GLAND SURGERY

REPROGRAMMING IMMUNITY: A META-ANALYSIS OF LIFESTYLE, NUTRITION, AND MICROBIOME INTERVENTIONS

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Abstract

Chronic low-grade inflammation is implicated in the pathogenesis of metabolic, cardiovascular, renal, and age-related diseases. Non-pharmacologic interventions-spanning lifestyle modification, nutritional strategies, and microbiome-directed therapies-have been proposed as upstream modulators of inflammatory physiology, yet cross-domain quantitative syntheses remain scarce. This systematic review and meta-analysis evaluated whether lifestyle, nutrition, microbiome-directed, and hybrid interventions reduce circulating inflammatory biomarkers relative to control conditions in adult populations. A systematic search of PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL (January 2011–April 2026) identified randomized or controlled intervention studies reporting C-reactive protein (CRP/hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), or lipopolysaccharide (LPS) endpoints. Fifteen studies met strict eligibility criteria. Random-effects meta-analyses were conducted using Hedges' g with inverse-variance weighting. All four biomarker families showed pooled effects favoring intervention. CRP/hs-CRP yielded the most robust estimate ($k = 11$; Hedges' $g = -0.51$, 95% CI [−0.81, −0.20]; $I^2 = 73.4\%$). IL-6 ($k = 6$; $g = -1.76$, 95% CI [−3.18, −0.33]; $I^2 = 96.3\%$), TNF-α ($k = 4$; $g = -1.50$, 95% CI [−2.61, −0.38]; $I^2 = 91.2\%$), and LPS ($k = 2$; $g = -0.75$, 95% CI [−1.45, −0.04]; $I^2 = 68.0\%$) showed large effects with considerable heterogeneity. Microbiome-directed interventions constituted the dominant evidence base. Non-pharmacologic interventions are associated with reduced inflammatory biomarker burden in adults, with the most stable evidence for CRP-family outcomes. These findings support a biomarker-centered interpretation of immune recalibration and highlight the need for domain-balanced trials with standardized inflammatory outcome reporting.

Keywords: meta-analysis, inflammation, C-reactive protein, microbiome, probiotics, lifestyle interventions, nutrition, immunomodulation, systematic review

1. Introduction

1.1 Immune Dysregulation as a Chronic Disease Substrate

Low-grade systemic inflammation over time has proved a common pathophysiological substrate behind a wide range of non-communicable diseases, such as type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, non-alcoholic fatty liver disease, obesity, and age-related cognitive decline (Furman et al., 2019; Hotamisligil, 20 Chronic inflammation is in contrast to acute inflammatory reactions, which dissipate after pathogen elimination or tissue repair, and is marked by sustained elevation of circulating pro-inflammatory mediators-such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha)-that persist in maintaining endothelial This chronic inflammatory condition frequently serves as a prognostic biomarker and a promising therapeutic target as it usually preclinically nears disease by decades. Notably, there is a growing body of evidence that suggests that non-pharmacologic interventions have the potential to change inflammatory physiology even before the onset of overt disease progression and provide complementary or adjunctive approaches to standard pharmacotherapy (Calder et al., 2017).

1.2 Defining “Reprogramming Immunity”

The reprogramming immunity concept needs to be strictly operationally defined to ensure rigor in science. The term is not used in the present review to refer to the general immune amplification or excessive stimulation of immune. Instead, it is a more precise definition of recalibration of chronic inflammatory signaling and hostenvironment immune regulation- a quantifiable change in the ratio of proinflammatory and antiinflammatory mediators which can be measured using validated circulating biomarkers. This is a crucial difference: there is a stronger evidence base to non-pharmacologic immune modulation to reduce inflammatory biomarkers, rather than completely remodel the immune phenotype. Formulating the notion in the context of biomarker-level recalibration safeguards the synthesis of overclaiming the synthesis and maintaining the mechanistic plausibility of the reviewed interventions.

1.3 Three Intervention Domains, One Biological Network

The three large areas of intervention have been tested on the ability to tune the chronic inflammatory signaling in adults. To begin with, interventions based on lifestyle, such as mindfulness meditation, acceptance-based psychological therapies, and structured physical activity programs, act more or less via neuroendocrine and autonomic mechanisms, regulating reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, sympathovagal balance, and stress-induced cytokine release (Black and Slavich, 2016 Second, nutritional interventions-including Mediterranean dietary patterns, caloric restriction, and protein-modified dietary plans-mechanisms of immunometabolic regulation; such as decreased adipose tissue inflammation and enhanced insulin sensitivity and modified substrate availability to activate immune cells (Christ et al., 2019). Third, microbiome-guided interventions-such as probiotics, synbiotics and fermented food interventions-operate via the gut-immune axis by enhancing intestinal barrier performance, lowering endotoxemia in the body, and altering host-microbe signaling pathways (Belkaid and Hand, 2014). Hybrid interventions are based on the elements of several of the domains and can involve either additive or synergistic upstream processes. Although the three domains have different direct pathways, they all lead to a common downstream result of acting to regulate low-grade systemic inflammation.

1.4 Biomarkers as the Measurable Bridge

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The current meta-analysis bases its quantitative synthesis on four main families of inflammatory biomarkers such as CRP/hs-CRP, IL-6, TNF-alpha, and LPS/endotoxin. CRP is a hepatically-produced acute-phase reactant that is the most commonly reported and clinically validated risk stratification reactant in cardiovascular risk (Ridker, 2016). One of the most important roles in the pathophysiology of hepatic CRP production is played by IL-6, which is both a pleiotropic cytokine and a key mediator of the synthesis of this potent cytokine. TNF-alpha is an upstream pro-inflammatory cytokine that is involved in the inflammation and insulin resistance of adipose tissue. LPS is a gram-negative bacterial cell wall component that is a mechanistically unique biomarker of gut barrier permeability and microbial translocation. Fecal calprotectin: Fecal calprotectin was left as a second mucosal marker to narrative synthesis. The data is best suited to the inflammatory burden as opposed to complete immune phenotyping.

1.5 Gap in the Literature

Although there is an increasing focus on non-pharmacologic immune modulation, the current evidence base is fragmented in single-domain reviews that seldom combine lifestyle, nutritional, and microbiome-directed interventions in a common analytical framework. Observational evidence and intervention evidence are often mixed, reporting of biomarkers is often inconsistent and limited quantitative syntheses have tried to compare across domains using standardized measures of effect size. The comparative role of each of the domains of intervention in the decrease of inflammatory biomarkers has not been assessed in a single meta-analysis (Minihane et al., 2015).

1.6 Objective and Hypotheses

The primary objective of this systematic review and meta-analysis is to evaluate whether lifestyle, nutrition, microbiome-directed, and hybrid interventions reduce inflammatory biomarker concentrations relative to control conditions in adult populations. Three a priori hypotheses guided the analysis: (a) pooled interventions will demonstrate a statistically significant reduction in inflammatory biomarker burden; (b) the strongest pooled signal will emerge for CRP-family outcomes; and (c) microbiome-directed studies will dominate both numerically and quantitatively within the strict evidence set.

2. Literature Review

2.1 Lifestyle Interventions and Neuroimmune Modulation

Psychological stress and chronic inflammation have well-described neuroendocrine mechanisms of interaction, specifically the HPA axis and the sympathetic–adrenal–medullary axis (Dhabhar, 2014). Sustained stress increases the cortisol in an unregulated manner that ironically enhances the expression of pro-inflammatory genes via the glucocorticoid resistance mechanisms (Cohen et al., 2012). Mind body interventions, such as mindfulness-based stress reduction, acceptance and commitment therapy and structured meditation, have been postulated to re-establish autonomic and to inhibit stress-induced inflammatory signalling. Systematic reviews have found small but significant decreases in CRP and IL-6 of mindfulness-based interventions (Bower and Irwin, 2016), although the effect sizes tend to disappear in controlled trials. The current data set has lifestyle interventions addressing psychological stress (Villalba et al., 2019), mild cognitive impairment (Ng et al., 2020), and end-stage renal disease (Alhawatmeh et al., 2024), which are clinically different settings where neuroimmune modulation has been studied.

2.2 Nutrition Interventions and Immunometabolic Recalibration

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Interventions based on dietary patterns regulate inflammatory signaling in a variety of immunometabolic pathways, such as decrease of visceral adiposity, enhancement of insulin sensitivity, regulation of oxidative stress, and change of substrate availability to activate immune cells (Christ et al., 2019). The biggest empirical evidence has been on the Mediterranean dietary pattern, showing the decreases of CRP, IL-6, and endothelial adhesion molecules in high-cardiovascular-risk populations when randomized (Estruch et al., 2018). Anti-inflammatory effects of polyphenols and monounsaturated fatty acids and dietary fiber are described as mechanistically based on their ability to inhibit the activation of NF-kB and stimulate anti-inflammatory production of eicosanoids (Schwingshackl and Hoffmann, 2014). The current amount of data contains a Mediterranean diet trial (Casas et al., 2014) and a protein-modified comparison in morbid obesity (Koelman et al., 2020).

2.3 Microbiome Interventions and Gut–Immune Signaling

The gut flora has a tremendous effect on systemic immune activity in three main ways: preservation of intestinal barrier integrity, control of short-chain fatty acid synthesis, and control of innate and adaptive immune responses at the mucosal interface (Belkaid and Hand, 2014). Dysbiosis-associated with a decrease in microbial diversity and pathobiont expansion-impaires the barrier function and allows translocation of bacterial endotoxin (LPS) into the systemic circulation, leading to inflammatory cascades controlled by TLR4 that elevate TNF-alpha, IL-6, and CRP (Cani et al., 2007). This endotoxemia of the metabolism has been found to be a contributory factor in inflammation associated with obesity, insulin resistance and cardiovascular risk. Probiotic interventions intend to regulate the microbial homeostasis through the introduction of useful strains that strengthen the tight junctional protein expression, murk out pathogenic organisms in their adhesion sites as well as create anti-inflammatory metabolites such as butyrate and propionate.

The prevalence of microbiome-guided interventions in the current dataset-eight of 15 studies and one microbiome/nutrition crossover-is indicative of the tremendous growth of clinical trial activity in this field in the last 10 years. The studies included have a wide range of clinical populations: type 2 diabetes (Chaithanya, 2025; Toejing et al., 2021; Mohamadshahi et al., 2014), hypercholesterolemia (Chaiyasut et al., 2021), peritoneal dialysis (Pan et al., 2021), NAFLD LPS is a mechanistically useful biomarker as it is a direct index of gut barrier permeability, and gives a proximal estimate of the microbiomeinflammation axis as opposed to a downstream acute-phase response. The clinical heterogeneity of these populations-including metabolically impaired groups of diabetic patients to otherwise healthy elderly with age-related inflammatory drift-is both an analytic richness and interpretive complexity to the current synthesis.

2.4 Rationale for Cross-Domain Synthesis

Although the three domains of intervention act via different proximal mechanisms, they all drive to the same goal of inflammatory control of chronic low-grade. The nodes of an immune regulatory network are neuroimmune, immunometabolic, and gut -immune pathways, which are interconnected (Dantzer et al., 2008). A cross-domain framework allows direct comparison of intervention efficacy based on standardized biomarker-level outcomes, which fills a critical gap where single-domain reviews have produced valuable evidence which, however, is compartmentalised.

The evidence base is limited by several gaps: the over-dependence of CRP-family markers to define the immune characterization depth; the small size of subgroups not subjected to microbiome interventions restricts domain-specific pooling; the variability of biomarker reporting formats makes

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harmonization difficult; the biomarker shifts in themselves as proxies of full immune remodeling are inherently limited.

3. Methods

3.1 Study Design and Reporting Framework

This study was conducted as a systematic review and meta-analysis following PRISMA 2020 guidelines (Page et al., 2021).

3.2 Eligibility Criteria

The requirements to be eligible were designed as per the PICOS. Participants were adults (18 years or older) with clinically defined and at-risk populations. The valid interventions included in four categories, namely, lifestyle (mindfulness meditation, acceptance-based therapies, structured exercise), nutrition (Mediterranean dietary patterns, protein-modified diets), microbiome-directed (probiotics, synbiotics, fermented food strategies), and hybrid interventions. Placebo, usual care, monitoring-only and active dietary comparators were used as comparators. The main results were CRP/hs-CRP, IL-6, TNF-a and LPS/endotoxin. Secondary outcomes were fecal calprotectin and other inflammatory markers directly reported. The only designs eligible were randomized controlled trials and controlled intervention studies. Observational studies, case reports, reviews and conference abstracts were excluded.

3.3 Information Sources and Search Strategy

Systematic searches were conducted across PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, and Cochrane CENTRAL, spanning January 1, 2011 through April 7, 2026. Supplementary searching included ClinicalTrials.gov and backward reference-list review. The strategy combined three conceptual blocks: (a) immune/inflammatory terms (immun*, inflamm*, CRP, hs-CRP, IL-6, TNF, cytokine*, endotoxin, LPS, calprotectin); (b) intervention terms covering all four domains; and (c) population/design filters restricting to adult human intervention studies.

3.4 Study Selection

The process of study selection was based on a stringent inclusion philosophy giving priority to experimental evidence that reported outcome of quantitative inflammatory biomarkers. The records found in databases and additional techniques were deduplicated with automated reference management software, with the rest of the potential duplicates being checked manually. Screening of Title and abstract was carried out independently and the ambiguous records were retained to undergo a full-text evaluation. The PICOS criteria above were used to conduct full-text eligibility assessment. Inclusions Studies were not included when they had only reported observational or cross-sectional associations, but an experimental manipulation was not done, when they had only quantitative data of biomarkers of immunity and had only pediatric or adolescent populations, or where the only endpoints of interest were mucosal or oral immunity and no systemic inflammatory markers were reported. Articles whose results included composite scores of immune values without the individual biomarker values were also filtered out unless one of the main biomarkers could be singled out. The last tight list of studies consisted of 15 studies that fulfilled all the eligibility requirements.

3.5 Data Extraction

A standardized form was used to extract data including: study ID, first author/year, intervention domain, intervention type, comparator, population/condition, study design, duration, biomarker

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outcomes, sample sizes, baseline and post-intervention means with dispersion, change scores, adjusted effect estimates with confidence intervals and notes. All the data were inputted in a structured workbook and matched with source publications.

3.6 Outcome Hierarchy and Biomarker Harmonization

A pre-specified hierarchy guided primary biomarker selection: (1) CRP/hs-CRP, (2) IL-6, (3) TNF-α, (4) LPS/endotoxin. Hedges' g was computed for cross-study comparison. Negative standardized effects favored intervention (lower inflammatory burden). CRP and hs-CRP were combined as a CRP-family outcome when using standardized effects.

3.7 Direct-Data Versus Sensitivity-Only Set

The primary direct-data synthesis included studies with raw post-intervention means or change-score means with appropriate dispersion measures. The sensitivity-only set comprised adjusted-only estimates (Raygan et al., 2018), transformed-scale outputs (Ng et al., 2020), median/IQR conversions (Lazou-Ahrén et al., 2025), secondary dose arms (Szulinska low-dose), and active-comparator complications (Koelman et al., 2020). This two-tier approach enhances transparency and protects primary estimates from methodological heterogeneity.

3.8 Statistical Analysis

DerSimonian-Laird estimator of between-study variance was used to perform random-effects meta-analyses, with a standardized meta-analytic workflow. Hedges g was the primary effect measure, a bias-corrected standardized difference between means that is recommended instead of Cohen's d in studies with small sample sizes since this measure uses a correction factor that decreases the upward bias in estimating the effects size. The combination of effect sizes was done with inverse-variance weighting, with weight being proportionately more in the pooled estimate of smaller studies (which have smaller standard errors). Three complementary measures of statistical heterogeneity were used: the I 2 statistic which is the percentage of total variability which can be attributed to between-study differences but not to sampling error, tau 2 which is an estimate of absolute between-study variance, and Cochran Q which is a formal test of whether there is any heterogeneity.

Biomarker family (CRP/hs-CRP, IL-6, TNF-alpha, LPS) subgroup analyses were performed. Pre-defined sensitivity analyses involved: (a) omission of adjusted-only effect measures to test the strength of the main synthesis; (b) omission of median/IQR-converted studies which assume distributional properties; (c) omission of active-comparator complications; (d) omission of CRP-family outcomes only to test the most clinically established biomarker. Where comparisons with a common control group were made in multiple studies- such as Makiel et al. (2025) with exercise-only and exercise-plus-diet with a common control group sharing a single control-control group sample- the sample sizes were divided in proportion to prevent artificial inflation of the effective sample size and to make the contribution effect sizes statistically independent. In the case of Casas et al. (2014), where there were over one arm of Mediterranean diet interventions versus a typical low-fat control, the active arms were summed in every biomarker analysis such that the trial would provide one independent comparison to the summative estimate.

4. Results

4.1 Study Selection

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The systematic search identified 1,620 records from database searching and 20 from supplementary methods (N = 1,640). Following removal of 480 duplicates, 1,160 records were screened by title and abstract, 978 were excluded, and 182 reports were sought for retrieval. Eight could not be retrieved, leaving 174 assessed for eligibility. After strict criteria application, 159 were excluded and 15 studies were retained (Figure 1).

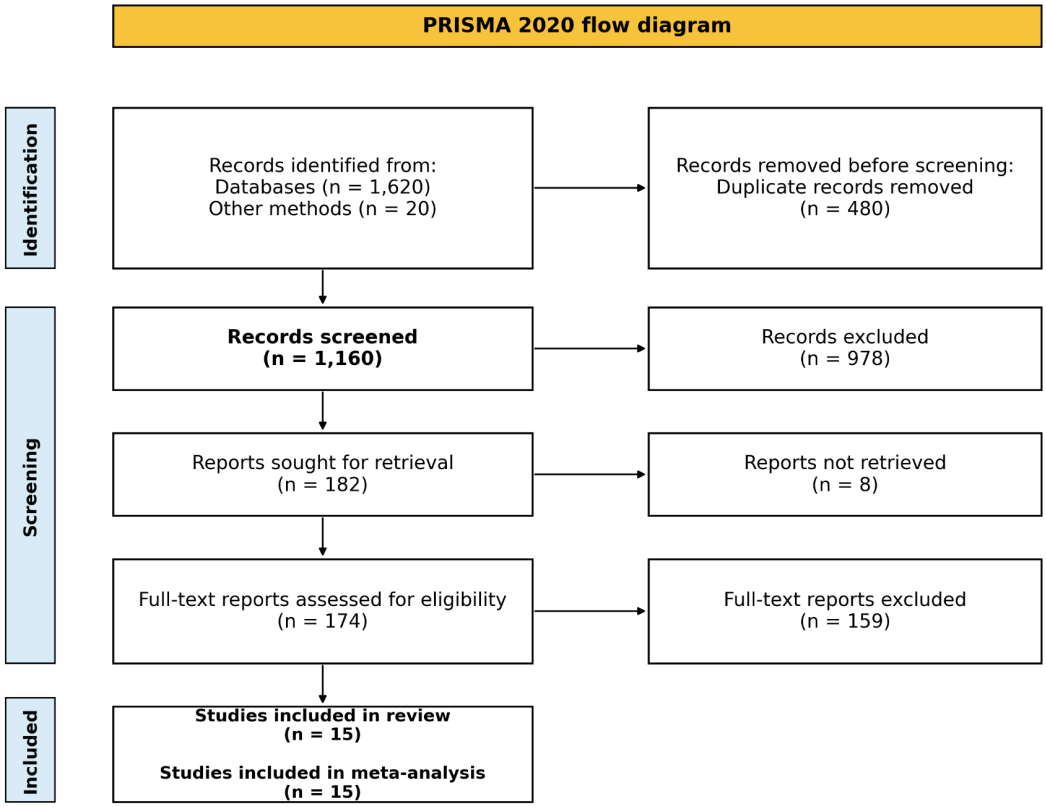

Figure 1. *PRISMA 2020 flow diagram summarizing study identification, screening, eligibility assessment, and final inclusion.*

4.2 Characteristics of Included Studies

The 15 included studies (Table 1) were published between 2014 and 2025, enrolled diverse adult populations across multiple countries, and were predominantly randomized and placebo controlled. Intervention duration ranged from 3 weeks to 12 months, with a median near 12 weeks. Sample sizes ranged from 22 to 164 participants. The evidence base was weighted toward microbiome-directed interventions (k = 8 plus one microbiome/nutrition crossover), with smaller lifestyle, nutrition, and hybrid subsets.

4.3 Biomarker Coverage and Evidence Distribution

CRP/hs-CRP was the most frequently reported biomarker (k = 11 effect sizes from 10 studies). IL-6 contributed six estimates from five studies; TNF-alpha four estimates from four studies; and LPS two estimates from two studies. CRP-family outcomes provided the deepest cross-domain coverage, whereas cytokine and endotoxin estimates were concentrated within microbiome studies. Figure 2 summarizes the imbalance in study distribution across intervention domains, and Figure 3 maps

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biomarker coverage across the included studies.

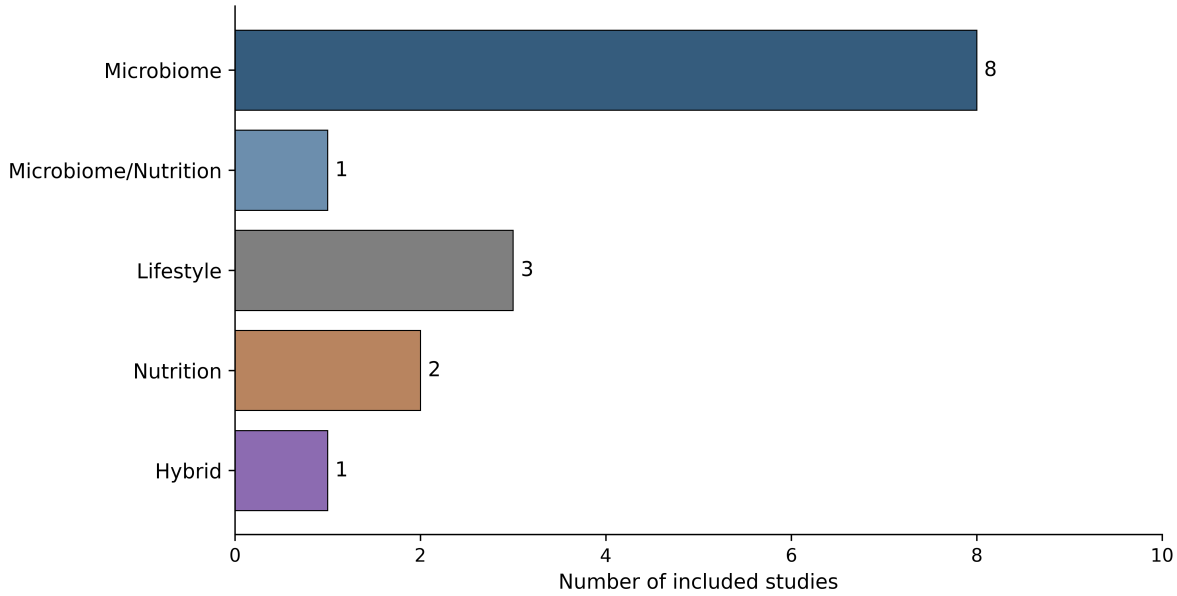

Figure 2. *Evidence distribution by intervention domain. The strict evidence set is weighted toward microbiome-directed interventions.*

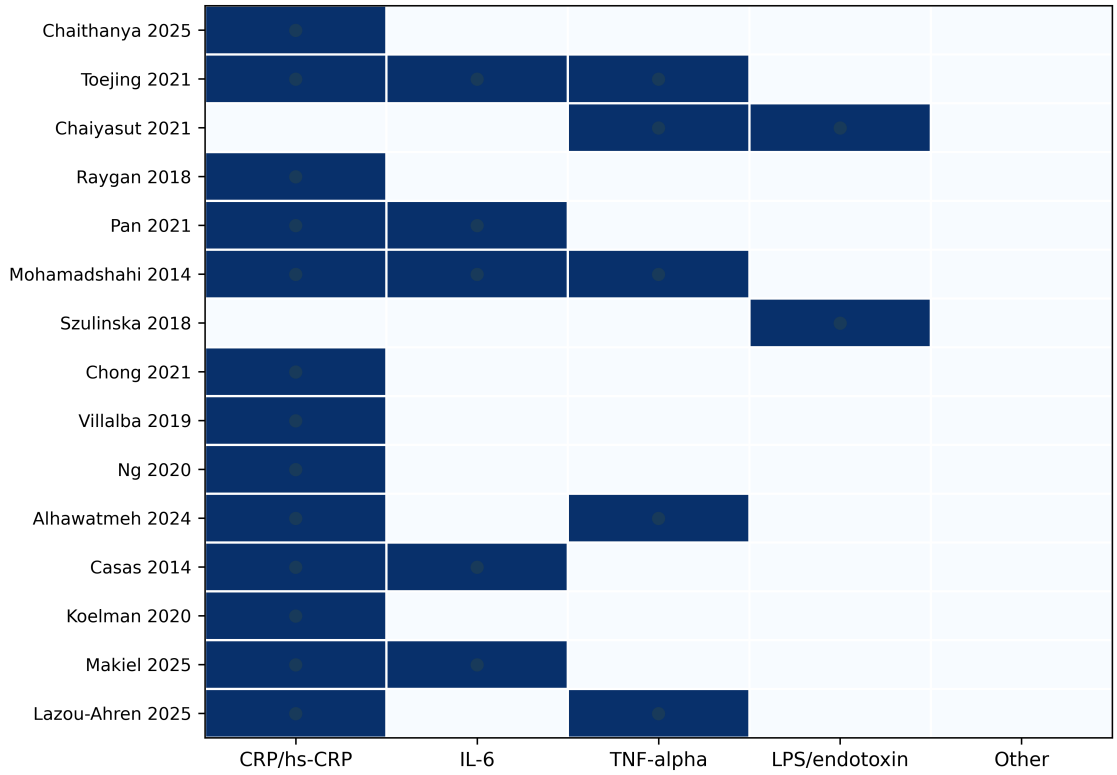

Figure 3. *Biomarker coverage heatmap across included studies. Filled cells indicate that the biomarker was reported for that study in the extraction workbook.*

4.4 Primary Pooled Effects by Biomarker Family

Random-effects meta-analysis revealed statistically significant pooled effects favoring

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intervention for all four biomarker families (Table 2; Figure 5). For CRP/hs-CRP, the pooled Hedges' g was −0.51 (95% CI [−0.81, −0.20]; k = 11; effective N = 786; I^2 = 73.4%; τ^2 = 0.179), representing the most stable estimate in the synthesis (Figure 4).

For IL-6, the pooled Hedges' g was −1.76 (95% CI [−3.18, −0.33]; k = 6; effective N = 386; I^2 = 96.3%; τ^2 = 3.035), representing a large reduction driven partly by the Casas et al. (2014) Mediterranean diet effect (g = −5.08). For TNF-α, the pooled Hedges' g was −1.50 (95% CI [−2.61, −0.38]; k = 4; effective N = 194; I^2 = 91.2%). For LPS, the pooled Hedges' g was −0.75 (95% CI [−1.45, −0.04]; k = 2; effective N = 106; I^2 = 68.0%).

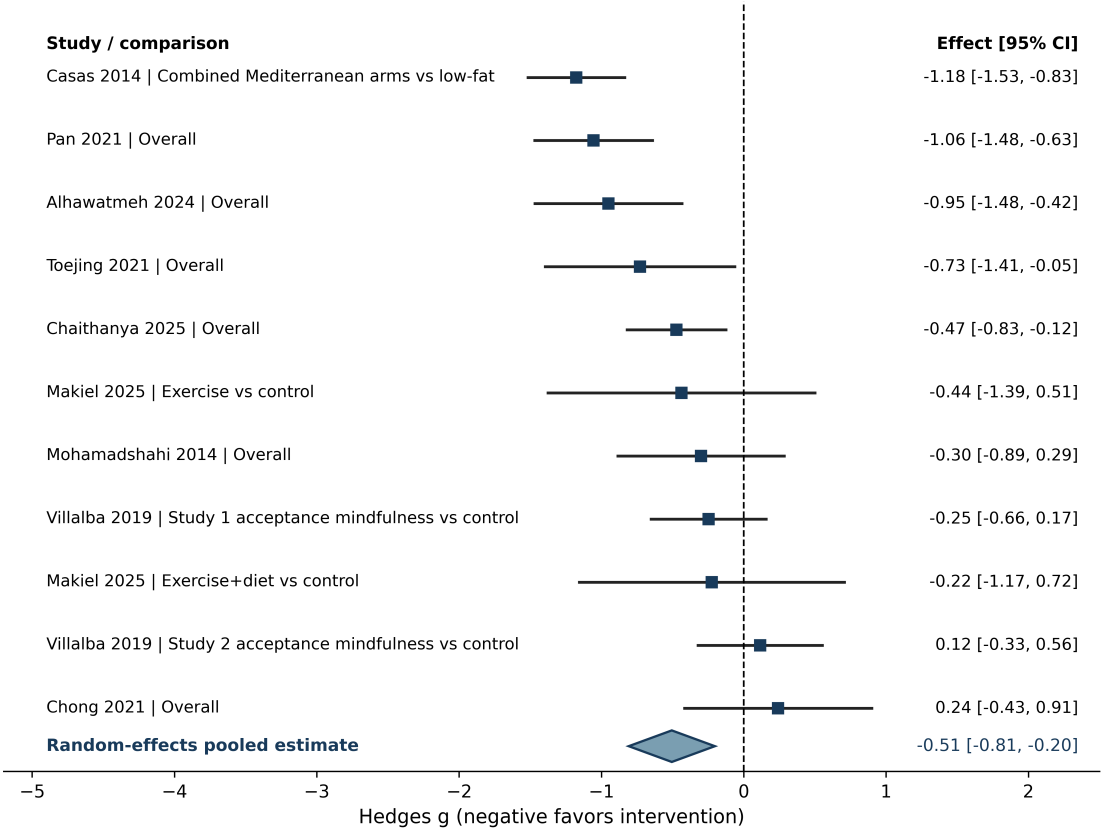

Figure 4. *Forest plot for CRP/hs-CRP primary direct-data synthesis. k = 11; I2 = 73.4%. The diamond represents the random-effects pooled estimate.*

4.5 Domain-Specific Interpretation

Microbiome interventions were the most consistent and numerically dominant domain, contributing six of 11 CRP-family estimates. Probiotic studies demonstrated simultaneous reductions across multiple biomarker families, consistent with the theoretical framework of gut barrier restoration reducing systemic inflammation through attenuated endotoxin translocation. For example, Toejing et al. (2021) reported statistically significant effects on LPS, TNF-α, IL-6, and hs-CRP simultaneously, providing multi-pathway evidence within a single trial. Pan et al. (2021) demonstrated one of the largest CRP reductions (g = −1.06) in a peritoneal dialysis population, suggesting that the anti-inflammatory potential of probiotics may be amplified in populations with compromised barrier function and elevated baseline inflammation. Conversely, Chong et al. (2021) reported a non-

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significant positive effect (g = 0.24) for hs-CRP in NAFLD patients receiving VSL#3, highlighting that not all probiotic formulations yield consistent anti-inflammatory effects across all clinical contexts.

Lifestyle interventions yielded a heterogeneous pattern that warrants nuanced interpretation. Alhawatmeh et al. (2024) reported large effects in ESRD patients (CRP g = −0.95; TNF-α g = −2.21), suggesting that mindfulness meditation may be particularly efficacious in populations with high baseline inflammatory burden driven by uremic toxicity. In contrast, Villalba et al. (2019) reported near-null effects across two independent acceptance-mindfulness trials in psychologically stressed but otherwise healthy adults (Study 1: g = −0.25; Study 2: g = 0.12), suggesting that the anti-inflammatory effects of mindfulness may depend on the severity of pre-existing inflammatory dysregulation rather than perceived stress alone.

Nutrition interventions were mechanistically important but quantitatively sparse. The Casas et al. (2014) Mediterranean diet trial produced one of the largest single-study effects in the entire dataset (IL-6 g = −5.08), though this outlier magnitude warrants cautious interpretation given that it may reflect the combined influence of multiple dietary components and the 12-month intervention duration. The hybrid domain (Makiel et al., 2025) showed moderate CRP reductions (exercise g = −0.44; exercise-plus-diet g = −0.22) and large IL-6 effects, but the small control group (n = 6) substantially limits precision and generalizability.

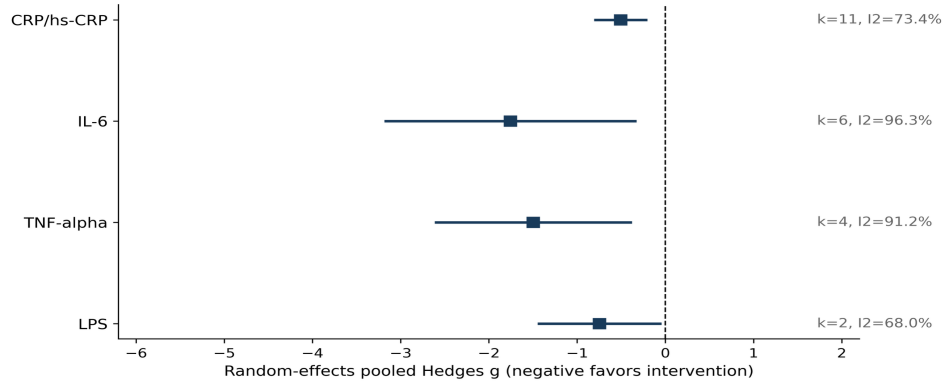

Figure 5. *Pooled standardized effects (Hedges g) by biomarker family with 95% confidence intervals. All estimates favor intervention (negative direction).*

4.6 Sensitivity Analysis and Heterogeneity

Five studies or arms were retained for sensitivity analysis rather than the primary direct-data synthesis (Table 3). Reasons included adjusted-only estimates, transformed scales, active-comparator complications, median/IQR reporting, and secondary dose-arm handling. This preserved comparability within the primary standardized mean-difference framework.

Substantial heterogeneity was observed across all biomarker families, as expected given the diversity of interventions, populations, comparators, durations, and reporting formats. CRP-family outcomes showed the most manageable heterogeneity. By contrast, IL-6 and TNF-α were influenced by several large study-specific effects, especially the Casas et al. (2014) IL-6 estimate, indicating real

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clinical and methodological diversity rather than simple random variation.

Table 1 *Characteristics of the 15 Strict Included Intervention Studies*

ID	Author, Year	Domain	Intervention	Comparator	Population	Design	Duration	Biomarkers
M01	Chaithanya, 2025	Microbiome	Multistrain probiotic	Placebo	Type 2 diabetes	RCT, DB, PC	24 wk	hs-CRP
M02	Toejing, 2021	Microbiome	L. paracasei HII01	Placebo	Type 2 diabetes	RCT, DB, PC	12 wk	LPS; TNF-α; IL-6; hs-CRP
M03	Chaiyasut, 2021	Microbiome	L. paracasei HII01	Placebo	Hypercholesterolemia	RCT, PC	12 wk	LPS; TNF-α; IL-10
M04	Raygan, 2018	Microbiome	Probiotic supplement	Placebo	T2DM + CHD	RCT, DB, PC	12 wk	hs-CRP
M05	Pan, 2021	Microbiome	Probiotic capsules	No-probiotic	Peritoneal dialysis	RCT	2 mo	hs-CRP; IL-6
M06	Mohamadshahi, 2014	Microbiome/ Nutrition	Probiotic yogurt	Regular yogurt	Type 2 diabetes	RCT, DB	8 wk	hs-CRP; IL-6; TNF-α
M07	Szulinska, 2018	Microbiome	Multispecies probiotic	Placebo	Obese postmenopausal	RCT	12 wk	LPS
M08	Chong, 2021	Microbiome	VSL#3 probiotic	Placebo	NAFLD	RCT, PC	10 wk	hs-CRP
M09	Villalba, 2019	Lifestyle	Acceptance mindfulness	No-treatment	Psychological stress	Two RCTs	8 wk	CRP
M10	Ng, 2020	Lifestyle	Mindful awareness	Health education	MCI	RCT	9 mo	hs-CRP
M11	Alhawatmeh, 2024	Lifestyle	Mindfulness meditation	Control	ESRD	RCT	8 wk	CRP; TNF-α; IL-6
M12	Casas, 2014	Nutrition	Mediterranean +	Low-fat diet	High CV risk	RCT	1 yr	CRP; IL-6

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ID	Author, Year	Domain	Intervention	Comparator	Population	Design	Duration	Biomarkers
			EVOO/nuts					
M13	Koelman, 2020	Nutrition	High-protein diet	Low-protein	Morbid obesity	Controlled	3 wk	CRP; IL-6; TNF-α
M14	Makiel, 2025	Hybrid	Exercise ± diet	Control	Abdominal obesity	RCT	12 wk	IL-6; hs-CRP
M15	Lazou-Ahrén, 2025	Microbiome	L. plantarum HEAL9	Placebo	Inflammaging	RCT, DB, PC	4 wk	CRP; TNF-α; IL-6

Note. RCT = randomized controlled trial; DB = double-blind; PC = placebo-controlled; CHD = coronary heart disease; MCI = mild cognitive impairment; ESRD = end-stage renal disease; CV = cardiovascular; NAFLD = non-alcoholic fatty liver disease.

Table 2 *Random-Effects Pooled Effects by Biomarker Family (Primary Direct-Data Synthesis)*

Biomarker Family	k	Effective N	Hedges' g	95% CI	I^2 (%)	τ^2	Direction
CRP/hs-CRP	11	786	**−0.51**	[−0.81, −0.20]	73.4	0.179	Favors intervention
IL-6	6	386	**−1.76**	[−3.18, −0.33]	96.3	3.035	Favors intervention
TNF-α	4	194	**−1.50**	[−2.61, −0.38]	91.2	1.174	Favors intervention
LPS	2	106	**−0.75**	[−1.45, −0.04]	68.0	0.175	Favors intervention

Note. Negative standardized effects favor the intervention group. High heterogeneity for IL-6 and TNF-α should be interpreted cautiously.

Table 3 *Studies or Arms Retained for Sensitivity Analysis Rather Than Primary Synthesis*

Study / Arm	Biomarker	Status	Handling Note
Raygan, 2018	hs-CRP	Adjusted-only estimate	Generic inverse variance candidate; no raw means/SD in extraction
Ng, 2020	hs-CRP	Adjusted beta, transformed scale	Not directly harmonizable with primary SMD framework
Koelman,	CRP	Active-	High-protein vs. low-protein without true no-

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Study / Arm	Biomarker	Status	Handling Note
2020		comparator diet	treatment control
Lazou-Ahrén, 2025	CRP; TNF-α	Median/IQR conversion	Distributional assumptions required for conversion
Szulinska, 2018 (low-dose)	LPS	Secondary sensitivity arm	High-dose arm entered primary synthesis to avoid double-weighting

Note. These records reflect adjusted-effect models, active-comparator designs, or median/IQR reporting that may be incorporated in sensitivity analyses.

5. Discussion

5.1 Principal Findings

This meta-analysis and systematic review offer evidence that non-pharmacologic interventions across lifestyle, nutrition, microbiome-directed and hybrid domains are linked to decreases in the levels of circulating inflammatory biomarkers in adult populations. CRP/hs-CRP produced the strongest quantitative signal, as an Hedges g of -0.51 (pooled) was statistically significant and had a moderate effect size across 11 comparisons. The large pooled effects are present in IL-6, TNF-a, and LPS with the large pooled effects being intervention-favored but with a high level of heterogeneity and smaller evidence bases. Microbiome-directed interventions are the most developed type of evidence and were the majority of included studies and were the most balanced in terms of biomarker family coverage.

5.2 Interpreting “Reprogramming Immunity”

The results uphold a tentative, biomarker-oriented approach to reprogramming immunity. The data do not indicate extensive immune remodelling or general immune-enhancing effects, but instead it supports the notion of low-grade inflammatory signalling modulations-that is, decreases in acute-phase proteins (CRP), pro-inflammatory cytokines (IL-6, TNF-a), and a gut-barrier permeability marker (LPS). Such framing is scientifically justifiable and clinically significant because a sustained decrease in these biomarkers has prospectively been linked to a lower cardiovascular risk, better metabolism, and less disease progression in various chronic diseases (Ridker, 2016).

5.3 Mechanistic Interpretation Across Domains

The cross domain framework shows convergence and divergence of the mechanistic pathways that these interventions use to regulate inflammation. The mechanism of action of microbiome-directed interventions seems to be mainly restoration of gut barrier integrity and decrease of endotoxin translocation, reflected by the LPS-reductions in probiotic trials, and the consistent improvements in multiple biomarker families in single, randomized trials. The fact that both Toejing et al. (2021) and Chaiyasot et al. (2021) used Lactobacillus paracasei HII01 and found a reduction of LPS and downstream inflammatory markers (TNF- 4, IL- 6) is in line with a mechanistic cascade starting at the gut barrier and continuing through TLR4- This signaling route offers a biologically credible way of systemic CRP suppression through upstream regulation of IL-6 signaling.

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The lifestyle interventions probably have a neuroimmune mechanism of action, however, baseline inflammatory dysregulation can influence the effect sizes. The big effects that are reported in ESRD would indicate increased impact where there is a high inflammatory burden. The mechanisms of action of nutritional interventions are likely to be adiposity, insulin sensitivity, and oxidative stress. The mixed evidence is encouraging yet too small to make definite conclusions.

5.4 CRP-Family Outcomes as the Primary Signal

The results of the CRP/hs-CRP should be highlighted as the most translatable to clinical use. CRP is the most regularly reported inflammatory biomarker, offers the most consistent pooled estimation in the current synthesis and has a direct clinical significance in the assessment of cardiovascular risk. CRP is, however, a flawed surrogate of more general immune activity: it is a hepatic acute-phase production whose primary cause is IL-6, fails to measure tissue-specific inflammation, and perhaps not a reorganization of the cellular immune that the title of this review suggests. Future research ought to complement CRP with multi-marker panels which incorporate immune cell phenotyping, resolution mediators and functional immune assays.

5.5 Strengths

This review has a number of strengths in terms of methodology. First, the inclusion criterion that only includes intervention studies would guarantee that all the pooled effects are obtained based on experimental evidence as opposed to observational evidence. Second, the multi-domain framework allows the comparison of categories within the framework of one analytical approach. Third, the direct-data and sensitivity-only evidence levels explicitly separated contribute to the improved data handling transparency. Fourth, the biomarker-family pooling approach utilises standardised effects in order to facilitate cross-outcome synthesis. Fifth, the disclosed nature of PRISMA place holder limitation and sources of heterogeneity offers a sincere interpretation scheme.

5.6 Limitations

There are a number of constraints that deserve a straight forward recognition. The narrow dataset contains only 15 studies which limits the statistical power of subgroup analysis, meta-regression, and formal inferences of publication bias like asymmetric funnel plot analysis or funnel test. The evidence base comprises a strong emphasis on microbiome-directed interventions, and a low representation of lifestyle, nutrition, and hybrid interventions, making it impossible to make meaningful domain-level meta-analytic comparisons other than descriptive reporting. The high heterogeneity-especially in the case of IL-6 ($I^2 = 96.3$) and TNF-alpha ($I^2 = 91.2$)-impares the accuracy and interpretability of pooled cytokine estimates, with the actual underlying effect being potentially much different across clinical settings and intervention regimes.

Synthesis was also limited to outcome-reporting variability. Other researchers reported adjusted-only estimates, transformed values or median/IQR summaries or active-comparator designs which could not be cleanly reconciled with the main framework. Moreover, changes of biomarkers in themselves are not sufficient to define shifts in immune-cell phenotype, control activity, or resolution-phase biology.

5.7 Implications for Research and Practice

The results have implications on the clinical practice and the research design in future. The clinical outcomes provide evidence that non-pharmacologic interventions-specifically microbiome-

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based and dietary interventions-should be used as an adjunct to pharmacologic therapy of chronic inflammatory diseases. The pattern of CRP-family-reductions in the areas of intervention has led to the possibility of recommending probiotic supplement, Mediterranean diet, or mindful-based-programs as an element of an integrated inflammatory risk management, especially in patients with a high baseline CRP who have higher cardiovascular risk.

To scientists, the synthesis puts into focus some pressing priorities. To begin with, future trials ought to be of a biomarker-standardized design, which reports raw means and standard deviations of all inflammatory outcomes, pre-register inflammatory outcome hierarchies, and incorporate multi-marker panels of CRP and pro-inflammatory cytokines, gut permeability, and immune cell phenotypes. Second, comparative trials based on domain balancing trials-direct comparison of lifestyle, nutrition, and microbiome interventions in a single randomized trial-would resolve the evidence asymmetry observed in this review and allow formal head-to-head comparison of their efficacies. Third, extended follow-up time with serial biomarker measurements at various times would help to determine whether the observed reductions are maintained, short-lived or dose-response relationships. Fourth, there would be a significant addition of new technologies-such as shotgun metagenomics to characterize microbiomes, flow cytometry to profile immune cell subsets, and multiplex cytokine assays-to uncover a deeper mechanistic understanding of future meta-analytic syntheses in this area.

6. Conclusion

This systematic review and meta-analysis demonstrate that lifestyle, nutrition, microbiome-directed, and hybrid interventions are associated with lower circulating inflammatory biomarkers in adults. The most robust and clinically translatable finding is the moderate pooled reduction in CRP/hs-CRP, supported by the largest evidence base and the most manageable heterogeneity. Larger pooled effects for IL-6, TNF-α, and LPS were also observed but were less stable.

Overall, the findings support a biomarker-centered interpretation of “reprogramming immunity” as recalibration of chronic inflammatory signaling rather than comprehensive immune remodeling. Future work should prioritize domain-balanced, multi-biomarker trials with standardized reporting and verified PRISMA counts.

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