level in monocytes surface could be a marker reflecting their pro-inflammatory or anti-inflammatory phenotypes [34]. Hence, we hypothesized that HLD-DR expression on T cells, B cells, and NK cells might have anti-inflammatory effects in OA setting, thereby exerting protective effects.

Gamma delta (γδ) T cells express TCRγδ on their surface, which enables them to recognize exogenous antigens. Their effects on modulating inflammation depend on the site and stage of the disease. They can also become activated without TCR ligands and rapidly trigger autoimmune inflammation [35]. It is reported that rheumatoid arthritis (RA) patients have increased numbers of IL-17-producing γδ T cells. Moreover, γδ T cells can induce osteoblasts to secrete RANKL, leading to bone and cartilage destruction [36]. Additionally, in synovial tissue from early-stage OA patients, restricted T cell receptor clonality was detected in infiltrated T cell in the perivascular area, which also indicates the minimal alteration of γδ T cells in OA patients [37]. Herein, Our results suggested that γδ T cells may increase the risk of OA progression, with specific mechanisms remaining unknown, which required additional investigation.

However, the interpretation and expansion of our findings should be approached with caution. It should be noted that our study has limitations; for instance, our analysis is based on GWAS data from European populations, potentially limiting the generalizability of our findings to non-European populations. Moreover, setting $P < 0.05$ as statistical significance may not be strict enough, applying more stringent corrections (e.g., Bonferroni or FDR) would indeed reduce false positives but might also obscure signals with moderate biological relevance. Our analysis demonstrated alignment in the direction and significance of beta coefficients across IVW and Weighted Median methods for most phenotypes (Supplementary Table 3). The beta coefficients span a range of magnitudes, with smaller values indicating subtle effects on OA. Given the corresponding significant p-values, we believe our findings suggest potential causal relationships. However, it also suggests the potential presence of uncertainties in the estimates, which could be attributed to factors such as sample size limitations and the use of weak instrumental variables. Our conclusions align with recent biological and clinical evidence on immunotherapy targets for alleviating osteoarthritis (OA) [38, 39]. However, it is crucial to emphasize that therapies targeting a single immune cell type appear insufficient. Instead, identifying specific immune cell phenotypes and developing comprehensive, rather than singular, treatment strategies targeting these groups appears more promising. Large-scale population-based immune datasets and systematic data collection on immune cell phenotypes at the pre-disease stage, followed by longitudinal cohort studies, are essential. Such efforts would be necessary for

translating findings from data-driven analyses to clinical validation, paving the way for developing comprehensive targeted therapies in OA pathogenesis.

Collectively, this study identified several immune cells causally associated with the knee OA risk by conducting two-sample MR analysis, which provided novel insights into the pathogenesis of OA and targets for developing treatment. However, as the GWAS data were limited to European populations, generalizability to other ancestries is uncertain. The MR estimates reflect lifelong exposure and may not capture short-term or context-specific immune changes. Additionally, we assumed linear effects across exposure levels, and non-linear relationships were not assessed. Moreover, the mechanisms by which these immune cells regulated OA development remained largely unknown. More studies are needed to address these questions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08735-4.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.
Supplementary Material 8.
Supplementary Material 9.
Supplementary Material 10.
Supplementary Material 11.

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Authors' contributions
Chenghao Gao and Hongxu Pu: Conceptualization, Methodology, Visualization, Original draft preparation. Yifan Zeng: Data curation, Software, Writing-Reviewing and Editing. Jun Xiao: Conceptualization, Supervision. All authors reviewed the manuscript.

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Data availability
Data in this study can be found at publicly archived datasets at https://gwas.mrcieu.ac.uk/ and https://www.ebi.ac.uk/gwas/.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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