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OBESITY AS AN IMMUNOMETABOLIC DISORDER: MECHANISMS OF IMMUNE IMPAIRMENT AND INCREASED SEVERITY OF INFECTIOUS DISEASES - A REVIEW OF CURRENT EVIDENCE

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ABSTRACT

Background: Obesity represents a major global health burden and is increasingly recognized as a complex immunometabolic disorder rather than a simple imbalance of energy intake and expenditure. Chronic low-grade inflammation, adipokine dysregulation, altered immune cell metabolism, and gut microbiota dysbiosis profoundly remodel immune responses in individuals with obesity. Growing evidence indicates that these alterations significantly affect susceptibility to infections, disease severity, and clinical outcomes, particularly in viral respiratory infections such as COVID-19 and influenza.

Aims: This narrative review aims to synthesize current epidemiological, mechanistic, and interventional evidence explaining why individuals with obesity experience more severe courses of infectious diseases. Particular attention is given to immunometabolic dysfunction, adipokine imbalance, inflammasome activation, microbiota-derived immune modulation, and the potential reversibility of immune impairment through metabolic interventions.

Methods: A comprehensive narrative literature review was conducted using PubMed, PubMed Central, Google Scholar, and ResearchGate. Eligible studies included randomized controlled trials, observational cohort and cross-sectional studies, mechanistic immunology research, microbiota studies, and systematic or narrative reviews focusing on adults with overweight or obesity. Evidence was synthesized qualitatively due to heterogeneity in study designs and outcomes.

Results: Across study types, obesity consistently emerged as an independent risk factor for immune dysfunction and severe infectious outcomes. Mechanistic studies demonstrated chronic activation of inflammatory pathways, including NLRP3 inflammasome signaling, leptin dominance with reduced adiponectin, impaired interferon responses, mitochondrial dysfunction, and exhaustion of T and NK cells. Microbiota studies revealed reduced diversity and depletion of short-chain fatty acid–producing bacteria. Clinical studies confirmed higher rates of hospitalization, intensive care admission, prolonged viral shedding, and mortality among individuals with obesity. Interventional studies showed that modest weight loss (5–10%) can partially restore immune function and reduce inflammatory burden.

Conclusion: Obesity profoundly impairs immune competence through interconnected metabolic, inflammatory, and microbiota-driven mechanisms, leading to increased susceptibility to infections and worse clinical outcomes. Although immunometabolic dysfunction is partially reversible, further long-term studies are required to determine its impact on clinical risk reduction.

KEYWORDS

Obesity, Immunometabolism, Infection Severity, Chronic Inflammation, Gut Microbiota, Vaccine Response

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Introduction

The rapidly increasing global prevalence of obesity has made understanding its immunological and clinical consequences a priority for translational research and public health. Obesity is no longer viewed solely as a disorder of energy balance; it is now recognized as a complex immunometabolic condition characterized by chronic, low-grade inflammatory activation ("meta-inflammation"), adipocyte dysfunction, dysregulated adipokine signaling, and extensive remodeling of immune responses at multiple cellular and molecular levels **[1]**.

Recent evidence confirms that the metabolic and inflammatory disturbances accompanying obesity substantially modulate the course of viral and bacterial infections, leading to increased susceptibility to infection, more severe disease, and a higher risk of complications **[2]**.

Mechanistically, expansion of adipose tissue results in adipocyte dysfunction and alterations in the adipokine profile, including a relative predominance of leptin (pro-inflammatory) over adiponectin (anti-inflammatory). This imbalance amplifies inflammatory signaling pathways and reprograms immune-cell metabolism **[2]**. Hyperactivation of the NLRP3 inflammasome and increased secretion of IL-1β and IL-18 promote mitochondrial dysfunction in immune cells and sustain chronic inflammation **[3]**. The resulting immunological phenotype is distinctive and includes an increased proportion of M1 macrophages, expansion

of effector-memory T cells with features of functional exhaustion, impaired natural killer (NK) cell activity, and attenuated production of type I and type III interferons **[4]**.

The gut microbiota also plays a critical role. Obesity is associated with reduced microbial diversity, an altered Firmicutes-to-Bacteroidetes ratio, and a depletion of short-chain fatty acid (SCFA)-producing bacteria, particularly butyrate-producing species **[5]**. SCFA deficiency impairs regulatory T cell (Treg) function and compromises intestinal barrier integrity, facilitating lipopolysaccharide (LPS) translocation and activation of Toll-like receptors **[6]**.

The clinical consequences of these disturbances are well documented. Cohort studies and meta-analyses have consistently demonstrated that obesity -particularly visceral obesity is associated with an increased risk of hospitalization, need for intensive care, and higher mortality in COVID-19 and influenza **[7]**. In addition, individuals with obesity more frequently exhibit prolonged viral shedding, which may have implications for transmission dynamics and the risk of severe complications **[8]**.

At the same time, interventional data suggest that improvement in metabolic status- through weight reduction, dietary interventions, or physical activity- may reverse some aspects of immunometabolic dysfunction. Moderate weight loss (5–10%) has been shown to reduce circulating levels of CRP, IL-6, and TNF-α and to normalize adipokine profiles, thereby promoting improved immune function **[9]**. However, these effects are heterogeneous and do not consistently translate into a clearly enhanced vaccine-induced immune response **[10]**.

Thus, the association between obesity, immune dysfunction, and infection severity is well established; nevertheless, critical research gaps remain. These include incomplete understanding of specific molecular pathways, the precise role of the gut microbiota, and the links between immunometabolic dysfunction and vaccine responsiveness **[11]**.

Aims

The aim of this narrative review is to provide a concise synthesis of contemporary epidemiological, interventional, and mechanistic evidence explaining why individuals with obesity experience more severe courses of infectious diseases. The review integrates data from randomized controlled trials, cohort and cross-sectional studies, and recent systematic reviews, analyzing the impact of metabolic dysregulation, chronic inflammation, impaired adipokine signaling, and microbiota alterations on immune system function. An additional objective is to assess the extent to which metabolic and microbiota-targeted interventions can partially reverse immunometabolic dysfunction and reduce the risk of severe infectious outcomes.

Research Questions

1. What are the principal molecular and cellular mechanisms through which obesity impairs immune responses and predisposes individuals to more severe infectious disease courses?
2. To what extent do alterations in gut microbiota composition and reduced SCFA production contribute to systemic immune dysregulation in individuals with obesity?
3. How strong and consistent is the clinical association between obesity (general and visceral) and infection severity, particularly in COVID-19 and influenza?
4. Do metabolic interventions (weight loss, dietary modification, physical activity) lead to reversal of selected immune defects, and does this translate into a reduced risk of severe infectious complications? How robust and durable are these effects?
5. How does obesity affect short- and long-term vaccine-induced immune responses (seroconversion, neutralizing antibody titers, and the rate of immune waning)? Which factors modify this effect?

Methods

Exclusion Criteria

Studies were excluded when they did not specifically address the interplay between obesity and immune function, when obesity was not clearly defined or stratified, or when infectious outcomes were not separated from metabolic comorbidities. Research focusing solely on pediatric populations, bariatric surgery without immunological endpoints, or animal work lacking translational relevance was also excluded. Mechanistic studies were omitted when they did not evaluate pathways pertinent to immunometabolic dysfunction, such as chronic inflammation, adipokine imbalance, dysbiosis, or interferon signalling **[12,13]**. Clinical studies were excluded if infectious outcomes were confounded by uncontrolled variables or if they lacked stratification by BMI or metabolic phenotype, which is essential in assessing obesity-related infection severity **[14,15]**.

Eligibility Criteria

Studies were eligible if they evaluated adults or adolescents with overweight or obesity and assessed immunological, metabolic, microbiota-related, or clinical infectious outcomes. Mechanistic and immunology-focused studies were included when they examined pathways such as leptin–adiponectin imbalance, NLRP3 inflammasome activation **[13]**, immune cell exhaustion **[12]**, and SCFA-mediated immunoregulation **[16,17]**. Clinical research was eligible when it explored infection severity, hospitalization, ICU admission, mortality, or viral shedding among individuals with obesity **[14]**. Interventional studies were included when weight reduction, dietary modification or physical activity influenced inflammatory markers or immune function. Vaccine-response studies were included when assessing antibody titres, neutralizing capacity, T-cell responses, or durability of immunity in individuals with elevated BMI **[18]**.

Search Strategy

The literature search was conducted between January 2024 and January 2025 using PubMed, PubMed Central (PMC), Google Scholar, and ResearchGate. Search terms combined concepts related to obesity, immunometabolism, viral pathogenesis, bacterial infection susceptibility, microbiota dysbiosis, SCFA deficiency and immune exhaustion. Foundational mechanistic evidence informing search keywords included chronic low-grade inflammation in obesity **[12]**, immune dysregulation linked to leptin dominance, inflammasome-driven IL-1β and IL-18 release **[13]**, impaired NK and interferon responses **[12]** and loss of SCFA-producing gut bacteria **[16]**. Clinical keywords were shaped by well-established data linking obesity to increased severity of COVID-19 and influenza **[15]** as well as prolonged viral shedding **[14]**. Search refinement continued iteratively until conceptual saturation was reached.

Study Types Included

This review incorporates randomized controlled trials, observational cohort studies, cross-sectional analyses, mechanistic immunology studies, microbiota research and systematic or narrative reviews. Randomized trials were particularly relevant where they demonstrated reversible aspects of immunometabolic dysfunction through weight reduction or metabolic improvement, including reductions in CRP, IL-6 and TNF-α and enhanced neutrophil and macrophage function. Cohort studies were included for their ability to evaluate real-world risk of severe outcomes in obesity across pathogens such as SARS-CoV-2 and influenza **[14,15]**. Cross-sectional studies were selected when they provided detailed immune phenotyping such as reduced naïve T-cell counts, NK-cell dysfunction and markers of immune exhaustion **[18,19]**. Mechanistic studies were incorporated where they elucidated metabolic–immune pathways, mitochondrial dysfunction and microbiota-driven inflammation **[16]**. Systematic reviews helped contextualize the broader biological and clinical implications **[20]**.

Data Collection Process

Titles and abstracts were screened for relevance to immunometabolic mechanisms, host defence, infection outcomes, microbiota alterations or metabolic interventions. Full-text articles were assessed with attention to methodological clarity, obesity classification, immune endpoints and adjustment for confounding variables. Key data extracted from mechanistic studies included inflammatory pathways, adipokine signalling, immune cell phenotypes and microbiota composition **[19,20]**. From interventional trials, emphasis was placed on changes in inflammatory markers, immune function and metabolic biomarkers following weight loss or dietary modification. For cohort studies, data extraction focused on hospitalization rates, ICU admission, mortality and viral shedding duration **[14,20]**. Vaccine studies contributed information on antibody titres, neutralizing activity and duration of immunity in individuals with obesity **[18]**.

Quality Assessment

A qualitative appraisal approach was used, consistent with standards for narrative evidence synthesis. Greater interpretative weight was assigned to high-quality cohort studies with rigorous adjustment for comorbidities **[14]** and to randomized trials showing clear causal links between metabolic improvement and immune restoration. Mechanistic studies were evaluated based on biological plausibility and consistency with clinical evidence, particularly those examining NLRP3 activation **[13]**, adipokine imbalance and SCFA deficiency **[17]**. Microbiota studies were assessed for methodological robustness, including sequencing techniques and control for dietary factors **[16]**. Systematic reviews were judged based on comprehensiveness and methodological transparency **[20]**.

Synthesis Approach

Because the included literature spanned diverse methodologies, populations and outcomes, quantitative pooling was not feasible. Instead, evidence was synthesised narratively, integrating immunological, metabolic and microbiota-driven pathways with real-world infectious outcomes to construct a cohesive explanatory framework. Mechanistic studies provided biological underpinnings of immunometabolic dysfunction, cross-sectional analyses described the immune phenotype of obesity, cohort studies defined clinical consequences, and randomized trials assessed reversibility through metabolic interventions. Systematic reviews were used to anchor points of convergence and highlight consistent mechanistic pathways across the literature **[20]**. This thematic synthesis approach is recommended in high-quality biomedical narrative reviews when heterogeneity precludes meta-analysis.

PRISMA Summary

The search process initially identified approximately 520 records. After removing duplicates and excluding studies unrelated to immune function, metabolic dysfunction or infection outcomes in obesity, 140 abstracts underwent eligibility screening. Eighty full-text articles were assessed in detail, and 58 studies ultimately met inclusion criteria across mechanistic, clinical, microbiota and interventional domains. This structured, PRISMA-aligned process ensured transparency and completeness while maintaining the flexibility necessary for a narrative synthesis. The final dataset integrates evidence from randomized trials, large-scale cohorts, cross-sectional analyses, microbiota studies and systematic reviews to capture the multidimensional relationship between obesity, immune dysregulation and infection severity **[12-20]**.

Results

1. Randomized Controlled Trials (RCTs)

Randomized controlled trials provide the most direct evidence that metabolic modifications and weight reduction can reverse selected immunometabolic disturbances observed in obesity. Interventions based on energy deficit, increased physical activity, or dietary therapy consistently lead to reductions in inflammatory markers such as CRP, IL-6, and TNF-α, even with relatively modest weight loss of approximately 5-10% **[21]**. These changes are accompanied by regulation of the adipokine axis, including decreased leptin and increased adiponectin levels, reflecting reduced inflammatory activity of adipose tissue. RCTs assessing immune function have demonstrated improvements in neutrophil activity, normalization of chemotaxis, and enhanced macrophage phagocytic capacity following weight reduction **[22]**. Reductions in oxidative stress and improvements in mitochondrial function within immune cells indicate that metabolic and immunological effects are tightly interconnected. Selected RCTs also report improvements in functional immune responses to pathogens or vaccination. After 8-12 weeks of metabolic intervention, patients exhibited increased T-cell activation following antigenic stimulation and favorable changes in interferon responses. Data on vaccine-induced immunity remain heterogeneous; however, some studies suggest that improvement of metabolic status prior to immunization enhances both humoral and cellular immune responses **[21]**. Importantly, RCTs demonstrate that even short-term metabolic interventions lead to measurable changes in immune phenotypes, including reduced expression of T-cell exhaustion markers, improved NK-cell function, and enhanced responsiveness of monocytes to pathogen-associated signals. These findings suggest that immunometabolic dysfunction in obesity is at least partially reversible.

2. Cohort Studies

Cohort studies provide a consistent body of evidence confirming that obesity- particularly visceral obesity is an independent risk factor for more severe courses of viral and bacterial infections. In numerous COVID-19 cohorts, patients with a BMI ≥30 exhibited a higher risk of hospitalization, faster progression to acute respiratory failure, increased need for mechanical ventilation, and higher mortality rates **[23]**. These associations persisted after adjustment for age, sex, and comorbidities. A particularly consistent finding across cohort studies is prolonged viral shedding in individuals with obesity, documented in both SARS-CoV-2 and influenza infections. Individuals with obesity may shed virus for several days longer than non-obese individuals, potentially increasing transmission risk and indicating impaired antiviral immune responses. Cohort studies further demonstrate that metabolic components of the metabolic syndrome including insulin resistance, NAFLD, hypertension, and dyslipidemia- worsen infectious outcomes independently of BMI **[24]**. These cohorts also assessed multiple inflammatory and immunological biomarkers associated with severe disease in patients with obesity, including elevated IL-6 levels, reduced T-cell responsiveness, diminished NK-

cell cytotoxicity, and dendritic cell dysfunction. Additionally, cohort analyses reveal a strong association between visceral adiposity (measured by waist circumference or waist-to-hip ratio) and infection severity, suggesting that not only the quantity but also the distribution of adipose tissue determines the immunological risk profile.

3. Cross-Sectional Studies

Cross-sectional studies provide detailed characterization of the immunological phenotype of obesity, documenting multiple abnormalities affecting both innate and adaptive immunity. Populations with obesity consistently exhibit elevated inflammatory markers (CRP, IL-6, TNF-α), reflecting chronic low-grade immune activation [25]. Analyses of T lymphocytes reveal reduced numbers of naïve T cells, expansion of memory T-cell populations, and increased expression of exhaustion markers such as PD-1 and TIM-3. Concurrently, studies demonstrate that NK cells in obesity exhibit reduced cytotoxic capacity and impaired production of type I and type III interferons [26], helping to explain increased susceptibility to viral infections. Gut microbiota studies in populations with obesity document characteristic features of dysbiosis, including reduced microbial diversity, an increased Firmicutes-to-Bacteroidetes ratio, and depletion of SCFA-producing bacteria, particularly butyrate producers [27]. Moreover, cross-sectional studies reveal increased lipotoxicity and oxidative stress in immune cells of individuals with obesity, impaired mitochondrial function in lymphocytes, and dysregulated glucose and fatty acid metabolism.

4. Systematic and Narrative Reviews

Systematic reviews emphasize chronic activation of the NLRP3 inflammasome, increased secretion of IL-1β and IL-18, and the regulatory roles of leptin and adiponectin in shaping immune responses **[22]**. Reviews focusing on the gut microbiota highlight that SCFAs- particularly butyrate are critical for maintaining tolerogenic immune responses and regulatory T-cell (Treg) function **[28]**. Their deficiency in obesity promotes activation of the gut–immune axis and represents an important mechanism exacerbating immune dysfunction. With respect to vaccine responses, reviews indicate that individuals with obesity may initially generate normal or even elevated antibody titers following vaccination; however, protective immunity wanes more rapidly, and cellular immune responses are more susceptible to early decline **[29]**. Narrative reviews extend these findings by emphasizing study heterogeneity while identifying a shared conclusion: obesity disrupts immune function across multiple dimensions- metabolic, hormonal, inflammatory, and microbiota-related.

5. Comparative Interpretation

Across study types, obesity consistently emerges as a major determinant of immune dysfunction and heightened vulnerability to infectious diseases. Randomized controlled trials offer high-quality mechanistic evidence, demonstrating that even modest weight loss improves inflammatory markers, adipokine balance, and innate immune cell function **[30,31]**. Cohort studies reinforce these findings in clinical settings, showing that individuals with obesity face substantially higher rates of severe infection, hospitalization, prolonged viral shedding, and mortality across multiple pathogens, including SARS-CoV-2 and influenza. Cross-sectional studies deepen mechanistic understanding by characterizing the immunological phenotype of obesity- chronic low-grade inflammation, impaired interferon responses, NK-cell dysfunction, lymphocyte exhaustion, and dysbiosis- all of which contribute to diminished host defense **[32,33]**. Systematic and narrative reviews integrate these data, highlighting strong biological plausibility and convergent evidence across models, while also noting persistent gaps such as heterogeneity of metabolic profiles, short duration of interventional studies, and variable methods of immune assessment. Collectively, the evidence indicates that obesity represents a multifaceted immunometabolic disorder that substantially increases infection severity and disrupts both innate and adaptive immunity. Although the complexity of immunometabolism poses challenges for causal inference, findings from clinical, observational, and mechanistic research collectively support a coherent causal framework linking obesity to impaired immune resilience and worse infectious outcomes.

Discussion

The findings presented in the *Results* section, together with previous literature, allow for a deeper reflection on the complex mechanisms linking obesity with impaired immune function and more severe courses of infectious diseases. In this discussion, the key mechanisms, the strength of the available evidence, limitations of existing studies, as well as clinical and research implications are addressed.

Mechanistic and immunological aspects of dysfunction

Immunometabolic mechanisms such as chronic inflammation of adipose tissue, alterations in adipokine secretion, inflammasome activation, and shifts in immune cell populations, appear to be central to explaining the increased susceptibility to infections observed in individuals with obesity. Numerous studies indicate that adipose tissue functions as an active endocrine and immunological organ which, under conditions of energy excess and adipocyte expansion, generates excessive production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and chemokines that recruit immune cells, leading to chronic, low-grade inflammation ("metaflammation") **[34–36]**.

Persistent inflammatory stimulation and an altered adipokine profile (e.g., elevated leptin and reduced adiponectin levels) may impair normal immune cell functions, affecting both innate and adaptive immunity. Such shifts can weaken the ability to respond effectively to infections, drive excessive production of inflammatory mediators, and promote oxidative stress, ultimately reducing the efficiency of immune responses **[36–38]**.

In addition, the gut microbiota and its interactions with the immune system play a significant role. In obesity, dysbiosis is frequently observed, characterized by reduced microbial diversity, shifts in taxonomic composition, impaired production of short-chain fatty acids (SCFAs), and abnormal intestinal barrier permeability **[39,40]**.

Reduced availability of SCFAs which exert anti-inflammatory and immunomodulatory effects- together with increased translocation of lipopolysaccharide (LPS), may lead to activation of Toll-like receptors and systemic inflammatory stimulation, further burdening immune homeostasis **[40–42]**.

Collectively, these mechanistic data provide a strong biological rationale for the clinically observed correlation between obesity and more severe infectious disease courses.

Clinical correlates and epidemiological significance

From a clinical and epidemiological perspective, numerous analyses including cohort studies, cross-sectional investigations, and systematic reviews confirm that obesity, particularly visceral obesity, is associated with an increased risk of severe infection, hospitalization, poorer clinical outcomes, and, in the context of viral pathogens such as SARS-CoV-2 and influenza viruses, prolonged viral shedding and impaired vaccine responses **[43–46]**.

The strength and consistency of this association across diverse populations indicate that obesity should be regarded as a significant and independent risk factor for infectious diseases, with direct implications for clinical practice, including prevention strategies, vaccination prioritization, and risk management **[43,44]**.

Potential of metabolic and microbiota-targeted interventions

Several interventional and lifestyle-based studies (weight reduction, dietary modification, physical activity) suggest that improvement in metabolic status may partially reverse immunometabolic dysfunction by reducing levels of pro-inflammatory mediators, normalizing adipokine profiles, and improving immune function. These findings raise hope that "revitalization" of the immune system and a reduction in the risk of severe infections may be achievable in individuals with obesity **[38,45]**.

Moreover, an increasing number of studies suggest that modulation of the gut microbiota (e.g., through diet, prebiotics, or probiotics) may represent a promising adjunct to interventional strategies. Restoration of a beneficial microbial composition and SCFA production may improve intestinal barrier integrity, reduce endotoxemia, and alleviate chronic inflammation **[39–42]**.

Limitations and gaps in the current literature

Despite the growing number of publications, several important limitations and gaps must be considered when interpreting the available evidence:

Heterogeneity of studies: Variability in obesity definitions (BMI versus visceral obesity), dietary and interventional protocols, and study populations complicates comparisons across studies and limits the formulation of universal conclusions **[45]**.

Causality versus correlation: Many studies are observational and correlational in nature, making it difficult to disentangle the direct effects of obesity on immunosuppression from the contribution of coexisting factors (e.g., micronutrient-poor diets, low physical activity, comorbid conditions) **[46]**.

Lack of long-term interventional data: Although some studies demonstrate that weight loss improves inflammatory and immunological markers, large-scale, long-term interventional trials are lacking, making it difficult to assess the durability of effects or their impact on hard clinical endpoints such as infection incidence, hospitalization, and mortality **[38,45]**.

Complexity of the gut microbiota and difficulty in identifying key mediators: The gut microbiota is highly dynamic and influenced by multiple factors (diet, genetics, environment). Although dysbiosis and reduced SCFA production are frequently observed, it remains unclear which specific microbial changes are most clinically relevant, limiting translational application **[39–42]**.

Lack of standardized assessments of immune response and definitions of "immunity" in obesity: Many studies focus primarily on inflammatory markers rather than functional immune outcomes (e.g., response to infection, vaccine efficacy) **[45,46]**.

Implications and recommendations for future research

Based on the current state of knowledge, the following directions for future research and action are recommended:

- Long-term, prospective interventional studies assessing not only immunological and metabolic changes but also meaningful clinical outcomes (infection incidence and severity, vaccine responses, hospitalizations).
- Studies investigating the gut microbiota as a therapeutic target, including dietary, prebiotic, and probiotic interventions that modulate microbial composition, SCFA production, and intestinal barrier function, with assessment of effects on immunocompetence.
- Standardization of definitions and measurement methods for immunological dysfunction in obesity, including biomarker panels and functional immune assays (e.g., vaccine response, immune performance tests).
- Identification of high-risk subpopulations, particularly individuals with visceral obesity, metabolic dysfunction, dysbiosis, and low physical activity, to target interventions where they may have the greatest impact.
- Integration of preventive and health-promoting strategies, including healthy diet, physical activity, microbiota-targeted interventions, and vaccination strategies, as components of comprehensive care for individuals with obesity.

Conclusions

Obesity should be regarded as a systemic immunometabolic disorder with profound consequences for host defence against infectious diseases. The evidence synthesized in this review demonstrates that chronic low-grade inflammation, adipokine imbalance, immune cell dysfunction, and gut microbiota dysbiosis collectively impair both innate and adaptive immune responses in individuals with obesity. These mechanisms provide a biologically plausible explanation for the consistently observed associations between obesity and increased infection severity, prolonged viral shedding, poorer clinical outcomes, and altered vaccine responses.

Importantly, data from interventional studies suggest that immunometabolic dysfunction is not entirely irreversible. Modest weight loss and metabolic improvement can attenuate systemic inflammation, normalize adipokine profiles, and partially restore immune cell function. However, the durability of these effects and their translation into meaningful reductions in infection-related morbidity and mortality remain insufficiently studied.

Future research should prioritize long-term, well-controlled interventional trials incorporating functional immune endpoints, standardized immunophenotyping, and clinically relevant outcomes such as infection incidence and vaccine effectiveness. Additionally, targeting the gut microbiota represents a promising adjunctive strategy to restore immune homeostasis in obesity. Recognizing obesity as a modifier of immune resilience has critical implications for public health policy, risk stratification, vaccination strategies, and the clinical management of infectious diseases.

Disclosure

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All authors have read and agreed to the published version of the manuscript.

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