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Atopic dermatitis: pathogenesis and therapeutic interventions

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Thesis

ATOPIC DERMATITIS:

PATHOGENESIS AND THERAPEUTIC INTERVENTIONS

by

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DEDICATION

I would like to dedicate this thesis to God and my wonderful family.

Thank you for always supporting and encouraging me.

ACKNOWLEDGMENTS

I would like to thank my professors Dr. Offner and Dr. Symes for making this a great MAMS year. I now love Biochemistry!

ATOPIC DERMATITIS:

PATHOGENESIS AND THERAPEUTIC INTERVENTIONS

TIOLUWA AKINJAIYEJU

ABSTRACT

Atopic dermatitis (AD), often called eczema, is the most common chronic inflammatory skin disease. Over two hundred million people worldwide have eczema, which mainly begins in early childhood by showing dermatological signs, including rashes, itchiness, redness, inflammation, and dry, cracked skin. As the skin condition is becoming more widespread, research shows that genetic and environmental factors, among others, are all involved in the mechanism of this disease and how to manage and treat it in the future.

There is no exact etiology of atopic dermatitis. However, clinicians believe that studying the various contributors, such as genetic predispositions, immune dysfunction, and environmental factors, will provide an analysis of the development of the heterogeneous disease.

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LIST OF ABBREVIATIONS

AD..Atopic dermatitis

CD .... Contact dermatitis

FLG... Filaggrin

ISAAC…..........................International Study of Asthma and Allergies in Childhood

TCS ....Topical Corticosteroids

TREAT...................... TREatment of ATopic Eczema (TREAT) Registry Taskforce

WWT.. Wet Wrap Therapy

INTRODUCTION

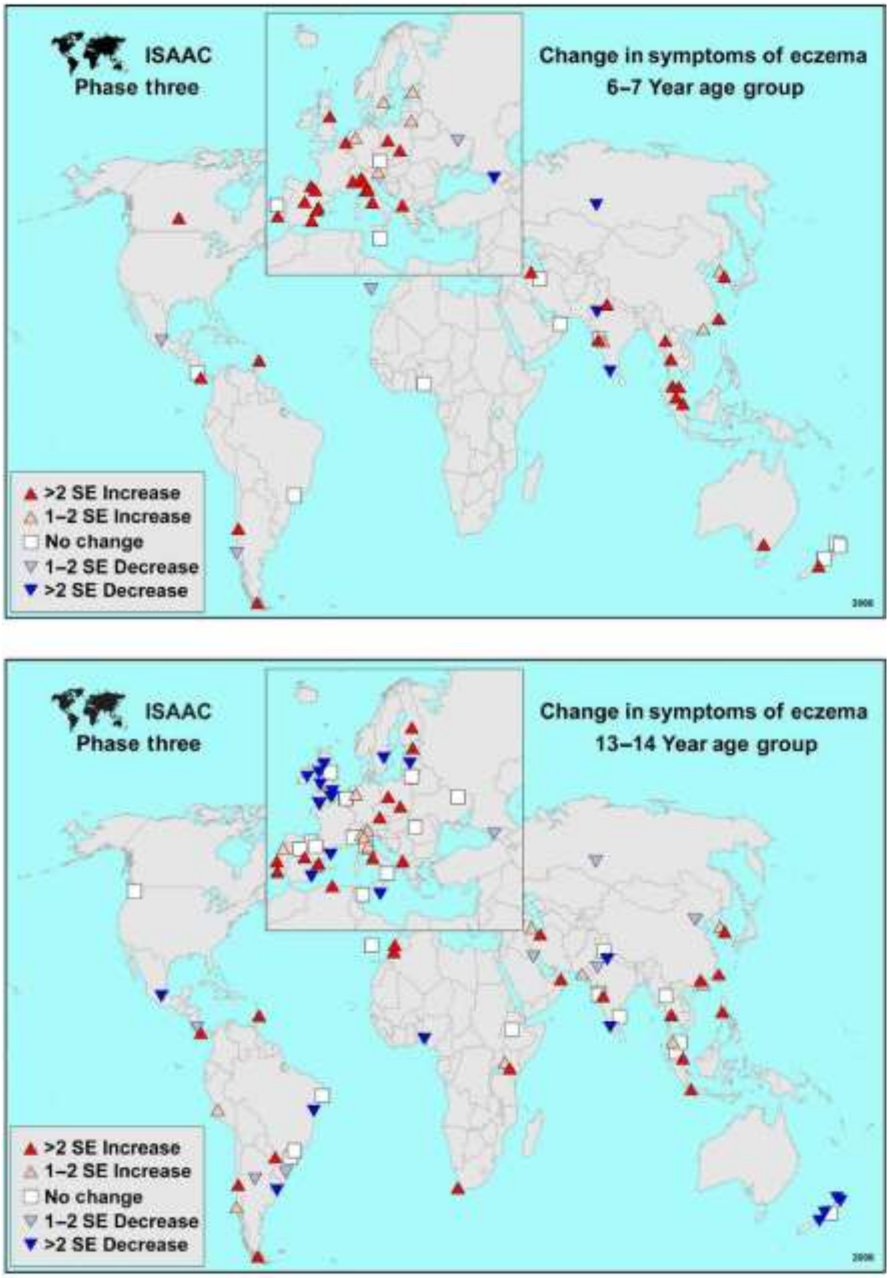
In the first part of this thesis, epidemiology, demographics, and origination will be explored. Analyzing these topics builds the foundation for clinical treatment and intervention, understanding the prevalence of the disease, and policies for gaining treatment.

Eczema is found in developed countries in 20% of children but it is not as prevalent in adults at about 3% worldwide. When looking at onset research indicates that eczema cases tend to be seen as early childhood with 90% being discovered before the age of five (IntechOpen - Open Science Open Minds). AD found in adults normally presents itself in 2 different ways the first being the version in which eczema from childhood becomes more severe as one ages. The other way is adult onset AD which is uncommon (IntechOpen - Open Science Open Minds). Many studies focus research on children in order to study the disease closer to the onset period as well as because it is more likely to be found in younger populations than older, **Illustration 1** displays a child with eczema.

Illustration 1. Atopic dermatitis of the flexural surfaces of the extremities. Children typically have manifestations of AD on the flexural surfaces of the extremities. (Illustration from Kapur, S et al., 2018)

The etiology of eczema can be studied by analyzing prevalence in various countries, environmental triggers, immune system regulation and genetic factors. Research from *New insights into the epidemiology of childhood atopic dermatitis* entails a question that is: why is there an increase in the prevalence of eczema. This is can be looked at via trend data, while AD is known to be prevalent in developing countries it is beginning to show the same patter in more developed nations. Contact with all elements of nature including the sun, microbiota, and plants can influence prevalency of diseases. Since atopic dermatitis is the most common type of chronic inflammatory disease in children so a commonly asked question is how to prevent environmental risk factors. Trend data from the article indicate that low income developing countries have previously shown to have significant numbers in children with eczema for example Africa and Asia (Flohr, C et al., 2014).

The article details a system in which Asthma and allergies can be tracked and documented for comparison called the International Study of Asthma and Allergies in Childhood (ISAAC). This allergy study allows for immediate and efficient comparison though three different phases. In phase one and three higher income locations and time trends are the focus. In phase two a physical test for dermatitis is completed. Results from ISAAC show that AD is on the rise regardless of the country's income in the 6-7 year old age groups after doing cross sectional study. Phase one (high income setting) indicated that 13-14 year olds with eczema was common but prevalences did not decrease or increase contrary to developing countries.



Reproduced with kind permission from the *J Allergy Clin Immunology*. Source: Williams H et al. Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008;121:947-54.

Figure 1. AD symptom prevalence. This figure depicts the worldwide change in AD symptom prevalence between ISAAC Phases One and Three. Figure taken from (Flohr, C et al., 2014).

Environmental Factors that Effect Atopic Dermatitis

It used to be said that inflammation of the nerves caused eczema creating the term neurodermatitis this caused many to believe that genetic predispsosition held all bearing in determining if one had eczema. While genetics play a major role, there is major evidence which indicates that environmental factors have a large role as well.

The human body comes into contact with many types of organisms meaning that food, bacteria, plants and more all can contribute to the human body's homeostasis. Passive or deliberate contact with microorganisms play a significant role in allergy progression. Being a microbiome, normally the human body has a lot of diversity however patients with AD have decreased diversity but demonstrate high levels of *pathogenic Staphylococcus aureus* (S. aureus) this deteriorates the skin creating dysbiosis. **Figure 2** presents evidence of the dysbiosis in patients with Atopic dermatitis.

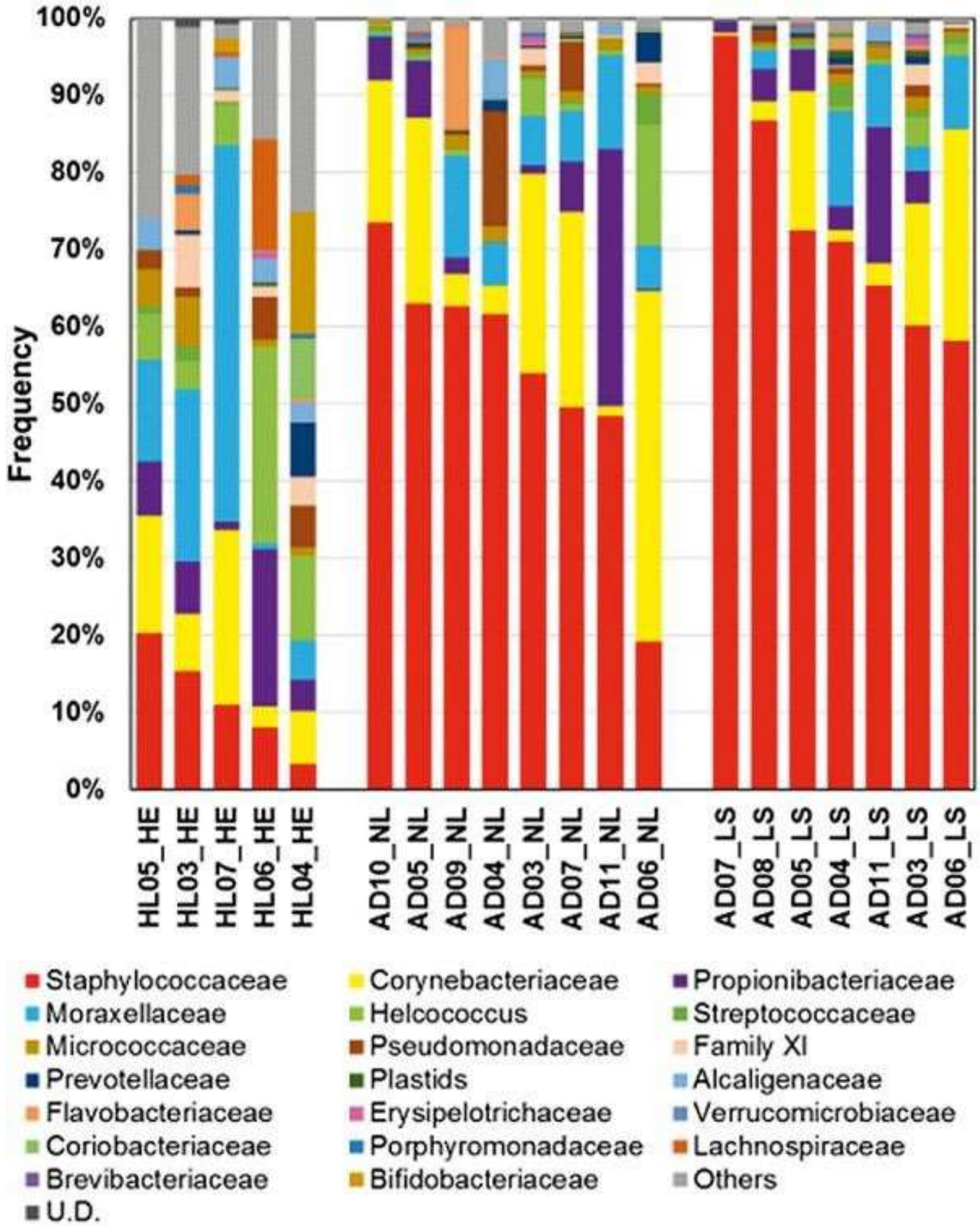


Figure 2. Microbiome analysis in healthy individuals and in AD patients. In healthy individuals the skin microbiome is colonized by different bacterial species. In patients with AD the diversity of the microbiome decreases. Dysbiosis of the skin flora is particularly pronounced in lesional skin. Figure from (Kapur et al., 2018).

Genetic Predispositions that Affect Atopic Dermatitis

Various mutations that negatively affect the skin barrier specifically in the filaggrin gene (FLG) have the most evidence AD skin is known to lack proteins like filaggrin and claudins as well as lipids like ceramide, cholesterol and fatty acids this is all clinically indicated in the loss of hydration and rapid water loss unlike healthy skin. Research explains the absence of the filaggrin gene as a “deficiency that contributes to inherent barrier defects in atopic skin that, in combination with the effects of inflammatory cytokines and environmental factors, results in the development of AD” (Kaufman, Guttman-Yassky, & Alexis, 2018, p. 341). The FLG LoF mutation is found in 50% of children who at least have moderate eczema leading reduced skin hydration (Chong A 2022). FLG mutations effect pH in the stratum corneum this pH imbalance can lead to allergic sensitization which is what explains research links to allergic rhinitis and asthma (Boguniewicz, M 2011).

Immune system Dysregulation affect on Atopic Dermatitis

Immunoglobulin E functions to mediate allergic reactions. Research indicates that patients with eczema display higher than normal levels of IgE and therefore a greater sensitization to allergens leading to elevated cytokine expression in various lesions as well as T cells (Boguniewicz, M 2011). Since not all patients with eczema have FLG mutations, such as those of African ancestry, (Kaufman, Guttman-Yassky, & Alexis, 2018) this further bolsters the ongoing argument of the question: “do skin barrier abnormalities precede immune dysregulation or do immune dysregulation precedes barrier changes” (Boguniewicz, M 2011). The following figure presents the pathophysiololgy of AD mainly focusing on immune abnormalities.

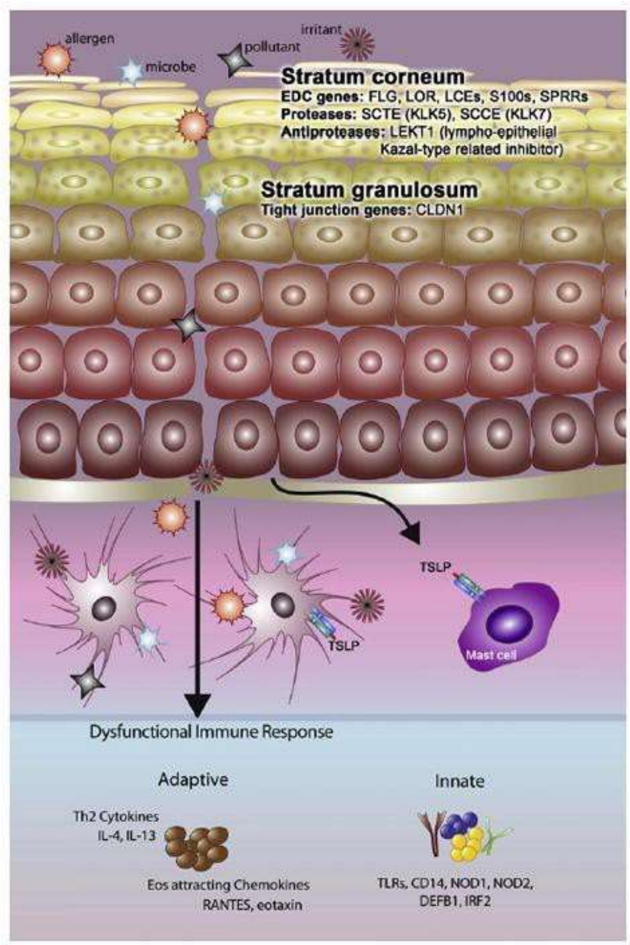


Figure 3. Complex pathophysiology of AD. Figure includes barrier and immune abnormalities Figure from (Boguniewicz, M et al., 2011)

Looking at these three overall aspects environmental triggers, immune system dysregulation, and genetic predispostions all contribute to the main causes of why patients have eczema. The following figure simply displays how the factors previously discussed interconnect in order to have an individual contract eczema.

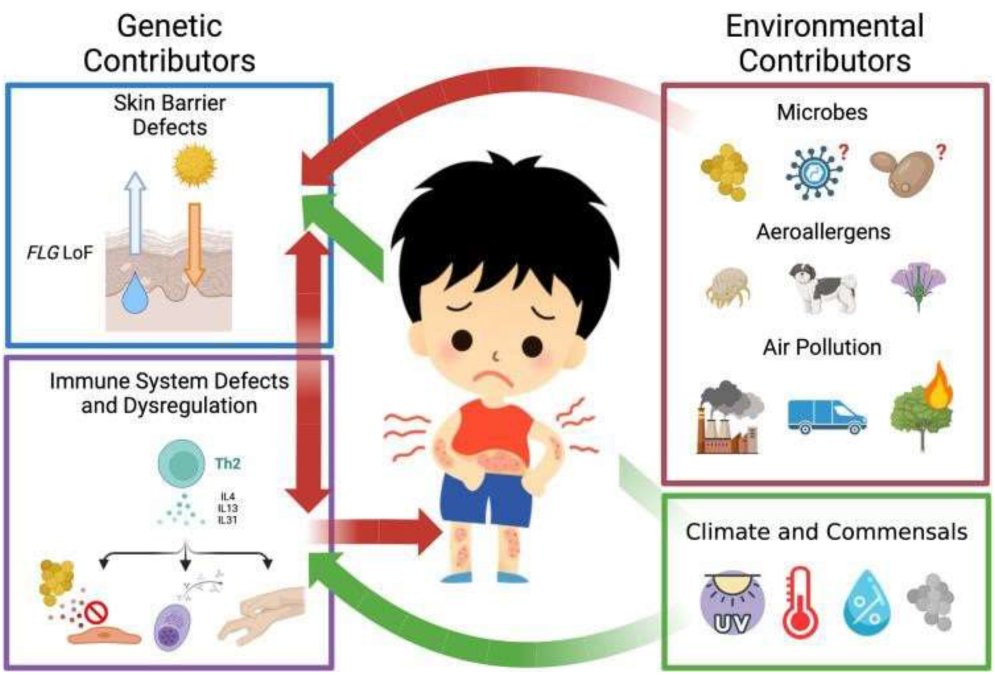


Figure 4. Genetic and Environmental Interplay. The interplay of genetic and environmental contributors in modulating the immune dysregulation of AD. Figure from (Chong, A. C et al., 2022)

PATHOGENESIS

Filagrin mutations often cause barrier defects and, therefore, facilitate allergen penetration and immune responses. Mutations cause keratinocytes to express downstream immune responses in the form of cytokines, such as IL-33 and IL-25 in AD, which stimulate the production of type 2 cytokines.

Nowadays, therapeutics aim to target type 2 cytokines like IL-4 and IL-3 because they cause inflammation in AD. Drugs such as Dupilumab, which targets the IL-4 receptor, have dramatically altered treatment for AD, which validates the role of cytokines in the pathogenesis of AD (Ong 2022). More recent information shows that systemic therapeutics are beginning to target adaptive immunity.

Mutations in the filaggrin gene are frequently associated with a compromised skin barrier function. This predisposes individuals to enhanced allergen permeability and subsequent immune reactivity. This genetic abnormality provokes keratinocytes to induce the secretion of key cytokines such as IL-25 and IL-33, culminating in the generation of type 2 cytokines in AD (**Figure 5**). Current therapeutic strategies are centered on the modulation of type 2 cytokines, particularly IL-4 and IL-3, recognized as drivers of inflammation in AD. Significant advancements, such as the production of Dupilumab targeting the Il-4 receptor, have transformed the treatment ability for AD (Ong 2022). Emerging research emphasizes a shift towards systemic therapeutic interventions aimed at modulating the adaptive immune response, specifically focusing on cytokines created by T cells.

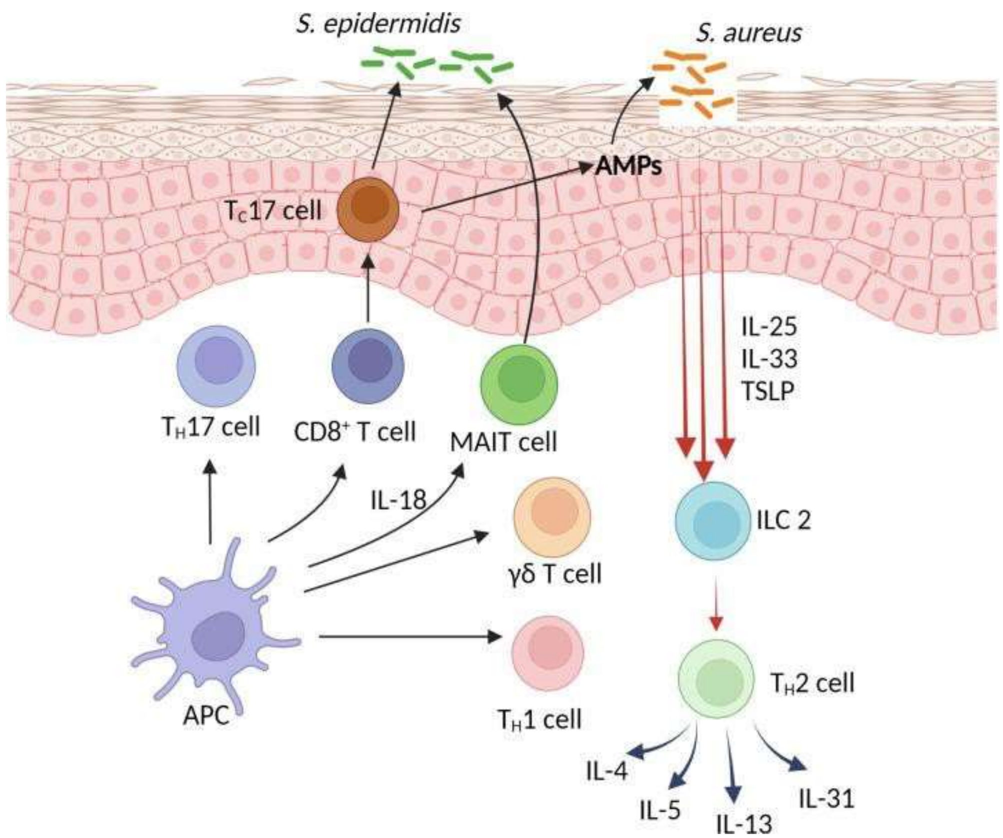


Figure 5. AD keratinocytes pathway. Keratinocytes express an increased level TSLP, IL-33 and IL-25 (Ong 2022 (36–38)). These cytokines act as alarmins that induce the production of IL-4, IL-5 and IL-13 from ILC2 and Th2 cells Figure from (Ong 2022).

CLINICAL MANIFESTATIONS ACROSS VARIOUS RACES

Atopic dermatitis presents itself in various forms depending on the skin type. Specific mutations or symptoms in one race may not be found in another- though both patients are diagnosed with the disease and receive different treatments to manage their symptoms. In the second part of this thesis, we will discuss how eczema presents itself in various races, including assessing the differences from the molecular level to the clinical level and treatment efficacy. Acknowleding these differences will provide healthcare personnel with the ability to cultivate preventative measures and treatments to various patient populations.

White, African American, & Black Individuals

AD appears clinically and molecularly distinct in ethnic skin due to contrasts in gene expression. African American and Black patients with eczema usually present with lichenification (thickened skin), itchy nodules, and follicular and papular bumps. In White individuals, flexural surfaces commonly exhibit lesions with eczema, but in Black individuals, the outer portions of the limbs commonly exhibit lesions. Research also shows that FLG mutations are rare in individuals of African ancestry (Kaufman et al., 2018). One is six times more likely to find the mutation in those of European ancestry than African. About 27.5% of null FLG mutations occur in those of European ancestry, whereas less than 5.8% occur in

African Americans. The following table displays the FLG null mutations in patients of African ancestry (Kaufman et al., 2018).

Table 1. Filaggrin null mutations in individuals of African Ancestry. Table from (Kaufman et al., 2018).

Race	Number studied	% with R501X	% with 2282del4	% with R2447X	% with S3247X	New (% affected)	Ethnic group	Ref.
Black	370 AD	3.2%	0.5%	0.7%	1.5%	N/A	African American	43
White	433 AD	13.8%	12.0%	1.4%	2.8%	N/A		
Black	60 AD	0	0	0	0	Q507X (1.7%) R3409X (1.7%) S3707X (1.7%)	African American	44
Black	187 AD/ADEH	3.2% Aa	3.2% Aa[a]	N/A	N/A	None	African American	42
	152 C	0	1.3%					
White	278 AD/ADEH	14% Aa, 1.4% aa	13.9% Aa, 1.8% aa					
	157 C	2.6% Aa	3.2% Aa					

The following illustrations, 6, 7, and 8, depict how eczema typically appears on Black individuals usually characterized by lesions with bumps on the extensor limbs.

Illustration 2 AD in a Black individual. Lichenified, hyperpigmented plaques due to atopic dermatitis on the extensor surface of the right forearm in a Black female. Illustration from (Kaufman et al., 2018).

Illustration 3. AD in A Black female individual. This image presents severe lichenification and follicular accentuation on the anterior leg and dorsal foot in a Black female. Illustration from (Kaufman et al., 2018).

Illustration 4. Lichen simplex chronicus with hyperpigmentation in Black skin. Illustration from (Kaufman et al., 2018).

Asian Individuals

Asian patients from Singapore and Malaysia, when affected by atopic dermatitis, typically show sandpaper-like lesions on their extensor surfaces, wrist dermatitis, and hyperkeratotic papules (Yong & Tay, 2017). Dermatitis often appears on the face and eyelids of female Asians. These findings contribute to our understanding of the unique presentation of atopic dermatitis in different ethnic groups, guiding clinicians in their diagnosis and treatment.

Hispanic Individuals

Hispanic individuals tend to have more papular Eczema on their extensor surfaces and are prone to more severe hyperpigmentation than non-Hispanic white individuals; this severity comes from SCORAD, which is a Scoring Atopic Dermatitis index. Like African American individuals, Hispanic individuals are also prone to post-inflammatory hyperpigmentation (Silverberg et al., 2013). The following figures, from the *Journal of Allergy and Clinical Immunology* display the differnces between symptoms of atopic dermatitis in patients of Asian and European ancestry.

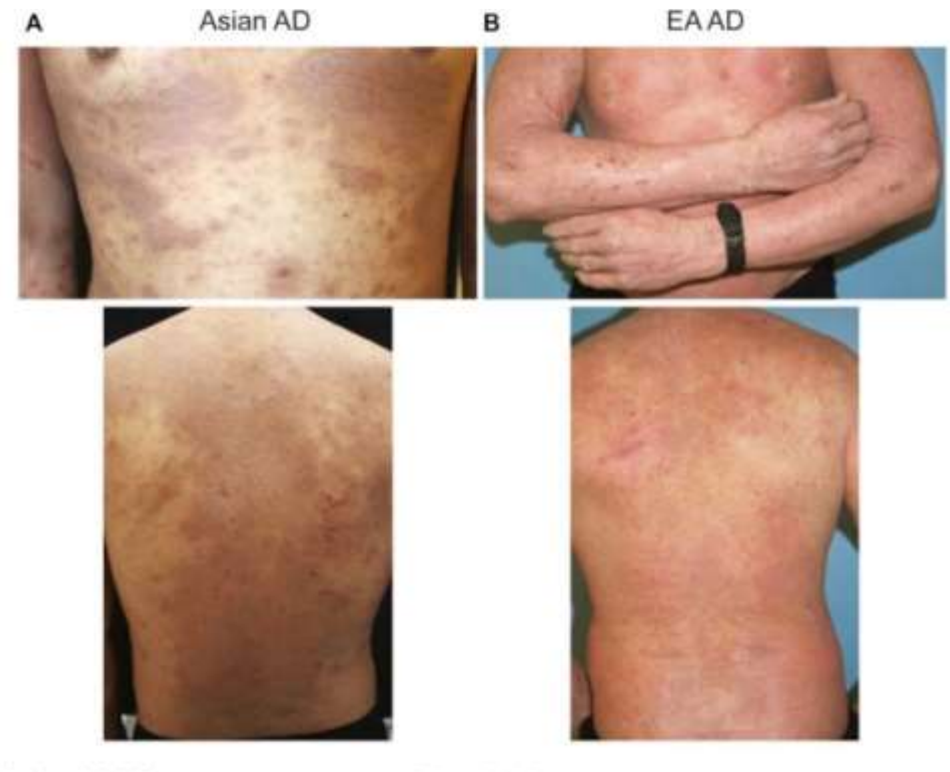


Illustration 5. Asian and European patients with atopic dermatitis. Asian individuals depict a more severe hyperpigmentation factor on the back and chest Illustration from (Noda et al., 2015).

INTERCONNECTING DISEASES

The Hanifin and Rajka criteria as well as the American Academy of Dermatology criteria are utilized to diagnose AD because they contain factors that detect various aspects, including features that detect pruritus and atypical AD presentations (Hanifin & Rajka, 1980). Other dermatological conditions that fall under Eczema diseases frequently appear similar to AD. Including AD, there are seven different types of Eczema, and while similar, they still have unique characteristics that allow clinicians to diagnose and treat them accordingly; in the following portion contact dermatitis (CD), which interconnects with AD, its qualities, mechanisms of diagnosis will briefly be discussed in order to understand how treatments can be prescribed to eczemas.

Contact Dermatitis

Contact dermatitis is a disease that develops when people come into contact with an exogenous agent. Like AD, there is sufficient evidence that contact sensitization likely develops during one's earlier years- and that children are more sensitive to allergens than adults due to their thinner skin (Borok et al., 2019).

In the past, AD and CD showed ambivalent results as to whether AD patients were more or less likely to have AD. Correa de Rossa et al., (2015) conducted a study to understand if patients with AD react differently.

De Rossa's experiment's methodology included immunohistochemistry and gene expression from two groups of patients, one with AD and one without. The groups were patch-tested with nickels, fragrances, and rubber. Then, immunostaining and PCR were used to evaluate all the data.

AD utilizes T cells in the immune system, specifically TH22, TH2, and sometimes TH1, while CD involves TH17, TH1, and TH22 pathways. Depending on the allergen, cutaneous allergic responses can be polarized. In patients with AD, the skin showed a much smaller amount of immune cells and fewer signs of genetic moderation, contrasting the non-AD group (Correa da Rosa et al., 2015). **Figure 3** explains the result of fewer T cells being seen in those with underlying AD. Though complicated, these results indicate that the link between AD and CD establishes that AD affects how the skin reacts to allergens, which furthers knowledge of treatment therapy.

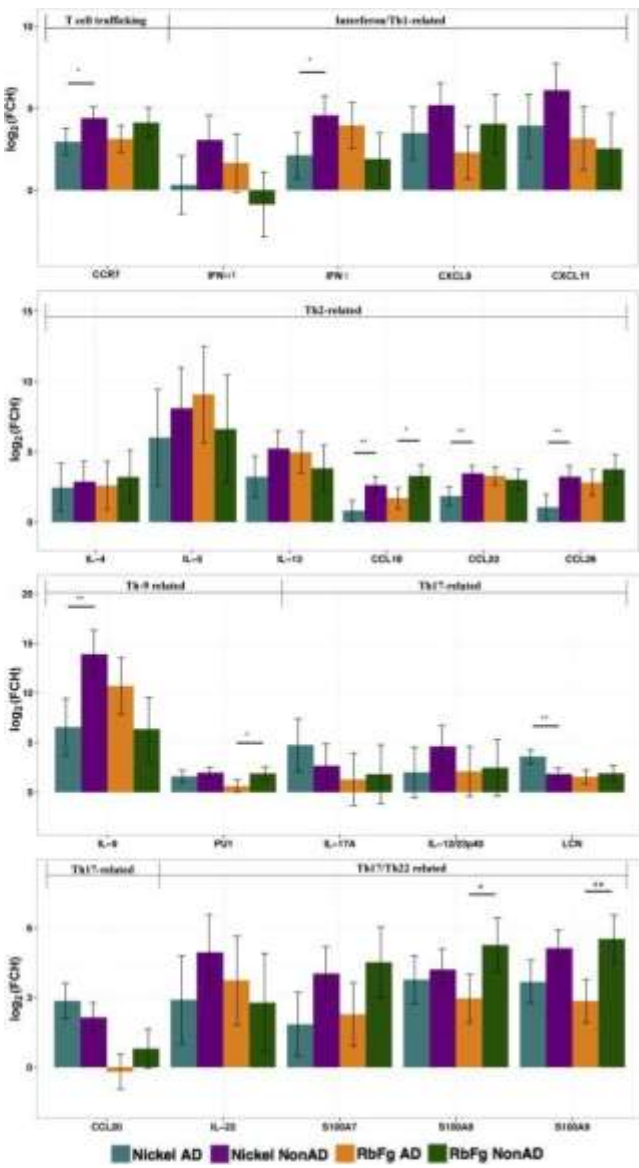


Figure 6. T cells in underlying AD. This figure explains the result of fewer T cells being seen in those with underlying AD. RT-PCR data adjusted for levels of immune activation in control skin confirmed decreased immune responses in patch-tested AD skin. RT-PCR was used to evaluate the expression of major cytokines and inflammatory markers. Data were grouped according to allergen type and AD status and by the major inflammatory and regulatory pathways represented. All data were adjusted for control values. *P*values of expression in the AD versus non-AD groups are indicated, if significant. **P* < .1 and ***P* < .05. Figure from (Correa da Rosa et al., 2015).

Illustrations 10, 11, and 12 show patients with contact dermatitis due to nickel and rubber. Unlike AD, CD can be anywhere that the exogenous agent has touched the body.

Illustration 6. Contact Allergy From Nickel. Illustration from DermNet New Zealand (Litchman et al., 2024)

Illustration 7. Contact Allergy From Rubber. DermNet New Zealand Illustration from (Litchman et al., 2024)**.**

Illustration 8. Nickel Contact Dermatitis. A classic presentation of periumbilical nickel contact dermatitis with ID reaction involving elbows. Illustration from (Litchman et al., 2024)

TREATING ATOPIC DERMATITIS: STRATEGIES AND INNOVATIONS

Historical Treatment of Atopic Dermatitis

Treating Eczema is not simple or the same for every patient. Each person who is diagnosed may react to treatment differently. There is no cure, so clinicians focus on preventing the growth of the disease and managing current symptoms that patients may exhibit. This section will explore the historical treatments, present treatment capabilities, and what research predicts the future will bring in curing this disease.

Historically, AD was treated using elementary medical practices mainly based on customary medicine. In ancient times, herbal preparations that included aloe vera and honey were commonly used to soothe inflammation and alleviate symptoms. These remedies are still around today and work just as well as they did then.

In the Medieval period, skin conditions made little progress in treatment, though animal ointments and herbal brews were used to balance bodily fluids, commonly believed to be the underlying cause of all diseases (Anderson, 2018).

Profound advancements were made in the early 19th and 20th centuries. One of the first topical remedies for inflammation, redness, and itching was coal tar. Due to its effectiveness, it was used for years. In the 1930s, corticosteroids were introduced and completely transformed the treatment of AD and inflammation (Leung et al., 2004).

Topical Treatment of Atopic Dermatitis

Today, the most common form of therapy for Eczema is topical treatment. Atopic dermatitis is typically managed through different forms of treatment tailored to various ethnicities, ages, and degrees of the disease. Currently, topical remedies are the reigning form of prevention and relief for patients. Nonpharmacologic interventions generally involve moisturizers. They typically attack xerosis and dry skin, a hallmark sign of Eczema, by using emollients to lubricate the skin and trap water to hydrate it. These emollients will help stop inflammation and prevent flare-ups and the progression of other symptoms (Eichenfield, L. F et al., 2014). Consequently, clinicians consider moisturizers the foundation of therapy for atopic dermatitis. The following table from the American Academy of Dermatology shows the strength of the recommendation of topical therapies in treating the disease (Eichenfield, L. F et al., 2014).

Recommendation	Strength of recommendation	Level of evidence	References
Use of moisturizers	A	I	9-16,18-21,126
Bathing and bathing practices	C	III	23,24,26,28,30
Application of moisturizers after bathing	B	II	24,25
Limited use of nonsoap cleansers	C	III	27-30
Against use of bath additives, acidic spring water	C	III	31,32,127
Wet-wrap therapy	B	II	34-41
Use of TCS	A	I	42-46
Consideration of a variety of factors in TCS selection	C	III	49,128,129
Frequency of application	B	II	51-53
Proactive use of TCS for maintenance	B	II	54-56
Need for consideration of side effects with use	A	I	57,58,66
Need for monitoring for cutaneous side effects with potent TCS	B	III	57,58,66
Specific routine monitoring for systemic side effects with TCS not needed	C	III	57,58,62,66
Addressing fears with use	B	III	67-69
Use of TCI	A	I	70,76,81
Use as steroid-sparing agents	A	I	82,83
Off-label use of TCI in those age <2 y	A	I	76,89
Counseling on local reactions with TCI and the preceding use of TCS	B	II	81,85,96
Proactive use of TCI for maintenance	A	I	54,93-95
Concomitant TCS and TCI use	B	II	82,83,106-109
Informing patients regarding theoretical risk of cutaneous viral infections with use	C	III	82,98
Awareness of black-box warning of TCI	C	III	98-101
Routine monitoring of TCI blood levels not needed	A	I	102,103
Against routine use of topical antistaphylococcal treatments	A	I	110-112
Bleach baths and intranasal mupirocin for those with moderate to severe AD and clinical infection	B	II	113
Against use of topical antihistamines	B	II	42,115-117

AD, Atopic dermatitis; *TCI*, topical calcineurin inhibitors; *TCS*, topical corticosteroids.

Table 2. Strength of recommendations for the use of topical therapies. Strength of recommendations for the use of topical therapies in the treatment of atopic dermatitis. Table from (Eichenfield, L. F et al., 2014)

Wet Wrap Therapy

While emollients are helpful, sometimes physicians have to prescribe topical corticosteroids (TCS). TCS target several different immune cells, like monocytes, dendritic cells, and T lymphocytes, to suppress proinflammatory cytokines. TCS are usually the subsequent step when patients' lesions do not effectively respond to regimented skincare, ointments, and moisturizers (Eichenfield, L. F et al., 2014).

Wet wrap therapy (WWT) involves TCS for rapid relief. A topical agent will be covered in a wetted layer of cloth followed by a dry cloth layer. WWT can occlude the topical agent for increased penetration and water retention. According to a study by Eichenfield et al. (2014), applying topical corticosteroids (TCS) via WWT was more effective than moisturizers. However, it is essential to use caution because mid to high-potency TCS can block neurological pathways, including the hypothalamic-pituitary-adrenal axis. This blockage occurs because the hypothalamus releases hormones, such as cortisol releasing hormone, which then travels to the anterior pituitary, stimulating the release of adrenocorticotropic hormone and ultimately leading to cortisol production in the adrenal glands. High potency TCS can lead to increased absorption and suppression of the hypothalamic-pituitary axis, resulting in low serum cortisol levels in the morning, which goes against the body's natural circadian rhythms, as cortisol levels are supposed to be highest in the morning.

Long-term treatment

There is a paucity of research concerning long-term treatments for AD, with most studies being limited to a duration of four weeks. The upcoming segment will delve into three extensive trials examining the efficacy of topical corticosteroid (TCS) treatment over a prolonged period and the comparative findings. In these three randomized controlled trials the comparisons are generally made with placebos or another TCS.

Trial 1

The initial trial conducted by the British Journal of Dermatology focused on adults with AD who had previously used the topical corticosteroid, fluticasone propionate 0.005%, for two weeks and experienced significant improvement. These patients were included in a study to determine if continued application for two consecutive days would sustain the benefits. The results indicated that those who continued to use fluticasone showed a slight worsening of AD over a sixteen-week period, but this was significantly less than those who used a placebo. The relapse rate for those on placebo was three times higher than for those on fluticasone. Overall, the study did not find any adverse effects on the participants' bodies, nor were there any signs of abnormal cortisol levels (J.B. Van Der Meer et al., 1999).

Trial 2

The second trial, conducted by K S Thomas et al. (2002) over an 18-week period, sought to determine whether a mild preparation of 1% hydrocortisone over seven days is less effective than a three-day burst of a potent 0.1% betamethasone valerate each week. Both groups applied their treatment only when needed.

The researchers did not find significant differences between the two groups of children. They noted their scratch-free days and calculated it to be 118.0 for the mild preparation group and 117.5 for the potent group. Both groups displayed some thinning in their skin thickness, but overall, all participants showed improvement in disease severity.

Trial 3

In the third trial by John Berth-Jones et al. (2003), the aim was to determine whether fluticasone propionate affects the time to relapse of atopic dermatitis during the maintenance phase. The patients in this study were ages 12-65 with moderate to severe AD. They were assessed using a typical lesion index and chosen depending on whether they were experiencing a flare-up.

In the initial stages of the study, the flare-up was treated with 0.05% fluticasone propionate ointment once or twice a day for four weeks. Individuals who achieved remission entered the maintenance phase. This phase encompasses a time when the same formulation from the first phase is used over a different period—in this case, two consecutive evenings per week for a maximum of 16 weeks. Furthermore, whether or not one was in the maintenance group, they applied an emollient daily. Patients who did not go into remission applied an emollient and a non-medicated cream twice weekly, while those in the remission group applied the emollient and the TCS twice weekly.
The maintenance group relapsed anytime after 16 weeks, while the other group relapsed after six weeks. Results indicate that the twice-weekly fluticasone propionate effectively kept treatment benefits consistent.

	Group using cream		Group using ointment	
	Daily emollient* plus twice weekly fluticasone propionate (n=70)	Daily emollient* plus twice weekly base (placebo) (n=84)	Daily emollient* plus twice weekly fluticasone propionate (n=68)	Daily emollient* plus twice weekly base (placebo) (n=73)
No (%) of patients having a relapse	13 (19)	54 (64)	27 (40)	41 (56)
% difference between placebo and fluticasone propionate (95% CI)	46 (32 to 59)		16 (0.2 to 33)	
Median time to relapse in weeks	>16	6.1	>16	6.1
Hazard ratio (base:fluticasone propionate)†	5.8 (95% CI 3.1 to 10.8, P<0.001)		1.9 (1.2 to 3.2, P=0.010)	
Number needed to treat‡	2.2		6.1	

*Twice daily (once daily on study treatment days) plus bath oil as required.

†Based on the probability of a relapse occurring at any time point in the study, on one treatment relative to the other.

‡Number of patients who have to be treated with fluticasone propionate to prevent one relapse that would have occurred on placebo.

Table 3. Fluticasone propionate cream reduces the risk of relapse of AD. A hazard ratio of 5.8 indicates that patients adding fluticasone propionate cream into their emollient maintenance routine reduce the risk of relapse of AD. Table from (Berth-Jones et al., 2003).

The three clinical trials provide valuable insights for healthcare professionals regarding the effective use of TCS for both short-term and long-term patient treatment. Although the trials' duration may be insufficient to ascertain adverse effects, they represent a significant real-world application of TCS in AD treatment. **Table 3** outlines the summary of analysis of time relapse in the maintenance phase.

Database of Measurement

Well-known treatments like systemic therapy and phototherapy in AD are commonly used for patients with moderate to severe Eczema. However, a study by the British Association of Dermatology (F.M. Vermeulen et al., 2019) determined that collaboration on collective compilations of patient information of those with AD in a standardized manner is necessary to have a definitive data pool that determines if phototherapy and systemic therapy are providing long-term effectiveness for patients.

Systematic reviews, conferences with clinicians, and reviews of preexisting databases were garnered to reach a consensus on how measurements should be assigned.

The TREatment of ATopic Eczema (TREAT) Registry Taskforce created a domain on 'what to measure.' After this, a finding process was performed to integrate the 'how and what to measure' into a national registry. The database included current systemic therapies for adults, including Dupilumab and ciclosporin, but there are no approved systemic therapies for children (F.M. Vermeulen et al., 2019). Phototherapy dosages were included when available. Current topical treatments, like corticosteroid potency, were included even though the classification system varies by country. The following table from the study depicts the domains of measurement instruments to be captured in eczema treatment registries (Atherton D. J. 2003).

Table 4. Core dataset of domains and measurement instruments

Domains	Domain items	How to measure	Comments
Demographics	Date of birth	1. Date	
	Date of enrolment into registry	2. Date	
	Gender	1. Male, female, other	
	Ethnicity	1. Country of birth of patient and parents 2. Ethnicity of patient (possibility to select two options): White (Europe, Russia, Middle East, North Africa, U.S.A., Canada, Australia), Black-African, Afro Caribbean, African American, Asian-Chinese, South Asian (India, Pakistan, Sri Lanka, Nepal, Bhutan, Bangladesh), Asian—other (Korea, China north of Huai River), Japanese, Hispanic or Latino, mixed—please specify, other—please specify	
	Educational status	1. ISCED classification (for both adults and children): ISCED 0: Early childhood education ISCED 1: Primary education ISCED 2: Lower secondary education ISCED 3: Upper secondary education ISCED 4: Post-secondary non-tertiary education ISCED 5: Short-cycle tertiary education ISCED 6: Bachelor's or equivalent level ISCED 7: Master's or equivalent level ISCED 8: Doctoral or equivalent level	This item will be assessed repeatedly Use the highest completed education level; from child or parents if a child or from the patient themselves if adult Will have to be translated for each country to its national educational classification
	Current occupation or education	1. Eurostat classifications 1–8: 1. employed, 2. self-employed, 3. disability pension (unable to work), 4. retired, 5. student or pupil, 6. engaged on home duties, 7. unemployed, 8. other—please specify	This item will be assessed repeatedly
AE diagnosis	How diagnosis AE is established	1. Clinically Y/N 2. Histopathology Y/N	
	Use of validated diagnostic criteria	1. Physician diagnosis alone, Hanifin & Rajka Criteria, U.K. Working Party Diagnostic Criteria, AAD/Eichenfield Criteria, Refined Millennium Criteria, Schultz-Larsen Criteria, Kang and Tian Criteria, Diepgen Criteria, Danish Allergen Research Centre Criteria, Saeki's JDA Criteria	Each country can decide which of these criteria they want to give as options
	Date of onset AE	1. Year	
Past AE treatments	Phototherapy	1. Y/N 2. NB-UVB, BB-UVB, UVB (unspecified), UVA, UVA1, UVAB, PUVA (oral or other), other (possibility to select multiple options) 3. How many courses (numerical), cumulative dose (J/cm^{-2}) (optional), when (start year) (optional), number of treatments within a course (numerical) (optional), outcome: a. effect (excellent (clearance), good, moderate, poor), b. reason to stop (insufficient response, loss of treatment response (after initial good response), side-effects, cumulative dose, disease remission, other) (select one option), c. adverse event (Y/N)	UVB (unspecified) if type is unknown This is only medical history. If (also) current it should be recorded under 'current AE treatments'

(continued)

Table 4. Core dataset of domains and measurement instruments continued

Domains	Domain items	How to measure	Comments
	Systemic therapy	1. Y/N 2. Ciclosporin, azathioprine, methotrexate, mycophenolate acid, systemic corticosteroids, dupilumab, omalizumab, other—please specify, investigational medication—please specify (possibility to select multiple options) 3. How many courses (numerical), when (start month + year) (optional), duration (free text), average treatment (maintenance) dose (optional), outcome: a. effect (excellent (clearance), good, moderate, poor), b. reason to stop (insufficient response, loss of treatment response (after initial good response), side-effects, cumulative dose, disease remission, other), c. adverse event (Y/N)	With definitions for average treatment (maintenance) dose (Fig. S4; see Supporting Information) This is only medical history. If (also) current it should be recorded under 'current AE treatments'
	Topical treatments for AE	1. Y/N 2. Corticosteroids, calcineurin inhibitors, tar ointments, crisaborole, other (possibility to select multiple options)	Only to be registered for the past year This is only medical history. If (also) current it should be recorded under 'current AE treatments'
	Day hospital care treatments for AE (outpatient)	1. Y/N 2. Duration (cumulative treatment days)	Only to be registered for the past year This is only medical history. If (also) current it should be recorded under 'current AE treatments'
	Hospitalization for AE	1. Y/N 2. Duration (cumulative days)	Only to be registered for the past year This is only medical history. If (also) current it should be recorded under 'current AE treatments'
Current AE treatments	Phototherapy	1. Y/N 2. NB-UVB, BB-UVB, UVA, UVA1, UVAB, PUVA (oral or other), other 3. Start date, cumulative dose (J/cm^{-2}), stop date	
	Systemic therapy	1. Y/N 2. Ciclosporin, azathioprine, methotrexate, mycophenolate acid, systemic corticosteroids, dupilumab, omalizumab, other—please specify, investigational medication—please specify (possibility to select multiple options) 3. Start date, start dose, current dose, stop date	With definitions for average treatment (maintenance) dose (Fig. S4; see Supporting Information)
	Topical treatments	1. Y/N 2. Corticosteroids, calcineurin inhibitors, tar ointments, crisaborole, other (possibility to select multiple options) 3. Classification of steroids and calcineurin inhibitors (optional) 4. Frequency ('how many times a week do you use it?') (optional)	If classification is registered use the national official potency classification
	Amount of topical creams/ointments used per week (g)	1. <30, 30–60, 60–100, >100	This is exclusive additive-free, bland emollients
Family history of AE or allergic diseases	Family history of AE or allergic diseases	1. Y/N 2. Atopic eczema, asthma, allergic rhinoconjunctivitis, atopic eye disease, eosinophilic oesophagitis, other (possibility to select multiple options)	Y if first-degree relative (parents or children) According to the patient or physician-diagnosed

(continued)

Table 4. Core dataset of domains and measurement instruments continued

Domains	Domain items	How to measure	Comments
Allergic comorbidities	Asthma	1. Physician diagnosed Y/N	
	Allergic rhinoconjunctivitis	1. Physician diagnosed Y/N	
	Atopic eye disease	1. Physician diagnosed Y/N	
	Eosinophilic oesophagitis	1. Physician diagnosed Y/N	
	Food allergies	1. Do you have a food allergy currently? Y/N 2. If yes, is at least one food allergy diagnosed by a doctor? Y/N 3. If yes, how was this diagnosis made? Double-blind placebo-controlled oral food challenge, open food challenge, skin prick tests, scratch tests, positive food allergen-specific IgE test, other (e.g. atopy patch test), unknown	
	Contact allergies	1. Have you ever been tested for contact allergies with patch tests? Y/N, unknown 2. If yes, what was the outcome? Positive, negative, unknown	
Other past and current comorbidities	Malignancies	1. Y/N 2. When (year) 3. Type of malignancy (free text) 4. Active, remission, relapsed	MedDRA categories will be used for this item as much as possible
	Serious infections	1. Y/N 2. When (year) 3. Type of infection (free text) 4. Active, latent, resolved (cured)	MedDRA categories will be used for this item as much as possible Includes 'medical history' (tuberculosis, HIV, hepatitis B or C); original item of domain baseline assessments
	Other significant illnesses	1. Y/N 2. When (year) 3. Type of illness (free text) 4. Active, remission, resolved (cured), relapsed	MedDRA categories will be used for this item as much as possible
Current concomitant medication (i.e. other than specific AE medication)	Antihistamines	1. Y/N 2. Oral, topical	
	Antibiotics	1. Y/N 2. Oral, topical	
	Other medication relevant for AE treatment response	1. Y/N 2. Which (free text)	Includes 'immunotherapy' Relevant according to judgement of treating physician
	Immunosuppressives for other inflammatory diseases	1. Y/N 2. Which (free text) 3. Indication: inflammatory bowel disease, rheumatoid arthritis, other—please specify 4. Start date, stop date 5. Current dose (free text)	
Baseline general AE questions	Exposures that trigger disease flares	1. Y/N 2. Stress, infection, weather conditions, sweating/exercise, exposure to aero-allergens, other (possibility to select multiple options)	
	Episodes of skin infection	1. Y/N 2. Bacterial skin infection (folliculitis, impetigo, etc.), viral skin infection (HSV infection, molluscum contagiosum, etc.) (possibility to select multiple options)	

(continued)

Table 4. Core dataset of domains and measurement instruments continued

Domains	Domain items	How to measure	Comments
	Days lost from usual activities (e.g. work, study)	1. Y/N 2. Days per month (free text)	Average number of days in the past 3 months
Baseline physical examination	Fitzpatrick skin type	1. I, II, III, IV, V, VI	
	Skin examination	1. Flexural eczema: select involved areas (individual patches have to be ≥ 1 cm): skin folds around the eye(s), neck (front), flexures of the arm(s), flexures of the leg(s), front of ankle(s), not applicable 2. Non-flexural eczema: select involved areas (individual patches have to be ≥ 2 cm and, excluding the face, on both sides): face, extensor of elbows, arms, extensor of knees, legs, hands, not applicable 3. Presence of (Y/N): (history of) pompholyx, discoid eczema, nodular prurigo, follicular eczema, ichthyosis, keratosis pilaris, palmar hyperlinearity, erythroderma, skin infection (if Y: bacterial/viral/fungal, sample taken Y/N)	For definitions on these phenotypical and morphological characteristics see Figure S3 (see Supporting Information)
Baseline physician- and patient-reported domains	Physician-assessed clinical signs	1. EASI 2. SCORAD (optional)	Objective or full SCORAD. If the full SCORAD is used, the objective and subjective SCORAD need to be reported separately
	Investigator/physician global assessment	1. vIGA-AD™ scale (five-point)	
	Patient-reported symptoms	1. POEM 2. Peak pruritus NRS (0–10) past 24 h 3. Peak VAS pain (0–10) past 24 h (optional)	
	Patient global assessment	1. Patient Global Assessment five-point	
	Generic quality of life score	1. EQ-5D (version 5L and Y)	Adults EQ-5D-5L; children EQ-5D-Y; caregivers (proxies) EQ-5D-Y and EQ-5D-5L Awaiting the index score for the EQ-5D-Y
	Skin-specific quality of life score	1. DLQI, CDLQI, IDQoL	DLQI > 16 years; CDLQI 4–16 years; IDQoL < 4 years
	Patient-reported satisfaction with AE care received	1. How satisfied are you with the care received for your AE since the last visit? (five-point Likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (five-point Likert scale)	The wording may change in the future if a validated measurement tool becomes available Satisfaction with care is broad and includes for instance satisfaction with treatment, physician and the hospital
	Impact of AE on the family	1. FDLQI	Needs to be filled out within the visit window (according to the patients visit) by adult family members or the partner of the patient Preferably the FDLQI is answered by the same person every time
Baseline investigations	Full blood count	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Normal/abnormal according to local standards
	Liver function	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Normal/abnormal according to local standards

(continued)

Table 4. Core dataset of domains and measurement instruments continued

Domains	Domain items	How to measure	Comments
	Kidney profile	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Normal/abnormal according to local standards
	Evaluating TPMT level before azathioprine use	1. Y/N, not applicable 2. Low or absent, intermediate, normal or high	
Baseline management	Main reasons for choosing specific treatment (systemic or phototherapy)	1. Existent comorbidities and/or results of baseline investigations including abnormal laboratory results, patient age, anticipation of pregnancy and other family planning issues for both males and females, history of prior systemic therapies (incl. response), drug safety and side-effect profile, therapeutic profile: a. speed of onset, b. magnitude of effect, c. better long-term control after drug is stopped, accessibility of the treatment (including licensing), patient preferences, other (possibility to select 3 options)	
	Relative contraindication (s) for selected treatment	1. Y/N 2. Which (free text)	
Follow-up general AE questions	Days lost from usual activities	1. Y/N 2. Days per month (free text)	Average number of days since the last visit
	Change in diagnosis after enrolment	1. Y/N 2. CTCL, other	
	Date of death and relation to AE	1. Date, not applicable 2. Not related, doubtful, possible, probable, very likely, definite	
Follow-up physical examination	Skin examination	1. Flexural eczema: select involved areas (individual patches have to be ≥ 1 cm): skin folds around the eye(s), neck (front), flexures of the arm(s), flexures of the leg(s), front of ankle(s), not applicable 2. Non-flexural eczema: select involved areas (individual patches have to be ≥ 2 cm and, excluding the face, on both sides): face, extensor of elbows, arms, extensor of knees, legs, hands, not applicable 3. Presence of (Y/N): (history of) pompholyx, discoid eczema, nodular prurigo, follicular eczema, ichthyosis, keratosis pilaris, palmar hyperlinearity, erythroderma, skin infection (if Y: bacterial/viral/fungal, sample taken Y/N)	Same comment(s) as for baseline item
Follow-up physician- and patient-reported domains	Physician-assessed clinical signs	1. EASI 2. SCORAD (optional)	Same comment(s) as for baseline item
	Investigator/physician global assessment	1. vIGA-AD™ scale (five-point)	
	Patient-reported symptoms	1. POEM 2. Peak pruritus NRS scale (0–10) past 24 h 3. Peak VAS pain (0–10) past 24 h (optional)	
	Patient global assessment	1. Patient Global Assessment five-point	
	Generic quality of life score	1. EQ-5D (version 5L and Y)	Same comment(s) as for baseline item
	Skin-specific quality of life score	1. DLQI, CDLQI, IDQoL	Same comment(s) as for baseline item

(continued)

Table 4. Core dataset of domains and measurement instruments continued

Domains	Domain items	How to measure	Comments
	Reporting of disease control	–	HOME results showed that for now this should be registered by repeated measurements of clinical signs, symptoms, quality of life and a patient global instrument (a specific instrument is not yet defined by HOME)
	Adherence to treatment between appointments	1. MARS (optional)	To be adjusted for AE, until then optional
	Patient-reported satisfaction with AE care received	1. How satisfied are you with the care received for your AE since the last visit? (five-point Likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (five-point Likert scale) 3. PsoSaT (optional)	PsoSat to be adjusted for AE Further comment(s) same as for baseline item
	Impact of AE on the family	1. FDLQI	Same comment(s) as for baseline item
Follow-up investigations	Full blood count	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Previously captured as 'safety bloods' Further comment(s) same as for baseline item
	Liver function	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Previously captured as 'safety bloods' Further comment(s) same as for baseline item
	Kidney profile	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Previously captured as 'safety bloods' Further comment(s) same as for baseline item
Follow-up adverse events	Severe adverse events	1. Y/N 2. Diagnosis (free text) 3. In case of a serious adverse event: death, life-threatening, hospitalization or prolonged hospitalization of existing hospitalization, persistent or significant disability, congenital anomaly, important medical event that requires medical intervention, not applicable (possibility to select multiple options) 4. Relatedness: not related, doubtful, possible, probable, very likely, definite 5. Action: Stop, switch of therapy, change in dosage, not applicable	MedDRA categories will be used for this item as much as possible Severe according to judgement of treating physician
Follow-up management	Reason for switching therapy	1. Efficacy, inefficacy, adverse event(s), interaction with other medication, child wish, patient request, other, not applicable (possibility to select multiple options)	
	Reason for discontinuation of therapy	1. Efficacy, inefficacy, adverse event(s), interaction with other medication, child wish, patient request, other, not applicable (possibility to select multiple options)	

AAD, American Academy of Dermatology; AE, atopic eczema; BB-UVB, broadband ultraviolet B; CDLQI, Children's Dermatology Life Quality Index; CTCL, cutaneous T cell lymphoma; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol five-Dimensional; FDLQI, Family Dermatology Life Quality Index; HSV, herpes simplex virus; HOME, Harmonising Outcome Measures for Eczema; IDQoL, Infant's Dermatitis Quality of Life Index; ISCED, International Standard Classification of Education; JDA, Japanese Dermatological Association; MARS, Medication Adherence Report Scale; MedDRA, Medical Dictionary for Regulatory Activities; N, no; NB-UVB, narrowband ultraviolet B; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure; PsoSat, Psoriasis Satisfaction questionnaire; PUVA, psoralen and ultraviolet A; QoLIAD, Quality of Life Index for Atopic Dermatitis; SCORAD, SCORing Atopic Dermatitis; TPMT, thiopurine methyltransferase; UVA, ultraviolet A; UVAB, ultraviolet A plus ultraviolet B; UVB, ultraviolet B; VAS, visual analogue scale; vIGA-AD, Validated Investigator Global Assessment scale for Atopic Dermatitis; Y, yes.

Table 4. Core dataset of domains and measurement instruments. Core dataset of domains, domain items and measurement instruments to be captured in national atopic eczema treatment registries Consensus on measurement of core dataset for AE treatment research registries, Table from (F.M. Vermeulen et al. 2019)

The clinical significances of this table show that the qualitative data, categorically standardized, allows worldwide access to a more in-depth understanding of the long-term effectiveness and safety of phototherapy and systemic therapy to accommodate future treatment (F.M. Vermeulen et al., 2019).

BEYOND THE SKIN: PSYCHOSOCIAL IMPACT OF ATOPIC DERMATITIS

Though AD contains much research regarding its treatment possibilities, pathogenesis, systemic involvement, and diverse impact on different races, one integral aspect that can be overlooked is the psychosocial impact of the disease. The chronic and widespread ability of AD can highly affect the emotional and mental well-being of many patients. The final section of this thesis will aim to analyze these psychosocial dimensions as well as the coping mechanisms that AD patients can employ for daily living.

Psychological and Emotional Impact

Several studies can link mental health diseases such as depression and anxiety to patients suffering from AD. This makes sense, as the emotional toll can seem cumbersome. Constant itching leads to pauses in everyday activity. Furthermore, perceived social stigmatization can aggravate the disease itself with scabs, tearing, and bleeding- but can also cause profound fatigue and irritability. The visibility of Eczema can make individuals more prone to mental health issues. The study by Yochai Schonmann et al., 2020 used data from the UK Clinical Practice Research Datalink to handpick over 1 million individuals with AD into three categories based on their eczema severity: mild, moderate, and severe. Each patient was then placed into a group with five other individuals without Eczema. This extensive and intricate database allowed clinicians to exclude further people who may have preexisting psychiatric diagnoses from the various cohorts. **Figure 7** expounds on the collection with a diagram of how the database categorizes individuals. The study focused on anxiety and depression separately. Altogether, the study sought to provide insight into whether AD increases the risk of new-onset depression or anxiety and whether the risk varies with the severity of the disease.

The findings of this study revealed that AD was associated with a 14% increased risk of depression and a 17% increased risk of anxiety. Results of the study also establish that patients with AD, regardless of severity, were more likely to develop depression and anxiety; the results are significant as they open yet another angle that clinicians can use to help patients manage their symptoms more efficiently.

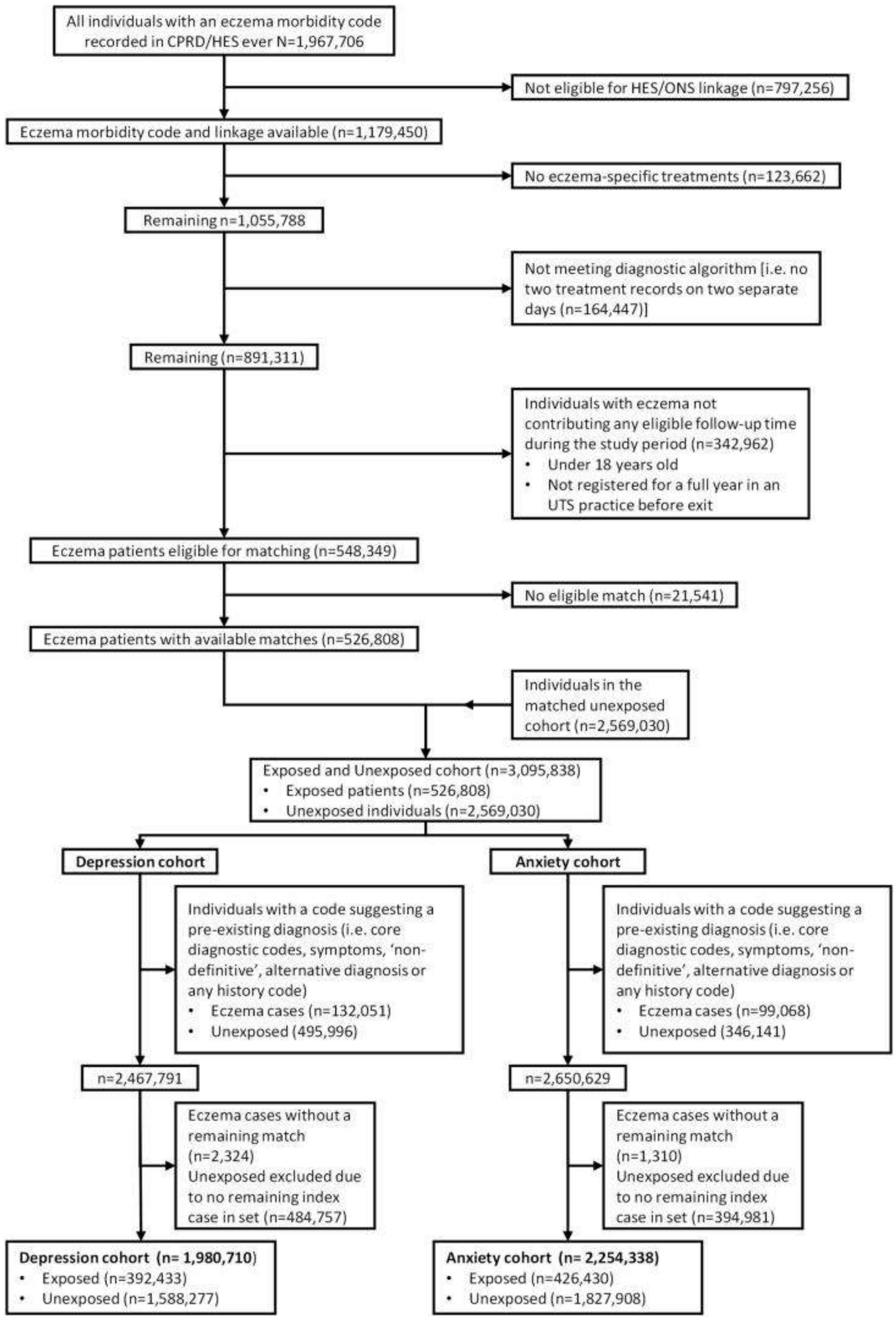


Figure 7: Flow diagram of group separation. This flow chart shows the creation of the cohort and reasons for exclusion (1998-2016). ONS, Office for National Statistics; UTS, up-to-standard. Figure from (Schonmann, Y et al., 2020)

Coping Mechanisms and Support Systems

In handling the psychosocial dimmension patients will look to coping mechanisms such as Cognitive behavioral therapy (CBT) and support groups. Studies have established that CBT is effective in ameliorating psychological stressors associated with AD (Revankar, R et al., 2022). Engaging in counseling and gathering with other patients to hear different perspectives from those who can identify with the disease via support groups is a credible means of managing the condition. Interacting in these groups is a valuable resouce because of the comunal understanding. Furthermore, stress management techniques have also been shown to mitigate unsettling emotions and enhance one's general well-being (Revankar, R et al., 2022).

Social and Occupational Challenges

AD can markedly impact workplace performance and impede career advancement by diminishing overall productivity. The need for regular medical consultations and the possibility of severe flare-ups may stunt career growth because afflicted individuals may avoid roles involving exposure to large crowds, public speaking, and irritants that irritate their condition. Implementing health screenings for AD individuals is of paramount importance as it enables early detection of various mental health disorders, which can speed up the process of ameliorating their symptoms and mental health issues. Fostering greater awareness of atopic dermatitis and mental health is essential for delivering significant improvements in the care of patients with this condition. AD can markedly impact workplace performance and interfere with career advancement by reducing productivity.

CONCLUSIONS AND FUTURE DIRECTIONS

The profound impact of Atopic dermatitis on individuals of diverse backgrounds underscores the pressing need for comprehensive research and collaborative efforts to pursue effective treatments. The primary goal of treatment should be to reduce inflammation, alleviate itching, and repair the skin barrier. Collaborative efforts between researchers and healthcare providers are needed to close the gap and improve outcomes for all patients with AD.

AD is multifaceted and requires a holistic approach to management. Advances in understanding the pathogenesis of the disease are essential because they have led to many treatment options, but there are other aspects, such as the mental health impact, environmental triggers, and equitable care, that lack studies. As someone who has witnessed others grapple with the persistent symptoms of pruritus, I understand it is imperative to acknowledge the uncharted territories surrounding the disease. The journey towards better management of atopic dermatitis is ongoing, and I am confident that continued research and innovation will lead to more effective treatments and yield innovative therapies that ultimately bring hope and healing.

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CURRICULUM VITAE

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