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Research Article

Bidirectional Two-Sample Mendelian Randomization Study Investigating Gut Microbiota and Kawasaki Disease

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Abstract

Background: Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a systemic immune-mediated vasculitis of unknown etiology. It predisposes to coronary artery disease. This study employs bidirectional Mendelian randomization (MR) to investigate interactions between KD and gut microbiota, thereby elucidating their causal relationships.

Methods: Based on publicly available genome-wide association study (GWAS) data, genetic variants associated with gut microbiota and KD were selected as instrumental variables. Causal effects were assessed via inverse-variance weighted (IVW), weighted median (WM), and MR-Egger methods. Heterogeneity testing, sensitivity analyses, and pleiotropy evaluation were performed.

Results: Forward MR analysis identified 14 microbial features with causal effects on KD, including: 5 protective taxa: e.g., OTU99_11 (Parabacteroides abundance) [OR: 0.351; 95% CI: 0.144–0.857; P = 0.022], 9 risk taxa: e.g., TestASV_42 (Alphaproteobacteria prevalence) [OR: 1.584; 95% CI: 1.046–2.397; P = 0.030]. Reverse MR (with KD as exposure) showed no significant causal effects on gut microbiota.

Conclusion: Bidirectional two-sample MR demonstrates putative causal links between gut microbiota and KD, providing mechanistic insights for KD pathogenesis and therapeutic targeting.

Kew Words: bidirectional mendelian randomization; gut microbiota; mendelian randomization; Kawasaki disease; gwas catalog

1.Introduction

Kawasaki Disease (KD), also known as mucocutaneous lymph node syndrome, is an acute, nonspecific vasculitis primarily affecting small arteries in children, with a particular predilection for the coronary arteries. Although the exact etiology of KD remains unclear, it is widely believed to involve a systemic immune response triggered by infectious agents[1]. Characteristic clinical manifestations include persistent high fever, bilateral conjunctival injection, cracked lips and oral mucosa, erythema and edema of the hands and feet, and polymorphous rash. In severe cases, cardiovascular complications such as coronary artery aneurysms may develop[2].

Epidemiological studies indicate that KD predominantly affects children under five years of age, with a higher incidence in males. Compared to Western countries, East Asian nations—especially Japan—exhibit significantly higher incidence rates. Additionally, KD demonstrates seasonal peaks during winter and spring, and higher incidence has been observed among populations with elevated socioeconomic status. Although KD incidence is rising in developing countries, it remains the leading cause of acquired heart disease in children from developed nations[3].

In recent years, the gut microbiota has emerged as a major research focus. Studies reveal that gut microorganisms influence numerous host biological processes, including metabolism, intestinal barrier function, and immune responses both locally and systemically. Alterations in its composition have been linked to the development of inflammatory and cardiovascular diseases, including Kawasaki Disease (KD)[4–6]. Research on the gut microbiota-KD relationship spans over two decades;

however, most existing studies examining the causal link between gut microbiota and KD risk are observational in nature and thus susceptible to bias from confounding factors and reverse causation. Consequently, there remains a lack of definitive mechanistic evidence elucidating the precise role of gut microbiota in KD pathogenesis.

This study employs Mendelian randomization (MR) analysis to systematically evaluate the causal relationship between gut microbiota and KD. Through bidirectional analysis, we not only investigate the potential impact of gut microbiota on KD but also assess the potential influence of KD on gut microbiota composition[7]. This comprehensive approach aims to delineate the mechanistic role of gut microbiota in KD pathogenesis, ultimately seeking to identify novel biomarkers and potential therapeutic targets for early intervention and personalized treatment of KD[8].

2. Materials and Methods

2.1 Research Program and Data Sources

This study employed a bidirectional two-sample Mendelian randomization (MR) approach to evaluate the causal relationship between gut microbiota and Kawasaki disease (KD). Single nucleotide polymorphisms (SNPs) were utilized as genetic instruments, satisfying three core MR assumptions:(1) Relevance: Strong association between instruments and exposure factors;(2) Independence: Instruments independent of confounding factors;(3) Exclusion restriction: Instruments influence outcomes solely through the exposure, without alternative pathways[9]. The study design incorporated summary-level GWAS data for 430 gut microbiota taxa and Kawasaki disease：（1）Forward MR analysis: Genetic variants associated with gut microbiota were selected to infer causal effects of microbiota on KD risk.（2）Reverse MR analysis: Genetic variants associated with KD were used to infer causal effects of KD liability on gut microbiota composition. The analytical framework is schematically presented in Figure 1.

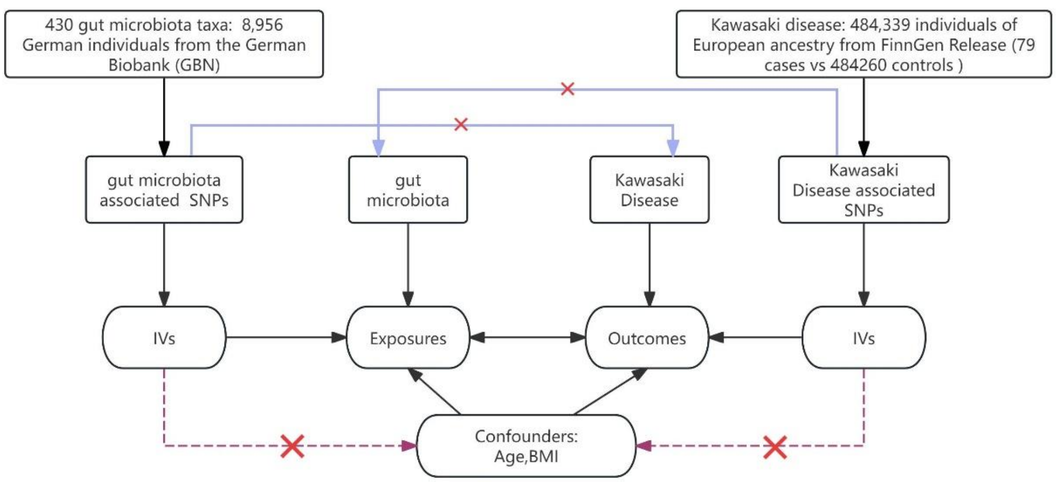


Figure 1: Hypothesis and study design of bidirectional MR for the association of gut microbiota with Kawasaki disease. BMI, body mass index; Genetic tool variables: SNPs, single nucleotide polymorphisms.

2.3 Genetic Instrumental Variables of Gut Microbiota

Gut microbiota data data were obtained from 8956 German(PopGen12, n = 724; FoCus, n = 957; SHIP, n = 2,029; SHIP-TREND, n = 3,382; KORA, n = 1,864) individuals by Ruhlemann et al. [10]. This study analyzed 430 microbial taxa (from phylum to genus level, examining both abundance and prevalence in fecal samples), identifying 38 genetic loci associated with individual bacterial features and overall microbiome composition.

2.4 Genetic Instrumental Variables in KD

The Kawasaki disease data were sourced from the FinnGen Release, comprising 79 Kawasaki disease cases and 484,260 healthy controls. To mitigate potential confounding from population stratification, all samples were restricted to individuals of European ancestry.

2.5 Selection of Genetic Instrumental Variables

To comply with Mendelian randomization (MR) assumptions (Figure 1), all GWAS-derived SNPs were independent and reached genome-wide significance ($P < 5\times10^{-8}$, $r^2 < 0.001$, clumping distance = 10,000 kb). Given the limited number of significant SNPs for gut microbiota traits, a relaxed threshold ($P < 1\times10^{-5}$) was employed for SNP selection, while reverse MR analyses used $P < 5\times10^{-5}$. Additionally, the study assessed whether there was an association with confounding factors (BMI). Obesity may lead to systemic chronic low-grade inflammation; therefore, BMI was used as a confounder[11]. To reduce the bias, we excluded SNP related to the age-related survival rate of recruitment[12]. Finally, instrument strength was evaluated using the F-statistic: $F = (\beta/SE)^2$. SNPs with $F \leq 10$ were excluded to mitigate weak instrument bias, retaining only variants with $F > 10$[13].

2.6 Two-Way MR Analysis

This study employed bidirectional Mendelian randomization to assess the directionality of associations between Kawasaki disease (KD) and gut microbiota using summary-level data. Forward MR: Instrumental variables (IVs) derived from gut microbiota-associated SNPs were used to estimate causal effects on KD. Reverse MR: KD-associated SNPs served as IVs to evaluate causal effects on microbial features.Causal estimates were primarily generated via inverse-variance weighted (IVW) regression, supplemented by weighted median (WM), MR-Egger, simple mode, and weighted mode methods [14].

2.7 Sensitivity Analysis

Heterogeneity was quantified using Cochran's Q statistic; significant heterogeneity (Q-test P < 0.05) prompted random-effects IVW models. Horizontal pleiotropy was assessed via MR-Egger intercept test (intercept P < 0.05 indicating pleiotropic bias). Leave-one-out sensitivity analyses evaluated robustness by iteratively excluding individual SNPs. Funnel plot symmetry was visually inspected to confirm result stability[15–17].

P < 0.05 was considered to indicate a significant association. Two-way analyses were conducted via the MRPRESSO (version 1.0) and TwoSampleMR (version 0.5.6) packages in R software (version 4.4.0). This report was written in accordance with the STROBE-MR statement guidelines.

3 Results

3.1 Influence of Gut Microbiota on the Risk of Developing KD

Table 1 presents statistically significant MR results using the inverse-variance weighted (IVW) method. IVW analysis identified causal associations between Kawasaki disease (KD) and 14 gut microbial features. Five microbiota taxa demonstrated protective effects against KD:OTU99_11 (*Parabacteroides*) abundance [OR: 0.351; 95% CI: 0.144, 0.857; P = 0.022], OTU99_62 (*Ruminococcaceae*) prevalence [OR: 0.392; 95% CI: 0.158, 0.971; P = 0.043], OTU97_33 (*Holdemanella*) prevalence [OR: 0.517; 95% CI: 0.296, 0.901; P = 0.020]. Conversely, nine taxa were identified as risk factors for KD: TestASV_42 (*Alphaproteobacteria*) prevalence [OR: 1.584; 95% CI: 1.046, 2.397; P = 0.030], TestASV_30 (*Paraprevotella*) abundance [OR: 1.690; 95% CI: 1.185, 2.408; P = 0.004], OTU97_26 (*Parasutterella*) prevalence [OR: 1.777; 95% CI: 1.087, 2.906; P = 0.022]. Complete analytical results are provided in Supplementary Table 1.

Exposure	Outcome	nSNP	OR	95%CI	P-value	P_FDR
TestASV_30 (Paraprevotella) abundance	MLNS	8	1.690	(1.185, 2.408)	0.004	0.986
OTU99_58 (Bacteroides) abundance	MLNS	9	1.925	(1.114, 3.328)	0.019	0.986
OTU97_33 (Holdemanella) prevalence	MLNS	8	0.517	(0.296, 0.901)	0.020	0.986
OTU99_11 (Parabacteroides) abundance	MLNS	12	0.351	(0.144, 0.857)	0.022	0.986
OTU97_26 (Parasutterella) prevalence	MLNS	7	1.777	(1.087, 2.906)	0.022	0.986
OTU99_26 (Parasutterella) prevalence	MLNS	7	1.777	(1.087, 2.906)	0.022	0.986
OTU97_86 (Phascolarctobacterium) abundance	MLNS	15	0.676	(0.484, 0.946)	0.022	0.986
P_Bacteroidetes abundance	MLNS	10	2.897	(1.137, 7.384)	0.026	0.986
TestASV_42 (Alphaproteobacteria) prevalence	MLNS	8	1.584	(1.046, 2.397)	0.030	0.986
OTU97_165 (Porphyromonadaceae) abundance	MLNS	9	0.600	(0.374, 0.964)	0.035	0.986
C_Bacteroidia abundance	MLNS	5	3.076	(1.043, 9.071)	0.042	0.986
O_Bacteroidales abundance	MLNS	5	3.076	(1.043, 9.071)	0.042	0.986
OTU99_62 (Ruminococcaceae) prevalence	MLNS	6	0.392	(0.158, 0.971)	0.043	0.986
G_Sutterella abundance	MLNS	6	3.814	(1.037, 14.033)	0.044	0.986

Note: MLNS: Mucocutaneous lymph node syndrome.

Table 1: The MR Results of Gut Microbiota and MLNS

3.1 Effect of KD Status on gut microbiota composition

Table 2 presents statistically significant MR results using the inverse-variance weighted (IVW) method. The IVW analysis did not identify causal associations between Kawasaki disease (KD) and any gut microbial features. All five analytical methods (IVW, weighted median, MR-Egger, simple mode, and weighted mode) yielded consistent null findings. After false discovery rate (FDR) correction, all results remained statistically non-significant. Complete analytical results are provided in Supplementary Table 2.

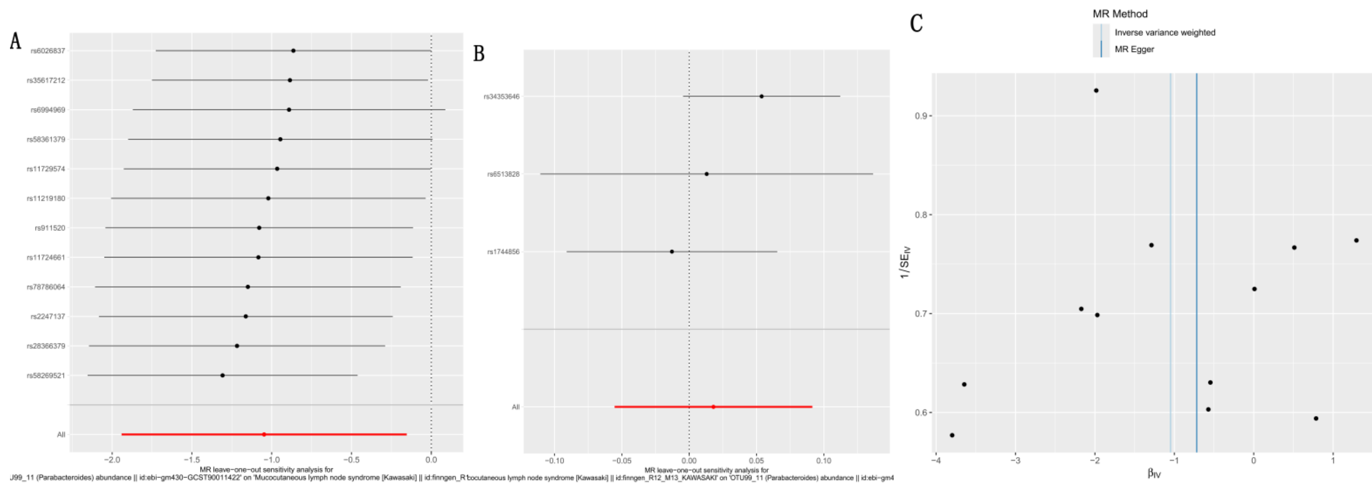
Exposure	Outcome	nSNP	OR	95%CI	P-value	P_FDR
MLNS	C_Bacteroidia abundance	3	0.029	(-0.004, 0.063)	0.082	0.606
MLNS	G_Sutterella abundance	3	0.000	(-0.061, 0.061)	0.995	0.995
MLNS	O_Bacteroidales abundance	3	0.029	(-0.004, 0.063)	0.082	0.606
MLNS	OTU97_165 (Porphyromonadaceae) abundance	3	0.055	(-0.114, 0.224)	0.525	0.875
MLNS	OTU97_257 (Mitsuokella) prevalence	3	-0.006	(-0.154, 0.142)	0.933	0.995
MLNS	OTU97_26(Parasutterella) prevalence	3	0.034	(-0.070, 0.139)	0.520	0.875
MLNS	OTU97_33 (Holdemanella) prevalence	3	-0.005	(-0.085, 0.075)	0.907	0.995
MLNS	OTU97_86 (Phascolarctobacterium) abundance	3	-0.079	(-0.195, 0.037)	0.182	0.683
MLNS	OTU99_11 (Parabacteroides) abundance	3	0.018	(-0.055, 0.091)	0.631	0.940
MLNS	OTU99_26 (Parasutterella) prevalence	3	0.034	(-0.070, 0.139)	0.520	0.875
MLNS	OTU99_58 (Bacteroides) abundance	3	0.006	(-0.061, 0.073)	0.863	0.995
MLNS	OTU99_62 (Ruminococcaceae) prevalence	3	0.028	(-0.108, 0.164)	0.689	0.940
MLNS	P_Bacteroidetes abundance	3	0.026	(-0.007, 0.059)	0.121	0.606
MLNS	TestASV_30 (Paraprevotella) abundance	3	0.058	(-0.059, 0.175)	0.330	0.875
MLNS	TestASV_42 (Alphaproteobacteria) prevalence	3	0.039	(-0.079, 0.158)	0.515	0.875

Note: MLNS: Mucocutaneous lymph node syndrome.

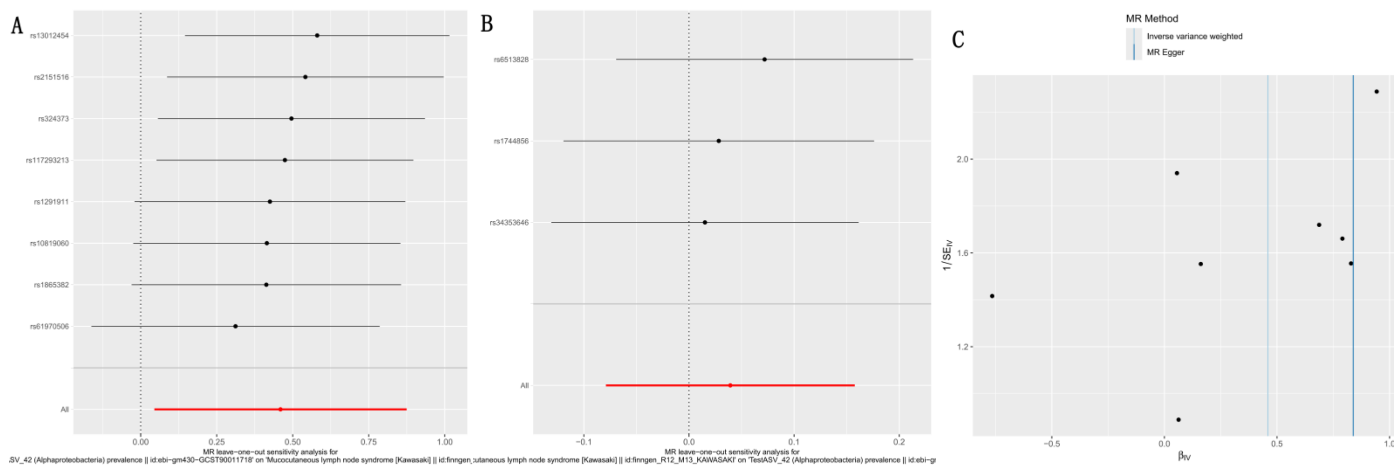
Table 2: The MR Results of MLNS and Gut Microbiota

3.2 Sensitivity Analysis

Heterogeneity analysis revealed significant bias in the association between Kawasaki disease (KD) and OTU99_62 (*Ruminococcaceae*) prevalence among previously significant results ($P < 0.05$). No evidence of horizontal pleiotropy was detected ($P > 0.05$). Complete heterogeneity and pleiotropy analyses are presented in Supplementary Tables 3-6. Leave-one-out analysis confirmed the stability of all results, demonstrating robustness against individual SNP influences (Supplementary Figures 1-2). The figure panels below depict sensitivity analyses for: Protective taxon: OTU99_11 (*Parabacteroides*) and Risk-associated taxon: TestASV_42 (*Alphaproteobacteria*)



Sensitivity analysis of bidirectional causal relationships between Kawasaki disease (KD) and OTU99_11 (*Parabacteroides*): (A) Leave-one-out plot for OTU99_11 in forward MR analysis. (B) Leave-one-out plot for OTU99_11 in reverse MR analysis. (C) Funnel plot of individual SNP estimates.



Sensitivity analysis of bidirectional causal relationships between Kawasaki disease (KD) and TestASV_42 (*Alphaproteobacteria*): (A) Leave-one-out plot for TestASV_42 in forward MR analysis. (B) Leave-one-out plot for TestASV_42 in reverse MR analysis. (C) Funnel plot of individual SNP estimates.

4. Discussion

This study systematically evaluated causal relationships between gut microbiota and Kawasaki disease (KD) using bidirectional two-sample Mendelian randomization (MR). Results revealed significant causal effects of gut microbiota on KD, though no reverse causation was detected.

The gut represents the largest interface between microbial factors and the host, harboring the highest bacterial density and most extensive lymphoid tissue. Gut microbiota, comprising trillions of bacteria, viruses, fungi, and archaea, participate in numerous physiological processes through host interactions—including regulation of the intestinal mucosal barrier, host metabolism, and immune responses[18,19]. These functions are primarily mediated by microbial metabolites such as short-chain fatty acids (SCFAs), bile acids, and trimethylamine N-oxide (TMAO)[20]. Dysbiosis-induced disruption of metabolite production can trigger inflammatory responses and metabolic diseases, including cardiovascular disease (CVD)[21].

KD is an acute febrile systemic vasculitis whose clinical features (e.g., acute fever) suggest infectious triggers may activate aberrant immune responses in genetically susceptible individuals, though its exact etiology remains unknown. Multiple lines of evidence implicate gut microbiota in KD pathogenesis: (1) Significantly elevated circulating levels of secretory IgA (sIgA), anti-cardiolipin, and anti-lipid A IgA in patients[22]. (2) Fecal microbiome analyses demonstrate reduced abundance of beneficial SCFA-producing bacteria alongside proliferation of pro-inflammatory taxa. Butyrate-producing *Clostridium*, for instance, limits Th17 differentiation and promotes Treg development via SCFA modulation—with SCFA depletion correlating with elevated Th17 and reduced Treg levels in KD[23]. (3) Pre-diagnostic antibiotic use for febrile symptoms disrupts microbiota composition, eliminating bacteria essential for host physiology[24]. Childhood antibiotic exposure associates with increased risk of immune-mediated disorders. While these studies suggest links between microbial shifts and KD development, consensus on this relationship remains elusive.

Previous research has identified specific microbiota associations with KD: Lactobacillus and Actinobacteria phylum as protective factors against coronary lesions, while Pseudomonadaceae serve as pathological markers, Actinobacteria dominate serum microbial homologs in acute KD[25], and murine models show Bacteroides-enriched and Bifidobacterium-enriched environments increase coronary inflammation[26]. Our MR analysis identified causal relationships between 14 microbial features and KD, including: 5 protective taxa (e.g., OTU99_11 [Parabacteroides]) and 9 risk taxa (e.g., TestASV_42 [Alphaproteobacteria]; OR: 1.584; 95% CI: 1.046–2.397; P = 0.030). Protective genera like Parabacteroides may inhibit KD through: (1) Anti-inflammatory metabolite regulation: Production of succinate/propionate activates GPR43/GPR109a receptors, suppressing NF-KB signaling and systemic inflammation (e.g., TNF-α, IL-6 release)[27–29]. (2) Immune homeostasis maintenance: Animal studies demonstrate promotion of Treg differentiation and suppression of Th17 hyperactivation—correcting the Th17/Treg imbalance central to KD vascular injury[30]. Risk taxa like Alphaproteobacteria may exert effects via: (1) Pro-inflammatory epitope mimicry: Structural similarity between bacterial LPS and host vascular antigens potentially triggers autoimmunity[31,32]. (2) Vascular endothelial injury: Metabolites like TMAO induce endothelial apoptosis and monocyte adhesion[33,34], exacerbating coronary inflammation—consistent with Yeung et al.'s "gut microbiota-mediated coronary susceptibility" hypothesis[26].

This study has the following limitations*:* (1) Discrepancies across MR methods indicate limited robustness of forward causal estimates, requiring further validation. (2) Liberal SNP threshold may yield weak instruments. (3) Restricted KD sample size (n = 79 cases) limits precision and generalizability. (4) Exclusive European ancestry precludes extrapolation to high-risk East Asian populations. Future studies should validate findings in multi-ethnic cohorts.

4 Conclusion

In this study, bidirectional Mendelian randomization (MR) analysis systematically evaluated causal relationships between gut microbiota and Kawasaki disease (KD) risk. Forward MR identified 14 microbial features with causal effects on KD, while reverse MR showed no significant effects of KD on gut microbiota composition. These findings indicate that abundance levels of specific gut microbes may influence KD initiation and progression. Although the roles of other microbiota remain incompletely characterized, they represent potential targets for future research and clinical intervention. Further investigations should elucidate the precise functions of these microbes across distinct KD disease stages.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Statement

After reviewing the guidelines and requirements, we confirm that this study was exempt from Institutional Review Board (IRB) approval in accordance with Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, February 18, 2023).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors state that the study was conducted without any involvement in commercial or financial interests that could be perceived as potential conflicts of interest.

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