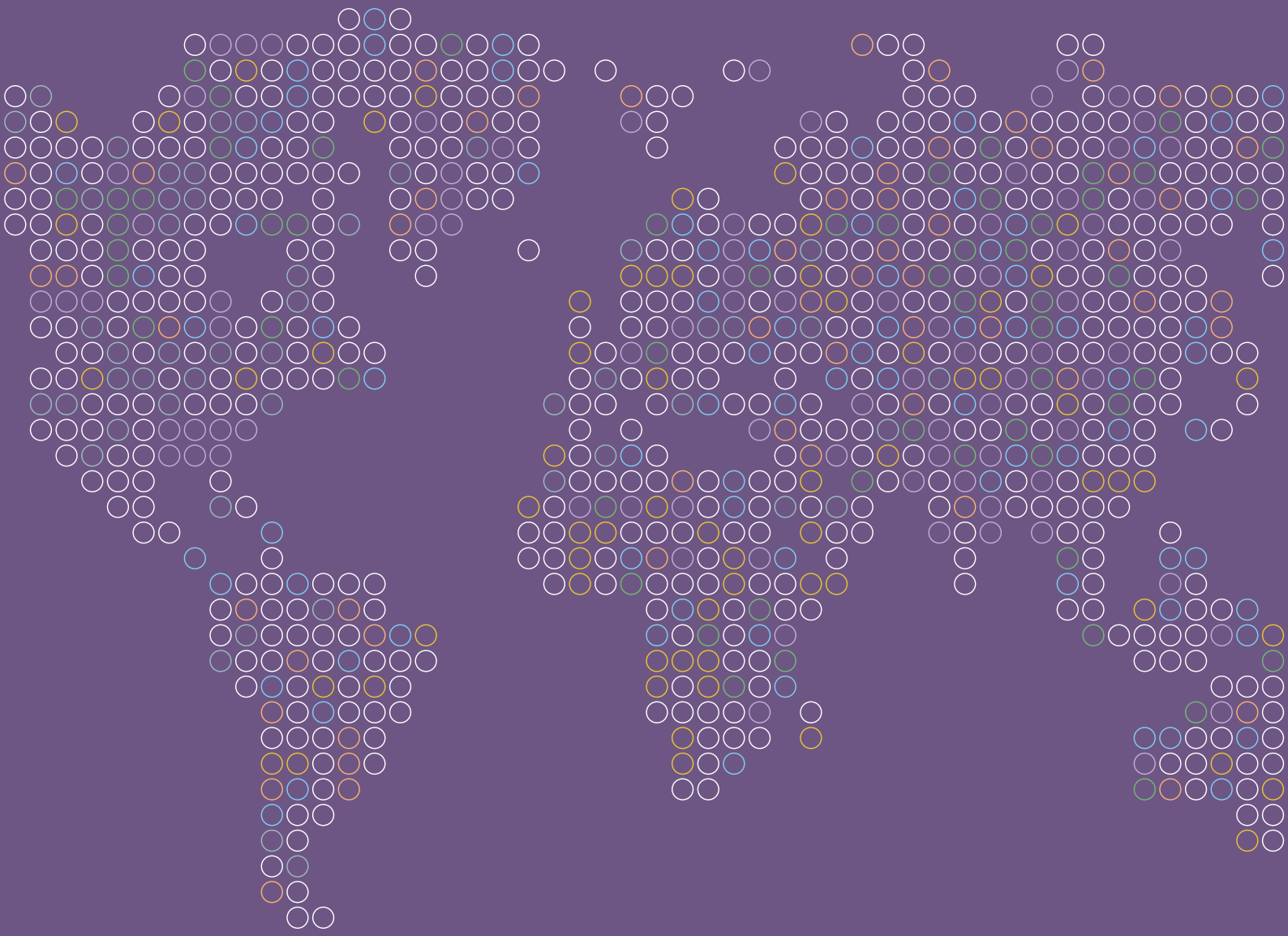
GLOBAL ATOPIC DERMATITIS ATLAS

Global Report on Atopic Dermatitis 2022



atopicdermatitisatlas.org

GLOBAL ATOPIC DERMATITIS ATLAS

Global Atopic Dermatitis Atlas
2022 Report

International League of Dermatological Societies
Willan House
4 Fitzroy Square
London W1T 5HQ
United Kingdom
Phone: +44 (0)20 7388 6515
Email: info@ilds.org

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the International League of Dermatological Societies concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. The geographical data and subsequent graphs/illustrations are based on the data of the Global Burden of Disease project (GBD), published by the Institute for Health Metrics and Evaluation (IHME), Population Health Building, Seattle, USA.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the International League of Dermatological Societies in preference to others of a similar nature that are not mentioned. The products mentioned are based on the World Health Organization (WHO) Model List of Essential Medicines - 22nd List (2021), the most current atopic dermatitis clinical practice guidelines, published peer-reviewed scientific papers on atopic dermatitis and the development of atopic dermatitis treatments, public information available from international trial registries (clinicaltrials.gov), or testimonials from patients, for none of which the International League of Dermatological Societies can take any responsibility.

All reasonable precautions have been taken by the International League of Dermatological Societies, such as external review, to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the International League of Dermatological Societies be liable for damages arising from its use.

Funding: This report was funded by the International League of Dermatological Societies.

Design and layout: David Webb

Contents

Foreword

Atopic dermatitis is a highly prevalent, non-communicable, chronic skin disease and ranks 15th among all non-fatal diseases with regard to disability-adjusted life years, and first among all skin diseases (based on Global Burden of Disease (GBD) estimates), with the main burden in children.

In numbers, about 223 million people are living with atopic dermatitis in 2022 (GBD 2022), of which around 43 million are aged 1-4. This illustrates the strikingly high prevalence in young children. In addition to the disease burden for the child and their caregivers, atopic dermatitis can also negatively affect the development of the child, education, and work. Atopic dermatitis is also often the precursor of food allergies, allergic rhinitis and asthma. Many adult and adolescent patients with atopic dermatitis suffer of psychological co-morbidities, such as social withdrawal, anxiety and depression. Furthermore, atopic dermatitis can lead to work impairment and financial burden.

The underlying pathophysiology of atopic dermatitis has been subject to a lot of research, suggesting a complex interplay between genetic, immunological, skin barrier, and environmental factors. Considerable progress has also been made in treating severe forms of atopic dermatitis.

Meanwhile, there is lack of data on how many people have atopic dermatitis, its severity, in which geographical locations, under which environmental circumstances, what their treatment needs are, and how it is treated. This knowledge is essential to combine with fundamental findings on the pathogenesis of atopic dermatitis, to improve health care and develop novel treatments and methods of disease prevention.

The International League of Dermatological Societies (ILDS) therefore initiated the Global Atopic Dermatitis Atlas (GADA) project, a collaboration between the ILDS, the International Society of Atopic Dermatitis (ISAD), the International Eczema Council (IEC), the European Taskforce for Atopic Dermatitis (ETFAD) and the International Alliance of Dermatology Patient Organizations (GlobalSkin).

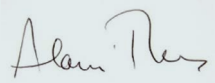
GADA intends to fill the current gaps in epidemiological data in three phases: (1) a systematic review of current epidemiological data; (2) reaching international consensus to standardize and improve epidemiological studies; and (3) developing research tools for fieldwork. We plan to conduct and equip epidemiological surveys with newly developed, standardized methodology, particularly focusing on geographical areas which lack data.

This global report on atopic dermatitis signals the start and remit of the GADA project. The report summarizes all known aspects of atopic dermatitis and presents the disparities regarding the burden of disease and care, resulting in unmet needs. Despite a common perception that atopic dermatitis would be mainly a 'Western' and industrialized country disease, this is not the case as shown in this global report. Recent treatment innovations have not solved existing inequalities, due to lack of access and affordability. These disparities need to be urgently addressed with universally accessible healthcare systems to provide personalized and targeted care for patients with atopic dermatitis who may depend on care across the lifespan. Governments and other stakeholders have a key role to play in addressing these pressing issues of access and affordability of current and future treatments.

> ***If you care, make it so that people can get the care they need. Do something right now. You have the power to change our lives.***

Quoting the people living with atopic dermatitis that are featured in this report: "If you care, make it so that people can get the care they need. Do something right now. You have the power to change our lives." The ILDS are working with GADA to represent of over 200,000 dermatologists and are engaged in the effort to improve patient outcomes for people with atopic dermatitis.

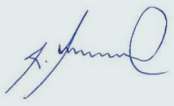
Carsten Flohr
Director
Global Atopic Dermatitis Atlas



Alain Taieb
President
International Society of Atopic Dermatitis

Prof Lars French
President
International League of Dermatological Societies

Mette Deleuran
Chair
European Taskforce for Atopic Dermatitis



Robert Bissonnette
President
International Eczema Council

Jennifer Austin
Chief Executive Officer
International Alliance of Dermatology Patient Organizations (GlobalSkin)

Acknowledgements

The realization of this report was supervised by Carsten Flohr, St. John's Institute of Dermatology, King's College London and Guy's & St Thomas' Hospitals, United Kingdom.

The report was prepared by Bernd Arents, Dutch Association for People with Atopic Dermatitis, The Netherlands; Esther van Zuuren, Dermatology Department, Leiden University Medical Center, The Netherlands; Zbys Fedorowicz, Veritas Health Sciences Consultancy, United Kingdom; and Olivia Hughes, School of Psychology, Cardiff University, United Kingdom.

The following people provided helpful comments and their expert critical review: Katrina Abuabara, Valeria Aoki, Jennifer Austin, Sebastian Barbarot, Robert Bissonnette, Mette Deleuran, Sandipan Dhar, Lars French, Christopher Griffiths, Alan Irvine, Kenji Kabashima, Peter Schmid-Grendelmeier, Tammi Shipowick, Alain Taieb, Jacob Thyssen, Gail Todd, and Andreas Wollenberg. They contributed in the capacity of their institutional affiliations, and by being represented through:

- The International League of Dermatological Societies (ILDS)
- The International Society of Atopic Dermatitis (ISAD)
- The International Eczema Council (IEC)
- The European Task Force on Atopic Dermatitis (ETFAD)
- The Global Psoriasis Atlas (GPA)
- The International Alliance of Dermatology Patient Organizations (GlobalSkin)

The authors of this report want to thank the Global Burden of Disease team at the Institute of Health Metrics and Evaluation (IHME), University of Washington, Seattle (USA) for allowing us to include some of their unpublished data on the global burden of atopic dermatitis and for drawing up maps for this report: Mohsen Naghavi, Authia Gray and Eve Wool. We are also grateful to the patients from around the world who kindly provided their very personal and heartfelt testimonials on living with atopic dermatitis, coordinated by GlobalSkin. Likewise, we sincerely thank all adults and carers of children with atopic dermatitis for giving their consent to use their images in this report.

GADA is truly a joint effort, meant for the benefit of patients, their carers and families, healthcare providers, and society at large.

Acronyms and abbreviations

CDLQI
The Children's Dermatology Life Quality Index

DALY
Disability-Adjusted Life Year

DFI
Dermatitis Family Impact

DLQI
The Dermatology Life Quality Index

EASI
The Eczema Area and Severity Index

EFA
The European Federation of Allergy and Airways Diseases Patients' Associations

EHR
Electronic Health Records

EMA
European Medicines Agency

EQ-5D
EuroQoL-5D

ETFAD
The European Task Force on Atopic Dermatitis

EU
European Union

FDA
Food and Drug Administration

FDLQI
The Family Dermatology Life Quality Index

FLG
Filaggrin

GADA
Global Atopic Dermatitis Atlas

GBD
Global Burden of Disease

GDP
Gross Domestic Product

GP
General Practitioner

GPA
The Global Psoriasis Atlas

HSV1
Herpes simplex virus 1

HOME
The Harmonising Outcome Measures for Eczema initiative

HRQoL
Health related quality of life

HTA
Health Technology Assessments

IADPO
The International Alliance of Dermatology Patient Organizations (GlobalSkin)

IDQOL
Infants' Dermatitis Quality of Life Index

IEC
The International Eczema Council

IGA
Investigator Global Assessment

IgE
Immunoglobulin E (type of antibody)

IHME
The Institute for Health Metrics and Evaluation

IL
Interleukin

ILDS
The International League of Dermatological Societies

ISAD
The International Society of Atopic Dermatitis

JAK
Janus kinase

NRS
The Numeric Rating Scale

NTD
Neglected tropical diseases

OECD
The Organization for Economic Co-operation and Development

PDE
Phosphodiesterase

POEM
The Patient-Oriented Eczema Measure

PO-SCORAD
The Patient Oriented Scoring Atopic Dermatitis scale

PROM
Patient-reported outcome measure

QoL
Quality of life

QoLIAD
Quality of Life Index for Atopic Dermatitis

SAWP
The Scientific Advise Working Party

SCORAD
The Scoring Atopic Dermatitis scale

SF-36
Short-Form 36

SSA
Sub Saharan Africa

TCI
Topical calcineurin inhibitors

TCS
Topical corticosteroids

UK
The United Kingdom

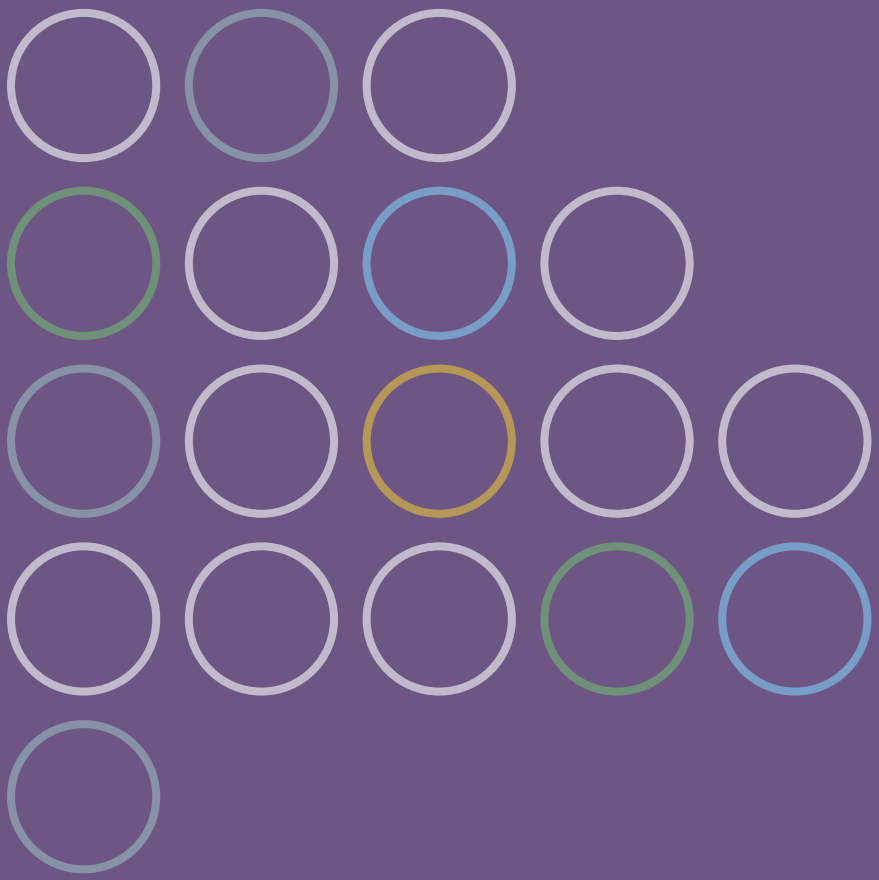
USA
The United States of America

UV
Ultraviolet light

WAO
World Allergy Organization

WHO
World Health Organization

Chapter 1.
Introduction



What is atopic dermatitis?

Atopic dermatitis is a common chronic, non-communicable skin disease characterized by dry skin, localized red scaly patches and intense itching as well as skin pain (1-3). Atopic dermatitis is also known as 'atopic eczema', 'neurodermatitis', or just simply as 'eczema' (1, 3).

Although the precise etiology has not been fully elucidated, there are many factors and triggers which may play a role. These include interactions between genetic and environmental factors, skin barrier disruption, microbiome alterations, and immune dysregulation (1, 2, 4, 5).

The prevalence of atopic dermatitis is high, affecting up to 20% of children and up to 10% of adults. The burden of disease ranks 15th worldwide for non-fatal diseases, and number one for skin diseases, measured in disability-adjusted life-years (DALYs) (1, 6, 7). Therefore, in 2022, atopic dermatitis is considered a common and burdensome skin disease with a complex pathogenesis. The associated burden of disease can have a significant impact on a person's physical well-being and quality of life.

The intensity of itch experienced can result in repeated scratching of the skin to relieve itch, often leading to more skin damage, and more itch (known as the itch-scratch-itch cycle; see Figure 1.1) (1, 2).

The skin lesions associated with atopic dermatitis are characterized by papules, oozing vesicles on red swollen skin (although redness is more difficult to discern in darker skin and may not always be apparent), crusting, and scaling (1, 2, 8). These lesions can merge into larger areas, sometimes as a result of extensive scratching. When lesions become chronic, they may result in thickening of the skin, known as lichenification (1, 2, 8).

Figure 1.1: Itch-scratch-itch cycle

Atopic dermatitis is a highly variable skin disorder with a wide spectrum of clinical manifestations, and typically fluctuates in severity between periods of flares and remissions (2, 3, 8). For the majority of people, atopic dermatitis becomes apparent in early childhood with most patients experiencing an onset of the disease before the age of five years, but it can also develop later in adult life, or reoccur following long periods of resolution (1, 2). In fact, high rates are increasingly reported among older adults (9, 10).

Atopic dermatitis has a typical age-related distribution, and the skin lesions can vary depending on disease stage, ethnicity, as well as geographic location (1, 2, 8, 11). In infants, the face, scalp, cheeks, and extensor sides of the arms and legs are frequently involved, but the whole body may be affected in severe cases (1, 2, 8). With increasing age, skin lesions are commonly found in areas such as the folds of the knees and elbows (flexural), neck, ears, wrists, ankles, and around the eyes (1, 2, 4, 8, 11). In adolescents and adults, the hands, feet, head, and neck are frequently affected which can impair the ability to work and perform daily life activities (4, 11). The features of atopic

dermatitis can also differ between geographical regions. For example, in Africa, more thickened and bumpy skin (papular lichenoid lesions) is reported, whereas in South East Asia, oozing lesions (exudative) are more prevalent (11), which is a sign of bacterial skin infection. In India and South East Asia, lichenification, and hypo- or hyperpigmentation of the skin are also common features in patients with atopic dermatitis (12).

People with atopic dermatitis often have an impaired quality of life and experience negative effects such as sleep disturbances from itching and scratching, skin pain, psychological distress, social restrictions, time consuming treatments, and reduced productivity at school or work (1, 2, 5, 8, 13). All these aspects can have financial consequences (see Chapter 3, Socioeconomic Burden).

There is a well-established association between atopic dermatitis and other atopic morbidities. 'Atopic' refers to the Greek word 'atopos' which means 'without place', and hints at the frequent occurrence of other related atopic diseases like asthma and allergic rhinitis (allergy to pollen, animals, house dust mite) (1, 8). This association is also known as the 'Atopic Triad', and consists of asthma, atopic dermatitis, and allergic rhinitis. However, only half of people with atopic dermatitis will have an allergic constitution with elevated antibodies to environmental allergens (5, 8).

The co-occurrence of atopic dermatitis, asthma and allergic rhinitis is not fully understood, but might be partly explained by a shared genetic origin (14). The association of atopic diseases with different ages of peak prevalence is referred to as the 'atopic march'. Following this conceptual model, the 'march' starts with atopic dermatitis, followed by IgE-mediated food allergies, and the later development of asthma and allergic rhinitis. Associated allergic comorbidities can result in considerable multimorbidity at a young age. However, we now know that this concept is an over-simplification, with patients taking many different disease trajectories (2, 4).

Both allergic and irritant contact dermatitis are frequently reported in patients with atopic dermatitis (4, 15, 16). In adults an association with immune-mediated conditions and decreased bone health has been reported, as well as metabolic disorders and cardiovascular diseases, although the latter two remain controversial (17). Together with the above, it can be concluded that atopic dermatitis is typically the first sign of atopy and is a complex disease with many health-related consequences, as visualized in Figure 1.2.

Management of atopic dermatitis depends on disease severity, the extent of the body-surface affected, and if there are coexisting conditions present (1). The starting point for treatment involves a stepped-care approach, beginning with patient education around the avoidance of irritants and triggers and the correct use of topical therapies, such as emollients and topical

Figure 1.2: Atopic dermatitis and associated diseases

corticosteroids, which require guidance for appropriate use (18). In severe cases, where atopic dermatitis has not been controlled with topical therapies, adjuvant therapies may be necessary, such as phototherapy and systemic treatment, but this decision depends on the person (including age, co-morbidities, use of other medication, pregnancy, or previous treatments). Atopic dermatitis is a chronic disease, which means that for some, treatment can be lifelong. Treatment should be tailored to the patient's most bothersome signs and symptoms at that time in their life, with the aim of improving quality of life and life goals (1). See Chapter 4, 'Principles of Managing Atopic Dermatitis'.

Why a global report on atopic dermatitis?

Based on Global Burden of Disease (GBD) data, atopic dermatitis has the highest burden among all skin diseases, making it an important public health problem worldwide. Although these GBD data are helpful to demonstrate and compare disease prevalence and burden, there are gaps in epidemiological data arising from the use of different methodologies and from a lack of data for some geographical settings, in particular lower resource countries (see Figure 1.3).

These inconsistencies in data impede precise estimates that are urgently needed to increase our understanding of atopic dermatitis. For instance, there are unexplained differences between geographic locations (altitude, longitude, urbanization) which could be explained by factors such as diversity of populations, lifestyle, pollution, sun exposure, and the influence of climate change. There is also a need for a greater understanding of the diverse individual burden and associated costs, as most existing research has been conducted in countries with a higher socio-demographic index and in people with more moderate-to-severe atopic dermatitis.

To address these gaps, the International League of Dermatological Societies (ILDS)

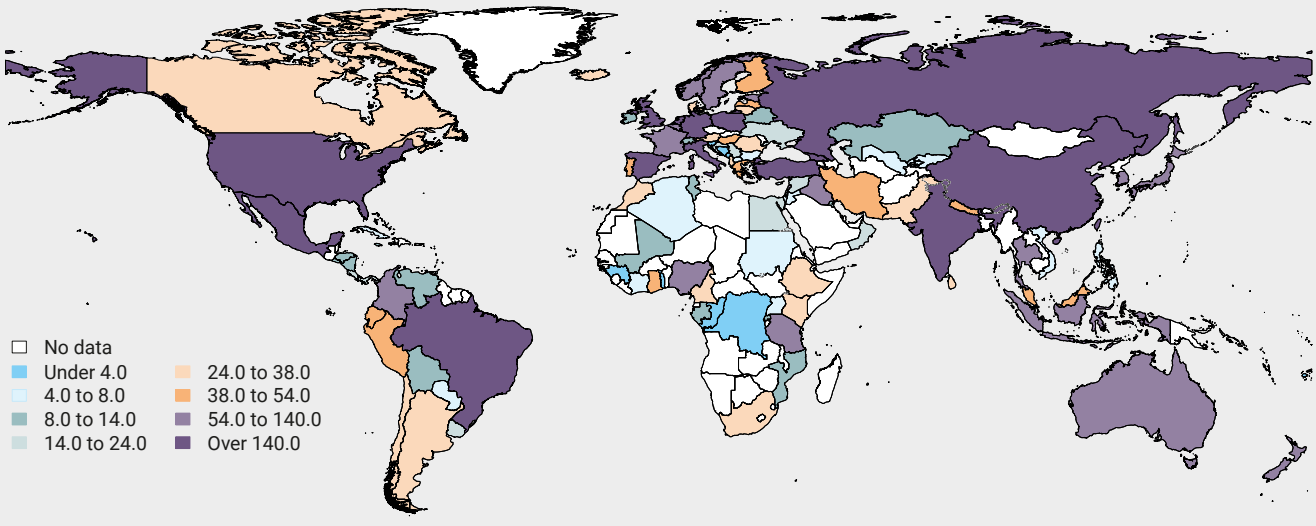


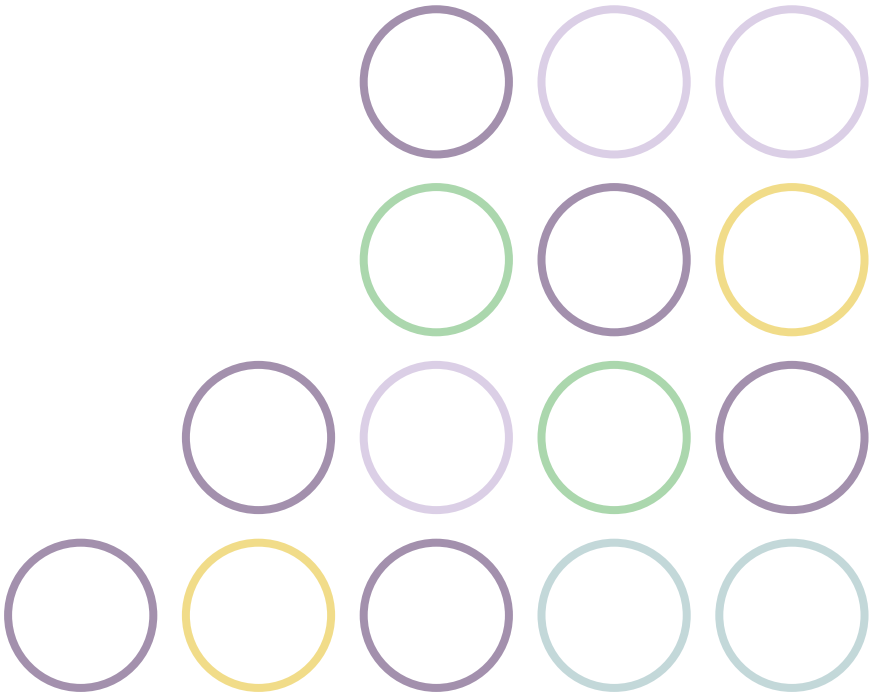
Figure 1.3: Total counts of data sources for atopic dermatitis, country-level, 1971-2017 *Source: IHME 2020 (19)*

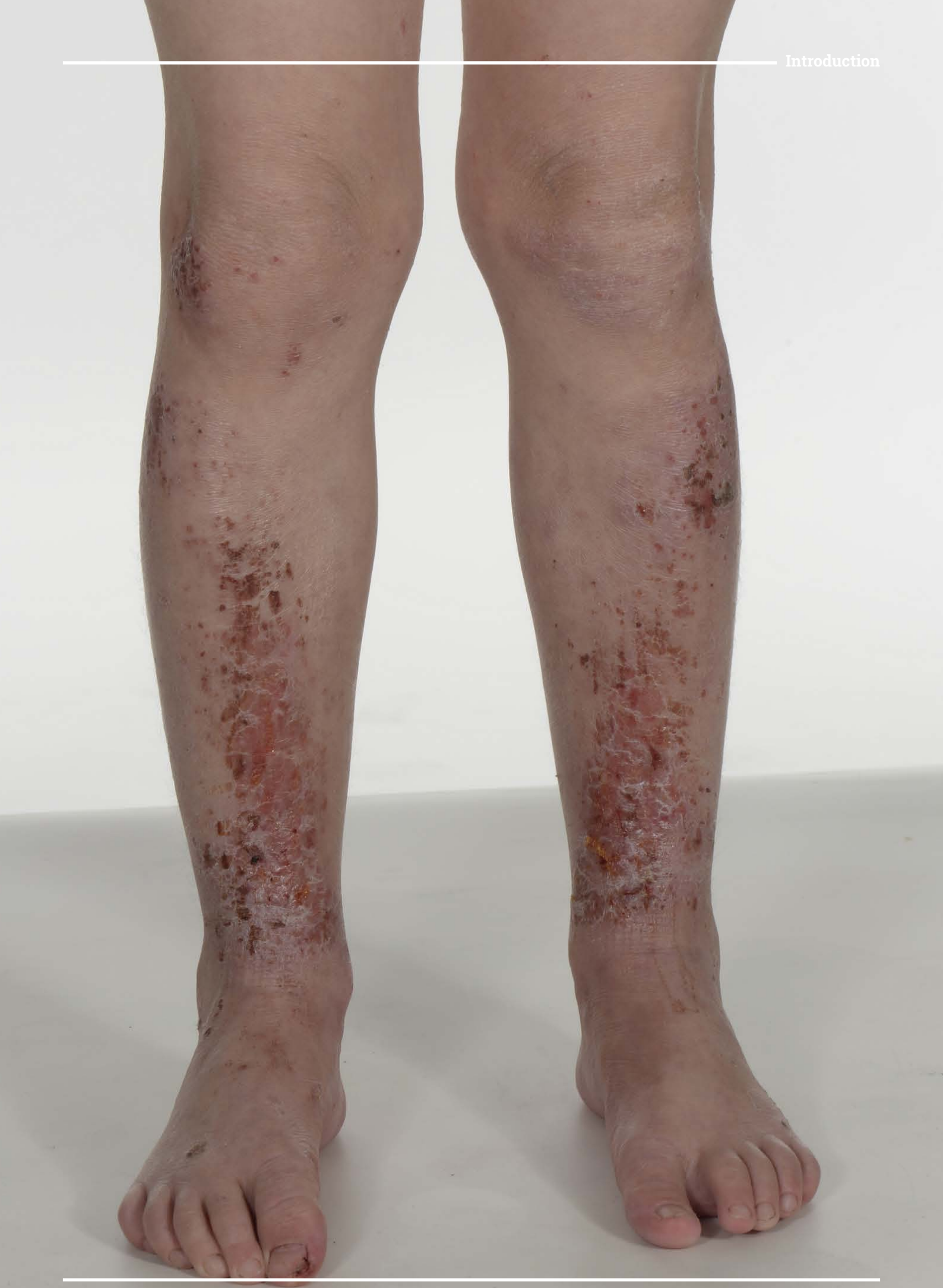
initiated the Global Atopic Dermatitis Atlas (GADA) project as a global resource, in close collaboration with the International Society for Atopic Dermatitis (ISAD), the International Eczema Council (IEC), the European Taskforce for Atopic Dermatitis (ETFAD) and the International Alliance of Dermatology Patient Organizations (GlobalSkin).

The GADA project will address the gaps in epidemiological data, develop research tools, conduct original fieldwork, and provide recommendations for governments, policymakers, health professionals, and patient organizations based on best available evidence. We plan to publish our future work in scientific papers, conferences, and on our website.

This global report on atopic dermatitis signals the start and remit of the GADA project and aims to give an overview of the current state of atopic dermatitis worldwide. This report summarizes the current evidence on atopic dermatitis with data on its impact on patients and their families, its comorbidities, its burden, and presents suggestions for how to reduce that burden. This report was launched at the ISAD Symposium in Montreal, October 17-19th 2022, and is now available on our website www.atopicdermatitisatlas.org.

The need for this report and the GADA project is clear. What is inherently different about atopic dermatitis when compared to other non-communicable diseases with high disease burden, is that it affects so many children and their carers and families. Therefore, we hope that GADA will help to serve, grow, and guide stakeholders as a global resource for dealing with atopic dermatitis, and ultimately contribute to the empowerment of patients and their carers, and benefit societies at large.





Chapter 2.
The burden of atopic dermatitis

Atopic dermatitis affects up to 20% of children and up to 10% of adults (20-25). Yet, the prevalence and disease burden of atopic dermatitis varies considerably between countries. The reasons for these variations are still poorly understood.

Prevalence and incidence

A striking aspect of atopic dermatitis is the higher prevalence in young children than in adults. Although atopic dermatitis is a chronic skin disease, some children will 'grow-out of it' at some point in their life and may no longer experience symptoms. Yet for many children, atopic dermatitis can persist into adulthood and last across the lifespan (26-29). The reasons for atopic dermatitis affecting people at different ages and the variations in onset, progression and remission are not clear, and have been subject to research (30-32). Therefore, measuring the prevalence and incidence of atopic dermatitis is complex.

Prevalence per age-group

The reported age-standardized prevalence per age-group based on the GBD data shows a bimodal curve, suggesting a high prevalence of atopic dermatitis in young children that declines towards adulthood, with an upward trend in later life.

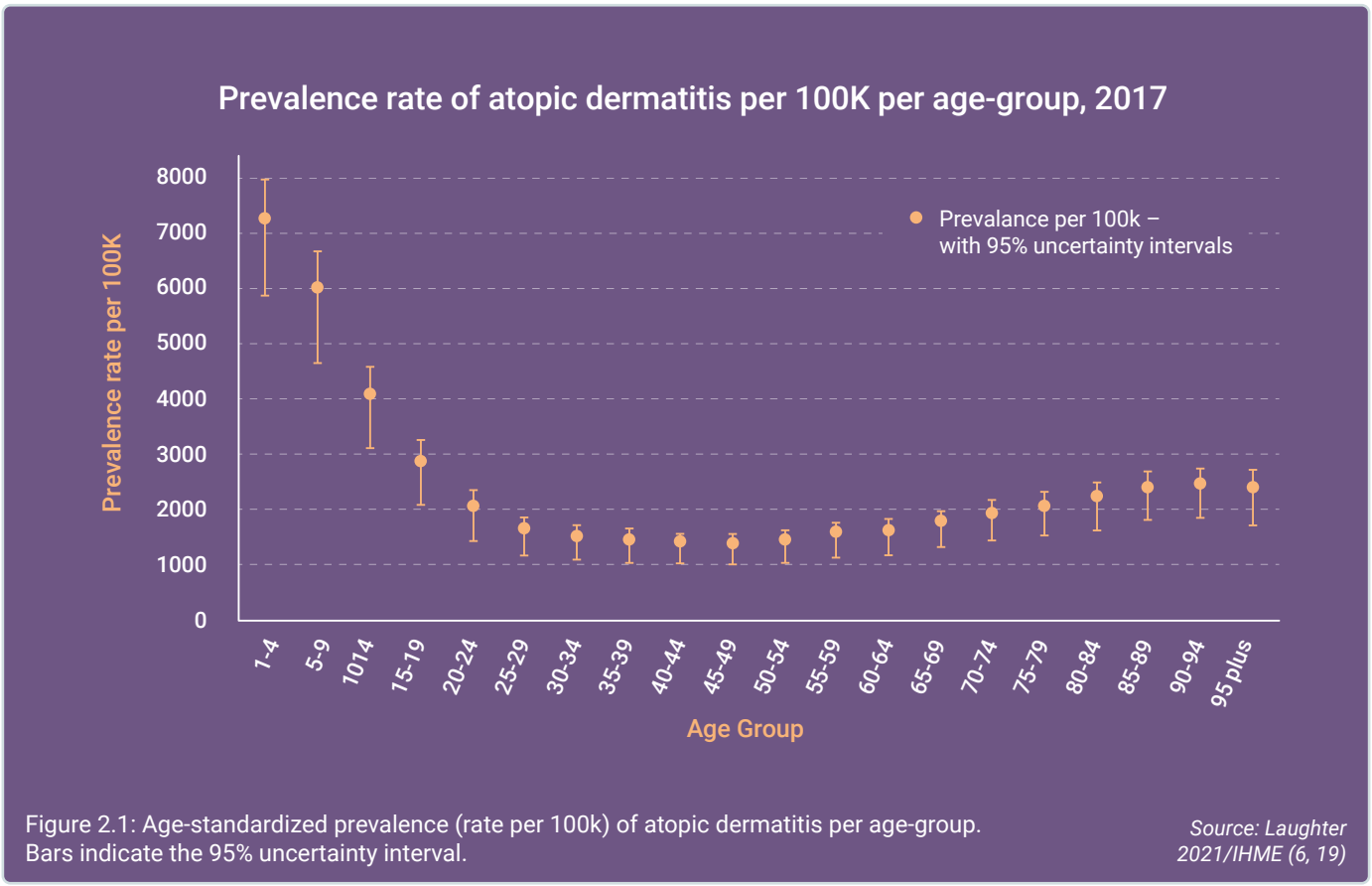


Figure 2.1: Age-standardized prevalence (rate per 100k) of atopic dermatitis per age-group. Bars indicate the 95% uncertainty interval.

Source: Laughter 2021/IHME (6, 19)

Prevalence per country

The prevalence of atopic dermatitis varies worldwide. Based on the 2017 GBD data, the five highest scoring countries are Sweden, United Kingdom, Iceland, Finland, and Denmark and the lowest five are Uzbekistan, Armenia, Tajikistan, China, and Kazakhstan (see Table 2.1)(6). The global variations are shown in Figure 2.2.

Country	Top 5 highest	Country	Top 5 lowest
Sweden	7,437.70 (7,206.63 - 7,686.35)	Kazakhstan	1,841.20 (1,697.87 - 1,992.02)
United Kingdom	6,472.34 (6,152.69 - 6,811.60)	China	1,855.53 (1,775.56 - 1,938.47)
Iceland	6,298.92 (5,945.31 - 6,667.08)	Armenia	1,936.72 (1,741.48 - 2,139.71)
Finland	6,000.77 (5,661.15 - 6,367.74)	Tajikistan	1,938.49 (1,742.37 - 2,139.20)
Denmark	5,799.08 (5,342.07 - 6,259.22)	Uzbekistan	1,939.80 (1,743.86 - 2,141.07)

Table 2.1 – Age-standardized prevalence rate per 100K (95% Uncertainty Interval) – Top 5 highest and lowest, 2017
Source: Laughter 2021/IHME (6, 19)

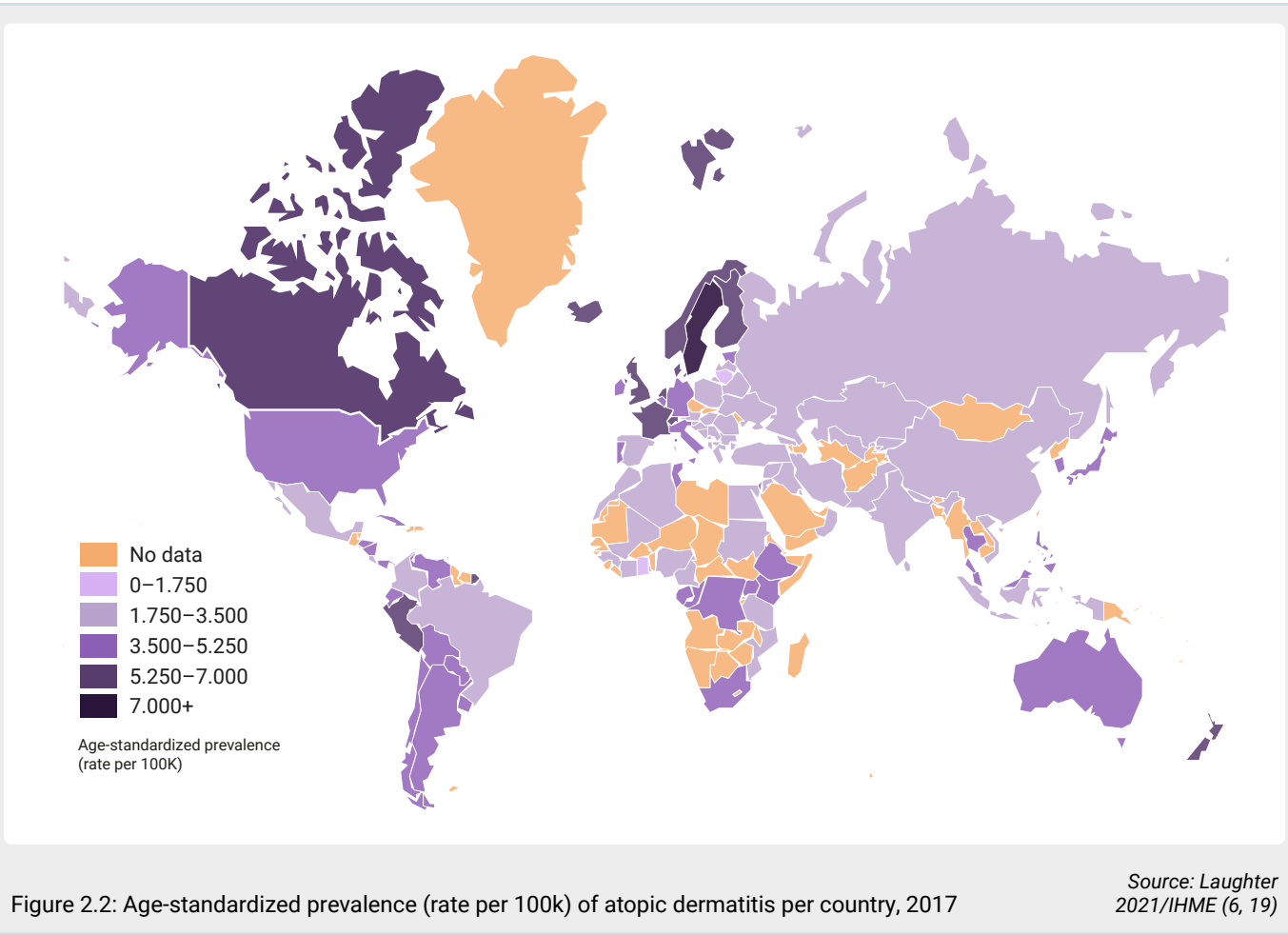


Figure 2.2: Age-standardized prevalence (rate per 100k) of atopic dermatitis per country, 2017

Source: Laughter 2021/IHME (6, 19)

Global disability burden from atopic dermatitis

The burden of atopic dermatitis, measured in disability-adjusted life-years (DALY's) is in line with the prevalence. Based on data from 2017, the five highest scoring countries are Sweden, United Kingdom, Iceland, Finland, and Denmark, and the five lowest are Uzbekistan, Armenia, Tajikistan, China, and Kazakhstan (see Table 2.2).

The DALY's per World Health Organization (WHO) region are shown in Figure 2.3. Despite a common perception that atopic dermatitis would be mainly a 'Western' and industrialized disease, this is not the case. The highest scoring region in DALY's is Andean Latin America and the fifth highest scoring region Southern Sub-Saharan Africa.

Country	Top 5 highest	Country	Top 5 lowest
Sweden	326.91 (177.70 - 547.39)	Uzbekistan	85.14 (45.23 - 144.49)
United Kingdom	284.15 (154.81 - 477.66)	Armenia	85.12 (45.83 - 142.94)
Iceland	276.98 (149.02 - 464.91)	Tajikistan	85.11 (46.06 - 143.20)
Finland	263.57 (143.55 - 442.67)	China	82.10 (44.21 - 138.01)
Denmark	254.63 (137.41 - 423.97)	Kazakhstan	80.91 (43.62 - 136.33)

Table 2.2 – DALY rate per 100K (95% Uncertainty Interval) – Top 5 highest and lowest, 2017
Source: Laughter 2021/IHME (6, 19)

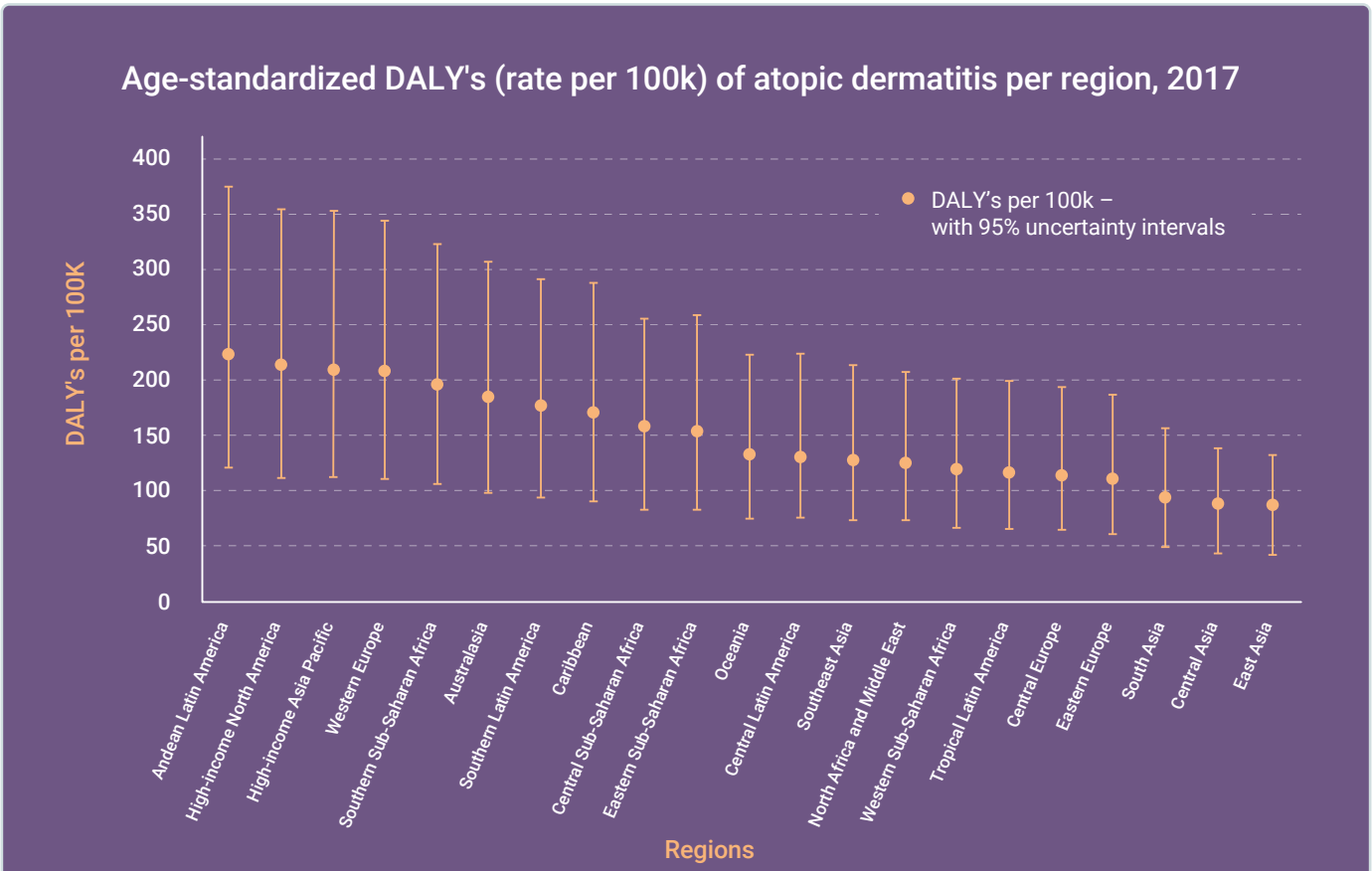


Figure 2.3: Age-standardized disability-adjusted life-year (DALY) rates for atopic dermatitis per 100K per region (in descending order of DALY rate). Bars indicate the 95% uncertainty interval.

Source: Laughter 2021/IHME (6, 19)

Prevalence and DALY's related to a country's income

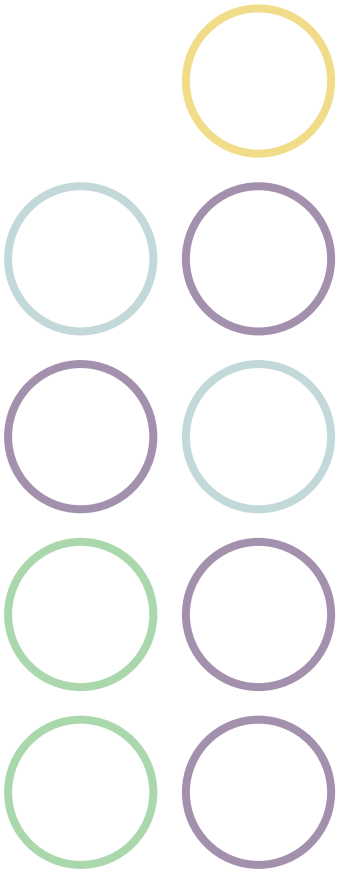
Atopic dermatitis is associated with a higher prevalence in countries with higher incomes. For 2017, it was calculated that there was a moderate positive correlation between Gross Domestic Product (GDP) and prevalence rates of atopic dermatitis (Pearson's r = 0.45)(6). Similarly, a moderate positive correlation between GDP and DALY's was found (Pearson's r = 0.46)(6).

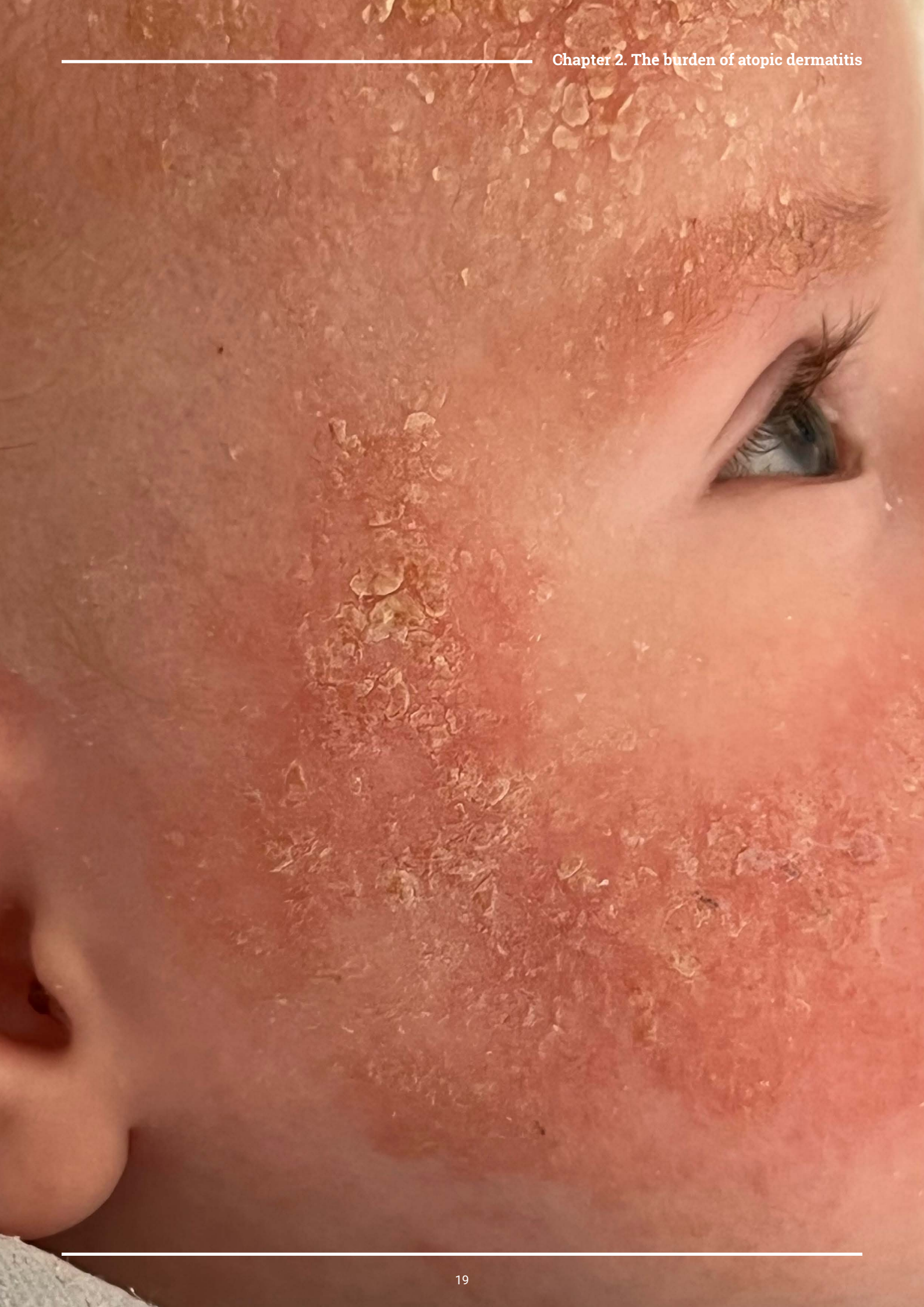
Is atopic dermatitis becoming more or less common?

This remains a complicated question. The ISAAC study assessed changes in prevalence of atopic dermatitis, asthma and rhino-conjunctivitis in children over a period of five years between 1997 and 2003 (33). The study suggested a significant (at least one Standard Error) increase in areas with previously low prevalence and plateauing in high prevalence areas, pointing to environmental drivers. Some countries (e.g., Spain) also had significant increases and decreases within the same country. Based on the GBD data from 1990-2017 there has not been an overall global increase in the prevalence and burden of atopic dermatitis in terms of rates (metrics are presented per 100,000 persons)(6). This means that relatively there has not been an increase in atopic dermatitis, but in absolute numbers there has been. This could be explained as the global population has increased from roughly 5.3 billion people in 1990, to 7.6 billion people in 2017.

Gaps in data

The methodology used by the GBD project to measure the prevalence and disease burden of atopic dermatitis is complex. Data input is based on published literature, claims databases, and national surveys, which all have unique strengths and limitations (21, 34, 35). The GBD has a method in place to combine these data into one repository. Once combined, data is further adjusted to disease severity and co-morbidities. This method is used to transform heterogeneous data into a model with metrics that reflects reality. In this model, lacking data is extrapolated and imputed based on the GBD's methodology. The number of data sources per country varies a lot, from none to over 140 (see Chapter 1, Figure 1.3). To better understand atopic dermatitis, these variations, gaps, strengths, and weaknesses in epidemiological data must be addressed.





Chapter 3.
How does atopic dermatitis affect peoples' lives?

Introduction

Atopic dermatitis is a common chronic skin disease causing significant itch, pain, disfigurement, and physical and psychological distress. There is no cure for atopic dermatitis, but it can be controlled with treatment for periods of time before it recurs.

The disease usually develops during childhood, but it can start at any age. The clinical presentation of atopic dermatitis can vary with age, season, and geographical location. Patients with atopic dermatitis often experience additional hay fever, asthma, food allergies, and other diseases such as chronic inflammatory conditions, autoimmune and cardiovascular diseases, and allergic and irritant contact dermatitis (1, 16). Patients and their families often share the burden of atopic dermatitis, and the disease can have an impact on all aspects of life. Sleep deprivation, inability to go to school or work, shame, anxiety and depression, social isolation, and extra financial costs can all have a detrimental effect on emotional, social, and economic well-being.

I live in Utah of the United States. I developed eczema when I was six years old and as I got older it progressively got worse. One of my worst days was when I woke up and my skin was really dry on my face, and it was so dry that like I couldn't even like open my mouth or like blink. And it was very painful. Eczema isn't just a rash on our skin it's not just a little itch on our back it's it affects everything.
Natalia, USA

I remember when I tried to get up in the morning. I couldn't even open my eyes. And when I tried to stretch my fingers, my fingers would bleed. And there is water oozing out as well.
Phoebe, Hong Kong SAR, China

From: Skin | Our Barrier to the World

Diagnosis

There are various diagnostic criteria for atopic dermatitis which are mainly used for research (1, 36-38). Examples include the Hanifin and Rajka criteria (39), UK Working Party criteria (40) and the Diagnostic Criteria for Atopic Dermatitis According to the American Academy of Dermatology (37). The diagnosis of the disease is made clinically and based on skin signs, distribution of the skin lesions, associated clinical findings, and whether there is a personal or family history of atopy (1, 18, 36, 37). Itch is a cardinal symptom of atopic dermatitis. Table 3.1 lists the typical features of atopic dermatitis, and Figure 3.1 demonstrates the clinical appearances.

Clinical Features	Description
Essential features[1]	
Eczema	Chronic or relapsing eczema with characteristic morphologic features and age specific patterns
Stage	Acute, subacute, or chronic
Severity	Mild, moderate, or severe
Pruritus	Itch
Important features[2]	
Early age at onset	Typically between 2 months and 6 months of age
Atopy	Personal or family history or both, IgE reactivity (elevated total or allergen-specific serum IgE or both, seen in up to 80% of patients)[†]
Xerosis	Dry to very dry skin
Associated features[3]	
Atypical vascular responses	Facial pallor or white dermographism, for example
Perifollicular lesions	Keratosis pilaris, perifollicular accentuation
Ocular or periorbital changes	Dennie-Morgan fold, Hertoghe's sign (lateral eyebrow thinning)
Other regional findings	Perioral changes, periauricular lesions, pityriasis alba, hyperlinear palms, ichthyosis
Scratching-related chronic lesions	Lichenification, prurigo lesions, scratch marks
Related conditions	
	Bacterial skin infections (impetigo, skin abscesses)
	Viral skin infections (eczema herpeticum, molluscum contagiosum)
	Fungal skin infections (dermatophytosis, candidiasis)
	Allergic disorders (asthma, rhinitis, rhinoconjunctivitis, food allergy)
	Quality-of-life impairment (sleep disturbance), anxiety, depression, suicidality
	Inflammatory bowel disease, rheumatoid arthritis, cardiovascular disease (debated)

Table 3.1. Diagnostic Criteria for Atopic Dermatitis According to the American Academy of Dermatology.[*]
There are a number of other sets of diagnostic criteria available, all rather similar.

[*] The information presented is modified from Ständer 2021 and Eichenfield et al 2014 (1, 37).
[1] Essential features are those required for the diagnosis of atopic dermatitis.
[2] Important features are those observed in most cases, adding support to the diagnosis.
[3] Associated features suggest the diagnosis but are too nonspecific to be used in defining or detecting atopic dermatitis for clinical and epidemiologic studies.
[†] Monitoring of IgE levels is not recommended for the routine assessment of disease severity.

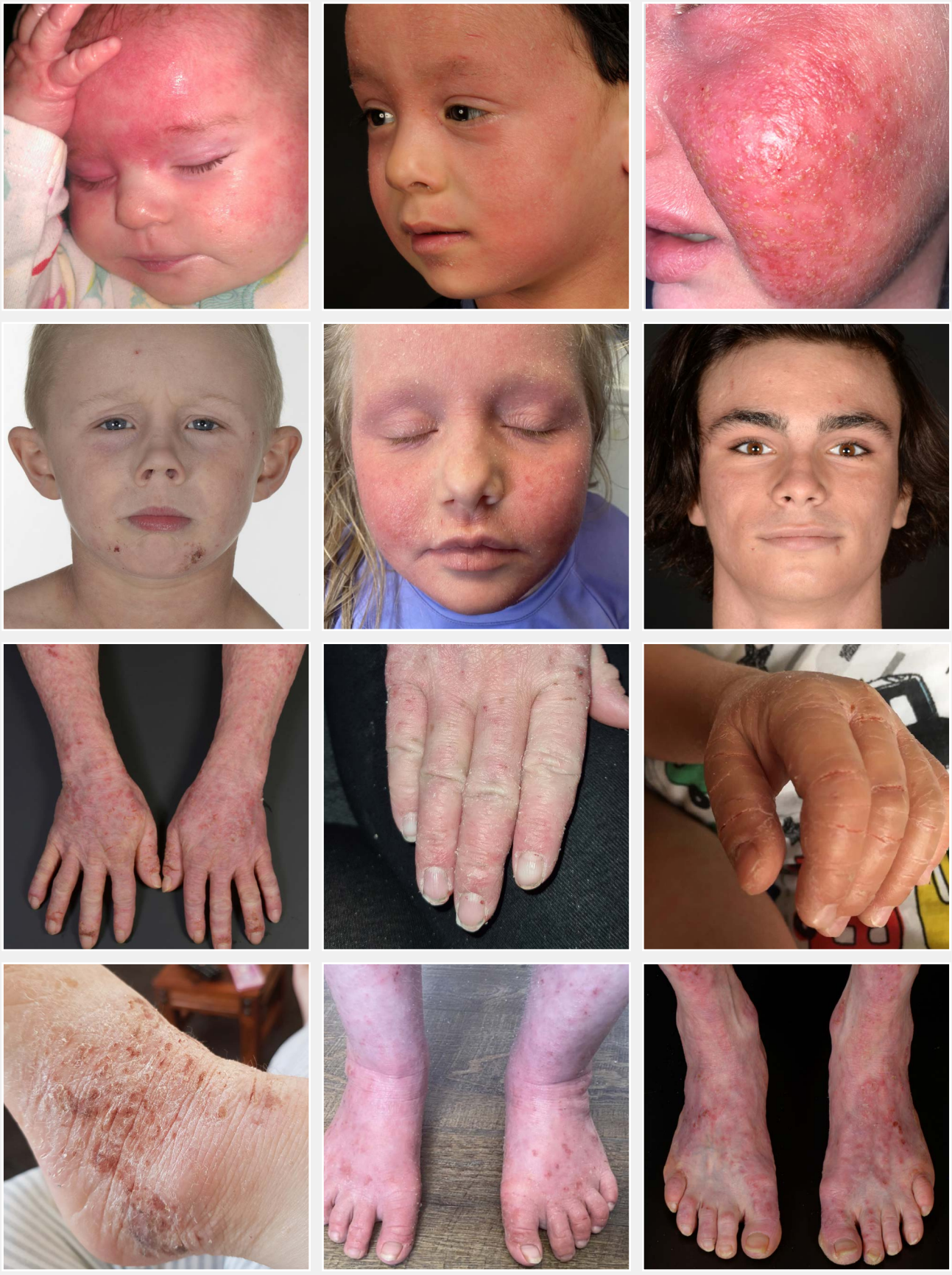


Figure 3.1: Clinical appearance of atopic dermatitis

Assessing disease severity

There are many existing tools to assess severity of atopic dermatitis, including the Investigator Global Assessment (IGA), the Eczema Area and Severity Index (EASI) and the Scoring Atopic Dermatitis (SCORAD) scales (41, 42). When assessing severity, physicians take dryness, redness, oozing, swelling, scratch marks, skin thickening, and extent of disease on various body parts into account (1).

There are also validated instruments available for patients with atopic dermatitis to score their disease severity themselves (patient-reported outcome measures or PROMs), such as the Patient-Oriented Eczema Measure (POEM), Patient Oriented SCORAD (PO-SCORAD), and the numerical rating scale (NRS)-itch (43, 44). In addition, there are a range of instruments to measure the impact on quality of life, some specific to atopic dermatitis, others more generic, such as the Dermatology Life Quality Index (42, 44).

The recommended outcome measures for atopic dermatitis are summarized in the Core Outcome Sets for clinical trials and clinical practice, which are published and maintained by the international Harmonising Outcome Measures for Eczema initiative (HOME)(43).

Associated diseases

People with atopic dermatitis are at a higher risk of developing both allergic and non-allergic comorbidities (15-17). There is a well-established association between atopic dermatitis and the development of allergic coexistent diseases such as hay fever and asthma (45, 46). Furthermore, food allergies affect children more frequently than adults (1, 15-17, 47). Recently, an association with eosinophilic esophagitis has been suggested (chronic inflammatory disease where the esophagus is triggered by pollen and food allergens), however, more research is needed to confirm this link (47).

Having atopic dermatitis makes patients vulnerable to bacterial, viral, or fungal skin infections from an impaired skin barrier. The skin of patients with atopic dermatitis is frequently colonized with the bacteria *S Aureus* (~70-90%) that can lead to sepsis and endocarditis (48). A well-known and common skin infection in atopic dermatitis caused by *S Aureus*, is impetigo (49). Common viral infections in atopic dermatitis include molluscum contagiosum, viral warts, and localized herpes simplex virus 1 (HSV1) infections (1, 16). In some cases, HSV1 infections can lead to a more generalized and potentially life-threatening form called 'eczema herpeticum', which needs immediate attention and systemic intervention. Concerns might also be warranted if the HSV1 infection affects the eye.

There are several additional comorbid diseases associated with atopic dermatitis, such as alopecia areata and urticaria (17). In children, adolescents, and adults, atopic dermatitis has been associated with lower bone density and consequently, a higher risk of bone fractures (50, 51). This seems to be at least in part unrelated to the use of topical and oral corticosteroids. Rheumatoid arthritis, inflammatory bowel diseases, and cardiovascular diseases have also been suggested to occur more frequently in people with atopic dermatitis, but the exact associations with these conditions continue to be debated (1, 15-17).

Psychological and mental health

Atopic dermatitis is a debilitating disease (52). Chronic or recurrent itch, skin pain, and disfiguring lesions can result in psychological distress, sleep disturbances, stigmatization, social embarrassment, and impaired quality of life (16, 53-55). These factors can result in people experiencing difficulties with concentration and may lead to poor school or work performance (54).

Children with severe atopic dermatitis have an increased risk of depression and internalizing behaviors (behaviors that result from negativity focused inward, such as social withdrawal, feeling unloved, and feelings of loneliness or guilt) (56). Similarly, a meta-analysis exploring the impact on children and adults demonstrated a positive significant association between atopic dermatitis, depression, and anxiety, as well as suicidal ideation (54). Another meta-analysis confirmed these results and reported that one in six people with atopic dermatitis experienced clinical depression, one in four had depressive symptoms, and one in eight had suicidal ideation (55). The association with mood disorders has been further evidenced in a study of 2,893 adults with atopic

dermatitis, reporting dramatically higher rates of depression and anxiety, but also indicating that these psychological conditions often go undiagnosed (53). The severity of atopic dermatitis may not be a straightforward predictor of psychological impact, as a large epidemiological study comparing patients with atopic dermatitis to people without the disease found that adults with atopic dermatitis were more likely to develop depression and anxiety, regardless of disease severity (52).

What I realized, if you don't take care of the child's self-esteem, then it is going to be very difficult, especially at an early age. So with Arsene we really work on his self-esteem. We show him that he's just as good as any other person and that it is not wrong to be sick.
Rachel, mother of son Arsene with atopic dermatitis, Kenya

From: Skin | Our Barrier to the World
©2022 GlobalSkin

Influences from the workplace

A history of atopic dermatitis is an important risk factor for developing hand eczema from a damaged skin barrier allowing greater penetration of irritating substances and allergens (57-60). Wet work (e.g., metal working, cleaning, nursing, and hair dressing) can lead to further deterioration of skin that might already be prone to dermatitis (59). This also applies to the skin coming into contact with hazardous substances like detergents, adhesives, or organic solvents. Allergens such as metals, hair dye, and flour can also worsen existing hand eczema in those with atopic dermatitis. A Swedish study demonstrated that when people with atopic dermatitis reported sick from work due to hand eczema, the mean duration of that sick leave was twelve weeks (59). Sometimes it might be necessary for a person to change jobs if their skin complaints persist, which could have an additional detrimental impact on psychological well-being. It is important that workplace exposures are addressed, and the skin is kept in the best possible condition with education, protective gloves, and barrier creams (59, 61).

Social participation

Atopic dermatitis can affect all aspects of life for people with the disease, but their caregivers, partners, and families may share the burden. The disease can have an impact on sleep, relationships, school/work, psychological well-being, and socializing (1, 18, 62). Visible skin lesions on the face and body can lead to social stigmatization and reduced self-esteem (63). More than half of people with moderate-to-severe atopic dermatitis experience disrupted sleep, depression, anxiety, and reduced quality of life and ability to work (63). A study of 602 adults with atopic dermatitis demonstrated that 51.3% felt that their lifestyle was limited due to their skin disease, with 39.1% avoiding social interactions as a result of their appearance, and the disease influenced daily life activities in 43.3% (64). Almost one in two adults with self-reported severe atopic dermatitis have described experiencing "a bit, to a great deal of burden" to their lifestyle, social interactions, and leisure activities (64).

My relationship with my husband? We have no intimacy, you know, because I feel very ugly. And he also cannot sleep the whole night because I was scratching. (...) So I know that my husband really loved me because I don't look perfect. (...) This is true love. I'm very lucky.
Martina, Slovenia

From: Skin | Our Barrier to the World
©2022 GlobalSkin

Socioeconomic burden

The socioeconomic burden of atopic dermatitis is a complex issue. There are costs directly related to the health care provided. Depending on the health care system, these costs are carried collectively (government, third party payers) or (partially) paid by the patient (out-of-pocket). The medically required use of moisturizers in atopic dermatitis is often seen as self-care, and there are additional costs incurred with food allergy diets, using hypoallergenic products for personal hygiene, and clothing or bedding, which are all out-of-pocket costs. The amount and personal impact of indirect costs arising from presenteeism, absenteeism, and loss of work, depends largely on a country's

social system. This complexity and variance in costs and socioeconomic burden is reflected in empirical literature and findings are often not generalizable.

A study from 2006 reported the annual cost of atopic dermatitis in the United States of America (USA) as close to $US 5.3 billion, of which $US 1.0 billion was for direct costs (65, 66). Two other USA studies reported costs totaling around $US 3300 per person per year in 2013, for children (direct and indirect)(67) and adults (health care utilization) (68). In another USA study, it was demonstrated that there are disparities in out-of-pocket costs between ethnicities, with black individuals experiencing higher costs and a greater financial impact (69). A recent paper on the costs for moderate-to-severe atopic dermatitis across Europe found expenses at €10.1 billion for health care (direct costs), €4.7 billion for personal out-of-pocket costs, and €15.2 billion for indirect costs, totaling €30 billion per year (70). In a recent systematic review, combining data from 27 studies, the total costs for adults with uncontrolled symptoms of moderate-to-severe atopic dermatitis reached €20,695 per-person-per-year (direct and productivity loss) in the European Union (EU) (71). Two other European studies have previously reported out-of-pocket costs for health care to be €351 per year for French adults (72) and €927 per year for adults with moderate-to-severe atopic dermatitis in nine EU-countries (73). In the latter study, the out-of-pocket costs for German patients were higher for atopic dermatitis than for psoriasis and rheumatoid arthritis (€941, €224, and €628, respectively) (73). Studies from the Asia-Pacific region have reported similar results, with direct costs per year ranging from $US 199 in Thailand to $US 1250 in South Korea, and the total household annual health costs for severe atopic dermatitis ranging from $US 600 in Vietnam to $US 4488 in Singapore (74, 75). Where assessed in these studies, it was consistently reported that costs increased with disease severity. Health care expenses increased around the first referral to the hospital and after a quick decrease stabilized at a higher level than before referral.

An unquantifiable aspect of the indirect socioeconomic burden of atopic dermatitis is the loss of education, and the loss of promotion and career opportunities. This includes people changing careers to more suitable (but potentially less paid and less satisfiable) jobs, which could contribute to disease burden from a sense of unused potential or reflecting on 'what could have been'. This not only results in individual loss, but also incurs a loss for society. This indirect socioeconomic impact may be especially poignant for people with atopic dermatitis, as the disease is so prevalent during childhood. Children may not be able to achieve their perceived 'potential' and may have to cope with disappointment if they cannot acquire a certain job or fulfil their future as they envisioned it, which they might have been capable of if they did not have atopic dermatitis.

Measuring the impact of atopic dermatitis on quality of life

The symptoms of atopic dermatitis, including itch and skin pain, are negatively correlated with health-related quality of life (HRQoL). These symptoms lead to sleep disturbances and impairment of daily activities such as work, school, sports, and socializing (37, 77). Atopic dermatitis has an impact on quality of life (QoL) of patients as well as their families (15). Caregiver burden is often overlooked and underrecognized, but the wider impact of the disease has received more attention in recent years (78).

There are many instruments available to measure the impact of atopic dermatitis on QoL (79, 80). There are generic validated instruments for overall assessment of the impact on health status, such as the EuroQoL-5D (EQ-5D) or Short-Form 36 (SF-36) (81). There are also dermatology-specific quality of life instruments, including the Dermatology Life Quality Index (DLQI), which is widely used and consists of 10 questions measuring the extent to which the skin disease has prevented a patient from engaging in daily activities including, work, sports, being intimate, and seeing friends.

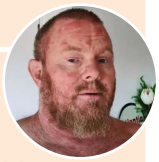
For children, the Children's Dermatology Life Quality Index (CDLQI) is used to measure the impact of skin disease on the lives of children, and the Family Dermatology Life Quality Index (FDLQI) is designed for family members or partners of patients with skin disease (78, 81). There are also disease-specific (atopic dermatitis) instruments such as the

proxy measure Infants' Dermatitis Quality of Life Index (IDQOL) for infants below the age of four years, the Quality of Life Index for Atopic Dermatitis (QoLIAD), the Dermatitis Family Impact (DFI) (81) and the Atopic Eczema Score of Emotional Consequences (82). The Harmonising Outcome Measures for Eczema (HOME) initiative decided at the VII meeting in 2019 in Tokyo that the DLQI (adults), CDLQI (children) and IDQOL (infants) are the recommended instruments for use in clinical trials (83).

A study of European patients from France, Germany, Italy, Spain, and the United Kingdom (UK) with moderate-to-severe atopic dermatitis indicated that atopic dermatitis impacted on QoL (as measured with the DLQI) with a moderate effect (score 6-10) and varied between 13.1% in Spain and 29.7% in the UK. A large effect (score 11-20) on QoL was reported in 14.7% in Spain and 23.9% in the UK, and an extremely large effect (score 21-30) was found on QoL scores between 4.4% in Spain and 33.3% in the UK (63). This impairment of QoL is in line with a 2019 study on burden of disease and individual suffering in nine EU-countries (13). Of those with severe disease, 88% stated that atopic dermatitis compromised their ability to face life.

Most studies on QoL have been carried out in Western countries, but a recent systematic review of Asian countries found that QoL of people with atopic dermatitis and their families were impaired to a similar degree as reported in Western countries (84). Furthermore, a study assessing the impact of atopic dermatitis on QoL in Saudi infants and children (as measured with the IDQOL) showed a mean score of 12.3 (scored 0-30, with higher scores indicating greater impact) suggesting serious impairment to QoL. This impairment was directly proportional to disease severity, and the items scoring highest were itch and scratching (85).

You have thoughts like I don't fit in or people are staring at my skin. Or sometimes you just like even I was at a point where I was like, I don't even want to be here anymore.
Natalia, USA



It wears thin, you know, and they're the times where you would like to just lie down and not feel anymore. We don't realize that our skin is our barrier to this world. You know you just take it for granted really. But it is. It stops everything. (…) Eczema in the family. I know it's always a different dynamic. My mother has been definitely my rock. She actually blames herself about my skin condition. Now having kids of my own, like, I can see where she's coming from. My little girl's four and she's slowly understanding that dad's got sore skin.
Rhys, New Zealand

From: Skin | Our Barrier to the World

Similar results were found from a web-based survey of children and adolescents from six months up to eighteen years old with atopic dermatitis (and their parents or caregivers) from eighteen countries (including North America, Latin America, Europe, Middle East/ Eurasia, and East Asia) conducted to evaluate the impact of atopic dermatitis on families (86). Scores on the DFI (0-30) varied from 7.1 to 8.6 for mild atopic dermatitis, to 17 to 17.2 for severe atopic dermatitis. Indeed, more severe atopic dermatitis may lead to a greater negative impact on physical, emotional, and economic aspects of family life across all age groups, and countries. A previous study in 2013 amongst children from Ukraine, Czech Republic, Singapore, the Netherlands, Brazil, and South Korea came to similar conclusions (87).

Many studies have investigated the association between atopic dermatitis and QoL, and although study designs differ, research findings have consistently and globally suggested that increased severity is associated with a greater negative impact on QoL. Furthermore, the detriment to QoL can affect a person's physical and psychosocial well-being, and impair all areas of daily life (88).

Chapter 4.
Quality health care for people with atopic dermatitis

Principles of managing atopic dermatitis

Atopic dermatitis is a chronic, incurable but treatable skin disease associated with intense itch, skin pain, sleep disturbances, and psychological conditions such as depression and anxiety.

There are many triggering factors for atopic dermatitis, including stress, irritants, allergens, infections, and changes in weather or season. These triggers can cause acute flares and have a significant impact on a person's quality of life. Flares are an integral part of disease trajectory, and based on the level of skin severity, treatment may be adjusted, modified, or intensified, as well as making lifestyle changes. Therefore, management approaches to atopic dermatitis should address both the periods of acute worsening and the chronic nature of the disease (1, 89).

Treatment of atopic dermatitis should be tailored to the patient based on their age, extent and severity of disease, stage of disease (acute or chronic), location of the lesions, and the patients' preferences, with attention to improving quality of life (1, 18). Management strategies for treating atopic dermatitis follow a stepped-care approach and include the use of emollients, topical treatments, phototherapy and/or systemic treatments (18, 89). In children with atopic dermatitis, it is also important that the caregivers receive adequate knowledge, skills, resources, and support to manage the treatment of their child at home and cope with the impact on family life (18).

Care for people with atopic dermatitis must go beyond the treatment of skin lesions and include addressing comorbidities, such as allergic rhinitis and asthma. Food allergies, allergic and irritant contact dermatitis, decreased bone health and autoimmune diseases are more frequently reported in people with atopic dermatitis, and these associated health conditions need to be taken into account. Health care providers should therefore treat people with atopic dermatitis as a whole person, and not just focus on the skin. This also extends to considering the burden of the skin disease on carers, and the impact on family life. Preferably, when treating atopic dermatitis, the principle of shared decision-making should be applied, which means that the patients' beliefs, lifestyle, and preferences are discussed when deciding on a treatment plan (1, 18).

People with atopic dermatitis are more likely to develop mental health conditions such as anxiety and depression, have an increased rate of suicidal ideation (54) and report more difficulties facing life (13). Psychological and educational interventions should be implemented to positively influence disease progression and improve overall psychological well-being (18, 90).

Treatment recommendations for atopic dermatitis follow a stepped-care approach, as shown in Figure 4.1 (18). These treatment recommendations can be adapted for countries based on local needs, availability of medication, potential benefits and harms, access to healthcare, costs, limitations, and advantages and inconveniences of the suggested therapeutic options.

Treating the whole person: beyond the skin manifestations

As previously outlined, care for people with atopic dermatitis must go beyond the treatment of skin lesions and include addressing comorbidities, and the impact on psychosocial well-being. Not being able to participate in social activities, experiencing impairments at school or work, intense itch, disrupted sleep, and potentially dangerous food allergies can all negatively impact on a person's mental health. Treatment should be personalized for patients' preferences to improve quality of life, and where co-morbid allergies and asthma are present, multidisciplinary team management may be required (18). Atopic dermatitis commonly

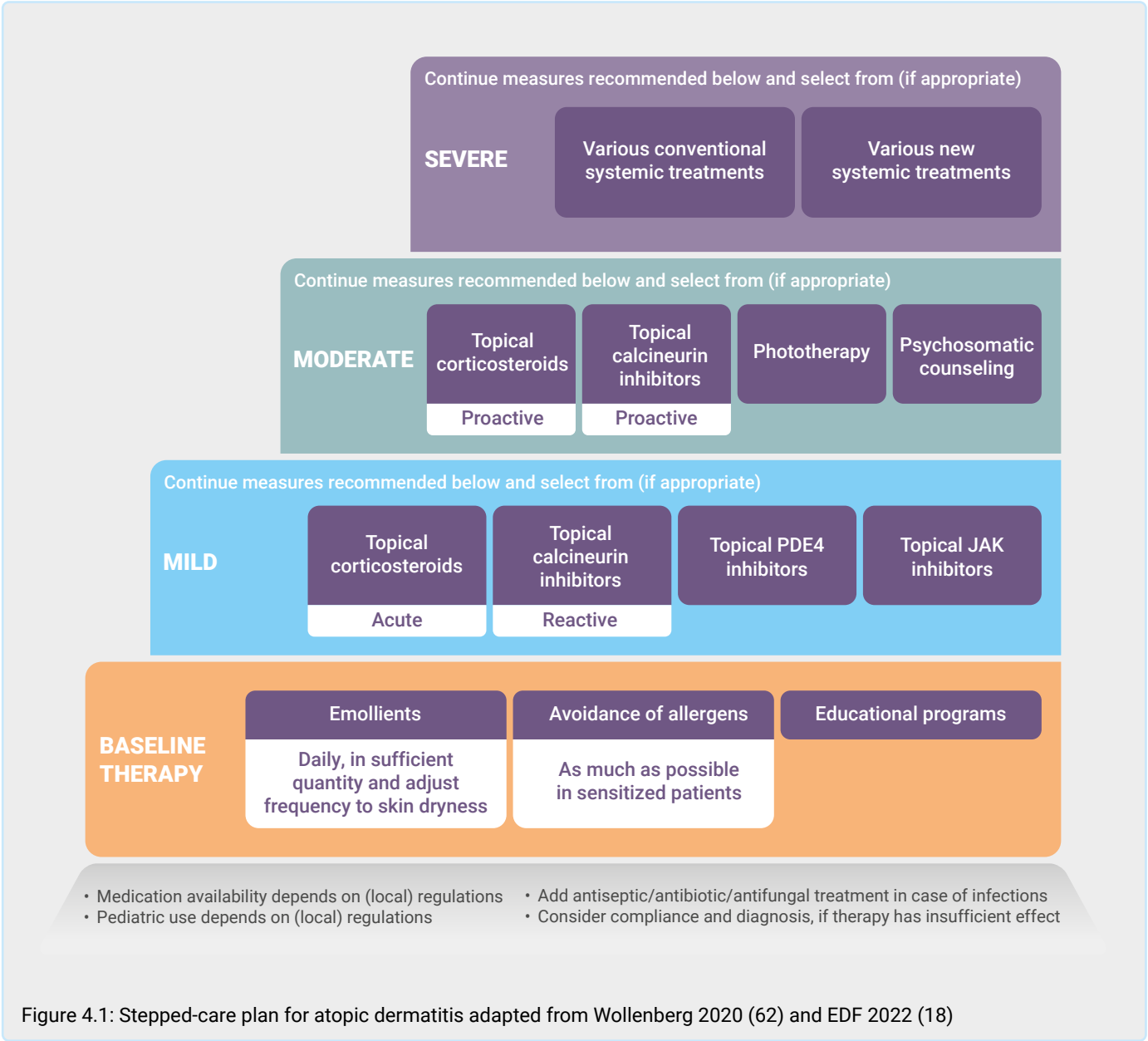


Figure 4.1: Stepped-care plan for atopic dermatitis adapted from Wollenberg 2020 (62) and EDF 2022 (18)

develops at a young age, can vary in severity, and is often lifelong. Therefore, treatment needs and goals will change across the lifespan. A patient-centric holistic approach can empower people with atopic dermatitis to manage their disease and improve treatment adherence, to achieve their life goals (1, 18). Treatment might also include psychotherapeutic support, habit reversal therapy to break the itch-scratch cycle, and stress reduction techniques (62).

Treating the skin manifestations

Management strategies for atopic dermatitis consist of general measures, baseline therapies, and active treatments to address inflammatory lesions (2, 18, 62). These general measures and baseline therapies apply to all people with atopic dermatitis (see Table 4.1), regardless of disease severity.

Educational programs

Educational programs have been developed to increase understanding of atopic dermatitis and treatment. People learning more about the disease can assist in promoting acceptance and coping for both the person diagnosed with the skin disease and their caregivers. These programs can help to improve skin barrier function, increase adherence to treatment, and ultimately reduce the burden of disease from affecting quality of life. The aim of educational interventions encompasses more than providing information, as they also involve the acquisition of skills to self-manage, self-assess (e.g. for skin infections), and self-adjust to topical treatments for long-term disease control (18, 91-94). By increasing knowledge and understanding of their disease, triggers, and treatment, and with the use of patient-reported outcome measures (PROMs) (e.g. PO-SCORAD), people with atopic dermatitis and their families can be empowered to take an active role in the shared management of the disease (95-97).

Emollient therapy

The use of emollients is the basis of treating atopic dermatitis, to moisturize the impaired skin barrier. The choice of emollient(s) should be based on the patient's preference, season and weather, time of application (day or night) and location on the body (face versus body) (2, 18, 89). Preferably, these emollients should not contain any contact allergens such as fragrances, plant ingredients or preservatives that are associated with increased risk of contact allergy. Emollients often contain a humectant such as urea or glycerol to promote hydration of the skin, and an occludent such as petrolatum to prevent evaporation (2). To restore the skin barrier and prevent flares, the daily use of liberal amounts of emollients is recommended, ideally immediately after showering or bathing with 'soft pat drying' (2, 18, 62). In tropical climates with high temperatures and humidity for the majority of the year, the strategy for the application of emollients needs to be tailored and judicious (98). Although historically, many

Educational programs	Cleansing and bathing Personal daily skin care Coping with stress Behavioral therapy
Avoidance of triggers and irritants	Reducing allergen and irritant exposure
Emollient therapy	Restoring the skin barrier
Therapy addressing potential skin infection	Depending on bacterial and/or viral infection
Wound care	Covering open or oozing wounds

Table 4.1: General measures and baseline therapies (1, 18, 62)

emollients have not contained active ingredients, most recently, several non-medicated products or 'emollients plus' with active ingredients (e.g., licochalcone A) have been made available (2, 18, 62).

Understanding triggers

Atopic dermatitis can be influenced by many triggers that differ between people, and identifying these individual triggers can be a challenge (18, 99, 100). Factors that can trigger flares or worsen atopic dermatitis include both endogenous (related to the body) and environmental (external) factors, such as environmental allergens (Table 4.2).

Triggers related to the body itself are difficult to avoid or influence. People with atopic dermatitis have (very) dry skin, often resulting from a genetic origin (101). The protein called filaggrin (FLG) is essential for keeping the skin barrier intact. People with atopic dermatitis are more likely to have a defective FLG gene, which causes a 'leaky' skin barrier, increases water loss, and consequently leads to dry skin.

As well as genes, changes in the amount and diversity of skin bacteria can play an important role in disease severity and disease flares (1, 102). In addition, the body's response to stress and the production of hormones can negatively impact the function of the skin barrier and can influence immune responses (99, 100). Although there is an increasing understanding of psychoneuroimmunology, less is known about effective strategies for mitigating the negative impact of stress and other triggers on atopic dermatitis (103, 104).

Environmental exposure to pollutants, irritants, and cutaneous infections (bacterial, viral, and fungal) can induce further skin barrier damage from making the skin vulnerable to the entrance of contact allergens and through toxin secretion that contributes to disease chronicity and flares (100, 105). Although flares are often reported after inhalation or skin contact with aeroallergens, it is very difficult to avoid exposure to pollen, house dust mites, and animal dander (18, 62). A study carried out in subtropical Guangzhou in China found that air pollution acutely triggered atopic dermatitis, and that children were more sensitive to this than adults (106). Irritants include chemicals and detergents, and irritating fibers such as wool (100, 105). Approximately 40-65% of people with atopic dermatitis will have one or more contact allergies (62). Some well-known contact allergens include ingredients in emollients (e.g., lanolin, wool alcohols), fragrances, preservatives, and topical corticosteroids (62). Some of these ingredients are also used in several topical treatment formulations. Both active and passive smoking are associated with an increased prevalence of atopic dermatitis, and therefore, the avoidance of tobacco smoke is recommended (18, 62, 107).

Food allergies occur in up to one-third of children with moderate-to-severe atopic dermatitis, however, the influence on disease severity and flares is complex. Adults with atopic dermatitis are more frequently sensitized for food allergens

Triggers related to the body itself	Triggers related to the environment
Skin barrier dysfunction (e.g. filaggrin skin barrier gene deficiency)	Exposure to allergens
Changes in the amount and diversity of skin bacteria	Food allergy
Altered functioning of the immune system	Hot and humid environment
Hormonal changes	Dry and cold environment
Stress	Sweating (physical exercise)
	Sun exposure
	Clothing with irritating fibers (wool)
	Air pollution

Table 4.2: Potential triggers that are implicated in atopic dermatitis (adapted from Girolomoni (100))

although the food allergens differ from children (108). Therefore, when deciding on a treatment plan, it is important to gather a detailed clinical history for food allergies and conduct allergy testing (e.g., skin prick tests, serum specific IgE testing) and, where required, food challenges (18, 62, 100, 109, 110). A study in Denmark showed half of a sample of 1,343 parents attempted to use dietary exclusions to manage atopic dermatitis in their children (109). These findings could suggest there may be unnecessary negative consequences for social life of families and the potential for nutritional deficiencies that could lead to impaired growth. Therefore, seeking guidance from a dietitian to avoid nutritional deficiencies is important.

Weather and seasons may also play a role in the disease burden. A drop in humidity and temperature leads to increased number of health care visits and medication use (111). Heat and sweating are amongst the most common triggers reported by people with atopic dermatitis for exacerbating itch (18, 99). Excessive sweating can lead to the occlusion of sweat pores and keratin plug formation, resulting in the irritation of atopic dermatitis lesions, itch, and localized inflammation (112). However, although there is conflicting evidence regarding the role of exercise in triggering atopic dermatitis, people with atopic dermatitis should not be discouraged from exercising regularly. Exercise has many beneficial effects for a person's physical health and psychological well-being (18). Other common triggers that can worsen atopic dermatitis are cold weather, sunlight, and dry air (62, 63).

In many cases, there may be multiple triggers, which makes identifying and avoiding all influencing factors even more difficult. Therefore, counseling for assisting with which triggers can be avoided is recommended, as well as considering adjustments to treatment intensity (stepping up in therapy) (99).

Therapy for skin infection

The skin of people with atopic dermatitis (especially the lesions) are frequently more colonized with the bacteria *S Aureus* and are therefore more susceptible to infection with *S Aureus*, even systemic ones. When this bacterium affects the skin extensively, a short course of systemic antibiotics is recommended and topical antiseptic products or bleach baths can be considered to prevent future bacterial infections (18, 113-115). Eczema herpeticum (a disseminated herpes simplex virus (HSV) infection) requires immediate systemic antiviral therapy such as acyclovir (18). Other viral infections should be treated according to local guidelines (18, 62).

Wound care

In atopic dermatitis, bandages can be used to protect the wound(s), absorb wound fluids, make scratching more difficult, and fixate applied topical products. Tubular bandages have been used for decades and are still applied today. However, these bandages can be difficult to attach with adhesives when there are creams and ointments on the surface of the skin. For this reason, bandages in the form of garments are available (e.g., made from cotton, sericin-free silk, viscose or micromodal). Some garments are formulated with antibacterial properties that may be beneficial to reduce *S Aureus* colonization and therefore improve symptoms (116-124). However, a study assessing the efficacy of antibacterial garments made of sericin-free silk demonstrated no added benefit for atopic dermatitis (125).

Medical treatment

Treatment recommendations for atopic dermatitis follow a stepped-care approach, as shown in Figure 4.1. Baseline therapy is required for all severities of atopic dermatitis. Mild atopic dermatitis is usually treated with topical anti-inflammatory medications, such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). More recent options include a topical phosphodiesterase 4 (PDE4 inhibitor), and a topical JAK-inhibitor. TCS are available in four potencies (WHO ATC code D07A: weak, moderately potent, potent, or very potent) (126) and in different formulations (cream, ointment, lotion, or foam) (18, 62, 127).

When choosing a TCS, the patient's age, disease severity, and body area should be considered. Moderately potent TCS can be safely used on most areas of the body. However, for sensitive areas of the body (such as the face, axillae, and groin) weak TCS or TCI are recommended (18, 62, 89). There are more considerations for young children, with weak TCS being advised for the face, and moderately potent TCS for the rest of the body. It is also important to address concerns of patients and/or their carers regarding fears of potential side effects of corticosteroids, which can impact treatment compliance (known as 'corticophobia') (18, 62,

89, 128-130). The most reported side effects of TCS are skin atrophy and stretch marks, but these are rare when used correctly.

Treatment for moderate atopic dermatitis involves continuing the measures for baseline therapy and mild atopic dermatitis, with an increased potency of TCS: usually from moderately potent to potent (or very potent with caution). When suitable education has not been provided, it is needed at this stage. Psychosomatic counselling is also recommended at this level, to teach people strategies to cope with their disease. These strategies might include techniques to manage stress, which can induce severe exacerbations as well contributing to a vicious circle of itching and scratching (18, 62). Moderate-to-severe atopic dermatitis recalcitrant to topical treatments, or when these are somehow contraindicated, can also be treated with phototherapy (ultraviolet light) such as narrow band UVB or medium UVA1 (18). However, caution is warranted in children and adolescents.

Topical anti-inflammatory treatments can be used reactively. Reactive use of anti-inflammatory treatments involves the topical application to lesional skin only, and the application will be tapered (or stopped) when the lesions improve or disappear (18, 62, 89). Another approach is proactive treatment which usually involves twice weekly application of topical anti-inflammatory treatments on previously affected skin areas, in combination with daily use of emollients on the entire body. This proactive approach is also known as maintenance therapy and is often used after an acute flare of the disease has been successfully treated (18).

For people with severe atopic dermatitis that have not responded to previous therapies in the stepped-care plan, systemic treatment could be considered. Conventional systemic treatments include cyclosporin, methotrexate, azathioprine, and mycophenolate mofetil (18). Systemic glucocorticosteroids should be avoided as much as possible, and only used as short rescue therapy (18). Although glucocorticosteroids produce a rapid treatment response, they have an unfavorable benefit/risk ratio, and their use should be restricted to short-term (a few weeks) (18). More recent systemic treatments include biologic therapies such as dupilumab or tralokinumab, and JAK inhibitors such as abrocitinib, baricitinib or upadacitinib. However, these medications are expensive and not globally available.

Of all the medications, only a small number of topical and systemic treatments for patients with atopic dermatitis are on the World Health Organisation (WHO) Model List of Essential Medicines (see Table 4.3) (131). From a global perspective this is understandable, especially regarding newer and more expensive medications. Despite this, there is a lack of inclusion of moderate potency TCS (ATC code D07AB; 126),

Core list[1]	
Anti-inflammatory and antipruritic medicines	
Betamethasone	Cream or ointment: 0.1% (as valerate)
Hydrocortisone	Cream or ointment: 1% (acetate)
Medicines affecting skin differentiation and proliferation	
Urea	Cream or ointment: 5% or 10%
Complementary list[2]	
Systemic therapies[3]	
Prednisone	Tablet: 5 mg or 25 mg (for immunosuppression)
Methotrexate	Tablet: 2.5 mg (as sodium salt) (for immunosuppression)
Azathioprine	Tablet: 50 mg (for immunosuppression)

Table 4.3: Atopic dermatitis treatment options on the WHO Model List of Essential Medicines 2021 *Source: WHO 2021 (131)*

[1] Minimum medicine needs for a basic health-care system.
[2] Medicines for which specialized diagnostic, monitoring, training or care may be needed.
[3] These medicines are not specifically included in the WHO Model List of Essential Medicines for dermatological conditions, but for the indications specified above.

which is problematic as they are a very important treatment option for both children and adults. For a child, a weak TCS will often not suffice for the treatment of moderate to severe disease, and a potent TCS could cause harm. This also applies to adults regarding their sensitive skin areas.

Complementary medicine

Many people with atopic dermatitis use complementary medicine. Complementary medicine encompasses a wide variety of treatments such as traditional Chinese medicine, homeopathy, Ayurveda, or traditional healing. However, these treatments are not recommended by healthcare professionals as they are not supported by sufficient evidence (18, 62).

Other treatment resources

The evidence for treating atopic dermatitis in this report is underpinned by the most recent guidelines (18) and scientific literature. All 40 international clinical practice guidelines on atopic dermatitis less than five years old are available through the **GUIDEMAP project** (7, 132).

Horizon scanning of new drugs in the pipeline and phase 2/3 trials

Atopic dermatitis is subject to a lot of research, both fundamental and exploring the use of new therapeutic interventions. In 2017, dupilumab became the first innovation after the licensing of TCI in 2000 and was the first biologic purely developed and registered for people with atopic dermatitis. Biologics are also known as targeted treatments as they target specific functions of the immune system. Both dupilumab as well as tralokinumab are monoclonal antibodies, and they are injected subcutaneously. The target of dupilumab is IL-4Rα, blocking both IL-4 and IL-13 signaling, whereas tralokinumab blocks IL-13. By blocking these pathways, biologics improve the severity of atopic dermatitis from reducing the inflammation process in the body.

Janus kinase (JAK) inhibitors are also targeted treatments, but work differently. JAK inhibitors block a part of the immune system called the JAK-STAT pathway, and some work with more precision than others. JAK inhibitors can be taken orally (tablets) and work more broadly by inhibiting the effects of several signaling molecules in the immune system. Abrocitinib, baricitinib and upadacitinib are oral medications licensed for use in atopic dermatitis. As well as being administered orally, delgocitinib and ruxolitinib are JAK-inhibitors that can be applied to the skin, with the same mechanism of action, but working locally on the skin.

There are currently many more therapeutic strategies and targets for the treatment of atopic dermatitis under development, as presented in Table 4.4 (for details see Appendix).

Strategy	Drug type and mode of application	Number of studies identified
Modulating the microbiome	Bacterial strains — topical	3
	Small molecule — topical	2
	Bacterial strains — oral	2
Targeting the innate immune response	Small molecule — topical	1
	Biologic — injection	7
Targeting the adaptive immune response	Biologic — injection	17
	Small molecule — oral	8
	Small molecule — topical	12
Targeting itching	Biologic — injection	2
	Small molecule — oral	3
Inhibiting Janus kinases	Small molecule — topical	8
	Small molecule — oral	4

Table 4.4: Current therapeutic pipeline for atopic dermatitis adapted from Bieber 2022 (133) and updated with data from clinicaltrials.gov (134).

Barriers to quality health care

There are many barriers to optimum treatment and delivering quality health care. These barriers are complex and can be divided into four main overlapping areas: the general perception of atopic dermatitis as a disease, the ability of people and/or their carers in (self)management, the organization of the country's health care system, and how health care is paid for.

General perception of atopic dermatitis

Due to the high prevalence of mild disease in children, atopic dermatitis may be seen as a mild skin condition 'they will grow out of'. This is not always the case. A systematic review concluded that in 20% of patients with atopic dermatitis, the disease persisted beyond eight years after diagnosis, and the persistence into adolescence and adulthood was more likely in people with more severe disease (26). Regarding severity, a study of children in the USA found that 67% had mild atopic dermatitis, 26% had moderate disease, and 7% had severe disease, with variation between states (135). A nationwide Danish study showed that approximately two out of three of children seen in a hospital setting had intermittent disease activity after 10 years (136). Between countries there are also many differences, as a recent international study (18 countries) in children demonstrated (137). Measured with POEM, between 35.8% and 66.1% had mild disease, between 28.8% and 55.0% had moderate disease, and overall, less than 15% had severe disease.

Despite decades of efforts, atopic dermatitis is still falsely conceived as contagious or a sign of a person being 'dirty', leading to stigmatization, exclusion, and bullying. Common myths also extend to treatment, and the mainstay use of topical corticosteroids. There is a lot of misinformation surrounding the use and side effects of these 'steroids', which has resulted in some people experiencing corticophobia (128-130). These misconceptions may be held by the patient or the carer, or could be unsolicited from other people, and consequently reinforced.

Ability of self-management

Treatment of atopic dermatitis is complex, time-consuming, and messy. For most people, treatment consists of avoiding triggers and regularly applying ointments. This can involve a lot of effort for people with atopic dermatitis and their carers, who may be part of the journey of finding out what triggers flare the disease, and which topical treatments work best. Maintaining intensive treatment regimens across the lifespan can be challenging, and often requires discipline. There are three main drivers to executing successful self-management: (1) knowledge of atopic dermatitis and treatments, (2) personal attitude/beliefs towards the disease and treatments (e.g., corticophobia, and psychological resilience), and (3) level of motivation (94). Even with these drivers considered, the management of treatment regimens can be burdensome for the patient, their carers, and for health care providers. An additional barrier could be the literacy and/or health literacy of people with atopic dermatitis and their carers. Therefore, health-related information and educational interventions should be accessible and understandable for all people, irrespective of background.

The health care system

Dermatologists are clinicians who specialize in the treatment of skin conditions. Yet, most people with atopic dermatitis will initially be assessed or treated within primary care (general physician/family doctor), although this is not always consistent between countries. There are variations in the number of primary care practitioners per country, and there may be other factors influencing access, such as the distance people must travel to that doctor (or take time off from work) or the doctor's knowledge of atopic dermatitis (138-144).

I remember going to the clinic and then I was told he has eczema. Then there's a lot of confusion, seeking medical help, from one dermatologist to another. We moved all over the country trying to get him help. I've done everything in my power to try get information and to try also to get him relief.

Rachel, mother of son Arsene with atopic dermatitis, Kenya

From: Skin | Our Barrier to the World

Where over-the-counter topical corticosteroids are available, treatment of mild atopic dermatitis might (after diagnosis) be seen as 'self-care', with an additional out-of-pocket expense. Depending on the healthcare system, the primary care practitioner usually refers a patient to the care of a dermatologist (or pediatrician/allergist); when a dermatologist is available and accessible, which is not the case for all geographic locations (138-142, 144). The distinction between first-line treatment (primary care) and second-line treatment (dermatologist/pediatrician/allergist) is important, as second-line treatments such as phototherapy and systemic treatments cannot be prescribed as 'first-line' (except for a short course of antibiotics or oral corticosteroids). For many countries, discrepancies in the availability of specialist services and treatments/prescriptions can be a significant barrier to accessing quality care.

Paying for health care

Along with inequalities in the availability of quality of health care, there is the issue of affordability. Costs of treatment mostly depend on a country's health policy, which consists of a myriad of aspects. However, when topical therapies are designated and available over-the-counter, they become an out-of-pocket expense.

The cost of visiting a health care provider and the treatments they prescribe, can also depend on the way health care is paid for. For example, are costs met by the government, a third party, or is there a co-payment for the patient? Although market authorizations, such as the European Medicines Agency (EMA) or Food and Drug Administration (FDA), seem straightforward, they are not. For instance, in Europe, the EU grants these authorizations after approval by the EMA, but despite this approval, not all medicines are reimbursed or affordable for all EU countries, especially systemic therapies. Similarly, when the FDA grants approval, it does not guarantee equal accessibility, and this is also the case for countries outside Europe and North America.

To date, health care for atopic dermatitis, including consulting a health care provider and availability of medication, is not universally accessible or affordable for everyone. This is problematic and is contributing to global health inequity for people with atopic dermatitis: *the care you can afford depends on where you live*.

Digital health care innovations

Digital health care innovations can be both a facilitator and a barrier. These interventions are often driven by local need, such as geographical distances. For example, where access to a dermatologist is sparse due to location and availability. As well as distance, there may be greater need for the delivery of remote health care as a result of the COVID-19 pandemic, to increase access to health care providers.

However, digital health interventions could be a barrier when dermatologists are unable to implement these innovations, or when people with atopic dermatitis are not able to use them due to lack of skills or an inability to afford the necessary technology (145). Another barrier could be the visual aspects related to the field of dermatology and atopic dermatitis, that often determine the course of treatment. For the future of dermatology and dermatology patients, this must be overcome.

Chapter 5. **Addressing the gaps, barriers and needs**

This report aimed to address the current state of atopic dermatitis and has (1) summarized the burden of atopic dermatitis for the person diagnosed and their caregivers, (2) highlighted the standards of what quality health care for people with atopic dermatitis should consist of, and (3) outlined the gaps and barriers to measuring and relieving that burden.

The origins of these barriers and their solutions are complex and involve an interplay between stakeholders; non-governmental organizations, governments, health care providers, medical societies, health care payers, and patient organizations (national, regional, and international). Although each party has their own responsibility, working together is essential. Moreover, the gaps and barriers are not unique to atopic dermatitis itself, and there are a lot of commonalities with other skin diseases, such as psoriasis, for which collaboration with stakeholders should be sought.

Gaps in epidemiological data and the GADA project

At present, there is lack of robust prevalence and burden data for many countries, and where data is available, direct comparisons are restricted by methodological diversity. For example, the way in which atopic dermatitis is diagnosed (e.g., questionnaire versus skin examination, population-based versus hospital-based sample). There are several gaps in our current understanding of the natural history and global burden of atopic dermatitis, in particular:

- Few studies have focused on the incidence of atopic dermatitis and on trends in the incidence over time.
- Robust disease severity data at the population level is sparse, and where available, it lacks standardization.
- Longitudinal data on individual disease course over time is also sparse, especially beyond childhood. It would be useful to offer better predictive information for patients and to identify factors that perpetuate disease.
- Few studies have assessed associated diseases, such as respiratory diseases, food allergies, and common psychological comorbidities (e.g., depression and anxiety) at the population level.
- Most of the studies contributing data on disease prevalence and burden have been conducted in Europe and the USA, with fewer studies identified from Asia, Africa, and South America.
- Little is known about atopic dermatitis in adults at the population level compared to pediatric cohorts, and prevalence and burden-related data is scarce.
- There are different clinical phenotypes of atopic dermatitis in skin of color versus white populations (e.g., flexural versus discoid versus follicular atopic dermatitis), and it remains unclear whether these variations are driven by environmental factors, or differences in cutaneous immunology, genetics, and the skin microbiome.

Further international research into atopic dermatitis is therefore necessary to fill these important gaps in knowledge. For this reason, we propose the establishment of an international research program to develop GADA that will derive estimates of the global epidemiology of atopic dermatitis (Phase 1). These estimates will determine core criteria for the conduct of population-based epidemiological studies (Phase 2) that can subsequently be used in future research to update GADA on a regular basis (Phase 3). Along with this, the GADA project will also provide an opportunity to develop e-tools for epidemiological research.

Phase 1

The increasing number of studies reporting on the epidemiology of atopic dermatitis and the heterogeneity of the results highlight the importance of developing systematic/standardized methods of synthesizing studies and assessing their validity. This will allow more robust estimations of the disease burden of atopic dermatitis to be conducted worldwide.

The aim of Phase 1 will be to develop GADA to generate estimates of prevalence of atopic dermatitis and its severity and associated diseases for different countries based on existing data, using rigorous methods previously adopted by the Global Psoriasis Atlas project and the International Diabetes Federation (146, 147).

Phase 2

In Phase 2, we will assemble an expert reference group with the aim of establishing consensus on core criteria for the design of future epidemiological studies of atopic dermatitis, and develop guidelines for the conduct and reporting of such work. For instance, the criteria are likely to address key issues (which have previously been inconsistently applied and/or reported), such as:

- Case definition (self-report via questionnaire, dermatologist diagnosis).
- Prevalence measure (point, period, lifetime prevalence).
- Age and sex distribution of the population (to allow comparison with other national demographic statistics).
- Ethnicity.
- Atopic dermatitis severity and quality of life assessed by patients/physicians, making use of e-tools (e.g., Patient-Oriented SCORAD app)(148).

Once core criteria for the design, conduct and reporting of epidemiological studies have been established, these will be published in peer-reviewed journals and disseminated internationally. These guidelines will improve the scope and quality of subsequent epidemiological studies of atopic dermatitis. Having these criteria will also allow GADA to be updated on a regular basis, to guide national and international efforts and set priorities on how to meet the challenges of this common and debilitating skin disease.

Phase 3

Phase 3 still requires mandate but could involve conducting epidemiological field studies in geographical areas that have not been adequately covered, such as Africa, Asia, and South America. In addition, we will consider conducting studies investigating the generation of skin microbiome, skin immunology and genetics, as well as examining co-morbidities (asthma, rhinoconjunctivitis, food allergies, depression, and anxiety) and patient quality of life.

The GADA project is hosted on an interactive website as an information hub for clinicians, patients, and policy makers worldwide, providing regular updates on disease burden and offering free access to the developed research tools for epidemiological studies on atopic dermatitis. We are also planning the development of field research training tools, and the translation of our resources into other languages.

Addressing the health care needs of people with atopic dermatitis

As discussed in chapter 4, there are many barriers to affordable, quality health care, resulting in many unmet needs. These unmet needs have been reported by patient organizations (149, 150) and researchers (151, 152). Addressing these barriers to quality care is complex, and there is no 'one-size-fits-all' solution. However, there are models of the health care chain that can assist in clarifying the responsibilities of involved stakeholders and provide a framework for the process that should be followed. An example of this is the Patient-Centered Health-care System Model proposed by WHO (153).

Patient-Centered Health-care System Model

In the global expert consultation of the WHO framework on patient and family engagement, the topic of patient-centric healthcare was addressed (153). The report provided a helpful illustration of the process, the stakeholders, and the importance of patient and family engagement for improving patient outcomes and quality of care for people with health conditions (see Figure 5.1).

Important outcomes for patients and their families

The most important outcomes for patients with atopic dermatitis and their families have been adequately and consistently addressed in the last decade by the Harmonising Outcome Measures for Eczema (HOME) Initiative (43). The HOME Core Outcome Set for atopic dermatitis in clinical trials has been adopted by researchers in recent years and has made it possible to compare study outcomes using meta-analyses. Specifically, for atopic dermatitis, there is a living network meta-analysis for systemic treatments based on those core outcomes (154-156).

Research and development

Patient engagement is a topic of interest in research and development. In the EU, the concept of patient involvement has been embedded for years in the governance and work processes of the European Medicine Agency (EMA). One such activity is asking patient representatives to participate in the procedures of the Scientific

Advise Working Party (SAWP). The role of the patient representative within SAWP procedures is to advice on research proposals, mostly at the point when studies are progressing from phase-2 to phase-3 trials. Patient engagement is important to ensure that proposed research is meaningful to patients' lives, is achievable, and ethical. Within the pharmaceutical industry, the added value of patient participation has also been recognized, as early patient input can lead to better study designs, better patient information, faster inclusion, and less drop-out. From a public research funder's point of view, patient engagement is often required to have funding awarded, in ensuring research proposals are meaningful to, and supported by, patients (157, 158).

Whilst, when research is being conducted on fundamental areas such as biomarkers and genetics, it is important to include patients to discuss feasibility and ethical aspects (159). The topic of ethics is current in atopic dermatitis as there is a substantial amount of research being carried out on biomarkers, genetics, endotypes and phenotypes of atopic dermatitis. To illustrate this anecdotally: at present, we do not know if young children who develop atopic dermatitis will have it severely, if they will have it for their whole life, and we do not know if they will develop asthma and allergies. If we could find out more about the progression of atopic dermatitis, would a parent want more information about the clinical course of their child's disease with a test? If this could be done, could these tests be made universally available, and affordable? For research like this, it is important that patient insights are embedded in the research process.

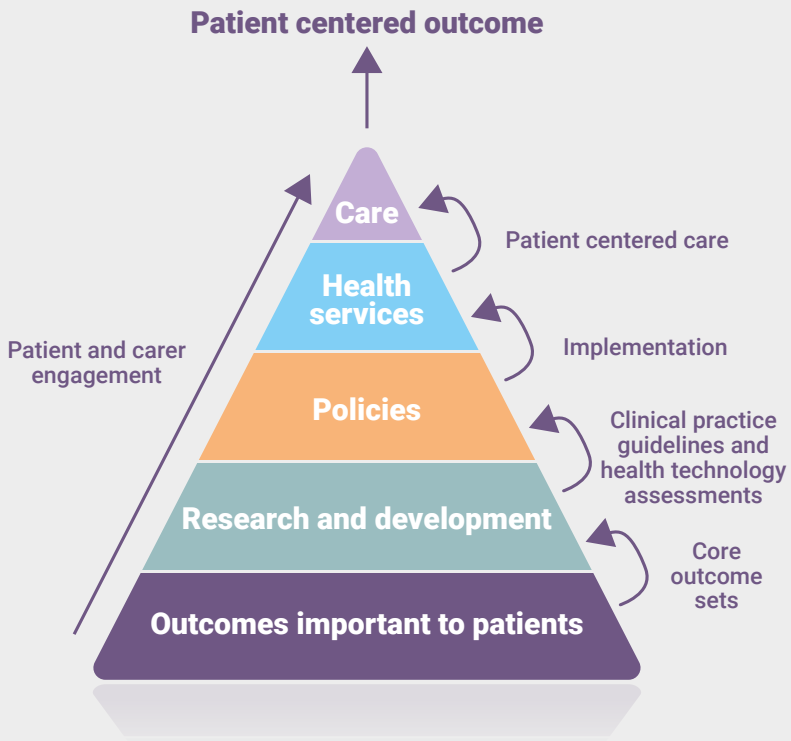


Figure 5.1: Patient-Centered Health-care System Model, adapted from the WHO (153)

As well as the need for research to develop new interventions for atopic dermatitis and increase understanding of fundamental aspects of the disease, there are also gaps in the evidence base for existing treatments. For example, we still do not know enough about treatments that have been used for decades such as phototherapy for atopic dermatitis (18) and the literature base could benefit from further comparisons of the efficacy of interventions (151).

Regardless of the methodology or subject of research conducted, the outcomes used should be based on the Core Outcomes for Trials for atopic dermatitis (43) to enable meta-analyses and systematic reviews to be carried out with robust evidence.

Policies

As shown in Figure 5.1, policies are based on clinical practice guidelines. When developed robustly, according to the most-up-to-date methodologies, they firstly provide the certainty of benefits and harms of diagnostics, treatments and interventions based on available evidence. Secondly, professional experience, local circumstances, local preferences, and local availability are weighed as an integral part of the process to formulate the strengths of recommendations (160-163). It is paramount that patients are part of the guideline development process, however, this is not always the case. A systematic review on atopic dermatitis guidelines found that less than 25% of the 40 current guidelines reported patient involvement (7). This prompted a plea by twelve patient advocates to include the patient voice in developing clinical practice guidelines for atopic dermatitis (164).

Developing new guidelines is a lengthy and time-consuming process. When possible, guidelines can be adapted based on previously published high quality guidelines (7). Or, when resources are adequate, a guideline can become a 'living' document, such as the recently published European (EuroGuiDerm) guideline on atopic dermatitis (18). Local reimbursement policies that can influence clinical practice guidelines (and vice versa) could benefit from collaboration between dermatological societies and patient organizations in conducting Health Technology Assessments (HTA) (165).

Importantly, what must be avoided and improved, is the current situation. Health care innovations in atopic dermatitis have created even more global disparity and inequity due to unavailability and unaffordability. This needs national and supra-national collaboration between governments, dermatological societies, third-party payers, and the companies providing the innovation to address these inequalities (medication and diagnostic/testing technologies).

Health services

One of the challenges of delivering quality patient-centered health care is timely incorporation and implementation of the latest interventions and diagnostic tools when new guideline recommendations have been released. Dermatological societies and health care organizations providing dermatological care should also be aware of how using patient engagement can enhance care for the individual patient and the available resources within an organization.

Delegation of care from doctors to (specialized) nurses or adequately trained physician assistants could be a feasible strategy to address issues of capacity, as well as the use of digital innovations for remote care. This is especially important for countries lacking physicians with training in dermatological care, or even lacking general physicians. For example, there is a reported shortage of dermatologists for most African countries (e.g., Namibia 0.8, Ghana 1.1, South Africa 3.0, Botswana 3.3, per one million people) compared to other parts of the world (United Kingdom 10, United States of America 36, Germany 65, per one million people) (139). Similar numbers are reported in the 2019 data of the Organization for Economic Co-operation and Development (OECD) on the number of doctors per country. The OECD found that Austria scored highest with 5.32 per 1,000 people, and South Africa scored the lowest with 0.79 (data from many countries is lacking) (166). Additionally, there are some concerns regarding physicians' knowledge of dermatology, although literature to substantiate this is sparse and hardly generalizable. A recent study of the curricula of USA medical schools demonstrated that dermatology training was not widely included (167). In the UK, it was reported that dermatology education was mandatory in approximately 80% of medical schools, resulting in a quarter of students graduating without exposure to clinical dermatology, and these estimates did not change between 2009 and 2016 (168). Regarding general physicians (GP), an Australian study suggested that trainees in GP find skin problems challenging, and indicated a need for more and better targeted undergraduate and trainee education in the field of dermatology (169).

Care

It can be deduced that the level of care delivered by health care providers to patients depends on many complex factors. Patient care is pictured in Figure 5.1 as the last step of the model, but it is the most crucial and personal one. The care provided by a health care professional must be centered around the individual patient's needs, with consideration of what can be accessed. This shared decision-making is based on knowledge, experience, communication skills, and available and applicable therapies, in a process of weighing their benefits and harms before a treatment plan is decided. For patients, this is the point of contact with health care delivery, and the way this is approached by the health care provider is essential to how patients manage their disease (e.g., adaptive coping and positive adjustment to illness) and use prescribed medication (e.g., adherence).

Depending on the needs of the patient, the role of the health care provider is to be informative and rational, whilst providing coaching with an empathetic understanding. Nevertheless, the level of care offered by health care providers depends on their working environment and can be influenced by the amount of time allocated for consultations, availability of staff, their knowledge, and what treatments are affordable. Although health care providers strive to do their best with every patient, what is realistically feasible depends on a complex system. Sadly, this does not always result in the patient receiving the best quality of care.

International Society of Atopic Dermatitis initiative to improve atopic dermatitis treatments in lower resource settings, such as Sub-Saharan Africa

On June 6th 2022, the International Society of Atopic Dermatitis (ISAD), the World Health Organization (WHO), the World Allergy Organization (WAO), the International League of Dermatological Societies (ILDS) and the Ministry of Public Health of Madagascar, held a meeting in Antananarivo, Madagascar, chaired by Alain Taieb, ISAD President. The meeting topic was entitled 'Atopic dermatitis and common skin disorders in sub-Saharan Africa (SSA)'.

The meeting is part of an initiative around improving the care and access to medicines for atopic dermatitis patients in lower resource settings driven by ISAD, in close collaboration with the WHO.

It was a follow-up to the inaugural workshop held in Geneva in 2019 (170), with the aim to launch a convergent plan of action in SSA targeting both skin neglected tropical diseases (NTDs) and common chronic skin diseases, in particular atopic dermatitis.

The decisions made at the meeting were:

1. To improve training and capacity building, for instance through updating WHO manuals and Apps, as well as the production of guidelines for the management of atopic dermatitis in lower resource countries, online courses on atopic dermatitis for the WHO platform, and translation of patient and physician leaflets on atopic dermatitis care in native languages; and
2. To improve drug accessibility, especially for emollients and oral methotrexate, but also new molecules, through inclusion on the WHO's essential medicines list (131) and by involving the manufacturers of those treatments.

'Global Accessibility to drugs for Atopic Dermatitis' will also be the topic of a satellite symposium at the ISAD 2023 symposium, Gdansk, Poland.

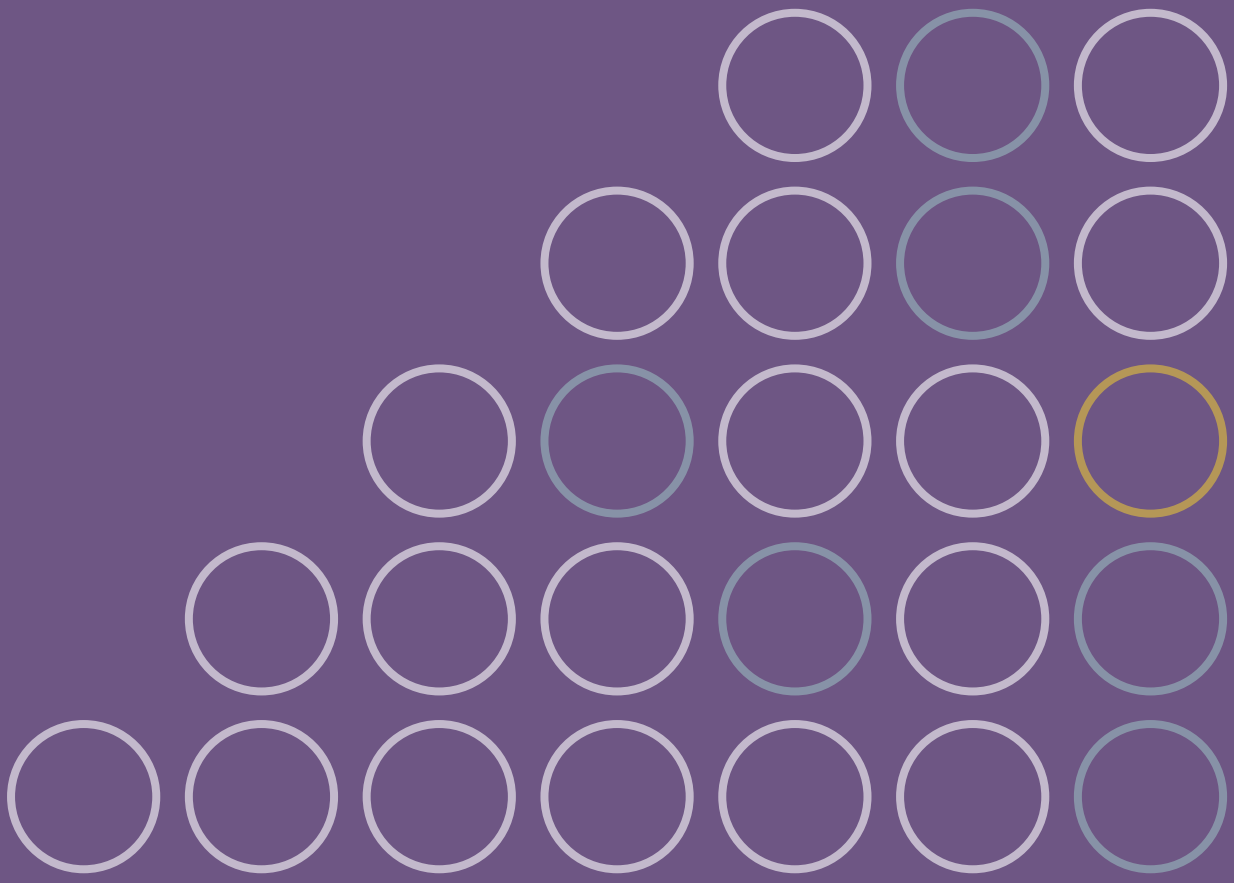
Addressing the general perceptions of atopic dermatitis

The societal misconceptions of atopic dermatitis being a mild skin condition that children will 'grow out of' or that it is contagious, are difficult to address. World Atopic Eczema Day has been held since 2018 on the 14th of September and is a global initiative. Patient organizations and their local dermatological societies use World Atopic Eczema Day to increase awareness of the challenges faced by people living with atopic dermatitis. The initiative is globally facilitated by the International Alliance of Dermatology Patient Organizations (GlobalSkin) and the European Federation of Allergy and Airways Diseases Patients' Associations (EFA). These awareness campaigns are of great importance for patients, their organizations, and for wider society (see Figure 5.2). Using understandable and accessible language, the annual campaign conveys messages in different media about what it is like to live with atopic dermatitis and emphasizes what is lacking. By highlighting aspects of atopic dermatitis that need to be better understood by the public, there is an effort to address societal misconceptions and reduce stigma.

Figure 5.2: World Atopic Eczema Day 2022 – social media cards


STANCE

Chapter 6.
Conclusion and considerations



The International League of Dermatological Societies (ILDS) initiated the Global Atopic Dermatitis Atlas (GADA) project in collaboration with the International Society of Atopic Dermatitis (ISAD), the International Eczema Council (IEC), the European Taskforce for Atopic Dermatitis (ETFAD) and the International Alliance of Dermatology Patient Organizations (GlobalSkin).

The inaugural 2022 GADA report kick starts the GADA project. The report summarizes current global data on the state of atopic dermatitis, and identifies gaps, barriers, and patients' (unmet) needs. The ILDS and all its collaborators are committed to addressing the gaps in epidemiological data over the coming years through the GADA project. Collaboration is a core value of ILDS and is a key concept in addressing the barriers and (unmet) needs of patients outlined in this report. Based on the findings from this report, considerations for stakeholders involved in the governance and provision of care for people with atopic dermatitis are summarized below.

Considerations for the World Health Organization

- Atopic dermatitis is a chronic non-communicable skin disease that can have a profound impact on the lives of patients, carers and families, and substantial financial implications for individuals and societies. Therefore, the severity of the disease-burden of atopic dermatitis should be recognized.
- To safely treat (young) children and sensitive areas of skin in adults (e.g., the face), the WHO Model List of Essential Medicines would benefit from the addition of a moderately potent topical corticosteroid (ATC-code D07AB).

Considerations for governments and policymakers

- People with atopic dermatitis should have access to affordable professional medical care.
- People with atopic dermatitis should have access to affordable, comprehensive, and personalized treatment.
- Current disparities in access to care and access to treatment, (inter)nationally or within national jurisdictions and (sub)populations, should be addressed and resolved.
- Medications on the current WHO Model List of Essential Medicines, including systemic therapies, are the bare minimum of what should be available for the treatment of atopic dermatitis.
- Information and education on atopic dermatitis should be provided to work towards increasing public awareness and reducing stigma, exclusion, and discrimination (e.g., through campaigns and educational programs).
- Patients' organizations, and their umbrella organizations, should be recognized, enabled, and supported.
- Patients' organizations, and their umbrella organizations when applicable, should be consulted in policy decision making.

Considerations for health care systems and health care professionals

- Health care professionals' associations should develop (or adapt/adopt) and maintain clinical practice guidelines, according to the required methodology and in collaboration with patients.
- Health care professionals' associations should provide (online) training for physicians from low- and middle-income countries to ensure adequate diagnosis and treatment of atopic dermatitis.
- Health care professionals' associations should collaborate with patients' organizations, (e.g., by serving on their Medical Advisory Boards) to help achieve shared goals.
- Health care providers should be given the appropriate time, training, and resources to educate people with atopic dermatitis and their carers in lay language about treating and managing the disease.
- Health care providers should implement health care delivery strategies such as remote and on-demand care, to address issues of capacity and travel distance, preferably in collaboration with patients.

- Every person with atopic dermatitis should be treated as whole, and not just their skin, with consideration of the wider burden of skin disease on everyday life.
- The principle of shared decision-making should be followed (e.g., discussing the patients' beliefs, lifestyle and preferences when deciding on a treatment plan).
- People with atopic dermatitis and their carers should receive adequate information, resources, and support to treat atopic dermatitis and cope with the impact the disease can have on quality of life.
- When resources allow, people with atopic dermatitis who have co-morbidities should be treated by multi-disciplinary teams.
- People with atopic dermatitis should have equal access to all available treatments and they should be affordable and practical for everyone.

Considerations for patients' organizations (national and international umbrellas):

- Patients' organizations should continue advocating for the rights of people with atopic dermatitis and their families, addressing issues such as social isolation, discrimination, exclusion, and stigma.
- Patients' organizations should be involved in raising public awareness of atopic dermatitis (e.g., through World Atopic Eczema Day), preferably in collaboration with governments, policymakers, and health care professionals' associations.
- Patients' organizations (especially local) should have a key role in providing (local) support to people with atopic dermatitis and their carers and should facilitate (online) platforms for mutual communication and recognition.
- Patients' organizations should have a role in holding governments and policymakers to account regarding their plans and commitments and should be able to challenge policies where appropriate.
- Patients' organizations should be able to collaborate with health care professionals' associations in the development of clinical practice guidelines, health technology assessments, and other formal policies regarding the care and treatment of atopic dermatitis.

Research considerations:

- All research should be conducted in partnership with patients, to ensure outcomes are meaningful to the lives of people with atopic dermatitis.
- All research should make use of the defined Core Outcomes for Trials for atopic dermatitis to provide robust evidence that can be compared between trials, and enable evidence synthesis in systematic reviews and meta-analyses.
- Academia and independent funding bodies should address research topics that are of less commercial interest, and focus on improving the evidence base on the prevention of atopic dermatitis, the development of comorbidities, and benefits and harms of existing therapies that have been used to treat the disease for decades.
- When not carried out by the pharmaceutical industry, academia and independent funding bodies should conduct robust clinical trials comparing active treatments and establish the added value of each treatment to position them in treatment algorithms within clinical practice guidelines.
- While clinical trials are intended to show efficacy of an intervention (e.g., compared to placebo or another active treatment) real-word data from patient registries is essential to demonstrate effectiveness and adverse events on a larger scale, with more long-

term patient follow up. Therefore, collection of real-world data on atopic dermatitis needs to be supported, encouraged, and ideally internationally harmonized in terms of outcomes measured (e.g. International TREAT registry taskforce).

- Academia should ensure the results of fundamental research are implementable within standard care and be of added value to the shared decision-making process around treatments for atopic dermatitis.
- The pharmaceutical industry should acknowledge the importance of including patients in their research and development programs from the earliest possible stages.
- The pharmaceutical industry should focus on mild-to-moderate atopic dermatitis, as there is currently a gap. In doing this, the appropriate products should be marketed, available and affordable.

Patients' closing words

As with the foreword, this chapter closes with the words of the patients whose stories have been featured in this report. These words were kindly made available by GlobalSkin from their powerful documentary 'Skin|Our Barrier to the World', that premiered on the 1st of September 2022, and have also been used for World Atopic Eczema Day 2022 (171).

Phoebe: *"I invite you, policy makers of the world, to please do something about it."*

Natalia: *"If there are treatments…"*

Rachel: *"…make it possible for people to access them."*

Martina: *"If support systems are in place…"*

Rhys: *"…make it so people can actually use them."*

Phoebe: *"If you care…"*

Arsene: *"…make it so people…"*

Natalia: *"…can get the care they need."*

Rachel: *"Do something right now. You have the power to change our lives."*

Help people living with atopic eczema in your country today.

From: Skin | Our Barrier to the World

References

1. Ständer S. Atopic Dermatitis. N Engl J Med. 2021;384(12):1136-43.
2. van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. Cochrane Database Syst Rev. 2017;2(2):CD012119.
3. Bosma AL, Ascott A, Iskandar R, Farquhar K, Matthewman J, Langendam MW, et al. Classifying atopic dermatitis: a systematic review of phenotypes and associated characteristics. J Eur Acad Dermatol Venereol. 202;36(6):807-19.
4. Ramírez-Marín HA, Silverberg JI. Differences between pediatric and adult atopic dermatitis. Pediatr Dermatol. 2022;39(3):345-53.
5. Bieber T, Paller AS, Kabashima K, Feely M, Rueda MJ, Ross Terres JA, et al. Atopic dermatitis: pathomechanisms and lessons learned from novel systemic therapeutic options. J Eur Acad Dermatol Venereol. 2022;36(9):1432-49.
6. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. Br J Dermatol. 2021;184(2):304-9.
7. Arents BWM, van Zuuren EJ, Vermeulen S, Schoones JW, Fedorowicz Z. Global Guidelines in Dermatology Mapping Project (GUIDEMAP), a systematic review of atopic dermatitis clinical practice guidelines: are they clear, unbiased, trustworthy and evidence based (CUTE)? Br J Dermatol. 2022;186(5):792-802.
8. Lax SJ, Harvey J, Axon E, Howells L, Santer M, Ridd MJ, et al. Strategies for using topical corticosteroids in children and adults with eczema. Cochrane Database Syst Rev. 2022;3(3):CD013356.
9. Chan LN, Magyari A, Ye M, Al-Alusi NA, Langan SM, Margolis D, et al. The epidemiology of atopic dermatitis in older adults: A population-based study in the United Kingdom. PLoS One. 2021;16(10):e0258219.
10. de Lusignan S, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C, et al. The epidemiology of eczema in children and adults in England: A population-based study using primary care data. Clin Exp Allergy. 2021;51(3):471-82.
11. Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. J Am Acad Dermatol. 2019;80(2):390-401.
12. Dhar S, Kanwar AJ. Epidemiology and clinical pattern of atopic dermatitis in a North Indian pediatric population. Pediatr Dermatol. 1998;15(5):347-51.
13. Ring J, Zink A, Arents BWM, Seitz IA, Mensing U, Schielein MC, et al. Atopic eczema: burden of disease and individual suffering - results from a large EU study in adults. J Eur Acad Dermatol Venereol. 2019;33(7):1331-40.
14. Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet. 2017;49(12):1752-7.
15. Appiah MM, Haft MA, Kleinman E, Laborada J, Lee S, Loop L, et al. Atopic dermatitis: Review of comorbidities and therapeutics. Ann Allergy Asthma Immunol. 2022;129(2):142-9.
16. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol. 2019;123(2):144-51.
17. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, et al. American Academy of Dermatology Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults. J Am Acad Dermatol. 2022;86(6):1335-6.e18.

18. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Bararot S, et al. Euroguiderm guideline on atopic eczema. Available at https://www.edf.one/home/Guidelines/EDF-EuroGuiDerm.html (last accessed 13 August 2022).
19. Institute for Health Metrics and Evaluation (IHME), 2020. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States. Available at https://vizhub.healthdata.org/gbd-results/ (last accessed 9 August 2022).
20. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI; ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124(6):1251-8.e23.
21. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One. 2012;7(7):e39803.
22. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. Allergy. 2018;73(3):696-704.
23. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. J Am Acad Dermatol. 2019;80(6):1526-32.e7.
24. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018;73(6):1284-93.
25. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132-8.
26. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. J Am Acad Dermatol. 2016;75(4):681-7.e11.
27. Ghio D, Muller I, Greenwell K, Roberts A, McNiven A, Langan SM, et al. 'It's like the bad guy in a movie who just doesn't die': a qualitative exploration of young people's adaptation to eczema and implications for self-care. Br J Dermatol. 2020;182(1):112-8.
28. Abuabara K, Margolis DJ. Do children really outgrow their eczema, or is there more than one eczema? J Allergy Clin Immunol. 2013;132(5):1139-40.
29. Thyssen JP, Corn G, Wohlfahrt J, Melbye M, Bager P. Retrospective markers of paediatric atopic dermatitis persistence after hospital diagnosis: A nationwide cohort study. Clin Exp Allergy. 2019;49(11):1455-63.
30. Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of mild to moderate atopic dermatitis. JAMA Dermatol. 2014;150(6):593-600.
31. Mulick AR, Mansfield KE, Silverwood RJ, Budu-Aggrey A, Roberts A, Custovic A, et al. Four childhood atopic dermatitis subtypes identified from trajectory and severity of disease and internally validated in a large UK birth cohort. Br J Dermatol. 2021;185(3):526-36.
32. Abuabara K, Ye M, Margolis DJ, McCulloch CE, Mulick AR, Silverwood RJ, et al. Patterns of atopic eczema disease activity from birth through midlife in 2 British birth cohorts. JAMA Dermatol. 2021;157(10):1191-9.
33. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43.
34. Flohr C, Weinmayr G, Weiland SK, Addo-Yobo E, Annesi-Maesano I, Björkstén B, et al. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. Br J Dermatol. 2009;161(4):846-53.
35. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351(9111):1225-32.

36. Reynolds M, Gorelick J, Bruno M. Atopic dermatitis: a review of current diagnostic criteria and a proposed update to management. J Drugs Dermatol. 2020;19(3):244-8.

37. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-51.

38. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. Br J Dermatol. 2008;158(4):754-65.

39. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980;92(Suppl):44-7.

40. Williams HC, Burney PG, Hay RJ , Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 1994;131(3):383–96.

41. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. J Allergy Clin Immunol. 2014;134(4):800-7.

42. Légaré S, Chagnon M, Palijan A, Kojok K, Bissonnette R. Sensitivity of clinician-assessed efficacy outcome measurement instruments in trials of topical therapies for atopic dermatitis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2022;36(2):196-212.

43. Harmonising Outcome Measures for Eczema (HOME). Available at http://www.homeforeczema.org/ (last accessed 14 August 2022).

44. Silverberg JI, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, et al. Validation of five patient-reported outcomes for atopic dermatitis severity in adults. Br J Dermatol. 2020;182(1):104-11.

45. Knudgaard MH, Andreasen TH, Ravnborg N, Bieber T, Silverberg JI, Egeberg A, et al. Rhinitis prevalence and association with atopic dermatitis: A systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2021;127(1):49-56.e1.

46. Ravnborg N, Ambikaibalan D, Agnihotri G, Price S, Rastogi S, Patel KR, et al. Prevalence of asthma in patients with atopic dermatitis: A systematic review and meta-analysis. J Am Acad Dermatol. 2021;84(2):471-8.

47. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. Front Immunol. 2020;11:1907.

48. Droitcourt C, Vittrup I, Kerbrat S, Egeberg A, Thyssen JP. Risk of systemic infections in adults with atopic dermatitis: A nationwide cohort study. J Am Acad Dermatol. 2021;84(2):290-9.

49. Alexander H, Paller AS, Traidl-Hoffmann C, Beck LA, De Benedetto A, Dhar S, et al. The role of bacterial skin infections in atopic dermatitis: expert statement and review from the International Eczema Council Skin Infection Group. Br J Dermatol. 2020;182(6):1331-42.

50. Wu D, Wu XD, Zhou X, Huang W, Luo C, Liu Y. Bone mineral density, osteopenia, osteoporosis, and fracture risk in patients with atopic dermatitis: a systematic review and meta-analysis. Ann Transl Med. 2021;9(1):40.

51. Egeberg A, Schwarz P, Harsløf T, Andersen YMF, Pottegård A, Hallas J, et al. Association of potent and very potent topical corticosteroids and the risk of osteoporosis and major osteoporotic fractures. JAMA Dermatol. 2021;157(3):275-82.

52. Schonmann Y, Mansfield KE, Hayes JF, Abuabara K, Roberts A, Smeeth L, et al. Atopic eczema in adulthood and risk of depression and anxiety: A population-based cohort study. J Allergy Clin Immunol Pract. 2020;8(1):248-57.e16.

53. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, et al. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults. Br J Dermatol. 2019;181(3):554-65.

54. Rønnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. J Am Acad Dermatol. 2018;79(3):448-56.e30.

55. Patel KR, Immaneni S, Singam V, Rastogi S, Silverberg JI. Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(2):402-10.

56. Kern C, Wan J, LeWinn KZ, Ramirez FD, Lee Y, McCulloch CE, et al. Association of atopic dermatitis and mental health outcomes across childhood: A longitudinal cohort study. JAMA Dermatol. 2021;157(10):1200-8.
57. Mora-Fernández V, Mercader Garcia P, Borrego Hernando L, González Pérez R, Córdoba Guijarro S, Giménez Arnau A, et al. Epidemiological, clinical, and allergy profile of patients with atopic dermatitis and hand eczema: Evaluation of the Spanish Contact Dermatitis Registry (REIDAC). Actas Dermosifiliogr. 2022;113(3):236-43.
58. Lloyd-Lavery A, Solman L, Grindlay DJC, Rogers NK, Thomas KS, Harman KE. What's new in atopic eczema? An analysis of systematic reviews published in 2016. Part 3: nomenclature and outcome assessment. Clin Exp Dermatol. 2019;44(4):376-80.
59. Thyssen JP, Schuttelaar MLA, Alfonso JH, Andersen KE, Angelova-Fischer I, Arents BWM, et al. Guidelines for diagnosis, prevention, and treatment of hand eczema. Contact Dermatitis. 2022;86(5):357-78.
60. Ruff SMD, Engebretsen KA, Zachariae C, Johansen JD, Silverberg JI, Egeberg A, et al. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. Br J Dermatol. 2018;178(4):879-88.
61. Papadatou Z, Williams H, Cooper K. Effectiveness of interventions for preventing occupational irritant hand dermatitis: a quantitative systematic review. JBI Database System Rev Implement Rep. 2018;16(6):1398-1417.
62. Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin-Weller M, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020;34(12):2717-44.
63. Girolomoni G, Luger T, Nosbaum A, Gruben D, Romero W, Llamado LJ, et al. The economic and psychosocial comorbidity burden among adults with moderate-to-severe atopic dermatitis in Europe: Analysis of a cross-sectional survey. Dermatol Ther (Heidelb). 2021;11(1):117-30.
64. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340-7.
65. Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. J Am Acad Dermatol. 2006;55(3):490-500.
66. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: Summary of a report for the National Eczema Association. J Invest Dermatol. 2017;137(1):26-30.
67. Filanovsky MG, Pootongkam S, Tamburro JE, Smith MC, Ganocy SJ, Nedorost ST. The financial and emotional impact of atopic dermatitis on children and their families. J Pediatr. 2016;169:284-90.e5.
68. Drucker AM, Qureshi AA, Amand C, Villeneuve S, Gadkari A, Chao J, et al. Health care resource utilization and costs among adults with atopic dermatitis in the united states: A claims-based analysis. J Allergy Clin Immunol Pract. 2018;6(4):1342-138.
69. Chovatiya R, Begolka WS, Thibau IJ, Silverberg JI. Financial burden and impact of atopic dermatitis out-of-pocket healthcare expenses among black individuals in the United States. Arch Dermatol Res. 2022;314(8):739-47.
70. Augustin M, Misery L, von Kobyletzki L, Armario-Hita JC, Mealing S, Redding M. Unveiling the true costs and societal impacts of moderate-to-severe atopic dermatitis in Europe. J Eur Acad Dermatol Venereol. 2022;36(Suppl 7):3-16.
71. Augustin M, Misery L, Kobyletzski LV, Mealing S, Redding M, Chuang CC, et al. Systematic literature review assessing the overall costs and societal impacts of moderate-to-severe atopic dermatitis in Europe. J Eur Acad Dermatol Venereol. 2022 Aug 3. Epub ahead of print.
72. Launois R, Ezzedine K, Cabout E, Reguai Z, Merrhand S, Heas S, et al. Importance of out-of-pocket costs for adult patients with atopic dermatitis in France. J Eur Acad Dermatol Venereol. 2019;33(10):1921-7.
73. Zink AGS, Arents B, Fink-Wagner A, Seitz IA, Mensing U, Wettemann N, et al. Out-of-pocket costs for individuals with atopic eczema: A cross-sectional study in nine European countries. Acta Derm Venereol. 2019;99(3):263-7.

74. Olsson M, Bajpai R, Wee LWY, Yew YW, Koh MJA, Thng S, et al. The cost of childhood atopic dermatitis in a multi-ethnic Asian population: a cost-of-illness study. Br J Dermatol. 2020;182(5):1245-52.

75. Tsai TF, Rajagopalan M, Chu CY, Encarnacion L, Gerber RA, Santos-Estrella P, et al. Burden of atopic dermatitis in Asia. J Dermatol. 2019;46(10):825-34.

76. Thyssen JP, Brenneche AW, Madsen ME, Pedersen MH, Trangbaek DJ, Vestergaard C. Societal costs of moderate-to-severe atopic dermatitis occurring in adulthood: A Danish register-based study. Acta Derm Venereol. 2021;101(9):adv00538.

77. Cheng BT, Paller AS, Griffith JW, Silverberg JI, Fishbein AB. Burden and characteristics of skin pain among children with atopic dermatitis. J Allergy Clin Immunol Pract. 2022;10(4):1104-6.e1.

78. Ali F, Vyas J, Finlay AY. Counting the Burden: Atopic dermatitis and health-related quality of life. Acta Derm Venereol. 2020;100(12):adv00161.

79. Vakharia PP, Cella D, Silverberg JI. Patient-reported outcomes and quality of life measures in atopic dermatitis. Clin Dermatol. 2018;36(5):616-30.

80. Lundin S, Bergström A, Wahlgren CF, Johansson EK, Andersson N, Ballardini N, et al. Living with atopic dermatitis as a young adult in relation to health-related quality of life and healthcare contacts: A population-based study. Acta Derm Venereol. 2022;102:adv00702.

81. Chernyshov PV, Tomas-Aragones L, Manolache L, Marron SE, Salek MS, Poot F, et al. Quality of life measurement in atopic dermatitis. Position paper of the European Academy of Dermatology and Venereology (EADV) Task Force on quality of life. J Eur Acad Dermatol Venereol. 2017;31(4):576-93.

82. Arents BWM, Mensing U, Seitz IA, Wettemann N, Fink-Wagner AH, de Carlo G, et al. Atopic eczema score of emotional consequences—a questionnaire to assess emotional consequences of atopic eczema. Allergo J Int. 2019;28:277-88.

83. Thomas KS, Apfelbacher CA, Chalmers JR, Simpson E, Spuls PI, Gerbens LAA, et al. Recommended core outcome instruments for health-related quality of life, long-term control and itch intensity in atopic eczema trials: results of the HOME VII consensus meeting. Br J Dermatol. 2021;185(1):139-46.

84. Huang J, Choo YJ, Smith HE, Apfelbacher C. Quality of life in atopic dermatitis in Asian countries: a systematic review. Arch Dermatol Res. 2022;314(5):445-62.

85. Alzolibani AA. Impact of atopic dermatitis on the quality of life of Saudi children. Saudi Med J. 2014;35(4):391-6.

86. Barbarot S, Silverberg JI, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. The family impact of atopic dermatitis in the pediatric population: Results from an international cross-sectional study. J Pediatr. 2022;246:220-6.e5.

87. Chernyshov PV, Jirakova A, Ho RC, Moed H, Caldeira AP, Alvarenga TM, et al. An international multicenter study on quality of life and family quality of life in children with atopic dermatitis. Indian J Dermatol Venereol Leprol. 2013;79(1):52-8.

88. Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. J Eur Acad Dermatol Venereol. 2014;28(6):719-26.

89. Silverberg JI. Atopic dermatitis in adults. Med Clin N Am. 2020;104(1):157–76.

90. Hua T, Kim LS, Yousaf M, Gwillim EC, Yew YW, Lee B, et al. Psychological interventions are more effective than educational interventions at improving atopic dermatitis severity: A systematic review. Dermatitis. 2022 Apr 28. Epub ahead of print.

91. Barbarot S, Stalder JF. Therapeutic patient education in atopic eczema. Br J Dermatol. 2014;170(Suppl 1):44-8.

92. Takaoka R, Coelho E. Patient education in atopic dermatitis: Why it is needed and how to improve it. Curr Derm Rep. 2018;7(4):221–6.

93. Ridd MJ, King AJL, Le Roux E, Waldecker A, Huntley AL. Systematic review of self-management interventions for people with eczema. Br J Dermatol. 2017;177(3):719-34.

94. Arents BWM. Eczema treatment: it takes time to do no harm. Br J Dermatol. 2017;177(3):613-4.

95. Armario-Hita JC, Artime E, Vidal-Vilar N, Huete T, Díaz-Cerezo S, Moro RM, et al. Patient-reported outcome measures in real-world atopic dermatitis studies in Spain: A systematic review. Actas Dermosifiliogr. 2022;113(7):685-704.

96. Sanchez J, Cherrez-Ojeda I, Galvan C, Garcia E, Hernández-Mantilla N, Londoño Garcia A, et al. the unmet needs in atopic dermatitis control in Latin America: A multidisciplinary expert perspective. Dermatol Ther (Heidelb). 2021;11(5):1521-40.

97. Greenwell K, Ghio D, Sivyer K, Steele M, Teasdale E, Ridd MJ, et al. Eczema Care Online: development and qualitative optimisation of an online behavioural intervention to support self-management in young people with eczema. BMJ Open. 2022;12(4):e056867.

98. Dhar S, Parikh D, Rammoorthy R, Srinivas S, Sarkar R, Inamadar A, et al. Treatment guidelines for atopic dermatitis by ISPD Task Force 2016. Indian J Paediatr Dermatol. 2017;18(3):174-6.

99. Silverberg JI, Lei D, Yousaf M, Janmohamed SR, Vakharia PP, Chopra R, et al. Association of itch triggers with atopic dermatitis severity and course in adults. Ann Allergy Asthma Immunol. 2020;125(5):552-9.e2.

100. Girolomoni G, Busà VM. Flare management in atopic dermatitis: from definition to treatment. Ther Adv Chronic Dis. 2022;13:20406223211066728.

101. Moosbrugger-Martinz V, Leprince C, Méchin MC, Simon M, Blunder S, Gruber R, et al. Revisiting the roles of filaggrin in atopic dermatitis. Int J Mol Sci. 2022;23(10):5318.

102. Wang V, Boguniewicz J, Boguniewicz M, Ong PY. The infectious complications of atopic dermatitis. Ann Allergy Asthma Immunol. 2021;126(1):3-12.

103. Solomon I, Ilie MA, Draghici C, Voiculescu VM, Căruntu C, Boda D, Zurac S. The impact of lifestyle factors on evolution of atopic dermatitis: An alternative approach. Exp Ther Med. 2019;17(2):1078-84.

104. Tamagawa-Mineoka R, Katoh N. Atopic dermatitis: Identification and management of complicating factors. Int J Mol Sci. 2020;21(8):2671.

105. Yue H, Umehara Y, Trujillo-Paez JV, Peng G, Nguyen HLT, Chieosilapatham P, et al. Exogenous factors in the pathogenesis of atopic dermatitis: Irritants and cutaneous infections. Clin Exp Allergy. 2021;51(3):382-92.

106. Wang HL, Sun J, Qian ZM, Gong YQ, Zhong JB, Yang RD, et al. Association between air pollution and atopic dermatitis in Guangzhou, China: modification by age and season. Br J Dermatol. 2021;184(6):1068-76.

107. Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: A systematic review and meta-analysis. J Am Acad Dermatol. 2016;75(6):1119-25.e1.

108. Manam S, Tsakok T, Till S, Flohr C. The association between atopic dermatitis and food allergy in adults. Curr Opin Allergy Clin Immunol. 2014;14(5):423-9.

109. Gerner T, Haugaard JH, Vestergaard C, Deleuran M, Jemec GB, Mortz CG, et al. Disease severity and trigger factors in Danish children with atopic dermatitis: a nationwide study. J Eur Acad Dermatol Venereol. 2021;35(4):948-57.

110. Dhar S, Srinivas SM. Food allergy in atopic dermatitis. Indian J Dermatol. 2016;61 (6):645-8.

111. Hamann CR, Andersen YMF, Engebretsen KA, Skov L, Silverberg JI, Egeberg A, et al. The effects of season and weather on healthcare utilization among patients with atopic dermatitis. J Eur Acad Dermatol Venereol. 2018;32(10):1745-53.

112. Haque MS, Hailu T, Pritchett E, Cusack CA, Allen HB. The oldest new finding in atopic dermatitis: subclinical miliaria as an origin. JAMA Dermatol. 2013;149(4):436-8.

113. Dhar S, Kanwar AJ, Kaur S, Sharma P, Ganguly NK. Role of bacterial flora in the pathogenesis and management of atopic dermatitis. Indian J Med Res. 1992;95:234-8.

114. Chopra R, Vakharia PP, Sacotte R, Silverberg JI. Efficacy of bleach baths in reducing severity of atopic dermatitis: A systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2017;119(5):435-40.

115. Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, et al. Bleach baths for atopic dermatitis: A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. Ann Allergy Asthma Immunol. 2022;128(6):660-8.e9.

116. Gauger A, Mempel M, Schekatz A, Schäfer T, Ring J, Abeck D. Silver-coated textiles reduce Staphylococcus aureus colonization in patients with atopic eczema. Dermatology. 2003;207(1):15-21.

117. Ricci G, Patrizi A, Bendandi B, Menna G, Varotti E, Masi M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. Br J Dermatol. 2004;150(1):127-31.

118. Gauger A, Fischer S, Mempel M, Schaefer T, Foelster-Holst R, Abeck D, et al. Efficacy and functionality of silver-coated textiles in patients with atopic eczema. J Eur Acad Dermatol Venereol. 2006;20(5):534-41.

119. Ricci G, Patrizi A, Mandrioli P, Specchia F, Medri M, Menna G, Masi M. Evaluation of the antibacterial activity of a special silk textile in the treatment of atopic dermatitis. Dermatology. 2006;213(3):224-7.

120. Senti G, Steinmann LS, Fischer B, Kurmann R, Storni T, Johansen P, et al. Antimicrobial silk clothing in the treatment of atopic dermatitis proves comparable to topical corticosteroid treatment. Dermatology. 2006;213(3):228-33.

121. Juenger M, Ladwig A, Staecker S, Arnold A, Kramer A, Daeschlein G, et al. Efficacy and safety of silver textile in the treatment of atopic dermatitis (AD). Curr Med Res Opin. 2006;22(4):739-50.

122. Koller DY, Halmerbauer G, Böck A, Engstler G. Action of a silk fabric treated with AEGIS in children with atopic dermatitis: a 3-month trial. Pediatr Allergy Immunol. 2007;18(4):335-8.

123. Stinco G, Piccirillo F, Valent F. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. Dermatology. 2008;217(3):191-5.

124. Park KY, Jang WS, Yang GW, Rho YH, Kim BJ, Mun SK, et al. A pilot study of silver-loaded cellulose fabric with incorporated seaweed for the treatment of atopic dermatitis. Clin Exp Dermatol. 2012;37(5):512-5.

125. Thomas KS, Bradshaw LE, Sach TH, Batchelor JM, Lawton S, Harrison EF, et al. Silk garments plus standard care compared with standard care for treating eczema in children: A randomised, controlled, observer-blind, pragmatic trial (CLOTHES Trial). PLoS Med. 2017;14(4):e1002280.

126. World Health Organisation Collaborating Centre for Drug Statistics Methodology. Available at https://www.whocc.no/atc_ddd_index/?code=D07A&showdescription=no (last accessed 12 August 2022).

127. Oakley R, Arents BWM, Lawton S, Danby S, Surber C. Topical corticosteroid vehicle composition and implications for clinical practice. Clin Exp Dermatol. 2021;46(2):259-69.

128. Koster ES, Philbert D, Zheng X, Moradi N, de Vries TW, Bouvy ML. Reducing corticosteroid phobia in pharmacy staff and parents of children with atopic dermatitis. Int J Clin Pharm. 2021;43(5):1237-44.

129. Lambrechts L, Gilissen L, Morren MA. Topical corticosteroid phobia among healthcare professionals using the TOPICOP Score. Acta Derm Venereol. 2019;99(11):1004-8.

130. Bos B, Antonescu I, Osinga H, Veenje S, de Jong K, de Vries TW. Corticosteroid phobia (corticophobia) in parents of young children with atopic dermatitis and their health care providers. Pediatr Dermatol. 2019;36(1):100-4.

131. World Health Organization Model List of Essential Medicines – 22nd List, 2021. Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.02). Available at WHO model list of essential medicines – 22nd list, 2021 (last accessed 12 August 2022).

132. Haw WY, Al-Janabi A, Arents BWM, Asfour L, Exton LS, Grindlay D, et al. Global Guidelines in Dermatology Mapping Project (GUIDEMAP): a scoping review of dermatology clinical practice guidelines. Br J Dermatol. 2021;185(4):736-44.

133. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nat Rev Drug Discov. 2022;21(1):21-40.

134. Clinicaltrial.gov. Available at https://clinicaltrials.gov/ (last accessed 2 August 2022).

135. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. Dermatitis. 2014;25(3):107-14.

136. Thyssen JP, Corn G, Wohlfahrt J, Melbye M, Bager P. Retrospective markers of paediatric atopic dermatitis persistence after hospital diagnosis: A nationwide cohort study. Clin Exp Allergy. 2019;49(11):1455-63.

137. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorioet P, et al. Atopic dermatitis in the pediatric population: A cross-sectional, international epidemiologic study. Ann Allergy Asthma Immunol. 2021;126(4):417-28. e2.

138. Alfawzan A, Altalhab S, Alkhowailed M. Dermatology workforce over a decade in Saudi Arabia: demographics, distributions, and future challenges. Hum Resour Health. 2022;20(1):29.

139. Tiwari R, Amien A, Visser WI, Chikte U. Counting dermatologists in South Africa: number, distribution and requirement. Br J Dermatol. 2022;187(2):248-50.

140. Rehman R, Mateen Z, Osto M, Mehregan D. Ethnic distribution of populations in the highest and lowest dermatologist-dense areas: is there more to the story? Dermatol Online J. 2022;28(1).

141. Glazer AM, Farberg AS, Winkelmann RR, Rigel DS. Analysis of trends in geographic distribution and density of US dermatologists. JAMA Dermatol. 2017;153(4):322-5.

142. Mosam A, Todd G. Dermatology training in Africa: Successes and challenges. Dermatol Clin. 2021;39(1):57-71.

143. Statista Research Department. Number of dermatologists in selected European countries in 2015. Published July 2021. Available at https://www.statista.com/statistics/873707/number-from-dermatologists-in-europe/ (last accessed 6 August 2022).

144. Rehman R, Mateen Z, Osto M, Mehregan D. Ethnic distribution of populations in the highest and lowest dermatologist-dense areas: is there more to the story? Dermatol Online J. 2022;28(1).

145. Ariens LF, Schussler-Raymakers FM, Frima C, Flinterman A, Hamminga E, Arents BW, et al. Barriers and facilitators to eHealth use in daily practice: Perspectives of patients and professionals in dermatology. J Med Internet Res. 2017;19(9):e300.

146. The Global Psoriasis Atlas. Available at https://www.globalpsoriasisatlas.org/ (last accessed 18 August 2022).

147. Guariguata L, Whiting D, Weil C, Unwin N. The International Diabetes Federation diabetes atlas methodology for estimating global and national prevalence of diabetes in adults. Diabetes Res Clin Pract. 2011;94(3):322-32.

148. Eczema Foundation. PO-SCORAD app. 2018. Available at: https://www.poscorad.com/ (last accessed 21 august 2022).

149. European Federation of Allergy and Airways Diseases Patients' Associations: Brussels, Belgium. Itching for life. 2018 Available from https://www.efanet.org/images/2018/EN_-_Itching_for_life_Quality_of_Life_and_costs_for_people_with_severe_atopic_eczema_in_Europe_.pdf (last accessed 20 August 2022).

150. Kimberly McCleary K of the Kith Collective. Understanding the lived experience of eczema - The "voice of the patient" report on the eczema Patient-focused drug development meeting. 2019, More than Skin Deep. Available from https://www.aafa.org/media/2628/more-than-skin-deep-voice-of-the-patient-report.pdf (last accessed 20 August 2022).

151. Abuabara K, Nicholls SG, Langan SM, Guttman-Yassky E, Reynolds NJ, Paller AS, et al. Priority research questions in atopic dermatitis: an International Eczema Council eDelphi consensus. Br J Dermatol. 2021;185(1):203-5.

152. Elsawi R, Dainty K, Smith Begolka W, Barta K, Butler L, Capozza K, Eftekhari S, et al. The multidimensional burden of atopic dermatitis among adults: Results from a large national survey. JAMA Dermatol. 2022;158(8):887-92.

153. World Health Organization. Global expert consultation on the WHO framework on patient and family engagement (WHO/HIS/SDS/2015.12). 2015, Geneva, Switzerland. Available at: https://www.who.int/publications/m/item/global-expert-consultation-on-the-who-framework-on-patient-and-family-engagement (last accessed 20 August 2022).

154. Drucker AM, Ellis A, Jabbar-Lopez Z, Yiu ZZN, Arents BWM, Burton T, et al. Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis. BMJ Open. 2018;8:e023061.

155. Drucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZN, Rochwerg B, et al. Systemic immunomodulatory treatments for patients with atopic dermatitis: A systematic review and network meta-analysis. JAMA Dermatol. 2020;156(6):659-67.

156. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, et al. Systemic immunomodulatory treatments for atopic dermatitis: Update of a living systematic review and network meta-analysis. JAMA Dermatol. 2022;158(5):523-32.

157. Anstey AV, Popli U, Hughes CL. Patient engagement with the BJD: why and how? Br J Dermatol. 2019;180(6):1274-6.

158. Heague M, Ray C, Bowers J, Guckian J, Arents BWM, Layton A. Patient and public involvement in dermatology research: A review. Am J Clin Dermatol. 2022;23(3):319-29.

159. Fritzsche MC, Buyx AM, Hangel N. Mapping ethical and social aspects of biomarker research and its application in atopic dermatitis and psoriasis: a systematic review of reason. J Eur Acad Dermatol Venereol. 2022;36(8):1201-13.

160. van Zuuren EJ, Arents BWM, Flohr C, Ingram JR. Publication of national dermatology guidelines as a Research Letter in the BJD: can less ever be enough? Br J Dermatol. 2020;182(6):1319-20.

161. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25.

162. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013;66(2):140-50.

163. Montori VM, Brito JP, Murad MH. The optimal practice of evidence-based medicine: incorporating patient preferences in practice guidelines. JAMA. 2013;310(23):2503-4.

164. Capozza K, Vastrup A, Proctor A, Roberts A, Picozza M, Manion R, et al. The sound of silence – where are the voices of patients in eczema guideline development? Br J Dermatol 2022 Aug 16; Epub ahead of print.

165. Garrett Z, Imaz-Iglesia I, Willemsen A. Building a model of health technology assessment cooperation: lessons learned from EUnetHTA joint action 3. Int J Technol Assess Health Care. 2022;38(1):e14.

166. The Organisation for Economic Co-operation and Development (OECD). Doctors per 1,000 people, 2019 - Country rankings. Available from: https://www.theglobaleconomy.com/rankings/doctors_per_1000_people/ (last accessed 20 August 2022).

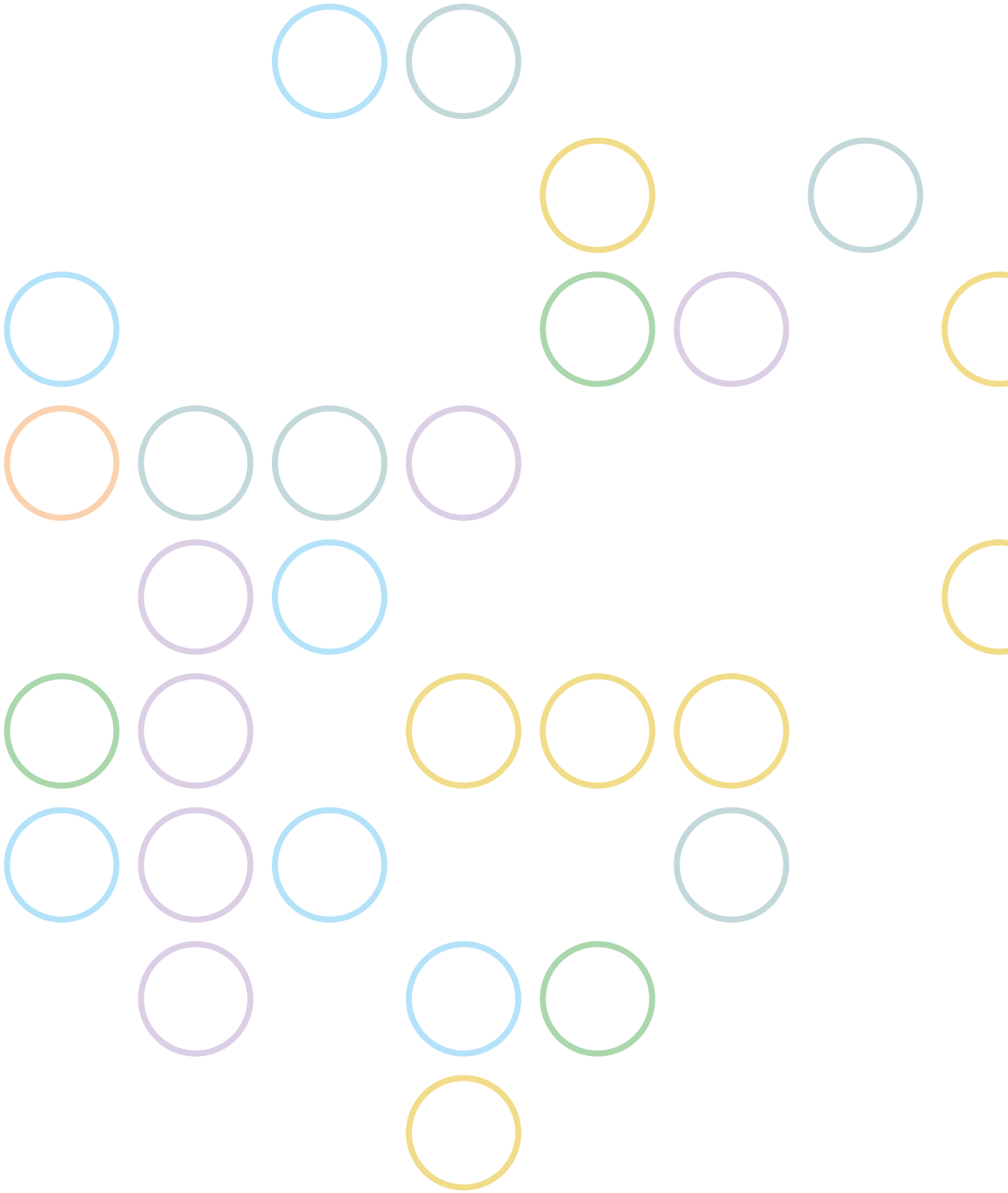
167. Cahn BA, Harper HE, Halverstam CP, Lipoff JB. Current status of dermatologic education in US medical schools. JAMA Dermatol. 2020;156(4):468-70.

168. Yaakub A, Cohen S, Singh, Goulding. Dermatological content of U.K. undergraduate curricula: where are we now? Br J Dermatol. 2017;176(3):836.

169. Whiting G, Magin P, Morgan S, Tapley A, Henderson K, Oldmeadow C, et al. General practice trainees' clinical experience of dermatology indicates a need for improved education: A cross-sectional analysis from the Registrar Clinical Encounters in Training Study. Australas J Dermatol. 2017;58(4):e199-e206.

170. Schmid-Grendelmeier P, Takaoka R, Ahogo K, Belachew W, Brown S, Correia J, et al. Position statement on atopic dermatitis in sub-Saharan Africa: current status and roadmap. J Eur Acad Dermatol Venereol. 2019;33(11):2019-28.

171. Global Skin. Atopic Eczema Documentary: Skin Our Barrier to the World. 2022. Available at https://www.youtube.com/watch?v=qYiJgUvWMRg (last accessed 22 August 2022).



Appendix

Current therapeutic pipeline for atopic dermatitis

Current therapeutic pipeline for atopic dermatitis adapted from Bieber 2022 (133) and updated with data from clinicaltrials.gov (134).

Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Modulating the microbiome	Bacterial strains — topical	B244 (AOBiome)	Nitric oxide donor	IIb	NCT04490109 (completed 2021)
		ShA9 (NIAID)	Targeted microbiome transplant	I/IIa	NCT03151148 (completed 2020)
		FB-401 (Forte Biosciences)	Bacterial replacement, anti- inflammation via TLR5 and TNFR activation	IIb	NCT04504279 (completed 2021)
	Small molecule — topical	CLS-001/ omiganan (Maruho Co)		II	NCT03091426 (completed 2017)
		ATx201/ niclosamide (Union Therapeutics)	Protonophore activity Cell membrane enhancer	II	NCT04339985 (completed 2020)
	Bacterial strains — oral	EDP1815 (Evelo)	Modulation of systemic inflammation	II	NCT05121480 (recruiting since 2021)
		STMC-103H (Siolta therapeutics)	Immunomodulation via microbiome manipulation	Ib	NCT03819881 (recruiting since 2019)

Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Targeting the innate immune response	Small molecule — topical	Tapinarof/ benvitimod (Dermavant)	AhR agonist	IIb	NCT05014568 NCT05032859 (recruiting since 2021)
	Biologic — injection	Tezepelumab (Amgen/ AstraZeneca)	TSLP	IIb	NCT03809663 (completed 2022)
		Etokimab (AnaptysBio)	IL-33	IIa	NCT03533751 (recruiting since 2018)
		REGN3500 (Regeneron)	IL-33	IIa	NCT03738423 (terminated-lack of efficacy)
		Astegolimab (Genentech)	IL-33	IIa	NCT03747575 (completed 2018)
		MEDI3506 (Astra Zeneca)	IL-33	IIa	NCT04212169 (started 2019)
		Bermekimab (Janssen)	IL-1α	II	NCT04021862 (completed 2020)
		Spesolimab (Böhringer Ingelheim)	IL-36R	IIa	NCT03822832 (completed 2020)

Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Targeting the adaptive immune response	Biologic — injection	GBR 830/ISB 830 (Glenmark/ Ichnos)	OX40	IIb	NCT03568162 (completed 2022)
		KHK4083 (Kyrin)	OX40	IIb	NCT03703102 (completed 2022)
		KY1005 (Kymab/ Sanofi)	OX40L	IIb	NCT05131477 (recruiting since 2021)
		Dupilumab (Regeneron/ Sanofi)	IL-4Rα	Approved globally (>6 yr)	NCT03346434 (completed 2021 for ≥6 mo to <6 yr)
		CBP-201 (Connect Biopharma)	IL-4Rα	IIb	NCT04444752 (completed 2021)
		AK120 (Akesobio)	IL-4Rα	II	NCT05048056 (recruiting since 2021)
		ASLAN004 (ASLAN)	IL-4Rα1	IIb	NCT04090229 (recruiting since 2021)
		Tralokinumab (LEO Pharma)	IL-13	Approved globally for adults	NCT03526861 (completed for adolescents 2021)
		Lebrikizumab (Allmiral/Lilly)	IL-13	III, staggered pediatric program ongoing	NCT04250350 (completed 2022)
		Benralizumab (AstraZeneca)	IL-5Rα	II	NCT04605094 (started 2020)
		Omalizumab (Novartis)	IgE	II	NCT02300701 (completed 2018)
		FB825/anti- CεmX (LEO Pharma/ Oneness Biotech)	mIgE	IIa	NCT04413942 (start 2020)
		Fezakinumab (IIT)	IL-22	IIa	NCT01941537 (completed 2019)
		LEO 138559 (LEO Pharma)	IL-22R1	IIa	NCT04922021 (start 2021)
		Secukinumab (Novartis)	IL-17a	IIa	NCT02594098, NCT03568136 (completed 2019 and 2020 resp.)
		Risankizumab (AbbVie)	IL-23	IIa	NCT03706040 (completed 2021)
		LY3471851 (Lilly)	rhIL-2 to Treg cells	Ib	NCT04081350 (start 2019)

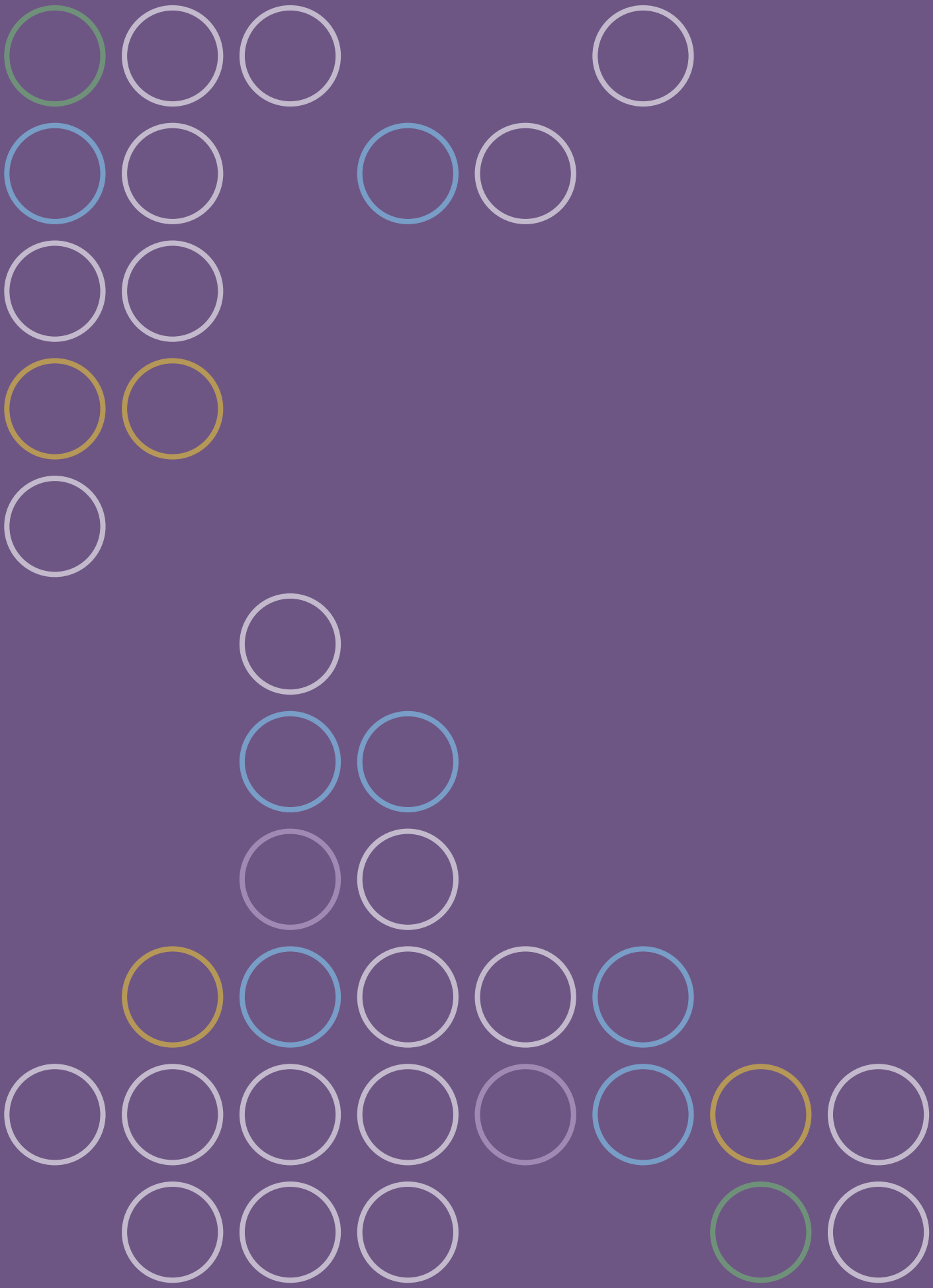
Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Targeting the adaptive immune response	Small molecule — oral	Adriforant (Novartis)	H4R	IIb	NCT03517566 (terminated-lack of efficacy)
		LEO 152020/ JW1601 (LEO Pharma)	H4R	IIb	NCT05117060 (start 2021)
		RPT193 (RAPT Therapeutics)	CCR4	IIb	NCT05399368 (recruiting since 2022)
		Etrasimod (Arena Pharma)	S1PR1, S1PR4, S1PR5	IIb	NCT04162769 (completed 2020)
		SCD-044 (Sun Pharma)	S1PR1	IIa	NCT04684485 (recruiting since 2020)
		LC51-0255 (LG Chem)	S1PR1	I	Not applicable
		BMS-986166 (Bristol Myers Squibb	S1PR1	IIb	NCT05014438 (recruiting since 2021)
		KT-474 (Kymera)	S1PR1	Ib	NCT04772885 (recruiting since 2021)

Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Targeting the adaptive immune response	Small molecule — topical	AKP-11 (Akaal Pharma)	S1PR1	IIb	ACTRN12617000763347 (completed 2017)
		Lotamilast (RVT-501 /E6005) (Dermavant)	PDE4	IIb	NCT03394677, NCT02950922 (completed 2018 and 2017 resp.) NCT03415282 (start 2018)
		Difamilast (OPA-15406 /MM36) (Otsuka)	PDE4	III	NCT0390897, NCT03911401 (both completed 2019)
		DRM02 (Dermira)	PDE4	IIb	NCT01993420 (completed 2014)
		LEO 29102 (LEO Pharma	PDE4	IIa	NCT01037881 (completed 2010)
		Roflumilast (AstraZeneca)	PDE4	IIa/IIb	NCT01856764 (completed 2014) NCT04773587, NCT04773600, NCT04845620 (all recruiting since 2021)
		Hemay-808 (Tianjin Hemay Pharmaceutical)	PDE4	IIa	NCT04352595 (start 2021, status unknown)
		PF-07038124 (Pfizer)	PDE4	IIa	NCT04664153 (completed 2021)
		BEN2293 (BenevolentAI Bio)	TRK	IIa	NCT04664153 (completed 2021) NCT04737304 (recruiting since 2020)
		HY209 (Shaperon)	GPCR19	II	NCT04530643 (completed 2021)
		VTP-38543 (Vitae Pharma)	Liver X receptor- β	IIa	(completed 2016)
		ALX 101 (Ralexar)	Liver X receptor	IIb	NCT03175354 (completed 2018) NCT03859986 (start 2019)

Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Targeting itching	Biologic — injection	Nemolizumab (Galderma)	IL-31	III	NCT03989349 NCT03985943 (start both 2019)
		Vixarelimab (Kiniksa Pharma)	OSMRβ	IIa/b	NCT03816891 (recruiting since 2019)
	Small molecule — oral	Serlopitant (Vyne)	NK1R	IIa	NCT02975206 (completed 2018)
		Tradipitant (Vanda)	NK1R	III	NCT03568331 (completed 2019) NCT04140695 (completed 2020)
		BLU-5937 (Bellus)	P2X3	II	NCT04693195 (completed 2021)
Inhibiting Janus kinases		Delgocitinib (Japan Tobacco/ LEO)	Pan-JAK	IIb in EU, approved in Japan	NCT03725722 (completed 2020)
		Ruxolitinib (Incyte)	JAK1/JAK2	III	NCT03745638 NCT03745651 (completed 2019 and 2020 resp.) NCT04921969 (recruiting since 2021)
		Cerdulatinib (RVT/ DMVT502) (Dermavant)	Pan-JAK/SYK	Ib	NA
		Brepocitinib (Pfizer)	JAK1/TYK2	IIb	NCT03903822 (completed 2020)
		ATI-1777 (Aclaris)	JAK1/JAK3	IIa	NCT04598269 (completed 2021)
		CEE321 (Novartis)	Pan-JAK	I	NCT04612062 (completed 2021)
		Jaktinib (Suzhou Zeigen Biopharma	Pan-JAK	IIa	NCT04539639 (recruiting since 2020)
		SHR0302 (Reistone Biopharma)	JAK-1	II/III	NCT04717310 (recruiting since 2020)

Strategy	Drug type and mode of application	Agent/company	Mode of action/ target	Clinical development phase in AD	Clinical trial ID
Inhibiting Janus kinases	Small molecule — oral	Baricitinib (Lilly)	JAK1/JAK2	Approved in EU for adults, staggered pediatric program ongoing	NCT03952559 (recruiting since 2019)
		Upadacitinib (AbbVie)	JAK-1	Approved in EU and US for adolescents and adults, staggered pediatric program ongoing	NCT03646604 (start 2019)
		Abrocitinib (Pfizer)	JAK-1	Approved in EU and US for adults and adolescents	NCT03627767 (completed 2020)
		SHR0302 (Reistone Biopharma)	JAK-1	II	NCT04162899 (completed 2020)

Legend: AhR, aryl-hydrocarbon receptor; BTK, Bruton tyrosine kinase; CCR4, C- C chemokine receptor 4; GPCR19, G protein-coupled receptor 19; H4R, type 4 histamine receptor; IL-4Rα, α- chain of the IL-4 receptor; IL-5Rα, α-chain of the IL-5 receptor; IL-13Rα1, α1 chain of the IL-13 receptor; IL-22R1, IL-22 receptor 1; JAK, Janus kinase; NK1R, neurokinin 1 receptor; NA, not applicable; OSMRβ, oncostatin M receptor-β; OX40L, OX40 ligand; PDE4, phosphodiesterase 4; P2X3, purinoreceptor 3 rhIL-2, recombinant human IL-2; resp., respectively; S1PR1, sphingosine 1- phosphate receptor 1; Treg cell, regulatory T cell; TRK, tropomyosin receptor kinase; TSLP, thymic stromal lymphopoietin.



atopicdermatitisatlas.org