REVIEW ARTICLE

Neuro-immune communication: a narrative review on vagus nerve stimulation and immunomodulation

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ABSTRACT

Background: The nervous and immune systems are intricately connected and engage in continuous bidirectional communication that is essential for maintaining physiological homeostasis. Recent advances have highlighted the pivotal role of the vagus nerve in the modulation of immune responses via the cholinergic anti-inflammatory pathway. This narrative review explores the mechanisms and clinical implications of vagus nerve stimulation (VNS) in regulating immune function, focusing on inflammatory and autoimmune diseases, pain modulation, and emerging applications in conditions such as COVID-19.

Methods: A comprehensive literature search was conducted using PubMed, Google Scholar, and Scopus to identify relevant preclinical and clinical studies of VNS and immunomodulation. Studies were selected on the basis of their relevance to neuro-immune communication, inflammatory markers, and clinical outcomes.

Results: Evidence from animal models and human trials demonstrates that VNS can reduce pro-inflammatory cytokines (e.g., TNF-α and IL-6), enhance anti-inflammatory mediators (e.g., IL-10), and improve disease outcomes in sepsis, rheumatoid arthritis, cardiovascular disease, diabetes, and chronic pain. Non-invasive VNS also has the potential to modulate immune responses in COVID-19. The psychoneuroimmunological perspective emphasizes the influence of neural activity and psychological stress on immune regulation.

Conclusion: VNS offers a novel and minimally invasive strategy for modulating immune function in a spectrum of diseases characterized by chronic inflammation and autonomic imbalance. As research progresses, stimulation protocols have been optimized. Expanding clinical trials will be key to fully realizing the therapeutic potential of neuro-immune modulation.

Keywords: Neuroimmune cross talking, VNS, Immunomodulation, Cholinergic Anti-inflammatory Pathway.

Introduction

Neuro-immune communication represents a complex and highly coordinated system of bidirectional interactions between the nervous and immune systems that is essential for maintaining physiological homeostasis [1-3]. Neural circuits can modulate both innate and adaptive immune responses, while immune mediators, which include cytokines and chemokines, can influence neural activity and behavior [1-3]. This dynamic interplay has been implicated in a wide range of physiological and pathological processes, including inflammation, infection, autoimmunity, and neurodegenerative disease[1-3].

Substantial evidence supports the role of neural reflex pathways in regulating immune function, particularly in the autonomic nervous system [4]. Both the sympathetic and parasympathetic pathways contribute to immune modulation, with the vagus nerve emerging as a key mediator of this neuro-immune interface through the cholinergic anti-inflammatory pathway [1-6].

Despite the significant advances in our understanding of neuro-immune interactions, some important gaps still remain. The precise mechanisms by which neural signals

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Received: 17 March 2026 | **Revised (1):** 06 Apr 2026 | **Revised (2):** 21 Apr 2026 | **Revised (3):** 09 May 2026 | **Accepted:** 14 May 2026

modulate human immune responses have not been fully elucidated; in addition, translation of these mechanisms into effective therapeutic strategies remains limited [1-3]. Furthermore, the clinical relevance of targeting the autonomic pathways in chronic inflammatory and autoimmune diseases is an area of active research.

Vagus nerve stimulation (VNS), originally developed to treat epilepsy and depression, has gained increasing attention as a potential bioelectronic therapy capable of modulating immune responses [7-11]. Both invasive and non-invasive VNS approaches have demonstrated anti-inflammatory effects in preclinical models and early clinical studies, suggesting their potential applications across a spectrum of inflammatory and immune-mediated conditions [7,9,10].

The aim of this narrative review is to provide a comprehensive overview of the mechanisms underlying neuro-immune communication, with a particular focus on the VNSs role in immunomodulation. We further examine the current evidence supporting its clinical applications, explore emerging therapeutic indications, and discuss the limitations and future directions of this evolving field. Narrative reviews aim to provide a critical and integrative interpretation of the literature, rather than an exhaustive quantitative synthesis.

Methods

Study design

This narrative review was conducted to provide a comprehensive and critical synthesis of the current evidence on VNS and its role in immunomodulation. Given the evolving and relatively novel nature of this field, the objective of this review was not to perform an exhaustive systematic analysis but rather to integrate and interpret available mechanistic and clinical evidence to highlight key concepts, therapeutic potential, and emerging applications.

Search strategy and timeframe

A literature search was performed using PubMed, Scopus, and Google Scholar to identify relevant studies published between 2000 and April 2025 (at the time of manuscript preparation). This timeframe was selected to capture both foundational discoveries in neuro-immune communication and more recent advances in bioelectronic medicine. The search strategy included combinations of the following keywords: “VNS,” “cholinergic anti-inflammatory pathway,” “neuro-immune communication,” “psychoneuroimmunology,” “inflammation,” “cytokines,” “rheumatoid arthritis,” “sepsis,” “cardiovascular disease,” “diabetes,” “COVID-19,” and “pain regulation.” Boolean operators (AND, OR) were used to optimize search sensitivity. In addition, reference lists of relevant articles were manually screened to identify additional pertinent studies.

Eligibility criteria

Studies were considered eligible if they investigated VNS or related neuro-immune mechanisms and reported immunological or clinical outcomes, including cytokine modulation and inflammatory markers. Both preclinical studies and human studies were included, encompassing clinical trials, systematic reviews, and meta-analyses. Only articles published in English were considered. Studies were excluded if they did not address VNS or neuro-immune interactions, lacked accessible full text, or consisted solely of editorial opinions without supporting data.

Study selection

Study selection was performed through an initial screening of titles and abstracts, followed by a full-text review of potentially relevant articles. When multiple reviewers were involved, selection was conducted through collaborative discussion and consensus. A total of approximately 120-150 studies were initially identified through database searching. Following relevance screening and removal of non-pertinent articles, approximately 60-80 studies were included in the final synthesis.

Data synthesis

Given the narrative nature of this review and the heterogeneity of available evidence, findings were synthesized thematically rather than quantitatively. Emphasis was placed on integrating mechanistic insights, including the cholinergic anti-inflammatory pathway and related molecular mediators, with clinical applications across different disease states. The predominance of preclinical data, variability in study design, and the limited number of large-scale clinical trials were taken into consideration during the interpretation of the findings.

Results and Discussion

The cholinergic anti-inflammatory pathway

Autonomic dysfunction is increasingly implicated in the pathogenesis of several inflammatory diseases, including rheumatoid arthritis, diabetes mellitus, and sepsis [4]. However, whether this dysfunction is the primary driver of inflammation or a secondary consequence of ongoing immune activation remains unclear [4]. The cholinergic anti-inflammatory pathway provides important insights into this relationship, suggesting that neural circuits, particularly those mediated by the vagus nerve, play a critical role in regulating immune responses and maintaining inflammatory homeostasis [1-5].

Experimental studies have demonstrated that VNS significantly reduces the release of pro-inflammatory cytokines, modulates coagulation pathways, and prevents organ dysfunction in sepsis and endotoxemia models [12]. In addition to suppressing inflammation, VNS has been shown to actively promote resolution through mechanisms such as enhanced efferocytosis and biosynthesis of specialized pro-resolving mediators (SPMs). These effects are partially mediated by pathways involving Alox15 and activation of the α7 nicotinic acetylcholine receptor (α7nAChR) on immune cells [13].

Mechanistic insights into the cholinergic anti-inflammatory pathway provide a critical framework for understanding the clinical effects of VNS across diverse disease states. Activation of the α7 nicotinic acetylcholine receptor (α7nAChR) on immune cells has been shown to inhibit the release of pro-inflammatory cytokines such as TNF-α and IL-6, while promoting anti-inflammatory mediators, including IL-10 [7,13]. Simultaneously, VNS-mediated activation of pro-resolving pathways, including Alox15-dependent lipid mediator biosynthesis, facilitates the resolution of inflammation rather than merely suppressing it [13].

These molecular and cellular mechanisms directly inform clinical observations in conditions such as rheumatoid arthritis, sepsis, and cardiovascular disease, where reductions in systemic inflammation and improvements in disease activity have been reported after VNS treatment [7,8,14-22]. Thus, the therapeutic potential of VNS is best understood as the translation of neuro-immune regulatory pathways into clinically measurable outcomes, bridging mechanistic biology with applied bioelectronic medicine [3,7].

Clinical applications of VNS

Sepsis

Short-term high-frequency VNS (e.g., 30 minutes) has shown immediate anti-inflammatory effects, making it a promising adjunct for acute sepsis management [7,9,10]. However, it can take several months to demonstrate a significant effect in epilepsy. In preclinical models of sepsis, VNS suppressed cytokine storms, stabilized hemodynamics, and improved survival rates. Small-scale human trials are underway to assess VNS's utility in sepsis management [8]. A schematic overview of the cholinergic anti-inflammatory pathway and its key mediators is provided in Figure 1.

Cardiovascular diseases

Studies have demonstrated an association between reduced vagal tone and increased inflammatory markers, supporting the role of autonomic dysfunction in cardiovascular disease [16,23]. VNS has been shown to improve heart rate variability and reduce inflammatory signaling in preclinical models [7,14]. However, clinical evidence remains limited and heterogeneous, with variability in study design, patient selection, and stimulation protocols, which complicates interpretation of its true therapeutic benefit in cardiovascular settings [7,24].

The observed interplay between autonomic dysfunction and systemic inflammation in cardiovascular disease highlights a broader pathophysiological framework that extends beyond a single organ system. In particular, the relationship between vagal activity, inflammatory signaling, and metabolic regulation suggests that similar neuro-immune mechanisms may also contribute to the development and progression of metabolic disorders such as diabetes mellitus [7,16]. Given the well-established role of chronic low-grade inflammation and autonomic imbalance in insulin resistance and glucose dysregulation, the potential immunomodulatory effects of VNS warrant consideration within the context of metabolic disease. This provides a conceptual basis for exploring the role of VNS in diabetes mellitus, where modulation of inflammatory pathways may influence both metabolic and systemic outcomes [7].

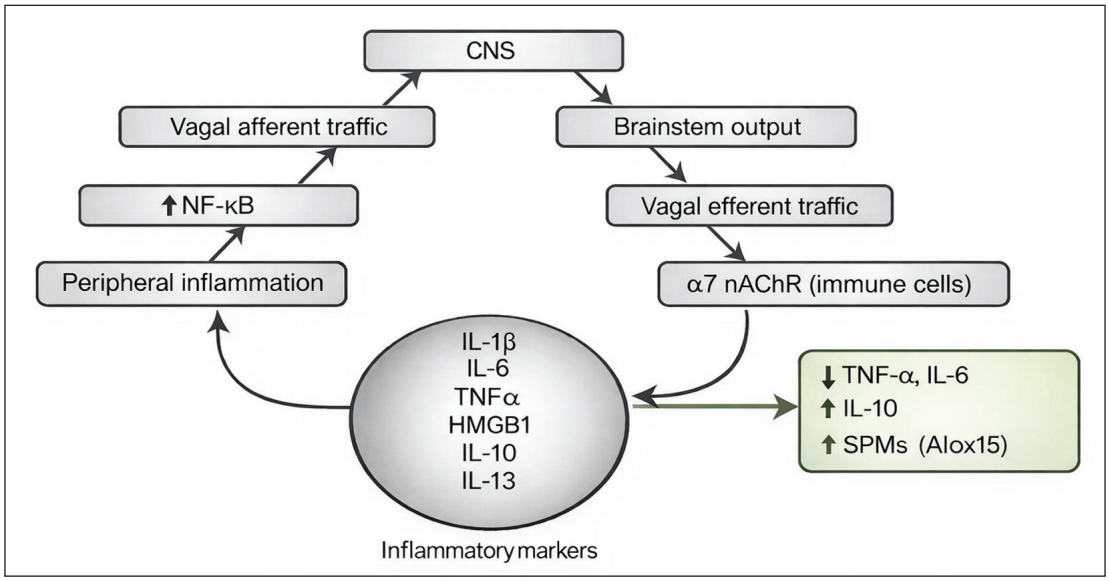

Figure 1. *Schematic representation of the cholinergic anti-inflammatory pathway. Peripheral inflammatory signals activate afferent vagal pathways to the brainstem, which in turn initiate efferent vagus nerve signaling. This results in acetylcholine release, which binds to α7 nicotinic acetylcholine receptors (α7nAChR) on immune cells, leading to suppression of pro-inflammatory cytokines (TNF-α, IL-6), enhancement of anti-inflammatory cytokines (IL-10), and promotion of inflammation resolution via specialized pro-resolving mediators (SPMs) through Alox15-dependent pathways [3,7,13]. Created by the authors using BioRender.com.*

Diabetes mellitus

The role of VNS in metabolic regulation remains an area of emerging interest. Preclinical studies suggest that vagal modulation may influence glucose homeostasis and inflammatory pathways associated with insulin resistance [7,25]. Nevertheless, current evidence is limited by a lack of robust clinical trials, and the extent to which these mechanistic findings translate into clinically significant metabolic improvements in humans remains unclear.

Rheumatoid arthritis

Early clinical trials indicate safety, tolerability, and potential efficacy [10]. Early trials in rheumatoid arthritis patients demonstrated that implanted VNS reduced TNF-α levels and improved disease activity scores, providing symptomatic relief even in cases refractory to biologic therapies [26]. Miniaturized VNS devices have shown promise as cost-effective alternatives to biologics in rheumatoid arthritis treatment [17].

VNS and pain: the psychoneuroimmunology perspective

Psychoneuroimmunology provides a unifying framework that links neural activity, psychological stress, and immune regulation, extending the concept of neuro-immune communication beyond reflexive pathways [27–30]. Chronic psychological stress and mood disorders have been consistently associated with dysregulation of autonomic function, particularly reduced vagal tone, which in turn contributes to a pro-inflammatory state characterized by elevated cytokines such as IL-6 and TNF-α [16,31]. This relationship reinforces the central role of the vagus nerve as a critical interface between emotional, neural, and immune processes [3,16,32].

In this context, VNS may exert therapeutic effects through direct modulation of immune pathways as well as by restoring autonomic balance and attenuating stress-induced inflammatory responses [7,27]. Pain perception, which is closely linked to immune activation, is influenced by pro-inflammatory cytokines that sensitize nociceptive pathways and contribute to both peripheral and central sensitization [27,31]. Therefore, the analgesic effects of VNS observed in clinical studies may reflect an integrated mechanism involving immunomodulation and the regulation of neural circuits [33,34].

VNS in COVID-19 and systematic review evidence

A recent meta-analysis evaluating non-invasive VNS (nVNS) in patients with COVID-19 demonstrated a significant increase in IL-10 levels, whereas no statistically significant changes were observed in CRP, IL-6, cortisol, or D-dimer levels [35]. These findings raise important questions regarding the clinical relevance of VNS-induced immunomodulation, as IL-10 elevation may not translate into a meaningful suppression of systemic inflammation. The absence of consistent changes in key inflammatory markers, such as IL-6 and CRP, may reflect either insufficient stimulation intensity or limited systemic efficacy of nVNS in acute inflammatory states [24,35-37].

Furthermore, the included studies were characterized by relatively small sample sizes, short follow-up durations, and heterogeneous stimulation protocols, all of which may have limited the statistical ability to detect clinically significant effects [17]. Differences in VNS modalities, including transcutaneous and invasive approaches, may also contribute to variability in outcomes, as invasive VNS is associated with more robust and sustained autonomic and immunological responses in other disease settings [24]. These limitations underscore the need for larger, well-designed, randomized controlled trials with standardized stimulation parameters to better define the role of VNS in COVID-19 and other acute inflammatory conditions.

Collectively, the clinical applications of VNS across diverse disease states suggest a shared mechanistic foundation centered on modulation of systemic inflammation and autonomic balance. Despite differences in disease-specific pathophysiology, conditions such as rheumatoid arthritis, sepsis, cardiovascular disease, and diabetes mellitus exhibit common features of chronic low-grade inflammation and dysregulated immune responses [4,7]. Across these conditions, VNS appears to exert its therapeutic effects primarily through activation of the cholinergic anti-inflammatory pathway, leading to suppression of pro-inflammatory cytokines and restoration of immune homeostasis [13]. However, the magnitude and consistency of these effects vary depending on disease context, study design, and stimulation parameters. Notably, while inflammatory modulation is consistently observed in preclinical models, clinical outcomes in human studies remain more variable, reflecting differences in patient populations and methodological heterogeneity [24]. These observations highlight an important conceptual framework in which VNS may be understood not as a disease-specific intervention, but rather as a systemic immunomodulatory strategy with broad applicability across inflammatory conditions. Nevertheless, further studies are required to delineate disease-specific responses and optimize therapeutic protocols for different clinical settings [7].

Conflicting evidence

Despite accumulating evidence supporting the immunomodulatory effects of VNS, findings across studies remain heterogeneous and, in some cases, conflicting. The variability in outcomes may be attributed to differences in study design, patient populations, disease states, and stimulation parameters [7,24]. Notably, invasive VNS appears to produce more consistent reductions in pro-inflammatory cytokines such as TNF-α and IL-6. Whereas nVNS has demonstrated more variable and sometimes modest effects [35,38].

Additionally, discrepancies in cytokine responses across studies suggest that the effects of VNS may be context-dependent and influenced by disease severity, intervention timing, and baseline autonomic function [4,7]. Some studies report significant anti-inflammatory effects, whereas others fail to demonstrate meaningful

changes in inflammatory biomarkers, highlighting the need for cautious interpretation of current evidence. These inconsistencies emphasize the importance of standardized methodologies and larger clinical trials to establish reproducibility and clarify the therapeutic potential of VNS [24].

To enhance the synthesis of the available evidence, a representative summary of key preclinical studies, clinical investigations, and systematic analyses related to VNS and immunomodulation is provided in Table 1. Given the emerging nature of the field, the current literature remains heterogeneous and is largely composed of preclinical and exploratory studies. To provide a more balanced comparison of currently available VNS approaches, Table 2 summarizes key differences between invasive and non-invasive modalities with emphasis on delivery method, clinical context, safety considerations, and the current strengths and limitations of the supporting evidence [7,17,24,35].

Emerging and experimental applications

VNS as a novel therapeutic strategy in glioblastoma and solid tumors: emerging and hypothesis-driven perspectives

The potential application of VNS in oncology represents an emerging and largely hypothesis-driven area of investigation. Recent conceptual and preclinical work suggests that VNS may influence tumor biology through modulation of systemic inflammation and immune responses, particularly via reduction of pro-inflammatory cytokines such as interleukin-6 (IL-6), attenuation of the senescence-associated secretory phenotype (SASP), and enhancement of antitumor immune activity [39].

Table1. *Summary of clinical and preclinical studies on VNS and Immunomodulation.*

Study (References)	Study Type	Population/Model	VNS Modality	Key Findings	Main Limitations
Czura and Tracey [4]	Foundational mechanistic review	Neuro-immune regulation	Conceptual	Established autonomic regulation and cholinergic anti-inflammatory pathway	Not a primary experimental study
Johnson and Wilson [7]	Narrative review	Multiple conditions	Invasive and non-invasive	Demonstrated anti-inflammatory effects of VNS and autonomic modulation across diseases	Heterogeneity across included studies
Caravaca et al. [13]	Preclinical experimental study	Animal inflammation models	VNS	Promoted resolution of inflammation via Alox15 and α7nAChR-dependent pathways	Preclinical findings may not fully translate to humans
Mastitskaya et al. [12]	Preclinical/ translational study	ARDS/COVID-19 models	VNS	Suggested VNS reduces cytokine storm and improves inflammatory control	Mostly theoretical
Sloan et al. [16]	Observational cohort study	CARDIA cohort	Indirect vagal tone assessment	Demonstrated inverse relationship between vagal activity and inflammatory markers	Observational; no direct VNS intervention
Bonaz [17]	Clinical review	Rheumatoid arthritis	Implanted VNS	Reduced inflammation and disease activity	Limited RCTs
de Araújo-Deca et al. [26]	Systematic review	RA patients	Mixed	Improved disease activity	Small samples
Taha et al. [35]	Meta-analysis	COVID-19	nVNS	↑ IL-10, no CRP/IL-6 change	Small trials
de Melo et al. [24]	Meta-analysis	Mixed	Various	Cytokine modulation	High heterogeneity
Straube et al. [33]	RCT	Migraine	tVNS	Pain reduction	No immune endpoints
Silberstein et al. [34]	Clinical trial	Migraine	nVNS	Headache prevention	Limited immune data
Brem [39]	Hypothesis	Oncology	Conceptual	Proposed VNS anti-tumor role	No clinical evidence

RCTs, randomized controlled trials; RA, rheumatoid arthritis; VNS, vagus nerve stimulation.

Table 2.*Comparison of invasive and non-invasive VNS.*

Feature	Invasive VNS	Non-invasive VNS
Mode of delivery	Surgically implanted device delivering stimulation to the cervical vagus nerve [6,17]	External transcutaneous stimulation (auricular or cervical) without surgical implantation [6, 24, 35]
Clinical experience	Established use in epilepsy and depression; emerging use in inflammatory diseases such as rheumatoid arthritis [6,17]	More recent use in exploratory settings including pain disorders and COVID-19-related inflammation [24, 33, 35]
Precision of stimulation	Controlled and programmable stimulation, but requires implantation and follow-up [6]	Easier to apply, but stimulation depth and consistency may vary across devices [6, 24]
Evidence in immunomodulation	Early clinical and mechanistic evidence suggests anti-inflammatory effects, but based on small studies [17, 26]	Mixed findings; increased IL-10 without consistent changes in other markers in some studies [35], overall heterogeneous evidence [24]
Safety considerations	Associated with surgical and device-related risks [6, 17]	Avoids surgery; generally well tolerated but dependent on adherence and protocol [6, 35]
Cost and accessibility	Higher cost due to implantation and follow-up [17]	Lower cost and more accessible in outpatient settings [17, 35]
Current limitations	Limited by small sample sizes and lack of large RCTs in inflammatory diseases [17, 26]	Heterogeneity in protocols, populations, and outcomes limits comparability [24,35]

These mechanisms are biologically plausible given the established role of chronic inflammation in tumor progression and immune evasion.

Preclinical studies have indicated that VNS may modulate immune cell activity, including cytotoxic T lymphocytes and natural killer cells, which are critical for tumor surveillance. However, it is important to emphasize that the current evidence base remains limited and is largely derived from experimental models and theoretical frameworks rather than robust clinical data [39].

Currently, no clinical trials support the oncologic application of VNS, and its role in cancer therapy remains unproven. Therefore, the proposed mechanisms should be interpreted with caution and considered primarily as hypothesis-generating rather than evidence-based.

Future research should focus on early-phase clinical studies and mechanistic validation to determine whether the immunomodulatory effects of VNS can be translated into meaningful therapeutic benefit in oncology.

Limitations

This narrative review had several inherent limitations that should be acknowledged. First, as a narrative rather than a systematic review, the methodology was subject to selection bias. The study inclusion was not based on a predefined protocol or quantitative synthesis, which may have influenced the representation of available evidence [7,9,10].

Second, a substantial proportion of evidence supporting VNS in immunomodulation is derived from preclinical studies and animal models, which may not fully translate into human physiology or clinical outcomes [13,40]. Although early clinical trials have demonstrated promising results, many are limited by small sample sizes, short follow-up durations, and a lack of standardized endpoints, reducing the strength and generalizability of the conclusions [17,35].

Third, there is considerable heterogeneity in VNS methodologies, including differences between invasive and non-invasive techniques, stimulation parameters, treatment duration, and patient populations. This complicates direct comparisons across studies and limits reproducibility [7,24].

Finally, the emerging applications discussed, particularly in oncology, remain largely hypothesis-driven and are supported by limited preclinical evidence with a notable absence of human clinical trials [39]. These factors highlight the need for more rigorous, standardized, and large-scale studies to validate the therapeutic potential of VNS in immunomodulation.

Conclusion

Neuro-immune communication represents a critical axis in health and disease, facilitating complex interactions between neural circuits and immune responses. VNS stands at the intersection of these two systems, offering a novel, minimally invasive approach to modulate immune responses. Through mechanisms centered on the cholinergic anti-inflammatory pathway and neural circuit regulation, VNS has demonstrated therapeutic potential in a range of inflammatory and autoimmune conditions. It dampens excessive immune activation and promotes resolution and repair processes. Growing evidence from animal models, early human trials, and systematic reviews supports the integration of VNS into clinical practice, particularly for conditions marked by chronic inflammation and autonomic dysregulation. However, larger standardized clinical studies are necessary to validate these findings, refine stimulation protocols, and ensure patient-specific safety and efficacy. As our understanding of neuro-immune interactions deepens, VNS may become a cornerstone of the evolving landscape of bioelectronic medicine [10,40].

List of Abbreviations

α7nAChR	α7 nicotinic acetylcholine receptor
Alox15	Arachidonate 15-lipoxygenase
ARDS	Acute respiratory distress syndrome
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
IL	Interleukin
NF-κB	Nuclear factor kappa B
nVNS	Non-invasive vagus nerve stimulation
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SASP	Senescence-associated secretory phenotype
SPMs	Specialized pro-resolving mediators
TNF-α	Tumor necrosis factor alpha
Tvns	Transcutaneous vagus nerve stimulation
VNS	Vagus nerve stimulation

Funding
None.

Conflict of interest
The author declares no conflict of interest.

Consent to participate
Not applicable.

Ethical approval
Not applicable.

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Supplementary content (If any) is available online.

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