Genetic and Immunological Determinants of Atopic Dermatitis: A Systematic Review

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Abstract: *Purpose*: The present work aimed to study the role of genetic and immunological factors in the development of atopic dermatitis (AD).

Material and Methods: A thorough systematic search of relevant information on AD presented in the PubMed, ResearchGate, Scopus, Web of Science, and Google Scholar databases for 2010-2023 was carried out. The total number of studies included was 50, with a primary focus on genetic association studies, epigenetic studies, and microbiome studies.

Results: The etiopathogenetic mechanisms of the pathogenesis remain under active investigation. It has been determined that the primary factors in the occurrence of AD pathology are the interaction between genetic abnormalities and environmental factors, including climatic factors (temperature, humidity), geographic location (urban vs. rural), air pollution (e.g., particulate matter, ozone), dietary influences (e.g., fat intake, allergens), and exposure to microbes (e.g., pets, infections). An imbalance of the normal intestinal microbiota is a significant predisposing factor. The pathogenetic basis of the disease is an inflammatory process with activation of the T-cell immune response and dysfunction of the genes encoding filaggrin, transglutaminase, and keratin. These disorders lead to increased permeability of the skin barrier and unhindered penetration of allergens. AD is a heterogeneous, multifaceted condition characterised by various endotypes, phenotypes, and clinical subtypes. It frequently commences in early childhood, during the maturation of the immune system and skin barrier. Typical symptoms encompass xerosis, erythema, and pruritus, with affected children exhibiting increased sensitivity to benign irritants, indicative of early immunological dysregulation.

Conclusion: AD substantially lowers quality of life and presents mental health risks, especially in young patients. The early onset underscores the necessity for swift action to facilitate immunological development and protect child health.

Keywords: Skin inflammation, epidermal barrier, hypersensitivity, keratinocytes, skin microbiome.

INTRODUCTION

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin disease marked by severe itching, erythema, and recurrent eczematous lesions. Current epidemiological data indicate that AD affects roughly 20% of the paediatric population and 2-7% of the adult population globally. A recent analysis of the Global Burden of Disease statistics reveals a notable rise in the prevalence of AD from 2000 to 2023, with increasing incidence rates observed in both economically developed nations and developing ones [1]. Patients with atopic dermatitis typically present within the first year of life, with 90% receiving a diagnosis before the age of five. The present classification of atopic dermatitis encompasses various criteria, including age, ethnicity, serum immunoglobulin E (IgE) levels, and filaggrin gene alterations.

The etiopathogenesis of atopic dermatitis is multifaceted, encompassing a complex interplay of genetic variables, external environmental impacts, skin barrier dysfunction, and immune system dysregulation. Research indicates that approximately 70 genes contribute to the disease's aetiology, with critical components including filaggrin, keratins, and transglutaminases, which are essential for the proper functioning of the epidermal barrier. Malfunction of these proteins results in a compromised skin barrier, permitting allergens and pathogens to penetrate the skin, hence facilitating disease progression. Staphylococcus aureus colonisation significantly worsens disease progression.

The studies have highlighted the age stratification of the prevalence of AD, emphasizing its significant presence in early childhood. A systematic review has shown that the 1-year prevalence of clinically diagnosed AD in infants shows significant geographical variability, ranging from 0.96% in Asia to 22.6% in Europe. The peak incidence is observed in the age group of 1 to 4 years, with approximately 80% of cases manifesting by the age of six years [2]. Epidemiological data from the United States indicate that 9.6 million children under the age of 18 years have a diagnosis of AD, with a peak prevalence in early childhood [3]. Although AD is traditionally associated with the pediatric population, its prevalence in the adult

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population also remains significant, with studies reporting rates ranging from 7.3% to 10.2% in the US adult population.

Nedoszytko *et al.* [4], Mu and Zhang [5], Ryguła *et al.* [6] noted that the development of the pathology is based on an inflammatory reaction driven by T cells and dysfunction of the skin barrier. Approximately 70 genes are involved in the pathogenesis of the disease. Filaggrin, transglutaminases, keratin, and intercellular proteins are key components that ensure the normal functioning of the epidermis. Dysfunction of these protein structures leads to pathological permeability of the skin barrier, which allows allergens and microorganisms to infiltrate the deep layers of the skin. Colonization of the skin with Staphylococcus aureus is an additional factor contributing to the progression of the disease. Metabolites produced in the gastrointestinal tract have a direct effect on skin receptors and interact with the commensal microflora.

The course of the acute form of the disease is characterized by the development of diffuse erythematous foci and papules. In the chronic course, the formation of plaques with excoriations and lichenification is observed. These symptoms lead to a deterioration in the general condition and psycho-emotional sphere of patients. Patients have a decrease in everyday productivity and overall quality of life. Depressive disorders, anxiety states, and sleep disorders are comorbid conditions, especially in moderate and severe disease. Nakashima *et al*. [7], Eichenfield *et al*. [8], and Napolitano *et al*. [9] noted that the basic therapy of patients with mild and moderate severity includes topical corticosteroids and local calcineurin inhibitors. Phototherapy is used to increase the effectiveness of treatment. In severe forms, the use of immunomodulatory agents (cyclosporine, methotrexate, azathioprine) and systemic corticosteroids is recommended. It should be emphasized that the use of the latter is associated with several serious side effects. Patients should be advised to eliminate provoking factors, such as woolen clothing, psycho-emotional stress, adverse climatic and environmental factors, and bad habits. Several researchers have described and proposed scales for assessing the severity of AD and the risk of developing comorbidities. In particular, Laska *et al.* [10], Chopra *et al.* [11], and Kuo *et al.* [12] in their works presented the SCORAD scale, the eczema area and severity index (EASI), the global assessment scheme (IGA), and Hanifin-Rike criteria (HRC).

A comprehensive review of the scientific literature on the pathogenesis of atopic dermatitis was conducted. Despite the significant number of studies devoted to the clinical features, microbiome aspects, and therapeutic approaches to atopic dermatitis, an integrative analysis of the immunological and genetic components of the disease remains insufficiently covered in the scientific literature. This study aimed to systematize and analyze the available data on the influence of genetic and immunological factors on the pathogenesis of atopic dermatitis. The study is aimed at identifying key genetic determinants involved in the development of atopic dermatitis. Additionally, to elucidate the role of epigenetic regulation in gene expression and its pathogenic implications, as well as to characterize immunological dysfunction and the mechanisms underlying pruritus in atopic dermatitis.

MATERIALS AND METHODS

Literature Search Strategy

The first stage of the study in October 2023 was a thorough, structured, systematic search for relevant information on atopic dermatitis in PubMed, ResearchGate, Scopus, Web of Science, and Google Scholar databases. In the course of the work, all available articles with the necessary information (clinical trials, randomized controlled trials, reviews, systematic reviews, and meta-analyses) presented from 2010 to 2023 in peer-reviewed journals in Polish, French, German, Spanish, and English were found and reviewed. The necessary information was searched using a combined set of keywords: “allergic reaction”, “immune response”, “type of immune response”, “hypersensitivity”, “inflammatory response”, “skin inflammation”, “epidermal barrier”, “stratum corneum”, “keratinocytes”, “skin microbiome”, “gut microbiome”, “non-IgE-mediated allergy”, “IgE-mediated allergy”, “epidemiology of atopic dermatitis”, “Aetiology of atopic dermatitis”, “Symptoms of atopic dermatitis”, “Mechanism of atopic dermatitis development”, “Diagnosis of atopic dermatitis”, “Treatment of atopic dermatitis”, “Prevention of atopic dermatitis”, “Complications of atopic dermatitis”, “Filaggrin”, “Immunogenetics of atopic dermatitis”, “Epigenetic regulation of gene expression”.

Data Selection and Screening Process

A thorough systematic review was conducted in accordance with the PRISMA guidelines (Appendix 1). The literature review initially identified 1,320

publications, which were assessed for relevance based on their title and abstract, publication date, and level of evidence. Bibliographic lists of relevant articles were also checked to identify additional sources. After removing 320 duplicates, 1,000 records were screened for eligibility. Publications that did not meet the chronological boundaries of the study (2010-2023) were excluded, leaving 850 records for further evaluation. Of these, 150 full-text articles were assessed for inclusion based on relevance, and 100 full-text articles were excluded due to irrelevance, methodological flaws, or failure to meet the inclusion criteria. Studies using animal models, or those containing outdated, unverified, or irrelevant data, were excluded from the final review. The remaining 50 articles were selected, which provided relevant and high-quality information on the epidemiology, etiology, risk factors, pathogenesis, clinical manifestations, diagnosis, therapeutic approaches, and prevention of AD. Both IgE-mediated and non-IgE-mediated allergic reactions were considered. Publications detailing the microbiome, the composition of the skin and intestinal microbiome in healthy individuals and AD patients, the genetic and epigenetic regulation of genes associated with AD, and the influence of allergic mediators on AD development were also included. The final set of 50 relevant articles fully met the established criteria (Figure **1**).

The PRISMA flowchart demonstrates the systematic methodology used in the study selection process, ensuring that only the most relevant and methodologically sound studies were included in the final analysis. The disciplined application of inclusion and exclusion criteria helped to minimize bias and increase the reliability of the consolidated results. Methodological rigor ensured that the conclusions drawn from the selected studies adequately reflected the current scientific consensus on the genetic and immunological determinants of the pathogenesis of atopic dermatitis.

Data Extraction and Analysis

After the selection procedure, the data gathered from the included papers were rigorously analysed and classified based on their relevance, research design, publication date, and degree of evidence. Key findings were analysed and verified to guarantee precision and dependability. To augment the rigour of the study, the reference lists of the chosen papers were reviewed for supplementary sources, and cross-referencing was conducted to uncover any pertinent studies that may have been overlooked in the first search.

RESULTS

Genetic Mutations and Barrier–Immune Crosstalk

Decreased ceramide concentrations have been reported in patients with bronchial asthma, particularly in individuals with filaggrin defects [13-15]. The cytokine cascade inhibits ceramide synthesis by increasing interferon-alpha (IFN-α) concentrations. Nedoszytko *et al*. [4] and Mu and Zhang [5] demonstrated that increased pH activates serine proteinases and inhibits the function of acid sphingomyelinase and β -glucocerebrosidase (key components of ceramide biosynthesis). Increased serine proteinase activity reduces lamina propria secretion by involving type II plasminogen activator and causes impaired transport and release of substances from the lamina propria. As a result of these processes, the stratum corneum is thinned. There is a reduction in the hydrocarbon chain length of ceramides, free fatty

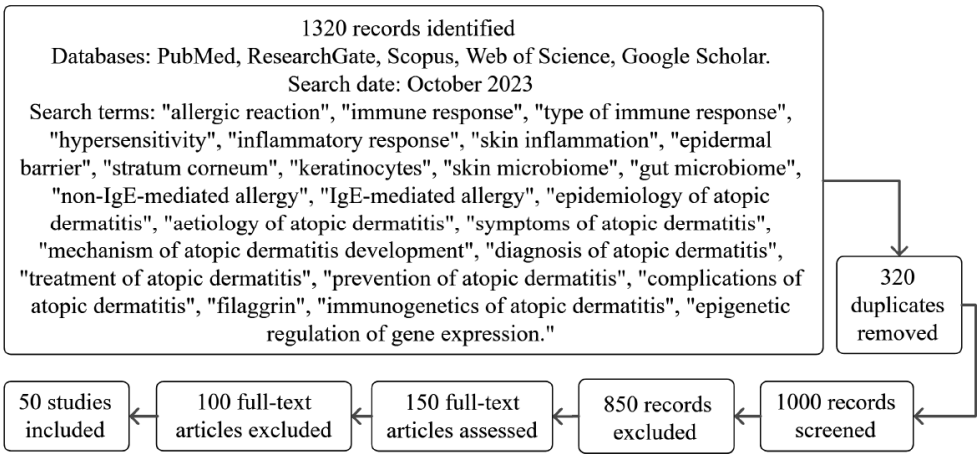

Figure 1: PRISMA flow diagram.

Table 1: Risk of Bias Assessment for Selected Studies

Study	Type of Study	Risk of bias
[13]	Review (biomarkers and endotype)	Low risk: Comprehensive review, well-structured synthesis of existing data, no major risks identified.
[14]	Review (translational advances in AD)	Low risk: Systematic review with a clear focus on the clinical application of findings, no significant biases.
[16]	Original research (clinical study)	Low risk: Randomized clinical trials and objective biomarker analysis
[18]	Original research (immunological study)	Low risk: Study using high-quality immunological markers. No apparent bias in sample selection or reporting.
[19]	Original research (clinical study)	High risk: Small sample size and retrospective design, potential selection bias.
[20]	Original research (clinical study)	High risk: Limited sample and observational design, lacks a control group.
[21]	Randomized clinical trial	Low risk: Randomized controlled trial design with clear methodology and ADequate controls.
[22]	Original research (lipids and microbiome study)	Low risk: Well-designed experiment with rigorous lipidomic analysis, providing robust data.
[23]	Review (online health information)	High risk: Online health information, not primary research; potential conflict of interest.
[24]	Cross-sectional study	Low risk: Cross-sectional study with a large sample and proper statistical handling.
[25]	Original research (clinical study)	High risk: Non-AD study, small sample, potential bias in participant selection.
[26]	Original research (genetic study)	Low risk: High-quality genetic analysis with proper controls, no major biases detected.
[27]	Original research (microbiome study)	Low risk: Well-conducted microbiome study with high-quality sequencing and appropriate analysis.
[28]	Original research (microbiome and genomics study)	Low risk: Genomic study with solid methodology and robust analysis.
[29]	Original research (microbiome study)	Low risk: Well-designed study focusing on microbiome biofilms with proper controls.
[30]	Cross-sectional study	Moderate risk: Cross-sectional design, not directly focused on AD but provides useful data.
[31]	Original research (cytokine study)	High risk: Not directly related to AD, and the study design is limited.
[32]	Review (omics approaches)	Low risk: Review with comprehensive omics approaches, no significant bias noted.
[33]	Original research (genetic study)	Low risk: Original research with well-controlled genetic data.
[34]	Review (pharmacology and mechanisms)	Low risk: Review of itch mechanisms relevant to AD, no bias found.
[35]	Review (therapeutics and mechanisms)	Low risk: Review with high-quality synthesis of Th2-related therapies for AD.
[36]	Review (cytokine study)	Low risk: Comprehensive review, no significant bias detected.
[37]	Original research (immunology study)	Low risk: Well-conducted original research with strong immunological data.
[38]	Review (immunology study)	Low risk: High-quality review of Type 2 inflammation and skin barrier dysfunction in AD.
[39]	Review (barrier dysfunction and microbiome)	Low risk: Comprehensive update with no major bias found.
[40]	Original research (obesity and dermatitis study)	Low risk: Original research with solid experimental controls.
[41]	Epidemiological study (global burden)	Low risk: Epidemiological study, data from large global datasets.
[42]	Microbiome study	Low risk: High-quality microbiome study with global data.
[43]	Microbiome and genomics study	Low risk: Microbiome and genomics study, high-quality data.
[44]	Microbiome and genetics study	Low risk: Well-designed study linking breast milk to gut microbiota and AD susceptibility.

(Table 1). Continued.

Study	Type of Study	Risk of bias
[45]	Genetic study	Low risk: Genetic study with strong methodology and appropriate controls.
[46]	Cohort study (dietary influence)	Moderate risk: Cohort study, potential biases in dietary data and self-reports.
[47]	Observational study (microbiome study)	Low risk: Observational study with solid microbial data and proper controls.
[48]	Bioinformatics study	Moderate risk: Bioinformatics study, may have biases due to secondary data processing.
[49]	Clinical study (immunology)	Low risk: Clinical study with robust neuroimmune findings.
[50]	Metagenomic study	Low risk: Metagenomic study with solid methodology and appropriate controls.
[51]	Review (microbiome study)	Low risk: Review with solid evidence and no major bias.
[52]	Microbiome study	Low risk: Microbiome study, using robust metagenomic and culture methods.
[53]	Clinical and microbiome study	Moderate risk: Clinical and microbiome study, potential bias in detection methods.
[54]	Cohort study (psoriasis)	Moderate risk: Retrospective cohort design, potential bias in selection and treatment allocation.
[55]	Mendelian randomization study	Low risk: Mendelian randomization study with robust statistical methods and clear analysis.
[56]	Randomized controlled trial (feeding regimen)	Low risk: Well-designed randomized trial with appropriate controls and statistical analysis.
[57]	Review (gut-skin axis)	Low risk: Well-conducted review with solid evidence supporting the gut-skin axis in AD.
[58]	Review (nutritional supplements for skin)	Moderate risk: Review with some potential bias in the selection of studies.
[59]	Review (microbiota and allergy)	Low risk: Well-conducted review with current insights on microbiota and allergies.
[60]	Systematic review and meta-analysis	Low risk: Systematic review and meta-analysis with clear methodology and appropriate inclusion/exclusion criteria.
[61]	Prospective cohort study (exposure to pollutants)	Low risk: Well-designed prospective cohort study with proper exposure assessment.
[62]	Clinical guide	Low risk: Well-established and validated tool for AD severity assessment.
[63]	Original research (microbiome study)	Low risk: Controlled microbiota study with a large sample size and appropriate methods.
[64]	Review (pathophysiology of AD)	Low risk: Comprehensive review with solid evidence on the pathophysiology of AD.

acids, and esterified fatty acids, which leads to structural abnormalities of the lipid profile and increased permeability of the epidermal barrier. Interleukin-22 is associated with excessive proliferation of epidermal cells and inhibition of terminal differentiation of keratinocytes. It induces the expression of S100A120 and S100A136, which leads to hyperplasia. Excessive secretion of IL-22 also correlates with the expression of keratin 6 and keratin 16, markers of proliferation and maturation of the epidermis [16-18].

Table **1** delineates the risk of bias evaluation for the papers incorporated in the review. The studies were assessed according to their design, methodology, and the existence of any potential biases that might affect the results. The evaluation classifies the risk of bias as low, moderate, or high according to recognized criteria for systematic reviews and clinical research studies.

The phenotype of atopic dermatitis is determined visually during clinical examination of the skin. The main skin manifestations of this pathology include eczematous lesions, dermatitis, facial hyperemia, and Hertoghe's symptom [19, 20]. The endotype of the disease is characterized by the state of the skin barrier, features of the immune response, the presence or absence of mutations of the filaggrin gene, and ceramide variants. The characteristic features of the endotype are a type 1 immune response, increased serum IgE concentration, impaired cellular immunity, food intolerance, as well as the dependence of clinical manifestations on environmental factors and the psycho-emotional state of the patient. Regardless of endotypes and phenotypes, there is a classification into subtypes of atopic dermatitis: external and internal, European-American and Asian, pediatric and adult subtypes.

Recent studies have shown that people with AD, particularly those with filaggrin (FLG) mutations, have lower levels of ceramides. In a comprehensive cohort investigation, individuals with AD and FLG mutations demonstrated a decrease of 30-40% in ceramide levels in the stratum corneum compared to healthy controls. Ceramide 1 (EOS) and ceramide 3 (NP), essential for skin barrier integrity, were seen to be reduced by roughly 40% and 30%, respectively, in patients with FLG mutations associated with AD [21]. In contrast, some studies indicate that levels of specific ceramide species, such as ceramide 7 (AS) and ceramide NS, may unexpectedly rise in particular subgroups of atopic dermatitis, underscoring the complexity and variability of lipid changes in the condition [22]. The ceramide species are essential for preserving the epidermal permeability barrier, and their substantial decrease correlates with elevated transepidermal water loss (TEWL) and greater vulnerability to environmental allergens and irritants.

AD is characterised by significant differences in clinical manifestations in newborns compared with older children. Infants present with pruritus, dryness, and scaling of the skin with erythema and edema, often accompanied by papules that may excoriate. These symptoms are predominantly localized to the face, scalp, and extensor surfaces of the extremities. As children age, the topography of the lesions changes with a shift to flexural areas, including the elbows and knees, neck, wrists, and ankles. In older children, lichenification of the affected skin may occur as a result of chronic scratching [23]. In addition, older children are prone to more frequent and severe exacerbations, which potentially negatively affect quality of life and psychological well-being. Approximately 67% of children with atopic dermatitis suffer from sleep disturbances, mainly due to intense itching [24]. These impairments can lead to increased daytime fatigue, attention deficits, and decreased academic performance. Chronic sleep deprivation in children with AD is associated with growth failure, as adequate sleep is essential for optimal growth and development.

The classification of atopic dermatitis into intrinsic and extrinsic types is based on serum IgE levels, while the European-American and Asian subtypes are classified by ethnicity. The pediatric and adult subtypes correspond to specific age categories. The extrinsic, European-American, and pediatric subtypes are dominated by a type 2 inflammatory response, whereas the intrinsic, Asian, and adult subtypes are dominated by types 1 and 3 inflammatory responses [25]. The extrinsic subtype is characterized by elevated IgE levels and is significantly more common than the intrinsic subtype (80% to 20%). In the extrinsic subtype, the skin barrier is disrupted by a mutation in the filaggrin gene. This promotes the penetration of protein antigens through the damaged stratum corneum, activation of the Th2 cell response, and production of interleukins IL-4 and IL-5, which leads to increased levels of IgE and eosinophils in the blood. The intrinsic subtype is characterized by increased expression of interferon-γ (IFN-γ) and interleukins IL-22/IL-17, as well as reduced levels of suprabasin in the stratum corneum of the epidermis [13, 14].

In heterozygous carriers of the gene, the risk of developing the disease increases by 7-8 times; however, it should be noted that in 40% of carriers of filaggrin gene mutations, atopic dermatitis does not manifest. This gene is expressed in the granular layer of the epidermis and is one of the key proteins of the stratum corneum. Its proteolytic cleavage releases urocanic and pyrrolidinecarboxylic acids.

The main functional properties of filaggrin include the synthesis of natural moisturizing factor, which ensures hydration of the stratum corneum of the epidermis and maintains its pH at 5.5; participation in keratinization processes and maintaining the antimicrobial peptide function of the skin. A decrease in the level of natural moisturizing factor leads to an increase in transepidermal moisture loss, dehydration, and the formation of microcracks in the epidermis [26]. As a result, conditions are created for the unhindered penetration of allergens and microorganisms; pH increase activates proteases and enhances epidermal desquamation. Activated proteases induce pro-inflammatory cytokines, which initiate an inflammatory response. Genes of the second and third groups cause dysfunction of innate and adaptive immunity, contribute to hyperactivation of the TLR system, excessive expression of Th2-profile cytokines, and impaired function of regulatory T lymphocytes. The fourth group combines genes expressed by keratinocytes under the influence of exogenous factors, in particular ultraviolet radiation or mechanical injury, and includes interleukins IL-25, TSLP, and IL-33. The fifth group is represented by genes encoding the synthesis of vitamin D [27-29].

Depending on the ratio of Th1, Th2, Th17/Th22, and Th22, two types of disease are distinguished. The Th2-dependent type is characterized by an increase in the level of eosinophils and IgE and is mainly found in children, while the Th1/Th17/Th22-dependent type is

more common in adults and is characterized by local skin inflammation and production of IL-17 and IL-22. The phenotype is not determined only by the presence of a mutation in the filaggrin gene, but also depends on the individual sensitivity and immune profile [20].

Immune Pathways and Cytokine Network

AD is frequently linked to the later development of additional allergy conditions, generally termed the "atopic march." Approximately 60% of children with AD develop one or more concomitant atopic conditions, such as asthma, allergic rhinitis, or food allergies [30]. Children with early-onset, severe, and chronic atopic dermatitis are at markedly increased risk of developing these disorders. Timely diagnosis and care may reduce the likelihood of future allergy illnesses, highlighting the significance of immunological monitoring in these individuals.

The immune response in AD is dominated by a Th2-mediated cytokine network, with IL-4, IL-13, and IL-31 serving crucial functions in the acute and subacute phases of the disease. Th2 cytokines facilitate the inflammation associated with AD, with IL-4 enhancing the Th2 response through the JAK-STAT signalling pathway. This cascade results in the synthesis of pro-inflammatory cytokines and chemokines, facilitating the recruitment of eosinophils, mast cells, and Th2 cells to the impacted tissues. The topical administration of JAK inhibitors has demonstrated efficacy in diminishing Th2-mediated dermal responses, reinstating skin barrier integrity, and mitigating itch, hence endorsing the therapeutic promise of targeting the JAK-STAT pathway in AD [7]. IL-13 plays a pivotal role in atopic dermatitis by inducing epithelial cell hyperplasia, enhancing the inflammatory response, and suppressing keratinocyte differentiation. This results in the distinctive thickening of the epidermis noted by patients. Additionally, IL-17, primarily generated by Th17 cells, contributes to localised skin inflammation by promoting the synthesis of pro-inflammatory cytokines and chemokines, which attract neutrophils to the affected area.

One of the key epithelial cytokines involved in AD pathogenesis is thymic stromal lymphopoietin (TSLP) [31]. TSLP is released by epidermal keratinocytes in response to environmental stimuli and serves as a vital alarm that stimulates the Th2 response [65]. Under typical circumstances, TSLP regulates the immunological response in the skin. However, in AD, its excessive synthesis results in an aberrant immune response, activating both innate and adaptive immune cells. Activation of TSLP facilitates dendritic cell maturation, thereby augmenting Th2 polarisation and resulting in a sustained inflammatory environment.

Innate lymphoid cells (ILCs), especially ILC2s, are crucial in the immunological dysregulation associated with AD. ILC2s exhibit sensitivity to cytokines, including IL-25, IL-33, and TSLP, which activate these cells, prompting the secretion of IL-4, IL-5, IL-9, and IL-13. These cytokines are essential for the onset and progression of allergic inflammation. In patients with atopic dermatitis, ILC2s are elevated, corresponding with disease severity and sustained inflammation [66, 67]. The activation of ILC2s is specifically associated with the worsening of atopic dermatitis in patients, as they play a crucial role in the inflammatory cascade by secreting cytokines that attract additional immune cells to the skin.

The Toll-like receptor 2 (TLR2) system, a crucial component of the innate immune system, also plays a role in the pathogenesis of AD [68]. Dysfunction of TLR2 in the skin of patients with atopic dermatitis, especially those with bronchial asthma, is associated with heightened colonisation by Staphylococcus aureus. This colonisation intensifies the disease by generating superantigens that activate T cells, resulting in increased Th2 skewing and IgE synthesis. Patients exhibit diminished TLR2 expression in macrophages and mononuclear cells, accompanied by a reduction in Th1/Th17-associated cytokines, including IFN-γ and IL-12, alongside an elevation in IL-5, a Th2-dependent cytokine.

Pruritus is a highly debilitating symptom of atopic dermatitis, profoundly affecting quality of life. The pruritus in atopic dermatitis is facilitated by a multifaceted interplay among epidermal cells, the immune system, and non-histaminergic sensory neurones. Th2 cytokines, including IL-4, IL-13, and IL-31, participate in pruritic pathways [69, 70]. IL-31 specifically interacts with IL-31 receptors on sensory neurones, amplifying itch perception and perpetuating the itch-scratch cycle. The central nervous system detects the itch signal and initiates a motor response characterised by scratching. Scratching causes epidermal injury, triggering the production of further pro-inflammatory cytokines and the activation of extra Th2 cells, thus sustaining the inflammatory feedback loop. Additionally, augmented cutaneous nerve fibre thickness in individuals with chronic atopic dermatitis lesions is a clinical characteristic linked to enduring

pruritus, even following the elimination of the initial trigger [32-34].

Despite the extensive research on immunological systems and cytokine networks in AD, numerous findings remain discordant among studies. Th2 dominance is typically linked to early-onset AD, although research indicates that Th1/Th17 pathways may be more influential in later stages or adult-onset AD [35, 36]. Research on the roles of IL-13 and IL-4 in different types of illnesses shows mixed results, with some studies suggesting that cytokine levels change over time [37]. Additionally, factors such as genetics, environmental germs, and external influences complicate the clear correlation between cytokine levels and disease severity. The variability in research methodology also contributes to these contradictory results. Cross-sectional research may identify temporal variations in immune responses that longitudinal studies would overlook. Furthermore, variations in patient cohorts, including age, ethnicity, and illness subtype, can substantially affect outcomes. Rectifying these methodological constraints is essential for enhancing our comprehension of immunological dysregulation in AD.

Epigenetic Regulation of Immune Responses

Over 70 genes have been linked to the pathophysiology of AD, involving various immunological and barrier-related mechanisms [38-40]. These genes can be categorised as epithelial barrier genes, innate immunity genes, acquired immunity genes, keratinocyte-expressed genes, and genes associated with epigenetic control, including DNA methylation and vitamin D synthesis (Table **2**).

The function of epigenetic regulation in the progression of AD is under investigation. Genetic mutations certainly play a role in disease progression, whereas epigenetic modifications, such as DNA methylation and histone alterations, regulate gene expression without changing the fundamental DNA sequence. These alterations are key to understanding the selective progression of AD, as they dictate the expression of genetic information in reaction to environmental influences.

A key method of epigenetic regulation in AD is DNA methylation, wherein the addition of a methyl group to DNA generally leads to the suppression of gene expression. DNA methylation plays a crucial role in various fundamental processes in AD, particularly in

Table 2: Genes Involved in the Pathogenesis of Atopic Dermatitis

Group of genes	Representatives	Key references	Effect size	Major gene variants	Study context
Epithelial barrier	Filaggrin, filaggrin 2, desmoglein, desmocollin, claudin, kallikreins, cathepsins, caspase 14, SPINK5, cystatin A.	Wang *et al*. [41], Kashaf *et al*. [42], Wang *et al*. [43]	FLG loss-of-function mutations are associated with a 5-8x increased risk of AD	FLG loss-of-function mutation (R501X, 2282del4)	European, East Asian, pediatric and adult AD
			40%-50% of moderate-severe AD cases have FLG mutations		
Innate immunity	TLR1, TLR2, TLR4, TLR6, TLR9, TLR10, CD14, NOD1.	Zhang *et al*. [44], Wang *et al*. [43]	TLR2: OR 1.4-2.1 for infections in AD	TLR2 variants linked to enhanced immune response	Pediatric, European; risk of infections
			CD14 polymorphism (C-159T): OR 1.3-1.7 for extrinsic AD	CD14 C-159T	Childhood onset/extrinsic AD
Acquired immunity	IL-4, IL-5, IL-13, IL2RA, IL-13RA IL-5RA, TSLPR, IL-4R, IL-18, IL-31; IL17A, TNFα, IL-22; STAT-6, FOXP3, LRRC32;	Zhong *et al*. [45], Lee *et al*. [46]	IL4 rs2243250: OR ~1.3-1.5 for AD	IL4 rs2243250, IL4R Q576R	Diverse; strong in Asian and European cohorts
			IL13 rs20541: OR 1.16 for AD susceptibility	IL13 rs20541, IL13RA1	GWAS and case-control studies
Alarmin/keratinocyte	IL-25, TSLP, IL-33.	Kozlovska *et al*. [71], Yang *et al*. [47]	TSLP increased: correlates with EASI/SCORAD severity	IL33 rs3939286	Lesional skin; severity related
Epigenetic/Vitamin D	KIF3A, CYP27A1, CYP2R1, VDR.	Yang *et al*. [48], Yosipovitch *et al*. [49]	VDR rs1544410: 10-20% reduced risk of AD	VDR rs1544410	Pediatric vitamin D supplementation trials

Source: compiled by the author based on Wang *et al.* [41], Kashaf *et al.* [42], Wang *et al.* [43].

the control of genes associated with keratinocyte development and innate immunological responses. In AD patients, modified DNA methylation patterns have been noted at various essential loci, including the FOXP3 promoter, which is implicated in regulatory T cell differentiation, and the RORC promoter, which governs Th17 cell differentiation. These alterations lead to immunological dysregulation, characterised by a lack of regulatory T cells and an overproduction of inflammatory cytokines, such as IL-17 [71].

DNA methylation also influences genes that govern skin barrier function. Filaggrin, an essential protein of the epidermal barrier, has been demonstrated to be subject to epigenetic regulation. Filaggrin mutations are well established in atopic dermatitis, and epigenetic processes, including methylation of the filaggrin promoter, can influence its expression and intensify barrier failure. The OAS cluster, which synthesises adenosine receptors, undergoes methylation in AD, hindering the innate immune response by disrupting interferon (IFN) signalling pathways [47, 48].

Recent shotgun metagenomic studies have transformed the understanding of the skin microbiome in AD, facilitating species- and strain-level resolution of microbial communities and their related functional pathways [50]. Employing whole genome sequencing (WGS), researchers have established that microbial dysbiosis may precede the clinical manifestation of AD, with notable alterations in the abundance of particular bacterial and fungal taxa, as well as metabolic pathways, detected years before illness onset [51]. In contrast to 16S rRNA gene sequencing, which predominantly identifies bacteria at the genus level and may overlook significant taxa or functional genes, shotgun metagenomics encompasses a wider range of microbial diversity, including fungi and viruses. It offers insights into strain-level variations and virulence factors, such as toxin genes in Staphylococcus aureus associated with disease severity [52]. Nonetheless, considerable methodological deficiencies endure: shotgun metagenomics is more resource-demanding, necessitates elevated DNA yields and advanced bioinformatics, and occasionally encounters challenges with host DNA contamination. Comparative analyses indicate that although 16S rRNA sequencing may overlook significant microbial diversity or pathogenic strains, WGS techniques can also exhibit detection limitations under specific sample conditions. Consequently, employing both methodologies concurrently is frequently essential for thorough community profiling and clinical correlations in AD [53].

A significant category of epigenetic regulators consists of microRNAs (miRNAs). MicroRNAs (miRNAs) are diminutive RNA molecules that modulate gene expression by binding to messenger RNA (mRNA), resulting in either its degradation or the inhibition of its translation. MicroRNAs are essential in modulating T cell differentiation, inflammation, and the maturation of keratinocytes in atopic dermatitis. Research has revealed elevated concentrations of miRNA-21, miRNA-146a, miRNA-155, and miRNA-223 in lesional skin specimens from patients with atopic dermatitis. These miRNAs modulate the expression of genes associated with immune response and inflammation. For example, miRNA 146a inhibits the IFN-γ induction pathway, thereby affecting the effectiveness of the antimicrobial immune response. MiRNA-155 is crucial for T cell proliferation, resulting in chronic inflammation, a characteristic of AD pathogenesis. Elevated levels of miRNA-155 are associated with disease severity and are believed to perpetuate persistent inflammation in AD lesions [72].

Notably, miRNA-155 targets IL-12 receptor β2 (IL12RB2), hence diminishing IL-12 signalling in AD. The disruption of IL-12 signalling contributes to the modulation of the immune response, favouring Th2 and Th17 pathways, which are pivotal in the pathogenesis of AD. In contrast, the downregulation of miRNAs, including miRNA-365, miRNA-375, and miRNA-193c, results in compromised immunological regulation, hence aggravating the disease [4, 54].

Vitamin D in its active form, called 1,25-dihydroxyvitamin D (calcitriol), works with the vitamin D receptor (VDR) to change how genes are expressed. In addition to its transcriptional effects, vitamin D influences epigenetic control by altering DNA methylation, histone alterations, and microRNA expression. Vitamin D specifically affects the DNA methylation of genes that help control the immune system, like IL-10 and IL-17, and plays a role in how these immune responses are regulated at the genetic level. As a result, vitamin D can affect genes involved in immune control, like IL-4, IL-5, and IL-13, in both how they are turned on and off and how they are modified, making vitamin D an important factor in keeping the immune system balanced in conditions like atopic dermatitis. The CYP27A1, CYP2R1, and VDR genes are primarily associated with vitamin D processing and also play a role in regulating immune responses, making them relevant to the study of epigenetics in AD development.

The epigenetic regulation of immunological responses in AD also encompasses the modulation of epithelial alarmins. TSLP, a cytokine secreted by keratinocytes in response to environmental stimuli, is essential for initiating the Th2 response in the skin. TSLP serves as a crucial mediator in the initial phases of inflammation by facilitating the development of naive T cells into Th2 cells. This epithelial immune signalling highlights the essential interaction between the skin barrier and the immune system in the aetiology of AD. IL-33 and IL-25, additional alarmins generated by keratinocytes, further promote type 2 immunity, intensifying the Th2-mediated inflammatory response in the dermis. Their release is increased during epidermal injury resulting from environmental irritants and persistent scratching [31, 65].

Furthermore, environmental factors like ultraviolet (UV) radiation, pollution, and microbial exposures significantly affect epigenetic pathways, especially in keratinocytes. UV light can modify histone modifications and DNA methylation patterns in epidermal cells, hence affecting the immunological response. These environmental stimuli influence epigenetic mechanisms to alter gene expression associated with barrier function and inflammation, hence sustaining the inflammatory cycle in atopic dermatitis.

Epigenetic regulation is pivotal in the aetiology of atopic dermatitis by influencing the expression of essential genes related to skin barrier integrity, immunological responses, and inflammation. The findings indicate that epigenetic medicines, including DNA methyltransferase inhibitors and miRNA-based treatments, may provide attractive prospects for future AD interventions. Nonetheless, additional research is required to elucidate the intricate interplay among genetics, epigenetics, and environmental influences on disease progression, as well as to formulate tailored medicines for the management of AD symptoms.

Investigations exploring epigenetic regulation in AD often encounter limitations due to limited sample sizes and insufficient longitudinal data, limiting the capacity to establish conclusive causal relationships. Research on DNA methylation and microRNA expression frequently concentrates on individual genes or limited gene panels, neglecting the intricacies of epigenetic relationships and their environmental stimuli. Consequently, although this research offers important clues about the molecular underpinnings of AD, the absence of standardised techniques for data collection and analysis hinders replication and comparison among investigations.

AD occurs due to the combination of genetic predispositions, immune system dysregulation, epigenetic alterations, and microbial imbalances, all shaped by environmental influences. Genetic abnormalities, especially in the filaggrin gene, compromise the skin barrier, facilitating the entry of allergens and microorganisms that incite an immunological response characterised by Th2 cytokines. This premature immune activation adds to the persistent inflammation typical of AD.

Besides hereditary considerations, epigenetic control is essential in modifying immune responses in AD. Alterations, including DNA methylation and modified microRNA expression, can compromise immune cell functionality, especially in regulatory T cells, resulting in an imbalance among Th1, Th2, and Th17 responses. These epigenetic alterations intensify inflammation and compromise the skin barrier, hence sustaining disease manifestations.

The microbiome, present in both the skin and gut, additionally affects immune responses. In patients with atopic dermatitis, an imbalance in the skin's microbes, leading to harmful bacteria like Staphylococcus aureus, causes increased inflammation and weakens the skin barrier. Microbial dysbiosis initiates immunological responses that exacerbate the inflammatory cycle in atopic dermatitis. Environmental variables, including air pollution, dietary habits, and early microbial exposures, combine with genetic and epigenetic elements to intensify disease. Pollutants such as polycyclic aromatic hydrocarbons cause oxidative stress and increase IgE production, which weakens the skin barrier and worsens inflammation. Conversely, early-life exposure to advantageous microorganisms through breastfeeding or environmental interaction can enhance immunological tolerance and diminish the likelihood of developing atopic dermatitis.

This conceptual model illustrates that a feedback loop, which includes genetic predisposition, epigenetic alterations, microbial dysbiosis, and environmental factors, propels the aetiology of AD. These elements interact to sustain skin barrier impairment and immune system activation, exacerbating the chronicity and severity of the condition. The model suggests that treatment should focus on different parts of this loop, like fixing the microbiota, changing epigenetic pathways, and repairing the skin barrier, to create better therapies for AD.

Future research should prioritise longitudinal studies to monitor the interactions of genetic, epigenetic, and microbiological changes over time in AD. Research should investigate personalised microbiome-based interventions, including probiotics and prebiotics, to restore immunological equilibrium. Epigenetic therapies, such as DNA methyltransferase inhibitors and microRNA-based strategies, present the potential to mitigate inflammation. Focusing on research about environmental changes, such as reducing exposure to pollutants and promoting a diverse diet early on, is crucial to prevent the onset of AD in people at high risk.

Gut Microbiome–Immune System Interactions

A healthy gut microbiota helps the immune system, improves nutrient absorption, and protects the body from infections by making short-chain fatty acids (SCFAs) and antimicrobial peptides, as well as adjusting mucosal immunity [73]. Dysbiosis, characterised by an excess of particularly pro-inflammatory microbial taxa, can exacerbate inflammation and increase susceptibility to allergic conditions. Research indicates that specific types of bacteria, including Mollicutes, Clostridia, Bifidobacteriales, and Christensenellaceae R7, are associated with a reduced risk of disease. Conversely, an overabundance of Clostridiaceae, Bacteroides, and Lachnospiraceae is linked to increased inflammation and a higher likelihood of allergies [55]. These findings suggest that specific microbial profiles can either promote immune homeostasis or contribute to the immunological dysregulation observed in AD.

Initial microbial exposures are crucial for immune system development and the building of immunological tolerance. Research indicates that infants who are exclusively breastfed for 3-4 months have a reduced likelihood of developing atopic dermatitis, particularly in the first four years of life [43]. The protective effect comes from human milk oligosaccharides, which help create a healthier gut environment and increase the number of regulatory T cells. These T cells promote immunological tolerance and reduce allergen sensitisation. Breastfeeding facilitates the colonisation of Bifidobacterium and Lactobacillus species, resulting in improved mucosal immunity and a diminished risk of allergy development.

A study by Boutsikou *et al*. [56] demonstrated that infants at heightened allergy risk who consumed a partially hydrolysed whey-based formula experienced a significantly lower incidence of atopic dermatitis during the first six months of life compared to those who received standard formula. Only 6.5% of infants with a familial tendency to AD who received hydrolysed formula developed the illness, compared to 22.7% of those who were breastfed. The results suggest that modifications to the diet can influence the microbiota, impacting immune development and potentially reducing the prevalence of allergic diseases. The reduced allergenicity of hydrolysed formulas and their ability to foster beneficial microbiota make them an ideal choice for high-risk newborns.

Skin Microbiome-Immune System Interactions

The skin microbiome is critical to preserving immunological balance. Commensal microorganisms on the skin affect keratinocyte function, enhance antimicrobial peptide synthesis, and strengthen innate immunity. Staphylococcus aureus, commonly found in individuals with atopic dermatitis, may cause skin irritation. Staphylococcus aureus produces exotoxins that act as superantigens, activating dendritic cells and directing the polarisation of naive T cells towards a Th2 phenotype, which is essential in the development of atopic dermatitis. The variation in skin immune responses, along with barrier dysfunction, leads to increased skin permeability and chronic inflammation, which are defining features of AD.

The skin microbiome is essential for preserving local immune homeostasis. Commensal bacteria, including Cutibacterium acnes, Corynebacterium, and Malassezia, engage with skin keratinocytes and immune cells to enhance barrier integrity and innate immune responses. Nonetheless, Staphylococcus aureus, sometimes disproportionately present in AD patients, disturbs this state of balance. S. aureus synthesises exotoxins that function as superantigens, resulting in Th2 polarisation, elevated IgE synthesis, and persistent inflammation in the dermis. This process aggravates skin barrier impairment and fosters the chronicity of atopic dermatitis. Additionally, the disruption of the skin microbiome, known as skin dysbiosis, is frequently associated with heightened skin permeability, facilitating allergen infiltration and amplifying the immune system's inflammatory response in AD [6; 74].

The methodological rigour of studies on microbiome dysbiosis in AD requires a comprehensive evaluation. For instance, 16S rRNA sequencing, a widely utilised technique, provides a limited view of microbial diversity by concentrating exclusively on a certain portion of the

bacterial gene, potentially neglecting substantial alterations within microbial communities. Shotgun metagenomics enhances the understanding of microbial function. Nonetheless, its application in AD research is limited by budgetary and technical challenges. Furthermore, sample size and patient demographics are significant sources of bias. Research focused solely on paediatric populations may overlook age-related immunological differences that could affect microbial compositions and immune responses.

These studies draw attention to the importance of gut microbiota in immune system development and its impact on AD pathogenesis. Future research should clarify the causal relationships between specific microbial taxa and immunological pathways in AD and assess the effectiveness of microbiota-targeted probiotics or prebiotics as therapeutic interventions to restore immune balance.

Clinical Phenotypes and Immune Profiles Across the Lifespan

AD is marked by clinical symptoms that evolve, illustrating the intricate interplay between immune system maturation and epidermal barrier integrity. In newborns and young children (0-2 years), the condition generally manifests as erythematous, exudative, and pruritic lesions, predominantly impacting the cheeks, forehead, and scalp, with occasional extension to the extensor regions of the limbs. A vesicular element is frequently noted, and subsequent bacterial infections may aggravate recurring excoriations. As children develop, the clinical presentation changes. In toddlers and children aged 2-12 years, the condition becomes more chronic, characterised by lichenification, xerosis, and hyperpigmentation. Lesions frequently impact the flexural areas, including the elbows, popliteal fossae, wrists, and ankles [8]. During adolescence, the condition may continue, characterised by more localised lesions that frequently resemble chronic hand eczema and impact the hands, feet, and face. At this point, relapses are often provoked by external stimuli, psychological stressors, and hormonal variations. These clinical shifts indicate modifications in immune activation and skin barrier function that are intricately associated with age and the maturity of the immune system, involving changes in Th2/Th1 equilibrium, cytokine profiles, and the activity of barrier proteins.

The environment significantly impacts the progression and development of AD, affecting both immune responses and the epidermal barrier. Maternal intake of fish during pregnancy, abundant in n-3 polyunsaturated fatty acids, is linked to a 30% decrease in the risk of childhood asthma, indicating a potential preventive immunomodulatory impact [57-59]. Likewise, interaction with domestic animals, particularly canines, has demonstrated a protective correlation with atopic dermatitis, but the precise processes are not fully understood. Research investigating the influence of environmental factors, including air pollution and tobacco smoke, on AD aetiology yields inconsistent findings. Some studies indicate a twofold rise in AD incidence due to prenatal exposure to these pollutants, while others propose that the extent of exposure or genetic predisposition may be more influential than previously acknowledged [60, 75]. Pollutants such as polycyclic aromatic hydrocarbons can produce oxidative stress, promote apoptosis, and increase IgE production, compromising the epidermal barrier and exacerbating inflammation [61, 76, 77].

Indoor environmental concerns, including insufficient ventilation, residential renovations, and dust mite allergens, further aggravate atopic dermatitis. Ozone exposure interacts with skin lipids, producing free radical chemicals that facilitate the inflammatory process. The administration of antibiotics during early childhood has been associated with an elevated prevalence of atopic dermatitis, presumably due to changes in the microbiota that enhance allergic sensitisation. These findings emphasise both the importance of environmental factors in immunological dysregulation and the contribution of microbiota-mediated immune control in the aetiology of atopic dermatitis.

The skin microbiome is essential for preserving immunological homeostasis. Cutibacterium acnes is prevalent in sebaceous regions, but Corynebacterium and Staphylococcus species are predominant in moist areas. Malassezia species, although a minor component, contribute to skin immunity. In breastfed newborns, the gut microbiota is augmented with bacteria that metabolise human milk oligosaccharides, facilitating immunological development. Formula-fed newborns exhibit less microbial diversity, perhaps hindering immune programming and heightening vulnerability to AD.

Nutritional factors throughout infancy and maternal dietary habits during gestation additionally affect the maturation of the immune system. The literature reveals contradictory evidence concerning the influence of breastfeeding on the risk of AD. Research indicates that exclusive breastfeeding for the initial 3-4

months offers protection against AD, especially in early childhood. However, some contend that prolonged nursing after six months correlates with a heightened risk of chronic AD [45]. These discrepancies may arise from methodological variations. Longitudinal studies demonstrate long-term protection, whereas cross-sectional studies may not account for the longitudinal impact of early dietary exposures. Moreover, research on breastfeeding is influenced by confounding variables, including familial history, environmental exposures, and microbiome composition, which are not consistently controlled for.

Recent data illustrate the importance of dietary composition in influencing immune function and preserving skin barrier integrity in children susceptible to atopic dermatitis [78]. Nutrients like long-chain polyunsaturated fatty acids (LC-PUFAs), especially omega-3 fatty acids derived from fish oil, demonstrate anti-inflammatory properties by regulating eicosanoid pathways and suppressing the production of pro-inflammatory cytokines such as IL-4 and IL-13 [79]. Omega-3 PUFA supplementation during pregnancy and early childhood has been linked to a diminished likelihood of allergic sensitisation and a reduction in the severity of AD symptoms. Conversely, increased intake of saturated fats and processed sugars may amplify Th2-dominant immune responses and worsen skin inflammation.

Micronutrients, including vitamin D, vitamin E, zinc, and selenium, are essential for maintaining skin integrity and regulating the immune system [80]. Vitamin D affects the expression of tight junction proteins and antimicrobial peptides, improving the epidermal barrier and regulating T-regulatory cell activity. Zinc is crucial for the proliferation of keratinocytes and the enzymatic function of metalloproteinases that facilitate wound healing and skin remodelling. A deficit in zinc or vitamin D has been associated with heightened transepidermal water loss and increased vulnerability to environmental allergens.

Moreover, dietary fibres and polyphenols affect the composition and metabolic function of the gut microbiota, thereby regulating systemic immune responses. A diet high in fibre increases the synthesis of SCFAs, including butyrate, which fortifies mucosal barrier integrity and inhibits the generation of inflammatory cytokines. Therefore, optimising dietary intake during crucial phases of immunological development may provide a non-invasive, supplementary method for reducing disease severity in paediatric AD.

Dietary treatments, including probiotic supplementation with Lactobacillus and Bifidobacterium, have demonstrated potential in mitigating AD symptoms by improving the gut-skin axis and regulating immunological responses. Omega-3 fatty acids, recognised for their anti-inflammatory properties, show potential in mitigating the severity of AD, while the evidence is mixed. The significance of vitamin D in the management of AD is currently being researched, with the first studies indicating potential benefits.

The correlation between dietary allergens and exacerbations of atopic dermatitis is intricate and well-documented. Common allergens, including cow's milk, eggs, almonds, and gluten, can provoke reactions in sensitised individuals. Nevertheless, routine elimination diets are not universally endorsed owing to the potential for nutritional deficits. Therefore, dietary adjustments must be individualised, informed by allergy assessments, and accompanied by nutritional oversight to guarantee effective immune modulation while preserving balanced nutrition.

From a public health standpoint, early nutritional treatments and environmental education are crucial for easing the burden of atopic dermatitis in children. Public health programs must prioritise promoting exclusive breastfeeding for the first six months of infancy, as advised by the World Health Organisation [81], due to its correlation with immunological tolerance and decreased incidence of atopic dermatitis. When breastfeeding is difficult, hydrolysed protein formulas should be contemplated for infants at elevated risk of developing allergies as a preventive strategy.

Additionally, community-based initiatives focused on maternal nutrition during pregnancy, such as guaranteeing sufficient consumption of omega-3 fatty acids, vitamin D, and foods high in antioxidants, are essential for fostering foetal immunological development and diminishing children's vulnerability to AD. School-based nutrition policies can provide a preventative function by controlling allergen exposure and promoting anti-inflammatory eating habits during early infancy. Public health campaigns ought to incorporate dermatological information, hygienic behaviours that maintain the skin barrier, and the proper application of emollients to mitigate disease exacerbations.

Incorporating nutritional counselling and allergy screening into standard paediatric treatment, especially for children with a familial predisposition to atopy, can enable the early detection of risk factors and the

Table 3: IGA Scale

Point	Characteristic features
0	No visible inflammatory response; there may be post-inflammatory signs of hyperpigmentation or hypopigmentation.
1	Almost imperceptible erythema, induration, papular changes, minimal lichenification, and no scab.
2	Slight but noticeable erythema, induration, papular lesions, lichenification, and absence of scab.
3	Dull red erythema, clearly visible indurations/papular lesions or lichenification; discharge and scab may be present.
4	Significant erythema of dark or bright red color, severe indurations/papular lesions or severe lichenification, widespread lesions, discharge, or scab.

Source: compiled by the author based on Melli *et al.* [63], Yosipovitch *et al.* [49], and Fujii [64].

application of tailored dietary adjustments. These integrative solutions highlight the significance of synchronised nutritional and public health policies for diminishing the prevalence and severity of paediatric AD.

Scales for Assessing the Severity of Atopic Dermatitis

The SCORAD scale can be used to assess the severity of the disease based on patient complaints and the results of a medical examination. The questionnaire contains three parts (A, B, and C). Part A is an assessment of the degree of damage according to Rule 9. The second part (B) contains six items and describes erythema, edema, cracking, lichenification, and dryness. The third part (C) includes two items that assess pruritus and insomnia. Each part is 20%, 60% and 20% respectively. There are three degrees of severity:

- mild – below 25 points;
- moderate 26-49 points;
- severe – over 50 points.

The EASI assesses the percentage of the body surface affected and the intensity of the skin lesions. At the first stage, the affected area is determined (head, neck, upper extremities, trunk, and lower extremities) and the corresponding score is assigned: 1 (1-9%), 2 (10-29%), 3 (30-49%), 4 (50-69%), 5 (70-89%) i 6 (90-100%). At the second stage, each of these areas is evaluated for the presence/absence of erythema, oedema/papules, exfoliation, lichenification, and a score from zero to three is assigned. The extent of damage to each individual site is determined by multiplying the sum of the region's intensity score by the region's score and the multiplier assigned to each area of residence. The result of the assessment is a total score, which is summed from each site. It ranges from 0 to 72.

The area and severity index scale can be used to assess the activity of the course, and when using SCORAD, dry skin, itching, and insomnia are also determined [75]. According to the IGA, patients are classified into 5 separate categories according to the degree of damage (Table **3**).

Thus, atopic dermatitis develops as a result of long-term systemic exposure to external and internal factors at all stages of human development. Environmental factors and the conditions in which an individual grows up have a significant impact. The manifestations of the disease depend on age and several personal factors.

DISCUSSION

The results of this study confirm and add to the existing scientific literature on the pathogenesis, clinical manifestations, and the influence of environmental factors on AD. There is a significant correlation between this study and the work of Bonamonte *et al*. [82], which recognized environmental variables as key determinants of the etiology and severity of AD. Bonamonte *et al*. emphasized the influence of environmental pollutants, allergens, and climatic factors on the exacerbation of AD symptoms. This conclusion was confirmed by the current study, which emphasized the role of air pollution, inadequate ventilation, and exposure to tobacco smoke. Similarly, Schram *et al*. [83] investigated the prevalence of AD in different geographical locations, finding a gradient in incidence between rural and urban areas. Their comprehensive study suggested that urban environments, characterized by elevated levels of pollution, stress, and a variety of allergens, are correlated with a higher incidence of AD. The current study substantiated this finding by highlighting the impact of urban pollutants on skin barrier dysfunction, impaired immunological responses, and activation of pro-inflammatory pathways.

Shinohara and Matsumoto [84] highlighted fetal exposure to tobacco smoke as a critical risk factor for the development of infantile AD. Their results demonstrated that exposure during the third trimester increases susceptibility to allergic disorders, a finding supported by the present study, which outlined mechanisms such as increased cell apoptosis and increased IgE production due to tobacco smoke exposure. Kim *et al*. [85] investigated the role of environmental pollutants by analysing how particulate matter exacerbates AD symptoms under different weather conditions. The current study established a link between elevated ozone levels and free radical generation with subsequent epidermal damage, highlighting the importance of air quality control for the prevention and treatment of AD. Lee *et al*. [86] studied the preventive effect of green residential areas on AD induced by prenatal air pollution. They suggested that exposure to green environments during pregnancy reduces the likelihood of developing atopic dermatitis in infants, potentially due to reduced exposure to pollutants and mitigation of psychological stress.

Goh *et al*. [87] presented a comprehensive review of therapeutic approaches to AD, emphasizing the need for an integrative strategy that combines pharmacotherapy, environmental modification, and psychological support. The study argued for this concept by examining the impact of environmental factors, including air pollution, dietary habits, and exposure to tobacco smoke, on the severity of the disease. The results highlighted the importance of personalized therapeutic protocols that take into account the systemic characteristics of AD. The authors emphasized the importance of biologics, especially monoclonal antibodies targeting specific cytokines (IL-4 and IL-13), as effective therapeutic alternatives. Current studies are investigating the immunological mechanisms associated with these cytokines and their role in epidermal dysfunction.

He and Guttman-Yassky [88] focused on the functional significance of JAK inhibitors in the treatment of AD, emphasizing their ability to block the JAK-STAT signaling pathway, which is critical for the development of the inflammatory response. Recent studies supported these findings, detailing the role of the JAK-STAT pathway in the pathogenesis of AD, particularly in enhancing the production of Th2-associated cytokines such as IL-4 and IL-13. While He and Guttman-Yassky focused on the clinical efficacy of JAK inhibitors, the present study shed light on the mechanisms by which these inhibitors reduce Th2-mediated inflammation, reduce the intensity of itching, and restore skin barrier function. Both studies acknowledged the potential adverse effects of JAK inhibitors, including an increased risk of infectious complications, while emphasizing their promise as a therapeutic option for patients with moderate to severe AD.

Stevens *et al*. [89] investigated the impact of KIF3A gene variations on skin barrier integrity and susceptibility to atopic dermatitis, finding that genetic alterations modify DNA methylation and gene expression, thereby disrupting the epidermal barrier. The current study correlated with previous findings by identifying multiple genes associated with the pathogenesis of atopic dermatitis, including those responsible for epithelial barrier function, modulation of the immune response, and DNA methylation.

Kern *et al*. [90] demonstrated that children with severe atopic dermatitis in childhood and adolescence have an approximately twice higher risk of developing depressive symptoms and internalizing behaviour. This correlation was observed even in mild forms of the disease, which emphasizes the need for early assessment of the mental state and appropriate medical care. The persistent nature of atopic dermatitis can cause frustration and decreased self-esteem, which exacerbates mental health problems.

Fan *et al*. [91] analysed the relationship between the composition of the maternal and neonatal gut microbiota and the development of atopic dermatitis in early childhood. Their results demonstrated that specific populations of gut microorganisms exert either protective or promoting effects on the pathophysiology of atopic dermatitis. Han *et al*. [92] studied the variation in gut microbiota between patients with atopic dermatitis who have gastrointestinal symptoms and those who do not, finding significant differences in microbial diversity and composition. Patients with atopic dermatitis who also have gastrointestinal symptoms have a more pronounced dysbiosis, characterized by a reduction in beneficial bacteria and an increase in pro-inflammatory microorganisms. Both studies demonstrated that an imbalance in the gut microbiota contributes to systemic inflammation by exacerbating epidermal barrier deficiency. Ye *et al*. [93] analysed the gut microbiota of patients with atopic dermatitis compared to healthy individuals, finding a significant reduction in microbial diversity in the former. Their study identified several bacterial taxa that show a decrease or increase in patients with atopic dermatitis,

including a reduction in Bifidobacterium and an increase in Clostridia and Bacteroides.

A notable recent advancement in AD treatment is the emergence of IL-4/IL-13 antagonists, including dupilumab, which specifically target immunological networks implicated in the disease's pathophysiology [94]. These biologics inhibit the activity of IL-4 and IL-13, pivotal cytokines implicated in the Th2 immune response that fosters the chronic inflammation observed in AD. This focused strategy seeks to inhibit the inflammatory cycle by diminishing IgE synthesis, eosinophilia, and keratinocyte activation, all of which are pivotal in the pathogenesis of AD. This study corroborates previous findings by highlighting the Th2-mediated inflammation and epidermal barrier dysfunction that are successfully alleviated by this therapy. Although dupilumab and other biologics present promising prospects, longitudinal studies are necessary to assess safety, efficacy, and potential adverse effects, including an elevated risk of infections [14].

Despite substantial progress, critical deficiencies persist in AD research. A significant constraint is the absence of non-European data in AD research. The predominant study on AD causality and therapy has focused on European, North American, and Asian populations, resulting in the under-representation of African, Latino, and Indigenous people [14]. These communities may possess distinct genetic variables, environmental exposures, and treatment responses that are insufficiently represented in existing literature. Research on these populations is essential to comprehending the impact of genetic polymorphisms on the disease and creating customised therapies for diverse communities.

A significant deficiency exists in research on paediatric atopic dermatitis, particularly concerning the longitudinal course of the condition and its genetic and epigenetic causes. AD is recognised as commencing in early childhood. Nonetheless, there is a restricted comprehension of how initial exposures, especially throughout the first years of life, build the immune system and affect disease progression. Longitudinal studies are essential to monitor immunological development and microbiome alterations in young children, as well as to uncover early biomarkers that may facilitate prompt diagnosis and intervention.

The present work highlights the complicated nature of AD pathogenesis, clarifying the interaction among hereditary factors, immune system dysfunction, and environmental stimuli. The advent of biologics aimed at IL-4 and IL-13 represents a substantial advancement in the management of moderate to severe AD. Integrating genetic and epigenetic knowledge in personalised medicine may enhance AD treatment. Comprehending genetic predispositions (e.g., filaggrin mutations) and epigenetic alterations (e.g., DNA methylation) can facilitate the customisation of medicines, such as JAK inhibitors, for specific patients, thereby providing more precise and efficacious treatments. This method may diminish dependence on trial-and-error while improving therapeutic efficacy and patient outcomes.

This review primarily examined research from Europe, North America, and Asia, with minimal representation from non-European areas like Africa and Latin America. This introduces a potential bias, as the prevalence, clinical symptoms, and environmental factors affecting AD may differ across geographic regions. Additional research is required in under-represented areas to improve the generalisability of results and to clarify further the cultural, genetic, and environmental variations in AD aetiology. Additional multinational research is required to address the deficiency in non-European data and comprehend the paediatric course of the disease. Moreover, incorporating epigenetics into AD research is crucial for elucidating the molecular mechanisms that regulate immune responses and for identifying possible biomarkers for early diagnosis and intervention.

CONCLUSIONS

AD is a heterogeneous and pervasive disorder that typically presents in early childhood, frequently within the initial years of life, while immune and skin barrier systems are still maturing. Considering that about 90% of cases are identified before the age of five, AD serves as both a dermatological disorder and a significant indicator of early-life immunological dysregulation. The symptoms, including severe itching, redness, dryness, and recurrent eczema, undermine skin integrity and profoundly disrupt sleep, emotional health, and neurodevelopment in affected children.

Causes and mechanisms of the disease include disruption of the normal functioning of genes (the main one is filaggrin, whose mutations have been described in 50% of patients with moderate and severe disease), exposure to environmental factors (tobacco smoke, toxic substances, ozone, antibiotics), disruption of the epidermal barrier and development of a type 2

inflammatory reaction. About 70 genes have been found to be associated with the development of the disease. Moreover, epigenetic regulation is also important, affecting gene expression, immune system functioning, and epidermal permeability. BP can complicate the course of many diseases.

Given the premature emergence and enduring impact of AD, treatments should emphasise paediatric health through preventive measures focused on the prenatal and early childhood stages. Nutritional interventions, such as maternal consumption of omega-3 fatty acids, promotion of breastfeeding, optimisation of vitamin D levels, and early regulation of microbiota, ought to be incorporated into mother and child health initiatives. Paediatric care must include allergy screening, nutritional counselling, and environmental sanitation to avert exacerbations and enhance barrier integrity. Instruments like SCORAD, EASI, IGA, and HRC are essential for evaluating disease severity and tracking therapeutic response.

The limitations of the present study are the insufficiently studied aetiology and pathogenesis of atopic dermatitis. In addition, the vast majority of studies are devoted to the European population, with less involvement of Asian and African groups.

Recommendations for future research and clinical practice:

- Emphasise research on early-life immune development and perinatal influences, encompassing maternal nutrition and newborns' dietary practices.
- Broaden research to encompass underrepresented populations to guarantee that findings have global relevance.
- Formulate comprehensive therapies that integrate genetic, immunological, microbial, and dietary approaches for early prevention.
- Execute public health initiatives aimed at enhancing air quality, minimising allergy exposure, and advancing maternal-child nutrition.
- Incorporate mental health assistance into paediatric dermatological protocols, especially for children with moderate to severe conditions.

In summary, the significant paediatric prevalence of atopic dermatitis requires a child-centred, multidisciplinary strategy that integrates dermatology, immunology, nutrition, and public health. Prioritising early prevention and immunological enhancement throughout pivotal developmental periods may diminish disease occurrence, severity, and long-term effects on child welfare.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

The author declares that generative AI or AI-assisted technologies were not used in any way to prepare, write, or complete this manuscript.

AUTHOR CONTRIBUTION

Maria Zofia Lisiecka contributed to the design and implementation of the research, the analysis of the results, and the writing of the manuscript.

Appendix 1: Completed PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			

Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 1, 3
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	p. 3-4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	p. 3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	p. 3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 3
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study, and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	p. 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	p. 3-4
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses.	p. 3-4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 3-4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	p. 3-4
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 3-4
Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 3-4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 3-4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p. 3
Study characteristics	17	Cite each included study and present its characteristics.	p. 3

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 4-6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	p. 4-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 4-6, 14-16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 7-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 4-6, p. 14-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 4-6, p. 14-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 4-6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 4-6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 18-20
	23b	Discuss any limitations of the evidence included in the review.	p. 18-20
	23c	Discuss any limitations of the review processes used.	p. 19-20
	23d	Discuss implications of the results for practice, policy, and future research.	p. 20
OTHER INFORMATION			
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 21
Competing interests	26	Declare any competing interests of review authors.	p. 21
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p. 21

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