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Effect of inflammatory factors on myocardial infarction

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Abstract

Background Cohort studies have increasingly shown associations between inflammatory markers and myocardial infarction (MI); however, the specific causal relationships between inflammatory markers and the development of MI remain unclear.

Methods and results By utilizing publicly accessible genome-wide association studies, we performed a two-sample Mendelian randomization (MR) analysis to explore the causal associations between inflammatory markers and myocardial infarction (MI). A random-effects inverse-variance weighted method was used to calculate effect estimates. The study included a total of 395,795 European participants for MI analysis and various sample sizes for inflammatory factors, ranging from 3,301 to 563,946 participants.Neutrophil count was found to increase the risk of MI (odds ratio [OR] = 1.08; 95% confidence interval [CI], 1.00–1.17; $p = 0.04$). C-reactive protein levels correlated positively with MI. No associations were observed with IL-1 beta, IL-6, IL-18, procalcitonin, TNF-α, total white cell count, or neutrophil percentage of white cells. Neutrophil count and C-reactive protein were inversely associated with lactate dehydrogenase: neutrophil cell count (OR 0.95; 95% CI, 0.93–0.98; $p < 0.01$) and C-reactive protein (OR 0.96; 95% CI, 0.92–1.00; $p = 0.02$). No associations of MI with myoglobin, troponin I, and creatine kinase-MB levels were found.

Conclusions This two-sample MR analysis revealed a causal positive association of MI with neutrophil count, C-reactive protein level, and the myocardial injury marker lactate dehydrogenase. These results indicate that monitoring C-reactive protein and neutrophil counts may be useful in management of MI patients.

Keywords C-reactive protein, Causal association, Inflammatory factor, Mendelian randomization, Neutrophil cell count

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Introduction

Inflammation is involved in all stages of atherothrombosis [1]. During ischaemia, cell death triggers inflammation, which is essential for cardiac repair, but which also contributes to ventricular remodelling. In the initial inflammatory phase, inflammation clears necrotic cell debris and the extracellular matrix, which is followed by fibroblast differentiation and scar tissue formation in the repair phase [2].

Macrophages play a crucial role in cardiac repair following myocardial infarction (MI). Macrophages promote healing in the heart by promoting lymph-angiogenesis, suppressing inflammation, and coordinating the repair process after MI [3]. In the chronic phase, angiopoietin-2 produced by macrophages promotes abnormal vessel remodelling and proinflammatory macrophages, worsening hypoxia and inflammation [4]. Macrophages also produce the anti-inflammatory cytokine interleukin (IL)-10, which is beneficial for myocardial infarction repair [5]. IL-10 decreases hyaluronidase-3 levels, reduces hyaluronan degradation, and limits collagen deposition in animal models. Moreover, IL-10 promotes fibroblast activation, including fibroblast proliferation, migration, and collagen production. Furthermore, in plaques from patients with atherosclerosis, both macrophages and T cells are activated and display evidence of IL-1β signalling [6].

Other inflammatory markers of myocardial injury include the following: A high white blood cell count to mean platelet volume ratio and neutrophil-to-platelet ratio, separately or in combination, have been associated with an increased risk of major adverse cardiovascular events in patients [7]. Moreover, the peak level of C-reactive protein (CRP) can serve as a predictive marker for transmural MI, and its predictive ability is comparable to that of peak creatine kinase-Myocardial Band (CK-MB) and high-sensitivity cardiac troponin T levels [8]. Lysine methyltransferase 2B, a lysine-specific methyltransferase, regulates histone H3 methylation at lysine 4 and activates the tumour necrosis factor-α (TNF-α)–nicotinamide adenine dinucleotide phosphate oxidase-2 axis by promoting riboflavin kinase gene transcription.

While associations between inflammation and MI have been reported, inflammatory factors may be mutually causal. Additionally, different inflammatory factors are expressed during the acute recovery and scarring phases of MI. However, it is unclear which inflammatory factors play important roles throughout the entire MI process.

Mendelian randomisation (MR) analysis is widely used to assess causal relationships between exposure and clinical outcomes. Unlike traditional observational studies, MR analysis can overcome reverse causation bias, because allelic randomisation occurs gamete formation, before disease onset. Genetic markers can be used as instrumental variables (IVs) of exposure to minimise the effects of confounding factors [9]. Genome-wide association studies (GWAS) facilitate the investigation of causality.

Using MR analysis, we aimed to identify inflammatory factors and markers associated with MI and myocardial injury. Detecting alterations in inflammatory markers among myocardial infarction patients, adjusting anti-inflammatory tactics, and enhancing prognosis.

Methods

Study design

There are three key assumptions in MR study design: (1) single-nucleotide polymorphisms (SNPs) are closely linked to inflammatory factors, (2) SNPs are not influenced by known confounding factors, and (3) SNPs solely impact MI occurrence through associated inflammatory factors.

Date sources

Our approach utilized data from GWAS. The data for MI (n=395,795) is sourced from the UK Biobank and the CARDIoGRAMplusC4D consortium [10]. IL-1β data (n=3,301) were obtained from the INTERVAL study [11]. IL-6 and IL-18 levels (n=21,758) were obtained from the report of Folkersen et al. [12]. The neutrophil percentage of white cells was obtained from the UK Biobank and INTERVAL studies [13]. CRP levels (n=204,402) were obtained from HapMap and 1000 Genomes imputed data [14]. The data for TNF-α levels (n=3,454) was sourced from the study results reported by Ahola-Olli et al. [15]. Procalcitonin (PCT) (n=3,301) data were obtained from an INTERVAL study [11]. White blood cell (WBC) (n=563,946) and neutrophil cell counts (n=563,946) were obtained from the Blood Cell Consortium.

The GWAS data used in this study were obtained from studies that have obtained approval from the respective ethical review boards. Therefore, ethical approval was not required for our study.

Selection SNPs and MR analysis

First, we selected SNPs associated with myocardial infarction (p-value less than $5\times10-8$). Second, we assessed the independence of the selected SNPs by examining pairwise linkage disequilibrium [16]. If the correlation coefficient (r2) was greater than 0.001 within a clustering window, we replaced the SNP with a stronger correlation to other SNPs, even if it had a higher p-value. Third, we calculated the F-statistic and selected SNPs with F-statistics greater than 10.

In the MR analysis, we primarily employed the inverse-variance weighted (IVW) analysis using a random-effects model, as well as the weighted median and MR-Egger tests. Sensitivity analyses were conducted on the data.

Table 1 Baseline characteristics of myocardial infarction and inflammatory factors

Trait	Year	Author	Population	Sample Size	No. of SNPs
WBC	2020	-	European	563,946	-
IL-6	2020	Folkersen L., et al.	European	21,758	11,782,139
IL-18	2020	Folkersen L., et al.	European	21,758	11,782,139
CRP	2018	Ligthart S., et al.	European	204,402	2,414,379
Neutrophil percentage of white cells	2016	Astle William J., et al.	European	171,542	29,166,313
IL-1β	2018	Sun Benjamin B., et al.	European	3,301	10,534,735
TNF-α	2016	Ahola-Olli Ari V., et al.	European	3,454	9,500,449
Neutrophil cell count	2020	-	European	563,946	-
PCT	2018	Sun Benjamin B., et al.	European	3,301	10,534,735
Myocardial infarction	2021	Hartiala JA., et al.	European	395,795	10,290,368

CRP level: C-Reactive protein level; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6 levels; IL-18: Interleukin-18 levels; PCT: Procalcitonin; TNF-α: Tumor necrosis factor-alpha; WBC: White blood cell count. SNP: single-nucleotide polymorphism

Table 2 Associations of genetically predicted inflammation factors with myocardial infarction

Inflammatory factors	No. of SNPs	OR (95% CI)	*P*
CRP	55	0.88(0.79–0.98)	< 0.01
IL-1β	2	1.07(0.99–1.15)	0.08
IL-6	2	0.92(0.73–1.14)	0.44
IL-18	8	1.01(0.95–1.07)	0.82
Neutrophil cell count	416	1.08(1.00–1.17)	0.04
Neutrophil percentage of white cells	134	1.03(0.92–1.14)	0.64
PCT	1	0.99(0.97–1.20)	0.16
TNF-α	N/A	N/A	N/A
WBC	478	1.06(0.99–1.14)	0.11

CRP: C-Reactive protein level; IL-1β: Interleukin-1 beta levels; IL-6: Interleukin-6 levels; IL-18: Interleukin-18 levels; PCT: Procalcitonin levels; TNF-α: Tumor necrosis factor alpha levels; WBC: White blood cell count; OR: odds ratio; CI: confidence interval; SNP: single-nucleotide polymorphism; N/A: not applicable

The weighted median method was considered reliable when there were more than 50% valid instrumental variables [17]. The MR-Egger method was used to assess the presence of horizontal pleiotropy in the selected instrumental variables [18]. The heterogeneity between instrumental variables was evaluated using the Cochrane Q statistic. A leave-one-out sensitivity analysis was performed to assess the impact of individual SNPs on the overall estimates. The same methods were used to validate the associations between the identified inflammatory factors and classical markers of myocardial injury.

All statistical analyses were conducted using the "TwoSampleMR" packages in R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

SNP selection

The studies that were included in the analysis were published from 2016 to 2020 and predominantly focused on European populations (Table 1). A total of 1,090 instrumental variables reached genome-wide significance levels, and all F-statistics were above 10 (Supplementary Table S1).

Myocardial infarction

IVW analysis revealed that an increase in genetically predicted inflammatory factors was inversely associated with MI. In particular, neutrophil cell count (odds ratio [OR] 1.08; 95% confidence interval [CI], 1.00–1.17; $p=0.04$) was significantly associated with MI, while suggestive evidence of a positive correlation between genetically predicted CRP and MI was also found (OR 0.88; 95% CI, 0.79–0.98; $p<0.01$) (Table 2). In contrast, no associations of IL-1β, IL-6, IL-18, PCT, TNF-α, neutrophil percentage of white cells, or WBC with MI were observed (Supplementary Fig. 1).

For the analysis of neutrophil count's relationship with myocardial infarction, the weighted median analysis showed consistent estimates but high heterogeneity. To address this, a random-effects model was used for the IVW meta-analysis. However, for C-reactive protein, which had poor heterogeneity, the MR-Egger analysis method was employed (Table 3). Supplementary Figures S2 and S3 present scatter and forest plots, respectively, illustrating the relationship between inflammatory factors and MI. These figures demonstrate consistent findings. Supplementary Figure S4 shows the results of the leave-one-out sensitivity analysis, which revealed that the overall estimates were not significantly influenced by any

Table 3 Associations between genetically predicted inflammatory factors and myocardial infarction in sensitivity analyses using the weighted-median and MR-Egger methods

Inflammatory factors	Weighted Median		MR-Egger		Pleiotropy		Heterogeneity	
	OR (95% CI)	*P*	OR (95% CI)	*P*	Intercept	*P*	Q	*P*
IL-1β	N/A	N/A	N/A	N/A	N/A	N/A	0.74	0.39
IL-6	N/A	N/A	N/A	N/A	N/A	N/A	4.02	0.04
IL-18	1.04 (0.96–1.12)	0.39	1.04 (0.90–1.19)	0.64	-0.0048	0.67	6.72	0.35
PCT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TNF-α	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
WBC	1.13 (1.02–1.25)	0.02	1.08 (0.92–1.25)	0.36	-0.0003	0.85	1071	< 0.01
Neutrophil cell count	1.14 (1.03–1.26)	0.01	1.06 (0.90–1.24)	0.48	0.0006	0.76	887	< 0.01
Neutrophil percentage of white cells	1.11 (0.97–1.26)	0.12	1.14 (0.86–1.51)	0.36	-0.0039	0.42	373	< 0.01
CRP	0.92 (0.82–1.02)	< 0.01	0.77 (0.66–0.91)	< 0.01	0.0100	0.04	192	< 0.01

CRP: C-reactive protein level; IL-1β: Interleukin-1 beta levels; IL-6: Interleukin-6 levels; IL-18: Interleukin-18 levels; PCT: Procalcitonin; TNF-α: Tumor necrosis factor alpha levels; WBC: White blood cell count; CI: confidence interval; MR: Mendelian randomization; N/A: not applicable; OR: odds ratio

Table 4 Associations between genetically predicted neutrophil cell count and cardiac biomarkers in sensitivity analyses using the weighted-median and MR-Egger methods

Outcome	Weighted Median		MR-Egger		Pleiotropy		Heterogeneity	
	OR (95% CI)	*P*	OR (95% CI)	*P*	Intercept	*P*	Q	*P*
Myoglobin	0.96 (0.88–1.05)	0.37	0.95 (0.85–1.06)	0.35	0.0004	0.75	513	< 0.01
Troponin I	1.09 (0.88–1.34)	0.44	1.02 (0.79–1.32)	0.89	0.0017	0.58	436	0.17
Creatine kinase-MB	0.92 (0.75–1.13)	0.45	0.91 (0.71–1.16)	0.44	0.0020	0.50	406	0.53
Lactate dehydrogenase	0.95 (0.91–0.99)	0.01	0.96 (0.90–1.01)	0.13	-0.0007	0.92	572	< 0.01

CI: confidence interval; MR: Mendelian randomization; OR: odds ratio

Table 5 Associations of genetically predicted neutrophil cell count with cardiac biomarkers

Outcome	No. of SNPs	OR (95% CI)	*P*
Myoglobin	412	0.96 (0.91–1.01)	0.17
Troponin I	411	1.09 (0.96–1.23)	0.20
Creatine kinase-MB	411	0.98 (0.86–1.10)	0.70
Lactate dehydrogenase	326	0.95 (0.93–0.98)	< 0.01

OR: odds ratio; SNP: single-nucleotide polymorphism.

single SNP. Supplementary Figure S5 shows a funnel plot indicating the absence of horizontal pleiotropy.

Markers of myocardial injury

The IVW analysis demonstrated a positive association of lactate dehydrogenase, an inflammatory marker associated with heart attacks, with neutrophil cell count (OR 0.95; 95% CI, 0.93–0.98; $p=0.002$) and CRP (OR=0.96; 95% CI, 0.92–1.00; $p=0.021$) (Tables 4, 5, 6 and 7). However, no significant associations were found with troponin I, myoglobin, or creatine kinase-MB (Supplementary Figs. 6, 7). The weighted-median and MR-Egger analyses yielded similar estimates, indicating no signs of directional pleiotropy for most biomarkers (Tables 4, 5, 6 and 7).

Discussion

In this two-sample MR analysis, we identified a causal positive of neutrophil count and CRP level with MI as well as with the myocardial injury marker lactate dehydrogenase.

Neutrophil count and MI

Animal experiments have shown that the occurrence of inflammation in MI may be due to the aggregation and release of specific molecules, S100A8 and S100A9, by neutrophils, which bind to Toll-like receptor 4 and activate nod-like receptor family pyrin domain-containing

Table 6 Associations between genetically predicted C-Reactive protein level and cardiac biomarkers in sensitivity analyses using the weighted-median and MR-Egger methods

Outcome	Weighted Median		MR-Egger		Pleiotropy		Heterogeneity	
	OR (95% CI)	*P*	OR (95% CI)	*P*	Intercept	*P*	Q	*P*
Myoglobin	0.98 (0.92–1.05)	0.65	0.96 (0.88–1.05)	0.34	-0.0001	1.00	78	0.01
Troponin I	1.07 (0.88–1.30)	0.48	1.07 (0.88–1.30)	0.57	-0.0041	0.47	54	0.42
Creatine Kinase-MB	1.05 (0.85–1.31)	0.63	1.11 (0.90–1.36)	0.35	< 0.0001	0.92	63	0.16
Lactate Dehydrogenase	0.97 (0.93-1.00)	0.08	0.96 (0.90–1.02)	0.15	< 0.0001	0.98	137	< 0.01

CI: confidence interval; MR: Mendelian randomization; OR: odds ratio

Table 7 Associations of genetically predicted C-reactive protein level with cardiac biomarkers

Outcome	No. of SNP	OR (95% CI)	*P*
Myoglobin	54	0.96 (0.90–1.02)	0.15
Troponin I	55	1.00 (0.88–1.14)	0.96
Creatine kinase-MB	55	1.11 (0.97–1.28)	0.13
Lactate dehydrogenase	49	0.96 (0.92–1.00)	0.03

OR: odds ratio; SNP: single-nucleotide polymorphism

protein 3 inflammasomes in neutrophils without immune stimulation, which promotes IL-1β secretion. The released IL-1β interacts with receptors (IL-1 receptor type 1) on haematopoietic stem cells and progenitor cells in the bone marrow, autonomously stimulating granulocyte production [19]. PDE4 is an enzyme responsible for hydrolysing intracellular cyclic adenosine monophosphate in the cell. In includes subtypes A–D, of which PDE4B plays a role in the interaction between neutrophils and endothelial cells, mediating the expression of cell adhesion molecules dependent on protein kinase A, neutrophil infiltration into the heart, and release of proinflammatory cytokines [20]. Neutrophils can be regulated by histidine decarboxylase/histamine via the H1R-SWI/SNF-PRMT1 pathway, which limits excessive oxidative reactions and neutrophil extracellular trap (NET) generation after MI [21]. By positive and negative validation studies, it has been shown that reducing neutrophil count can reduce scar formation and improve cardiac function in animal experiments, and that myeloperoxidase is a key factor in polymorphonuclear neutrophil-mediated cardiac remodelling [22]. Previous studies have shown that neutrophils release NETs into infarct-related arteries [23]. Additionally, the levels of NET-related tissue factors were significantly higher in coronary plasma samples [23]. These findings suggest that NETs are associated with ST-segment elevation MI (STEMI) and adverse cardiac events. In our study, the elevation of neutrophil count was associated with MI, but was not directly related to cytokines, such as ILs. The underlying mechanism may involve the regulation of inflammatory responses through IL-1 and PDE4B, leading to the occurrence of MI. Neutrophil count is correlated with lactate dehydrogenase levels, but not with early markers of acute MI, suggesting that increased lactate dehydrogenase levels may be the result of an inflammatory response involving neutrophil aggregation.

C-reactive protein and MI

CRP is an acute-phase mediator that activates the classical complement pathway, leading to elimination of pathogens or damaged/dead cells [24]. In low CRP levels, the presence of neutrophil-related pathways suggests the presence of an additional inflammatory risk beyond the conventional NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) pathways [25]. CRP levels in non-obstructive coronary artery MI are independently linked to a range of cardiovascular risk factors, comorbidities, and myocardial damage [26]. The levels correlated with the severity of coronary artery lesions and left ventricular ejection fraction (LVEF) 1 month after acute myocardial ischaemic events [27]. The extent of CRP elevation serves as a predictive indicator of the 1-year prognosis following MI [28]. In a large cohort of patients with rheumatoid arthritis without a history of cardiovascular events, an increase of 20 mg/L in CRP concentration was associated with a 1% increase in the 10-year risk of cardiovascular events [29].

In our MR study, we found that CRP was an exposure factor associated with MI and that it correlated with elevated lactate dehydrogenase levels. CRP is closely related to both the occurrence and prognosis of MI, further confirming the importance of dynamic clinical monitoring of CRP levels and of the need to take the necessary measures to improve prognosis. Animal studies have confirmed that plasma exchange can be performed 2 days after acute MI to reduce CRP levels specifically and reduce myocardial damage further [30].

The experimental evidence from animal studies has indicated the value of specific removal of inflammatory factors in individuals with a higher inflammatory response after acute MI. A previous study showed that CRP apheresis could effectively reduce CRP levels in patients with STEMI, without any significant side effects [31]. This suggests that CRP apheresis can disrupt the detrimental effects of STEMI and improve the long-term prognosis of patients after STEMI [31].

Dynamic monitoring of neutrophil counts and CRP level changes in patients with MI, particularly during the acute phase after MI, can help in adjustment of treatment plans. Anti-inflammatory therapies and, if necessary, measures such as clearing inflammatory factors, can improve prognosis. Recently, several large-scale randomized controlled trials (RCTs) have demonstrated the efficacy of anti-inflammatory medications in secondary prevention of atherosclerotic events. For instance, the CANTOS trial showed that canakinumab, an IL-1β inhibitor, significantly reduced the risk of recurrent cardiovascular events [32]. Similarly, the COLCOT trial indicated that colchicine reduced the incidence of major cardiovascular events in patients with recent acute coronary syndrome [33]. Our study further supports the pathogenic role of inflammation in myocardial infarction (MI), particularly highlighting the positive causal associations of neutrophil count and C-reactive protein (CRP) with MI. These findings, consistent with the outcomes of these RCTs, underscore the potential of targeting the neutrophil and CRP pathways as therapeutic strategies in managing MI patients. Future research should further explore the clinical benefits of these anti-inflammatory treatments in MI management [34–36]. It is important to acknowledge that neutrophil count and CRP levels can be highly variable in daily clinical practice and are influenced by factors such as infections and autoimmune disorders. Therefore, the timing of assessment of these inflammatory markers in relation to the occurrence of myocardial infarction is crucial [37–39]. Future studies should consider these variables to better understand the causal relationship.

Our study identified a causal positive association between neutrophil count and C-reactive protein (CRP) levels with myocardial infarction (MI). While high-sensitivity troponin (hs-Tn) is a precise and well-established biomarker for diagnosing acute myocardial infarction, our findings suggest that CRP and neutrophil count can serve as additional markers for assessing MI risk, particularly in preventive screening.Hs-Tn is extremely precise in diagnosing acute myocardial infarction. It is the "gold standard" for detecting myocardial injury [40]. Although CRP and Neutrophil Count are less specific than hs-Tn, they provide valuable information about systemic inflammation and immune response, which are crucial in the pathophysiology of atherosclerosis and plaque instability [41, 42]. Integrating CRP and neutrophil count with hs-Tn and other known risk factors (such as cholesterol levels, blood pressure, and smoking status) can enhance the accuracy of risk stratification models. This multimarker approach may help identify high-risk individuals who could benefit from more aggressive preventive measures [43]. Regular monitoring of CRP and neutrophil count in high-risk populations can help identify individuals with subclinical inflammation, allowing for timely interventions to prevent myocardial infarction [44]. While CRP and neutrophil count are useful inflammatory markers, they are not specific to myocardial infarction and can be elevated in various inflammatory conditions. Therefore, they should be used as complementary markers alongside more specific biomarkers like hs-Tn [45]. More studies are needed to validate the clinical utility of these biomarker combinations in different populations and to develop and refine comprehensive risk scores [46].

In our two-sample Mendelian randomisation (MR) analysis, we identified a causal positive association between myocardial infarction (MI) and neutrophil count as well as C-reactive protein levels. These findings align with a recent unsupervised machine learning clustering analysis that identified distinct phenotypes in patients undergoing percutaneous coronary intervention, particularly an inflammatory phenotype characterised by elevated neutrophil and C-reactive protein levels [47].

Our MR study elucidates the mechanistic underpinning by revealing causal relationships between specific inflammatory markers, such as neutrophil count and CRP, and MI. This further substantiates the inflammatory hypothesis in the progression of atherosclerosis, echoing the classification results observed in machine learning analysis [48]. The concordance between genetic and machine learning approaches bolsters the importance of these inflammatory markers as indicators for predicting and managing cardiovascular events, thus providing a valuable foundation for future gene therapy research. We will continue to highlight these associations in the manuscript and explore the potential implications of these findings for future therapeutic strategies, particularly in the precision medicine approach to identifying and targeting high-risk patient groups [49].

This study had several limitations. The potential influence of directional pleiotropy cannot be fully ruled out. In the case of CRP, a pleiotropic effect was observed in the MR-Egger intercept test, which led to its utilization. Additionally, the focus of GWAS databases on European populations may limit the generalizability of our findings to other ethnicities. Nevertheless, the European ancestry of our study population minimizes the likelihood of ethnic bias impacting our results.

Conclusion

This two-sample MR analysis revealed an association of neutrophil count with MI as well as with the myocardial injury marker lactate dehydrogenase. Moreover, we show evidence of a positive correlation of genetically predicted CRP with MI, as well as with lactate dehydrogenase. These results imply that monitoring CRP and neutrophil counts may provide new opportunities for the management of patients with MI in future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04122-4.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
Not applicable.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wei Li, Tao Xu, Zhenghua Luo, Haiyan Zhou, Zonggang Duan, Xinlin Xiong and Mengjun Huang. The first draft of the manuscript was written by Qingyi Zeng and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets and materials used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The GWAS data used in this study were obtained from studies that have obtained approval from the respective ethical review boards. Therefore, ethical approval was not required for our study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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