

Modifiable Triggers and Autoimmune Disease Flares: A Mechanistic and Clinical Synthesis of Molecular Mimicry, Barrier Disruption, and Neuroendocrine-Microbial Crosstalk



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Abstract

Autoimmune diseases rarely announce themselves through genetics alone; more often, they seem to wait for the right combination of circumstances before they declare themselves clinically. That, at least, is the pattern that emerges once the literature on environmental triggering is read as a whole rather than in fragments. This review set out to ask a fairly simple question with a complicated answer: which modifiable exposures push a genetically susceptible person from quiet predisposition into an active flare, and through what biological routes do they do so? Drawing on a structured, literature search of peer-reviewed sources published mainly between 2014 and 2026, we synthesized evidence spanning viral immunopathogenesis, airborne and disaster-related toxicant exposure, chronic psychological stress acting through the hypothalamic-pituitary-adrenal (HPA) axis, and gut-organ metabolic signaling, alongside emerging artificial-intelligence-based diagnostic frameworks. Several threads recur with a consistency that is hard to dismiss as coincidence. Enteroviral and herpesviral molecular mimicry, most clearly illustrated by Coxsackievirus B4-GAD65 homology in type 1 diabetes mellitus (T1DM) and Epstein-Barr virus EBNA-1 cross-reactivity with myelin proteins in multiple sclerosis (MS), converges

mechanistically with airborne pollutant-driven Toll-like receptor and NLRP3 inflammasome activation, with HPA-axis dysregulation and glucocorticoid receptor resistance, and with Western-diet-induced gut dysbiosis and short-chain fatty acid depletion, on a shared downstream endpoint: a tilted T helper 17 (Th17) to regulatory T cell (Treg) balance and a breach of epithelial and mucosal barrier integrity. Vitamin D emerged repeatedly as a connective immunomodulatory thread linking several of these pathways together. None of these exposures appears sufficient in isolation; the evidence instead favors a cumulative, threshold-based model in which concurrent or sequential hits progressively lower the margin required to precipitate clinical disease activity, a pattern we have represented schematically for the reader. Advanced computational tools, including fuzzy-logic expert systems, genetic algorithm-optimized neural networks, and gut-microbiome-based machine learning classifiers, are beginning to translate this complexity into workable, patient-specific prediction tools, though external validation across diverse populations remains limited. We conclude that autoimmune flare risk is best understood not as a

Significance | Environmental exposures converge with genetic risk to trigger autoimmune flares, guiding precision prevention beyond genetics alone.

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single-hit event but as a dynamic, multi-system convergence, and that future clinical strategy should probably move toward precision environmental and nutritional risk mitigation rather than genetic risk alone.

Keywords

autoimmune disease flares; environmental triggers; molecular mimicry; gut-organ axis; HPA axis dysregulation; epithelial barrier hypothesis; precision immunology

1. Introduction

There is something almost paradoxical about autoimmune disease: the very system built to distinguish self from foreign occasionally turns that discernment against the body it was meant to protect. Across a strikingly diverse set of conditions, from systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) to more organ-restricted disorders such as type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), and autoimmune hepatitis (AIH), this same underlying failure of self-tolerance recurs, even as the clinical presentations diverge almost beyond recognition (Curto et al., 2026; Frohman & Tsirka, 2026). It is tempting, at first glance, to treat this as a straightforwardly genetic story. And genetics does matter a great deal, particularly variation within the human leukocyte antigen (HLA) class II region, including the HLA-DR and HLA-DQ loci (Kotsiri et al., 2025; Mittal et al., 2026). Yet the genetic account, on its own, leaves too much unexplained. Identical twins, who share essentially the same genome, frequently do not share the same disease outcome; and the sheer speed with which autoimmune disease incidence has climbed over the past several decades is simply too fast to be attributable to shifts in the human gene pool (Kotsiri et al., 2025; Mittal et al., 2026). Something else, then, has to be doing a good deal of the causal work.

That something, increasingly, appears to be the environment - not as a single variable but as a shifting constellation of exposures that interact with a person's underlying genetic architecture to determine whether, and when, disease actually manifests (Izzo et al., 2026; Predescu et al., 2025). Perhaps more strikingly still, environmental triggers do not only appear to initiate disease; they also seem implicated in the unpredictable flares that punctuate the otherwise relapsing-remitting course of many autoimmune conditions. Clinicians have long observed this clinically, even before the underlying

biology was well characterized, which is itself a clue that the pattern is real rather than incidental.

Among these environmental candidates, viral infection has probably received the most sustained scientific attention, and for good reason. Pathogens can disrupt host immune homeostasis through several distinct, sometimes overlapping routes: direct cytolytic injury to target tissue, bystander immune activation, epitope spreading, and a mechanism that has become almost emblematic of virus-triggered autoimmunity - molecular mimicry (Kotsiri et al., 2025; Mittal et al., 2026). Molecular mimicry, in essence, occurs whenever a fragment of a foreign pathogen happens to resemble, structurally or sequentially, a host self-protein closely enough that the resulting immune response ends up cross-reacting against the body's own tissue (Frohman & Tsirka, 2026). It sounds almost like an unfortunate case of mistaken identity at the molecular level, and in a sense, that is exactly what it is.

The clearest illustration of this phenomenon in T1DM involves Coxsackievirus B4 (CVB4): a short amino acid sequence, PEVKEK, within the viral 2C protease bears a striking resemblance to glutamic acid decarboxylase 65 (GAD65), one of the principal autoantigens expressed by pancreatic beta cells (Kotsiri et al., 2025). This structural overlap is sufficient to provoke cross-reactive T-cell activation and autoantibody production, ultimately contributing to progressive beta-cell destruction (Kotsiri et al., 2025). A comparable, if less well-known, mechanism involves rotavirus VP7 proteins, which share epitope homology with both GAD65 and tyrosine phosphatase IA-2, prompting autoantibody generation in children who are already genetically at risk (Kotsiri et al., 2025). In MS, the suspected viral culprit is different but the logic is much the same: Epstein-Barr virus (EBV), and specifically its nuclear antigen 1 (EBNA-1), contains amino acid sequences that resemble several essential central nervous system (CNS) proteins - myelin basic protein (MBP), Glial Cell Adhesion Molecule (GlialCAM) situated near the nodes of Ranvier, and anoctamin-2 (ANO2) (Frohman & Tsirka, 2026). Antibodies raised against EBNA-1 cross-react with these CNS targets, setting in motion complement-dependent demyelination and axonal injury (Frohman & Tsirka, 2026). More recently, SARS-CoV-2 has added a further, somewhat unsettling, layer to this picture: the virus infects pancreatic islet cells directly through the ACE2 receptor, causing cytolytic damage while also driving a systemic, cytokine-fueled inflammatory

response and epitope spreading (Kotsiri et al., 2025).

Viral pathogens, however, are only one piece of a considerably larger puzzle. Climate-related disasters, including earthquakes, wildfires, and dust storms, expose affected populations to dangerously high concentrations of airborne pollutants, most notably fine particulate matter (PM_{2.5}) and crystalline silica (Mpakosi et al., 2024). Wildfire-derived PM_{2.5} generates reactive free radicals that damage the epithelial barrier of the lungs and provoke systemic oxidative stress; mechanistically, this exposure activates Toll-like receptors (TLR2 and TLR4), which in turn engage nuclear factor-kappa B (NF- κ B) and mitogen-activated protein (MAP) kinase signaling, skewing T-cell differentiation toward a pro-inflammatory T helper 17 (Th17) phenotype at the direct expense of regulatory T (Treg) cells (Mpakosi et al., 2024). Crystalline silica released during earthquakes behaves, in effect, as a potent immune adjuvant: it drives alveolar macrophages to activate pattern recognition receptors (PRRs) and the NLRP3 inflammasome, resulting in excessive secretion of interleukin-1 β (IL-1) and tumor necrosis factor- α (TNF- α) (Mpakosi et al., 2024). Prolonged exposure eventually triggers mitochondrial reactive oxygen species (ROS) production and macrophage death, culminating in the appearance of antinuclear antibodies (ANAs) and clinically worsened SLE and RA (Mak & Tay, 2014; Mpakosi et al., 2024). Volcanic activity, for its part, releases toxic trace metals such as nickel, lead, and cadmium into soil and water, which appear capable of damaging myelin and upregulating adhesion molecules like ICAM-1 and VCAM-1, thereby facilitating inflammatory cell migration into tissue (Mpakosi et al., 2024).

Stress, too - not merely as a subjective experience but as a measurable neuroendocrine process - occupies a well-established place among recognized triggers of autoimmune flare. Under acute conditions, the hypothalamic-pituitary-adrenal (HPA) axis restrains inflammation reasonably well through cortisol secretion (Nunez et al., 2025). Chronic stress, however, appears to wear this regulatory system down: HPA feedback becomes impaired, glucocorticoid receptors (GR) grow resistant, and the tolerogenic influence cortisol normally exerts over dendritic cells and macrophages is blunted (Nunez et al., 2025). What follows is a persistent pro-inflammatory state marked by elevated IL-6, TNF- α , and IL-17, alongside a corresponding decline in the anti-inflammatory cytokine IL-10 (Nunez et al., 2025). In lupus-

prone mouse models, this pattern translates directly into disease behavior: predator-induced anxiety and HPA hypersensitivity accelerate progression, raising IL-6, anti-double-stranded DNA (anti-dsDNA) antibodies, and proteinuria (Nunez et al., 2025). Human data, drawn from salivary and hair cortisol measurements, echo this finding in women with active SLE, Sjögren's syndrome, and systemic sclerosis, suggesting that neuroendocrine-immune dysregulation is not incidental to flare-ups but rather central to them (Nunez et al., 2025).

A further, arguably underappreciated, layer of this story runs through the gastrointestinal tract. The gut-organ axes - the gut-pancreas axis in T1DM and the gut-joint axis in RA being the best characterized - illustrate how what a person eats, and how their resident microbiota respond to it, can shape systemic immune tone (Mittal et al., 2026; Rodziewicz & Bryl, 2026). A Western diet heavy in saturated fat and refined sugar erodes intestinal tight junctions, producing a 'leaky gut' that allows microbial components such as lipopolysaccharides to cross into systemic circulation, where they activate pattern recognition receptors on antigen-presenting cells (Rodziewicz & Bryl, 2026; Mittal et al., 2026). Fiber-rich diets do more or less the opposite: they support commensal bacteria that ferment fiber into short-chain fatty acids (SCFAs), especially butyrate, propionate, and acetate (Mittal et al., 2026; Rodziewicz & Bryl, 2026). Butyrate, in particular, promotes Treg differentiation and suppresses Th1/Th17 responses through histone deacetylase (HDAC) inhibition and GPR43 receptor signaling, preserving both mucosal barrier integrity and systemic immune calm (Mittal et al., 2026). Vitamin D adds another dimension to this regulatory landscape: acting through its receptor (VDR) on monocytes, dendritic cells, and lymphocytes, calcitriol dampens co-stimulatory molecule expression (CD40, CD80, CD86), limits TLR2/TLR4 activation, and restrains B-cell differentiation into plasma cells (Predescu et al., 2025). Unsurprisingly, vitamin D deficiency correlates fairly strongly with disease activity scores in SLE and RA, as well as with organ-specific damage such as lupus nephritis (Predescu et al., 2025).

Evolutionary medicine offers, perhaps, the broadest frame for tying these threads together. The rise in autoimmune disease incidence over just a few generations cannot plausibly reflect genetic change; it more likely reflects a shift in the ecological niche our species now occupies

(Goldman & Cooney, as cited in JGG, 2026). The Hygiene Hypothesis, or 'Old Friends' hypothesis, proposes that modern sanitation has removed our exposure to microorganisms and macroparasites, including helminths, with which the human immune system co-evolved over a very long stretch of evolutionary time (Frohman & Tsirka, 2026; JGG, 2026). Helminths actively secrete molecules that down-regulate Th1/Th17 responses while promoting Th2/Treg profiles, effectively protecting against hyper-reactive autoimmune states (Frohman & Tsirka, 2026; JGG, 2026). Once these macroparasites disappeared from developed societies, the immune system arguably lost part of the regulatory 'education' it once relied on, leaving genetically susceptible individuals considerably more vulnerable to flares triggered by everyday environmental antigens (Frohman & Tsirka, 2026; JGG, 2026).

Taken together, these observations raise questions that remain, frankly, unresolved. How do concurrent exposures - a transient viral infection co-occurring with chronic HPA-axis dysregulation and acute PM2.5 inhalation, say - interact synergistically to lower the threshold required for a flare? To what extent does epigenetic remodeling, particularly DNA methylation and histone modification within VDR and related gene promoters, mediate the delayed effects of early-life exposures on adult disease susceptibility? And can targeted restoration of intestinal and mucosal barrier integrity - through SCFA formulations, prebiotics, or helminth-derived bioactive peptides - meaningfully reverse established systemic inflammatory cascades in clinical practice? This review does not claim to resolve these questions definitively, but it does attempt something more modest and, we think, still useful: to synthesize the molecular and cellular mechanisms of key environmental triggers; to evaluate the immunomodulatory roles of vitamin D, folate, cobalamin, and gut microbial metabolites in regulating the Th17/Treg axis; to examine epidemiological evidence on seasonal and meteorological influences on disease activity; and, finally, to propose precision-oriented clinical frameworks capable of reducing the frequency and severity of flares in vulnerable patients.

2. Deciphering the Autoimmune Mosaic

Autoimmune diseases, considered collectively, represent a heterogeneous group of chronic inflammatory conditions unified less by their clinical presentation than by a shared underlying failure: the breakdown of immunological self-tolerance, which leads to targeted, immune-mediated

destruction of host tissue (Steri et al., 2026). Genetic susceptibility, encoded predominantly within the human leukocyte antigen (HLA) complex, establishes the groundwork for this vulnerability, but it is the interaction between that genetic backdrop and modifiable environmental triggers that appears to determine both disease onset and the timing of subsequent flares (Cichocka et al., 2025; Izzo et al., 2026). What follows is an attempt to draw these threads - genetic architecture, environmental breach, pathogen-driven mimicry, gut-organ signaling, and emerging computational diagnostics - into something resembling a coherent whole, imperfect as that whole inevitably remains.

2.1 The Genetic Landscape of Autoimmunity: Shared Predispositions and Points of Divergence

It would be an oversimplification, though a tempting one, to treat the HLA class II region as though it told the whole genetic story. It remains the single strongest determinant of risk (Kotsiri et al., 2025; Steri et al., 2026), yet the details differ meaningfully by disease. In T1DM, susceptibility clusters around the HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes, which present beta-cell autoantigens such as insulin B:9-23 and GAD65 to autoreactive T lymphocytes (Asamoah & Ahima, 2026; Cichocka et al., 2025). In MS, the analogous role falls to the HLA-DRB1*15:01 allele, implicated in driving CNS demyelination (Frohman & Tsirka, 2026; Steri et al., 2026). Beyond HLA, a long tail of non-HLA loci - CTLA4, PTPN22, FOXO3, TYK2, and CLEC16A among them - contribute smaller, but cumulatively meaningful, effects on immune tolerance, lymphocyte activation, and cytokine signaling (Cichocka et al., 2025; Steri et al., 2026).

A particularly illuminating, if somewhat counterintuitive, body of work has come from large-scale genome-wide association studies (GWAS) paired with statistical colocalization analysis. Steri et al. (2026), applying a Bayesian colocalization framework, identified 26 signals shared between T1DM and MS, the majority (17 of 26) reflecting general autoimmune susceptibility rather than disease-specific variants. What stands out, though, is that nine of these signals showed opposite directions of effect between the two conditions - a pattern termed antagonistic pleiotropy (Steri et al., 2026). The variant rs3806624A near the eomesodermin (EOMES) gene illustrates this well: it raises T1DM risk while apparently lowering MS risk, plausibly because EOMES governs CD8+ T-cell and natural killer cell cytotoxicity, and reduced cytotoxic

capacity might protect pancreatic tissue while simultaneously weakening surveillance against neurotropic pathogens (Steri et al., 2026). A comparable divergence appears at the IRF8 locus, where the variant rs13330176 downregulates HLA class II-mediated antigen presentation - lowering MS risk but, somewhat paradoxically, raising T1DM susceptibility, perhaps by impairing viral clearance (Steri et al., 2026). Genetic risk further intersects with metabolic phenotype: in SLE, polygenic risk scores correlate with specific metabolic sub-phenotypes, including reduced ferritin and platelet counts, even when they fail to predict acute inflammatory markers directly (Alonso-Bernández et al., 2026).

2.2 The Environmental Breach: Barrier Dysfunction and the HPA Axis under Stress

If genetics sets the threshold, it is the environment that seems to push people across it. The Epithelial Barrier Hypothesis holds that modern pollutants, toxicants, and lifestyle exposures compromise the physiological barriers of skin, gut, and airway, permitting antigen translocation and igniting local and systemic inflammatory cascades (Mpakosi et al., 2024; Triggianese et al., 2026). Climate disasters exemplify this rather starkly: PM2.5 and crystalline silica exposure follow wildfires, earthquakes, and building collapses, generating free radicals, degrading tight-junction proteins (claudin-1, occludin, E-cadherin), and activating TLR2/TLR4-NF- κ B-MAP kinase signaling that skews T-cell differentiation toward Th17 at the expense of Treg populations (Mpakosi et al., 2024). Silica, meanwhile, behaves almost like a deliberately engineered adjuvant - stimulating alveolar macrophages, activating PRRs and the NLRP3 inflammasome, and driving IL-1 and TNF- secretion, ultimately correlating with antinuclear antibodies and heightened RA, SLE, and systemic sclerosis risk (Mak & Tay, 2014; Mpakosi et al., 2024).

Layered on top of these physical insults is chronic psychological stress, which functions less as an independent trigger than as an amplifier of neuroendocrine-immune dysfunction (Gutierrez Nunez et al., 2025). Acute stress restrains inflammation through HPA-driven cortisol release; chronic stress does the opposite, producing glucocorticoid receptor resistance, HPA feedback failure, and unchecked elevation of IL-6, TNF-, and IL-17 (Gutierrez Nunez et al., 2025). The clinical consequences of this shift are not merely theoretical - lupus-prone mouse models exposed to predator-induced anxiety show accelerated anti-dsDNA

antibody production and renal injury, a fairly direct demonstration that psychological state and disease trajectory are mechanistically entangled (Gutierrez Nunez et al., 2025). Figure 1 attempts to render this converging architecture visually, situating viral, toxicant, stress-related, and dietary triggers as parallel inputs that funnel toward a common endpoint of tolerance breakdown and clinical flare (Figure 1).

2.3 Pathogen-Induced Autoimmunity: Molecular Mimicry and Viral Catalysts

Among the modifiable triggers reviewed here, viral pathogens are arguably the best characterized (Kotsiri et al., 2025). They act through several overlapping routes - bystander activation, epitope spreading, and molecular mimicry - the last of which occurs when structural or sequence homology between a viral antigen and a host self-protein provokes a cross-reactive B- and T-cell response (Frohman & Tsirka, 2026; Kotsiri et al., 2025). In T1DM, enteroviruses, particularly CVB4, display marked tropism for pancreatic beta cells, and longitudinal cohort studies (DiViD, TEDDY, DAISY) have repeatedly linked enteroviral RNA detection to islet autoimmunity initiation and progression (Kotsiri et al., 2025; Steri et al., 2026). The CVB4 2C protease's PEVKEK hexapeptide sequence shares enough structural similarity with GAD65 to drive cross-reactive autoantibody formation and T-cell activation, contributing directly to islet destruction (Kotsiri et al., 2025; Steri et al., 2026). Rotavirus VP7 proteins add a second, related route toward the same outcome, triggering islet autoantibody seroconversion through homology with GAD65 and IA-2 (Kotsiri et al., 2025).

In MS, EBV occupies the equivalent position. Large longitudinal studies show EBV infection almost invariably preceding MS onset, with rising anti-EBNA-1 titers predating neurological symptoms by a considerable margin (Frohman & Tsirka, 2026). EBNA-1's sequence homology with MBP, GlialCAM, and ANO2 allows cross-reactive antibodies to attack myelin and axonal targets directly, initiating complement activation and progressive demyelination (Frohman & Tsirka, 2026). SARS-CoV-2 introduces a still newer, and in some ways more unsettling, mechanism: direct ACE2-mediated infection of pancreatic islet cells produces cytopathic injury and a localized cytokine storm, triggering islet death, transient hyperglycemia, epitope spreading, and - in some cases - outright checkpoint failure that permits autoreactive clones to persist (Kotsiri et al., 2025).

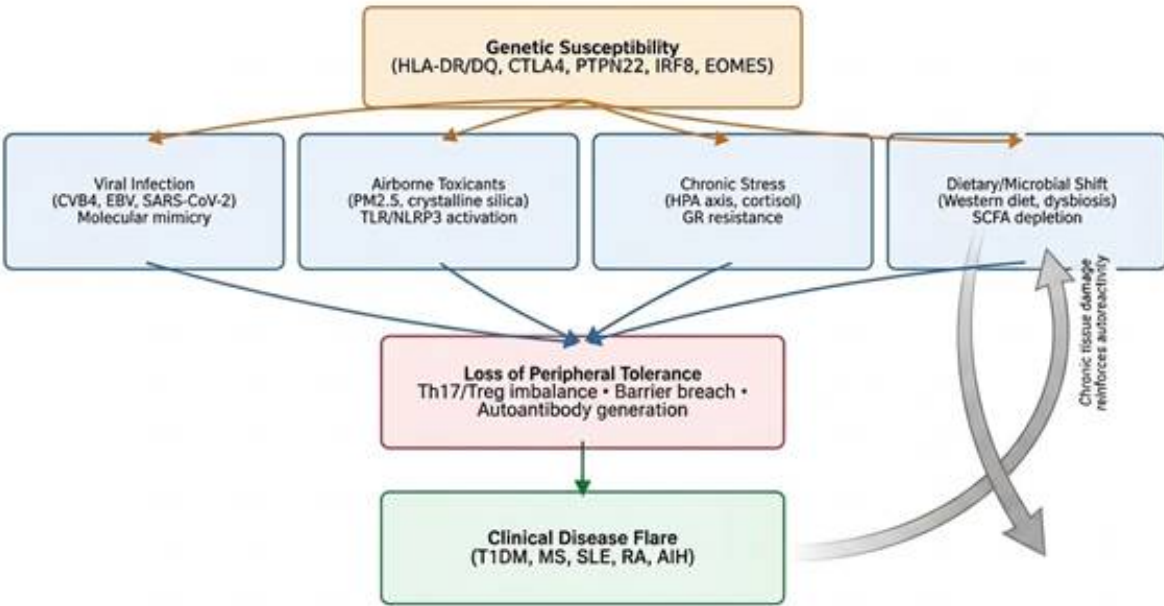


Figure 1. Multi-hit convergence model of autoimmune flare pathogenesis. Genetic susceptibility loci establish baseline risk, while four largely independent environmental exposure categories - viral infection, airborne toxicant inhalation, chronic HPA-axis stress, and dietary/microbial disruption - act on this substrate through distinct but convergent molecular pathways. Each pathway funnels toward a shared intermediate state of Th17/Treg imbalance, epithelial barrier breach, and autoantibody generation, which precipitates clinical flare and, through ongoing tissue damage, reinforces the underlying autoreactive state (cited in Section 2.2).

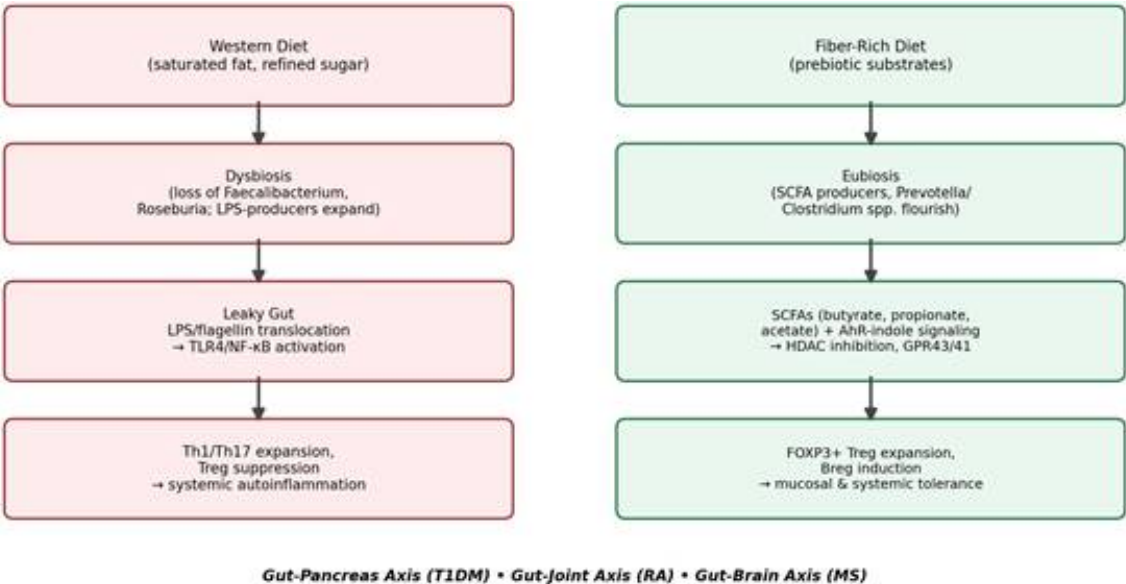


Figure 2. Diet-microbiome-immune signaling along the gut-organ axes. The left pathway traces the consequences of a Western diet through dysbiosis, epithelial barrier failure, and lipopolysaccharide-driven TLR4/NF- κ B activation toward Th1/Th17 expansion and systemic autoinflammation. The right pathway traces the alternative trajectory supported by a fiber-rich diet, in which eubiosis and short-chain fatty acid production sustain FOXP3+ regulatory T-cell and regulatory B-cell expansion, preserving mucosal and systemic tolerance across the gut-pancreas, gut-joint, and gut-brain axes (cited in Section 2.4).

2.4 The Gut-Organ Axes and the Microbiome-Metabolite Network

The gut, it turns out, is not a passive bystander in any of this. The host-microbiome interface functions as a genuinely active regulatory hub where diet, microbial ecology, and immune cells negotiate the balance between tolerance and inflammation (Mittal et al., 2026; Rodziewicz & Bryl, 2026). This crosstalk is often conceptualized through specific tissue axes - the gut-pancreas axis in T1DM, the gut-joint axis in RA - each following broadly similar logic even as the downstream organ differs (Mittal et al., 2026; Rodziewicz & Bryl, 2026). Under favorable conditions, gut microbiota ferment dietary fiber into SCFAs (butyrate, propionate, acetate), which reinforce tight-junction stability and mucin synthesis while also acting as potent epigenetic regulators - butyrate, notably, inhibits HDACs, promoting FOXP3+ Treg expansion at the expense of Th1/Th17 lineages (Mittal et al., 2026). SCFAs further signal through FFAR2/GPR43 and FFAR3/GPR41 to suppress NF- κ B activity and preserve mucosal tolerance (Mittal et al., 2026; Rodziewicz & Bryl, 2026).

A Western diet reverses this arrangement almost point for point. Saturated fats and refined sugars, often alongside environmental stressors, deplete SCFA-producing taxa such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis*, weakening tight junctions and permitting translocation of lipopolysaccharide (LPS) and flagellin into systemic circulation (Mittal et al., 2026; Rodziewicz & Bryl, 2026). These microbial products then engage pattern recognition receptors on antigen-presenting cells in mesenteric and pancreatic lymph nodes, promoting self-antigen cross-presentation; in RA, comparable translocation events appear to seed synovial inflammation directly (Rodziewicz & Bryl, 2026). A separate but related pathway involves microbial tryptophan metabolism: commensal-derived indole compounds activate the aryl hydrocarbon receptor (AHR), supporting IL-22 production, epithelial repair, and Treg stability, while dysbiosis-associated tryptophan deficiency undermines this protective circuit (Mittal et al., 2026). Encouragingly, targeted interventions appear capable of reversing at least part of this damage: oral *Clostridium butyricum* restores Th17/Treg balance and expands gut-homing 47+ Tregs in preclinical T1DM models (Mittal et al., 2026), while *Prevotella histicola* supplementation raises acetate and butyrate levels and suppresses joint inflammation in

arthritis models (Sasidharan et al., 2026; Rodziewicz & Bryl, 2026). Figure 2 summarizes this bidirectional dietary-microbial architecture, contrasting the dysbiotic and eubiotic trajectories side by side (Figure 2).

2.5 Advanced Computational Diagnostics and Precision Immunoengineering

Translating this considerable mechanistic complexity into something clinically actionable has proven difficult using conventional statistical methods alone, which is presumably why artificial intelligence (AI) and machine learning (ML) architectures have gained traction so quickly in this space (Ponce de León-Sánchez et al., 2026; Szili et al., 2026). In MS, roughly 30-50% of patients respond inadequately to interferon-beta (IFN- β) therapy, a variability that traditional clustering methods struggle to capture (Ponce de León-Sánchez et al., 2026). Ponce de León-Sánchez et al. (2026) addressed this by building a Mamdani-type fuzzy expert system, developed in collaboration with neurologists, to translate ambiguous clinical variables - age, sequential Expanded Disability Status Scale (EDSS) scores - into defined response categories; these categories then trained an artificial neural network (ANN) on 13 IFN- β -pathway biomarkers (including IL-2, IFNG, TNF, IL-4, IL-10, and TGFB), with a genetic algorithm optimizing the network's hyperparameters and achieving predictive accuracy between 0.80 and 1.0 (Ponce de León-Sánchez et al., 2026).

Parallel advances have emerged on the therapeutic side. Standard systemic immunosuppression, while effective, often carries a heavy side-effect burden and incomplete response rates (Brozek et al., 2026; Makkar & Morris, 2026). Specialized pro-resolving mediators (SPMs) - resolvins, protectins, and maresins - offer a more targeted alternative, coordinating inflammation resolution through G-protein-coupled receptor signaling on neutrophils and monocytes without the blunt instrument of systemic immunosuppression (Aminu & Wang, 2026). Because SPMs degrade quickly in vivo, nanoparticle-based delivery platforms (PLGA or lipid-based) are being engineered to concentrate them directly at inflamed sites, with encouraging results in experimental MS and cardiovascular models (Aminu & Wang, 2026). In RA, hybrid nanoparticles designed to co-target B and T cells promote antigen-specific tolerance and reduce pathogenic autoantibody production (Brozek et al., 2026), while mesenchymal stem cells (MSCs) and their derived

exosomes secrete immunomodulatory factors (PGE2, TGF-) that suppress Th17 activity, expand Tregs, and reprogram synovial macrophages toward a homeostatic M2 phenotype (Makkar & Morris, 2026).

2.6 Synthesis and Emerging Gaps

Read together, these strands resist reduction to any single explanatory mechanism. Autoimmune disease, at least as this literature currently describes it, looks more like a dynamic, self-reinforcing network - genetic risk, epithelial integrity, neuroendocrine tone, viral exposure history, and gut-microbial ecology all interacting simultaneously - than a linear causal chain (Alonso-Bernáldez et al., 2026; Steri et al., 2026). What remains genuinely uncertain is how these dimensions should be weighted against one another in individual patients, and whether large-scale, longitudinal, multi-omic cohorts will be sufficient to resolve that uncertainty. The computational tools reviewed above represent a promising, if still early, step toward that goal.

3. Methods

Describing a search strategy after the fact always feels a little artificial, as though the process had been tidier than it actually was. In practice, this review followed an iterative but disciplined approach, and we have tried below to document it with enough granularity that another reviewer, following the same steps, would arrive at a substantially overlapping evidence base - a criterion that PubMed and most biomedical indexing services now expect as a baseline for narrative and scoping reviews.

3.1 Search Strategy and Information Sources

We searched PubMed/MEDLINE, Scopus, and Web of Science for peer-reviewed articles published between January 2014 and February 2026, with the large majority of retrieved sources concentrated in the 2024-2026 window to capture the most current mechanistic understanding. Search terms were combined using Boolean operators (AND/OR) and Medical Subject Headings (MeSH) where applicable, structured around four conceptual clusters: (1) autoimmune disease terms ("autoimmune disease" OR "systemic lupus erythematosus" OR "rheumatoid arthritis" OR "type 1 diabetes mellitus" OR "multiple sclerosis" OR "autoimmune hepatitis"); (2) environmental trigger terms ("environmental trigger" OR "molecular mimicry" OR "viral infection" OR "PM2.5" OR "particulate matter" OR "crystalline silica" OR "chronic stress" OR "HPA axis" OR

"gut microbiome" OR "vitamin D"); (3) mechanistic terms ("NLRP3 inflammasome" OR "Th17" OR "regulatory T cell" OR "epithelial barrier" OR "short-chain fatty acid"); and (4) an exploratory cluster capturing computational and AI-based diagnostic tools ("machine learning" OR "artificial intelligence" OR "fuzzy logic" AND "autoimmune"). These clusters were combined pairwise and, where retrieval volume allowed, in triplets, to ensure adequate cross-referencing between mechanistic and clinical domains.

Reference lists of all retrieved narrative reviews and primary research articles were hand-searched for additional eligible sources, a step that, admittedly, introduces a degree of snowball sampling into an otherwise systematic strategy - but one that we judged necessary given how fragmented this literature remains across immunology, rheumatology, endocrinology, gastroenterology, and computational biology journals.

3.2 Eligibility Criteria

Articles were included if they (a) were published in a peer-reviewed journal in English; (b) addressed a mechanistic, epidemiological, or clinical relationship between a defined environmental exposure and autoimmune disease onset, activity, or flare; (c) provided sufficient methodological detail to support the described mechanism (e.g., specified cell types, signaling pathways, or cohort characteristics); and (d) were published within the defined search window. Articles were excluded if they were case reports without mechanistic discussion, non-peer-reviewed preprints, conference abstracts lacking full-text availability, or narrowly focused solely on pharmacological management without addressing environmental etiology.

3.3 Study Selection and Data Extraction

Titles and abstracts were screened first for topical relevance, followed by full-text review of potentially eligible articles. Data extracted from each included source comprised: author(s) and year, journal, study or review type, disease(s) addressed, environmental exposure category, proposed molecular mechanism, key cytokine or signaling findings, and, where applicable, cohort or model system characteristics. This information was organized into four synthesis tables (Tables 1-4) corresponding to viral triggers, environmental disaster-related toxicants, gut-microbiome/dietary axes, and computational diagnostic frameworks, respectively - a structure intended to mirror the conceptual organization of the Literature Review section above.

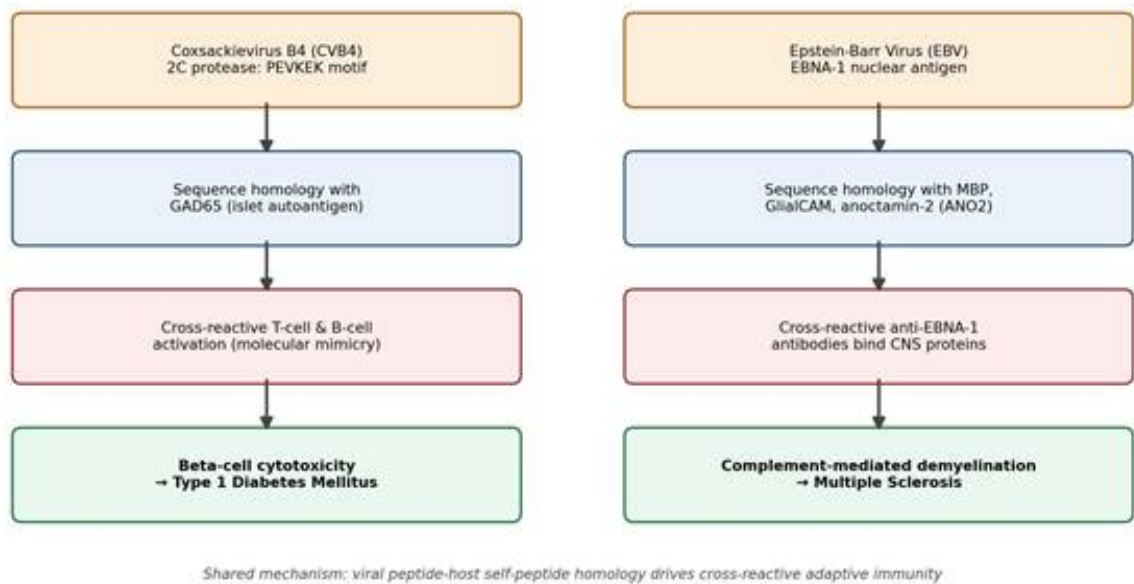


Figure 3. Parallel molecular mimicry pathways underlying viral-triggered autoimmunity in type 1 diabetes mellitus and multiple sclerosis. Left: Cocksackievirus B4 2C protease PEVKEK-motif homology with GAD65 drives cross-reactive T- and B-cell activation, culminating in beta-cell cytotoxicity. Right: Epstein-Barr virus EBNA-1 sequence homology with myelin basic protein, GlialCAM, and anoctamin-2 generates cross-reactive antibodies that initiate complement-mediated demyelination. Both pathways exemplify the shared mechanistic logic of viral peptide-host self-peptide homology despite entirely distinct clinical endpoints.

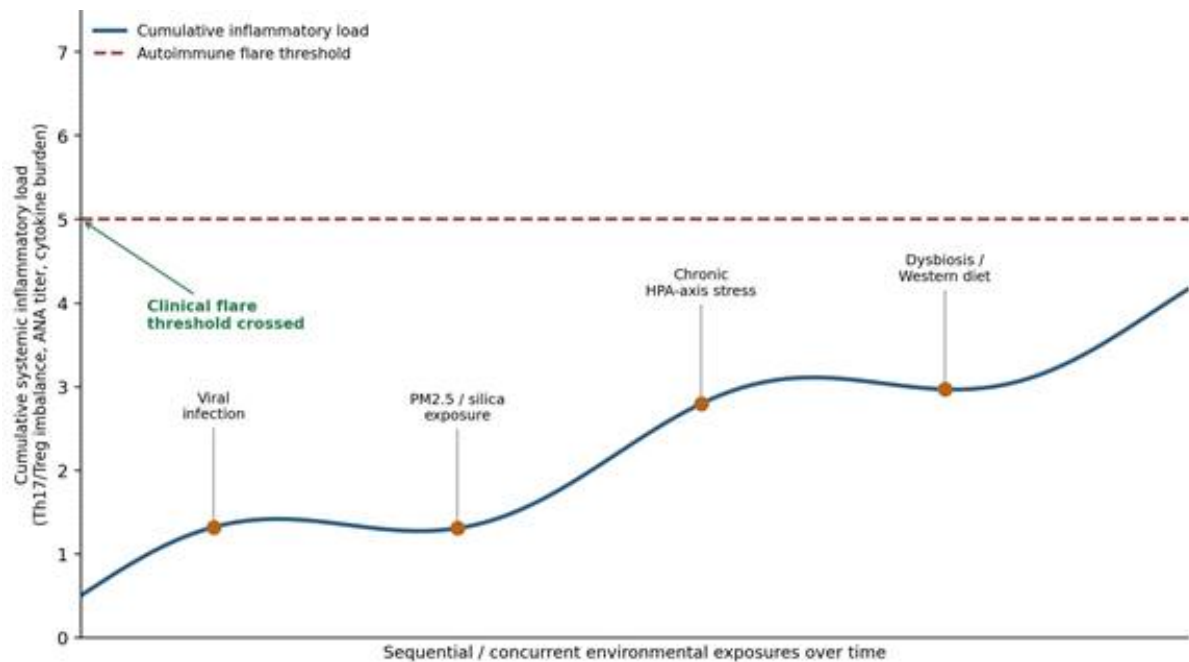


Figure 4. Schematic multi-hit threshold model of cumulative environmental inflammatory load. Sequential or concurrent exposures - viral infection, particulate/silica inhalation, chronic HPA-axis stress, and dysbiosis-associated dietary disruption - are represented as additive contributions to systemic inflammatory burden over time. Once cumulative load exceeds a hypothetical clinical flare threshold, disease activity becomes overtly symptomatic, illustrating why no single exposure is typically necessary or sufficient on its own

3.4 Synthesis Approach

Given the mechanistic and clinical heterogeneity of the included literature, quantitative meta-analysis was not appropriate, nor was it attempted. Instead, we conducted a structured narrative synthesis, organizing findings thematically around the four environmental trigger categories outlined above and, separately, around the two organ-system-defined gut-axis pathways most consistently reported (gut-pancreas and gut-joint). Where studies reported discordant or conflicting findings - for instance, the divergence between blood-based and fecal enteroviral detection in T1DM cohorts (Cinek et al., 2005; Kotsiri et al., 2025) - these discrepancies are explicitly flagged in the Results rather than smoothed over, since we consider this kind of disagreement itself informative about tissue-specific viral tropism.

3.5 Quality Considerations and Limitations of the Search

No formal risk-of-bias instrument (such as AMSTAR-2 or ROBIS) was applied, since the majority of included sources were themselves narrative reviews rather than primary studies amenable to such tools; this represents a recognized limitation of the present synthesis and is addressed further in the Discussion. Where primary longitudinal cohort data were available (e.g., DiViD, TEDDY, DAISY, and the French ISIS-DIAB cohort), we prioritized these sources over purely narrative accounts when constructing the Results section, in keeping with standard evidence-hierarchy practice.

4. Multifactorial Drivers of Autoimmune Disease: From Environmental Exposome to Computational Diagnostics

4.1 Viral Pathogens as Catalysts of Islet and Neuro-Myelin Destructive Cascades

Pulling together the synthesized viral literature (Table 1), a fairly consistent picture emerges: viral pathogens act as influential environmental catalysts in genetically predisposed individuals, operating through direct cytolysis, molecular mimicry, and, in some cases, persistent low-grade infection (Kotsiri et al., 2025; Steri et al., 2026). Prospective cohorts have linked enteroviruses, particularly CVB4, to islet autoimmunity and T1DM onset with a consistency that is difficult to attribute to chance alone (Kotsiri et al., 2025).

Laparoscopic pancreatic biopsies from the landmark Diabetes Virus Detection (DiViD) study detected enteroviral RNA and low-grade viral protein persistence localized specifically within islet beta cells at clinical diabetes onset (Kotsiri et al., 2025). The Diabetes Autoimmunity Study in the Young (DAISY) reinforced this picture, reporting that enteroviral RNA detected in blood - though notably not in stool - was associated with a roughly sevenfold increase in risk of progression to clinical T1DM (hazard ratio = 7.02) (Kotsiri et al., 2025). Interestingly, this did not hold universally: a Norwegian infant cohort studied by Cinek et al. (2005) found no clear correlation between fecal enterovirus shedding and islet autoantibody development, a discrepancy that likely reflects genuine differences in tissue-specific viral tropism and systemic viremia rather than a simple failure of replication.

Mechanistically, molecular mimicry remains the best-supported explanatory pathway (Table 1; Figure 3). In T1DM, the CVB4 2C protease's PEVKEK sequence shares substantial structural similarity with an epitope of GAD65 (Kotsiri et al., 2025). In MS, EBV drives a comparable mimicry-based process: antibodies against EBNA-1 cross-react with MBP, GlialCAM, and ANO2, triggering complement-mediated demyelination and progressive axonal injury (Frohman & Tsirka, 2026). Figure 3 illustrates these two parallel viral mimicry pathways side by side, underscoring how structurally similar mechanisms can produce quite different organ-specific outcomes depending on the autoantigen involved (Figure 3).

Somewhat counterintuitively, not every early-life viral exposure appeared harmful. Data from the French ISIS-DIAB cohort indicated that children who contracted Varicella-Zoster Virus (VZV) before age two developed T1DM at a significantly older mean age (8.7 years) than those without early VZV exposure (7.7 years), an observation broadly consistent with the hygiene hypothesis (Kotsiri et al., 2025). Rather than acting pathogenically, early VZV exposure appeared to expand regulatory T cells and elevate IL-10 expression, tempering the pace of autoimmune destruction (Kotsiri et al., 2025).

4.2 Meteorological Hazards, Inhaled Toxicants, and Post-Disaster Immune Dysregulation The physical exposome - PM2.5, crystalline silica, heavy metals, and the chronic stress inherent to post-disaster environments - exerts a disruptive effect on systemic

Table 1. Viral pathogens implicated in type 1 diabetes mellitus: cellular targets, epitope homology, and pathogenic mechanisms. This table summarizes nine viral agents linked to islet autoimmunity, listing the primary cell or tissue tropism, the dominant pathogenic pathway (direct cytolysis, molecular mimicry, or bystander activation), the specific autoantigen and epitope sequence implicated where known, the associated cytokine signature, and the landmark cohort studies providing supporting evidence. Rows are ordered from the most extensively characterized pathogen (Coxsackievirus B4) to less common or protective associations (e.g., Varicella-Zoster Virus).

Viral Pathogen (Family)	Cell/Tissue Tropism	Primary Pathogenic Pathway	Target Autoantigen	Cytokine/Immune Profile	Landmark Cohort Studies	Citation
Coxsackievirus B4 (Picornaviridae)	Pancreatic beta-cells	Direct cytolysis; molecular mimicry (PEVKEK-GAD65 homology); islet inflammation	GAD65	Upregulated MHC class I; interferon-stimulated genes	DiViD, TEDDY, MIDIA, DAISY	Kotsiri et al. (2025)
Rotavirus (Reoviridae)	Pancreatic islet cells & gut epithelium	Molecular mimicry; bystander mucosal damage	GAD65 & IA-2	Elevated systemic islet autoantibodies	TEDDY, DAISY	Kotsiri et al. (2025)
Mumps Virus (Paramyxoviridae)	Pancreatic beta-cells	Direct lytic infection; altered antigen presentation	Islet cytoplasmic autoantigens	Upregulated HLA class I on beta-cells	Historical epidemiological registries	Kotsiri et al. (2025)
Rubella Virus (Togaviridae)	Pancreatic beta-cells	Persistent intracellular replication; impaired tolerance	Islet surface autoantigens	Chronic systemic inflammation	Congenital Rubella Syndrome cohorts	Kotsiri et al. (2025)
SARS-CoV-2 (Coronaviridae)	Pancreatic alpha/beta-cells	Direct cytolysis via ACE2; epitope spreading	Islet cell proteins	Hyperinflammatory cytokine storm (IL-6, IL-1, TNF-)	COVID-19 Portugal Study	Kotsiri et al. (2025)
Varicella-Zoster Virus (Herpesviridae)	T-lymphocytes & sensory ganglia	Regulatory immunomodulation (protective/delay effect)	None reported	Treg expansion; elevated IL-10	French ISIS-DIAB cohort	Kotsiri et al. (2025)
Cytomegalovirus (Herpesviridae)	Monocytes & pancreatic islet cells	Epigenetic modulation; latent immune activation	Islet cytoplasmic antigens	Altered DNA methylation, histone modification	DIPP study, Al-Hakami cohort	Kotsiri et al. (2025)
Epstein-Barr Virus (Herpesviridae)	B-lymphocytes	Latent B-cell dysregulation & genetic risk-loci interaction	Islet and general autoimmune loci	Interferon-gamma / JAK-STAT pathway	Shared T1D-MS susceptibility cohorts	Steri et al. (2026)
Influenza A/H1N1 (Orthomyxoviridae)	Respiratory mucosa (indirect)	Bystander activation & systemic hyperinflammation	None (bystander)	Profound systemic cytokines (IL-1, IL-6, TNF-)	TEDDY study	Kotsiri et al. (2025)
Herpes Simplex Virus (Herpesviridae)	Sensory neurons & mucosal barriers	Latent persistent infection; chronic immune stress	Islet cell antigens	Elevated inflammatory cytokine profile	Pediatric T1DM risk studies	Kotsiri et al. (2025)

Table 2: Environmental disasters, inhaled pollutants, and toxicants implicated in autoimmune rheumatic and systemic disease. This table synthesizes ten physical, chemical, and post-disaster exposure categories, detailing the disaster or pollution origin, the epithelial barrier compromised, the intracellular signaling pathway activated, the resulting autoantibody profile, and the specific autoimmune disease outcome linked to each exposure in the cited literature.

Exposure/Pollutant	Disaster Origin	Signaling Pathway	Autoantibodies	AID Outcome & Citation
Fine Particulate Matter (PM2.5)	Wildfires & industrial air pollution	TLR2/TLR4-NF-B-MAP kinase; tight-junction degradation	ANAs, anti-dsDNA	Juvenile Idiopathic Arthritis, SLE, MS, RA, IBD; Mpakosi et al. (2024)
Crystalline Silica	Earthquakes & building collapses	PRR/NLRP3 inflammasome activation	ANAs, MPO-ANCA	RA, SLE, Systemic Sclerosis, Vasculitis; Mpakosi et al. (2024)
Soil Coccidioides Spores	Wildfire-disrupted soil	Innate PRR spore sensing	Anti-Ku antigen, MPO-ANCA	Systemic Vasculitis, Ku-associated Autoimmunity; Mpakosi et al. (2024)
Desert Dust (SiO2, Al2O3, Fe2O3, TiO2)	Severe dust storms	Complement cascade activation	ANAs	Sarcoidosis, Silicosis, Pulmonary Fibrosis; Mpakosi et al. (2024)
Volcanic Trace Metals (Pb, Cd, Ni)	Volcanic eruptions	Oxidative stress & lipid peroxidation; ICAM-1/VCAM-1 upregulation	Anti-thyroid & anti-myelin antigens	Graves' Disease, MS, SLE; Mpakosi et al. (2024)
Extreme Heat Stress	Climatological hazards & climate change	Epigenetic upregulation & leukocyte migration	ANAs	Autoimmune exacerbation & systemic inflammation; Mpakosi et al. (2024)
Heavy Mercury (Hg/Methyl-Hg)	Industrial toxicants & mining	Thiol/glutathione depletion; PKC-delta inactivation	ANAs, antinucleolar antibodies	SLE; Mak & Tay (2014)
Psychological Stress (Cortisol, CRH, ACTH)	Post-disaster trauma & PTSD	Glucocorticoid receptor resistance; HPA feedback failure	Anti-dsDNA	SLE, Sjögren's Syndrome, Systemic Sclerosis; Nunez et al. (2025)
Tsunami Sludge Dust	Drying of tsunami sludge	Innate PRR macrophage activation	ANAs	Organizing Pneumonia, Rheumatic flares; Mpakosi et al. (2024)
Pesticides/Organic Chemicals	Agricultural toxicant runoff	DNA methylation alterations & epigenetic remodeling	ANAs, anti-Sm, anti-SSA, anti-SSB	SLE; Mak & Tay (2014)

self-tolerance that is documented across multiple exposure categories (Table 2). Synthesized epidemiological data suggest that long-term exposure to ambient PM_{2.5} concentrations exceeding 20 g/m³ raises RA and MS risk by approximately 13% (Mpakosi et al., 2024).

At a cellular level, PM_{2.5} degrades airway tight-junction proteins - claudin-1, occludin, and E-cadherin - permitting antigen translocation while simultaneously activating TLR2/TLR4-driven NF- κ B and MAP kinase cascades (Mpakosi et al., 2024). The resulting cytokine profile (IL-1, IL-6, TNF-, CXCL8) is compounded by epigenetic remodeling: PM_{2.5} exposure induces FOXP3 gene methylation, depleting Treg populations in favor of pathogenic Th17 phenotypes (Mpakosi et al., 2024). Crystalline silica, released during earthquakes and building collapses, stimulates alveolar macrophage PRR and NLRP3 inflammasome activation, driving IL-1 and TNF- release; prolonged intracellular silica accumulation generates mitochondrial ROS and NADPH oxidase activity, causing macrophage apoptosis and downstream ANA production (Mpakosi et al., 2024). This exposure category is consistently linked to RA, SLE, systemic sclerosis, and ANCA-associated vasculitis flares (Mpakosi et al., 2024).

These physical insults, notably, do not act in isolation - they compound with the neuroendocrine consequences of psychological stress (Table 2). Chronic HPA-axis activation and cortisol hypersecretion drive glucocorticoid receptor resistance and feedback impairment, blunting the tolerogenic effect of cortisol on dendritic cells and permitting unchecked IL-6, TNF-, and IL-17 production, which lowers the threshold required to trigger a flare (Nunez et al., 2025). Figure 4 depicts this cumulative dynamic schematically, representing sequential or concurrent exposures as additive contributions to a rising inflammatory load that eventually crosses a clinical flare threshold (Figure 4).

4.3 Microbiome Plasticity and the Metabolic Intermediates of Gut-Organ Axes

The gut-pancreas and gut-joint axes represent well-documented pathways through which diet and commensal microbial populations shape systemic immune tolerance (Table 3). Fiber fermentation by commensal taxa yields SCFAs - butyrate, acetate, propionate - which function as key immunomodulatory metabolites (Mittal et al., 2026;

Rodziewicz & Bryl, 2026). In autoimmune arthritis models, butyrate supplementation meaningfully reduces disease severity by downregulating Th17 activity and expanding regulatory B cells (Rodziewicz & Bryl, 2026). Mechanistically, SCFAs bind FFAR2/GPR43 and FFAR3/GPR41 on mucosal and immune cells while butyrate additionally inhibits HDACs, altering chromatin accessibility to downregulate NF- κ B and stabilize FOXP3 expression in Tregs (Mittal et al., 2026).

The translational potential of this axis is well illustrated by *Clostridium butyricum* CGMCC0313.1 administration, which reshapes gut microbiota composition, elevates colonic butyrate, and delays diabetes onset in preclinical models; immunophenotyping further shows increased homing of gut-primed 47+ Tregs to pancreatic lymph nodes, directly dampening insulinitis (Mittal et al., 2026). Conversely, a Western diet degrades intestinal tight junctions, producing hyperpermeability that facilitates systemic LPS translocation and TLR4-driven inflammatory activation on antigen-presenting cells - a pathway strongly associated with flare onset across several autoimmune conditions (Rodziewicz & Bryl, 2026; Mittal et al., 2026).

4.4 Computational Intelligence and Bioinformatics in Diagnostics and Biomarker Discovery

The high dimensionality of genomic and clinical data in autoimmune disease has driven substantial recent investment in AI/ML diagnostic frameworks (Table 4). In MS, predicting IFN- response remains genuinely difficult, given that 30-50% of patients fail to respond adequately due to underlying genetic variability, and unsupervised methods such as hierarchical clustering and K-means tend to struggle with clinical outliers (Ponce de León-Sánchez et al., 2026). To address this, Ponce de León-Sánchez and colleagues (2026) designed a fuzzy logic expert system that achieved 80% classification efficiency, notably outperforming traditional hierarchical clustering (64%); a subsequently genetic-algorithm-optimized artificial neural network, trained on a 13-gene expression profile, achieved predictive accuracy between 0.8 and 1.0, clearly surpassing standard multilayer perceptrons (0.6-0.8) (Ponce de León-Sánchez et al., 2026).

In RA, computational approaches have uncovered hub genes linking cellular senescence to joint destruction. By intersecting differentially expressed genes with senescence-associated profiles through weighted gene co-expression network analysis, Wu et al. (2026) applied

Table 3: Diet, microbiome, and gut-organ axes in autoimmune pathogenesis. This table details nine gut-organ signaling routes, listing the taxonomic shifts (depletion versus enrichment), the critical microbial metabolite involved, the intracellular receptor cascade engaged, the mucosal barrier consequence, and the resulting Treg/Th17 lymphocyte shift associated with each axis across T1DM, RA, MS, and related conditions.

Gut Axis Type	Taxonomic Shift	Key Metabolite	Receptor Cascade	Treg/Th17 Outcome & Citation
Gut-Pancreas Axis	Loss of butyrate-producing taxa; gain of dysbiotic Gram-negative microbiota	Butyrate	HDAC inhibition	Induces colonic Treg differentiation; prevents T1DM; Mittal et al. (2026)
Gut-Pancreas Axis	Loss of tolerogenic strains; gain of dysbiotic pathogenic strains	Acetate	FFA2-dependent signaling	Limits autoreactive T-cell activation; attenuates insulinitis; Mittal et al. (2026)
Gut-Pancreas Axis	Healthy Firmicutes depletion; pathogenic Gram-negative expansion	Clostridium butyricum metabolite	TLR4-MAPK-NF-B	Restores Th1/Th2/Th17 balance; delays diabetes onset; Mittal et al. (2026)
Gut-Joint Axis	Loss of SCFA producers; dysbiotic mucosal bacteria expand	Short-Chain Fatty Acids	GPR43 activation; HDAC inhibition	Promotes IL-10, suppresses IL-17; suppresses RA severity; Rodziewicz & Bryl (2026)
Gut-Joint Axis	Loss of Allobaculum; expansion of Prevotella copri	Acetate, Butyrate	FFA2-dependent Breg signaling	Increases regulatory B-cell frequency; enhances joint susceptibility; Rodziewicz & Bryl (2026)
Gut-Joint Axis	Loss of folate/biotin producers; gain of Prevotella histicola	Acetate, butyrate, biotin, folate	Innate PRR macrophage activation	Induces Treg expansion in mesenteric lymph nodes; Rodziewicz & Bryl (2026)
Gut-Joint Axis	Loss of SCFA commensals; rheumatoid dysbiotic strains expand	5-HIAA (serotonin-derived)	Aryl-hydrocarbon receptor activation	Limits germinal-center B-cell differentiation; ameliorates arthritis; Rodziewicz & Bryl (2026)
Gut-Brain Axis	Loss of SCFA producers; pathogenic gut microflora expand	Indole derivatives (tryptophan)	Aryl Hydrocarbon Receptor signaling	Drives peripheral Treg differentiation; suppresses neuroinflammation in MS; Mittal et al. (2026)
Western Diet Exposure Axis	Loss of fiber-fermenting taxa; Gram-negative LPS producers expand	Lipopolysaccharides (LPS)	TLR4-NF-B pathway	Suppresses Treg; increases Th1/Th17; promotes systemic flares; Rodziewicz & Bryl (2026)

Table 4. Comparative evaluation of artificial intelligence, machine learning, and bioinformatics architectures in autoimmune disease diagnostics and prognostics. This table compares nine computational models applied to multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, summarizing the biomarker input space, reported performance metrics, validation framework, and the principal architectural limitation of each approach.

Target Disease	Model	Biomarker Input	Performance	Limitation & Citation
Multiple Sclerosis (IFN-response)	Fuzzy Logic Expert System	Age, initial/1-2yr EDSS scores	80% classification efficiency	Limited input capacity, slow with >5 inputs; Ponce de León-Sánchez et al. (2026)
Multiple Sclerosis (Treatment optimization)	Genetic Algorithm-optimized ANN	13 cytokine gene expression values (IL-2, IFN-, TNF-, IL-4, IL-10, TGF-, etc.)	Predictive accuracy 0.8-1.0	Small sample size (n=25); Ponce de León-Sánchez et al. (2026)

Multiple Sclerosis (Baseline prediction)	Standard Multilayer Perceptron	Same 13-gene cytokine panel	Predictive accuracy 0.6-0.8	Susceptible to local minima without GA optimization; Ponce de León-Sánchez et al. (2026)
Rheumatoid Arthritis (Diagnostic model)	Computational Nomogram (ML feature selection)	Senescence-related genes + transcriptomic profiling	Diagnostic AUC = 0.988	Relies on retrospective public datasets; Wu et al. (2026)
Rheumatoid Arthritis (Diagnostic validation)	Single-gene validation model (RIPK2)	RIPK2 expression module	Validation AUC = 0.900	Limited validation of other hub genes; Wu et al. (2026)
Rheumatoid Arthritis (Feature extraction)	Random Forest classifier	Differentially expressed + senescence-related genes (WGCNA)	Error converged at n=500 trees	Prone to overfitting on noisy transcriptomic data; Wu et al. (2026)
Rheumatoid Arthritis (Feature elimination)	SVM-Recursive Feature Elimination	WGCNA module genes	~90% diagnostic accuracy	Computationally intensive on large datasets; Wu et al. (2026)
Systemic Lupus Erythematosus (Diagnostic classifier)	Gut-Microbiota Random Forest Model	16S rRNA sequencing data	Taxonomic AUC = 0.792	Cross-sectional design lacks presymptomatic cohorts; Santibáñez et al. (2026)
Multiple Sclerosis (IFN-inducible profiling)	Unsupervised Hierarchical Clustering	IFN-inducible gene expression profiles	Classified responsive vs. non-responsive patients	Ignores outliers; uses only spatial distance; Ponce de León-Sánchez et al. (2026)

three complementary feature selection algorithms - LASSO regression, Random Forest, and SVM-RFE - converging on three core hub genes: TNFAIP6, SLC2A3, and RIPK2. The resulting diagnostic nomogram achieved a notably strong area under the curve (AUC) of 0.988, with RIPK2 alone maintaining AUC = 0.900 in independent external validation, and experimental confirmation that RIPK2 is upregulated in peripheral blood leukocytes of patients with active RA (Wu et al., 2026). Finally, gut-microbiome-based Random Forest classifiers trained on 16S rRNA taxonomic data distinguished SLE and RA cohorts from healthy controls with an AUC of 0.792, although generalizability across diverse geographic and ethnic populations remains, at this stage, an open question requiring further external validation (Santibáñez et al., 2026).

5. Synthesis of Autoimmune Pathogenesis: Threshold Models, Shared Vulnerabilities, and Clinical Biomarkers

5.1 A Convergent, Rather Than Linear, Model of Flare Pathogenesis

Reading across the results assembled here, it becomes progressively harder to defend a single-cause model of autoimmune flare pathogenesis. What emerges instead - and this is not a wholly new idea, but the accumulated evidence makes it considerably harder to dismiss - is something closer to a threshold model, in which viral exposure, toxicant inhalation, chronic stress, and dietary-microbial disruption each nudge cumulative inflammatory load upward until a clinical tipping point is reached (Figure 1; Figure 4). None of these exposures, taken alone, appears reliably sufficient to trigger disease in most individuals; the DiViD, TEDDY, and DAISY cohort data on enteroviral RNA detection illustrate this reasonably well, since a meaningful fraction of children carrying enteroviral RNA never progress to clinical T1DM (Kotsiri et al., 2025). What likely distinguishes progressors from non-progressors is probably the coincidence of viral exposure with an already-primed neuroendocrine or metabolic state - though we should be honest that this remains, for now, a plausible inference rather than a demonstrated causal pathway.

5.2 Molecular Mimicry as a Recurring but Not Universal Mechanism

Molecular mimicry (Table 1; Figure 3) offers perhaps the

most mechanistically satisfying explanation available for viral-triggered autoimmunity, if only because the sequence homologies involved - CVB4's PEVKEK motif and GAD65, EBNA-1 and MBP/GlialCAM/ANO2 - are so structurally specific that a coincidental explanation seems unlikely (Frohmán & Tsirka, 2026; Kotsiri et al., 2025). Yet mimicry alone cannot account for every viral association identified in this review. SARS-CoV-2's direct ACE2-mediated cytolysis of islet cells, for instance, operates through cytopathic injury and cytokine storm rather than sequence homology per se (Kotsiri et al., 2025), and the apparently protective effect of early VZV exposure runs in the opposite direction entirely, suggesting that viral-immune interactions are considerably more context-dependent than a single unifying mechanism would suggest (Kotsiri et al., 2025). This heterogeneity, we would argue, is itself an important finding: it cautions against overgeneralizing from any one pathogen-disease pairing to the field as a whole.

5.3 The Epithelial Barrier and Neuroendocrine Axis as Shared Vulnerability Points

Across the toxicant, stress, and dietary literature synthesized in Table 2 and Table 3, a genuinely recurring theme is barrier disruption - whether airway epithelium under PM2.5 assault, intestinal tight junctions under a Western diet, or, in a looser sense, the HPA axis's regulatory 'barrier' against unchecked cytokine production (Mpakosi et al., 2024; Nunez et al., 2025; Rodziewicz & Bryl, 2026). It is tempting to view these as three unrelated phenomena occurring in three different organ systems, but the downstream signaling convergence on NF- κ B activation, Th17/Treg imbalance, and autoantibody production (Figure 1) argues instead for a shared final common pathway, even where the initiating exposure differs substantially. If that interpretation holds, it would imply that therapeutic strategies aimed at reinforcing barrier integrity - broadly construed, whether epithelial, mucosal, or neuroendocrine - might have utility across multiple, seemingly unrelated autoimmune conditions rather than being disease-specific.

5.4 Clinical and Translational Implications

Several of the findings synthesized in Table 3 and Table 4 point toward reasonably near-term clinical application. SCFA-based and probiotic interventions (*Clostridium butyricum*, *Prevotella histicola*) have shown disease-modifying effects in preclinical models that, while not yet definitively replicated in large human trials, are promising

enough to justify continued investigation (Mittal et al., 2026; Rodziewicz & Bryl, 2026). Vitamin D supplementation, given its correlation with disease activity scores across SLE and RA, likewise represents a low-cost, comparatively low-risk intervention worth prioritizing in future randomized trials (Predescu et al., 2025). The computational diagnostic tools reviewed in Table 4 - particularly the genetic-algorithm-optimized neural network for IFN- response prediction and the RIPK2-based RA nomogram - suggest that precision, biomarker-guided treatment selection is becoming technically feasible, even if external validation across broader, more demographically diverse populations remains an unmet need (Ponce de León-Sánchez et al., 2026; Wu et al., 2026).

5.5 Limitations

This review carries the limitations inherent to any narrative synthesis built substantially from other narrative reviews rather than from a systematic meta-analysis of primary data: publication bias, uneven reporting quality across included sources, and the absence of a formal risk-of-bias assessment (as noted in Section 3.5) all constrain the strength of the conclusions that can reasonably be drawn. Much of the gut-microbiome and SCFA evidence, moreover, derives from preclinical animal models, and translation to human disease-modifying efficacy is not yet firmly established. We have tried, throughout to flag areas of genuine uncertainty rather than present a falsely unified narrative, but readers should weigh the strength of evidence unevenly across the different exposure categories discussed here.

6. Conclusion

Autoimmune disease flares, taken as a whole, look less like the product of a single decisive trigger and more like the cumulative outcome of several converging pressures acting on an already genetically primed system. Viral molecular mimicry, airborne toxicant-driven barrier and inflammasome activation, chronic HPA-axis dysregulation, and gut-microbial dysbiosis each contribute independently documented mechanistic routes toward a shared downstream endpoint - Th17/Treg imbalance, epithelial or mucosal barrier breach, and autoantibody generation - that ultimately precipitates clinical disease activity across T1DM, MS, SLE, RA, and related conditions. No single exposure reviewed here appears both necessary and sufficient; rather, the evidence favors a threshold or 'multi-

hit' framework in which concurrent or sequential exposures progressively narrow the margin separating quiescent disease from active flare. Encouragingly, several of these pathways - vitamin D signaling, SCFA and probiotic-based microbiome modulation, and emerging AI-driven diagnostic and prognostic tools - are already clinically actionable or close to it, offering plausible, comparatively low-risk avenues for flare prevention that extend meaningfully beyond genetic risk stratification alone. Future research should prioritize large-scale, longitudinal, multi-omic human cohorts capable of testing these interaction effects directly, validating predictive computational models across diverse populations, and ultimately supporting a shift toward precision, environmentally informed autoimmune disease prevention and management.

Author Contributions

R.B.S.M.N.M. contributed to the conception and design of the review, literature search, analysis and synthesis of the relevant evidence, and drafting of the manuscript. L.W.Z. contributed to the literature search, interpretation of evidence concerning molecular mimicry, environmental exposures, barrier disruption, and autoimmune mechanisms, and critical revision of the manuscript. A.A. contributed to the analysis and interpretation of evidence related to neuroendocrine signaling, microbial interactions, environmental triggers, and emerging diagnostic approaches, and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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