Journal of Environmental Studies and Health Research
An open-access International Journal

Review Article

Autoimmune Disorders on the Rise: Pathways to Understanding and Prevention

Robert C. Sizemore [1, *], Md S. Zaman [1,2]

[1]Department of Biological Sciences, Alcorn State University, Lorman, MS 39096, USA

[2]Department of Biology, South Texas College, McAllen, TX 78501, USA

**Corresponding email: sizemore@alcorn.edu*

Cite: Sizemore, R.C., Zaman, M.S. (2025). Autoimmune Disorders on the Rise: Pathways to Understanding and Prevention. Journal of Environmental Studies & Health Research, 1 (1), 1-19. https://www.doi.org/10.5281/zenodo.14827061 - 6 Jan 2025

Abstract

Autoimmune disorders occur when the immune system mistakenly attacks the body's self-tissues due to a breakdown in tolerance mechanisms that prevent self-reactivity. Autoimmune diseases disproportionately impact females, who represent approximately 78% of autoimmune patients. The increasing prevalence of autoimmunity, as evidenced by rising antinuclear antibody (ANA) biomarkers, is concerning. Between 2011-2022, approximately 15 million people in the U.S. were diagnosed with autoimmune disorders, with 34% having more than one autoimmune disease. Key mechanisms contributing to autoimmunity include abnormalities in thymic selection, where autoreactive T cells escape deletion, and failure of regulatory T cells (Tregs) to suppress harmful immune responses. Environmental factors, such as viral infections or chemical exposures, may alter self-antigens, causing the immune system to misidentify them as foreign through molecular mimicry. In rare cases, anatomically sequestered antigens, normally hidden from immune surveillance, are released, leading to autoimmunity. Inappropriate expression of major histocompatibility complex (MHC) molecules on non-antigen-presenting cells can aggravate autoimmune conditions. Additionally, the interplay of genetics, hormones, and gut microbiota may play a role in causing autoimmune conditions. Autoimmune diseases may not be entirely preventable. However, strategies such as healthy diet, stress management, exercise, toxin avoidance, gut health support, and routine health check-ups can reduce risk or delay onset. This review explores the factors driving the rise of autoimmune disorders, their prevalence, the mechanisms behind their development, and preventive measures to reduce the risk or delay autoimmune onset. Understanding these mechanisms may lead to improved treatments, given the significant impact of autoimmunity on global health.

Keywords: Autoimmune disorders, ANA, thymic selection, Tregs, molecular mimicry, autoimmunity, MHC.

Introduction

The basic principle of the immune response is to defend the host against any foreign invaders. Although we are preprogrammed to respond to anything from outside the body, we normally do not respond to any of our self-tissue even though we all have the innate ability to mount an immune response to anything that currently exists, has existed, or will exist (Justiz Vaillant et al., 2024). Thus, although we have the ability to self-react, we develop tolerance early in life to our self-tissue to prevent this from occurring (Singh et al., 2016). When tolerance breaks down, immune reactions to self-tissue bring about what is commonly referred to as an autoimmune disease (Theofilopoulos et al., 2017). We feel that it may be preferable to say "autoimmune disorder" since "disease" often implies something infectious and transmissible, neither of which is the case with autoimmunity. In short, whenever there is a breakdown in any of how self-reactivity is checked it will result in the immune system attacking the host (Theofilopoulos et al., 2017),

The concept of autoimmunity has led to more speculation and hypotheses than any other area in the field of immunology. Although we can describe the pathogenesis of various autoimmune diseases, their etiology often remains elusive. Of particular note is the fact that autoimmune diseases impact approximately 8% of the population, with women accounting for 78% of those affected (Fairweather and Rose, 2004). In the case of systemic lupus (an autoimmune disease), approximately 70 - 90% of patients are female (McDonald et al.2015). Left-handed individuals are more likely to develop autoimmune problems than right-handed people (Geschwind and Behan, 1982). In the past few years, we have seen a dramatic increase in the number of individuals with these disorders (Miller, 2023). In this article, we will discuss the possible reasons for this dramatic increase in occurrence and why females are more susceptible.

Autoimmune disorders are currently considered to be the third leading cause of morbidity in developed countries (Chang et al., 2023). A 2024 study revealed that approximately 15 million people, or 4.6% of the U.S. population, were diagnosed with at least one autoimmune disease between January 2011 and January 2022. Of those individuals, 34% were diagnosed with multiple autoimmune diseases (Abend et al., 2024). Even more concerning, autoimmunity is becoming increasingly prevalent, with some studies estimating an annual increase of 3 to12% (Murray, 2024).

Sufficient research on the rise of autoimmune diseases is lacking. In 2020, researchers noted that antinuclear antibodies (ANAs), commonly used as biomarkers for autoimmune disorders, are increasing in prevalence in the United States (Dinse, et al., 2022). This increase was particularly prevalent among males, non-Hispanic whites, adults 50 and older, and adolescents (Dinse, et al., 2022). ANA can be an indicator of diseases such as systemic lupus erythematosus, scleroderma, Sjogren's disease, rheumatoid arthritis, and polyarteritis nodosum, among others (Bloch, 2024). Among adolescents aged 12 to 19 years, the incidence of ANA has increased almost 300% (NIH Medline, 2020). In the past 40 years, the prevalence of type 1 diabetes in adults has almost doubled (Murray, 2024). Another study revealed that from 1980 to 2019, the incidence of type 1 diabetes was 15 per 100,000 people and the prevalence was 9.5% worldwide (Mobasseri et al., 2020). Globally, the estimated number of people with multiple sclerosis increased by 30% between 2013 and 2022 (Graf et al., 2024). From 2006 to 2021, the prevalence of inflammatory bowel disease (IBD) rose by 46% (Murray, 2024).

Potential Mechanisms of How Autoimmune Disease Occurs

As stated earlier, autoimmune diseases occur when the immune system mistakenly attacks the body's self-tissues. Some possible factors that could lead to autoimmune disorders are discussed here. Together, these circumstances can disrupt the delicate balance of immune regulation and contribute to the development of autoimmune diseases (Figure 1).

Abnormality in the Thymic Selection Process

Thymic selection is an essential part of the development of self-tolerant and functional T lymphocyte cells. This process occurs in the thymus, where immature T cells undergo positive, negative, and agonist selection stages (Parish and Health, 2008; Vrisekoop et al., 2014). Positive selection ensures the functionality of T cells to make strong encounters with foreign antigens, while negative and agonist selections enforce self-tolerance (Kurd and Roby, 2016). This ensures that T cells recognize foreign antigens and self-major histocompatibility complex (MHC) proteins, and eliminates autoreactive T cells that can mistakenly attack self-antigens (Caforio et al., 1990; Stoakes, 2025).

Abnormalities in the thymic selection process can lead to the escape of autoreactive T cells (Parish and Health, 2008; Vrisekoop et al., 2014). Typically, negative selection removes T cells that bind strongly to self-antigens, preventing autoimmunity. However, if negative selection is faulty, such as impaired expression of self-antigens in the thymus, autoreactive T cells may enter the peripheral circulation (Griesemer et al., 2010; Watanabe, et al., 2020). Upon entering the circulation, autoreactive T cells encounter self-antigens and become activated, causing autoimmune attacks on tissues and organs (Yan and Mamula, 2002).

One potential cause of failure of thymic selection is genetic mutations in the *autoimmune regulator gene* (AIRE). AIRE is a transcription factor that helps the thymus display a wide variety of self-antigens. If AIRE function is compromised, fewer self-antigens are presented to T cells, leading to inadequate removal of autoreactive T cells and subsequent autoimmune responses (Anderson and Su, 2010). Other factors, such as disrupted signals for T-cell development, imbalances in cytokine signals, and costimulatory molecules, can also disrupt the selection process (O'Shea and Murray, 2008; Watanabe, et al., 2020).

Breakdown of regulatory T cells or other regulatory mechanisms

Regulatory T cells (Tregs) are responsible for suppressing excessive immune responses and preventing autoimmune diseases (Goswami et al., 2022). Tregs express a protein called transcription factor FoxP3, which plays a crucial role in the development, function, and ability to suppress the immune response (Mertowska et al., 2022). Tregs are essential for suppressing extreme responses against self-antigens by inhibiting autoreactive T cells that escape thymic selection and controlling inflammation and immune responses. When Tregs fail to function or are not properly regulated, the immune system can lose its tolerance, leading to the development or worsening of autoimmune diseases (Sakaguchi et al., 2008; Oparaugo et al., 2023). This failure in immune tolerance plays a significant role in the pathogenesis of various autoimmune diseases, including systemic lupus erythematosus (SLE), and type 1 diabetes (Goswami et al., 2022).

Tregs help maintain immune tolerance in several ways, including releasing the immunosuppressive cytokines interleukin-10 (IL-10) and Transforming Growth Factor- β (TGF- β), which directly suppress active T cells, and influence antigen-presenting cells (APCs) (Goswami et al., 2022). If Tregs are not fully functional or are in insufficient numbers, autoreactive T cells can become overactive, attack self-antigens, and cause autoimmune inflammation. This loss of control can result in genetic mutations, and changes in gene regulation, and affect the development, stability, or function of Tregs (Rajendeeran and Tenbrock, 2021).

Mutations in FoxP3 may impair Treg development and function, causing severe autoimmune reactions in many organs (Georgiev et al., 2019). Additionally, genetic variations in genes such as interleukin 2 (IL-2) and CTLA-4 (cytotoxic T-lymphocyte antigen-4) could affect Treg activity and increase the risk of autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis (Hossen et al., 2023). IL-2 is essential for the development, proliferation, and activation of Tregs, whereas CTLA-4, a protein that decreases T cell activation, acts as a “brake” in the immune response.

Chronic inflammation can weaken Treg cells, decreasing their ability to suppress harmful immune responses or turning them into proinflammatory cells. This change, called Treg plasticity, can cause Tregs to lose control over autoreactive T cells, leading to tissue damage. Additionally, malfunctions in other immune regulators, such as Programmed death-1 (PD-1), a protein found on T cells, and CTLA-4, which helps Tregs maintain immune balance, can decrease immune control (Buchbinder and Desai, 2016).

Alteration of self-antigens by chemicals or viruses

Changes to self-antigens caused by external agents like chemicals or viruses, may lead to the development of autoimmune diseases. These changes can cause failure of the immune system to recognize self-antigens, leading to the activation of immune cells that mistakenly attack self-tissues (Sundaresan et al., 2023; Maoz-Segal and Andrade, 2015). A well-known example is drug-induced lupus, where drugs, such as procainamide or hydralazine create altered antigens that appear foreign, stimulating the immune system to attack them (Pietrangelo, 2019).

Viruses can also change self-antigens through molecular mimicry or by altering proteins after they are generated. In molecular mimicry, viral proteins look like self-antigens, so when the immune system fights the virus, it might also attack similar self-proteins, leading to tissue damage and autoimmunity (Habib et al., 2023). For example, in multiple sclerosis, the immune system may mistakenly attack myelin, the protective layer around nerves, due to a viral infection (Gray, 2010). This may also occur with bacterial infections such as rheumatic heart disease, where the immune system's response to *Streptococcus* infection may mistakenly attack heart tissues due to cross-reactivity (WHO, 2020).

Additionally, viral infections can cause inflammation and tissue damage, which can expose or alter normally hidden self-antigens (cryptic epitopes). This exposure can trigger an abnormal immune response (Sundaresan et al., 2023). Viruses can also change self-antigens through processes, such as glycosylation (attachment of carbohydrates, or glycans, to proteins and lipids) or protein cleavage (breaking the peptide bonds between amino acids in a protein), creating new antigens that the immune system sees as foreign (Li et al., 2021).

Release of sequestered antigen

Anatomically sequestered areas evolved to protect them from inflammatory responses during infection (Hong and Van Kaer, 1991). However, this situation (sometimes called immune privilege) can backfire when normally hidden self-antigens are released into the bloodstream and the immune system starts to recognize them as foreign and trigger an immune response (Theofilopoulos et al., 2017). Typically, this is not a major situation but one that can occur occasionally.

During fetal life, we are exposed to self-antigens which results in the induction of tolerance to them. It is thought that there are a few antigens that are anatomically sequestered (i.e., hidden away so that the immune system never sees them). The lens of the eye and sperm are sequestered and not normally seen by the immune system (Han et al., 2016; Hong and Van Kaer, 1999; Zhou and Caspi, 2010). Sometimes when men undergo vasectomy, sperm can enter the circulation and induce antibody formation, which can lead to inflammation of the testes (Han et al., 2016). However, this is transient and dissipates fairly quickly.

Inappropriate Expression of MHC Molecules on Non-antigen-pressing Cells

The Major Histocompatibility Complex (MHC) molecules are typically present on specialized antigen-pressing cells (Stoakes, 2025). However, if MHC molecules appear on cells that are not supposed to display them, such as epithelial and endothelial cells, they can then present self-antigens to immune cells and potentially trigger autoimmune responses (Caforio et al., 1990; Stoakes, 2025).

This is considered to be a probable cause in many cases. Gamma interferon (IFN-γ) has been shown to induce the expression of MHC class II molecules (Wijdeven et al., 2018). This could cause cells, which are not normally APCs to present self-antigens to the immune system. Furthermore, costimulatory molecules may be induced (Sandilands et al., 2006). Overall, this could lead to the activation of the immune system to self-antigens.

This occurs in several cases, which may be why autoimmune disorders often follow infections. Infection can increase the production of IFN-γ, which increases the expression of class II MHC molecules (Mertowska et al., 2023). As discussed below, this is another possible reason that viral infections such as COVID-19 can initiate autoimmune disorders (Kocivnik and Velnar, 2022).

This is also why IFN-β is used for the treatment of multiple sclerosis (it downregulates class II MHC expression) (Christophi et al., 2009). Thus, patients who take these drugs often benefit from the suppression of class II MHC expression (and general suppression of the immune system) (Kasper and Reder, 2014).

This is also one reason why women may have more autoimmune problems. Estrogen apparently promotes the production of IFN-γ giving women a stronger immune system but unfortunately increasing their susceptibility to autoimmune problems (Mayo Clinic, 2005; Rubtsov et al., 2010). This is why the incidence of autoimmune diseases such as multiple sclerosis (MS) often increases after pregnancy (Moulton, 2018). Early studies suggested that estrogen-containing birth control pills can increase the risk of autoimmune disorders such as systemic lupus, but recent studies suggest no increased risk for people with stable lupus (Williams, 2017).

The Interplay of Genetics, Hormones, and Gut Microbiota

The prevalence of autoimmune diseases in women could also be due to an interplay between genetic, hormonal, and gut microbial factors (Taneja, 2023) with unknown mechanisms. Women have two X chromosomes, while men have one, which may cause their immune systems to work differently. One of the X chromosomes is inactivated in each cell so that females do not get a double dose of proteins (which could prove deadly). This inactivation is achieved through the production of Xist and only occurs when a cell has two mismatched X chromosomes. Thus, this does not occur in males where there is only one X chromosome. Xist is a long non-coding RNA molecule that will bind to and inactivate one of the X chromosomes. But other proteins and nucleotides such as DNA can bind to Xist. These complexes can trigger an immune response that could mistakenly attack the self-tissues (Dou, et al., 2024; Goldman, 2024).

Sex hormones, such as estrogen and progesterone, which vary between men and women, may also play a role (Taneja, 2018). As we noted previously, estrogen promotes the production of IFN-γ which can boost the immune response, suggesting why women have a stronger immune system but higher rates of autoimmune diseases (Harding and Heaton, 2022). Some researchers suggest that the stronger immune response in women may be an evolutionary trait, to help with pregnancy, even though it increases the risk of autoimmune diseases (Moyer, 2021).

Recent research highlights the role of gut microbiota in the development of autoimmune diseases. The gut microbiome is sexually dimorphic, meaning it differs between men and women. These gut bacteria and sex hormones influence each other, affecting the immune system (Rosser et al., 2022). Additionally, there is a bidirectional relationship between sex hormones and the gut microbiota, with each influencing the other's composition and function (Castillo-Izquierdo, 2022).

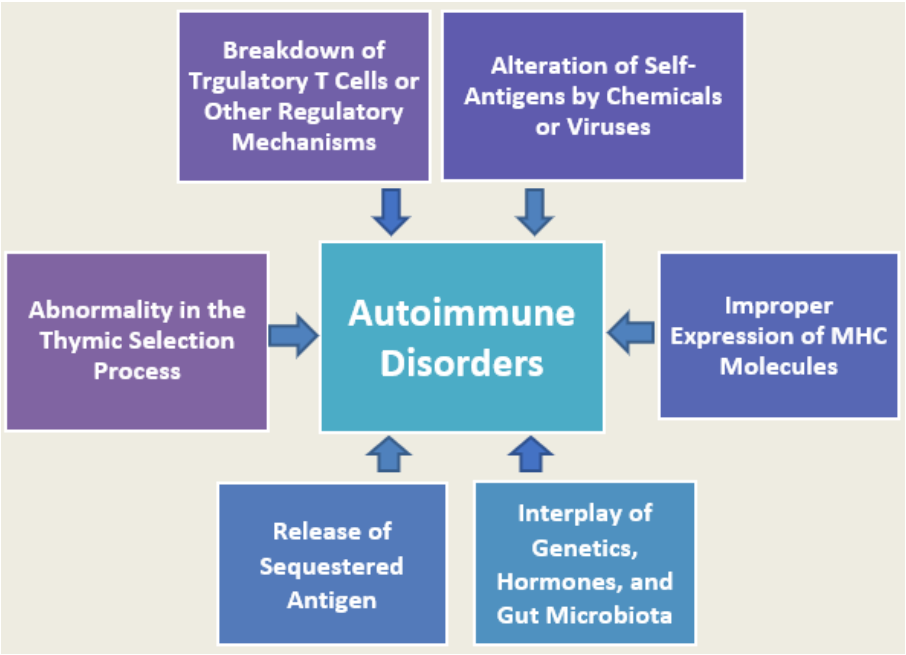

Figure 1: Potential mechanisms of autoimmune diseases.

Prevention Strategies for Autoimmune Diseases

As discussed earlier, autoimmune diseases are a diverse group of conditions that occur when the immune system mistakenly attacks the body's self-tissues, leading to inflammation, tissue damage, and impaired function of the affected organs. Despite the complex and largely genetic nature of these diseases, several strategies can potentially help reduce their risk or delay their onset (Gregersen and Olsson, 2009). Here, we explore key prevention strategies.

Maintaining a healthy diet

A balanced and nutritious diet plays a significant role in supporting a healthy immune system, reducing inflammation, and thus reducing the risk of autoimmune conditions.

- Anti-inflammatory Food: Diets rich in fruits, vegetables, whole grains, and healthy fats, such as omega-3 fatty acids, have been shown to help reduce systemic inflammation. Foods like fatty fish (salmon, sardines), nuts, seeds, olive oil, and leafy greens may have protective effects (Kelsey, 2021).
- Reducing the Consumption of Processed Food: High levels of processed foods, sugar, trans fats, and refined carbohydrates can promote inflammation and may trigger or worsen autoimmune responses (DISC, 2024). Limiting these foods can help maintain immune system balance.
- Gluten and Dairy Sensitivities: Some autoimmune diseases, particularly celiac disease and certain forms of arthritis, may be triggered by gluten or dairy products (Summit Rheumatology, 2025). For individuals with sensitivities, avoiding these foods may help reduce symptoms or prevent disease onset.

Maintaining a Healthy Gut Microbiome

The gut plays a crucial role in immune system function. An imbalanced gut microbiome has been linked to the development of autoimmune diseases (Wu and Wu, 2012). The microbiome influences how the immune system reacts to pathogens, as well as how it distinguishes between harmful invaders and the body's self-cells (Lambring et al., 2019).

- Probiotics and Prebiotics: Consuming probiotic food, such as yogurt may help support healthy gut flora. Prebiotic foods such as garlic, onions, and bananas also support the growth of beneficial gut bacteria (Bladh, 2024).
- Avoiding Overuse of Antibiotics: Excessive use of antibiotics can disrupt the balance of the gut microbiome (Dahiya and Nigam, 2023). It is essential to use antibiotics only when necessary and under medical supervision.

Stress Management

Chronic stress is known to affect immune function (Segerstrom and Miller, 2004); thus the body's response to prolonged stress can alter immune system responses. The following strategies can be used to maintain a healthy stress level.

- Exercise: Exercise is essential for maintaining overall health. Exercise helps regulate stress hormones such as cortisol. Chronically elevated stress hormones can contribute to immune dysfunction (Mayo Clinic, 2022). Research indicates that consistent physical activity may reduce the risk of developing conditions like rheumatoid arthritis and lupus by helping to keep the immune system in balance (Frade et al., 2021).
- Meditation: Meditation, deep breathing exercises, and yoga can help reduce stress and promote relaxation. These practices have been shown to reduce inflammation and help balance immune system activity (Chang, 2024).
- Adequate Sleep: Ensuring adequate and high-quality sleep is essential for a healthy life. Poor sleep or chronic sleep deprivation can increase inflammation and negatively impact immune function (Garbarino et al., 2021).

Environmental Factors and Toxin Avoidance

Certain environmental factors, including toxins and pollutants, have been linked to the onset of autoimmune diseases. Exposure to chemicals, pesticides, heavy metals, and other pollutants may trigger or aggravate immune system dysfunction (Kharrazian, 2021).

- Reducing Exposure to Chemicals: Avoiding exposure to harmful chemicals can help minimize the risk of immune dysfunction (Kharrazian, 2021).
- Minimizing Air Pollution: Studies suggest that exposure to air pollution may contribute to the development of autoimmune diseases like rheumatoid arthritis and lupus (Adami et al., 2022). Taking measures, such as limiting exposure to polluted air, avoiding high-traffic areas, or using quality indoor air filters, can be beneficial.

Preventative Health Care

Regular health check-ups are essential for identifying early signs of diseases, including autoimmune diseases. Early detection can lead to more effective treatment, potentially preventing the progression of disease (NIH, 2005).

Genetic and Family History Awareness

Autoimmune diseases can be influenced by genetic factors (Pisetsky, 2023). Thus, individuals with a family history of autoimmune conditions should be vigilant with respect to their health. Understanding genetic risks, working with healthcare providers to monitor for early signs, and genetic testing (when available) for predisposition to autoimmune diseases can help prevent or manage autoimmune diseases (Pisetsky, 2023; Gregersen and Olsson, 2009).

Discussion

One of the most fundamental processes that maintains immune tolerance is *thymic selection***.** Thymic selection ensures that T cells which play a crucial role in immune defense, are properly trained to recognize

foreign antigens while ignoring the body's self-tissues (Parish and Health, 2008; Vrisekoop et al., 2014). When this selection process fails, *autoreactive T cells* that attack the body's tissues can escape into circulation, leading to autoimmune diseases (Parish and Health, 2008; Vrisekoop et al., 2014). Mutations in genes such as AIRE can compromise thymic selection and increase the likelihood of autoimmunity (Anderson and Su, 2010). This failure to eliminate harmful T cells illustrates the delicate balance of the immune system and the consequences when self-tolerance is not properly established.

Regulatory T cells (Tregs) play a crucial role in preventing excessive immune responses and maintaining self-tolerance (Goswami et al., 2022). If Treg function is disrupted, often due to genetic mutations like in FoxP3, autoreactive T cells can attack the body, leading to autoimmune disorders such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis (Sakaguchi et al., 2008; Mertowska et al., 2022; Oparaugo et al., 2023).

Autoimmune diseases can also be triggered when external factors, like chemicals or viruses, modify self-antigens, causing the immune system to attack the body's tissues (Sundaresan et al., 2023; Maoz-Segal and Andrade, 2015). Molecular mimicry, where viral proteins resemble self-antigens, is another mechanism involved, particularly in conditions like multiple sclerosis (Gray, 2010; WHO, 2020).

The release of sequestered antigens, such as those from the eye or sperm, can also lead to autoimmunity when these previously hidden antigens are exposed (Harakal et al., 2022; Han et al. 2016; Zhou and Caspi 2010). Additionally, the abnormal expression of MHC molecules on non-immune cells, such as epithelial cells, can cause the immune system to attack self-tissues (Caforio et al., 1990; Stoakes, 2025). IFN-γ can upregulate the expression of MHC molecules and women may be more susceptible to autoimmune diseases due to higher estrogen levels, which promote IFN-γ production (Mayo Clinic, 2005; Williams, 2017).

Regardless of the possible etiology, it is clear that autoimmune disorders are on the rise (Dinse et al., 2022). Recent studies suggest that post-COVID-19 recovery may increase the risk of new autoimmune diseases, possibly due to persistent SARS-CoV-2 infection and increased cytokine production (Pacheco et al. 2019), as well as molecular mimicry (Lakota et al., 2021).

Environmental pollutants, including air pollution, heavy metals, pesticides, and industrial chemicals, have been increasingly linked to the development and exacerbation of autoimmune diseases (Berend, 2016;). Exposure to particulate matter in polluted air can cause inflammation in the respiratory system, which might trigger an immune response that becomes dysregulated over time (Berend, 2016). Chronic inflammation from repeated exposure to environmental toxins may lead to the immune system mistakenly attacking the body's tissues (Thompson, et al., 2015). Additionally, heavy metals have been shown to alter immune cell function and promote the production of autoantibodies (Wang et al., 2021).

Toxic chemicals can bind to immune and endocrine receptors throughout the body and promote immune dysregulation. For example, they can bind to nucleic acids and promote anti-nuclear autoimmunity (Kharrazian, 2021). Moreover, toxins can interfere with the normal function of regulatory T cells (Tregs) (Ohue and Nishikawa, 2019). Without proper Treg function, the immune system may become hyperactive, resulting in autoimmune reactions.

Microplastics and nanoplastics in the environment could potentially influence autoimmune diseases (Yang et al., 2022). Studies have suggested that these particles can affect the production of cytokines and other

immune signaling molecules, creating an imbalance that may favor autoimmune responses (Weber et al., 2022). The increase in microplatics and nanoplastics throughout the world could have devastating long-term effects on the future health of humans and other species (Zaman et al.,2019; Zaman and Sizemore, 2020).

Moreover, the chemical additives found in plastics, such as phthalates and bisphenol have been linked to endocrine disruption, which can alter the regulation of immune responses. In particular, bisphenol A (BPA) has been shown to influence the function of T cells and regulatory T cells (Tregs) (Gao, et al., 2020). Additionally, BPA can alter hormone signaling pathways that regulate immune function, further increasing the risk of autoimmune diseases (Hong, et al., 2024).

As microplastics, nanoplastics, and various pollutants continue to accumulate in the environment, their role in immune dysregulation underscores the need for a better understanding of their long-term effects on public health, particularly in relation to autoimmune disorders.

The rising prevalence of autoimmune diseases in the population raises important questions. The increased rates of autoimmune markers such as antinuclear antibodies (ANA) in recent decades, especially among adolescents and adults over 50, suggest that environmental factors, genetic predispositions, or lifestyle changes may be contributing to the surge (Dinse et al., 2022). The global rise in conditions like type 1 diabetes, multiple sclerosis, and inflammatory bowel disease highlights the growing burden of autoimmune diseases on public health (Da-Peng et al., 2023).

Despite advances in understanding autoimmune disorders, many aspects of their etiologies remain elusive. The complexity of the immune system, the interactions between genetics, environmental triggers, and hormonal influences, and the potential for immune dysregulation to occur at multiple levels all contribute to the difficulty in pinpointing the exact causes of autoimmune diseases. Further research into the immune system's regulatory mechanisms, the role of environmental factors, and the development of more precise diagnostic and therapeutic approaches will be essential in addressing this growing health concern.

While autoimmune diseases cannot always be entirely prevented, various strategies can reduce the risk of their development or delay their onset. Maintaining a healthy diet, managing stress, staying physically active, avoiding toxins, supporting gut health, and ensuring regular medical check-ups all play a critical role in preventing autoimmune diseases. By adopting a proactive approach to health and focusing on these prevention strategies, individuals can enhance their overall well-being and potentially reduce the risk of autoimmune diseases in the future (Iddir et al., 2020; Shao et al., 2021).

Limitations in Autoimmune Disorder Studies

Studies on autoimmune disorders face various challenges that make it difficult to fully understand their mechanisms. One key challenge is the complexity of the immune system itself, which involves many different cells and pathways. When the immune system malfunctions and causes autoimmune diseases, it is hard to pinpoint the exact disruptions in the complex interactions between genetic, hormonal, and environmental factors.

Another challenge is the variation in symptoms among patients with the same autoimmune disease. Even within the same disorder, symptoms can vary widely, making it difficult to develop treatments that work for everyone.

Environmental factors, such as pollution and toxins, also complicate research, as it is hard to accurately measure long-term exposure and its impact on the immune system.

Finally, some autoimmune diseases like dermatomyositis, Goodpasture syndrome, Guillain-Barre syndrome, and myasthenia gravis are rare, making it difficult to gather enough patients for research. Small studies with limited funding may not produce strong results. Therefore, larger, long-term studies with diverse populations are needed to improve the understanding and treatment of autoimmune diseases.

Conclusions

Autoimmune diseases are becoming a significant public health concern. The immune system's failure to recognize and tolerate the body's own tissues, particularly due to problems in processes, such as thymic selection and regulatory T cells, are leading to diseases, such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis.

Triggers such as environmental pollution, toxins, and infections further worsen these immune issues. Factors like microplastics and chemicals that disrupt hormones also add to the problem, making it more difficult to understand how autoimmune diseases develop.

As autoimmune diseases become more common around the world, it is crucial to better understand how these various factors affect the immune system. Even though scientists have made progress, many questions about these diseases remain unanswered. Ongoing research is important to find out more about the influence of genetics, environmental factors, and immune system regulation.

Looking forward, personalized medical treatments, early detection, and new ways to treat autoimmune diseases will be key to managing them. Preventing exposure to harmful environmental factors, promoting healthy living, and supporting the immune system early on can help reduce the chances of these diseases.

Acknowledgments: *Not applicable.*

Patents: *Not applicable.*

Institutional Review Board Statement: *Not applicable.*

Informed Consent Statement: *Not applicable.*

Conflicts of Interest: *None.*

References

Abend, A.H., He. I., Bahroos. N., Christianakis. S., Crew. A.B., Wise. L.M., et al. (2025). Estimation of prevalence of autoimmune diseases in the United States using electronic health record data. J Clin Invest. 12, e178722. https://www.doi.org/10.1172/JCI178722

Adami, G., Pontalti, M., Cattani, G., Rossini, M., Viapiana, O., Orsolini, G. et al. (2021). Association between long-term exposure to air pollution and immune-mediated diseases: A population-based cohort study. RMD Open. https://doi.org/10.1136/rmdopen-2021-002055

Anderson, M. S., Su, M. A. (2011). Aire and T cell development. Current Opinion in Immunology, 23 (2), 198–206. https://doi.org/10.1016/j.coi.2010.11.007

Berend, N. (2016). Contribution of air pollution to COPD and small airway dysfunction. Respirology, 21(2), 237–244. https://doi.org/10.1111/resp.12645

Bladh, A. (2024). Easy guide: Prebiotic and probiotic food for gut health. Femme Pharma. https://femmepharma.com/easy-guide-prebiotic-and-probiotic-foods-for-gut-health/#:~:text=Key%20Foods%20for%20Gut%20Health,serving%20of%20yogurt%20or%20kefir

Bloch, D.B. (2024). Patient education: Antinuclear antibodies (ANA) (Beyond the basics). UpToDate. https://www.uptodate.com/contents/antinuclear-antibodies-ana-beyond-the-basics/print

Buchbinder, E.I., Desai, A. (2016). CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. American Journal of Clinical Oncology, 39 (1), 98-106. https://doi.org/10.1097/COC.0000000000000239

Caforio, A. L., Stewart, J. T., Bonifacio, E., Burke, M., Davies, M. J., McKenna, W. J., et al. (1990). Inappropriate major histocompatibility complex expression on cardiac tissue in dilated cardiomyopathy: Relevance for autoimmunity? Journal of Autoimmunity, 3 (2), 187–200. https://doi.org/10.1016/0896-8411(90)90140-N

Castillo-Izquierdo, A. D., Mayneris-Perxachs, J., Fernandez-Real, J. M. (2022). Bidirectional relationships between the gut microbiome and sexual traits. American Journal of Physiology-Cell Physiology, 322, C1223-C1229. https://doi.org/10.1152/ajpcell.00116.2022

Chang, R., Yen-Ting, C. T, Wang, S. I., Hung. Y. M., Chen, H. Y., Wei, C. J. (2023). Risk of autoimmune diseases in patients with COVID-19: A retrospective cohort study. eClinicalMedicine, 56, 101783. https://doi.org/10.1016/j.eclinm.2022.101783

Chang, R., Yen-Ting, C. T, Wang, S. I., Hung. Y. M., Chen, H. Y., Wei, C. J. (2024). Neurobiological and anti-aging benefits of yoga: A comprehensive review of recent advances in non-pharmacological therapy. Experimental Gerontology, 196, 112550. https://doi.org/10.1016/j.exger.2024.112550

Christophi, G. P., Panos, M., Hudson, C. A., Tsikkou, C., Mihai, C., Mejico, L. J., et al. (2009). Interferon-beta treatment in multiple sclerosis attenuates inflammatory gene expression through inducible activity of the phosphatase SHP-1. Clinical Immunology, 133 (1), 27-44. https://doi.org/10.1016/j.clim.2009.05.019

Dahiya, D., Nigam, P. S. (2023). Antibiotic-therapy-induced gut dysbiosis affecting gut microbiota-brain axis and cognition: Restoration by intake of probiotics and synbiotics. International Journal of Molecular Sciences, 24 (4), 3074. https://doi.org/10.3390/ijms24043074

Da-Peng, L., Yan-Xun, H., Yi-Sheng, H., Yu, W., YuChen, L., Zi-Yue, F., Hai-Feng, P., Fan, C. (2023). A global assessment of incidence trends of autoimmune diseases from 1990 to 2019 and predicted changes to 2040. Autoimmunity Reviews, 22, 103407. https://doi.org/10.1016/j.autrev.2023.103407

Dinse, G. E., Parks, C. G., Weinberg, C. R., Co, C. A., Wilkerson, J., Zeldin, D. C., Chan, E. K. L., Miller, F. W. (2020). Increasing prevalence of antinuclear antibodies in the United States. Arthritis & Rheumatology, 72 (6), 1026-1035. https://doi.org/10.1002/art.42330

DISC. (2024). The American standard diet and its impact on inflammation and chronic pain. DISC Centers of America Gallatin. https://gallatindisccenter.com/the-american-standard-diet-and-its-impact-on-inflammation-and-chronic-pain/#:~:text=In%20today's%20fast%2Dpaced%20world,off%20infection%20or%20promote%20healing

Dou, D. R., Zhao, Y., Belk, J. A., Zhao, Y., Casey, K. M., Chen, D.C., et al. (2024). Xist ribonucleoproteins promote female sex-biased autoimmunity. Cell, 1;187 (3):733-749.e16. https://www.doi.org/10.1016/j.cell.2023.12.037

Fairweather, D., Rose, N. R. (2004). Women and autoimmune diseases. Emerging Infectious Diseases, 10 (11), 2005-2011. https://doi.org/10.3201/eid1011.040367

Frade, S., O'Neill, S., Greene, D., Cameron, M. (2021). Exercise as adjunctive therapy for systemic lupus erythematosus. Cochrane Database of Systematic Reviews, 2021 (10), CD014816. https://doi.org/10.1002/14651858.CD014816

Gao, L., Dong, Y., Lin, R., Meng, Y., Wu, F., Jia, L. (2020). The imbalance of Treg/Th17 cells induced by perinatal bisphenol A exposure is associated with activation of the PI3K/Akt/mTOR signaling pathway in male offspring mice. *Food and Chemical Toxicology*, 137, 111177. https://doi.org/10.1016/j.fct.2020.111177

Garbarino, S., Lanteri, P., Bragazzi, N. L., Magnavita, N., Scoditti, E. (2021). Role of sleep deprivation in immune-related disease risk and outcomes. Communications Biology, 4 (1), 1304. https://doi.org/10.1038/s42003-021-02825-4

Georgiev, P., Charbonnier, L. M., Chatila, T. A. (2019). Regulatory T cells: The many faces of Foxp3. Journal of Clinical Immunology, 39 (7), 623-640. https://doi.org/10.1007/s10875-019-00684-7

Geschwind, N., Behan, P. (1982). Lefthandedness: Association with immune disease, migraine, and developmental learning disorder. Proceedings of the National Academy of Sciences, 79, 5097-5100.

Goldman, B. (2024). Stanford Medicine-led study shows why women are at greater risk of autoimmune disease. Standford Medicine Newsletter. https://med.stanford.edu/news/all-news/2024/02/women-autoimmune.html#:~:text=In%20every%20cell%20in%20a%20woman's%20body%2C,proteins%20are%20produced%20from%20that%20chromosome%20pair.&text=Research%20throws%20light%20on%20the%20mystery%20of,generate%20antibodies%20to%20a%20woman's%20own%20tissues

Goswami, T. K., Singh, M., Dhawan, M., Mitra, S., Emran, T. B., Rabaan, A. A., et al. (2022). Regulatory T cells (Tregs) and their therapeutic potential against autoimmune disorders-Advances and challenges. Human Vaccines & Immunotherapeutics, 18 (1), 2035117. https://doi.org/10.1080/21645515.2022.2035117

Graf, J., Akmatov, M. K., Meuth, S. G., Tremlett, H., Holstiege, J. (2024). Updated multiple sclerosis incidence, 2015–2022. JAMA Neurology, 81 (10), 1100-1102. https://doi.org/10.1001/jamaneurol.2024.2876

Gray, L. (2010). Virus infection may trigger unusual immune cells to attack the brain and spinal cord in multiple sclerosis. University of Washington. https://www.washington.edu/news/2010/06/10/virus-infection-may-trigger-unusual-immune-cells-to-attack-the-brain-and-spinal-cord-in-multiple-sclerosis/#:~:text=The%20authors%20explained%20that%20it's,myelin%20protein%20and%20a%20pathogen.

Gregersen, P. K., Olsson, L. M. (2009). Recent advances in the genetics of autoimmune disease. Annual Review of Immunology, 27 (1), 363-391. https://doi.org/10.1146/annurev.immunol.021908.132653

Griesemer, A. D., Sorenson, E. C., Hardy, M. A. (2010). The role of the thymus in tolerance. Transplantation, 90 (5), 465-474. https://doi.org/10.1097/TP.0b013e3181e7e54f

Habibi, M. A., Nezhad Shamohammadi, F., Rajaei, T., Namdari, H., Pashaei, M. R., Farajifard, H., et al. (2023). Immunopathogenesis of viral infections in neurological autoimmune disease. BMC Neurology, 23 (1), 201. https://doi.org/10.1186/s12883-023-03239-x

Han, D., Liu, Z., Yan, K. (2016). Immunology of the testis and privileged sites. In Encyclopedia of Immunobiology (Vol. 5, pp. 46-53). https://doi.org/10.1016/B978-0-12-374279-7.19009-5

Harakal, J., Qiao, H., Wheeler, K., Rival, C., Paul, A. G. A., Hardy, D. M., et al. (2022). Exposed and sequestered antigens in testes and their protection by regulatory T cell-dependent systemic tolerance. Frontiers in Immunology, 13, 809247. https://doi.org/10.3389/fimmu.2022.809247

Harding, A. T., Heaton, N. S. (2022). The impact of estrogens and their receptors on immunity and inflammation during infection. Cancers (Basel), 14 (4), 909. https://doi.org/10.3390/cancers14040909

Hong, S., Van Kaer, L. (1999). Immune privilege: keeping an Eye on Natural killer T Cells. Journal of Experimental Medicine, 190 (9), 1197–1200. https://doi.org/10.1084/jem.190.9.1197

Hong, Y., Wang, D., Lin, Y., Yang, Q., Wang, Y., Xie, Y. (2024). Environmental triggers and future risk of developing autoimmune diseases: Molecular mechanism and network toxicology analysis of bisphenol A. Ecotoxicology and Environmental Safety, 288, 117352. https://doi.org/10.1016/j.ecoenv.2024.117352

Hossen, M. M., Ma, Y., Yin, Z., Xia, Y., Du, J., Huang, J. Y., Huang, J. J., Zou, L., Ye, Z., Huang, Z. (2023). Current understanding of CTLA-4: From mechanism to autoimmune diseases. Frontiers in Immunology, 14, 1198365. https://doi.org/10.3389/fimmu.2023.1198365

Iddir, M., Brito, A., Dingeo, G., Fernandez Del Campo, S. S., Samouda, H., La Frano, M. R., Bohn, T. (2020). Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: Considerations during the COVID-19 crisis. Nutrients, 12 (6), 1562. https://doi.org/10.3390/nu12061562

Justiz Vaillant, A. A., Sabir, S., Jan, A. (2024). Physiology, immune response. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK539801/

Kasper, L. H., Reder, A. T. (2014). Immunomodulatory activity of interferon-beta. *Annals of* Clinical and Translational Neurology, 1 (8), 622-631. https://doi.org/10.1002/acn3.84

Kelsey, E. (2021). Fight harmful inflammation with these 10 healthy eating tips. MedStar Health. https://www.medstarhealth.org/blog/foods-that-fight-inflammation#:~:text=%E2%80%A2%20Practice%20Balanced%20Eating%20The%20Mediterranean%20diet,less%20emphasis%20on%20meats%20and%20refined%20carbs

Kharrazian, D. (2021). Exposure to environmental toxins and autoimmune conditions. Integrative Medicine (Encinitas), 20 (2), 20-24. PMID: 34377090; PMCID: PMC8325494.

Kocivnik, N., Velnar, T. (2022). A Review Pertaining to SARS-CoV-2 and Autoimmune Diseases: What is the connection? Life, 12 (1918). https://doi.org/10.3390/life12111918

Kurd, N., Robey, E. A. (2016). T-cell selection in the thymus: A spatial and temporal perspective. Immunological Reviews, 271 (1), 114-126. https://doi.org/10.1111/imr.12398

Lakota, K., Perdan-Pirkmajer, K., Hočevar, A., Sodin Semrl, S., Rotar, Ž., Čučnik, S., Žigon, P. (2021). COVID-19 in association with development, course, and treatment of systemic autoimmune rheumatic diseases. Frontiers in Immunology, 11, Article 611318. https://doi.org/10.3389/fimmu.2020.611318.

Lambring, C. B., Siraj, S., Patel, K., Sankpal, U. T., Mathew, S., Basha, R. (2019). Impact of the microbiome on the immune system. Critical Reviews in Immunology, 39 (5), 313-328. https://doi.org/10.1615/CritRevImmunol.2019033233

Li, Y., Liu, D., Wang, Y., Su, W., Liu, G., Dong, W. (2021). The importance of glycans of viral and host proteins in enveloped virus infection. Frontiers in Immunology, 12, Article 638573. https://doi.org/10.3389/fimmu.2021.638573

Maoz-Segal, R., Andrade, P. (2015). Molecular mimicry and autoimmunity. In Infection and autoimmunity (pp. 27–44). https://doi.org/10.1016/B978-0-444-63269-2.00054-4

Mayo Clinic. (2005). Genetic variant may explain why women develop multiple sclerosis more than men. ScienceDaily. https://www.sciencedaily.com/releases/2005/01/050128224022.htm

Mayo Clinic. (2022). Stress management. Mayo Clinic. https://www.mayoclinic.org/healthy-lifestyle/stress-management/in-depth/exercise-and-stress/art-20044469#:~:text=Exercise%20can%20provide%20stress%20relief,your%20body%20and%20your%20life

McDonald, G., Cabal, N., Vannier, A., Umiker, B., Yin, R. H., Orjalo, A. V. et al. (2015). Female bias in systemic lupus erythematosus is associated with the differential expression of X-linked Toll-like receptor. Frontiers in Immunology, 6, 457. https://doi.org/10.3389/fimmu.2015.00457

Mertowska, P., Mertowski, S., Podgajna, M., Grywalska, E. (2022). The importance of the transcription factor Foxp3 in the development of primary immunodeficiencies. Journal of Clinical Medicine, 11 (4), 947. https://doi.org/10.3390/jcm11040947

Mertowska, P., Smolak, K., Mertowski, S., Grywalska, E. (2023). Immunomodulatory role of interferons in viral and bacterial infections. International Journal of Molecular Sciences, 24 (12), Article 10115. https://doi.org/10.3390/ijms241210115

Miller, F. W. (2023). The increasing prevalence of autoimmunity and autoimmune diseases: An urgent call to action for improved understanding, diagnosis, treatment, and prevention. Current Opinion in Immunology, 80, Article 102266. https://doi.org/10.1016/j.coi.2022.102266

Mobasseri, M., Shirmohammadi, M., Amiri, T., Vahed, N., Hosseini Fard, H., Ghojazadeh, M. (2020). Prevalence and incidence of type 1 diabetes in the world: A systematic review and meta-analysis. Health Promotion Perspectives, 10 (2), 98-115. https://doi.org/10.34172/hpp.2020.18.

Moulton, V. R. (2018). Sex hormones in acquired immunity and autoimmune disease. Frontiers in Immunology, 9, Article 2279. https://doi.org/10.3389/fimmu.2018.02279

Moyer, M. W. (2021). Why nearly 80 percent of autoimmune sufferers are female. Scientific American. https://www.scientificamerican.com/article/why-nearly-80-percent-of-autoimmune-sufferers-are-female/

Murray, M. (2024). A major health crisis: The alarming rise of autoimmune disease. National Health Council. https://nationalhealthcouncil.org/blog/a-major-health-crisis-the-alarming-rise-of-autoimmune-disease/

NIH Medline. (2020). Autoimmunity in adolescents tripled in recent decades. NIH MedlinePlus. https://magazine.medlineplus.gov/article/autoimmunity-in-adolescents-tripled-in-recent-decades#:~:text=For%20those%20aged%2012%20to%2019%2C%20positive,lifestyle%20or%20the%20environment%20may%20be%20involved

NIH. (2005). Progress in autoimmune diseases research. National Institutes of Health - The Autoimmune Diseases Coordinating Committee. https://www.niaid.nih.gov/sites/default/files/adccfinal.pdf

Ohue, Y., Nishikawa, H. (2019). Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? *Cancer Science*, 110(7), 2080-2089. https://doi.org/10.1111/cas.14069

Oparaugo, N. C., Ouyang, K., Nguyen, N. P. N., Nelson, A. M., Agak, G. W. (2023). Human regulatory T cells: Understanding the role of Tregs in select autoimmune skin diseases and post-transplant nonmelanoma skin cancers. International Journal of Molecular Sciences, 24 (2), Article 1527. https://doi.org/10.3390/ijms24021527

O'Shea, J. J., Murray, P. J. (2008). Cytokine signaling modules in inflammatory responses. Immunity, 28 (4), 477-487. https://doi.org/10.1016/j.immuni.2008.03.002

Pacheco, Y., Acosta-Ampudia, Y., Monsalve, D. M., Chang, C., Gershwin, M. E., Anaya, J. M. (2019). Bystander activation and autoimmunity. Journal of Autoimmunity, 103, Article 102301. https://doi.org/10.1016/j.jaut.2019.06.012

Parish, I. A., Heath, W. R. (2008). Too dangerous to ignore: Self-tolerance and the control of ignorant autoreactive T cells. Immunology and Cell Biology, 86 (2), 146-152. https://doi.org/10.1038/sj.icb.7100161

Pietrangelo, A. (2019). Drug-induced lupus: What is it and are you at risk? Healthline. https://www.healthline.com/health/lupus/drug-induced-lupus

Pisetsky, D. S. (2023). Pathogenesis of autoimmune disease. Nature Reviews Nephrology, 19 (8), 509-524. https://doi.org/10.1038/s41581-023-00720-1

Rajendeeran, A., Tenbrock, K. (2021). Regulatory T cell function in autoimmune disease. Journal of Translational Autoimmunity, 4, Article 100130. https://doi.org/10.1016/j.jtauto.2021.100130

Rosser, E. C., de Gruijter, N. M., Matei, D. E. (2022). Mini-review: Gut-microbiota and the sex-bias in autoimmunity - Lessons learnt from animal models. Frontiers in Medicine (Lausanne), 9, 910561. https://doi.org/10.3389/fmed.2022.910561

Rubtsov, A. V., Rubtsova, K., Kappler, J. W., Marrack, P. (2010). Genetic and hormonal factors in female-biased autoimmunity. Autoimmunity Reviews, 9 (7), 494-498. https://doi.org/10.1016/j.autrev.2010.02.008

Sakaguchi, S., Yamaguchi, T., Nomura, T., Ono, M. (2008). Regulatory T cells and immune tolerance. Cell, 133 (5), 775-787. https://doi.org/10.1016/j.cell.2008.05.009

Sandilands, G. P., McCrae, J., Hill, K., Perry, M., Baxter, D. (2006). Major histocompatibility complex class II (DR) antigen and costimulatory molecules on in vitro and in vivo activated human polymorphonuclear neutrophils. Immunology, 119 (4), 562-571. https://doi.org/10.1111/j.1365-2567.2006.02471.x

Segerstrom, S. C., Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. Psychological Bulletin, 130 (4), 601-630. https://doi.org/10.1037/0033-2909.130.4.601

Shao, T., Verma, H. K., Pande, B., Costanzo, V., Ye, W., Cai, Y., Bhaskar, L.V.K.S. (2021). Physical activity and nutritional influence on immune function: An important strategy to improve immunity and health status. Frontiers in Physiology, 12, 751374. https://doi.org/10.3389/fphys.2021.751374

Sharma, C., Bayry, J. (2023). High risk of autoimmune diseases after COVID-19. Nature Reviews Rheumatology. https://doi.org/10.1038/s41584-023-00964-y

Singh, S. P., Wal, P., Wal, A., Srivastava, V., Tiwari, R., Sharma, R. D. (2016). Understanding Autoimmune Disease: An Update Review. International Journal of Pharmaceutical Technology and Biotechnology, 3 (3), 51-65.

Stoakes, S. F. (2025). Functions of MHC in the immune system. News Medical Life Sciences. https://www.news-medical.net/life-sciences/Functions-of-MHC-in-the-Immune-System.aspx#:~:text=Certain%20MHC%20molecules%20are%20associated,targeting%2C%20resulting%20in%20disease%20association

Summit Rheumatology. (2025). Celiac disease and rheumatoid arthritis: How are autoimmune conditions related. Summit Rheumatology. https://summitrheumatology.com/patient-lifestyle/celiac-disease-and-rheumatoid-arthritis/

Sundaresan, B., Shirafkan, F., Ripperger, K., Rattay, K. (2023). The role of viral infections in the onset of autoimmune diseases. Viruses, 15(3), 782. https://doi.org/10.3390/v15030782

Taneja, V. (2018). Sex hormones determine immune response. Frontiers in Immunology, 9, 1931. https://doi.org/10.3389/fimmu.2018.01931

Taneja, V. (2023). Microbiome: Impact of sex on function and characteristics of gut microbiome. In M. Legato (Ed.), Principles of gender-specific medicine (pp. 313-329). Academic Press.

Theofilopoulos, A. N., Kono, D. H., Baccala, R. (2017). The multiple pathways to autoimmunity. Nature Immunology, 18 (7), 716-724. https://doi.org/10.1038/ni.3731

Thompson, P. A., Khatami, M., Baglole, C. J., Sun, J., Harris, S. A., Moon, E. Y., et al. (2015). Environmental immune disruptors, inflammation and cancer risk. *Carcinogenesis*, 36(Suppl 1), S232–S253. https://doi.org/10.1093/carcin/bgv038

Vrisekoop, N., Monteiro, J. P., Mandl, J. N., Germain, R. N. (2014). Revisiting thymic positive selection and the mature T cell repertoire for antigen. Immunity, 41(2), 181-190. https://doi.org/10.1016/j.immuni.2014.07.007

Wang, Z., Sun, Y., Yao, W., Ba, Q., Wang, H. (2021). Effects of cadmium exposure on the immune system and immunoregulation. Frontiers in Immunology, 12, 695484. https://doi.org/10.3389/fimmu.2021.695484

Watanabe, M., Lu, Y., Breen, M., Hodes, R. (2020). B7-CD28 co-stimulation modulates central tolerance via thymic clonal deletion and Treg generation through distinct mechanisms. Nature Communications, 11 (1), 6264. https://doi.org/10.1038/s41467-020-20070-x

Weber, A., Schwiebs, A., Solhaug, H., Stenvik, J., Nilsen, A. M., Wagner, M., et al. (2022). Nanoplastics affect the inflammatory cytokine release by primary human monocytes and dendritic cells. *Environment International*, 163, 107173. https://doi.org/10.1016/j.envint.2022.107173

WHO. (2020). Rheumatic heart disease. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/rheumatic-heart-disease#:~:text=Overview,valves%20caused%20by%20rheumatic%20fever

Wu, H. J., Wu, E. (2012). The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes, 3 (1), 4-14. https://doi.org/10.4161/gmic.19320

Yan, J., Mamula, M. J. (2002). Autoreactive T cells revealed in the normal repertoire: Escape from negative selection and peripheral tolerance. Journal of Immunology, 168 (7), 3188-3194. https://doi.org/10.4049/jimmunol.168.7.3188

Yang, W., Jannatun, N., Zeng, Y., Liu, T., Zhang, G., Chen, C., Li, Y. (2022). Impacts of microplastics on immunity. Frontiers in Toxicology, 4, 956885. https://doi.org/10.3389/ftox.2022.956885

Wijdeven, R. H., van Luijn, M. M., Wierenga-Wolf, A. F., Akkermans, J. J., van den Elsen, P. J., Hintzen, R. Q., Neefjes, J. (2018). Chemical and genetic control of IFNγ-induced MHCII expression. EMBO Reports, 19 (9), e45553. https://doi.org/10.15252/embr.201745553

Williams, W. V. (2017). Hormonal contraception and the development of autoimmunity: A review of the literature. The Linacre Quarterly, 84 (3), 275-295. https://doi.org/10.1080/00243639.2017.1360065

Zaman, M. S., Sizemore, R., Zaman, R. (2019). Microplastics in the environment: Ecological interactions and consequences. Advances in Science and Technology, 13(1&2), 22-28.

Zaman, M. S., Sizemore, R. (2020). Potential biological and health effects of nanoplastics. Advances in Science and Technology, 14 (1&2), 1-7.

Zhou, R., Caspi, R. R. (2010). Ocular immune privilege. F1000 Biology Reports, 2 (3). https://doi.org/10.3410/B2-3