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Review

Meta-COVID Era Nutrition: A Prevention and Education Strategy for Immune and Metabolic Resilience

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Abstract

The COVID-19 pandemic highlighted the interplay between metabolic health and infectious disease outcomes, with conditions such as obesity, insulin resistance, micronutrient deficiencies, endothelial dysfunction, and sarcopenia associated with increased risk of severe illness and mortality. This study synthesizes evidence from immunology, metabolic medicine, clinical nutrition, microbiome research, and public health to examine the role of nutrition in supporting resilience in the post-COVID (“Meta-COVID”) context. Mechanistic pathways, including inflammatory signaling (e.g., NF-κB, NLRP3), immune regulation, mitochondrial function, and gut-lung axis interactions, are reviewed to illustrate how nutritional status may influence host defense. Key nutrients, including vitamin D, zinc, selenium, vitamin C, and omega-3 fatty acids, are discussed for their roles in modulating immune and inflammatory responses. Dietary patterns such as the Mediterranean diet are associated with improved metabolic health, reduced inflammation, and enhanced microbiome diversity. In addition, adequate protein intake and resistance exercise are considered important for mitigating sarcopenia and supporting immune function. The findings suggest that integrating nutritional strategies into clinical and public health frameworks may contribute to improved resilience against infectious and chronic diseases.

Keywords: COVID-19; inflammation; Mediterranean diet; immune modulation; sarcopenia; metabolic syndrome; public health nutrition

1. Introduction

The global impact of COVID-19 extended beyond viral transmission dynamics to expose underlying vulnerabilities in population metabolic health. Early epidemiological evidence identified obesity, type 2 diabetes mellitus, hypertension, cardiovascular disease, and advanced age as major predictors of severe outcomes [1,2]. A large meta-analysis involving more than 400,000 individuals confirmed that obesity independently increased the risk of hospitalization, intensive care admission, and mortality [3]. These associations were not incidental nor purely demographic; rather, they reflected a shared biological substrate linking chronic metabolic dysfunction to immune dysregulation.

Chronic low-grade inflammation, commonly referred to as “metaflammation”, is a defining feature of obesity and metabolic syndrome [4]. Expanded adipose tissue undergoes macrophage

infiltration and increased secretion of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) [5]. This elevated baseline inflammatory state predisposes individuals to dysregulated immune responses during viral infection. In severe COVID-19, it became evident that uncontrolled host immune activation, rather than direct viral cytotoxicity alone, was a major driver of acute respiratory distress syndrome and multi-organ dysfunction [6].

Metabolic dysfunction also compromises endothelial integrity. SARS-CoV-2 infection has been characterized as a vascular and endothelial disease due to widespread endothelial inflammation and microthrombosis [7]. Pre-existing insulin resistance reduces nitric oxide bioavailability, promotes oxidative stress, and impairs vascular homeostasis, thereby increasing susceptibility to thrombo-inflammatory complications [8]. These vascular alterations further amplify the systemic consequences of dysregulated immune activation.

Micronutrient status represents an additional critical determinant of immune competence. Vitamin D deficiency, highly prevalent worldwide, has been associated with increased susceptibility to respiratory infections and adverse COVID-19 outcomes [9,10]. Through vitamin D receptor (VDR)-mediated transcriptional regulation, vitamin D modulates both innate and adaptive immunity, suppressing nuclear factor kappa B (NF- κ B) activation while promoting antimicrobial peptide synthesis [11]. Zinc plays an essential role in interferon signaling and T-cell maturation, and its deficiency impairs antiviral responses [12]. Selenium contributes to redox homeostasis through its role in selenoproteins such as glutathione peroxidases and has been associated with modulation of viral pathogenicity [13]. Vitamin C further supports immune defense through its antioxidant properties and its role in neutrophil function [14]. Collectively, these micronutrients contribute to the regulation of immune responses and inflammatory balance.

Dietary patterns influence both micronutrient availability and broader metabolic and inflammatory pathways. Diets characterized by high intake of ultra-processed foods, refined carbohydrates, and industrial fats are associated with increased oxidative stress, metabolic endotoxemia, and chronic inflammation [15,16]. In contrast, the Mediterranean diet has consistently demonstrated anti-inflammatory and cardiometabolic benefits [17,18]. Its high content of fiber, polyphenols, and unsaturated fats supports short-chain fatty acid production, enhances regulatory T-cell differentiation, and promotes a balanced immune response [19]. These dietary effects extend beyond isolated nutrients, operating through synergistic interactions that influence multiple physiological systems.

In addition to metabolic and inflammatory regulation, skeletal muscle health plays a fundamental role in immune competence. Sarcopenia, defined as the progressive loss of muscle mass and strength, reduces amino acid availability necessary for lymphocyte proliferation and immune protein synthesis, thereby increasing vulnerability to infection [20]. During the COVID-19 pandemic, hospitalization and immobilization accelerated muscle catabolism through activation of proteolytic pathways, further compromising immune resilience [21]. Preservation of muscle mass is therefore critical not only for functional capacity but also for sustaining effective immune responses.

Emerging evidence also highlights the role of gut microbiota in modulating disease severity and recovery. Dysbiosis, characterized by reduced abundance of beneficial commensal bacteria, has been observed in patients with COVID-19 and is associated with increased inflammatory burden [22]. The gut-lung axis provides a mechanistic framework through which dietary components, particularly dietary fiber, influence pulmonary immune responses via microbial metabolites such as short-chain fatty acids [23]. These interactions further underscore the systemic nature of nutrition-immune crosstalk.

Collectively, these findings indicate that nutritional status operates across multiple interconnected mechanistic pathways, including inflammatory signaling (NF- κ B and NOD-like receptor family pyrin domain containing 3 (NLRP3)), interferon-mediated antiviral responses, mitochondrial bioenergetics, endothelial nitric oxide regulation, mTOR (mechanistic target of rapamycin)-dependent lymphocyte proliferation, and microbiota-derived immune modulation.

These pathways form an integrated network through which nutrition shapes both immune competence and metabolic stability, ultimately influencing susceptibility to infectious disease.

In this context, the Meta-COVID era, defined as the phase following the acute pandemic crisis, demands a transition from reactive healthcare models toward resilience-based prevention strategies. While substantial research has examined individual risk factors and clinical outcomes, an integrated understanding of how nutrition modulates immune and metabolic resilience across biological systems remains limited. Therefore, the aim of this study is to synthesize multidisciplinary evidence from immunology, clinical nutrition, metabolic medicine, microbiome research, and public health in order to establish nutrition as a central determinant of host resilience and to support the development of systems-based preventive frameworks for future health challenges.

2. Research Methodology and Sources

This study adopts a narrative integrative review methodology, synthesizing evidence from multiple scientific domains to construct a comprehensive framework linking nutrition with immune and metabolic resilience in the Meta-COVID era.

2.1. Study Design

The research is based on a structured narrative review designed to integrate findings from clinical nutrition, immunology, metabolic medicine, microbiome research, and public health. This methodological approach was selected due to the inherently multidisciplinary nature of the topic, where mechanistic, clinical, and population-level evidence must be interpreted collectively rather than in isolation. By combining diverse strands of evidence, the study aims to provide a systems-level understanding of how nutrition influences resilience to infectious and chronic diseases.

2.2. Data Sources and Search Strategy

Scientific literature was systematically identified through major biomedical and interdisciplinary databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search strategy employed combinations of keywords related to nutrition, immune function, and COVID-19, including “COVID-19 AND nutrition”, “immune function AND micronutrients”, “Mediterranean diet AND inflammation”, “gut microbiota AND respiratory infection”, “sarcopenia AND immune response”, and “metabolic syndrome AND COVID-19 outcomes”.

The search process prioritized publications from 2010 to 2026 in order to capture both foundational research and recent advances, with particular emphasis on studies published after 2020 that address COVID-19-related mechanisms and outcomes.

2.3. Inclusion Criteria

Studies were included based on predefined criteria to ensure scientific relevance and methodological quality. Eligible sources comprised peer-reviewed journal articles, including human clinical studies, meta-analyses, and systematic reviews. Mechanistic studies were also included where they provided biologically plausible insights into immune, metabolic, or inflammatory processes. In addition, reports from recognized public health organizations were considered when relevant to population-level outcomes and policy implications.

2.4. Exclusion Criteria

Studies were excluded if they were non-peer-reviewed, anecdotal in nature, or lacked methodological transparency. Publications not directly related to nutrition, immune function, or metabolic health were also excluded in order to maintain thematic coherence and scientific rigor.

2.5. Analytical Framework

A systems-based conceptual framework was applied to integrate evidence across multiple biological and public health domains. Specifically, the analysis focused on inflammatory signaling pathways (including NF-κB and NLRP3), immune regulation, metabolic health, skeletal muscle physiology, and gut microbiota interactions, as well as broader public health systems.

Emphasis was placed on dietary patterns, nutrient interactions, and cross-system effects rather than isolated variables. This integrative approach enabled the identification of interconnected pathways through which nutrition influences immune competence and metabolic stability. The key components of the methodological framework are summarized in Table 1.

2.6. Limitations

As a narrative review, this study does not include quantitative meta-analysis or a formal risk-of-bias assessment. However, methodological rigor is supported through the inclusion of high-quality peer-reviewed sources, consistency across disciplines, and strong mechanistic plausibility linking the reviewed evidence. These elements enhance the reliability of the integrative framework despite the absence of statistical synthesis.

2.7. Rationale for Methodological Approach

The complexity of COVID-19 outcomes, arising from interactions among metabolic status, immune function, and environmental factors, necessitates a systems-based methodological approach. Reductionist frameworks that focus on isolated variables are insufficient to capture these multidimensional interactions.

Accordingly, this study employs a multidimensional integrative framework that combines evidence from clinical nutrition, immunology, metabolic medicine, microbiome research, and public health. Literature is systematically identified, filtered according to predefined criteria, and synthesized using a systems-based analytical approach. The resulting synthesis is translated into a conceptual resilience model linking dietary patterns, metabolic health, immune function, and policy-level interventions in the Meta-COVID era. The overall methodological approach is illustrated in Figure 1.

Table 1. Integrated Methodological Framework for the Meta-COVID Nutrition Model.

Component	Description	Purpose in Study	Key Sources/Fields
Study Design	Narrative integrative review	To synthesize multidisciplinary evidence across biological and public health domains	Clinical nutrition, immunology, public health
Literature Type	Peer-reviewed articles, meta-analyses, clinical trials, epidemiological studies	Ensure scientific validity and reliability	PubMed, Scopus, Web of Science
Time Frame	Primarily 2010–2025 (focus on post-2020 COVID-19 research)	Capture both foundational and pandemic-related evidence	COVID-19 literature, chronic disease research
Search Strategy	Keyword-based search using combined terms (e.g., “nutrition AND COVID-19”, “microbiota AND immunity”)	Identify relevant interdisciplinary studies	Biomedical databases
Inclusion Criteria	Human studies, mechanistic relevance, high-quality reviews, public health reports	Ensure relevance to immune and metabolic resilience	WHO reports, clinical trials
Exclusion Criteria	Non-peer-reviewed studies, low methodological quality, unrelated topics	Maintain scientific rigor	-
Analytical Approach	Systems-based integration of biological pathways and population-level data	Link nutrition to immune, metabolic, and public health outcomes	Systems biology, epidemiology

Core Biological Domains	Inflammation, immunity, metabolism, microbiota, muscle physiology	Provide mechanistic foundation	Immunology, endocrinology
Dietary Focus	Whole dietary patterns (Mediterranean diet, fiber-rich diets) rather than isolated nutrients	Reflect real-world applicability	Nutritional epidemiology
Public Health Integration	Education, policy, food systems, health equity	Translate biological findings into population strategies	Public health, policy research
Outcome Framework	Immune resilience, reduced inflammation, metabolic stability	Define preventive health model	Meta-COVID resilience concept
Limitations	Non-systematic design, absence of quantitative meta-analysis	Acknowledge methodological constraints	Narrative review methodology

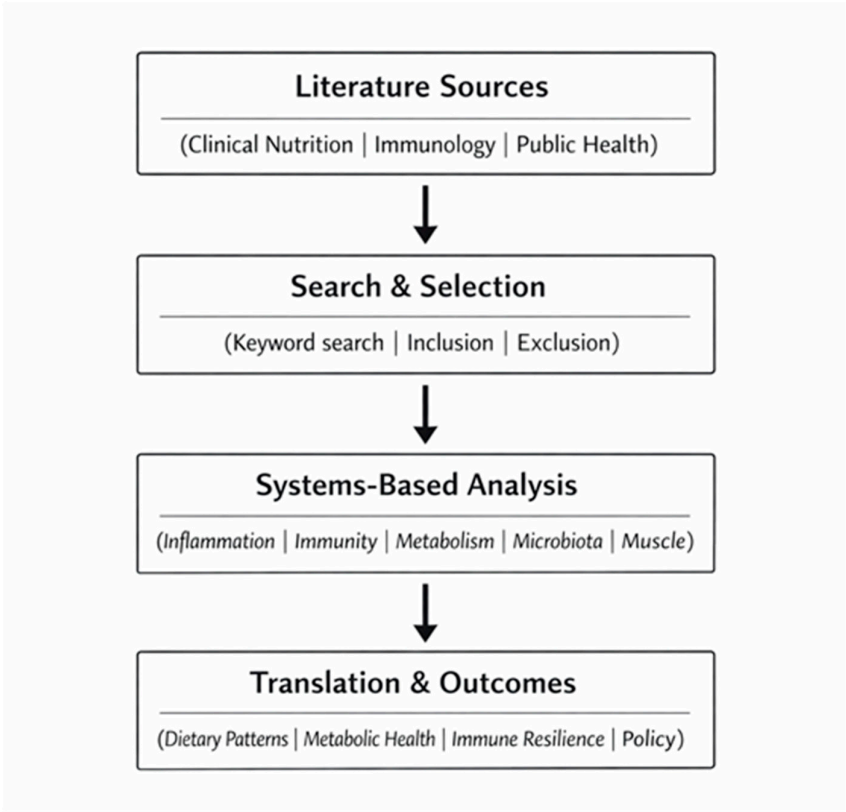


Figure 1. Methodological Integration Model. This figure presents the integrative methodological framework of the study, from literature identification and selection to systems-based analysis and translation into nutritional, clinical, and public health outcomes relevant to Meta-COVID resilience.

3. Immunological and Molecular Mechanisms Linking Nutrition to Viral Resilience

The immune response to viral infection is an energy-intensive and tightly regulated process that requires coordinated activation of both innate and adaptive pathways. Nutritional status influences immune cell differentiation, cytokine signaling, redox homeostasis, mitochondrial bioenergetics, and antiviral defense mechanisms across multiple regulatory nodes [24,25]. In severe COVID-19, dysregulated inflammatory responses, rather than viral replication alone, emerged as the primary drivers of tissue damage [6]. Understanding how nutrients modulate these interconnected pathways is therefore central to the development of resilience-oriented strategies in the Meta-COVID era.

3.1. Innate Immunity, Pattern Recognition, and Inflammatory Amplification

Innate immune activation is initiated through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which detect viral RNA and trigger intracellular signaling cascades. Activation of TLR3, TLR7, and TLR8 leads to downstream stimulation of NF- κ B and interferon regulatory factors (IRFs), promoting the production of pro-inflammatory cytokines and type I interferons [26].

In COVID-19, excessive activation of NF- κ B and the NLRP3 inflammasome has been strongly implicated in hyperinflammatory responses characterized by elevated levels of IL-6, IL-1 β , and TNF- α [27]. Activation of NLRP3 leads to caspase-1-mediated maturation of IL-1 β and IL-18, thereby amplifying inflammatory cascades. Pre-existing metabolic inflammation may further prime inflammasome responsiveness, effectively lowering the threshold for cytokine storm development.

Vitamin D exerts immunomodulatory effects through binding to the VDR, which forms a heterodimer with the retinoid X receptor (RXR) to regulate transcription of immune-related genes. It suppresses NF- κ B activation by inhibiting p65 nuclear translocation and upregulating I κ B α expression, while also attenuating NLRP3 inflammasome activation and reducing IL-1 β production [9,28]. A large individual participant meta-analysis demonstrated that vitamin D supplementation reduces the risk of acute respiratory tract infections, particularly in individuals with baseline deficiency [11]. Observational data during the COVID-19 pandemic further associated low serum 25(OH)D concentrations with increased disease severity [10].

Zinc plays a critical role in immune cell development and antiviral defense. It stabilizes cellular membranes, supports thymic hormone activity, and regulates gene expression through zinc-finger transcription factors [29]. Zinc deficiency impairs TLR-mediated signaling and reduces type I interferon production [12]. Experimental evidence suggests that increased intracellular zinc concentrations can inhibit RNA-dependent RNA polymerase activity in coronaviruses [30]. Additionally, zinc modulates NF- κ B activation through inhibition of I κ B kinase (IKK), thereby attenuating inflammatory amplification [31].

Selenium contributes to immune regulation through its role in selenoproteins such as glutathione peroxidases and thioredoxin reductases, which are essential for maintaining intracellular redox balance [32]. Oxidative stress enhances NF- κ B activation and inflammasome signaling, whereas selenium deficiency compromises antioxidant defense and has been associated with increased virulence of RNA viruses due to mutation-promoting oxidative damage [33,34]. Ecological analyses during the COVID-19 pandemic reported correlations between regional selenium status and recovery rates, although causality remains to be established [13].

3.2. Adaptive Immunity and Lymphocyte Metabolism

Adaptive immune responses involve clonal expansion of T and B lymphocytes, antibody production, and differentiation into memory cells [35]. These processes are highly dependent on amino acid availability, mitochondrial adenosine triphosphate (ATP) production, and metabolic signaling pathways such as the mechanistic target of rapamycin complex 1 (mTORC1) [36].

mTORC1 integrates signals from amino acids, insulin, and growth factors to regulate protein synthesis and cell proliferation. Leucine serves as a key activator of mTORC1 through Rag GTPase-mediated lysosomal recruitment [37]. Inflammatory cytokines such as IL-6 can impair mTOR signaling, thereby reducing anabolic capacity and immune cell proliferation [38]. Protein-energy malnutrition consequently diminishes lymphocyte proliferation and immunoglobulin synthesis, whereas adequate protein intake ensures sufficient substrate availability for effective adaptive immune responses [39,40].

Omega-3 polyunsaturated fatty acids (PUFAs) contribute to immune regulation through mechanisms distinct from classical anti-inflammatory suppression. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) serve as precursors to specialized pro-resolving mediators (SPMs), including resolvins and protectins [41,42]. These mediators actively promote the resolution phase of inflammation by reducing neutrophil infiltration, enhancing macrophage efferocytosis, and restoring

tissue homeostasis. Impaired resolution pathways may contribute to prolonged inflammatory damage in severe viral infections [43], suggesting that adequate omega-3 intake supports balanced immune responses without compromising pathogen clearance [44].

3.3. Mitochondrial Antiviral Signaling and Bioenergetics

Mitochondria serve as central hubs in antiviral immunity [45]. The mitochondrial antiviral signaling protein (MAVS), located on the outer mitochondrial membrane, activates interferon production following detection of viral RNA [46]. Viral disruption of mitochondrial dynamics impairs interferon responses and increases reactive oxygen species (ROS) generation [47].

Elevated ROS levels activate NF- κ B and NLRP3 pathways, thereby amplifying inflammatory cascades. Antioxidant nutrients, including vitamins C and E, selenium, and dietary polyphenols, modulate redox-sensitive transcription factors and help maintain oxidative balance [14]. In severe infections, plasma vitamin C concentrations decline significantly due to increased metabolic demand [48], suggesting that restoration of antioxidant capacity may attenuate oxidative amplification loops.

3.4. Endothelial Function and Immunothrombosis

COVID-19 is characterized by prominent vascular pathology, including endothelial inflammation and microthrombosis [7]. Endothelial nitric oxide synthase (eNOS) plays a key role in regulating vascular tone and platelet aggregation [49]. Oxidative stress reduces nitric oxide bioavailability, promoting vasoconstriction and thrombotic risk.

Dietary patterns rich in bioactive compounds, such as the Mediterranean diet, have been shown to improve endothelial function and reduce oxidative stress [50]. Components including extra virgin olive oil polyphenols and omega-3 fatty acids enhance nitric oxide bioavailability and support vascular integrity [17]. Preservation of endothelial function may therefore mitigate thrombo-inflammatory complications during viral infections [51].

3.5. Gut-Derived Immune Modulation

The gut microbiota plays a central role in systemic immune regulation through the production of metabolites such as short-chain fatty acids (SCFAs) [52]. These metabolites, particularly butyrate, exert immunomodulatory effects by inhibiting histone deacetylases, promoting regulatory T-cell differentiation, and suppressing NF- κ B activation [19]. SCFAs also influence hematopoiesis and alveolar macrophage function, linking gut-derived signals to pulmonary immunity via the gut-lung axis [23].

Dysbiosis observed in COVID-19 patients is associated with reduced abundance of beneficial commensal bacteria and diminished SCFA production, contributing to impaired immune regulation [22]. Dietary fiber intake therefore indirectly modulates immune responses through microbial metabolism [53].

3.6. Integrated Mechanistic Network

Nutritional status influences immune resilience through multiple interconnected biological pathways [54]. These include regulation of NF- κ B and NLRP3 inflammasome activity [55]. It also affects interferon-mediated antiviral responses. Nutritional status contributes to mTOR-dependent lymphocyte proliferation [56]. It supports mitochondrial bioenergetics and redox balance. In addition, it helps preserve endothelial nitric oxide signaling [57]. Finally, it modulates immune function through microbiota-derived mechanisms [58].

Disruptions in nutritional status or metabolic health can amplify inflammatory signaling and impair immune regulation, whereas balanced dietary patterns support coordinated immune activation and resolution [59]. In the Meta-COVID era, effective prevention strategies must therefore target this integrated network holistically rather than focusing on isolated nutrients. The complex

mechanistic interactions linking nutrition with immune and metabolic regulation are illustrated in Figure 2.

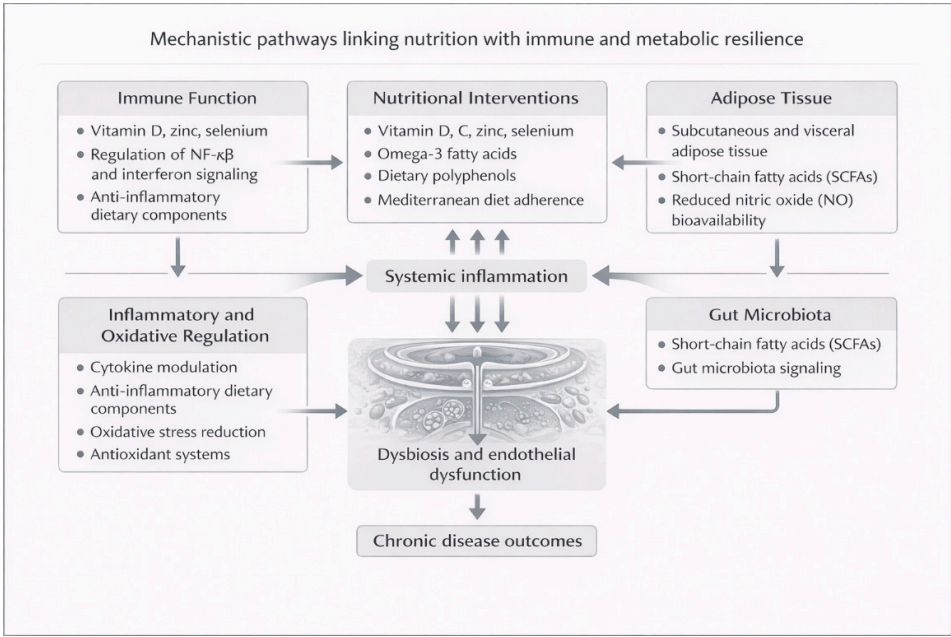


Figure 2. Mechanistic Pathways Linking Nutrition to Immune and Metabolic Stability. Nutritional inputs regulate immune activation through modulation of NF-κB signaling, inflammasome activation, interferon responses, mTOR-mediated lymphocyte proliferation, mitochondrial oxidative phosphorylation, endothelial nitric oxide bioavailability, and microbiota-derived short-chain fatty acid production. Dysregulation at these nodes amplifies inflammatory responses and metabolic instability. This figure integrates the principal biological pathways discussed in Sections 3–6.

4. Dietary Patterns, Metabolic Syndrome, and Systemic Inflammation

The COVID-19 pandemic did not generate metabolic vulnerability, it exposed it. The disproportionate severity of disease observed among individuals with obesity, insulin resistance, and cardiovascular disease underscores the biological convergence of chronic metabolic dysfunction and acute viral pathology [3,8]. Dietary patterns represent one of the most powerful upstream determinants of this convergence.

Unlike isolated micronutrient interventions, whole dietary patterns exert cumulative and synergistic effects on inflammatory signaling, endothelial function, adipose tissue biology, glucose metabolism, and gut microbiota composition [60,61]. In the Meta-COVID era, preventive strategies must therefore shift toward pattern-based nutritional frameworks capable of modulating systemic inflammatory tone and enhancing metabolic resilience [62].

4.1. Ultra-Processed Diets and Pro-Inflammatory Physiology

Ultra-processed foods (UPFs), characterized by refined carbohydrates, added sugars, industrial seed oils, and food additives, are strongly associated with obesity, metabolic syndrome, and cardiovascular disease [15]. Their physiological effects extend well beyond caloric excess.

High-glycemic-load meals induce rapid postprandial glucose excursions and compensatory hyperinsulinemia [63]. Acute hyperglycemia increases mitochondrial superoxide production, leading to oxidative stress and activation of NF-κB-mediated transcription of pro-inflammatory cytokines [64,65]. Repeated glycemic fluctuations sustain chronic inflammatory signaling and impair endothelial function [66].

Advanced glycation end products (AGEs), abundant in highly processed and thermally treated foods, bind to the receptor for AGE (RAGE), triggering oxidative and inflammatory cascades [67–69]. Activation of RAGE enhances NF- κ B signaling and contributes to vascular injury, which is particularly relevant in COVID-19–associated endothelial dysfunction [70].

Dietary saturated fats further exacerbate inflammation by increasing intestinal permeability and promoting metabolic endotoxemia [71]. Translocation of lipopolysaccharides (LPS) from the gut activates Toll-like receptor 4 (TLR4), stimulating inflammatory cytokine production [16,72]. This low-grade endotoxemia contributes to metaflammation and insulin resistance [73].

Collectively, these mechanisms create a pro-inflammatory metabolic environment that lowers the threshold for dysregulated immune responses during viral infection.

4.2. Insulin Resistance, Adipose Tissue, and Immune Dysregulation

Insulin resistance is a central component of metabolic syndrome [74]. Hyperinsulinemia disrupts eNOS signaling, reducing nitric oxide bioavailability and promoting vascular oxidative stress [75,76]. Impaired endothelial function compromises microvascular circulation and may exacerbate hypoxemic injury during respiratory infections [77].

Adipose tissue functions as an active endocrine organ. In obesity, adipocyte hypertrophy and macrophage infiltration increase secretion of pro-inflammatory cytokines, including IL-6, TNF- α , and monocyte chemoattractant protein-1 (MCP-1) [4,78]. Elevated leptin levels promote Th1 immune polarization, whereas reduced adiponectin diminishes anti-inflammatory signaling [79].

Furthermore, adipose tissue expresses angiotensin-converting enzyme 2 (ACE2), the cellular entry receptor for SARS-CoV-2 [80]. Increased adipose mass may therefore provide an expanded viral reservoir and prolong inflammatory signaling [81].

Weight reduction through dietary modification has been shown to decrease C-reactive protein (CRP) concentrations, improve insulin sensitivity, and restore adipokine balance [82,83]. These changes collectively reduce baseline inflammatory tone and enhance immune resilience.

4.3. The Mediterranean Dietary Pattern

The Mediterranean diet represents one of the most extensively studied dietary models for anti-inflammatory and cardiometabolic protection [84]. It is characterized by high consumption of plant-based foods, including fruits, vegetables, whole grains, legumes, nuts, and seeds; the use of extra virgin olive oil as the primary fat source; moderate intake of fish; and limited consumption of red and processed meats.

4.3.1. Clinical Evidence

The PREDIMED randomized controlled trial demonstrated an approximately 30% reduction in major cardiovascular events among high-risk individuals adhering to Mediterranean dietary patterns [17]. Meta-analyses consistently report reductions in inflammatory biomarkers, including CRP, IL-6, and adhesion molecules [85].

Observational analyses conducted during the COVID-19 pandemic have suggested inverse associations between adherence to the Mediterranean diet and mortality rates across populations [86]. Although these findings are ecological in nature, they are supported by strong mechanistic plausibility.

4.3.2. Polyphenols and Inflammatory Suppression

Polyphenols, including hydroxytyrosol, resveratrol, and flavonoids, exert potent anti-inflammatory effects by inhibiting NF- κ B activation and reducing oxidative stress [87]. These compounds also enhance endothelial nitric oxide availability and reduce LDL oxidation [88].

4.3.3. Monounsaturated Fats and Insulin Sensitivity

Oleic acid, the predominant fatty acid in olive oil, improves membrane fluidity and modulates inflammatory gene expression [89]. Substituting saturated fats with monounsaturated fats has been shown to improve insulin sensitivity and lipid profiles [90,91].

4.3.4. Omega-3 Fatty Acids and Resolution

Marine-derived omega-3 fatty acids contribute to the synthesis of specialized pro-resolving mediators, which facilitate the controlled resolution of inflammation [41,92]. These mediators actively limit excessive immune responses, promote clearance of inflammatory debris, and support the restoration of tissue homeostasis without impairing host defense mechanisms [93].

4.3.5. Dietary Fiber and Microbiota

High dietary fiber intake promotes the production of short-chain fatty acids, which enhance regulatory T-cell differentiation and suppress pro-inflammatory signaling pathways [18].

4.4. Glycemic Stability and Immune Competence

Acute hyperglycemia impairs key components of innate immunity, including neutrophil chemotaxis, phagocytosis, and complement activation [94]. Glycemic variability generates greater oxidative stress than sustained hyperglycemia alone [95,96]. Low-glycemic-index diets attenuate postprandial glucose excursions and reduce inflammatory burden [97,98]. Maintenance of glycemic stability may therefore enhance immune efficiency and limit inflammatory amplification during infection [99].

4.5. Comparative Dietary Effects

Dietary patterns exert differential effects on immune function and metabolic regulation through complex and interrelated biological mechanisms. Pro-inflammatory dietary patterns, characterized by high consumption of ultra-processed foods, refined carbohydrates, saturated fats, and low fiber, promote oxidative stress, metabolic endotoxemia, and chronic activation of inflammatory signaling pathways, including NF- κ B and the NLRP3 inflammasome [15,16].

These dietary profiles are closely associated with insulin resistance, adipose tissue inflammation, and endothelial dysfunction, all of which contribute to impaired immune regulation and increased susceptibility to severe infectious outcomes [8,100]. Postprandial hyperglycemia and lipid overload further amplify reactive oxygen species production and inflammatory cytokine release [101,102].

In contrast, anti-inflammatory dietary patterns such as the Mediterranean diet are associated with reduced circulating inflammatory markers, improved insulin sensitivity, and enhanced endothelial function [17,85]. These effects are mediated through high intake of fiber, polyphenols, monounsaturated fats, and omega-3 fatty acids, which collectively modulate immune signaling, promote resolution of inflammation, and support microbiota diversity [18].

Importantly, dietary effects operate across interconnected systems, including metabolic regulation, vascular function, and gut-derived immune modulation. This systems-level interaction highlights the limitations of single-nutrient approaches and supports prioritization of whole dietary patterns in preventive strategies. These comparative effects are summarized in Table 2. It should be noted, however, that much of the current evidence is derived from observational and ecological studies, and controlled intervention trials are required to establish causality.

Table 2. Comparative Effects of Pro-Inflammatory and Anti-Inflammatory Dietary Patterns on Immune and Metabolic Health.

Domain	Pro-Inflammatory Dietary Pattern	Anti-Inflammatory Dietary Pattern (Mediterranean)	Mechanistic Impact	Key References
Diet Composition	Ultra-processed foods, refined carbohydrates, saturated fats	Whole foods, fiber-rich, unsaturated fats, polyphenols	Nutrient quality shapes metabolic and immune pathways	[15]
Inflammation	↑ Chronic low-grade inflammation (↑ IL-6, TNF-α)	↓ Inflammatory markers (↓ CRP, IL-6)	Modulation of NF-κB and inflammasome activity	[17,28]
Metabolic Function	Insulin resistance, hyperglycemia	Improved insulin sensitivity	Regulation of glucose metabolism and lipid homeostasis	[8]
Oxidative Stress	↑ ROS production	↓ Oxidative stress via antioxidants	Redox balance and mitochondrial protection	[14]
Endothelial Function	Endothelial dysfunction	Improved endothelial integrity	Nitric oxide availability, vascular protection	[7]
Gut Microbiota	Dysbiosis, reduced diversity	Increased diversity, SCFA production	Gut-immune axis regulation	[19]
Immune Response	Dysregulated, hyperinflammatory response	Balanced immune activation and resolution	Immune signaling and cytokine control	[25]
Clinical and Epidemiological Outcomes	Higher risk of severe COVID-19	Reduced risk and improved recovery	System-wide resilience	[86]

4.6. Dietary Patterns and Long-COVID

Persistent fatigue and systemic inflammation observed in long-COVID may reflect sustained mitochondrial dysfunction and inflammatory dysregulation [103]. Anti-inflammatory dietary patterns rich in antioxidants and omega-3 fatty acids may support recovery processes, although robust interventional evidence remains limited.

4.7. Integrated Dietary Prevention Model

The available evidence supports prioritization of dietary patterns based on whole, minimally processed foods, high dietary fiber intake (≥25–30 g/day), replacement of saturated fats with healthier fat sources such as olive oil and fish, reduction of glycemic load, maintenance of adequate micronutrient density, and achievement of caloric balance to support healthy body weight. These components do not act independently but operate synergistically across inflammatory, metabolic, vascular, and microbial pathways, reinforcing the importance of integrated dietary strategies in enhancing resilience in the Meta-COVID era. At a broader level, the sustainability and organization of food systems play an important role in shaping dietary patterns and supporting long-term population health, with resource-efficient and circular approaches contributing to more resilient nutrition systems [104,105].

5. Sarcopenia, Muscle-Immune Crosstalk, and Protein Metabolism

Skeletal muscle is increasingly recognized as a central organ of immune competence, metabolic regulation, and systemic resilience. During the COVID-19 pandemic, hospitalization, prolonged immobilization, systemic inflammation, and reduced nutritional intake contributed to accelerated muscle catabolism, particularly among older adults and critically ill patients [21]. In the Meta-COVID era, prevention of sarcopenia is not merely a functional concern but a foundational component of immune resilience.

5.1. Muscle as an Immunometabolic Organ

Beyond its role in locomotion, skeletal muscle functions as an endocrine organ that secretes myokines with systemic immunomodulatory effects [106]. Interleukin-15 (IL-15) promotes natural

killer (NK) cell development and supports CD8⁺ T-cell survival [107,108], while other myokines such as irisin and myonectin contribute to metabolic homeostasis and regulation of inflammatory tone [109].

Skeletal muscle also serves as a critical reservoir of amino acids, particularly glutamine, required for lymphocyte proliferation and macrophage function [110]. During catabolic stress, accelerated muscle proteolysis depletes these amino acid stores, potentially compromising adaptive immune responses and impairing host defense [111].

5.2. Inflammation-Induced Muscle Catabolism

Acute infection and systemic inflammation activate the ubiquitin–proteasome system (UPS), leading to increased degradation of myofibrillar proteins [112]. Pro-inflammatory cytokines such as IL-6 and TNF- α stimulate the expression of muscle-specific E3 ubiquitin ligases, including MuRF1 and Atrogin-1, thereby accelerating muscle breakdown [113].

At the same time, inflammatory signaling suppresses anabolic pathways mediated by insulin-like growth factor-1 (IGF-1) and the mechanistic target of rapamycin complex 1 (mTORC1) [114]. This combined effect, enhanced proteolysis alongside reduced protein synthesis results in rapid muscle loss during severe infection [115]. In hospitalized COVID-19 patients, substantial reductions in muscle mass and strength have been documented within weeks, particularly in intensive care settings [21].

5.3. mTOR Signaling and Anabolic Resistance

mTORC1 integrates signals from amino acid availability, insulin, and mechanical stimuli to regulate protein synthesis and cellular growth. Leucine is a key activator of mTORC1 through lysosomal recruitment mechanisms [37].

Aging is associated with anabolic resistance, characterized by a diminished muscle protein synthesis response to dietary protein intake [116,117]. Inflammatory cytokines further impair mTOR signaling, compounding muscle loss during illness [118]. As a result, higher protein intake per meal, typically 25-30 g of protein containing approximately 2.5-3 g of leucine, may be required to effectively stimulate muscle protein synthesis [119].

5.4. Protein Requirements in Illness and Recovery

Standard dietary protein recommendations of 0.8 g/kg/day are insufficient during periods of inflammatory stress or aging. Current evidence suggests that protein requirements increase to approximately 1.0-1.2 g/kg/day in healthy older adults and 1.2-1.5 g/kg/day during illness or recovery, with intakes up to 2.0 g/kg/day in severe catabolic states [39].

The distribution of protein intake across meals is also important. Evenly distributed protein consumption enhances anabolic efficiency compared with skewed intake patterns [117]. High-quality protein sources, including dairy products, eggs, fish, legumes, and soy, provide essential amino acids necessary for both muscle maintenance and immune function.

5.5. Resistance Exercise and Muscle-Immune Synergy

Mechanical loading stimulates mTOR signaling independently of insulin, thereby enhancing muscle protein synthesis [120]. Resistance exercise also induces transient release of IL-6 from contracting muscle, which promotes anti-inflammatory cytokine production (such as IL-10) and suppresses TNF- α [109].

This response differs fundamentally from chronic IL-6 elevation observed in metabolic syndrome. Consequently, resistance training exerts immunoregulatory effects that extend beyond musculoskeletal health. In post-COVID rehabilitation, structured resistance exercise programs have been shown to improve muscle mass, functional capacity, and quality of life [121].

5.6. Sarcopenic Obesity

Sarcopenic obesity, characterized by the coexistence of excess adiposity and reduced muscle mass, represents a particularly high-risk metabolic phenotype [122]. In this condition, adipose-driven inflammation coexists with diminished amino acid availability and impaired metabolic flexibility [123].

This dual burden amplifies vulnerability to both infectious and cardiometabolic complications. Effective nutritional strategies must therefore simultaneously address fat reduction and preservation of muscle mass to improve overall metabolic and immune resilience.

5.7. Vitamin D and Muscle Function

Vitamin D receptors are expressed in skeletal muscle, and deficiency has been associated with reduced muscle strength and increased risk of falls [124,125]. Adequate vitamin D status may support muscle performance while also contributing to immune regulation, highlighting its dual role in musculoskeletal and immune health.

5.8. Mitochondrial Dysfunction and Post-Viral Fatigue

Persistent fatigue following COVID-19 has been linked to mitochondrial dysfunction and impaired oxidative phosphorylation [47]. Skeletal muscle mitochondria are particularly susceptible to inflammatory stress and oxidative damage, which may contribute to reduced energy production and prolonged recovery [126].

Nutrients that support mitochondrial function, including B-complex vitamins, magnesium, and omega-3 fatty acids, may facilitate recovery processes, although robust evidence from randomized trials remains limited [127].

5.9. Clinical Implications for Meta-COVID Recovery

An integrated rehabilitation approach should incorporate adequate protein intake, optimized amino acid distribution across meals, progressive resistance exercise, maintenance of sufficient vitamin D status, and adherence to anti-inflammatory dietary patterns [128]. Early nutritional intervention during hospitalization is particularly important, as it may mitigate rapid muscle loss and improve long-term functional and clinical outcomes [129].

5.10. Key Insights and Implications

Skeletal muscle should not be viewed as a peripheral component of immune function, but rather as a central immunometabolic organ essential for maintaining systemic homeostasis. Beyond its structural role, muscle tissue serves as a dynamic reservoir of amino acids required for immune cell proliferation, acute-phase protein synthesis, and tissue repair during infection.

Preservation of muscle mass is critical for sustaining metabolic flexibility and enabling the organism to respond effectively to the increased energetic and anabolic demands associated with immune activation. In addition, skeletal muscle contributes to immune regulation through the secretion of myokines, which exert anti-inflammatory and immunomodulatory effects across both innate and adaptive immune pathways.

Loss of muscle mass, particularly in the context of aging, chronic disease, or acute illness, is associated with impaired immune competence, delayed recovery, and increased susceptibility to adverse clinical outcomes. The coexistence of sarcopenia and metabolic dysfunction further amplifies this vulnerability, underscoring the need for integrated strategies that address both muscle health and systemic inflammation.

From a nutritional perspective, adequate protein intake, optimal amino acid availability, and resistance-based physical activity represent key interventions for preserving muscle integrity. These strategies not only support musculoskeletal health but also enhance immune resilience through interconnected metabolic pathways.

In the Meta-COVID era, muscle health should be recognized as a foundational component of preventive nutrition frameworks. Integrating muscle-preserving strategies into dietary guidelines and public health policies represents a critical step toward strengthening host resilience against both infectious and chronic diseases.

6. Gut Microbiota, the Gut-Lung Axis, and Immune Crosstalk

The gastrointestinal microbiota constitutes a dynamic ecological system intricately involved in immune regulation, metabolic homeostasis, and inflammatory balance. Bidirectional communication between the gut and the respiratory system, referred to as the gut-lung axis, has emerged as a key determinant of susceptibility to respiratory infections, including COVID-19 [23,130]. Nutritional modulation of microbial composition and metabolite production therefore represents a central pillar of resilience in the Meta-COVID era.

6.1. Microbiota-Driven Immune Education

The gut microbiota plays a fundamental role in immune system development and tolerance from early life onward [131]. Commensal microorganisms interact with pattern recognition receptors, shaping the differentiation of regulatory T cells (Tregs) and maintaining the balance between pro- and anti-inflammatory responses [132,133].

SCFAs, particularly acetate, propionate, and butyrate, are produced through fermentation of dietary fiber [134]. Butyrate functions as a histone deacetylase inhibitor, modulating gene transcription in immune cells and promoting Treg differentiation [19]. Through these epigenetic mechanisms, dietary composition directly influences systemic inflammatory tone.

In addition, SCFAs enhance epithelial barrier integrity by increasing tight junction protein expression and mucin production [135]. Maintenance of barrier function limits translocation of LPS, thereby reducing systemic endotoxemia and inflammatory amplification [136].

6.2. Dysbiosis in COVID-19

Alterations in gut microbial composition have been consistently reported in patients with COVID-19. Zuo et al. [22] observed reduced abundance of beneficial commensals, such as *Faecalibacterium prausnitzii*, alongside increased levels of opportunistic pathogens. The degree of dysbiosis was positively correlated with inflammatory markers and disease severity.

Reduced populations of SCFA-producing bacteria may weaken anti-inflammatory signaling and impair immune regulation [137]. Notably, microbiota alterations have been shown to persist beyond the acute phase of infection in individuals experiencing long-COVID symptoms, suggesting sustained microbial imbalance [138]. Although causality remains to be fully established, strong mechanistic plausibility supports a contributory role of dysbiosis in exaggerated inflammatory responses.

6.3. Intestinal Barrier Integrity and Metabolic Endotoxemia

The intestinal epithelium represents a critical immunological interface. Disruption of tight junction integrity increases intestinal permeability, commonly referred to as “leaky gut,” allowing translocation of microbial products such as LPS into systemic circulation [139].

Metabolic endotoxemia activates Toll-like receptor 4 (TLR4) signaling, triggering NF- κ B-mediated cytokine production [16,118]. This pathway provides a mechanistic link between ultra-processed dietary patterns and systemic inflammation.

In contrast, SCFAs enhance tight junction integrity and reduce endotoxemia [140]. Consequently, fiber-rich dietary patterns exert protective effects by preserving barrier function and limiting inflammatory amplification [141].

6.4. *The Gut-Lung Axis*

Communication between the gut and lungs occurs through circulating microbial metabolites, migration of immune cells, and shared mucosal immune pathways [142].

Experimental studies have demonstrated that high-fiber diets increase circulating SCFA levels, which modulate bone marrow hematopoiesis and enhance antiviral immune responses in the lungs [23]. SCFAs influence dendritic cell function and reduce Th2-mediated inflammation [143].

In the context of COVID-19, systemic inflammation may disrupt intestinal barrier integrity, further exacerbating dysbiosis and reinforcing inflammatory feedback loops [144]. Dietary strategies that enhance microbial diversity may therefore attenuate hyperinflammatory responses and improve host resilience [145].

6.5. *Polyphenols as Microbiota Modulators*

Polyphenols present in fruits, vegetables, olive oil, and legumes exhibit prebiotic-like effects. Microbial metabolism of these compounds generates bioactive metabolites with anti-inflammatory properties [146].

The Mediterranean diet, rich in both polyphenols and dietary fiber, has been associated with increased abundance of SCFA-producing bacteria and reduced systemic inflammation [147]. This synergistic interaction between dietary components and microbial ecology highlights the importance of whole dietary patterns rather than isolated supplementation strategies.

6.6. *Probiotics and Clinical Evidence*

Meta-analyses of randomized controlled trials indicate that certain probiotic strains may modestly reduce the duration and incidence of upper respiratory tract infections [148]. Proposed mechanisms include enhanced mucosal IgA production and modulation of cytokine responses [149].

However, evidence specific to COVID-19 remains limited and appears to be strain-dependent [150]. Current data therefore support prioritization of dietary diversity and fiber intake as primary strategies for fostering endogenous microbial resilience.

6.7. *Microbiota and Long-COVID*

Persistent symptoms following acute COVID-19 infection may involve ongoing low-grade inflammation and mitochondrial dysfunction [103]. Reduced production of butyrate may impair both energy metabolism and immune regulation [151].

Dietary approaches emphasizing fiber intake, fermented foods, and plant diversity may support microbiota restoration and functional recovery, although long-term interventional studies are still needed to confirm these effects [152].

6.8. *Microbial Metabolites and Host Metabolism*

Microbial metabolites play a central role in linking gut ecology with host metabolic function. SCFAs activate G-protein-coupled receptors, including GPR41 and GPR43, thereby influencing insulin sensitivity and lipid metabolism [19]. Improved metabolic control contributes to a reduction in baseline inflammatory tone.

Conversely, trimethylamine-N-oxide (TMAO), a metabolite derived from microbial metabolism of choline and carnitine, has been associated with increased cardiovascular risk [153]. Dietary patterns rich in plant-based foods are associated with reduced TMAO production, aligning with both cardiometabolic and immune benefits.

6.9. *Microbiota-Supportive Nutritional Strategy*

Evidence supports dietary strategies that promote microbial diversity, enhance SCFA production, and strengthen mucosal immune regulation [154]. These include adequate dietary fiber

intake, high plant diversity, regular consumption of fermented foods, reduction of ultra-processed foods, and sufficient intake of omega-3 fatty acids [155]. Together, these components contribute to a more resilient and balanced microbiota.

6.10. Integrated Perspective

Nutrition shapes microbial ecology, which in turn influences the production of metabolites that regulate immune cell differentiation [156]. These immune responses affect systemic inflammatory tone, ultimately determining susceptibility to infectious disease and overall resilience [157].

In the Meta-COVID era, microbiota-targeted nutrition should be integrated into broader preventive frameworks that link dietary patterns, metabolic health, and immune function at the systems level.

7. Education, Public Health Infrastructure, and Policy Integration in the Meta-COVID Era

The biological evidence linking nutrition to immune resilience is robust and multidimensional. However, translating this knowledge into measurable population health outcomes requires effective education, health system integration, and coordinated policy implementation. The COVID-19 pandemic exposed critical gaps not only in metabolic health but also in health literacy, healthcare preparedness, and preventive infrastructure [158–160].

7.1. Health Literacy as a Determinant of Resilience

Health literacy represents a fundamental determinant of dietary behavior and long-term metabolic health. Individuals with limited nutritional knowledge are more likely to adopt ultra-processed dietary patterns, contributing to chronic inflammation and increased disease susceptibility [15].

During the COVID-19 pandemic, widespread misinformation, particularly regarding “immune-boosting” supplements, highlighted the urgent need for evidence-based nutrition education [161]. Dietary pattern-based education has been shown to be more effective than isolated nutrient messaging and leads to more sustainable behavioral change [61]. Future educational frameworks should therefore emphasize integrated concepts such as inflammatory regulation, microbiota diversity, glycemic stability, and muscle preservation.

7.2. Early-Life and School-Based Interventions

Early-life nutrition plays a critical role in shaping lifelong metabolic health and disease risk [82]. School-based interventions have demonstrated effectiveness in improving dietary behaviors and reducing long-term cardiometabolic risk.

Educational strategies should extend beyond theoretical knowledge to include practical competencies such as meal planning, food label interpretation, and understanding the relationship between diet, immune function, and chronic disease. Embedding these principles early in life supports intergenerational health resilience.

7.3. Integration into Healthcare Systems

Despite strong evidence linking nutrition to disease outcomes, it remains underrepresented in routine clinical practice [162]. Many healthcare professionals receive limited formal training in nutrition, which constrains their ability to provide effective dietary guidance [163].

Integration of nutrition into healthcare systems should include routine nutritional screening, assessment of sarcopenia and metabolic risk, and the development of interdisciplinary care models involving physicians, dietitians, and rehabilitation specialists. Strengthening preventive care infrastructure is essential for improving long-term population resilience [164].

7.4. Digital Health and Tele-Nutrition Expansion

The rapid expansion of telemedicine during the COVID-19 pandemic created new opportunities for scalable and personalized nutrition interventions [165]. Digital platforms can facilitate dietary monitoring, behavioral support, and real-time feedback on metabolic health indicators.

Evidence suggests that tele-nutrition interventions can achieve outcomes comparable to in-person care, particularly in weight management and metabolic improvement [166]. However, unequal access to digital technologies may exacerbate existing socioeconomic disparities, underscoring the need for equitable implementation strategies.

7.5. Structural Food Environment and Policy Measures

Dietary behavior is strongly shaped by structural determinants, including food availability, pricing, and marketing environments [19]. Ultra-processed foods are often more accessible and affordable, particularly among lower-income populations [167].

Policy interventions such as subsidies for nutrient-dense foods, taxation of sugar-sweetened beverages, and regulation of food marketing have demonstrated effectiveness in improving dietary patterns and reducing disease burden [168]. Addressing these structural drivers is essential for enabling healthier choices at the population level.

7.6. Socioeconomic Inequality and Nutritional Vulnerability

The COVID-19 pandemic disproportionately affected socioeconomically disadvantaged populations, highlighting the intersection between food insecurity, chronic disease, and immune vulnerability [169,170].

Food insecurity is associated with both obesity and micronutrient deficiencies, while chronic psychosocial stress contributes to increased inflammatory signaling and metabolic dysregulation [171]. These overlapping vulnerabilities underscore the need for integrated social and nutritional policies that address both access and quality of food.

7.7. Nutrition in Pandemic Preparedness Frameworks

Traditional pandemic preparedness strategies have focused primarily on surveillance, vaccination, and acute care capacity [172]. However, the COVID-19 crisis demonstrated that healthcare systems must also be prepared for resource constraints and supply chain disruptions, particularly in critical care settings [173].

Rapid-response innovations, including the development and decentralized manufacturing of essential medical equipment such as ventilators, highlighted the importance of adaptable and resilient infrastructure during health emergencies [174,175]. Integrating such technological preparedness with population-level metabolic health strategies may strengthen overall system resilience.

7.8. Toward a Systems-Based Public Health Model

Achieving sustainable impact requires integration across individual behavior, healthcare systems, food environments, and policy structures [176,177]. Systems-based approaches enable the translation of scientific knowledge into practical interventions and support long-term metabolic and immune resilience [178].

In parallel, advances in sustainability science and circular resource management highlight the importance of efficient use of biological and material resources across systems [179,180]. Although originating from industrial and environmental domains, such approaches provide valuable conceptual frameworks for designing resilient and sustainable food and health systems. In this context, resource recovery approaches represent an additional dimension of system resilience, supporting the sustainable utilization of biological resources and contributing to more robust and adaptive food systems [181].

Despite growing evidence, the translation of nutritional knowledge into population-level outcomes remains constrained by structural and socioeconomic barriers [182]. Food environments, accessibility, and health system limitations may reduce the effectiveness of individual-level interventions. Therefore, future strategies must operate simultaneously across biological, behavioral, technological, and policy domains to achieve meaningful and equitable health outcomes. This can be accomplished through coordinated actions, including integration of nutrition into primary care, implementation of population-level dietary policies, expansion of digital health and tele-nutrition platforms, investment in education and community-based interventions, and alignment of food system sustainability with public health objectives.

8. Discussion

The evidence synthesized in this review supports a unifying principle: the severity of infectious diseases is strongly influenced by underlying metabolic and nutritional status [3,8,24,157,158]. Nutritional adequacy modulates key biological pathways involved in host defense, including inflammatory signaling through NF- κ B and inflammasome activation, interferon-mediated antiviral responses, mTOR-dependent lymphocyte proliferation, mitochondrial bioenergetics, endothelial nitric oxide regulation, adipose tissue inflammatory activity, and microbiota-derived immune signaling [6,24–28,38,45,47,52,154].

These systems operate as an interconnected network rather than as isolated mechanisms. Chronic low-grade inflammation associated with poor dietary patterns and metabolic dysfunction predisposes the host to immune dysregulation [4,5,15,16,60]. Sarcopenia reduces the availability of amino acids necessary for effective adaptive immunity and recovery from acute illness [20,21,39,54,106,109]. Dysbiosis impairs regulatory immune function and weakens gut-derived immune modulation, while endothelial dysfunction further amplifies thrombo-inflammatory processes [7,22,23,52,130,132,144]. Collectively, these interactions suggest that nutritional vulnerability is not limited to deficiency states alone, but includes broader disruptions in dietary quality, metabolic integrity, muscle health, and microbial homeostasis [24,25,40,59].

Within this framework, the Mediterranean dietary pattern emerges as a central integrative model. Its anti-inflammatory, cardiometabolic, microbiota-supportive, and antioxidant properties reflect the synergistic effects of whole dietary structures rather than isolated nutrients [17,18,50,84,85]. This is particularly relevant in the context of infectious disease resilience, where fiber, polyphenols, monounsaturated fats, omega-3 fatty acids, and micronutrient density act across multiple biological systems simultaneously [19,41–43,85,87,90,91,147,154]. Observational evidence also suggests an inverse association between Mediterranean diet adherence and COVID-19-related outcomes, although causal inference remains limited [86].

Importantly, the findings of this review support a shift away from reductionist approaches centered solely on individual nutrients or supplements. Although micronutrients such as vitamin D, zinc, selenium, and vitamin C are clearly involved in immune regulation, their effects occur within a broader nutritional matrix [9–14,24,25,28]. Whole dietary patterns provide cumulative and interactive effects that cannot be fully replicated by isolated supplementation strategies [17,18,61,162].

The Meta-COVID era therefore presents an opportunity to transition from reactive treatment models toward resilience-based prevention frameworks. However, despite strong mechanistic and epidemiological support, much of the current evidence linking nutrition to COVID-19 outcomes remains observational [3,8,24,28,158]. Heterogeneity in study design, dietary assessment methods, population characteristics, and clinical endpoints further complicates interpretation [162]. Accordingly, while biological plausibility is strong, definitive causal conclusions remain premature.

At the same time, the implications of this review extend beyond COVID-19 itself. The pandemic highlighted the broader importance of metabolic health, health literacy, public health preparedness, and system resilience in shaping outcomes during crisis conditions [165,169,172]. In this sense, nutrition should be understood not as a peripheral lifestyle variable, but as a foundational component of immune competence, chronic disease prevention, and population resilience [24,28,59,176].

9. Limitations

Several limitations should be considered when interpreting the findings of this review. First, the available evidence is dominated by observational studies, mechanistic investigations, and indirect clinical associations rather than randomized controlled trials specifically designed to assess nutritional interventions in viral infections [24,28,86,103,162]. This limits the ability to establish causality with confidence.

Second, considerable heterogeneity exists across the literature in terms of study populations, nutritional exposures, definitions of dietary patterns, biomarker selection, and outcome measures. Such variability reduces comparability across studies and complicates efforts to define optimal nutritional strategies for infectious disease resilience [59,162].

Third, nutrition-related exposures are inherently multidimensional. Dietary components rarely act in isolation, and their effects are strongly influenced by background metabolic health, age, physical activity, body composition, microbiota composition, and socioeconomic conditions [59,60,160,169,171]. This complexity makes reductionist interpretation difficult and reinforces the need for systems-based models.

Finally, population-level translation is constrained by structural determinants including food insecurity, unequal access to healthy foods, variable health literacy, and limitations in healthcare integration [160,163,167–171,182]. These factors may substantially influence both nutritional status and the feasibility of implementing preventive dietary strategies.

10. Future Directions

Future research should prioritize well-designed randomized controlled trials that examine the effects of dietary patterns, targeted nutritional interventions, and muscle-preserving strategies on infectious disease susceptibility, severity, and recovery [39,121,129,162]. Particular attention should be given to Mediterranean-style diets, protein adequacy in older and catabolic populations, microbiota-supportive interventions, and nutritional strategies relevant to long-COVID recovery [84,103,127,141,148,154].

Longitudinal and translational studies are also needed to clarify how metabolic health optimization influences preparedness for future pandemics and other systemic health threats [158,172]. Advances in microbiome science, immunometabolism, and nutrient signaling may help identify more precise biomarkers of resilience and response [35,36,57,62,154].

In parallel, future work should extend beyond biological mechanisms to implementation science and policy translation. Research is needed to determine how nutrition programs can be effectively scaled, integrated into healthcare systems, and adapted to diverse socioeconomic contexts [178,182]. Digital health, tele-nutrition, community-based interventions, and interdisciplinary care models may offer scalable pathways for improving access and long-term adherence [165,166,178].

Finally, resilient prevention frameworks should increasingly consider the intersection of public health, sustainability, and food system design. Systems thinking, circular resource management, and resource recovery approaches may help support more adaptive and sustainable nutrition environments at the population level [104,176,178–181].

11. Conclusions

The COVID-19 pandemic revealed a fundamental and often underrecognized principle: vulnerability to infectious disease is not random, but is profoundly shaped by underlying metabolic and nutritional status. The disproportionate burden of severe outcomes among individuals with obesity, insulin resistance, micronutrient deficiencies, sarcopenia, endothelial dysfunction, and dysbiosis reflects the convergence of multiple biological pathways that predispose to immune dysregulation and exaggerated inflammatory responses. Although much of the current evidence remains observational, the consistency of findings across epidemiological, clinical, and mechanistic domains supports the concept that metabolic health is a modifiable determinant of infectious disease

resilience. Importantly, these risk factors rarely occur in isolation; rather, they interact within a systems-level network linking diet, metabolism, immune function, musculoskeletal health, gut microbiota, and environmental context. A Meta-COVID prevention framework must therefore move beyond reductionist strategies and adopt an integrative systems-based approach. This includes prioritizing nutrient-dense dietary patterns, supporting adequate protein intake and skeletal muscle preservation, promoting microbiota diversity, improving health literacy, and addressing the structural determinants that shape dietary behavior and health outcomes. Without attention to these broader determinants, individual-level interventions are unlikely to achieve sustained population-level impact. The implications extend beyond COVID-19. Future preparedness strategies have traditionally focused on surveillance, vaccination, and acute care capacity, yet the pandemic demonstrated that host resilience and healthcare system adaptability are equally important. In this context, nutrition should be recognized not as an adjunctive therapy, but as a foundational component of preventive health infrastructure embedded within healthcare systems, education, policy, and sustainable food environments. In the Meta-COVID era, nutrition is best understood as a central determinant of biological resilience. Advancing this paradigm will require rigorous intervention research, interdisciplinary collaboration, and sustained policy commitment to strengthen population resilience against both infectious and chronic disease.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full term
ACE2	Angiotensin-Converting Enzyme 2
AGEs	Advanced Glycation End Products
ATP	Adenosine Triphosphate
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
DHA	Docosahexaenoic Acid
eNOS	Endothelial Nitric Oxide Synthase
EPA	Eicosapentaenoic Acid
IGF-1	Insulin-Like Growth Factor 1
IKK	IκB Kinase

IL	Interleukin
IRFs	Interferon Regulatory Factors
LPS	Lipopolysaccharide
MAVS	Mitochondrial Antiviral Signaling Protein
MCP-1	Monocyte Chemoattractant Protein-1
mTOR	Mechanistic Target of Rapamycin
mTORC1	Mechanistic Target of Rapamycin Complex 1
NF-κB	Nuclear Factor Kappa B
NK	Natural Killer
NLRP3	NOD-Like Receptor Family Pyrin Domain Containing 3
PRRs	Pattern Recognition Receptors
RAGE	Receptor for Advanced Glycation End Products
ROS	Reactive Oxygen Species
RXR	Retinoid X Receptor
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCFAs	Short-Chain Fatty Acids
SPMs	Specialized Pro-Resolving Mediators
TLR	Toll-Like Receptor
TMAO	Trimethylamine N-oxide
TNF-α	Tumor Necrosis Factor Alpha
Tregs	Regulatory T Cells
UPS	Ubiquitin-Proteasome System
UPFs	Ultra-Processed Foods
VDR	Vitamin D Receptor

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