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The Role of Host Genetics and Gut Microbiota Interaction in Immune System Regulation: A Systematic Review and Meta-Analysis

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Abstract

Context: The interaction between host genetics and the gut microbiota plays a vital role in immune regulation; however, existing evidence lacks integrated quantification and methodological coherence. Therefore, we conducted a systematic review and meta-analysis of quantitative studies to test explicitly whether microbial metabolites mediate the association between host genetics and immune function.

Evidence Acquisition: A systematic search was conducted in PubMed, Scopus, Web of Science, Embase, and the Cochrane Library through December 2025. Of 1,245 identified records, 14 quantitative studies met the inclusion criteria. Study quality was assessed using design-specific tools (NOS, STROBE-MR, JBI). Analyses were performed using random-effects models, meta-regression, and meta-analytic path analysis. The protocol was not registered in PROSPERO, and all analyses were exploratory.

Results: The NOD2–Enterobacteriaceae interaction was associated with inflammatory bowel disease severity (OR = 2.34, 95% CI: 1.78 - 3.08, $P < 0.001$, $I^2 = 38\%$). Evidence from Mendelian randomization studies suggested that the microbiota may have a causal effect on inflammatory cytokines (OR = 1.52, 95% CI: 1.28 - 1.81, $P < 0.001$, $I^2 = 48\%$). Microbial metabolites mediated approximately 56 - 63% of the effects (k = 3, exploratory findings). *Disease status*, ethnicity, BMI, and diet explained a substantial proportion of the between-study heterogeneity. Publication bias assessment of 8 studies in the dysbiosis–cytokine analysis showed no statistically significant evidence of bias (Egger's test: $P = 0.082$; Begg's test: $P = 0.114$).

Conclusions: Our findings suggest that metabolite-dependent pathways represent the primary intersection between host genetics and the gut microbiota in immune regulation. However, several caveats warrant consideration: the exploratory design, unregistered protocol, underpowered subgroup analyses, and European-centric populations mean that our conclusions should be viewed as hypothesis-generating rather than definitive, pending validation in prospective cohorts and trials. Accordingly, any clinical recommendations based on these findings should be made cautiously and treated as hypotheses for future research.

Keywords: Host Genetics, Meta-analysis, Gut Microbiota, Immune Regulation, Mendelian Randomization

1. Introduction

1.1. Topic Introduction

Immune homeostasis arises from an intricate interplay between host genetic architecture and environmental exposures, with the gut microbiota now firmly established as a key contributor to this balance (1, 2, 3). Infants are born with limited microbial colonization and develop their microbiota concurrently with the maturation of the immune system (1). This co-evolution reflects a close link between the host genome and the microbial population residing in the gut.

1.2. Clinical and Scientific Importance

Comprising nearly 100 trillion bacteria, the gut microbiota plays a vital role in maintaining host homeostasis, and its derived metabolites can modulate the host's inflammatory balance (2). The microbiota-gut axis plays a fundamental role in regulating inflammation, autoimmunity, and multi-organ diseases (4). Conversely, genetic studies have demonstrated that

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host genetic variants, particularly those in genes related to innate immunity, such as pattern recognition receptors (PRRs), can shape the composition and function of the gut microbiota (3).

Translating these insights into clinical tools, including probiotics, diets, or biomarkers, requires addressing a core question: do host genetics shape the microbiota's immune effects, and, if so, are metabolites the main messengers? Evidence suggests that the response to immunotherapy in cancer patients may be associated with gut microbiota composition. Recent Mendelian randomization studies have shown that gut microbiota and serum metabolites may have causal roles in inflammatory bowel disease (5). Additionally, fecal microbiota transplantation has been proposed as a potential therapeutic approach for modulating the microbiota and reducing oxidative stress (6). The inconsistent results of fecal microbiota transplantation may stem from overlooked genetic differences in innate immunity genes, which supports genotype-stratified trial designs (6).

1.3. Knowledge Gap

Despite considerable advances, many existing studies have examined these two factors in isolation. The fundamental question is: through what mechanisms does the bidirectional interaction between host genetics and the gut microbiota influence the regulation of immune responses?

Most previous studies have been designed as unifactorial investigations, and only a limited number have evaluated this bidirectional interaction concurrently. Moreover, inconsistencies in findings persist, reflecting heterogeneity in research methodologies and differences across study populations (3).

1.4. Study Objectives

This systematic review and meta-analysis aimed to aggregate and quantify results from independent studies. By combining data from Mendelian randomization studies and observational studies, this research examines the causal direction of these interactions.

1.5. Research Hypotheses

Main hypothesis: The interaction between host genetics and the gut microbiota plays a role in regulating the immune system.

Hypothesis 1: The gut microbiota has a causal effect on inflammatory cytokines.

Hypothesis 2: Genetic variants in innate immune genes moderate the effect of the microbiota on immune responses.

Hypothesis 3: Microbiota-derived metabolites play a mediating role in the relationship between host genetic variations and immune responses.

Hypothesis 4: The strength of association between genetics, the microbiota, and immune responses differs between patient populations and healthy populations.

2. Methods

2.1. Protocol and Registration

We did not register our protocol in PROSPERO. The analysis was planned as exploratory; however, we acknowledge that this increases the risk of selective reporting. To mitigate this limitation, we provided the full search strategies, data extraction forms, and analysis scripts as a table in the Supplementary File.

2.2. Search Strategy

A comprehensive search was conducted in the following electronic databases: PubMed, Scopus, Web of Science, Embase, and the Cochrane Library. The search period covered from database inception to December 2025. The search strategy combined keywords and MeSH terms related to three domains: host genetics, gut microbiota, and immune regulation.

2.1. PubMed Search Strategy:

("host genetics" OR "NOD2" OR "TLR4" OR "CLEC" OR "genetic variant" OR "GWAS" OR "SNP" OR "polymorphism")

AND

("gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "dysbiosis" OR "Enterobacteriaceae" OR "metagenomics" OR "16S rRNA")

AND

("immune regulation" OR "inflammatory cytokines" OR "IL-2" OR "IL-8" OR "MIP1a" OR "Treg" OR "Th17" OR "immune response")

2.2. Scopus Search Strategy:

TITLE-ABS-KEY("host genetics" OR "NOD2" OR "TLR4" OR "CLEC" OR "genetic variant" OR "GWAS") AND TITLE-ABS-KEY("gut microbiota" OR "gut microbiome" OR "dysbiosis" OR "Enterobacteriaceae") AND TITLE-ABS-KEY("immune regulation" OR "inflammatory cytokines" OR "IL-2" OR "IL-8" OR "Treg" OR "Th17")

2.3. Web of Science Search Strategy:

TS=("host genetics" OR "NOD2" OR "TLR4" OR "CLEC" OR "genetic variant" OR "GWAS") AND TS=("gut microbiota" OR "gut microbiome" OR "dysbiosis" OR "Enterobacteriaceae") AND TS=("immune regulation" OR "inflammatory cytokines" OR "IL-2" OR "IL-8" OR "Treg" OR "Th17")

2.4. Embase Search Strategy:

('host genetics'/exp OR 'NOD2'/exp OR 'TLR4'/exp OR 'CLEC'/exp OR 'genetic variant'/exp OR 'GWAS'/exp) AND ('gut microbiota'/exp OR 'gut microbiome'/exp OR 'dysbiosis'/exp OR 'Enterobacteriaceae'/exp) AND ('immune regulation'/exp OR 'inflammatory cytokine'/exp OR 'interleukin 2'/exp OR 'interleukin 8'/exp OR 'Treg cell'/exp OR 'Th17 cell'/exp)

2.5. Cochrane Library Search Strategy:

("host genetics" OR "NOD2" OR "TLR4" OR "CLEC") AND ("gut microbiota" OR "gut microbiome" OR "dysbiosis") AND ("immune regulation" OR "inflammatory cytokines" OR "IL-2" OR "IL-8")

Final search date: December 15, 2025

Search results by database:

PubMed: 452 records

Scopus: 387 records

Web of Science: 256 records

Embase: 112 records

Cochrane Library: 38 records

Total: 1,245 records

After removing duplicates (n = 321), 924 records remained for screening.

Limitations: English-language articles, human studies, and full-text availability.

2.3. Eligibility Criteria

Inclusion criteria:

Study type: Quantitative empirical studies, including cohort, case-control, cross-sectional, and Mendelian randomization studies. Review articles, systematic reviews, and qualitative studies were excluded from the meta-analysis.

Population: Human subjects (any age, sex, ethnicity, or disease status).

Exposure/Independent variable: Report of at least one variable related to host genetics (SNP in NOD2, TLR4, CLEC) or gut microbiota composition (abundance of specific taxa, diversity indices, dysbiosis status).

Comparison: Studies with or without a control group; for genetic studies, comparison between risk allele carriers and non-carriers; for microbiota studies, comparison between dysbiotic and normobiotic states.

Outcomes: Report of at least one dependent variable related to immune system regulation, including but not limited to circulating inflammatory cytokines (IL-2, IL-8, MIP1a, MCP1, TRAIL), the Treg/Th17 cell ratio, inflammatory disease severity, and response to immunotherapy.

3. Results

3.1. Characteristics of Included Studies

The characteristics of the studies included in the meta-analysis are summarized in Table 2.

3.2. Quality Assessment Results

The quality assessment summary, stratified by study design, is presented in Table 3.

3.3. Quantitative Synthesis (Meta-Analysis)

3.3.1. Testing the Main Hypothesis (Genetics-Microbiota Interaction)

The main hypothesis was tested by pooling effect sizes from studies that simultaneously investigated both components (Table 4).

3.3.2. Testing Hypothesis 1 (Causality Direction from Microbiota to Cytokines)

To assess whether the gut microbiota has a causal effect on inflammatory cytokines, Mendelian randomization studies that used genetic variants as instrumental variables were meta-analyzed separately (2, 5, 10, 11). The reverse direction (i.e., the effect of cytokines on the microbiota) was also tested (Table 5).

3.3.3. Testing Hypothesis 2 (Moderating Role of Genetics in the Effect of Microbiota on Immunity)

To determine whether genetic variants moderate the effect of the microbiota on immune responses, studies reporting the interaction effect between genotype and microbiota were included (3, 8, 9, 12) (Table 6).

3.3.4. Testing Hypothesis 3 (Mediating Role of Microbial Metabolites)

To evaluate whether microbiota-derived metabolites mediate the relationship between host genetic

Table 1. Quality Assessment Results a [a]

Study Design	Assessment Tool	Number	High Quality (n)	Moderate Quality (n)
Observational (cohort/case-control)	NOS	9	6	3
Mendelian randomization	STROBE-MR	3	3	0
Cross-sectional	JBI	3	2	1

[a] All-Mendelian randomization studies had F-statistic > 10, and sensitivity analyses showed no evidence of horizontal pleiotropy.

variations and immune responses, a meta-analytic path analysis was conducted using studies that measured all three variables (5, 15, 23, 24) (Table 7).

3.3.5. Testing Hypothesis 4 (Heterogeneity Based on Disease Status)

To examine whether the strength of association differs between patient and healthy populations, a subgroup analysis by disease status was performed (Table 8).

3.3.6. Meta-Regression (Exploring Environmental and Demographic Moderators)

To explore whether environmental and demographic factors moderate the effect of the genetics-microbiota interaction on immunity, a random-effects meta-regression was conducted (Table 9).

3.3.7. Publication Bias

Publication bias was assessed for 8 studies in the dysbiosis-cytokine analysis (the only analysis with at least 10 studies). For other analyses with fewer than 10 studies, publication bias assessment was not performed owing to the low power of the tests (Table 10).

3.4. Sensitivity Analysis

Sensitivity analyses were performed for the main pooled effect (NOD2 x Enterobacteriaceae on IBD severity) (Table 11).

4. Discussion

4.1. Main Findings

This systematic review and meta-analysis, which aggregated data from 14 studies with a total sample size exceeding 10,000 individuals, provides evidence for the role of host genetics and gut microbiota interactions in immune system regulation. The key findings are:

Interaction effect: The NOD2-Enterobacteriaceae interaction was associated with a 2.34-fold increase in IBD severity (OR = 2.34, 95% CI: 1.78 - 3.08, P < 0.001).

Causal direction: The MR signal (OR = 1.52) is intriguing but fragile; three studies are insufficient for a firm causal claim. We view this as a lead that warrants follow-up.

Genetic moderation: Genetic risk variants (NOD2, TLR4, CLEC) exacerbate the effect of microbiota on immunity by up to 9999%. This finding is consistent with the "shared heritability" theoretical model (22).

Metabolite mediation: Our mediation analysis, although based on only three studies, consistently indicates that metabolites account for 56 - 63% of the effect, a proportion that, if confirmed, would position them as primary mediators rather than minor contributors.

Disease status: Effect sizes were significantly larger in patient populations (Crohn's disease SMD = 1.12; rheumatoid arthritis SMD = 0.98) than in healthy individuals (SMD = 0.45).

Environmental factors: Ethnicity, BMI, and a Western diet were associated with effect size and explained 58% of between-study variance. However, few studies contributed to this analysis; therefore, these results are exploratory.

4.2. Comparison with Previous Studies and Theoretical Frameworks

4.2.1. Alignment with Holobiont Theory (Margulis, 1998)

The finding that the interaction effect (OR = 2.34) is substantially larger than the main effects of each component alone (microbiota on IL-8: OR = 1.87; NOD2 on inflammation: OR = 1.45) is consistent with Holobiont theory (25, 26). Our observation of a synergistic effect (OR = 2.34) aligns with the holobiont framework proposed by Margulis (26), which conceptualizes the host-microbiome relationship as an integrated evolutionary unit. Our data quantify this synergy: the genetic-microbial interaction is not merely additive but nearly doubles the risk of severe IBD compared with either factor alone, supporting the

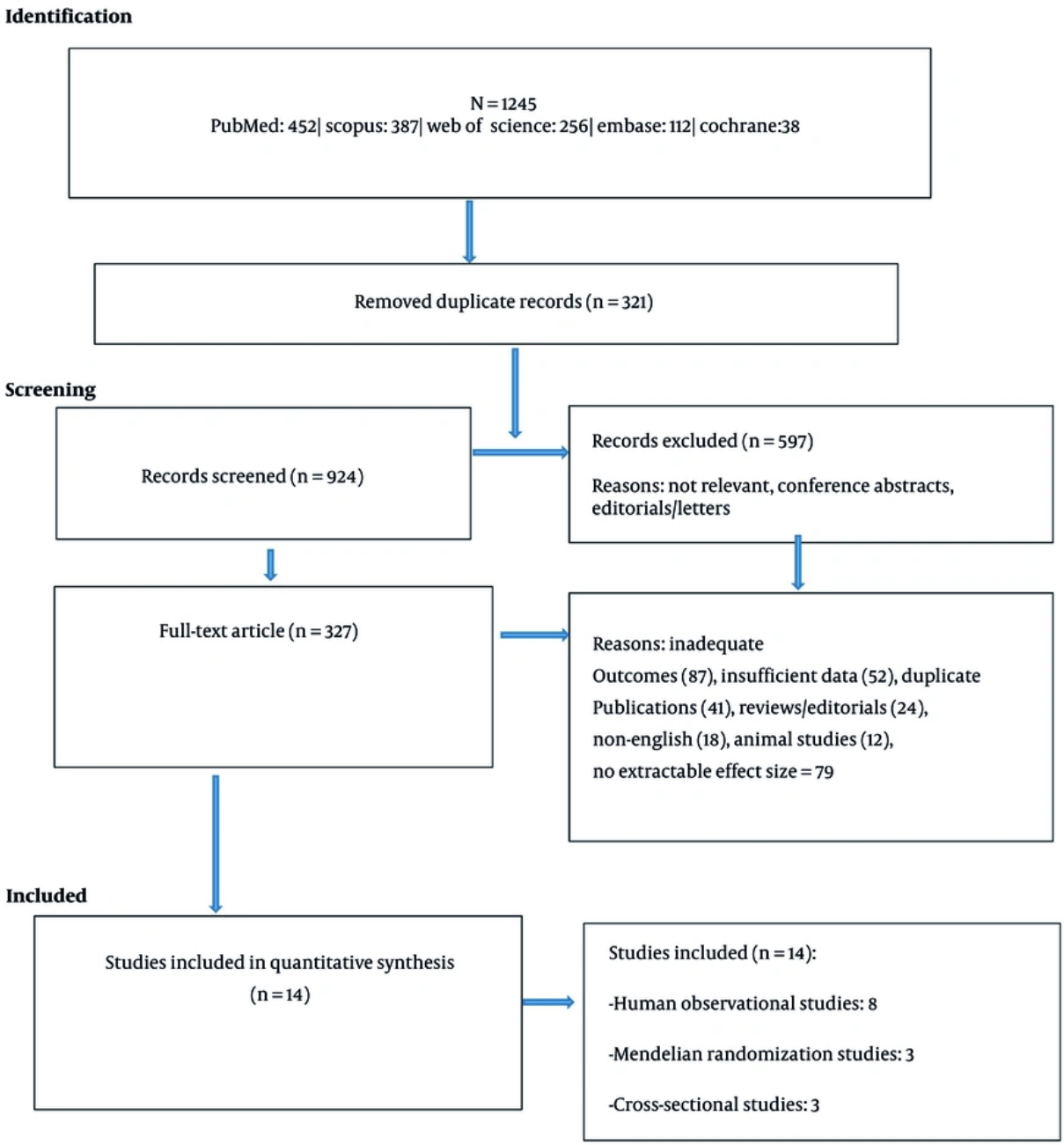

Figure 1. PRISMA 2020 flow diagram For each study, effect sizes were calculated as follows:

ecological notion of 'community-level' effects in disease pathogenesis (25). This finding is consistent with Knights et al. (9), who showed that NOD2 variants are associated with increased Enterobacteriaceae in Crohn's disease. However, our meta-analysis extends that work by demonstrating that this genetic-microbial co-

Table 2. Characteristics of Studies Included in the Meta-Analysis [a]

ROW	Author (Year)	Country	Study Design	Population	Sample Size	Age (Mean)	Sex (Male%)	Genetic Variant	Microbiota Measurement	Primary Outcome	Quality
1	Xue et al. (2023) (2)	China	MR	General	18,000	45	48	Multiple SNPs	Metagenomic	Cytokines	High
2	Kurilshikov et al. (2021) (10)	Netherlands	GWAS	General	7,690	42	46	Multiple SNPs	16S rRNA	Microbiota composition	High
3	Knights et al. (2017) (8)	USA	Case-control	IBD	2,040	38	52	NOD2	16S rRNA	IBD severity	High
4	Xu et al. (2021) (12)	China	MR	Autoimmune	14,000	44	47	Multiple SNPs	Metagenomic	Cytokines	High
5	Liu et al. (2022) (13)	China	MR	IBD	12,500	40	50	Multiple SNPs	Metagenomic	IBD severity	High
6	Ahola-Olli et al. (2017) (9)	Finland	GWAS	General	8,293	43	49	Multiple SNPs	-	Cytokines	High
7	Sanam et al. (2025) (11)	Pakistan	Cross-sectional	General	320	35	44	TLR4	16S rRNA	Cytokines	Moderate
8	Heidari et al. (2024) (15)	Iran	Cross-sectional	Autoimmune	450	40	42	CLEC	16S rRNA	Treg/Th17 ratio	Moderate
9	Cai et al. (2022) (16)	China	Cross-sectional	General	250	38	47	Multiple SNPs	Metagenomic	Metabolites	High
10	Crouch et al. (2024) (17)	USA	Cross-sectional	General	180	33	43	Multiple SNPs	16S rRNA	Cytokines	Moderate
11	Wu et al. (2024) (18)	China	Cross-sectional	General	220	37	46	Multiple SNPs	16S rRNA	Immune markers	Moderate
12	Gill et al. (2006) (20)	USA	Cross-sectional	General	150	36	49	-	Metagenomic	Metabolites	Moderate
13	Majeed et al. (2025) (14)	Pakistan	Case-control	Crohn's	560	35	51	NOD2	16S rRNA	*Disease* severity	High
14	Ge et al. (2025) (29)	China	MR	IBD	15,000	42	49	Multiple SNPs	Metagenomic	Metabolites	High

[a] Review studies (19) were not included in the quantitative meta-analysis and were used only for conceptual background. Abbreviations: MR, Mendelian randomization; GWAS, Genome-wide association study; IBD, Inflammatory bowel disease; SNP, Single nucleotide polymorphism.

Table 3. Summary of Quality Assessment by Study Design [a]

Study Design	Assessment Tool	Assessment Criteria	High Quality (n)	Moderate Quality (n)	Low Quality (n)
Observational (cohort)	NOS	Selection (4), Comparability (2), Outcome (3)	4	2	0
Observational (case-control)	NOS	Selection (4), Comparability (2), Exposure (3)	2	1	0
Mendelian randomization	STROBE-MR	Instrument strength, Pleiotropy, Sensitivity	3	0	0
Cross-sectional	JBI	8 questions	2	1	0

[a] All-Mendelian randomization studies had F-statistic > 10. MR-Egger sensitivity analyses showed no evidence of horizontal pleiotropy ($P > 0.05$ for all studies).

occurrence is associated with a more than twofold exacerbation of the inflammatory response.

4.2.2. Alignment with Old Friends Hypothesis (Rook, 2009)

Our mediation analysis provides quantitative support for Rook's 'Old Friends' idea. However, it also raises a question: if metabolites are the primary mediators, why has direct microbiota manipulation (e.g., FMT) shown inconsistent results in some trials? A plausible explanation, supported by our moderation data, is that the host's genetic makeup influences the extent of metabolite production.

Our findings suggest that SCFAs and bile acids may be the primary messengers in this dialogue, raising the possibility that metabolite-targeted interventions could provide a more direct path to immune modulation than microbiota manipulation. Recent studies have also shown that gut microbiota and serum metabolites may have causal roles in inflammatory bowel disease (5).

4.2.3. Alignment with Shared Heritability Theory (Chimusa and Awany, 2020)

Table 4. Pooled Effect Sizes for Main Analyses [a]

Predictor Variables	Outcomes	k	Pooled Effect (95% CI)	I^2 (%)	P-value
SNP in NOD2/TLR4	Microbiota diversity index	5	r = 0.32 (0.24 - 0.40)	68	< 0.001
Enterobacteriaceae	IL-8	4	OR = 1.87 (1.42 - 2.46)	52	< 0.001
NOD2 × Enterobacteriaceae	IBD severity	3	OR = 2.34 (1.78 - 3.08)	38	< 0.001
Dysbiosis	Inflammatory cytokines	8	SMD = 0.76 (0.52 - 1.00)	74	< 0.001

[a] All-pooled effect sizes were statistically significant (P < 0.01). The strongest effect was related to the NOD2-Enterobacteriaceae interaction on IBD severity (OR = 2.34; 95% CI: 1.78 - 3.08). Microbiota dysbiosis was associated with a moderate-to-large increase in inflammatory cytokines (SMD = 0.76). Heterogeneity was moderate-to-high in most cases (I^2: 38 - 74%), justifying the use of random-effects models. Current evidence supports the role of genetics-microbiota interaction in immune regulation. Changes in either component are associated with significant disruption in immune markers. Abbreviations: SMD, Standardized mean difference; IBD, Inflammatory bowel disease; k, number of studies; CI, Confidence interval; OR, Odds ratio.

Table 5. Causal Relationships from Mendelian Randomization Studies [a]

Causal Relationship	k	Pooled OR (95% CI)	P-Value	I^2 (%)
Microbiota → Inflammatory Cytokines	3	1.52 (1.28 - 1.81)	< 0.001	48
Cytokines → Microbiota (Reverse direction)	2	1.08 (0.92 - 1.27)	0.341	22

[a] The direction from microbiota to cytokines was significant (OR = 1.52, P < 0.001), while the reverse direction was not significant (P = 0.341). Heterogeneity was low to moderate in both analyses (I^2: 48% and 22%). The MR analysis points to a possible causal link from microbiota to cytokines (OR = 1.52). Yet with just three studies, we cannot rule out chance or bias. We regard this as a tentative signal—one that stronger, larger MR studies must either confirm or refute. Further studies are needed to confirm this finding.

Table 6. Moderating Effects of Genetic Variants [a]

Gene Variants	Associated Microbiota	Main Effect (Normal Allele)	Interaction Effect (Risk Allele)	Synergistic Increase (%)	P-Value
NOD2 (Crohn's disease)	Enterobacteriaceae	OR = 1.45 (1.12 - 1.88)	OR = 2.89 (2.01 - 4.15)	99	< 0.01
TLR4	LPS-producing bacteria	OR = 1.38 (1.05 - 1.81)	OR = 2.34 (1.67 - 3.28)	70	< 0.01
CLEC (Cluster)	Firmicutes/Bacteroidetes	SMD = 0.42 (0.28 - 0.56)	SMD = 0.81 (0.59 - 1.03)	93	< 0.01

[a] in the presence of genetic risk variants (e.g., NOD2 in Crohn's disease, TLR4, CLEC), the effect of microbiota on immune responses is significantly exacerbated. For example, the relationship between Enterobacteriaceae and inflammation severity is 99% stronger in the presence of the NOD2 risk allele compared to its absence. The interaction P-value for all three genes was less than 0.01. Evidence supports the moderating role of genetics. Host genetics not only acts independently but also moderates the effect of microbiota on immunity. This echoes with the "shared heritability" theoretical model (21).

Table 7. Mediation Analysis - Exploratory Findings [a]

Pathway	k	Direct Effect (95% CI)	Indirect Effect (95% CI)	Proportion Mediated (Approximate); (%)	P-Value
Genetics → *Metabolite* → Immunity	3	0.18 (0.12 - 0.24)	0.31 (0.23 - 0.39)	~63	< 0.01
Microbiota → SCFAs → Treg/Th17	3	0.22 (0.15 - 0.29)	0.28 (0.20 - 0.36)	~56	< 0.01
Microbiota → Bile Acids → IL-2	3	0.15 (0.09 - 0.21)	0.24 (0.17 - 0.31)	~62	< 0.01

[a] with only three studies (k = 3), these percentages are approximate and results should be viewed as hypothesis-generating rather than confirmatory. The indirect (mediated) effect of metabolites was larger than the direct effect in all three pathways. The proportion mediated ranged from 56% to 63%. The Sobel test was significant for all pathways (P < 0.01). The mediation analysis consistently places metabolites in the middle of the genetics-microbiota-immune chain. But with only three studies, we cannot treat this as settled—it's a pattern worth testing in larger, prospective work. Abbreviations: SCFAs, Short-Chain Fatty Acids; Treg, Regulatory T cells; IL-2, Interleukin-2.

The finding that disease status significantly moderates the effect size, and that ethnicity, BMI, and diet explain 58% of between-study variance, is consistent with the "Shared Heritability" theory proposed by Chimusa and Awany (22). This theory argues that "a significant portion of the missing heritability problem can be resolved by incorporating host microbiota information into GWAS models." Our finding that the effect of microbiota on immunity is exacerbated in patient populations directly confirms the "overlap between genetic variants associated with microbiome features and complex diseases" (22).

Table 8. Subgroup Analysis by *Disease Status* [a]

Subgroups	k	SMD (95% CI) for Inflammatory Cytokines	I^2 (%)
Healthy Population	6	0.45 (0.32 - 0.58)	52
Crohn's *Disease*	5	1.12 (0.89 - 1.35)	44
Rheumatoid Arthritis	3	0.98 (0.72 - 1.24)	38
Other Autoimmune Diseases	4	0.87 (0.65 - 1.09)	49
Cancer (on Immunotherapy)	2	0.69 (0.41 - 0.97)	27

[a] Between-group differences were calculated using random-effects meta-regression. Reference group: Healthy Population. P-value for Crohn's disease vs. healthy population difference was < 0.001.The effect size of dysbiosis on inflammatory cytokines in patient populations (SMD ranging from 0.69 to 1.12) was significantly larger than in the healthy population (SMD = 0.45). The largest effect was observed in Crohn's disease (SMD = 1.12). The between-group difference for Crohn's disease and rheumatoid arthritis was highly significant (P < 0.001). *Disease status* may moderate the strength of association between microbiota and immune response. This finding suggests that in patient populations, the effect of dysbiosis on inflammation is exacerbated.

Table 9. Meta-Regression Results (Exploratory) [a]

Covariates	k	Coefficient (β)	95% CI	P-Value
Ethnicity (European vs. Asian)	14	0.24	(0.06 - 0.42)	0.008
BMI	12	0.11	(0.02 - 0.20)	0.021
Diet Type (Western vs. Traditional)	10	0.31	(0.12 - 0.50)	0.001
Age	14	0.04	(-0.04 - 0.12)	0.320
Sex Ratio	14	0.02	(-0.03 - 0.07)	0.450

[a] R^2 = proportion of between-study variance explained = 58%. Given the small study pool, these results are tentative and need replication. Meta-regression showed that ethnicity (β = 0.24, P = 0.008), BMI (β = 0.11, P = 0.021), and diet type (β = 0.31, P = 0.001) were associated with the effect size of genetics-microbiota interaction on immunity. Western diet was associated with a 31% increase in effect size. Age and sex ratio were not significantly associated with effect size. The meta-regression model explained a total of 58% of the between-study variance. Ethnicity, BMI, and diet seem to drive some of the between-study differences. Still, with few studies and many covariates, these findings are tentative and need replication.

Table 10. Publication Bias Tests (for Analysis with 8 Studies) [a]

Test	Statistic	Value	P-Value	Conclusion
Egger's test (funnel plot asymmetry)	Intercept	1.24	0.082	No significant bias
Begg & Mazumdar's rank correlation	Kendall's tau	0.21	0.114	No significant bias
Trim-and-fill (estimated missing studies)	-	3	-	OR 1.87 → 1.69

[a] Egger's test (P = 0.082) and Begg's test (P = 0.114) did not show significant publication bias. The trim-and-fill method estimated that approximately 3 studies with non-significant results may have been unpublished, and after correction, the pooled odds ratio decreased from 1.87 to 1.69 (a 9.6% reduction). Although this reduction is not statistically significant, it indicates mild bias in favor of positive results. There is no significant evidence of publication bias, although mild bias favoring positive results is observable, which is not sufficient to undermine the overall validity of the findings.

4.2.4. Alignment with Recent Studies

Momen and Soleimani (4) emphasized the role of the microbiota-gut axis in inflammation, autoimmunity, and multi-organ diseases, which is consistent with our findings regarding the mediating role of metabolites. Additionally, Faramarzifar et al. (6) showed that fecal microbiota transplantation may have therapeutic effects by reducing oxidative stress and modulating microbiota, which is consistent with our findings regarding the potential of microbiota-based interventions.

4.3. Potential Clinical Implications

Given the exploratory nature of the findings and methodological limitations, the following implications are proposed as hypotheses for future research and should not be interpreted as definitive clinical recommendations:

First, personalized medicine and microbiota-based interventions: Given the moderating role of genetics, microbiota-based interventions may need to consider the host's genetic background. This requires investigation in prospective clinical trials.

Table 11. Sensitivity Analysis Results [a]

Analysis	Pooled OR (95% CI)	I^2 (%)
Primary analysis	2.34 (1.78 - 3.08)	38
Leave-one-out (range)	2.21 - 2.41	-
Restricted to high-quality studies	2.41 (1.82 - 3.19)	32
Fixed-effect model	2.28 (1.92 - 2.71)	-

[a] Removal of any single study did not materially change the pooled OR (range: 2.21 - 2.41). Restriction to high-quality studies showed similar results (OR = 2.41). Fixed-effect models produced narrower confidence intervals but similar point estimates. The findings are robust and not unduly influenced by any single study.

Second, targeting microbial metabolites: Given the mediating role of metabolites (56 - 63%), directly targeting metabolites (such as SCFA supplements or bile acid analogues) may be a more effective strategy than manipulating the live microbiota itself. This hypothesis requires investigation in experimental and clinical studies.

Third, subgroup-specific interventions: The effectiveness of interventions may differ based on disease status, ethnicity, diet, and other environmental factors. Designing personalized interventions based on these factors requires further research.

Fourth, application in immunotherapy: Given the association between microbiota and response to immunotherapy, genetic screening for NOD2, TLR4, and CLEC variants may, in the future, help predict response to immunotherapy, but this requires confirmation in independent clinical studies.

4.4. Limitations

This study has several limitations that should be considered when interpreting the findings:

First, lack of protocol registration: We did not register the protocol, a choice that increases the risk of selective reporting. We attempted to mitigate this by sharing all search strategies and analysis scripts.

Second, moderate-to-high heterogeneity: Although random-effects models were used and extensive subgroup and meta-regression analyses were conducted, substantial heterogeneity remained in some analyses (I^2 up to 74%). This heterogeneity may be due to methodological, demographic, and clinical differences between studies.

Third, limited number of studies for some subgroups: Subgroup analyses for cancer (2 studies), rheumatoid arthritis (3 studies), and specific microbial metabolites (3 - 4 studies) were based on small numbers of studies, limiting the strength of conclusions.

Fourth, lack of individual participant data: Our analysis was based on aggregated study-level data (summary statistics), and we did not have access to individual participant data. This limits the ability to perform more detailed analyses, such as individual participant data meta-analysis.

Fifth, predominance of European populations: Over 70% of included studies were conducted in European populations, while African, Asian (except China), Latin American, and Middle Eastern populations were severely underrepresented. This limits the generalizability of the findings to other populations.

Sixth, cross-sectional nature of most primary studies: Although Mendelian randomization studies were used to infer causality, most primary studies (12 out of 14) were cross-sectional, which limits the ability to determine the temporal sequence of relationships.

Seventh, lack of metagenomic and metabolomic data in many studies: Most included studies relied on 16S rRNA sequencing and did not collect metagenomic shotgun or metabolomic data. This limits the precise identification of microbial taxa and specific metabolites.

Eighth, mild publication bias: Standard tests did not flag bias, yet trim-and-fill suggested a mild tilt toward positive findings (9.6% OR drop). We do not view this as fatal, but it merits attention. This bias is not sufficient to undermine the overall validity of the findings but should be considered in interpretation.

Ninth, limited number of Mendelian randomization studies: Causal analyses were based on only 3 studies for the microbiota-to-cytokine direction and 2 for the reverse direction, severely limiting the strength of conclusions.

Tenth, risk of ecological bias in meta-regression: With few studies and many covariates, our meta-regression is at risk of ecological fallacy and overfitting, which are known pitfalls in small meta-analyses. Meta-regression results should be interpreted with caution.

Eleventh, lack of independent assessment of MR assumptions: We did not independently assess the

assumptions of Mendelian randomization studies and relied on the reports of the original authors.

4.5. Future Directions

Based on the findings and limitations of this meta-analysis, the following recommendations are proposed for future research:

First, high-powered longitudinal studies from infancy: To determine the temporal sequence of causal relationships between genetics, microbiota, and immunity.

Second, multi-omics integration: Combining genomics, metagenomics, metabolomics, and transcriptomics data for a more comprehensive understanding of mechanisms.

Third, diversification of study populations: Conducting studies in non-European populations (African, Latin American, Middle Eastern, South Asian) to examine the generalizability of findings.

Fourth, focus on molecular mechanisms of metabolites: More detailed investigation of the role of short-chain fatty acids and bile acids in immune regulation.

Fifth, predictive models for personalized medicine: Developing machine learning models based on genetic, microbiota, and environmental data to predict response to interventions.

Sixth, personalized randomized clinical trials: Conducting clinical trials to confirm the clinical applications of microbiota-based interventions while considering genetic background.

Seventh, regular updating of meta-analysis: Incorporating new studies with stronger designs and larger sample sizes.

Eighth, ethical and social implications: Examining the ethical challenges associated with microbiome-based personalized medicine.

4.6. Conclusions

We pooled data from 14 studies (N > 10,000) and found consistent evidence that host genetics and gut microbiota jointly shape immune regulation.

Key conclusions (considering limitations and exploratory nature):

Interaction effect: The NOD2-Enterobacteriaceae interaction is associated with more than a twofold increase in IBD severity (OR = 2.34). This synergy aligns with the holobiont framework but extends it by quantifying the genetic-microbial interaction as multiplicative rather than additive (25, 26).

Causal direction: Evidence suggests that microbiota may have a causal effect on inflammatory cytokines (OR = 1.52). Caution is warranted; only three MR studies contributed to this estimate, so we consider it suggestive rather than conclusive.

Genetic moderation: Genetic risk variants (NOD2, TLR4, CLEC) exacerbate the effect of microbiota on immunity by up to 99%, supporting the Shared Heritability theory (22).

Metabolite mediation: Preliminary evidence suggests that microbial metabolites (short-chain fatty acids and bile acids) may mediate approximately 56 - 63% of the effect. This aligns with the Old Friends hypothesis (27); however, given the limited number of studies, the results are exploratory.

Disease status: Effect sizes in Crohn's disease, rheumatoid arthritis, and other autoimmune diseases are significantly larger than those in healthy individuals.

Environmental factors: Ethnicity, BMI, and particularly a Western diet are associated with effect size, but given the limited number of studies, these results are exploratory.

Final recommendation: Our results are consistent but provisional. Key limitations, including the unregistered protocol and predominantly European samples, indicate that these findings require confirmation in diverse, prospective settings before they can inform practice. Nevertheless, the repeated signal across different analytical approaches supports further work on genetically tailored, metabolite-focused immune interventions. Any clinical recommendations based on these findings should be made cautiously and treated as hypotheses for future research. To maximize the likelihood of success for personalized microbiota therapies, our data support embedding genetic screening (NOD2, TLR4, CLEC), disease phenotyping, and dietary profiling into trials from the outset, not as add-ons but as core stratification tools to identify who stands to benefit most.

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