Occurrence and treatment patterns in children with atopic dermatitis and subsequent comorbidity in the form of severe acne
- a nationwide prescription registry study

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Til Pete, Henrik, Victoria og William

- *Nei, jeg bare tuller! Dere skal få noe annet.*

Summary

Background

Over the last decades, research has demonstrated that atopic dermatitis is prevalent. To our knowledge, however, there is scarce literature based on large-scale studies of the incidence and treatment patterns of atopic dermatitis in children and rarely on real-world data. In addition, knowledge about the occurrence of severe acne and the tolerability of acne treatment in individuals with atopic dermatitis is scant. A better understanding of the risk factors, predictors, and comorbidities faced by patients may facilitate a more personalized medical approach to the effective treatment of atopic dermatitis, potentially improving patient outcomes and helping to reduce the costs and burdens associated with the disease.

Aims

Using a national health registry based on prescription data, we aimed to provide up-to-date, population-based estimates of incidence and prevalence, risk predictors, disease burden, and an extensive overview of treatment patterns in the pediatric population of Norway. We also aimed to provide updated nationwide prevalence estimates for severe acne vulgaris in patients with atopic dermatitis and compare them with those without atopic dermatitis. We also aimed to evaluate the tolerability of isotretinoin in patients with atopic dermatitis.

Methods

Paper I included all Norwegian children aged up to six years between January 1, 2009, and December 31, 2015. In *Paper II*, all Norwegian children aged up to eleven years were included between January 1, 2014, and December 31, 2020. Finally, in *Paper III,* all children aged 4-6 were followed for 17 years until age 20-22 in 2020. Children with atopic dermatitis were identified using an algorithm based on medical diagnoses and disease-specific medications from the Norwegian Prescription Database (NorPD). Population statistics from Statistics Norway (SSB) were broken down by birth year, sex, and age (based on the annual mid-year population in Norway). Data on Norwegian climate statistics with long-term temperatures were retrieved from the Norwegian Meteorological Institute.

Results

The result from this nationwide study suggests a rise in the incidence rate of atopic dermatitis in Norwegian children during the study period, especially in children younger than one year (*Paper I).* Atopic dermatitis occurred earlier in boys than in girls before the age of two years *(Paper I).* Over one in six children under six years of age was affected by atopic dermatitis in Norway during the study period (from 2009 to 2014) *(Paper I).* More children with atopic dermatitis received their first treatment in winter or spring than in summer *(Paper I).* Most pediatric patients in Norway are treated with mild topical corticosteroids for a limited period *(Paper II).* Although the prevalence of atopic dermatitis was highest in the youngest children, these pediatric patients were least likely to be treated with potent topical corticosteroids *(Paper II).* Male sex and early onset of atopic dermatitis were associated with a long-term treatment course and treatment with antihistamines, potent topical corticosteroids, and skin infections *(Paper II)*. Systemic corticosteroids and other systemic treatments were sparingly used in children *(Paper II).* Severe acne was associated with atopic dermatitis in young adults older than 17 years at the population level *(Paper III).* We discovered a considerably increased use of topical corticosteroids in patients with a long-term course of atopic dermatitis while receiving isotretinoin treatment *(Paper III).*

Conclusions

The research included in this thesis shows that the risk of being treated for atopic dermatitis before the age of six is high (and possibly increasing). The high number of prescriptions, especially in the first years of life, indicates a high burden. Although most patients have a mild disease course, this study demonstrates that atopic dermatitis in children is a public health problem in Norway.

One effective method for treating atopic dermatitis is through the application of topical corticosteroids. However, Norway differs from other countries, such as the United States, in that systemic corticosteroids are not as commonly prescribed.

Although patients with atopic dermatitis suffer from dry skin, treatment of severe acne was associated with atopic dermatitis at the population level in young adults over 17 years of age. The results indicate that patients with a long-term course of disease (most likely severe atopic dermatitis) tolerated isotretinoin similarly to patients with a short-term course of disease (most likely mild atopic dermatitis).

Norsk sammendrag

Bakgrunn

Det er få storskalastudier av forekomst og behandlingsmønster av atopisk dermatitt hos barn. Kunnskapen om forekomst av alvorlig akne og tolerabiliteten av ankebehandling hos pasienter med atopisk dermatitt begrenset. En bedre forståelse av risikofaktorene, prediktorene og komorbiditetene kan føre til en bedre, mer effektiv og mer individuelt tilpasset behandling. Det kan redusere kostnader og byrden forbundet med sykdommen.

Mål

Ved å bruke et nasjonalt helseregister basert på reseptdata, hadde vi som mål beregne oppdaterte, populasjonsbaserte forekomst og prevalens, risikoprediktorer, sykdomsbyrde og behandlingsmønstre i den pediatriske befolkningen i Norge. I tillegg hadde vi som mål å gi oppdaterte landsdekkende prevalensestimater for alvorlig akne vulgaris hos pasienter med atopisk dermatitt og å sammenligne dette med befolkningen uten atopisk dermatitt. Vi hadde også som mål å undersøke tolerabiliteten av behandling med isotretinoin hos pasienter med atopisk dermatitt.

Metoder

Artikkel I inkluderte alle norske barn i alderen opptil seks år mellom 1. januar 2009 og 31. desember 2015. *I artikkel II* ble alle norske barn i alderen opp til elleve år inkludert mellom 1. januar 2014 og 31. desember 2020. I *artikkel III*, ble alle barn i alderen 4-6 fulgt i 17 år til alderen 20-22 i 2020. Barn med atopisk dermatitt ble identifisert ved hjelp av en algoritme basert på medisinske diagnoser fra resepter og sykdomsspesifikke medisiner fra Norsk Reseptdatabase (NorPD). Befolkningsstatistikk fra Statistisk sentralbyrå (SSB) ble fordelt på fødselsår, kjønn og alder (basert på den årlige halvårsbefolkningen i Norge). Data om norsk klimastatistikk med langtidstemperaturer er hentet fra Meteorologisk institutt.

Resultater

Resultatet fra denne landsomfattende studien tyder på en økning i forekomsten av atopisk dermatitt hos norske barn i løpet av studieperioden, spesielt hos barn yngre enn ett år *(artikkel I)*. Atopisk dermatitt oppstod tidligere hos gutter enn hos jenter før fylte to år *(artikkel I)*.

Over ett av seks barn under seks år ble rammet av atopisk dermatitt i Norge i løpet av studieperioden (fra 2009 til 2014) (*artikkel I).* Flere barn med atopisk dermatitt fikk sin første behandling om vinteren eller våren enn om sommeren *(artikkel I).* De fleste pediatriske pasienter i Norge behandles med milde topikale kortikosteroider i en kortvarig periode *(artikkel II).* Selv om forekomsten av atopisk dermatitt var høyest hos de yngste barna, var det minst sannsynlig at disse pediatriske pasientene ble behandlet med potente topikale kortikosteroider *(artikkel II).* Mannlig kjønn og tidlig debut av atopisk dermatitt var assosiert med et langvarig behandlingsforløp og behandling med antihistaminer, potente topikale kortikosteroider og hudinfeksjoner *(artikkel II).* Systemiske kortikosteroider og andre systemiske behandlinger ble i liten grad skrevet ut til barn, særlig om en sammenlikner med bruken i USA *(artikkel II).* Behandling av alvorlig akne var assosiert med atopisk dermatitt hos unge voksne over 17 år på populasjonsnivå *(artikkel III).* Vi oppdaget et økt bruk av topikale kortikosteroider hos pasienter med et langvarig forløp av atopisk dermatitt mens de fikk behandling med isotretinoin *(artikkel III).*

Konklusjoner

Resultatene i artiklene viser en høy risiko (og muligens økende) for å bli behandlet for atopisk dermatitt før fylte seks år. Det høye antallet resepter, spesielt i de første leveårene, indikerer en høy belastning i unge alder. Selv om de fleste pasienter har et mildt sykdomsforløp, tyder funnene i studiene på at atopisk dermatitt hos barn er et folkehelseproblem i Norge.

En effektiv metode for å behandle atopisk dermatitt er gjennom påføring av topikale kortikosteroider. Vi fant at Norge skiller seg imidlertid fra andre land, som for eksempel USA, ved at systemisk bruk av kortikosteroider ikke er like vanlig å foreskrive.

Selv om pasienter med atopisk dermatitt generelt lider av tørr hud, ble behandling av alvorlig akne assosiert med atopisk dermatitt på befolkningsnivå hos unge voksne over 17 år. Resultatene tyder på at pasienter med langvarig sykdomsforløp (mest sannsynlig alvorlig atopisk dermatitt) tolererte isotretinoin på samme måte som pasienter med kortvarig sykdomsforløp (mest sannsynlig mild atopisk dermatitt).

Abbreviations

AD	Atopic dermatitis
ADHD	Attention Deficit Hyperactivity Disorder
AEDS	Atopic eczema/dermatitis syndrome
A.D.	Anno Domino
ATC	Anatomical Therapeutic Chemical (classification system for medicines)
BMI	Body mass index
CI	Confidence Interval
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
DALYs	Disability-adjusted life years
DAGs	Directed Acyclic Graphs
DDD	Defined Daily Dose
EAACI	European Academy of Allergology and Clinical Immunology
EASI	Eczema Area and Severity Index
HR	Hazards Ratio
HSV	Herpes Simplex Virus
ICD	International Classification of Disease system
ICD-10	International Classification of Diseases, version 10
ICPC-2	International Classification of Primary Care, version 2
IGA scale	Investigator Global Assessment Scale
IgE	Immunoglobulin E
IR	Incidence Rate
IRR	Incidence Rate Ratio
ISAAC	The International Study of Asthma and Allergies in Childhood
JAK	Janus Kinase
NMI	National Meteorological Institute
NorPD	Norwegian Prescription Database
NPR	National Population Register
OR	Odds Ratio
OTC	Over the Counter

POEM	Patient-Oriented Eczema Measure
PY	Person Years
RH	Relative Humidity
SD	Standard Deviation
SSB	Statistics Norway
STROBE	STrengthening The Reporting of OBservational studies in Epidemiology
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
TEWL	Transepidermal water loss
WAO	World Allergy Organization
WHO	World Health Organization

Lists of papers

This thesis is based on three original research articles, referred to by Roman numerals (Paper I - III).

I. Mohn CH, Blix HS, Halvorsen JA, Nafstad P, Valberg M, Lagerlov P. Incidence Trends of Atopic Dermatitis in Infancy and Early Childhood in a Nationwide Prescription Registry Study in Norway. JAMA Netw Open 2018; 1: e184145.

II. Mohn CH, Blix HS, Brænd AM, Nafstad P, Nygard S, Halvorsen JA. Treatment Patterns of Atopic Dermatitis Medication in 0-10-Year-Olds: A Nationwide Prescription-Based Study. Dermatol and Therapy (Heidelb) 2022; 12: 1639-1657.

III. Mohn CH, Blix HS, Brænd AM, Nafstad P, Halvorsen JA. Prevalence of Isotretinoin Therapy in Adolescents and Young Adults With and Without Atopic Dermatitis: A Nationwide Prescription-based Population Study. Acta Derm Venereol. 2023 Jun 13;103:9424.

1 GENERAL INTRODUCTION

Atopic dermatitis – an overview

Atopic dermatitis, is the most common cause of the worldwide burden of skin disease with significant morbidity, including itching and impairment of personal and family quality of life [1]. Despite these profound implications, skin diseases still receive relatively little attention at the national and global levels.

The inflammatory skin condition known as atopic dermatitis is characterized by red, itchy, swollen, cracked, and irritated skin and can be lifelong [2-4]. In addition to skin symptoms, atopic dermatitis increases the risk of several comorbidities, such as progression to other atopic diseases e.g., asthma and allergic rhino-conjunctivitis [5-8]. The disease is also associated with several non-allergic/non-atopic comorbidities, including anxiety, attention deficit hyperactivity disorder, depression, infections, and suicidality [9, 10].

Specific genes associated with atopic dermatitis have been identified, and individuals with a family history have a higher risk of developing the disease. Temperature changes (e.g., cold, dry weather), allergens and irritants (e.g., dust, pollen, pet dander, certain cleaning products and hard water), and other environmental factors can irritate the skin and trigger a flare-up of the disease, worsening symptoms. Some studies have also suggested an association between stress and atopic dermatitis. Atopic dermatitis can have an unpredictable and fluctuating course for many patients.

The complex pathophysiology includes a epidermal dysfunction, altered microbiome, T-cell-driven inflammation [11]. The exact cause of atopic dermatitis is not completely understood.

Atopic dermatitis is more prevalent in the youngest children but can appear at any age. Estimates of the prevalence of atopic dermatitis range from 0 to 24% [12]. Studies have found that it affects up to 20% of children and 10% of adults in high-income countries [11].

The disease burden of atopic dermatitis goes far beyond the skin symptoms. Atopic dermatitis represents a substantial financial burden for patients, their families, and society and the disease can impact the quality of life of patients, caregivers and partners [13-18]. Moreover, The use of health care resources is extensive, and treatment are frequently very time-consuming for the patients and caregivers. Currently, this disease has no cure, and the only treatment is to prevent and relieve symptoms.

Nomenclature

The lack of consensus on nomenclature leads to inconsistency and confusion in research and clinical practice. According to a recent meta-analysis, "eczema" and "atopic dermatitis" are the most commonly used terms for atopic dermatitis [19]. Although the terms atopic dermatitis and eczema and are often referred to as synonyms [20] when retrieved from PubMed, they contain different outcomes and address various topics in their respective corpora [21]. There are several causes and types of eczema, e.g., atopic dermatitis, contact dermatitis (irritant or allergic), discoid and dyshidrotic eczema, neurodermatitis, seborrheic eczema and stasis dermatitis.

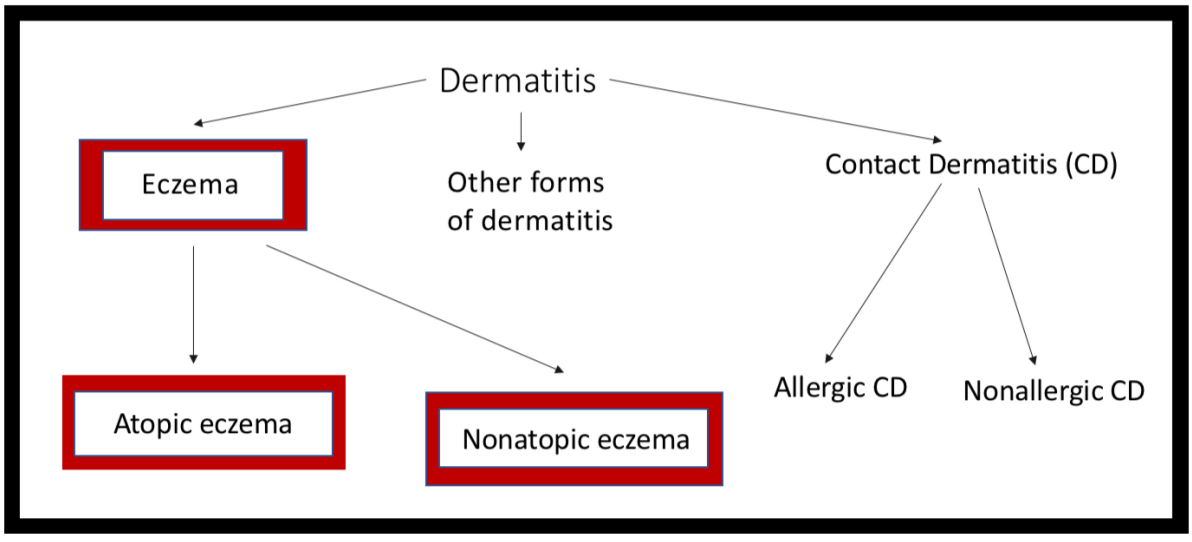

Figure 1 Under the umbrella "dermatitis", the term eczema has been agreed upon to replace the transitional term atopic eczema/dermatitis syndrome (AEDS). Atopic eczema is eczema in a person of the atopic constitution [22]. The figure is inspired by Dr. Emma Johannson, a dermatologist at Karolinska University Hospital.

In 2001, the European Academy of Allergology and Clinical Immunology (EAACI) proposed the nomenclature "Atopic eczema/dermatitis syndrome" (AEDS) [23]. In 2004, the World Allergy Organization (WAO) introduced the umbrella term *"dermatitis*" for local inflammation of the skin [22]. The organization also proposed that the term *eczema* includes *atopic eczema* and *non-atopic eczema*, the former meaning "*eczema in a person with an atopic constitution"* [24]. The requirement for IgE testing to determine the diagnosis, violates scientific and clinical standards and is associated with increased healthcare costs, which dermatologists have not welcomed [24].

In popular scientific presentations and in conversations with patients and caregivers, the term atopic eczema may be used more naturally [25]. However, because *eczema* is a nonspecific term describing the morphologic manifestation of various types of dermatitis, Kantor et al. recommend that the more specific term *atopic dermatitis* to be used in publications, medical education, and patient education [26]. Therefore, the term *atopic dermatitis* is consistently used in this thesis independently of IgE sensitization.

Historical aspects of atopic dermatitis

The heterogeneity of the clinical presentation of atopic dermatitis may be one reason for the different terminology used to describe the disease. The first known Egyptian papyrus addressing general medical issues dates from antiquity, about 1500 BC, and comprises material on various treatments for severe skin itching [27]. Maybe the earliest record of an individual, Emperor Augustus, having skin atopy is by Gaius Suetonius Tranquillus (anno domino [A.D.] 69), who made it part of his writing *The Twelve Caesars* (*De vita Caesarum*) [28]. The term eczema was first used centuries later by the Greek physician Aëtius of Amida (A.D. 543). Eczema in Greek; έκζεμα, means to boil [29].

In modern times, the first scientific treatise on skin diseases, *De morbis cutaneis* was published in 1572 by the physician Girolamo Mercuriale (1530-1606), describing a skin disease corresponding to what is now termed atopic dermatitis [30]. Jean-Louis Alibert (1768-

1837), a dermatologist in France, wrote descriptions of weeping and pruritic skin in pediatric patients (*teigne muqueuse, achor muqueuse)* [31].

Willan (1757-1812) and Bateman (1778-1821), two dermatologists, introduced a paradigm shift in the comprehension of the diseases of the skin [32, 33]. The two expanded the term eczema to mean "*an eruption of minute vesicles, noncontagious, crowded together; and which from the absorption of fluid they contain form into thin flakes or crusts*" [33]. In 1903, French dermatologist Luis-Anne-Jean Brocq was the earliest to distinguish the condition from other forms of eczema by calling it "neurodermatitis" [34]. Robert Cooke (1880-1960) and Arthur Coca (1875-1959), acknowledged the relationship between asthma allergic and rhinitis, coined the term *atopy* in 1923 [33]. In the field of dermatology, Marion Sulzberger (1895-1983) and Fred Wise (1881-1950) are known for their contribution to the introduction of the term "atopic dermatitis" in 1933.[33].

Etiology

Atopic dermatitis is a heterogeneous disease and the pathophysiology is multifactorial and complex [35]. Genetic disposition, environmental factors [36-39], immunologic responses and dysregulations (altered Th1/Th2 balance) and defective skin barrier function are some of the critical components of atopic dermatitis [39-43]. Interleukin-33 is a proinflammatory cytokine that is overproduced in the keratinocytes of patients with atopic dermatitis and often triggers the itch-scratch cycle of atopic dermatitis [44]. Mutations in the gene encoding filaggrin (FLG) are the best-known genetic abnormality predisposing to atopic dermatitis [45]. However, the key driver is controversial and still debated [46]. The epidermal and dermal immune systems and the skin microbiome support the function of the physical skin barrier. An imbalance of all three factors characterizes the disease. The pathophysiology of atopic dermatitis is thought to be influenced by changes in proteases and protease inhibitors, as well as by changes in the composition of epidermal lipids consisting of cholesterol, free fatty acids and ceramides [47-49].

Skin barrier disruption, manifesting as dry skin, is one of the primary pathologic findings in atopic dermatitis and one of its defining characteristics [49]. Even though the detailed

mechanism of pathogenesis remains unknown, over the past ten years, significant advances in the research of atopic dermatitis have increased our understanding of atopic dermatitis and provided support for the concept of the disease as an inflammatory skin condition with a systemic component [43]. Animal and human research has revealed that skin barrier disruption is inherited and increases the passage of allergens and other potentially toxic substances into the upper layer of skin, as well as an increase in transepidermal water loss [49, 50].

Clinical presentation

Because atopic dermatitis is a complex and heterogeneous disease, patients present a broad spectrum of clinical manifestations. Although the heterogeneity of atopic dermatitis is now widely recognized, there is no consensus on the different subtypes [51, 52]. The main clinical features include xerosis and lesions with poorly defined erythematous patches, papules, and plaques that may show edema or scales [53]. Pruritus is a central symptom of atopic dermatitis. Crusty erosions may result from scratching, and oozing is a sign of secondary infection [53]. The course of the disease can fluctuate from initially brief disease to relapsing-remitting disease, chronic or persistent atopic dermatitis, or extended periods of remission with subsequent relapse [11]. The disease can have a wide spectrum [11], and clinical features can range from minimal atopic dermatitis to generalized erythroderma in severe cases [54]. Lesions may co-occur at different stages [54]. The clinical presentation of atopic dermatitis may vary depending on the patient's age, skin type (i.e., pigmentation), location, ethnicity, other comorbidities, topical treatments used, and (duration of) disease activity. Other signs of atopic dermatitis include periorbital pigmentation, alopecia of the eyebrows, and the Dennie-Morgan sign (infraorbital fold under the eyelids) [53].

Individuals who have atopic dermatitis typically have dry skin. Pruritic, red, swollen, peeling skin with exudation, crusting, or erythematous papules characterize acute atopic dermatitis, while dry skin patches and scaly or excoriated erythematous papules are signs of subacute or chronic lesions [55]. Chronic scratching can lead to skin lichenification and fissures that often appear hyperpigmented (postinflammatory hyperpigmentation) [56]. Hypopigmentation,

pityriasis alba, is also common (sometimes mistakenly thought to be caused by topical corticosteroids).

Moreover, eczematous lesions typically have an age-dependent distribution [57, 58]. Diagnosis of atopic dermatitis may be tricky in infants who may have few (or none) objectively visible lesions at the time of medical examination, especially because pruritus, the main feature of atopic dermatitis, is not obvious [59].

In infants, the lesions often occur on the forehead, scalp, and cheeks [55]. In children up to two years of age, the extensor regions, cheeks, or scalp are more likely to be affected, leaving out the diaper area [55]. Older children and teenagers often have a flexural distribution, especially in the antecubital and popliteal fossa, the volar aspect of the neck, ankles, and wrists, and an "atopic dirty neck" (reticular pigmentation), whereas in adults the lesions tend to be more localized, with lichenified plaques in the skin flexures [55].

Predictors of risk

Established risk factors for developing atopic dermatitis include genetic factors such as atopy in the family (atopic dermatitis, asthma, or allergic rhinitis) and loss-of-function variants in the filaggrin gene. Environmental factors such as water hardness, chlorinated water [60], cold/warm weather (according to seasons), living in urban vs. rural areas, early child daycare, and pets are also known risk factors.

The early debut of atopic dermatitis is more likely to have IgE-mediated sensitization, severe early disease, a family predisposition to atopy, low income, darker skin pigmentation, considerably increased occurrence of loss-of-function mutations in the filaggrin gene higher disease activity, increased persistence, prolonged hospitalization, along with poor disease control for atopic dermatitis [61-67]. However, the three latter factors mentioned are poorly studied [66, 67].

Moreover, a few studies have shown that there is a possibility that more boys than girls are treated for atopic dermatitis at a young age [68-70]. Based on the 2020 Swedish systematic review, the prevalence of atopic dermatitis in girls before one year of age was 24% versus 35% in boys [71]. A research project from Denmark, suggest that the male sex appears to be associated with higher prevalence rates, and a higher burden of disease at a young age [72]. The male sex has also been found to be a predictor of excessive transepidermal water loss at three months in a study conducted in Norway fairly recently [73]. However, among children of school age, the prevalence was approximately 8% in boys and 11% in girls [71]. The female sex appears to be associated with a longer disease course [71, 74].

The severity of atopic dermatitis

Atopic dermatitis causes the most disability associated with skin disease and causes significant morbidity worldwide [1]. One of the most common chronic inflammatory skin diseases occurring in early childhood in the Western world is atopic dermatitis, ranking 15th among all non-fatal diseases and having the highest burden of disease among skin conditions as measured by disability-adjusted life years (DALYs) [55, 75, 76]. The burden of atopic dermatitis goes far beyond rashes, xerosis, and pruritus and affects all parts of one's life, including one's ability to sleep, relationships, performance at work or school, and other social activities. Atopic dermatitis is also associated to sleep difficulties (primarily owing to pruritus), lower work productivity, depression, and anxiety, all of which impose an additional burden on patients and caretakers physically and financially [75, 77-80].

Presently, there are more than 60 scales (instruments) in the literature for assessing the severity of atopic dermatitis [81]. When assessing the extent and severity of atopic dermatitis, the severity scoring systems/rating scales: the *Eczema Area and Severity Index* (EASI) and the *Investigator Global Assessment* (IGA) *Scale* are most commonly used [82, 83].

Although patients retain their atopic predisposition throughout their life, the disease is usually mild with brief periods of exacerbation [84-87]. Wollenberg and his collogues (y. 2018) discovered that approximately 10% of patients have severe disease (all ages included)[88]. A

2021 U.S. study evaluated the percentage of severe atopic dermatitis in children younger than six years in 18 countries to be 3.1%- 11.0% (except Israel; 24.9%) [89]. Although the prevalence and severity of atopic dermatitis varied by age group and country, overall, less than 15% were estimated to be severely affected [89].

The literature on the severity of the disease is sparse, especially in patients younger than two years [87, 90]. In an analysis of a 2020 study, Paller et al. [87] found that among children and adolescents, the most commonly treated age group for atopic dermatitis was 0-1 years old [87]. Another recent Danish study on the disease burden of atopic dermatitis (measured as the number of days with symptoms and medical treatment) confirms that the highest disease burden occurs in the first years of life, especially at one year of age [72]. While the burden of the disease increases with severity, even mild to moderate atopic dermatitis is related to a significant physical and economic burden [91-94].

Atopic dermatitis diagnostic criteria

Several scoring systems, diagnostic criteria, and tools for the purpose of diagnosing atopic dermatitis have been translated, validated, and put into use in various nations. The major clinical criteria for the diagnosis of atopic dermatitis were first developed by Hanifin and Rajka in 1980 using patients treated in hospitals [95]. These criteria (revised 2003) are most frequently cited in studies and have been validated several times [96, 97].

The *United Kingdom Working Party criteria* were defined in 1994 (revised in 2005) as a refinement of Hanifin and Rajka's original criteria to make them more suitable for population-based studies and easier to apply in the clinical setting [97, 98]. The diagnostic "*William´s criteria*" were developed by the United Kingdom Working Party [99].

The main features and criteria for the diagnosis, are the presence of atopic dermatitis at predilection sites, pruritus, chronic and recurrent nature, a personal - or a family history of allergic disease, and dry skin. The criteria are used in daily clinical practice, clinical trials,

and epidemiological studies. The criteria of Hanifin and Rajka and the United Kingdom Working Party are the most validated and used to date [97, 98, 100, 101].

Epidemiological measurements of atopic dermatitis

It remains challenging to obtain valid measures of the incidence, prevalence, natural course, and distribution of atopic dermatitis in a population. Although incidence refers to the number of new disease events in a given period, diagnosing atopic dermatitis in the early stages can be challenging because of the heterogeneous clinical picture of the disease [102].

Prevalence is usually defined as the proportion of the population with a disease [64]. Many studies that examined prevalence as part of a broader analysis reported wide variation in the prevalence of atopic dermatitis in pediatric populations [89, 103, 104]. Discrepancies between outcomes may be due to numerous factors, including variations in defined age groups, classifications/diagnostic methods used, varieties in prevalence described (point, period, or lifetime), aspects of reporting (self-report or clinical examination), differences within and between populations (population heterogeneity), variations in study methods and definitions of cases/participants with different clinical manifestations, and nomenclature of atopic dermatitis used [55, 105]. For this reason, there are no reliable estimates of the worldwide prevalence of atopic dermatitis and its trends over time. Without a pathognomonic biomarker, clinical signs and history are required for diagnosing atopic dermatitis, and physician assessment is regarded as the gold standard [12].

General population health surveys (questionnaire/telephone based on self-assessment of symptoms), hospital settings including outpatients, atopic dermatitis diagnosis codes in administrative data (i.e., prescription database and diagnoses made by physicians), and medical records are the data sources for large-scale epidemiologic studies of atopic dermatitis. For practical reasons, physiologic measures of atopic dermatitis (predominantly based on the *Investigator Global Assessment scale* (IGA scale) and the *Eczema Area and Severity Index* (EASI) are rarely available in large-scale epidemiologic studies [82].

In large-scale studies, standardized clinical trials involving subjects with and without atopic dermatitis are impractical for ethical, economic, and practical reasons. Many patients with atopic dermatitis have periods without visible skin lesions or bothersome symptoms, so the timing of clinical trials is critical in determining whether a subject has symptoms (skin lesions) of atopic dermatitis. Therefore, a point prevalence (over a short period of time) most likely underestimates the number of patients who have the disease, and a period prevalence (over a longer period of time) should be preferred. Consequently, the heterogeneity of the disease, determined by remission and relapse of clinical symptoms in the same individual over time, is then reflected in the prevalence determined.

The use of real-world data from national registries offers the potential for large sample sizes (and thus generalizability and robustness) and long-term, close follow-up epidemiologic studies in a real-world clinical setting [106]. Registry-based research allows for continuous, automated, and accurate assessment of events over time without impacting participants (children and their families). Information is collected in databases, reducing the risk of selective reporting (selection bias) and eliminating recall bias [107]. However, the fact that registry data are mostly collected for administrative purposes limits the information available. Moreover, the information collected is not tailored to the research question.

Incidence, prevalence, course and cumulative lifetime prevalence

The increase in atopic dermatitis in the Nordic countries has been described since the 1950s [108-112]. Three questionnaire-based studies of asthma, atopic dermatitis, and allergy in school-aged children were conducted by Selnes et al. in Troms and Finnmark counties (northern Norway). The self-reported atopic eczema/dermatitis syndrome (AEDS) study revealed a prevalence of 13.4%, 21.1%, and 20.8% in 1985, 1995, and 2000, respectively [110, 111]. A Danish study monitored the prevalence of atopic dermatitis from 1996 to 2002 and estimated that the prevalence of atopic dermatitis in children was approximately 14% [113].

Recent studies in Western countries, including the Nordic countries, suggest that the incidence in young children has leveled off at 15-20% [13, 108, 109, 114-116]. A Scandinavian research group observed that the incidence rate of atopic dermatitis in Danish and Swedish children remained virtually unchanged, from 1.05% in 1998 to 1.06% in 2011 and from 1.05% in 2007 to 0.99% in 2010, respectively [55, 114]. In Germany, children aged 9 to 11 have an incidence rate of 1.7% and those aged 16 to 20 have a recurrent incidence rate of 2.4% [55] .

Phases one and three of the International Study of Asthma and Allergy in Childhood (ISAAC) found that atopic dermatitis was increasing, especially in Western and developing countries. According to phase three (2009), the global prevalence ranged from approximately 1% to 25%, with the highest prevalence rates in Sweden, Latin America, and Africa [117]. Another researcher noted in 2020 that though estimates in high-income countries are stabilizing, the prevalence of atopic dermatitis is increasing worldwide [11]. However, a 2022 review (Nature) of 45 studies of the prevalence of atopic dermatitis (all ages) between 1992 and 2013 found no clear trend [12]. The study also found a 12-month prevalence for atopic dermatitis of 9.2% [12].

The burden of disease in the population is highest in early childhood [118]. The recent meta-analysis in Nature showed that the prevalence is considerably higher (over 16%) in children between the age of 0-5 years than in older age groups [12]. The disease often manifests during the first two years of life but can occur at any age [11, 60, 119]. In 60-65% and 80-85% of affected children, the disease breaks out before the age of 1-2 and 5 years, respectively [11, 120-122]. Onset in adulthood is rare.

Over the past five decades, researchers in several countries have described that atopic dermatitis is increasing in developing and some developed countries (62-66), with several contradictions [123-127]. In addition, statistics have demonstrated that atopic dermatitis is prevalent, particularly in urban areas of developing nations undergoing fast demographic change and in already established industrialized countries undergoing rapid demographic change [123].

In a UK study analyzed data from 1994 to 2013 of more than eight million persons aged 0 to 99 years, the cumulative lifetime prevalence was 9.9% [102]. Moreover, the highest prevalence (the risk of active disease) of atopic dermatitis was found in younger children and older adults as seen in Figure 2 [102]. A Danish study of 972,836 children found a lifetime prevalence of atopic dermatitis of 13% in children aged five years born between 1997 and 2011 [114].

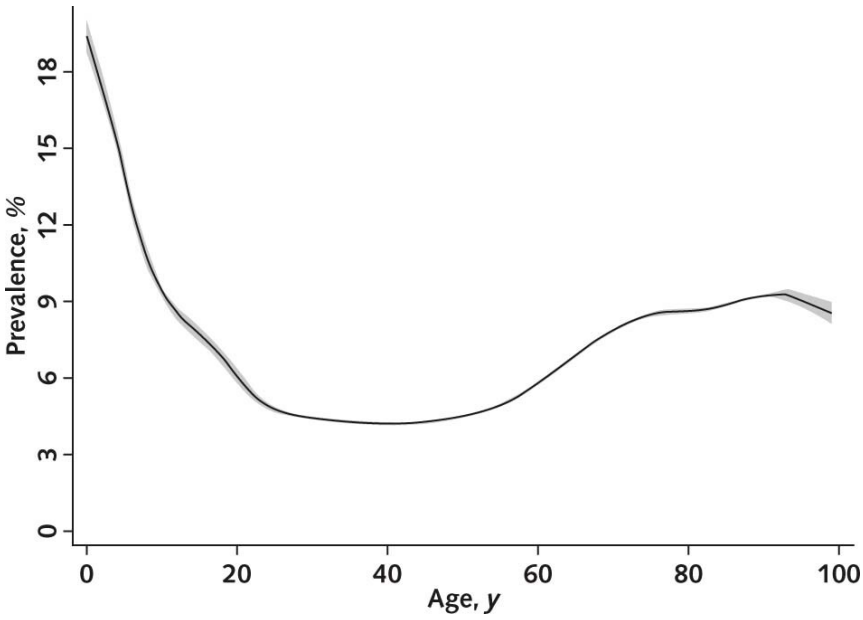

Figure 2. Local polynomial smoothed plot with shading indicating the 95% CIs generated from cross-sectional calculations of the prevalence of active atopic dermatitis at each age [102]. Active disease was defined by a visit or prescription code during each year of follow-up among patients who previously met the definition of atopic dermatitis (characterized by ≥1 of the following diagnosis codes: M111.00 [atopic dermatitis/eczema], M1120.0 [infantile eczema], M113.00 [flexural eczema], M114.00 [allergic/intrinsic eczema], and M12z100 [eczema not otherwise specified]) and were assigned ≥2 treatment codes for any atopic dermatitis-related therapy on separate dates [102].

The course of atopic dermatitis

Despite being a substantial cause of the global non-fatal disease burden, there is limited knowledge of the natural course of atopic dermatitis. The fact that patients with atopic dermatitis can present and progress through the disease in various ways indicates a complicated reality and unpredictability in disease courses. On an individual level, the course of the disease is uncertain. There is no consensus on how subgroups should be identified.

Of those affected, atopic dermatitis occurs in 45% of children before the age of 6 months, in 60% in the first year of life, and in at least 85% before the age of 5 years [128]. In children in whom the disease begins before age two years, symptoms persist in 20% of cases, and another 17% have intermittent symptoms until age seven years as seen in Figure 3 [63].

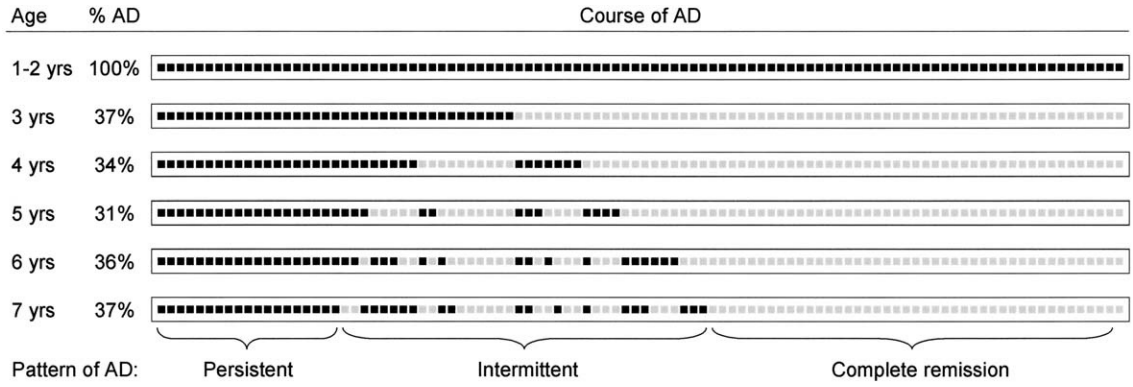

Figure 3. The natural course of AD up to age seven in children with early disease manifestation (≤2 years) [63]. Each symbol represents 1% of the children with early AD, and the natural course of each 1% subsample can be traced vertically. Filled squares represent subjects with AD in the respective period [63].

Although the incidence of atopic dermatitis peaks in infancy, the concept of atopic dermatitis as a disease that resolves in early childhood has changed to the understanding that atopic dermatitis can have a heterogeneous course [11, 118, 129]. Although the course of the disease

is uncertain, it is recognized that the onset of atopic dermatitis is typically in early childhood before the age of two years [12, 130, 131]. Fairly recently, research has shown that the disease can persist or even begin in adults or older individuals [3, 12, 132].

In most patients, atopic dermatitis resolves in late childhood/early adolescence (up to 50-75%) [11, 63, 126, 133]. According to three European birth cohorts, roughly 50% of infants with atopic dermatitis were in remission later in childhood [63, 134, 135]. Nevertheless, in the majority of patients with symptoms in adolescence, the disease persisted into late adolescence and adulthood [68, 114, 136, 137]. Twenty percent of childhood atopic dermatitis cases were found to have persistent disease eight years after diagnosis. In comparison, less than five percent of cases were found to have persistent disease twenty years after diagnosis, according to a pooled analysis of 45 studies that involved 110,000 subjects [120]. However, another study found that up to 40-60% of affected individuals may relapse later in life, often in the form of hand eczema [61, 62, 138, 139]. A recent study from Finland showed that of subjects who had symptoms before the age of seven, 37.4% had symptoms and 25.6% had active disease into adulthood [140].

Season, environmental and climatic factors

There are conflicting data on the prevalence of atopic dermatitis in genetically similar populations [115, 124]. One study found striking differences between different regions of Germany. The prevalence rates of atopic dermatitis were higher in western Germany than in eastern Germany (12,9% vs. 8,2%) [141]. Accordingly, black Caribbean children residing in London had a higher prevalence of atopic dermatitis compared to children of the same ethnicity living in Jamaica (Kingston) (14.9% versus 5.6%) [142]. These studies and an observational study from Finland of children with atopic dermatitis [141, 143] suggest that environmental rather than genetic alterations may have exacerbated the disease and led to an increased prevalence.

Seasonal change in atopic dermatitis is a frequently occurring phenomenon in a temperate climate [114, 144-148]. Physicians are aware that climatic factors such as seasons, temperature fluctuations, humidity, and sun exposure play an important role in the disease

severity of atopic dermatitis, also as an indirect effect of latitude [39, 113, 127, 144, 148-153]. There is a negative correlation between atopic dermatitis and outdoor temperature and a positive correlation between atopic dermatitis and latitude [148]. Although the effect of seasonal variations in atopic dermatitis is well established, it is still not fully understood how seasonal cycles affect the occurrence of atopic dermatitis and many other chronic diseases [145, 154],

Henriksen et al. found that the seasonal difference in the incidence of atopic dermatitis was pronounced in Denmark and Sweden, with a peak in winter and spring and the lowest level during summer [114]. Two other studies from Denmark showed that the winter season was associated with worsening atopic dermatitis [113, 155, 156]. In another recent Danish study, children with severe atopic dermatitis were least likely to report worsening during winter but most likely to report exacerbation due to cold and dry weather [60]. Because children with severe atopic dermatitis are prone to experience numerous flare-ups and the skin has little time to recover, one possible hypothesis is that they are less susceptible to exacerbations due to trigger factors and therefore experience fewer exacerbations in winter than children with mild atopic dermatitis [60, 157].

According to an experimental study, the water content of the stratum corneum of infants was significantly higher in early summer than in fall [158]. The author speculates whether the ambient temperature alters the water content and barrier function of the skin. An interesting 2015 study by Danish researcher found that low temperatures and humidity lead to an overall reduced and more diminished skin barrier reduction and increased weakness to mechanical stress [156]. In addition, the researcher described that due to the release of pro-inflammatory cytokines and cortisol by keratinocytes and the increase in the number of dermal mast cells, the skin was more sensitive to skin irritants and allergens, as shown in Figure 4 [156].

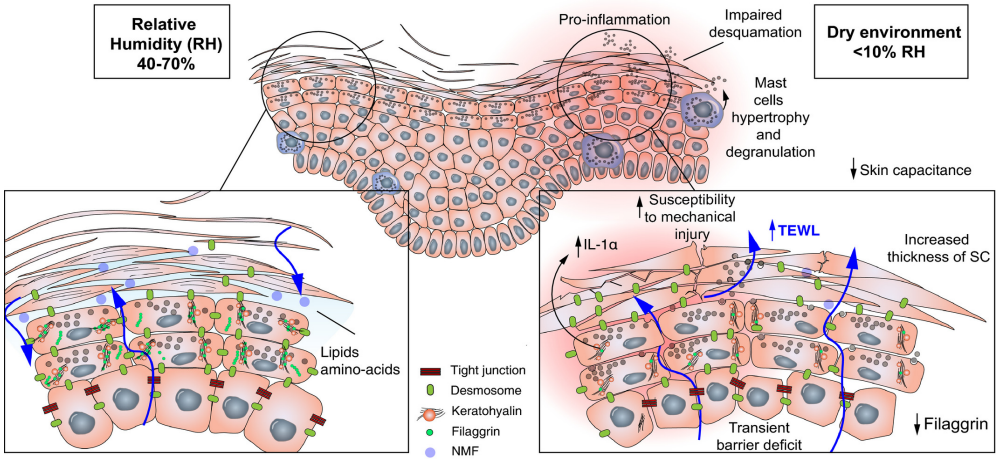

Figure 4. The short-term effect of dry environment (relative humidity<10%) on skin barrier function and composition [156].

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Foelster-Holst et al. showed for the first time that there might be a direct relationship between skin exposure to pollen allergens and the manifestation of atopic dermatitis and pruritus [146]. The association between relapse of atopic dermatitis and skin contact with pollen has been later studied several times in the literature, e.g., association with birch and grass pollen [159-161].

Comorbidities of atopic dermatitis

Atopic dermatitis is associated with a variety of comorbidities, as shown in Figure 5. Pediatric and adult patients with atopic dermatitis are known to be strongly associated with allergic IgE-mediated diseases such as asthma, allergic rhinoconjunctivitis and food allergies [56]. Associations between atopic dermatitis and other atopic and allergic diseases have been known for a long time and even contribute to the diagnostic criteria for atopic dermatitis [56, 95, 99]. However, it is still uncertain whether the associations between allergic diseases are causal or whether they are thwarted by shared genetics or shared environmental conditions [162].

Roughly 80% of patients with atopic dermatitis have increased IgE levels [163].

The concept of the atopic march was primarily proposed to characterize the progression of pediatric allergic disorders, with atopic dermatitis preceding the onset of asthma and allergic rhinitis [164]. Longitudinal and cross-sectional studies have supported the conception of the atopic march, which has provided a context for understanding the pathophysiologic mechanisms of these diseases [8, 165]. In this context, atopic diseases are thought to follow a sequential course, with the debut often presenting symptoms of atopic dermatitis as the first clinical manifestation [166, 167].

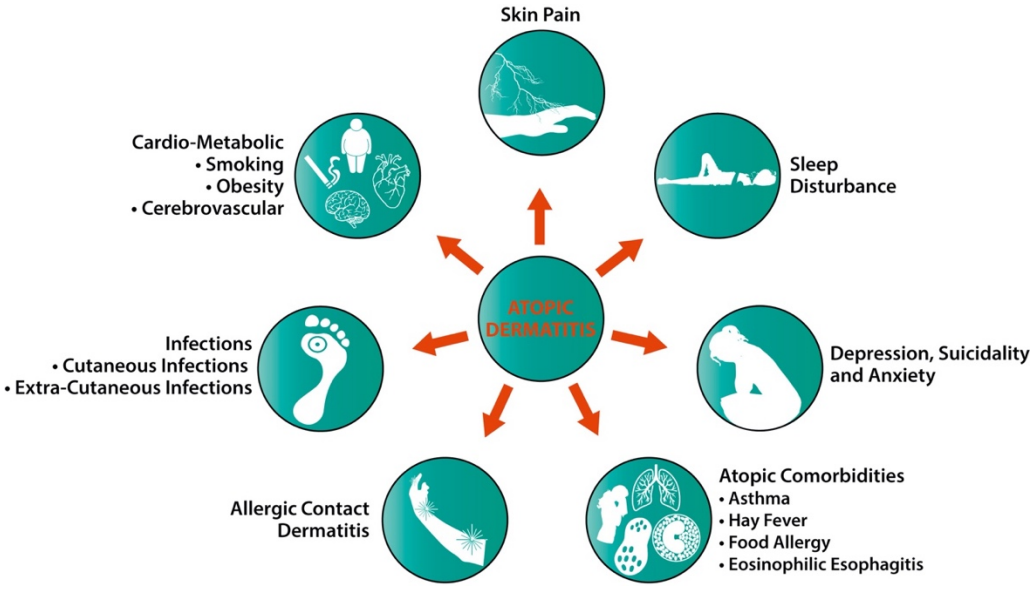

Figure 5 . Common comorbidities of atopic dermatitis.
Atopic dermatitis is associated with substantial burden and comorbidities. Identifying atopic dermatitis comorbidities is essential for proper disease management and improving overall patient outcomes [10].

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As atopic disorders are heterogeneous diseases caused by complex and not yet wholly understood interactions involving genetic, environmental, and epigenetic elements, it is common understanding that the atopic march is not a distinct path but an umbrella term for several pathways [168]. There is abundant evidence that a literal interpretation of the atopic march, as initially described, does not adequately capture the vast heterogenicity of the natural course in different patient groups [168, 169]. Moreover, the researchers note that the atopic march concept is unproven to explain these associations [164]. Instead, researchers

suggest that subgroups of patients with atopic dermatitis are more likely to develop IgE-mediated allergy [164]. Furthermore, allergic disorders do not necessarily develop in the order indicated. The "march" of the disorder may extend over several decades, with asthma appearing in adulthood, several years after one had atopic dermatitis as a child [169]. Another example is that patients with asthma may develop atopic dermatitis later [170]. Thus, the sequence is arbitrary [171].

Several recent studies of individuals who have atopic dermatitis are of an amplified risk of being diagnosed with certain nonallergy-related comorbidities. This is particularly true for alopecia areata [172], vitiligo, and urticaria [173]. There is an increased risk for type I diabetes mellitus and malignancies [174], attention-deficit/hyperactivity disorder (ADHD) [175], and epilepsy [176]. The risk for rheumatoid arthritis and inflammatory bowel disease is probably increased but not exceptionally high [177]. In addition, large-scale epidemiologic research has found a significantly higher likelihood of ocular issues in this patient group having atopic dermatitis compared to the general population (depending on severity)[178]. Blepharitis, cataracts, retinal detachment, keratoconjunctivitis, keratoconus, glaucoma, and ophthalmic herpes simplex virus infections are potential complications [178].

Reportedly, adults with atopic dermatitis have a higher risk of being diagnosed with anxiety and depression, and an increased risk of suicide and cardiovascular risk factors (smoking and cardiovascular disease, appear more prevalent in individuals with severe disease) [56, 179]. However, the majority of studies examining the relationship between smoking and alcohol consumption are cross-sectional, making it challenging to prove causality [56].

Cutaneous comorbid infection

Complications with skin infections in individuals with atopic dermatitis are well known and include bacterial, viral, or fungal skin and soft tissue infections, i.e., eczema herpeticum, candidiasis of the skin/nails and vulva/urogenital area [180, 181]. Cellulitis, skin abscesses, and impetigo are common soft tissue infections in atopic dermatitis. Staphylococcus aureus is the most typical cause of these infections, which is also listed in some diagnostic criteria for atopic dermatitis [95]. According to hospitalization statistics in the United States, atopic dermatitis is also related to severe skin infections (defined as those that result or require hospitalization or are life-threatening) [56].

Herpes simplex virus type 1 (HSV-1) can cause eczema herpeticum infection and is a potentially fatal consequence of atopic dermatitis [181]. Patients with atopic dermatitis are more than twice as likely to be affected by HSV infections as the general population [182]. Eczema herpeticum and bacterial skin infections are more common in inadequately controlled dermatitis, and preventive treatment (such as topical corticosteroids) can decrease the risk of these infections [183]. Because it may appear with widespread vesicles and skin erosion, eczema coxsackium should be evaluated as a differential diagnosis for eczema herpeticum. [184]. Molluscum contagiosum is a poxvirus belonging to the molluscipoxvirus subfamily, and skin barrier defects predispose patients with atopic dermatitis to molluscum contagiosum [185].

Previous and recent studies indicate that atopic dermatitis is related to a higher risk of extracutaneous infections in adults and children [186-191]. An increase in patients with atopic dermatitis suffering from bacteremia, osteomyelitis, septic arthritis, and endocarditis has also been observed [181]. Atopic dermatitis has also been associated with an increased risk of influenza or pneumonia in adults [190]. In addition, a previous analysis found that adults with atopic dermatitis were more likely to be vaccinated but still had higher rates of influenza and pneumonia than adults without atopic dermatitis [189, 190]. According to a meta-analysis conducted in 2019, both children and adults with atopic dermatitis have a higher likelihood of developing ear infections (with an odds ratio of 1.29), throat infections (with an odds ratio of 2.31), and urinary tract infections (with an odds ratio of 2.31) [190, 191].

Acne vulgaris – a comorbidity of atopic dermatitis?

General introduction

Although acne vulgaris (acne) is humans' most common chronic inflammatory skin disease, the complex pathogenic mechanisms are still not fully understood [192]. The known factors that play a major role in the pathophysiology of acne are hyperkeratinization and follicular congestion with sebum and keratinocytes, microbial colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), increased and fluctuating [193]

sebum production and complex inflammatory mechanisms (inflammatory mediators) [192, 194]. In addition, both individuals with acne and those with atopic dermatitis have ceramide deficiency, which is associated with hyperkeratinization of the follicles and contributes to skin barrier dysfunction, and to the formation of comedones [193, 195-200].

The diminished and altered barrier function of atopic dermatitis patients raises the question of to what extent severe acne affects this patient group and how tolerable acne treatment is. Isotretinoin and topical retinol treatment decrease sebum excretion in the stratum corneum and can cause excessive dryness, which can aggravate atopic dermatitis and cause flare-ups [201]. There are few thorough analyzes of acne in adolescent and adult patients with atopic dermatitis. However, there is increasing evidence that atopic dermatitis is a systemic inflammatory disease with an increased risk of infection [202].

Definition, the severity and classification of acne

The severity of acne is assessed based on the patient's clinical presentation and quality of life evaluation. Acne manifests as comedones, papules, pustules, nodules, cysts, and secondary signs such as scarring, hyperpigmentation and erythema [203]. Acne is classified based on the patient's age, the lesion's morphology (comedonal, nodulocystic, inflammatory, mixed, etc.), its distribution (trunk, face or both), and its severity (postinflammatory erythema, or hyperpigmentation, or extent, presence, or absence of scarring) [204].

The EU Guideline group [205] has classified acne patients to make treatment recommendations based on disease activity. However, there are no universal, standardized classification/grading system for acne severity [206]. More than 25 unique classification systems are currently used [206, 207].

Epidemiology and acne in the population with and without atopic dermatitis

The prevalence of acne varies by country and age group, and estimates range from 35% to nearly 100% of adolescents who have had acne at some point in their lives [206]. A recent meta-analysis published in 2020 (Nature), found that the prevalence of acne ranged from 26.8% in a German study to 96% in Brazil [206]. Until 2020, there were no studies on the occurrence of severe acne in individuals with atopic dermatitis [208]. In Danish research by Halling et al, a total of 482 individuals participated in a prevalence study of acne vulgaris in

individuals with atopic dermatitis (*n*=52) and individuals without atopic dermatitis (*n*=430) [208]. The study concluded that individuals with a history of atopic dermatitis had the exact prevalence and distribution of acne as individuals without atopic dermatitis. In 2022, another Danish study by Thyssen et al. examined the prevalence, incidence, and risk of acne in 6600 adolescents and adults with atopic dermatitis in a matched cohort study [209]. The prevalence for acne was estimated to be 3.9% in patients with atopic dermatitis and 3.7% in the general population (all ages included) [209]. In addition, the study found that the likelihood of having severe acne was lower in younger patients with atopic dermatitis and increased according to age [209].

Topical and systemic treatments for acne

Topical treatment should always be prescribed unless isotretinoin is used. Benzoyl peroxide has a bactericidal effect on Cutibacterium acnes (including resistant strains) and keratolytic activity. Benzoyl peroxide is superior to placebo (or no treatment) for treating acne. [210]. Adapalene has antimicrobial and anti-inflammatory activity and a synergistic effect in combination with benzoyl peroxide [207]. Azelaic has antibacterial properties and reduces follicular hyperkeratosis [211]. Clindamycin has antibacterial and anti-inflammatory properties and should be combined with benzoyl peroxide because of the risk of developing resistance (the maximum duration of use is three months). Topical retinoids have comedolytic and anti-inflammatory effects by inhibiting leukocyte migration and cytokine production and downregulating toll-like receptors [212, 213].

Oral antibiotics can be prescribed for moderate to severe acne when topical treatments do not produce the desired results. In conjunction with topical agents such as adapalene or benzoyl peroxide, systemic tetracycline preparations (lymecycline) are recommended. Tetracycline is an effective acne treatment, likely because of its anti-inflammatory properties. Combined with topical therapy, hormonal preparations, such as contraceptives, may effectively treat female acne [214].

Isotretinoin is a natural metabolite of vitamin A and is a systemic treatment introduced in the 1980s. Isotretinoin is a prescription medication taken for a limited period, usually 6-12 months. The drug acts on all four pathogenetic factors for developing acne; follicular epidermal hyperproliferation/obstruction of the follicle, excessive sebum production,

Cutibacterium acnes activity, and inflammation [215]. Indications are severe forms of acne (e.g., nodular, nodulocystic acne, or acne with risk of permanent scarring) that cannot be controlled with adequate standard treatment with systemic antibacterial drugs/topical treatment, severe forms of acne vulgaris, other specified/unspecified acne (conditions: the user must have severe acne, e.g., scarring, nodulocystic, or deep papulopustular acne), acne conglobata, acne varioliformis, or keloid acne [216]. The recurrence rate is 20-60% in patients treated with a total of 120-150 mg/kg isotretinoin [217]. Despite sufficient response to a single course of isotretinoin, only 40% are cured, while 60% require topical or a new course of treatment. Response to conventional therapy appears to be better after treatment with isotretinoin [218].

Treatment guidelines for atopic dermatitis

General guidelines

Treatment of atopic dermatitis depends on the patient's age and symptoms and the disease's severity, as seen in Figure 6 (the 2022 European Guidelines). One typical sign of atopic dermatitis is itching (pruritus). There is no cure for atopic dermatitis, but the majority of patients can have their symptoms alleviated and under control by combining moisturizer and topical corticosteroids. The primary treatment of atopic dermatitis aims to relieve symptoms by introducing lipids into the upper epidermis to restore and improve the skin barrier while avoiding individual trigger factors [219]. Optimal topical treatment is critical for disease control. Moisturizers are essential and should be applied daily, more than once, to prolong the time before relapses occur, resulting in a more extended disease-free period [220-222]. Several dermatoses associated with scaly and dry skin, such as atopic dermatitis, ichthyosis, xerosis, seborrheic dermatitis, and psoriasis, have shown considerable clinical improvement with the use of urea-containing formulations, according to several clinical studies [223].

Topical corticosteroids

Topical corticosteroids are first-line anti-inflammatory therapy for acutely skin-inflamed lesions (active disease) as needed (itching, new flare-ups/control of acute exacerbations) [50,

224, 225]. Rapid discontinuation of topical corticosteroids increases the risk of exacerbations and withdrawal/rebound effects. Therefore, topical corticosteroids should be discontinued gradually. Weekend therapy (proactive) is probably better than no topical corticosteroids/reactive application to prevent eczema flare-ups [226]. Topical corticosteroids, available in creams and ointments and liquid form, have an anti-inflammatory effect and inhibit cell proliferation, capillary dilation, edema formation, and pruritus [50, 227, 228]. For weeping areas, it is recommended to use a topical cream. Using a topical ointment on dry sites and the hands and feet is preferable. Liquid cortisone (liniment, emulsion, or solution) is typically prescribed for hairy areas.

Topical corticosteroids come in a variety of potencies. The potency of topical corticosteroids is classified from mild (Class I) to super-potent (Class IV), according to Nieder et al. [229, 230]. There are several potencies of topical corticosteroids. According to Nieder et al., the potency of topical corticosteroids ranges from mild (Class I) to extremely potent (Class IV) [230]. This classification is utilized throughout Europe (excluding France - the order is reversed) but varies globally. In contrast, the United States acknowledges seven groups, ranging from VII (weakest) to I (super-potent) [230].

The choice of potency is determined by the application site/body site, the disease's severity, the patient's age, lesion characteristics and recalcitrance, and patient preferences. It is essential to choose a preparation with sufficient potency to control inflammation. Weak topical corticosteroids are used to treat mild atopic dermatitis and areas of thin skin (skinfolds etc.), whereas potent topical corticosteroids are applied to more severe, thickened and chronic lesions [227]. The majority of children with atopic dermatitis can be effectively treated with mild or moderate preparations. Moreover, most adults can be treated with moderate to potent topical corticosteroids. Moderate to potent topical preparations can be applied to the face, armpits, groin, and anogenital area, while moderate to very potent preparations can be applied to the rest of the body. Very potent preparations are rarely indicated in patients with atopic dermatitis [231].

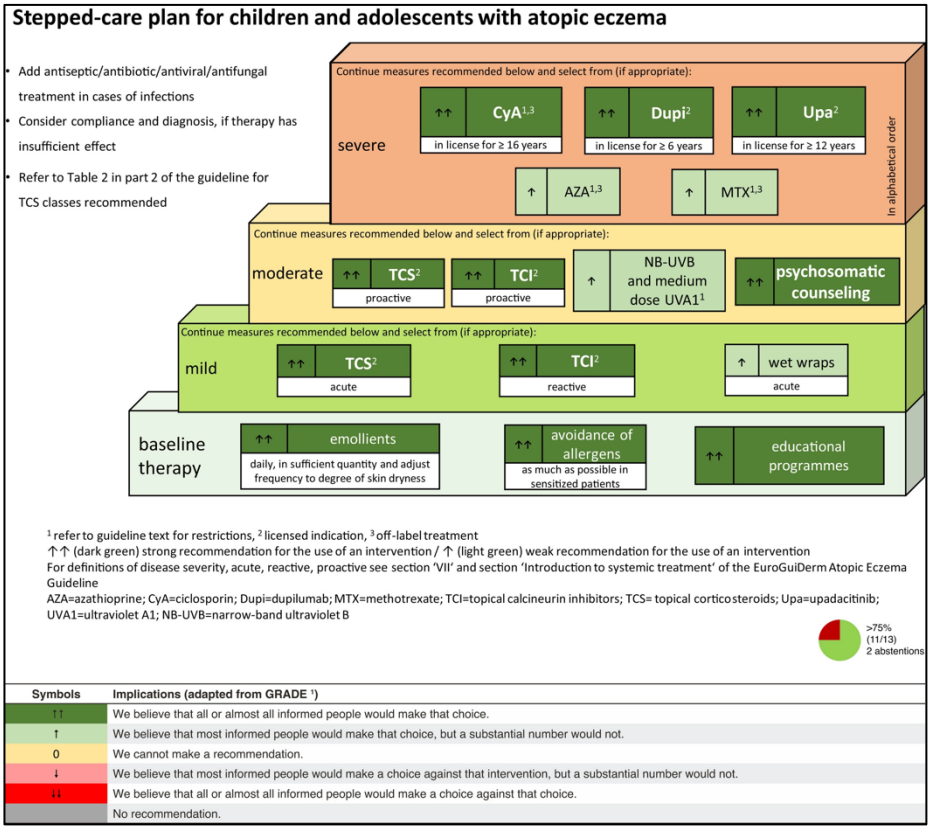

Figure 6. Stepwise plans for treating atopic dermatitis in children and adolescents according to the European guideline (EuroGuiDerm) [230].

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Topical calcineurin inhibitors

Tacrolimus ointment and pimecrolimus cream are the two topical calcineurin inhibitors approved in Norway to treat atopic dermatitis. Tacrolimus 0.03% ointment and pimecrolimus 1% cream is approved in the EU for the age group 2 years and older (tacrolimus 0.1% for age 16 and older) [232, 233]. Treatment with topical calcineurin inhibitors is a second-line therapy compared with topical glucocorticoids. Studies in patients using tacrolimus and pimecrolimus show decreased episodes with atopic dermatitis outbreaks [234]. Although topical calcineurin inhibitors and topical glucocorticoids have immunosuppressive properties, their mechanisms of action are distinct. Topical calcineurin inhibitors inhibit the phosphorylase enzyme calcineurin's activity, preventing T lymphocytes' activation [235]. Topical calcineurin inhibitors, unlike topical corticosteroids, do not cause skin atrophy and

are, therefore, particularly suitable for long-term prophylactic treatment and on sensitive areas such as face and skin folds [236].

Antiseptic agents

Infection with staphylococci is common in patients with atopic dermatitis. Signs of infection may include severe redness, increased secretions, and crusting [237, 238]. However, it can be difficult to distinguish an outbreak of atopic dermatitis from infected atopic dermatitis. Well-treated atopic dermatitis has a lower concentration of yellow staphylococci than aggressive active disease [239]. Therefore, in severe atopic dermatitis, it is essential to start treatment with topical corticosteroids that reduce yellow staphylococcal colonization [227]. Nevertheless, an infection may contribute to a lack of response to treatment with topical corticosteroids. In the case of superinfection, topical antiseptic agents are recommended and are preferable to topical antibiotic therapy [240].

Other treatment options

The vast majority of individuals with atopic dermatitis are affected by mild and, to a lesser extent, moderate disease. Basic treatment and reactive therapy consisting of topical corticosteroids and calcineurin inhibitors have a favorable benefit-risk ratio and usually keep disease activity under control [85, 222]. In combination with proactive basic therapy, oral steroids and immunosuppressants are only marginally indicated. Crisaborole is currently (2023) not approved in Norway or the EU but is under review by the European Medicines Agency (EMA).

Phototherapy should be considered when topical treatments including baths and wet wraps cannot control atopic dermatitis. Climatic therapy (treatment travel) is offered in Norway for some selected patients with atopic dermatitis. If phototherapy and topical treatment fail, second-line therapies such as systemic immunosuppressive treatment can be necessary for adults and children [241]. The most researched agents used in pediatric patients are azathioprine, mycophenolate mofetil, cyclosporine, and methotrexate [241, 242].

For decades, the only treatments for atopic dermatitis were topical corticosteroids, topical calcineurin inhibitors, and systemic immunosuppressants in patients with moderate-to-severe disease [243]. A growing number of innovative and promising newer targeted biologic

therapies are developing [244]. Biologic therapy such as dupilumab demonstrates good results in patients with moderate-to-severe atopic dermatitis. Still, the high cost of the drugs is a burden for patients with atopic dermatitis [245]. More recently, second-line systemic therapies for atopic dermatitis, such as Janus kinase (JAK) inhibitors, have become available [11]. However, they are infrequently used and are not approved for pediatric patients (< 12 years) [11]. Targeted therapies promise to control the disease, even in patients with recurrent disease [35]. However, there is still no cure because the causes of the disease are complicated [35].

Knowledge gaps and rationale for the study

Epidemiologic research is critical in explaining the risk factors of atopic dermatitis because incidence and prevalence can provide information about the burden of the disease in adults, adolescents, and children in different geographic regions in terms of quality of life, morbidity and life expectancy [55, 246]. However, the worldwide occurrence of atopic dermatitis in the last ten years has not yet been comprehensively described [55].

By 2021, according to Hade et al. [55], point prevalence data for recent years for atopic dermatitis were only available from Africa (Gabon, Ghana, Namibia, Rwanda, Senegal, and Tunisia), North and South America (Brazil, Canada, Latin America and the United States of America (USA), Asia (China, India, Japan, South Korea, Malaysia and Taiwan) and Europe (Denmark, France, Germany, Poland, Sweden, United Kingdom) and Oceania (Australia and New Zealand).

When the first paper *(Paper I)* was published, the incidence data on atopic dermatitis from the 21st-century data were studies from Denmark [247] and Sweden [114], Scotland [248], Italy [249], and the United Kingdom [250, 251]. To our knowledge, the Swedish study from Henriksen et al. [114] was the only article that reported the medications prescribed to define the incidence of atopic dermatitis. Epidemiologic studies of childhood and adult atopic dermatitis in different continents are still needed [55].

Knowledge of the predictive factors of disease is critical for personalized prognosis, health care planning, hypothesis generation, and future studies of atopic dermatitis prevention. An invited commentary [252] by Simpson et al. on our first published paper *(Paper I, 2018)* [68] emphasized that more details about risk predictors are needed to develop interventions to prevent the epidemic increase of atopic dermatitis in our population. Reducing the incidence of atopic dermatitis will alleviate the disease and decrease the risk of related comorbidities [68].

Despite the extensive studies of atopic dermatitis, little is known about factors associated with the persistence and severity of the disease [3, 119, 136, 253]. Moreover, the disease course of atopic dermatitis is not yet fully understood [12, 130, 131]. Sex differences in pediatric patients diagnosed with asthma are well known. However, few large-scale longitudinal investigations on atopic dermatitis address age-related sex differences children [69, 70, 254, 255]. Sebum content, skin hydration and skin surface pH in young children have been tested repetitively by age and sex without consistent results. [256-258]. The factors contributing to the different phenotypes, the generally low adherence rate to topical corticosteroids, comorbidities, and the chronic relapsing nature of the disease lead to complicated disease courses and outcomes that need further investigation. It is well known that children with severe and early-onset disease have a lower quality of life and a higher risk of comorbidities than children with mild disease [85, 259]. However, there is insufficient evidence on whether and how the disease's onset impacts its course and comorbidities.

There is little literature on the treatment patterns of pediatric patients with atopic dermatitis, particularly children younger than two years of age [87, 90]. Siegfried et al. (2018) noted in their review that there is a lack of knowledge about the treatment of severe atopic dermatitis, long-term and combination treatments, and systemic corticosteroids in children [90]. Therefore, an overview of the onset, treatment patterns, and progression of atopic dermatitis is needed. Nevertheless, the literature on the frequency of moderate to severe atopic dermatitis in the pediatric and adult population according to age remains sparse [260].

Despite the discovery of filaggrin gene mutations, researchers claim that the environment may play a key role in the pathophysiology of the disease [36-39]. The rapid increase in atopic dermatitis in recent decades suggests that alteration cannot be ruled out in genetically predisposed individuals. However, the substantial differences in the reported incidence of

atopic dermatitis across and within nations and between seasons in areas with temperate climates imply that these differences cannot be explained solely by genetics [68, 114, 144-147]. A complete understanding of how seasonal cycles influence the incidence of many chronic diseases is still scarce.

Despite increasing confirmation that atopic dermatitis is a systemic inflammatory disease with an increased risk of infection, there are few comprehensive analyses of real-world dermatologic comorbidities in adolescents and adults with atopic dermatitis [202]. Moreover, barrier function is reduced and altered in patients with atopic dermatitis. Consequently, it begs the questions of how severely acne affects individuals with atopic dermatitis and how tolerable the acne treatment is. Topical treatment with retinol and isotretinoin may cause excessive dryness and decreased sebaceous secretion in the stratum corneum, possibly aggravating atopic dermatitis and necessitating more aggressive therapy of atopic dermatitis [201]. Isotretinoin and other retinoids may alter immunologic activity, which is interesting in an inflammatory condition such as atopic dermatitis. Until 2021, there were no studies on the prevalence of acne vulgaris in patients with atopic dermatitis [208]. To our knowledge, no nationwide study of acne in patients with atopic dermatitis has ever been conducted. The tolerability (defined as the patient perspective of adverse drug reactions [261]) of isotretinoin in patients with atopic dermatitis has not been adequately studied in the literature.

The last literature search was performed November 2022.

2 AIMS

Aim I

To analyze a national health registry based on prescription data to determine the onset of atopic dermatitis (incidence rate) by age and sex and the proportion of affected children under six years of age (incidence proportion) in the total Norwegian pediatric population (Paper I).

There are few nationwide studies on the incidence of atopic dermatitis in children. To our knowledge, there are no nationwide studies of atopic dermatitis in Norwegian children.

Aim II

To analyze the onset (incidence) of atopic dermatitis in the pediatric population with atopic dermatitis in relation to the season of the year (Paper I).

A complete understanding of how seasonal cycles influence the incidence of many chronic diseases, including atopic dermatitis, is still scarce. An epidemiological study is needed to identify possible factors associated with the heterogeneity of atopic dermatitis.

Aim III

To provide up-to-date, nationwide population-based estimates of prevalence and an overview of treatment patterns in pediatric patients with atopic dermatitis, in terms of early or late onset of disease and by age and sex (Paper II).

There is little literature on the burden of atopic dermatitis with treatment patterns by age and disease course as a function of early and late-onset atopic dermatitis. The existing literature is rarely based on real-world data and subgroups are often small, reducing the study's statistical power.

Aim IV

To establish up-to-date population-based 12-month prevalence estimates for severe acne in adolescence and young adults with atopic dermatitis and resemble these estimates for severe acne with those without atopic dermatitis in the Norwegian population up to 23 years of age (Paper III).

Epidemiologic nationwide prevalence rates for severe acne in patients with atopic dermatitis are not available to our knowledge. There is a need for more knowledge about the risk and severity of acne in this patient group. Existing studies are not based on up-to-date data.

Aim V

To estimate the tolerability of isotretinoin in adolescence and young adults with topic dermatitis (Paper III).

Because of the widespread prevalence and chronicity of both atopic dermatitis and acne, physicians regularly prescribe isotretinoin to patients with atopic dermatitis. To our knowledge, there are limited data on the tolerability of isotretinoin treatments in patients with atopic dermatitis. The definition of tolerability is described in Chapter: Definitions, proxy measures, and classifications.

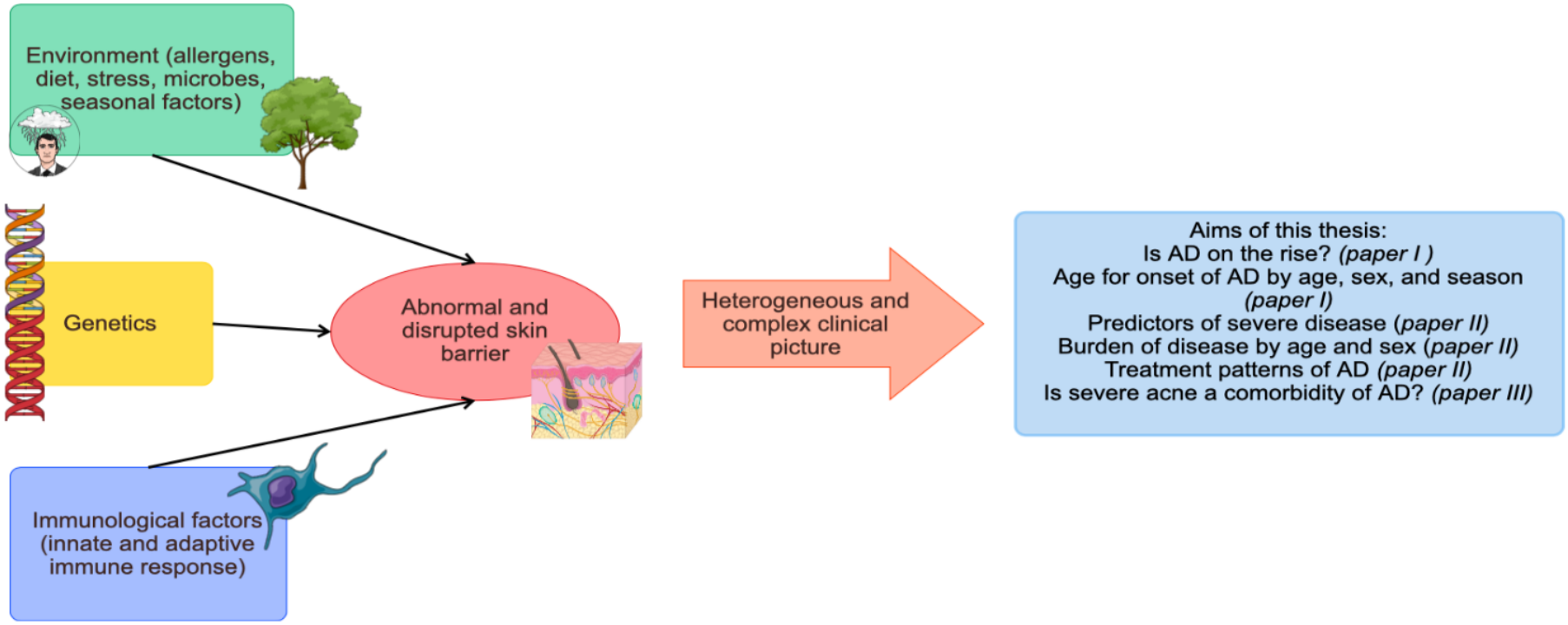

Figure 7. The figure illustrates how various factors influence atopic dermatitis and how they contribute to the heterogeneity and complexity of the disease, leading to different disease courses, manifestations, disease severity, onsets, occurrences and comorbidities that need to be further investigated, resulting in the aims of this thesis. Although the heterogeneity of atopic dermatitis is now a more recognized phenomenon, further research is needed to understand the predictive factors of the disease, which are critical for personalized prognosis, health care planning, and future atopic dermatitis prevention studies. It is important to study the distribution of atopic dermatitis severity, risk factors for severity, and treatment patterns to improve outcomes and disease progression.

3 MATERIALS AND METHODS

Source of data used in Papers I, II and III

All three Papers in this thesis are based on data retrieved from the *Norwegian Prescription Database* (NorPD) [262] and *Statistics Norway* (SSB) [263]. In the first published article *(Paper I),* we also included data from the *National Meteorological Institute* (NMI) [264].

Norwegian Prescription Database (NorPD)

(Norwegian: Reseptregisteret)

In recent years, health databases of prescribed medications from national registries have become available for scientific investigation. The Norwegian Prescription Database (NorPD) is an extensive and comprehensive database that covers the Norwegian population (5,475,240 inhabitants on January 1, 2023) and monitors all prescribed medications dispensed by pharmacies in Norway [263, 265]. The Prescription Register is a Norwegian prescription-based drug register maintained by the National Institute of Public Health since January 1, 2004 [266]. Medicines used in hospitals and to physicians (for use in their practices) are not included in the register, but drugs dispensed in nursing homes are. All pharmacies in Norway register prescriptions electronically, and is submitted to NorPD in monthly reports through Statistics Norway [266]. The register contains information on the patient, pharmacy, prescriber, drug dispensed, and other drugs dispensed that belong to the individuals. Statistics Norway replaces the prescriber's patient identification number and identification number with a unique pseudonym, making it possible to track a patient (without knowing the identity) over time [266]. In this way, the database provides comparative longitudinal data using a unique personal identifier. NorPD is an essential source of information on medication use in Norway for various purposes, including research, quality assurance, policy analysis and decision-making [267].

The NorPD lists variables [268], where the researcher can query the variables needed to conduct a study/research project. Data on individuals who received a prescription for topical corticosteroids or topical calcineurin inhibitors with Anatomical Therapeutic Classification

(ATC) [269] code D07A or D11AH01/D11AH02 were obtained from NorPD. All prescriptions were assigned a pseudonymous identification code. Information on the patients' sex, patient year and month of birth, sex, municipality and county (only retrieved in the first database – *Paper I*), month and year of death, the date of drug dispensing, the ATC classification code, the defined daily dose (DDD) [269], the number of packages and the size (quantity) of the prescription, the price and the quantity of the product (gram/kg/quantity) and other drugs dispensed to these patients were retrieved [268]. All reimbursement prescriptions were coded using the International Classification of Diseases (ICD-10) or the World Health Organization's International Classification of Primary Care (ICPC-2) codes [269].
From 2004 to 2008, "Refusjonspunkt" was the general medical coding system used by general practitioners in Norway. Since March 2008, physicians have been required to include a diagnosis code (ICPC-2 or ICD-10) on reimbursed prescriptions. The “Refusjonspunkt” coding system was not as accurate as ICD-10 / ICPC-2 and is not presented in the Papers.

Data received from the NorPD were reviewed for coding errors and omissions. Prescriptions without personal identification (pseudo-anonymized) were not included in the main analyses but were still analyzed and used for sensitivity analyses. The NorPD database was used in all included Papers.

Statistics Norway and the National Population Register

(Norwegian: Statistisk Sentralbyrå og Folkeregisteret)
Statistics Norway (ssb.no) is the national statistical institute of Norway. Statistics Norway is a professionally independent institution responsible for collecting, compiling and publishing official statistics on the population, society and economy at the local, regional, and National levels [263]. Statistics Norway processes data from more than 100 public registers. One of these is the National Population Register which also reports to the Norwegian Tax Administration [270]. The National Population Register contains information on all persons who live or have lived in Norway.

Statistics Norway holds an unrestricted access website called the *Statistics Bank*, where the information for this study was obtained [271]. The *Statistic Bank* at Statistics Norway contains detailed tables with time series and is available to the public to produce a selection of figures and save them in various file formats. Data on the population from the National Population Register has been downloaded from Statistics Norway (based on year, age, and sex) and used in *Paper I- III.* Furthermore, the statistics include all live births where one parent resides in Norway at the time of birth. Statistics Norway contains data on the average middle population (the average size of the population at the beginning and end of the year), defined as the average population size in the respective age group.

The Norwegian Meteorological Institute

The Norwegian Meteorological Institute is a government agency under the Ministry of Climate and Environment, founded in 1866 [264]. Norwegian climate statistics with monthly mean temperatures implemented and analyzed in the dataset *(Paper I)* were retrieved from the Norwegian Meteorological Institute in 2017. The Meteorological Institute monitors climate, forecasts weather, and conducts research. The website from which the 2017 weather statistics were obtained is no longer available [264].

Algorithm for defining individuals with atopic dermatitis

The algorithm was inspired by Henriksen et al. [114]. The algorithm was modified by the corresponding author and coauthors to better fit the research question and Norwegian conditions and the Norwegian Prescription Database (NorPD).

Individuals were considered to have AD if they met at least one requirement for either criteria 1 or 2:

- *Criterion 1 - based on disease-specific diagnoses:*
    - ≥ 1 (ICD-10) L20 "Atopic dermatitis"
    - ≥ 1 (ICPC-2) S87 "Dermatitis/atopic dermatitis"
- *Criterion 2 - based on disease-specific medication (ATC-codes):*
    - ≥ 1 dispensed prescription for D11AH "Agents for dermatitis, excluding corticosteroids" (tacrolimus or pimecrolimus) without any of the following prescription exclusion criteria [a)]
    - ≥ 2 dispensed prescriptions for D07 "Corticosteroids, dermatological preparations" for topical use (min. 14 days apart) within 12 months without any of the following prescription exclusion criteria.

Prescription exclusion criteria:

Individuals WITHOUT a diagnosis of (ICD-10) L20 "Atopic dermatitis" or (ICPC-2) S87 "Dermatitis/atopic dermatitis": Dispensed prescriptions with diagnoses:

- ICD-10: L21 "Seborrhoeic dermatitis", L22 "Diaper dermatitis", L23 "Allergic contact dermatitis", L24 "Irritant contact dermatitis", L25 "Unspecified contact dermatitis", L26 "Exfoliative dermatitis", L27 "Dermatitis due to substances taken internally", L28 "Lichen simplex chronicus and prurigo", L40–L45 "Papulosquamous disorders", L53 "Other erythematosus conditions", L55 "Sunburn", L56 "Other acute skin changes due to ultraviolet radiation", L80 "Vitiligo", L90 "Atrophic disorders of the skin", L93 "Lupus erythematosus".

- ICPC-2: S86 “Dermatitis seborrhoeic”, S88 “Dermatitis contact/allergic”, S89 “Diaper rash”, S80 “Solar keratosis/sunburn”, S82 “Exfoliative dermatitis”, S08 “Skin color change”, S91 “Psoriasis”, S99 “Skin disease, other”.

Non-AD criteria (exclusion criteria)

Individuals with co-occurring medical skin diagnoses (that might lead to identical treatment) or with co-occurring disease-specific medication (primarily prescribed for other diseases) were NOT considered to have AD and were excluded by the following non-AD Criteria:

- *Co-occurring skin diagnoses (based on ICD-10 or ICPC-2):*

  ≥ 1 diagnosis of either:

  - ICD-10: L40–L45 “Papulosquamous disorders”, L80 “Vitiligo”, L90 “Atrophic disorders of the skin”, L93 “Lupus erythematosus”
  - ICPC-2: S91 “Psoriasis”
- Co-occurring disease-specific medication (based on ATC):

  ≥ 1 dispensed prescription for either:

  - D05 “Antipsoriatics”, D02AF “Salicylates acid preparations”, D07AD “Corticosteroids, very potent (group IV)” including clobetasol b)

Note:

a) Calcineurin inhibitor ointment (0.03%) is indicated for adults, adolescents, and children from the age of 2 years and is prescribed for moderate-to-severe atopic dermatitis [272]
b) Prescriptions of corticosteroid group IV (without being diagnosed with atopic dermatitis) because atopic dermatitis is not treated singly with group IV.

Study population

Table 1.
Data on the study population and settings in the Papers included in this thesis.

	Paper I	Paper II	Paper III
Study design	Observational study	Observational study	Observational study
Data source	NorPD NMI* Statistics Norway	NorPD - Statistics Norway	NorPD - Statistics Norway
Study population	Norwegian population	Norwegian population	Norwegian population
Year of outcome measured	1st Jan. 2009 – 31st Dec. 2014 (15)[a]	1st Jan. 2014– 31st Dec. 2020	1st Jan. 2014 – 31st Dec. 2020
Main factors analyzed	The increase of atopic dermatitis in the child population.	Treatment patterns and prevalence. Predictors for severity and long-term atopic dermatitis.	Prevalence of severe acne in patients with/without atopic dermatitis (based on treatment with isotretinoin).
Statistical analyses	Poisson regression, Chi-square (X^2) test	Poisson regression, Chi-square (X^2) test	Poisson regression, Chi-square (X^2) test
Study population	*n*= 63,460	*n*= 176,458	*n*= 32,371
Age during outcome period (years)	age < 6 years	ages 0–10 years	age 4 – 22 years

NorPD: Norwegian Prescription Database; NMI: Norwegian Meteorological Institute

(a) The outcome of interest was incidence. NorPD data from 2004 - 2008 were used as washout period to ensure that patients had not received topical treatment for atopic dermatitis prior to the study period.

Paper I

The study included all children under the age of six years old years residing in Norway from January 2009 to December 2015. Data from 2004 to 2008 were used as washout periods to ensure patients had not received treatment before the study period. The number of children in the annual study population, aged under six years, increased from 357 451 in 2009 to 373 954 in 2015. A total of 63 450 children had atopic dermatitis, according to the algorithm. Children who had received atopic dermatitis-specific medications before December 2008 were excluded from this study.

Paper II

The included population was Norwegian children from birth to ten years of age from January 2014 to December 2020. The study population included 683,468 patients in 2014 and decreased to 672,188 in 2020. There was a total of 176,458 children aged 0 to 10 years who had been treated for atopic dermatitis, according to the algorithm, during the study period. A birth cohort totaling 59,335 children born in 2014 was followed for six years and analyzed as a subgroup analysis.

Paper III

The third study involved individuals born between 1998 and 2000. In the year 2004, there were 60,316 children aged four years old, 59,667 children aged five years old, and 61,324 children aged six years old years old among the population in Norway. There were 66,813, 66,164, and 67,817 individuals in Norway who were 20 years old, 21 years old, and 22 years old correspondingly in the year 2020. All individuals aged 4-6 in 2004 were followed for 17 years until 20-22 years old in 2020. According to the algorithm, the total number of patients with atopic dermatitis included 10,689 patients from the 1998 birth cohort, 10,697 patients from the 1999 birth cohort, and 11,025 patients from the 2000 birth cohort (a total of 32,371 patients).

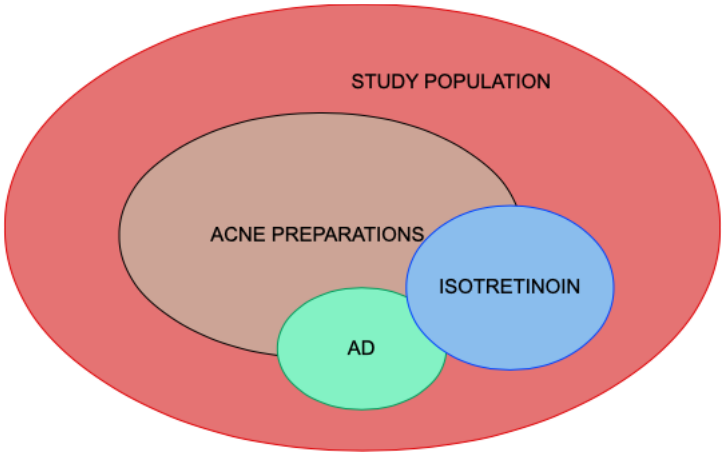

Figure 8 The figure displays the study population in *Paper III*. Part of the study population was treated with acne preparations and/or isotretinoin. The aim was to compare individuals with and without atopic dermatitis (AD) treated with isotretinoin. In addition, the proportion of individuals treated with acne preparations in the population with AD was analyzed.

Study design and methods

As far as analytic studies are concerned, the randomized controlled trial is an almost unbeatable study design for determining whether or not an intervention has the desired effect. [275, 276]. Randomized controlled trials are at the top of the traditional hierarchy for classifying research designs, followed by cohort studies, case-control studies, case reports, and case series [275]. Nevertheless, the research question is the most important consideration in the choice of study design [275]. An experimental study design was neither feasible nor appropriate to answer the current research question. Therefore, an observational study (also called an epidemiological study [277]), was completed. Our aim was to study the epidemiology by comparing the impact of the disease on the population over time (monitoring changes in the disease over time and according to age, sex, season, and year), treatment patterns, risks, and comorbidities of atopic dermatitis in an uncontrolled setting without influencing the study participants. We also wanted to analyze smaller subgroups of individuals and needed a large population to not losing power (significance). Using the entire population as a sample, reduced the risk of selection bias [278].

We also wanted to examine the treatment patterns of atopic dermatitis to determine the burden of the disease and to see what type of treatment was prescribed. Treatment of atopic dermatitis usually does not occur in a single episode but over long periods, and the data, therefore, had to be time-dependent [279]. We aimed to obtain as detailed a history of medication use as possible for the entire Norwegian population in the selected age groups. Therefore, a pharmacoepidemiologic study with secondary data from the NorPD was an appropriate choice.

The study design in all three papers was observational studies. It may be unclear whether all studies in the three papers can be described as cohort studies in the usual sense [280]. In the studies described in this thesis, the cohorts were open because individuals migrated (emigrated/immigrated), and a marginal proportion died. The size of the study population and the source population (age/year-specific Norwegian population) differed for each age and annual cross-section. Although the analysis is retrospective, the NorPD data were collected prospectively [228].

All studies were based on data from NorPD. All prescriptions for topical treatment of atopic dermatitis with ATC code D07, D11AH01, or D11AH02 were retrieved. Individuals were identified by their drug exposure status based on ATC codes on disease-specific prescriptions or whether patients had been diagnosed with atopic dermatitis. If patients had been diagnosed with atopic dermatitis according to the algorithm, they were defined as having atopic dermatitis *(paper I – III).* Individuals were followed for an extended period of time to determine when they developed the desired outcome. Exposure was generated when the individual filled a prescription for the drug of interest (Table 1).

Table 2. All dispensed drugs with ATC code that was analyzed in the *papers I – III.*

Dipsensed drugs (with ATC codes) analysed	Paper I	Paper II	Paper III
Antibiotics for topical use (D06A)		x	
Antiseptics and disinfectants including hydrogen peroxide (D08AX01)		x	
Calcineurin inhibitors including ciclosporin (L04AD01)		x	
Combined corticosteroid/antibiotic preparations (D07C)		x	
Cyproterone and estrogen treatment (G03HB01)			x
Dibrompropamidine (D08AC01)		x	
Doxycycline (J01AA02)			x
Dupilumab (D11AH05)		x	
Folic acid analogues including methotrexate (L01BA01)		x	
Interferons including interferon gamma (L03AB03).		x	
Isotretinoin (D10BA01)			x
Lymecycline (J01AA04)			x
Other anti-acne preparations for topical (D10AX)			x
Other immunosuppressants including azathioprine (L04AX01)		x	
Oxytetracycline (J01AA06)			x
Pimecrolimus (D11AH02)	x	x	x
Potassium permanganate (D08AX06)		x	
Selective immunosuppressants including mycophenolic (L04AA06)		x	
Systemic antibiotics (J01AA0)			x
Systemic antihistamines (R06A)		x	
Tacrolimus (D11AH01)	x	x	x
Tetracycline (J01AA07)			x
Topical antiinfectives (D10AF)			x
Topical corticosteroids, combinations with antibiotics (D07C)	x	x	x
Topical corticosteroids, combinations with antiseptics (D07B)	x	x	x
Topical corticosteroids, other combinations (D07X)	x	x	x
Topical corticosteroids, plain (D07A)	x	x	x
Topical retinoids (D10AD)			x

Paper I - selection of prescriptions and patients

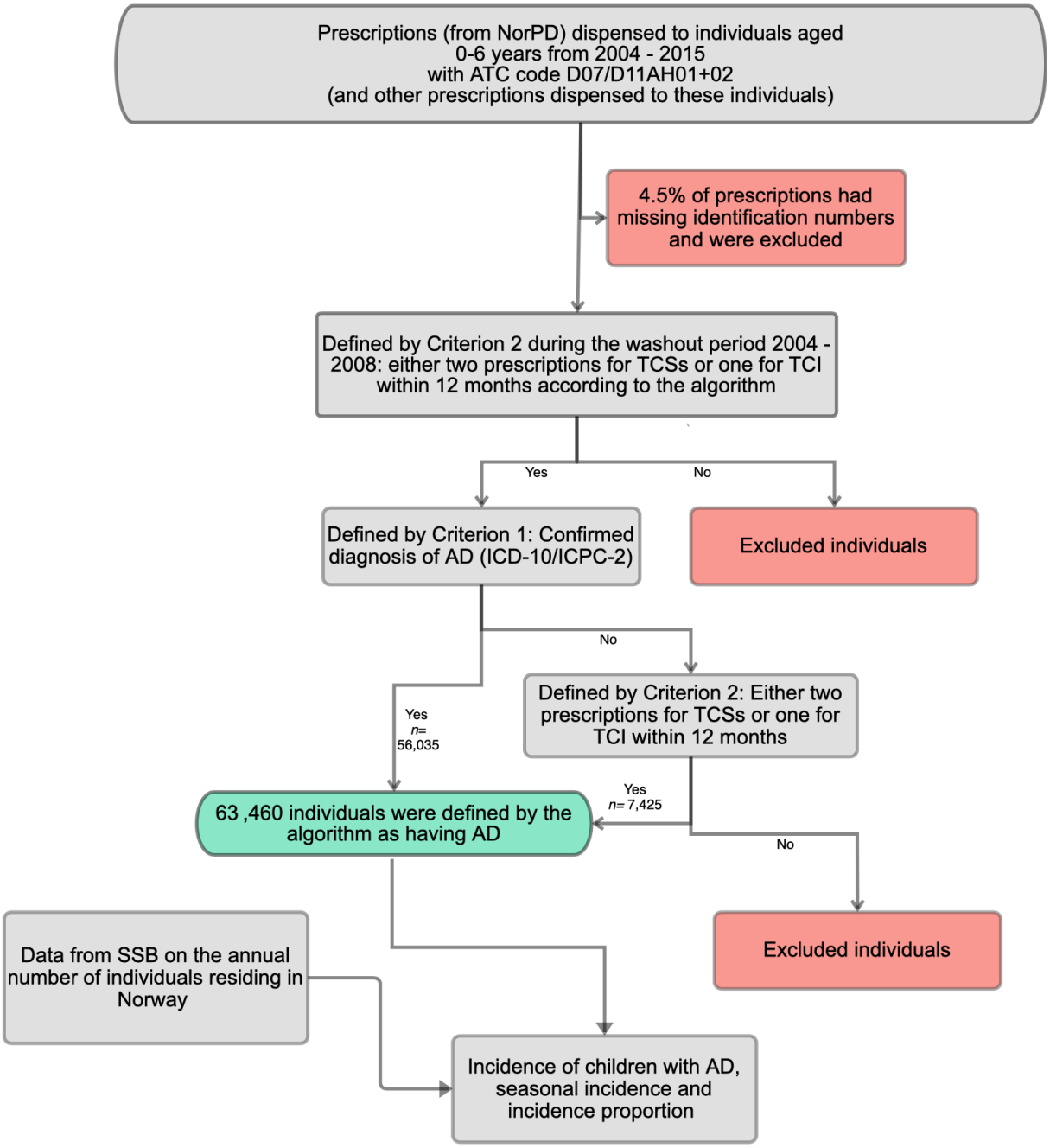

Figure 9 Flowchart illustrating the selection of prescriptions and patients in *Paper I.* After the prescriptions have been analyzed, the number of individuals defined by the algorithm (n=) is shown in the flowchart. The analysis in *Paper I* included a wash out period from 2004 – 2008.
AD: Atopic Dermatitis; NorPD: Norwegian Prescription Database; SSB: Statistics Norway; TCS: Topical Corticosteroids; TCI: Topical Calcineurin Inhibitor

Paper II - selection of prescriptions and patients

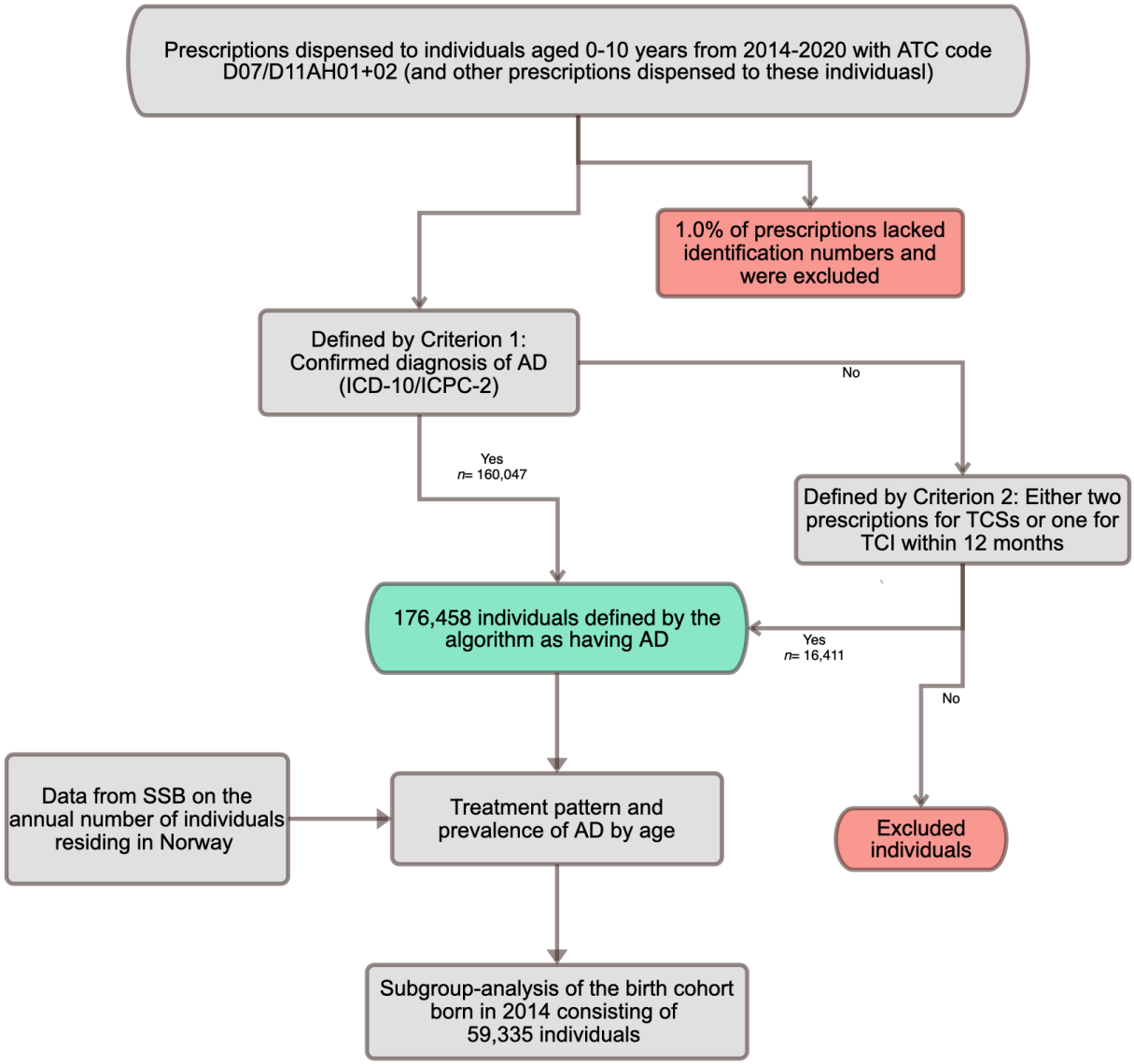

Figure 10 Flowchart illustrating the selection of prescriptions and patients in *Paper II*. After the prescriptions have been analyzed, the number of individuals defined by the algorithm (n=) is shown in the flowchart. AD: Atopic Dermatitis; NorPD: Norwegian Prescription Database; SSB: Statistics Norway; TCS: Topical Corticosteroids; TCI: Topical Calcineurin Inhibitor

Paper III - selection of prescriptions and patients

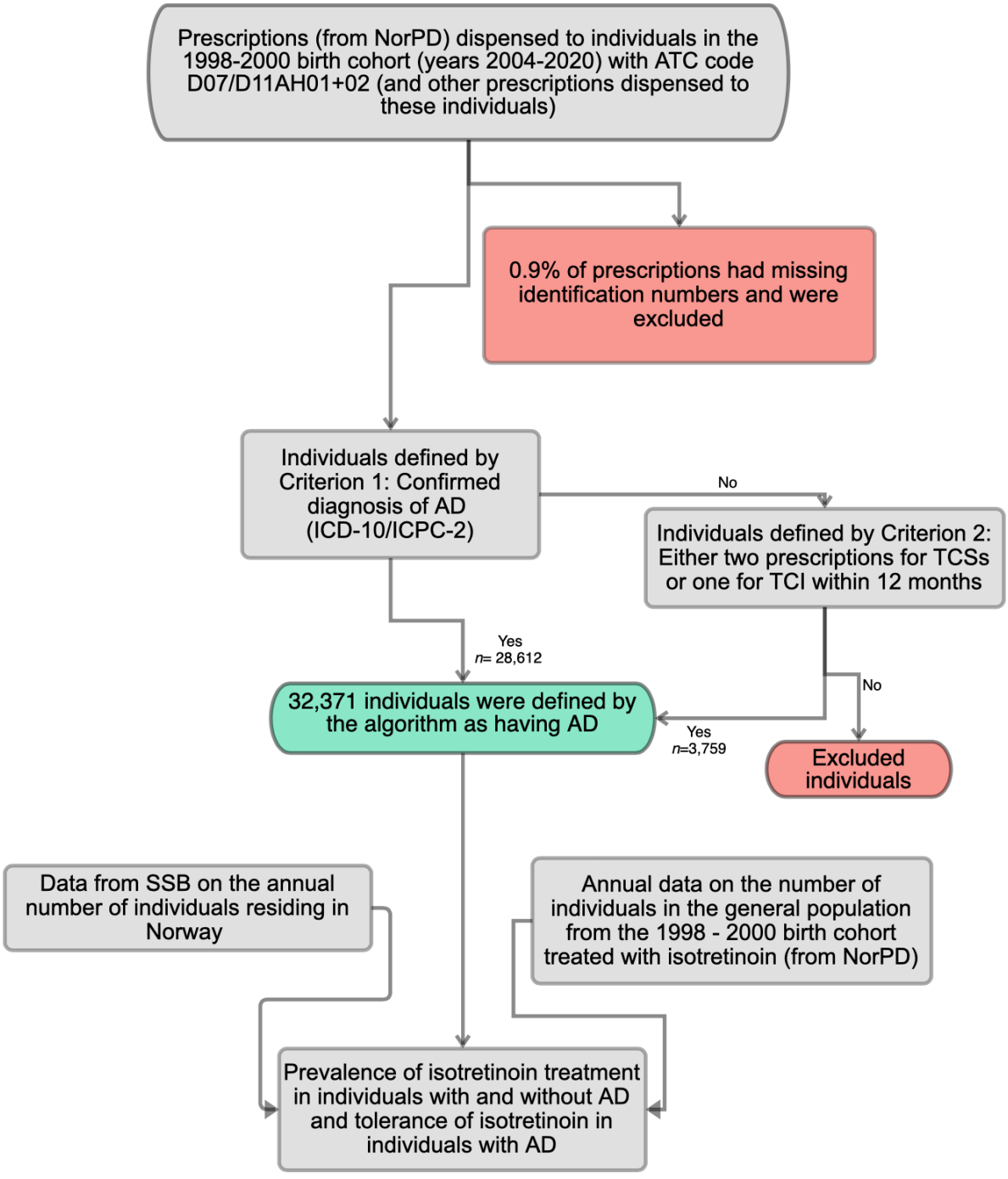

Figure 11 Flowchart illustrating the selection of prescriptions and patients in *Paper II.* After the prescriptions have been analyzed, the number of individuals defined by the algorithm (n=) is shown in the flowchart. AD: Atopic Dermatitis; NorPD: Norwegian Prescription Database; SSB: Statistics Norway; TCS: Topical Corticosteroids; TCI: Topical Calcineurin Inhibitor

Definitions, proxy measures and classifications

The definition of "dispensed prescriptions" is written synonymously with "received," "treated," “filled” and "the use of" (*Papers I – III)*.

When referring to patients or individuals with atopic dermatitis in *Papers I - III*, atopic dermatitis is defined according to the algorithm described in Chapter 2 in this thesis with the subtitle: *Algorithm for defining individuals with atopic dermatitis.*

Individuals, children, and pediatric patients are also used synonymously in *Papers I - III* and in this thesis.

Paper I

Defining the onset of atopic dermatitis

The incidence in the year, age, or season that the patient received the first topical treatment (topical corticosteroids or topical calcineurin inhibitor) for atopic dermatitis was defined as the onset of atopic dermatitis.

Paper II

Defining the burden of atopic dermatitis

The prevalence of dispensed topical treatment (topical corticosteroids or topical calcineurin inhibitor) according to age was defined as the burden of atopic dermatitis by age and subgroups in the population.

Classification of skin infection

Patients with atopic dermatitis who were dispensed medications for combined corticosteroid and antibiotic preparations, antiseptics, and disinfectants, including hydrogen peroxide

potassium permanganate and antibiotics for topical use were defined as having a skin infection.

Classification of the level of received topical corticosteroids.

The maximum potency of topical corticosteroid treatment received during the observation period classified the population with atopic dermatitis into three levels. Sole treatment of a low-potency topical corticosteroid (group I) was required to reach Level 1. The second level was defined as using moderate potent topical corticosteroid (group II) as the highest potency. Level 3 was classified as a topical corticosteroid that was either potent or very potent (group III or IV). A more potent topical corticosteroid (level) overruled a less potent one.

Papers II and III

Classification of individuals by the duration (persistence) of topical treatment of topical corticosteroids or topical calcineurin inhibitors.

Patients were classified by duration of treatment (number of years treated with topical corticosteroids or topical calcineurin inhibitors) based on prescriptions dispensed. The scientific literature has several different definitions and measurements of treatment persistence, which suggests that there isn't a universally accepted standard for either of these concepts [281, 282].

Paper III

Defining individuals as having acne

Topical preparations were classified based on their components. Topical retinoids, topical anti-infectives, and other anti-acne preparations for topical use such as azelaic acid were defined as topical acne preparations. Combination preparations containing retinoids for topical application fell under the category of topical retinoids (e.g., the combination of adapalene or clindamycin and benzoyl peroxide was categorized as a topical retinoid). Systemic antibiotics, cyproterone, estrogen, isotretinoin, and were defined as systemic acne preparations. Systemic antibiotics (antibacterial for systemic use) for the treatment of acne

vulgaris were doxycycline, lymecycline, oxytetracycline, and tetracycline. Because the systemic antibiotics belong to the same antibiotic class, the drugs were studied as a group defined as *tetracyclines*. To exclude the treatment of sexually transmitted diseases, etc., only dispensed packs containing more than fifty tablets were included in the study. Individuals treated with antiinfectives, azelaic acid, cyproterone and estrogen, isotretinoin, tetracyclines, or topical retinoids were defined as *having acne.*

Defining individuals as having severe acne

According to The Norwegian Directorate of Health [216], isotretinoin is only indicated for treating severe acne vulgaris. Individuals who received prescription for isotretinoin were classified as having a severe form of acne, according to the study.

Defining persistence of isotretinoin

The [WHO] Collaborating Center for Drug Statistics Methodology has determined that a daily dose of 30 mg of isotretinoin should be considered a defined daily dose (DDD) and was thus used as the daily maintenance dose in the study [269]. The period that elapsed between the date of the initial prescription and the date on which the drug was presumptively discontinued is defined as "drug persistence". According to DDDs, days were added to the dispensed prescription's last date.

Defining discontinuation of isotretinoin

The measure of tolerability of isotretinoin was defined as the discontinuation rate of isotretinoin in the subgroups (according to the length of topical treatment of atopic dermatitis in years). For the purpose of determining whether or not a patient has stopped (discontinued) receiving therapy, a cutoff of 16 weeks has been established. Generally, 16 to 24 weeks of treatment is sufficient [283].

Defining attempts of isotretinoin

The data were divided by the number of attempts. If it had been three months since the predicted date of discontinuation of therapy, then it was regarded that a subsequent treatment attempt had been made. The date of the following prescription marked the beginning of the subsequent attempt.

Main outcome measures

Outcome measures in *Papers I - III* were all defined by the prescriptions dispensed from the NorPD. More specifically, subjects who were dispensed a drug were defined as using or being treated with the drug in *Paper I - III*. Once the algorithm included individuals in the studies, the variables were dichotomous: either 0 for no dispensing or 1 for dispensing one or more prescriptions.

Paper I

Incidence rate

The outcome of interest was the incidence rate per person-year (PY). The incidence rate of atopic dermatitis was defined as the number of new events (without prior prescriptions dispensed in the period 2004 to 2008) (PY) with at least one prescription per year (2009 to 2014(15)) or per age group (under six years) or season as the numerator.

Year-, age-, and sex-specific data on the Norwegian midyear population per year (or age) were used as denominators (individuals at risk). We calculated the incidence rate per PY by age, sex, season, and calendar year and their interactions. The size of the study population and the source population (age/year/sex-specific data on the Norwegian population at-risk risk) differed for each age/year.

Incidence proportion

The primary outcome of interest was incidence proportions. Incidence proportions were estimated by dividing the number of new events of atopic dermatitis by the number of individuals at risk during a period from 2009 to 2014 in patients aged 0-6 years. According to the algorithm, individuals defined as having atopic dermatitis could not have received disease-specific treatment before 2009. The dominator consisted of the Norwegian population at risk in the same time period.

Incidence rate ratio

The primary outcome of interest was the incidence rate ratio *(Paper I)*. Incidence rates between different age groups, sexes, seasons, and years of individuals with atopic dermatitis were compared.

Papers II and III

Prevalence Proportion

The primary outcome *(Papers II and III)* of interest was a 12-month prevalence of atopic dermatitis and severe acne, which refers to the total number of individuals treated with disease-specific medications at a given age group or year as the nominator. The number of the Norwegian population in the corresponding period (by age or year) was used as the dominator to define individuals with atopic dermatitis per age *(Paper II)* and severe acne in the population without atopic dermatitis *(Paper III).* The size of the study population and the source population (Norwegian population) differed for each age and year. Point prevalence was examined as a function of age, sex, and year. The number of individuals with atopic dermatitis receiving isotretinoin *(Paper III)* was defined as the proportion of the belonging birth cohort with atopic dermatitis. The terms; point prevalence, proportion, and rate are sometimes also used as synonyms in this thesis [280].

The proportion of drug types dispensed

Individuals were classified according to the types of medications dispensed. For each medication category *(Papers II and III)*, the proportion of all prevalent users was calculated by subgroup.

Persistence

The overall length of treatment in years for atopic dermatitis was analyzed to assess the duration of disease-specific treatment in subgroups of the 2014 birth cohort *(in Paper II)* and the 1998-2000 birth cohort *(Paper III).* We analyzed the number of patients who received regular treatment for atopic dermatitis *(Papers II–III)*. The number of patients with atopic

dermatitis by subgroup as nominator was compared with the denominator in each group to determine the proportion in each group.

To determine the drug persistence of isotretinoin *(Paper III),"was defined as the duration between the date of the first prescription and the presumed discontinuation date (days, according to DDDs, were added to the date of the last prescription)"* [274].

Prevalence Rate Ratio and Relative risk
Another outcome of interest *(Papers II and III)* was the relative effect measures based on the occurrence ratios [280]. Prevalence rates and proportions were compared among different populations, age groups, subgroups, sexes, and years.

Statistical analysis

I used the Poisson regression procedure in all three papers to calculate the outcome with 95% CIs, using Stata/ MP software version 14.2 *(Papers I and II)* and 17.0 *(Paper III);* StataCorp LLP. Incidence rates per PY, incidence rate ratios, 12-month prevalence rates, risk ratios and prevalence rate ratios were calculated. Statistical significances were tested with $\chi 2$ tests. $P < .05$ (2-sided test) was considered statistically significant. The denominator was from the population from which the numerator was derived. Year-, age- and sex, and subgroup-specific analyzes were performed.

When reporting descriptive statistics for categorical variables, frequency (percent) was used. The data were stratified by age and sex, year, whether treatment was started early or late (onset), the number of years treatment was received (the course), the season, subgroups or birth cohorts, and interactions. The mean, standard deviation (SD), or median was used to report descriptive statistics for continuous variables.

Sensitivity analyses, together with a statistician, were performed. All steps of the analysis are written down and saved in the Stata do files so that the work can be reproduced in detail *(Paper I- III).*

Ethical considerations

In study is approved by the Regional Committees for Medical and Health Research Ethics in Southeast Norway (Ref: REK: 1927) and the Norwegian Social Science Data Services (NSD).

Because registry-based research does not impose any obligations (physical or nonphysical) on study participants, study participants can be expected to gain more from this research than they lose. Individuals participating in registry-based research do not have to invest time or take research-related risks. While it is clear that study participants can gain much from registry-based research, they can suffer significant losses if integrity is violated. To thoroughly evaluate the potential impact of the research, a comprehensive risk-benefit analysis was conducted. The analysis considered both the advantages and disadvantages of registry-based research, focusing on the potential impact on patients and the health care system as a whole. After careful consideration, it was concluded that the benefits of this type of research far outweighed the potential disadvantages. Ultimately, registry-based research has the potential to significantly improve patient outcomes and increase the overall efficiency of the healthcare system.

Prescription data from the NorPD are defined as pseudorandomized, but because of the many overlapping variables, it is not possible to determine whether the data set is truly anonymous. In most cases, data from the NorPD are considered indirectly identifiable information. Data were generally accessed, managed, and analyzed pseudonymously through a secure and password-protected portal. This approach serves to protect personal information.

Scientific inference

The inability to replicate medical research results is discussed in both the scientific and lay press. The scientific community is continually working to improve the quality of research through peer review recommendations [284] and checklists such as the *Consolidated Standards of Reporting Trials* (CONSORT) and the Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) [285-289]. The STROBE *(Paper I - III*) and the CONSORT checklists *(Paper III)* were followed.

Funding sources

This research was carried out at the Department of General Practice, part of the Institute of Health and Society at the University of Oslo. The Norwegian Research Foundation for General Practice provided financial support for the study. In October of 2021, Sanofi Genzyme provided the research project with a grant.

4 SYNOPSES OF THE PAPERS

Paper I

Mohn CH, Blix HS, Halvorsen JA, Nafstad P, Valberg M, Lagerlov P.
Incidence Trends of Atopic Dermatitis in Infancy and Early Childhood in a Nationwide Prescription Registry Study in Norway.
JAMA Network Open 2018

Methods

This cohort study included all Norwegian children younger than six years of age between January 1, 2009, and December 31, 2015. This population-based prescription registry analysis found that children with atopic dermatitis were identified based on disease-specific medications and medical diagnoses using data from the NorPD.

Results

The increase and proportion of children with atopic dermatitis (Aim I)

- Throughout the study period (2009 - 2014 (15)), there was a steady increase in children with atopic dermatitis.
- We found an overall increase of 16.8% (IRR, 1.17; CI, 1.14-1.20) from 2009 to 2015 in Norwegian children with atopic dermatitis. The increasing trend was mainly due to pediatric patients younger than one year. In this age group, the incidence rate increased by 42.0% (IRR, 1.42; CI, 1.32-1.53).
- The increase showed no significant difference between boys and girls.
- We observed that there was an interaction between age and sex and that boys had a 53.2% (IRR, 1.53; CI, 1.49-1.57) higher incidence rate than girls in the first year of life. At one year of age, boys had a 15.1% (IRR, 1.15; CI, 1.12-1.19) higher incidence rate than girls. At two years of age, there were no significant differences.
- The incidence rate of atopic dermatitis was highest in both sexes' first year of life.
- Overall, in pediatric patients under years of age, the incidence proportion of atopic dermatitis was 17.4% (CI, 17.2%-17.7%) during the six years of the study period.

The seasons and incidence of atopic dermatitis (Aim II)

- Winter and spring were the seasons with the highest incidence of atopic dermatitis.
- The IRR for winter and spring was 1.16 (CI, 1.13-1.19) and 1.41 (CI, 1.38-1.45), respectively.

Conclusion

This nationwide study showed a substantial increase in the incidence of atopic dermatitis in Norwegian children, especially in children under the age of one. Our results showed that atopic dermatitis onset was earlier in boys than in girls. The sex differences evened out after the age of two years. The burden of atopic dermatitis was substantial during the study period, with over one out of every six children under the age of six affected by the disease. The findings imply that seasonal environmental factors may contribute to the onset and exacerbation of the disease.

Paper II

Mohn CH, Blix HS, Brænd AM, Nafstad P, Nygard S, Halvorsen JA.
Treatment Patterns of Atopic Dermatitis Medication in 0-10-Year-Olds: A Nationwide Prescription-Based Study.
Dermatology and Therapy 2022

Methods

This study included all Norwegian children younger than ten years of age between January 1, 2004, and December 31, 2020. In this population-based prescription registry study, children with atopic dermatitis were identified based on disease-specific medications and medical diagnoses data retrieved from the NorPD. A subgroup analysis of the 2014 birth cohort was also conducted.

Results

Treatment patterns in Norway under the age of eleven (Aim III)

- Of the 176,458 children with atopic dermatitis during the study period, almost all patients (99.2%) received topical corticosteroids, many of them received potent topical corticosteroids (37.1%). Only a minority received topical calcineurin inhibitors (5.1%) and systemic corticosteroids (2.1%).
- Although the body surface increases with age, the average number of prescriptions per child and the average number of grams of topical treatments prescribed steadily decreased with age.
- The overall use of systemic immunosuppressants (including systemic corticosteroids) dispensed among the Norwegian pediatric population was marginal.
- The 12-month prevalence of atopic dermatitis ranged from 11.1% (CI 11.1-11.3) at one year to 4.5% (CI, 4.4-4.5) at 10 years.
- Statistics showed a significant preponderance of boys treated for atopic dermatitis at age four years. The average prescriptions per year per child and the average grams of topical treatments prescribed decreased steadily with age.

- The proportion of children per age group who received potent topical corticosteroids or topical calcineurin inhibitors increased with age.

Predictors of risk in the 2014 birth cohort (Aim III)

- Of the 59,335 live births in Norway (2014), 24.8% (CI, 24.5-25.1) of the children were treated for atopic dermatitis before the age of 6 years.
- In the birth cohort of 2014, 6.5% (CI, 6.1-6.9) were dispensed drugs for atopic dermatitis annually, minimum for 5 years (or longer).
- Significantly more boys (17.9% (CI, 6.5-27.9) than girls received treatment for at least 5 years (or longer).
- 12.4% (CI, 6.5-18.0) more potent topical corticosteroids and 6.4% (CI, 1.2-11.3) more treatments for skin infections were dispensed for boys compared with girls
- Relative to late-onset individuals, a greater proportion (18.9% (CI, 7.5-29.0)) of children with early-onset atopic dermatitis still received treatment at age five. Accordingly, more children (15.7% (CI, 7.1-23.4)) with early onset disease were receiving potent topical corticosteroids, and a greater proportion (44.4% (CI, 36.5-51.2)) of early-onset individuals were being treated for skin infections.
- 39.7% (CI, 28.9-48.8) more children with early with early-onset than late-onset atopic dermatitis received regular medications.
- When analyzing antihistamines taken before 6 years of age, we found that 20.9% (CI, 12.2-28.7) more early-index-age children than late index age individuals received antihistamines.

Conclusions:

Most children with atopic dermatitis were treated for a mild disease for a brief period of time. The highest burden of atopic dermatitis occurred before the age of two. In children aged one year, the prevalence of atopic dermatitis peaked. While the prevalence of atopic dermatitis was higher at younger ages, these children were least likely to be treated with potent topical corticosteroids. Early disease onset and male sex were associated with long-term treatment and more frequent treatment with potent topical corticosteroids, treatment of skin infections,

and antihistamines. Early disease onset and male sex are potential predictors of severe atopic dermatitis and prolonged disease course.

Paper III

Mohn CH, Blix HS, Brænd AM, Nafstad P, Halvorsen JA.
Prevalence of isotretinoin therapy in adolescents and young adults with and without atopic dermatitis: a nationwide prescription-based population study
Acta Dermato-Venereologica 2023

Methods

All Norwegian children were followed for 17 years between January 1, 2004, and December 31, 2020, at ages 4 to 22 years (the 1998-2000 birth cohort). In this population-based prescription registry study, medical diagnoses and disease-specific medications identified children with atopic dermatitis based on data retrieved from the NorPD. The prevalence of isotretinoin therapy was compared in adolescence and young adults with and without atopic dermatitis.

Results

Prevalence of acne *(Aim IV)*

- Of patients with atopic dermatitis, 28.2% were treated for acne (all preparations included), of whom 7.6% were dispensed treatment indicated for severe acne (isotretinoin).
- Treatment with isotretinoin peaked at 1.9% (0.01; CI, 0.01-0.01) in patients without atopic dermatitis at age 18 years, while it further increased to 2.2% (0.02, CI, 0.02-0.02) in patients with atopic dermatitis at age 22 years.
- After age 17 years, significantly more patients with than without atopic dermatitis were treated with isotretinoin with increasing age, from 16.2% (1.16; CI, 1.07 - 1.26) at age 18 years to 42.8% (1.43; CI, 1.24-1.65) at age 22 years.

Tolerability of isotretinoin treatment (Aim V)

- 54.1% of patients with atopic dermatitis treated with isotretinoin received topical corticosteroids/topical calcineurin inhibitors during isotretinoin treatment.

- In patients with a short-term course of atopic dermatitis, only 48.2% received topical corticosteroids/topical calcineurin inhibitors during isotretinoin treatment, compared with 92.3% in patients with a long-term course of atopic dermatitis.
- Patients receiving long-term topical treatment for atopic dermatitis were less likely to be treated with isotretinoin.
- No notable variations were found regarding discontinuation rates or the number of treatment attempts with isotretinoin according to the treatment course duration in atopic dermatitis.

Conclusions:

In conclusion, at the population level, severe acne was associated with atopic dermatitis in young adults after the age of 17. Fewer patients with long-standing atopic dermatitis received isotretinoin.

The findings suggest that individuals with severe and persistent atopic dermatitis and those with mild and short-lived atopic dermatitis tolerated the drug. However, we observed that patients with a chronic condition of atopic dermatitis were more likely to require topical corticosteroids while undergoing isotretinoin therapy compared to those with a short-term condition.

5 DISCUSSIONS

Measuring the incidence and prevalence in patients with atopic dermatitis

We found that the incidence rate of pediatric patients with atopic dermatitis aged 0-6 years increased by 16.8% between 2009 and 2014, as shown in figure 12. In addition, the increase in children under one year of age was 42% during the study period.

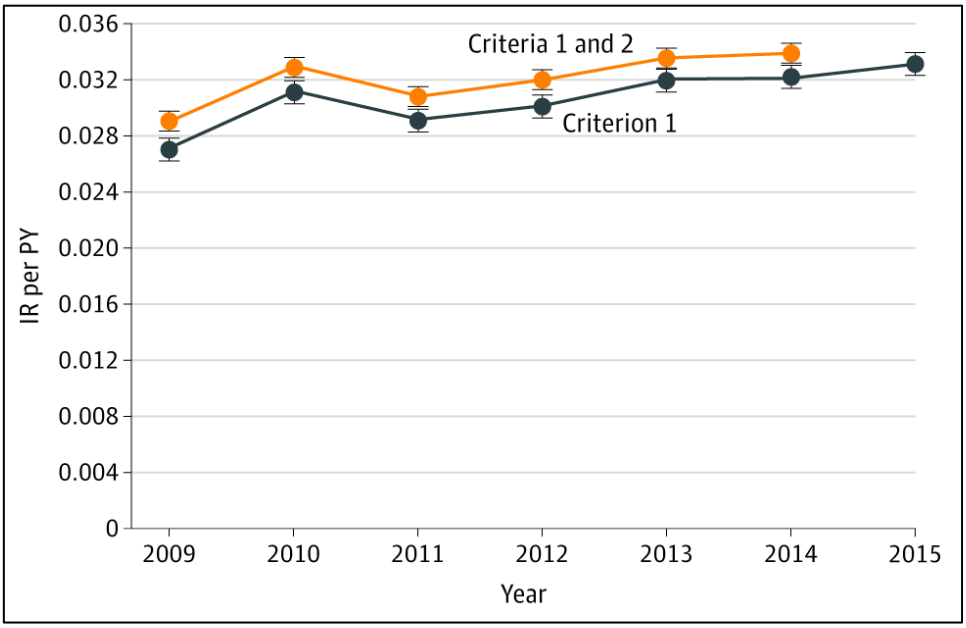

Figure 12. Incidence rate (IR) per person-year (PY) of atopic dermatitis during the first six years of life. The upper curve shows the incidence rate per person-year using reimbursed (criterion 1) and non-reimbursed (criterion 2) drugs as a proxy for atopic dermatitis; the lower curve (year 2009-2015) shows the incidence rate for reimbursed drugs only (criterion 1).

Before age six years, atopic dermatitis affected more than 1 in 6 children. In addition, the burden of atopic dermatitis was defined by prevalence, as illustrated in the figure below in figure 13. The figure shows the substantial increase found in *Paper I*, especially since 2013.

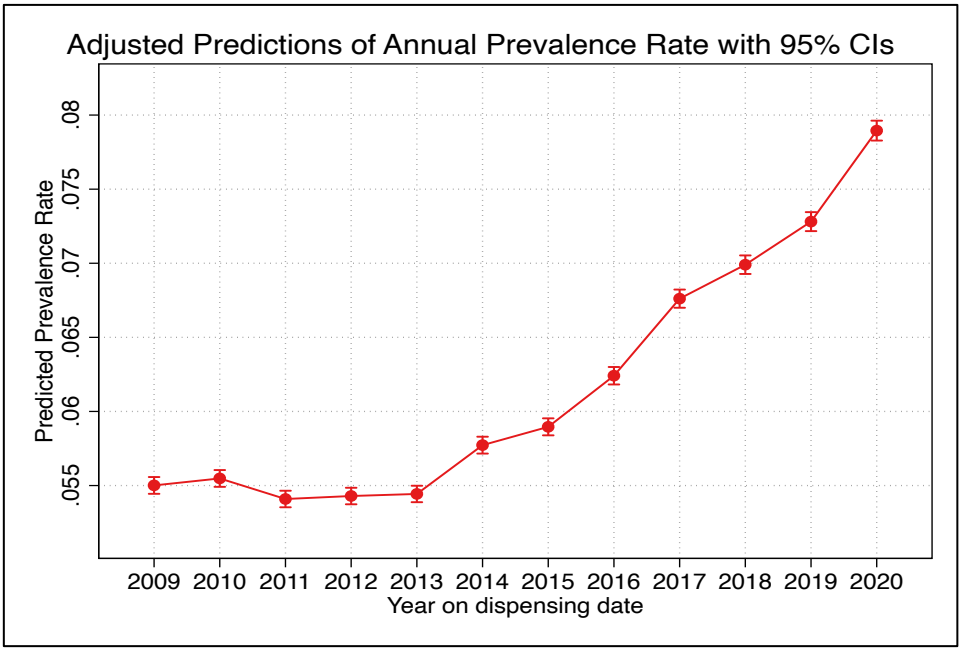

Figure 13. Annual prevalence rate in children with atopic dermatitis year 2009 - 2020, ages 0-10. Data are from the Norwegian Prescription Database from January 1, 2009, to December 31, 2020. Error bars indicate 95% CI. The curve shows prevalence determined by reimbursable (criterion 1) and non-reimbursable (criterion 2) medications as proxies for atopic dermatitis.

One must be cautious when drawing conclusions from trends over time. A change in surveillance programs could have been associated with the increased number of children with atopic dermatitis *(Papers I and II)*. The Norwegian infant healthcare program in Norway applies to all children from birth to school entry (0-5 years) in Norway. During this period, they are offered 14 consultations at a community health center. To our knowledge, scheduled visits to the health care program did not change in the relevant ages. Another important aspect to consider is that the criteria for diagnosing atopic dermatitis can change, However, the most commonly used criteria remained the same during the study period in which the occurrence of atopic dermatitis was measured. The 1980 Hanifin and Rajka criteria were revised in 2003, and the 1994 United Kingdom Working Party criteria were revised in 2005 [98]. However, it is unlikely that these criteria are commonly used by general practitioners.

An issue related to the availability of primary care physicians (fastlege), which has increased over the years, could potentially affect the number of children treated with topical corticosteroids. The number of primary care physicians per population has increased from 8.4% primary care physicians per 10,000 population in 2009 to 9.2% in 2020, an increase of approximately 9.5% [263]. However, during the same period, we found that the annual prevalence rate among pediatric patients with atopic dermatitis aged 0-10 years increased from 5.5% to 7.9% from 2009 to 2020, a 30.4% increase. If the number of pediatric patients with atopic dermatitis is increasing more than the number of general practitioners in Norway, then there is reason to suspect that the number of pediatric patients with atopic dermatitis is indeed increasing.

Over time, the internet has become an essential source of both information and misinformation. False information is spread, which may lead to corticophobia (phobia of corticosteroids) [290]. Topical corticosteroids are an effective and safe treatment for numerous dermatologic conditions [291]. A recent study in 2023 found that risk factors for corticophobia included misinformation, lack of education about topical corticosteroids, fear of potential side effects, urban residence, higher education, higher income, a higher number of primary care physician visits before a dermatologic examination, and lack of dermatology clinic continuity [290]. One can speculate whether parental anxiety is exceptionally high in the youngest children, leading to individuals may receive topical treatment but not use it (nonadherence to prescribed medication). This could partially explain why the burden of atopic dermatitis remains high among the youngest children, even when they receive treatment, as shown in Figure 14. Another possibility is that the chronicity of the disease has increased. I have found no evidence for the latter. Furthermore, in recent decades, the number of physicians per 1,000 population in Norway has increased, which could lead to more treatments and there has been a significant change in the way medicalization is approached [292]. Although medicalization must be considered, the effects may not be as severe in the relatively young population addressed in *Papers I- III* compared with older age groups (medicalization of aging). In addition, the consequences of these effects are also likely to be less visible over such a short period of time.

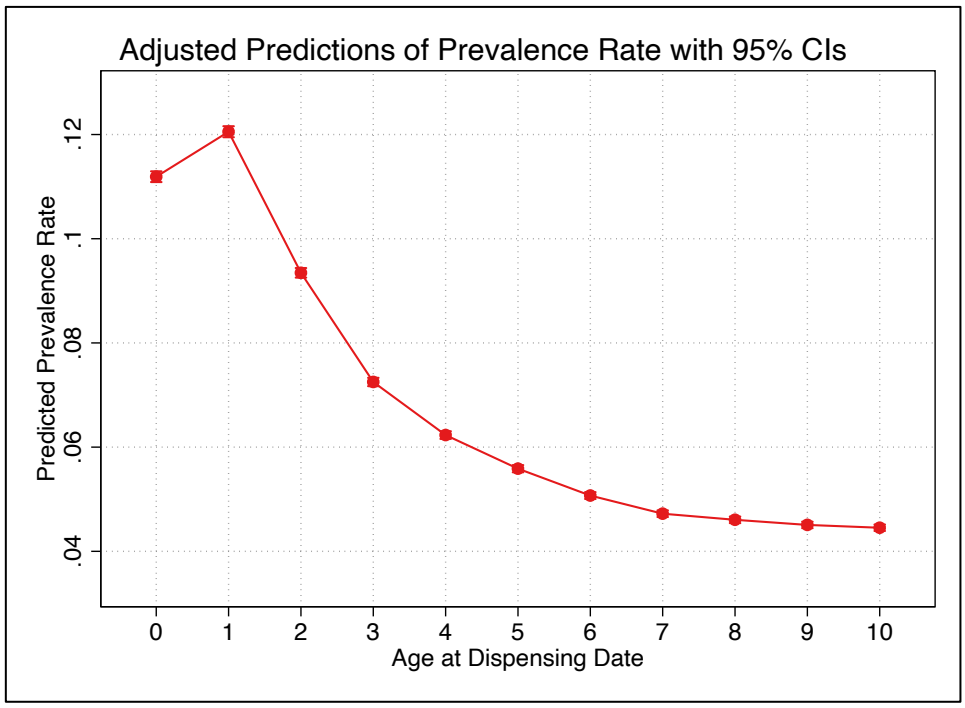

Figure 14. Prevalence rates in children with atopic dermatitis by age group at the time of the dispensed prescription from 2014-2020. Data are from the Norwegian Prescription Database from January 1, 2104, to December 31, 2020. Error bars indicate 95% CI. The curve shows prevalence determined by reimbursable (criterion 1) and non-reimbursable (criterion 2) medications as a proxy for atopic dermatitis.

As noted earlier, we found that the overall burden of atopic dermatitis was highest in the youngest age groups *(Papers I and II)*, as seen in figure 14. Although speculative, the overall high prevalence of children with atopic dermatitis noted in this work may be due to ineffective provided treatment. Other reasons could also include forgetfulness, patients' dislike of treatment and bathing, complicated instructions, the time required to apply treatment, phobia of corticosteroids, or inadequate understanding of the disease or treatment, as mentioned earlier [293]. The lack of precise laboratory or histologic findings, limited knowledge of clinical criteria, and the diversity and variability of the disease remain the most frequent causes of misdiagnosis, according to a 2021 review [294]. Most patients with atopic dermatitis are initially evaluated and treated by their general practitioner, who may be less familiar with atopic dermatitis guidelines, diagnosis, preventive care, and available treatment options [294]. Although several countries have adopted or even developed guidelines for diagnosing and treating atopic dermatitis, not all physicians who treat atopic dermatitis are

familiar with these guidelines, and not all clinics use established diagnostic criteria to make the diagnosis [294]. In addition, clinics probably rarely use established tools to assess disease severity [294, 295]. Although more and more patients are receiving treatment on topical corticosteroids (leading to an increase in incidence and prevalence, as observed in *Paper I-II*), explaining the basic principles of management and treatment and providing sufficient information on preventive measures is crucial to improving the overall outcome, especially for this disease [296]. Conventional treatments should always be supplemented by therapeutic education, which can be delivered in the form of nurse-led workshops, video training, and educational programs such as the Eczema School (Eksemskolen at the Department of Dermatology at Rikshospitalet, Norway) [296]. It is currently unknown whether patients (and caregivers to patients) with atopic dermatitis in Norway are inadequately informed. There is an obvious need for further investigation. However, although speculative, this could possibly be part of the explanation for why the burden of atopic dermatitis remains high in the youngest children, even after treatment with topical corticosteroids.

Although researchers confirmed that the prevalence of atopic dermatitis is considerably higher in the youngest children, these children had the lowest probability of receiving potent topical corticosteroids in our study *(Paper II)* [87]. As mentioned earlier, a hypothetical question arises as to whether inadequate topical treatment leads to treatment failure in infants and young children, which may partially explain their predominance. Although the thin skin of younger children may absorb the steroid more readily, there is limited evidence of clinically significant suppression of the hypothalamic-pituitary-adrenal (HPA) axis by the weaker or even the (very) potent topical corticosteroids when used as approved [297-301]. Although some clinical studies suggest that potent topical corticosteroids have a higher risk of suppressing adrenal function than weak and moderate topical corticosteroids, systemic effects are dissipated more rapidly if the skin barrier is restored more quickly [88]. Overall, treatment with potent compared with mild topical corticosteroids has resulted in more rapid improvement and increased disease control, with no difference in side effects [302]. This ultimately may lead to leads to less use of topical corticosteroids and, in general, fewer prescriptions and fewer visits to the general practitioner (suggesting that this may perhaps be more cost-effective) [88, 297-300, 302, 303]. Most children with atopic dermatitis are treated by their general practitioner [303]. A recent study showed that most general practitioners were not confident recommending potent topical corticosteroids [304]. In summary, guidelines for

the potency of topical corticosteroids according to the anatomical site of administration and the severity of the disease must be more age-specific, particularly in children under the age of two [305].

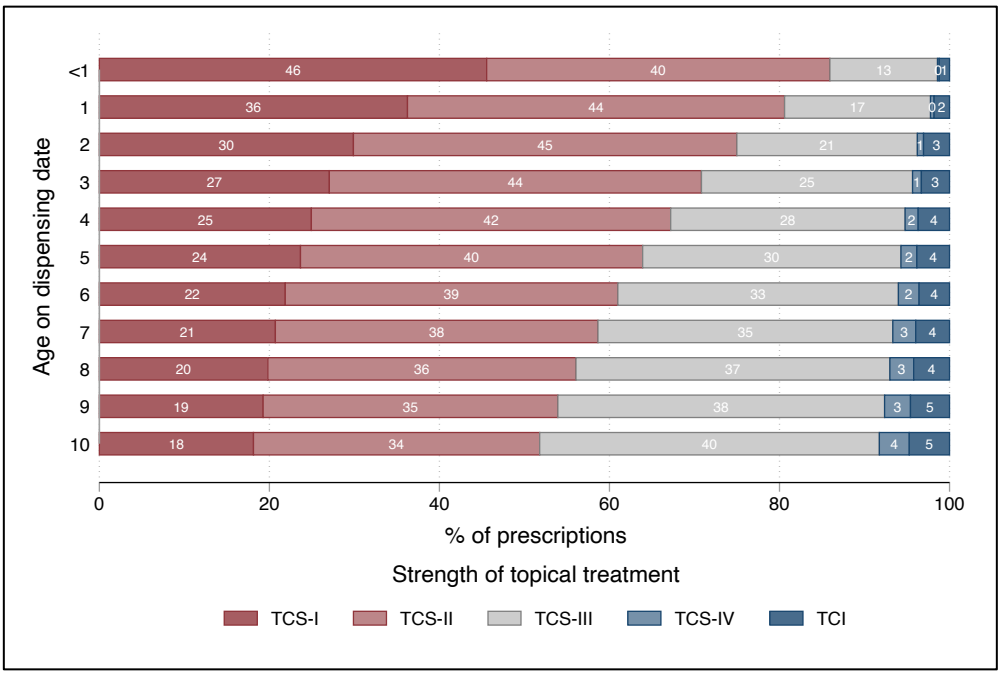

Figure 15. The relative proportion (in percent) of all dispensed atopic dermatitis treatments for children 0-10 (by age) years using topical corticosteroids and topical calcineurin inhibitors from 2014-2020. Data are from the Norwegian Prescription Database from January 1, 2014, to December 31, 2020. Bars represent the percentage of topical corticosteroids (presented in groups I- IV by potency) and topical calcineurin inhibitors (TCI) dispensed to children aged 0-10 years.

It has been discussed that the potential improved awareness of atopic dermatitis among nurses and clinicians in recent years may result in even the slightest symptoms being recognized as atopic dermatitis, leading to an "increased acceptance of having eczema. Increased patient (and caregiver) awareness of atopic dermatitis would also lead to earlier and more consultations/visits to the physician. Consequently, more diagnoses would be made, and more treatments prescribed. Furthermore, our results may be consistent with the hypothesis that the raise in the number of children treated for atopic dermatitis is due to better awareness of the symptoms of the disease, leading to the recognition of more patients with milder disease who

receive a shorter duration of treatment. In other words, the number of identified patients with atopic dermatitis may have increased without an actual increase in affected patients. Moreover, we use treatment (prescriptions) as a proxy to describe the occurrence of the disease. We also use these outcomes to represent the burden of disease in the population. But it is treatment that helps alleviate the symptoms of the disease. Therefore, our findings that more individuals are being treated for atopic dermatitis may also show that more children with atopic dermatitis are getting the help they need. Better awareness and recognition of even mild symptoms of atopic dermatitis could encourage caregivers to bring their children to the doctor earlier, even for milder symptoms. If this is the case, we could observe an increase in early-recognized atopic dermatitis in the youngest age groups. In the older age groups, the incidence of atopic dermatitis would decrease accordingly. However, the incidence in older children (2-5 years) was stable from 2009 to 2014 *(Paper I).*
Perceptions and awareness of disease may indeed change during long periods of observation, making longitudinal studies of recorded disease and disease-specific treatments uncertain. However, in our research, these effects are unlikely to be significant because our surveillance showed an increase in incidence within a relatively short period of time.

In summary, several factors may have added to the increasing trend of atopic dermatitis observed in *Paper I- II.* These may include increased awareness of atopic dermatitis, increased urbanization, changes in counseling practices, improved health care and access to it, increased environmental exposure, inadequate information about preventive measures and treatment guidelines for atopic dermatitis, or misinformation or inadequate strength of topical corticosteroids offered. In either case, the increasing trend of atopic dermatitis is a critical problem with significant public health implications. The interpretation of these findings is that there may have been an increase in atopic dermatitis, particularly in pediatric patients younger than one year of age, and that the burden of atopic dermatitis is most likely persistently higher in the early years of life. It is likely that several interrelated causative factors, along with a real increase of atopic dermatitis in pediatric patients, are responsible for this increasing trend found in *Paper I and II.*

Predictors of risk

We discovered an interaction between age and sex *(Paper I)*; we observed that boys had a much higher likelihood than girls of receiving treatment for atopic dermatitis at a younger age. In addition, boys were more likely to receive treatment for skin infections and antihistamines, and they also had an elongated disease course of atopic dermatitis compared to girls *(Paper II).* A Danish study came to the same conclusion, concluding that the condition was more severe in males than in females [72]. To our knowledge, no previous nationwide study has examined sex disparities in prescribing medications for atopic dermatitis before the age of 2 years (as of 2018). However, the sex disparity in atopic dermatitis is a phenomenon that has also been noted in previous studies before the age of 6 months [70, 254]. The predominance of boys in the treatment of atopic dermatitis at an early age reflects previous and recent studies [68-70, 306]. A recent study that was conducted in Norway found that the male sex was a predictor of transepidermal water loss at the age of three months [73]. We found that atopic dermatitis appears to occur earlier in boys than in girls *(Paper I)* but not after age 2. Compared to males, the point prevalence of atopic dermatitis in one-year-olds girls was 24%, while it was 35% in boys *(Paper II).* Asthma shows the same trends with sex differences as atopic dermatitis. The prevalence is higher in boys and are twice as likely as girls to require hospitalization [307].

There is a different distribution of predilection sites in girls and boys with atopic dermatitis in infancy [306]. Let us assume that boys are more likely to develop atopic dermatitis at a younger age than girls. In this case, they are theoretically more likely to see a doctor and consequently be diagnosed with atopic dermatitis earlier. Another hypothesis is that boys are more likely than girls to express pain/discomfort at a younger age [308-310]. Just as ADHD is often more subtle in girls than in boys, there may also be a difference in the presentation of itching or skin pain caused by atopic dermatitis. Finally, there are studies showing that more boys than girls have a higher prevalence of Ige-mediated food allergies before the age of 3-5 years [311]. It is unclear whether rashes associated with food allergies may have contributed to an overestimation of the prevalence of atopic dermatitis in boys in our studies *(Papers I – II)*.

Nearly one in five patients *(Paper II)* received early-onset treatment for atopic dermatitis in the birth cohort of 2014. The results *(Paper II)* indicate that children with early-onset atopic dermatitis are at increased risk for developing a more severe form of atopic dermatitis.

Patients with early-onset atopic dermatitis received more topical corticosteroids and calcineurin inhibitors (higher number of prescriptions and grams) and received potent (or very potent) topical corticosteroids and were treated more frequently for skin infections. Although antihistamines were primarily prescribed for allergies, they are also often prescribed for atopic dermatitis. Patients with early-onset atopic dermatitis had significantly higher use of antihistamines than individuals who presented with late-onset treatment *(in Paper II).* Nevertheless, a previous study found that patients with early-onset atopic dermatitis had a significantly higher chance of developing asthma and seasonal allergies than those with late-onset atopic dermatitis [119]. Moreover, compared with individuals who developed atopic dermatitis later in life, patients who developed the condition at a younger age had an increased risk of receiving topical therapy by age five *(Paper II).* According to a Danish researcher that observed the severity of atopic dermatitis in pediatric patients, early-onset atopic dermatitis in patients less than one year of age, are at increased risk for severe disease [65]. In addition, previous studies suggest that pediatric patients who develop early-onset atopic dermatitis have a considerably increased risk of having filaggrin loss-of-function mutations and longer duration of atopic dermatitis and hospitalizations, increased disease persistence, and poorer disease control [66, 67]. The results in *Papers I-II* are supported by all the findings from the aforementioned studies.

Seasonality of atopic dermatitis

The debut of atopic dermatitis (corresponding to the first prescription of topical therapy for the treatment of atopic dermatitis) was higher in winter and spring *(Paper I)*. This study may indicate a possible relationship with outdoor temperature or temperature-related factors. Meteorological statistics showed that the 2010 winter season was particularly cold in both Norway and Sweden [312]. In 2010, over-the-counter sales of hydrocortisone for topical use and prescriptions of glucocorticoid inhalers for children reached an all-time high in Norway [313]. In this particular year, the incidence of atopic dermatitis was the highest compared with previous and subsequent years from 2009 – 2012 *(Paper I).* In addition, atopic dermatitis and asthma incidence peaked in Sweden (Henriksen et al.) in precisely the same year [114].

Previous scientific studies in European countries [148] and Scandinavian countries (Denmark and Sweden) show a seasonal change in the frequency of atopic dermatitis, with clear peaks in winter (December – February) and spring (Mars – May) and the lowest values in summer (June – August). In Norway, outdoor temperatures are coldest in January, which was the month when most cases of atopic dermatitis occurred (*Paper I).* During the entire observation period, the average outdoor temperature in winter and spring in Norway was -6.3°C (20.67°F) and 3.17°C (37.71°F), respectively. In a fairly recent study, the water content of the stratum corneum of infants showed considerable seasonal variation (higher in early summer than in fall) [158]. Although speculative, water content could be a consequence (indirect or direct) of the influence of ambient temperature.

During the spring, a considerable amount of pollen is released, especially from Alder, hazel, and birch. About 20% of the Norwegian population has symptoms of allergy. Foelster-Holst et al. have shown for the first time that there may be a direct relationship between skin exposure to pollen allergens and the manifestation of atopic dermatitis and pruritus [146]. The relationship between flare-ups of atopic dermatitis and allergy to birch and grass pollen has been studied several times in the literature [38, 145-147]. The release of pollen in the air due to warmer outdoor temperatures could possibly explain some of the increased flare-ups in pediatric patients with atopic dermatitis in the spring noted in this study.

More research is needed to evaluate the effects of the season on the skin barrier. Our findings indicate that seasonal environmental factors influence the onset of the disease and possibly its exacerbation. Both vitamin D and UV light have been shown to reduce the inflammatory immune response due to their anti-inflammatory properties [314-316]. Many individuals with atopic dermatitis feel better when exposed to the sun in the summer. However, the effect of sunlight on patients with atopic dermatitis varies [317]. In addition, indoor climate may also have an impact on atopic dermatitis. When the weather is cold in winter, more people stay longer in houses, kindergartens, etc. The air in the homes must be warmed, and the air becomes drier (low humidity). Dry air (low humidity) can remove moisture from the skin and worsen atopic dermatitis [156]. Many other possible environmental factors could be related to the outcome of the seasonal incidence rate of atopic dermatitis. The various elements in this relationship could be confounded by natural antigens in the air, seasonal viruses, or lower humidity and sunshine duration, which could be associated with xerosis, psychological stress,

and itching [318]. Nevertheless, further studies are needed to investigate the seasonal variability of this skin condition.

Risk for severe acne in patients with atopic dermatitis

As noted earlier, the prevalence of atopic dermatitis is known to decrease in adolescence [133, 134, 319-321]. Despite the increasing awareness that atopic dermatitis is a systemic inflammatory condition with an increased risk of infection, the risk for acne in this patient group has been poorly studied. Thyssen et al. [209] estimated that the risk of acne in patients with atopic dermatitis increases slightly with age, especially in those over 40. The study also found that the risk of severe acne (isotretinoin treatment) was lower in younger patients and adolescents with atopic dermatitis but increased with age. In addition, the study discovered greater overall prevalence estimates for individuals with atopic dermatitis treated for acne (all acne preparations) compared to the general population. These findings are consistent with our findings. Among populations with and without atopic dermatitis in children and adolescents younger than 18 years old, we could not detect any statistically significant variations in the one-year-prevalence of isotretinoin therapy. Between the ages of 18 and 22 years old, there was hardly any change in the prevalence of isotretinoin use among patients who suffered from atopic dermatitis. On the other hand, there was a large drop in the number of individuals in the population who were treated with isotretinoin for severe acne who did not have atopic dermatitis. Isotretinoin was prescribed to a considerably higher proportion (42%) of individuals who had atopic dermatitis at the age of 22 for the treatment of severe acne compared to patients who did not have atopic dermatitis. Since atopic dermatitis is associated with very dry skin and acne is associated with very oily skin, one might assume that the risk for acne is lower when a patient has atopic dermatitis. Instead, our findings imply that severe acne is a comorbidity in adults with atopic dermatitis after the age of 17, which runs counter to the previously stated assumptions.

The skin microbiota, skin barrier abnormalities, and immune system dysregulation are just a few of the many elements involved in the pathogenesis of atopic dermatitis, which predisposes affected individuals to cutaneous and extracutaneous infections [202, 322]. High levels of sebum favor the growth of Cutibacterium acne, a bacterial species associated with the inflammatory aspects of acne [206]. Patients with atopic dermatitis appear to have

decreased sebum-lipid metabolism [197, 323-325]. However, Cutibacterium acne is also a sentinel of the healthy microbiome of human skin [326]. Alterations in the microbiome are associated with dysbiosis and diseases, including atopic dermatitis, psoriasis, rosacea, and acne [327]. It is conceivable that individuals experiencing atopic dermatitis may employ comedogenic moisturizers or ointments to alleviate dry skin, which could potentially result in the emergence of acne. However, it is important to acknowledge that this is not the sole cause for the increased incidence of acne in individuals with atopic dermatitis beyond the age of 17. On the contrary, dryness or skin irritation may lead to disruption of the stratum corneum barrier, resulting in increased transepidermal water loss (TEWL) and the development of inflammation [328]. In addition, there is evidence that moisturizers can independently contribute to improving the signs and symptoms of acne [329].

According to our results, boys with atopic dermatitis had an increased risk of skin infections at a young age *(Paper II).* However, girls were more likely to take acne medications from the age of 15 years (all preparations included - Supplementary Figure SI) *(Paper III).* It could be that girls at this age are more concerned about their skin than boys. However, after age 18, there was also a significant difference in one-year prevalence between females and males treated for severe acne with isotretinoin, which continued to increase with increasing age. Although some studies suggest that acne severity does not differ significantly by sex [330], researchers have documented that the female sex (adult) poses a persistence risk for acne [74]. Adult acne more often affects females, unlike juvenile acne, where males predominate [331]. A review article (2020, Nature) showed mixed results regarding acne risk according to sex. Lower sebum levels than in males [206] and cosmetic acne might contribute to a higher prevalence of acne in adult females, independent of the diagnosis of atopic dermatitis [332, 333]. The role of exogenous progestin in the development of acne is unclear [334, 335], and of interest because of the widespread use of contraceptives. Increased sebum production has been associated with higher progesterone levels in females. Sebum production in females during the menstrual cycle and premenstrual episodes has been attributed partly to progesterone, although this remains to be proven experimentally [336].

Tolerability of isotretinoin in patients with atopic dermatitis

Isotretinoin is known to have several adverse effects. Some of the most common adverse mucocutaneus effects of isotretinoin are dry lips, xerosis (dry skin,) and pruritus (itching) [337, 338]. Xerosis and pruritus occur generally more often in patients with atopic dermatitis than those without. Isotretinoin can provoke retinoid dermatitis, an adverse effect that varies in severity according to the dosage. It is essential for people with atopic dermatitis to keep their skin well moisturized in order to avoid developing retinoid dermatitis and flare-ups of their condition. Isotretinoin medication was discontinued by a total of 17.4% of patients diagnosed with atopic dermatitis, according to the findings of our research on the tolerability of acne treatment *(Paper III)*. There were no statistically significant differences in the percentage of atopic dermatitis patients who discontinued isotretinoin treatment based on the length of time they had been taking topical treatment for atopic dermatitis. We concluded that individuals with atopic dermatitis who had a history of receiving topical treatment for atopic dermatitis for almost ten years or longer could tolerate isotretinoin just as well as patients with a shorter history ranging from one to four years. Unfortunately, there were limitations in the data set, so we were not able to study discontinuation of drug treatment with isotretinoin in individuals without atopic dermatitis *(Paper III)*. However, according to the findings of a study that was conducted in Saudi Arabia in the year 2020, around 17% of acne sufferers stopped taking isotretinoin because of its side effects [339]. These findings align with what was discovered in *Paper III*, and they may also suggest that individuals with atopic dermatitis tolerate isotretinoin and patients who do not have atopic dermatitis.

We found that the discontinuation rate was the same as in the Belgian study *(Paper II)* [340]. There is complete overlap between the research periods, and the treatment criteria (guidelines) are the same in both countries. It's possible that some patients with atopic dermatitis who participated in our study were given a "lower dose" of isotretinoin treatment for a longer period to minimize the number of adverse effects they experienced. This could be one factor contributing to the low rate of patients who stopped taking the medication. The timing of isotretinoin discontinuation was estimated based on days added to the date of the last isotretinoin treatment, according to the package size and DDDs. If patients were taking a lower dosage than 30 mg, the duration of isotretinoin treatment might have been estimated to be shorter than the actual time used to consume the last pack(s) dispensed.

Various measures and definitions regarding therapy persistence have been suggested in the literature, reflecting the lack of a clear consensus [281, 282]. Patients with atopic dermatitis were classified according to the duration of dispensed treatment with topical corticosteroids and topical calcineurin inhibitors to estimate the severity of the disease (in *Papers II and III*). Patients with severe atopic dermatitis tend to experience numerous disease flare-ups and are more likely to rely on topical corticosteroids and calcineurin inhibitors to relieve their symptoms. Therefore, patients with atopic dermatitis who have received frequent topical treatments for atopic dermatitis are likely to be more burdened by the disease.

It is known that moisturizers can alleviate retinoid-induced skin irritation as an adjunctive treatment [341]. While it is only speculation, patients with long-standing (and most likely more severe disease) treated for atopic dermatitis (probably have a more severe disease) may apply creams or moisturizers more frequently, perhaps as a daily routine. Regular use of moisturizers could prevent irritation and flare-ups of atopic dermatitis and thus also improve the tolerability of isotretinoin. Another Danish researcher hypothesizes that the skin of patients with atopic dermatitis who experience frequent flare-ups is less susceptible to exacerbations due to trigger factors because it has little time to recover [60, 157]. This could also possibly explain why individuals with a long-term history of atopic dermatitis (who likely had a more severe condition) tolerated isotretinoin equally to those with a shorter duration of treatment. An additional intriguing hypothesis proposes that the anti-inflammatory impact of isotretinoin may also have some influence, albeit to a lesser degree, on the inflammation caused by atopic dermatitis.

Chronic hand eczema can be treated with alitretinoin, a vitamin A-associated retinoid (9-cis-retinoic acid). Alitretinoin acts by binding to two types of receptors in cells (intracellular retinoic acid receptors), RAR and RXR [342]. In comparison, isotretinoin binds only to the RAR receptors. For effective treatment of chronic hand eczema, both receptor types must be addressed. Nevertheless, research suggests that isotretinoin may have anti-inflammatory and immunomodulatory properties that could influence its tolerability in individuals with atopic dermatitis [343].

In the group of patients treated with isotretinoin *(Paper III),* there was a substantial rise in dispensed prescriptions of moderate-potency and potent topical corticosteroids throughout the

first seven months. The majority of the medications dispensed were potent topical steroids More than half of patients with atopic dermatitis who received isotretinoin were treated with topical corticosteroids/ calcineurin inhibitors. Nearly 50% of patients with a short-term treatment course for atopic dermatitis received topical corticosteroids or calcineurin inhibitors while treated with isotretinoin. Contrarily, over 90% of patients with a long-term treatment course for atopic dermatitis received corticosteroids or calcineurin inhibitors during isotretinoin treatment. According to the findings, the tolerability of the medication isotretinoin was the same in patients receiving long-term or short-term therapy for atopic dermatitis. Yet, the findings also indicate that individuals treated for atopic dermatitis for a longer period (long-term treatment course) most likely had a higher need for topical corticosteroids during their treatment with isotretinoin.

Flowchart presenting predictors of risk for atopic dermatitis based on the findings in this thesis.

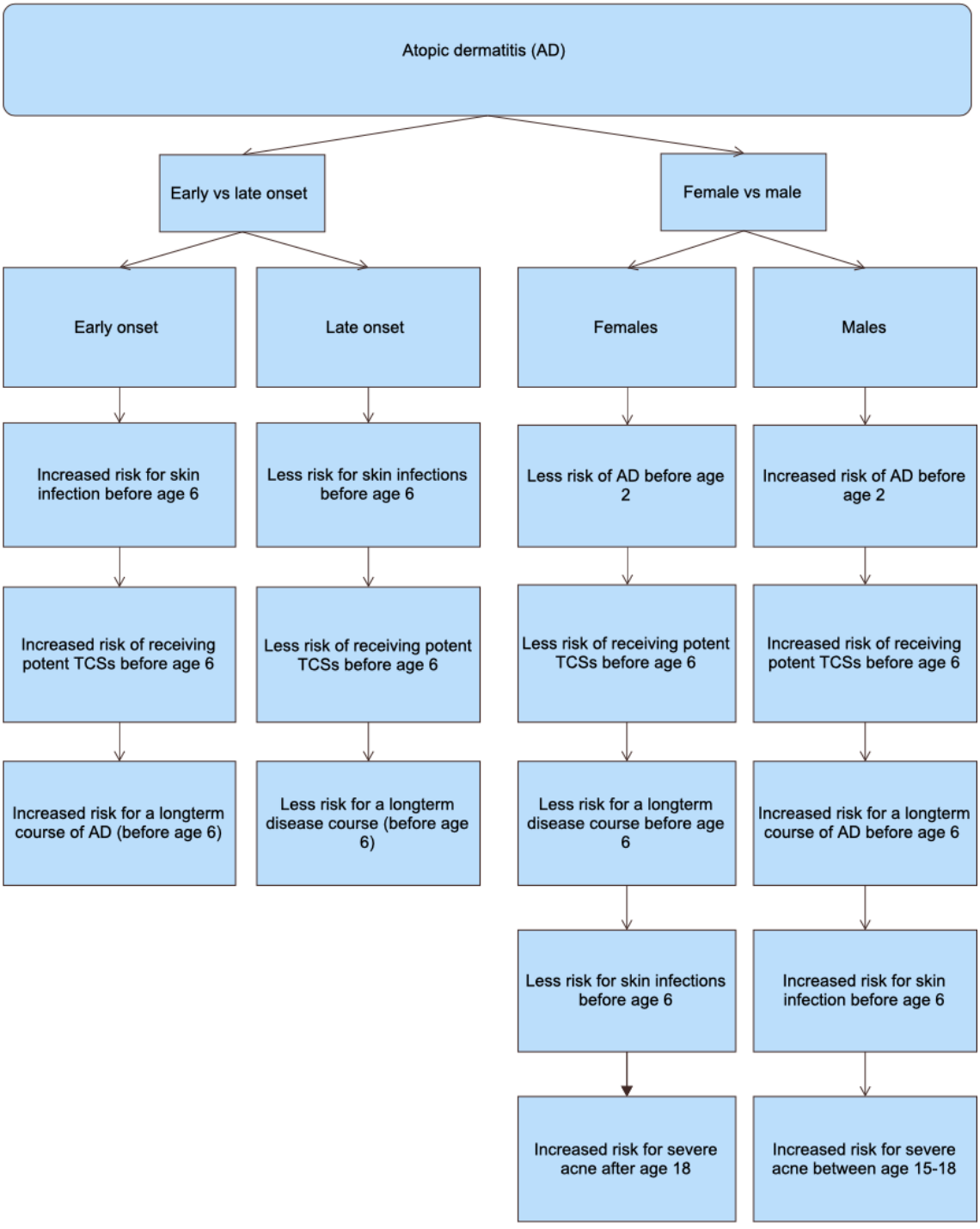

Figure 16 A complete overview of the increased risk in relation to sex or early or late onset of atopic dermatitis presented in *Paper II and III* in this thesis.

Dispensed prescriptions used as a proxy measure, and the validity of the algorithm

Proxies can be used for replication studies, long-term follow-up of health interventions, or to answer relevant research questions. In the three papers in this thesis, we used medical diagnoses and disease-specific medications to identify individuals with atopic dermatitis through an algorithm. In *Paper I*, we used the algorithm (the algorithm was described in an earlier chapter in this thesis) to determine the incidence rate (IR) of atopic dermatitis by age and sex (and seasonality) in the entire Norwegian pediatric population. In the second Paper *(Paper II)*, the algorithm was used to provide *"up-to-date, population-based prevalence estimates and predictors of risk and disease burden and a comprehensive overview of treatment patterns and course for paediatric patients with atopic dermatitis*". In the final Paper *(Paper III),* the algorithm provided up-to-date population-based prevalence estimates of atopic dermatitis in the Norwegian population up to 23 years of age.

Using prescription data for atopic dermatitis medications as a proxy for atopic dermatitis is a common research practice and can serve multiple purposes. Potential advantages of this method include accessibility, large sample size (generalizable and robust results), cost-effectiveness, and the ability to follow patients over time. However, it is essential to remember that significant limitations are associated with using prescription data as a proxy for disease such as atopic dermatitis.

The use of prescription databases covering an entire population to identify children with atopic diseases is a powerful epidemiologic research tool [104, 344-348]. Data on prescriptions filled by pharmacists have been gathered for many years in the Nordic nations, and this information is easily accessible to researchers. Notwithstanding the many benefits they offer administrative databases that can be utilized to carry out substantial research, although they were not developed for the purpose of research [106]. Longitudinal electronic prescription databases may lack essential details on health status and risk factors for treatment outcomes, which may introduce bias if not adjusted for [280]. The patient health status characteristics we want to consider may not always be directly observable, but they may be better observed through a set of algorithms. Topical steroids are often prescribed for children

with relatively common skin conditions (e.g., dermatitis, seborrheic dermatitis, contact dermatitis, and atopic dermatitis), raising concerns about using medications for atopic dermatitis as a proxy [347]. Due to the fact that topical steroids are also used to treat skin illnesses other than atopic dermatitis, the treatment with topical corticosteroids is not regarded as disease-specific. Thus, it has a low likelihood of reaching a high level of specificity. However, drug sensitivity (use of topical corticosteroids in those with the disease) is considered relatively high. To exclude other skin diseases, we used an algorithm that excludes diseases that require the same treatment as atopic dermatitis. In each of the three papers we published, the algorithms were used as a proxy adjustment to conduct a methodical search of the recorded codes for diagnoses and disease-specific prescriptions to locate individuals affected with atopic dermatitis. [280, 349]. In contrast to topical corticosteroids, the specificity of topical calcineurin inhibitors is considered relatively high. However, according to the results, sensitivity is considered low because topical calcineurin inhibitors are not much used in patients with atopic dermatitis *(Paper II).*

The mildest topical corticosteroids (group I) can be purchased without a prescription (over the counter in Scandinavian countries, which may further reduce the algorithm's sensitivity. Yet, purchasing drugs over the counter is a significantly more expensive option, with the annual cost for individuals with moderate disease activity ranging from €673 (euro) to €818 in 2014 [18]. Factors such as a well-developed, government-funded healthcare system, a high number of practicing physicians per capita, and the fact that Norwegian children with chronic diseases (including atopic dermatitis) are eligible for prescription drug reimbursement ensure that this study is highly likely to include children with atopic dermatitis from all socioeconomic strata and that the children can receive necessary medical treatments and medications free of charge. When compared to the cost of reimbursable medicines, the cost of medicines that may be purchased over the counter is significantly higher. However, it is possible that patients with very mild forms of the disease, who require only minor or occasional treatment, purchase the treatment as over-the-counter medications. As a result, there is a possibility that some patients who have a fairly mild version of the disease will not be included in the database. In addition, it is possible that people who have mild cases of atopic dermatitis will not be prescribed any drugs to treat their condition for reasons that have nothing to do with the disease itself (e.g., corticophobia).

Several studies use primary care data with proxies to identify patients with atopic dermatitis [104, 248, 350-355]. While more studies are using ICD-10 codes as proxies to measure atopic dermatitis in the population [114, 356-358], fewer studies base their studies on ICD-10 and ICPC-2 as well as disease-specific dispensed prescriptions. The survey from Henriksen et al. introduced an algorithm to define children with atopic dermatitis [114]. According to the study's findings, incidence rates of atopic dermatitis were relatively constant throughout the study periods in both Sweden and Denmark (1997-2011). The refined and updated algorithm formed the basis for dispensing medications as a proxy for atopic dermatitis and the diagnosis used *(Paper I – III)*. The algorithm used in the surveys in this thesis's studies is based on ICD-10 and ICPC-2, not just ICD-10, as in the study by Henriksen et al. The ICPC-2 is a coding system accepted by WHO [359] and is now used worldwide. Family physicians/general practitioners play a key role in the health care system in Norway. The general practitioner treats about 97% of patients with atopic dermatitis in the UK [86]. Although the UK is known for having few dermatologists, the number of patients in Norway treated by their general physician is probably also high. Most secondary care treatments are based on referrals from primary care physicians. In many healthcare systems, primary care is the main point of contact for patients, which means that diagnoses received in primary care may be more similar to the open population (as a less regulated group) than in the hospital setting. In addition, dermatologists are mainly found in larger cities and are not always accessible to individuals in rural areas in Norway. Accordingly, database researchers should consider including primary care diagnoses in epidemiologic studies to increase the sensitivity of the proxies.

Several studies have validated data on prescriptions dispensed for atopic dermatitis treatments as a proxy for atopic dermatitis, considering the sensitivity, specificity, and predictive value [106, 344-347, 360, 361]. According to the findings of a validation research, receiving two or more prescriptions for topical corticosteroids each year yielded a sensitivity value of approximately forty percent and a positive predictive value of approximately sixty percent [346]. The non-atopic dermatitis criteria, also known as the prescription exclusive criteria and the non-AD criterion, were applied in our research in order to boost the positive predictive value further.

As mentioned earlier, the algorithm used in our studies is inspired by the algorithm from the research of Henriksen et al. [114]. The algorithm was validated in a Danish study by telephone interviews with caregivers of pediatric patients (identified by the algorithm) [360]. Despite the high risk of recall error (studies have shown that validation by questionnaires performs poorly), the study was validated by telephone interviews. The validation study found that the sensitivity and specificity of the algorithm was 74.1% and 73%, respectively. [106]. Compared with the proposed values, the algorithm in our studies should cover a higher proportion of children with atopic dermatitis because Henriksen et al. did not include ICPC-2 in the algorithm, resulting in a higher sensitivity value in our work.

The use of the algorithm based on criterion 2 (based on disease-specific prescriptions) identified a small percentage of our patients with atopic dermatitis, ranging from 9.3% to 11.7% in our studies *(Paper I - III).* The remainder of individuals with atopic dermatitis in our studies were based on diagnoses made by a physician. A 2017 study found that "*the positive predictive value (PPV) for a physician-confirmed diagnosis"* of atopic dermatitis was 86% (95%CI, 80-91) and was higher in children (90%) than in adults (82%) [362].

The mainstay treatment for atopic dermatitis is topical corticosteroids [363]. Since 2016, a carbamide-containing moisturizer has been available on reimbursement prescription for patients diagnosed with moderate to severe atopic dermatitis. The algorithm did not include the treatment due to the study's time frame. The treatment of atopic dermatitis is described in an earlier chapter of this thesis.

Despite the importance of proxies in pharmacoepidemiologic research, we have taken into consideration that we have incomplete data on possible confounders (i.e., markers of smoking status, body mass index, clinical disease severity, functional status, and use of over-the-counter medications) [349]. As mentioned earlier, all Norwegian children (up to age 16) receive free medical care and medications, which might possibly increase the algorithm's sensitivity. Because there are no socioeconomic differences in children's use of medical care in Norway, we consider this another strength of our study. However, compared to the general population, it is difficult for us to know whether all children and adults with atopic dermatitis are represented for the entirety of the study period, and epidemiologic postulates concerning risk cannot be determined by this analysis alone. The concept of validity is a difficult topic,

especially since there are no specific tests that can provide answers. Consequently, the validity of identifying children with atopic dermatitis through adjusted proxies is questioned, and other algorithms need to be developed that consider sensitivity, specificity, and predictive value [344].

Missing identification number from the NorPD

Although all prescriptions dispensed by Norwegian pharmacies to Norwegian residents are recorded in NorPD, the registry contains a small proportion of prescriptions with missing registered identification numbers. The prescriptions with missing identification numbers cannot be followed over time. In 2004 (the first year of NorPD), the percentage of invalid or missing prescriptions with 11-digit birth numbers was 3.7% [266]. In 2005-2007, this percentage was about 2.0% in 2008, and in 2009 it was close to 1.4%, and in 2010-2016, the percentage of missing identification numbers was less than 1.0% (0.3% in 2016) [266]. Prescriptions with missing identification numbers were 4.5% in *Paper I* and 0.9%-1.0% in *Papers II and III*. The missing identification numbers were excluded because they led to overestimations of the occurrence of atopic dermatitis (because of increasing number of patients). Birth announcements with birth numbers sent in paper form could take up to 21 days in 2016, according to The Norwegian Tax Administration [270]. Thus, the proportion of very young children who received medications by prescription could not all be tracked and may have been underestimated because a higher proportion of very young children did not receive the correct 11-digit birth number in the prescription register [364]. Sensitivity analyses were performed to determine the robustness of the research by examining the extent to which missing data affected the results, for all ages, by sex, and by years. The estimated number of individuals with atopic dermatitis and the estimated increase in atopic dermatitis should be considered minimum values, especially in *Paper I* (most of the missing identification numbers appeared in *Paper I*). However, because atopic dermatitis is defined as a chronic condition, the likelihood that an affected child will later seek medical treatment is considered a realistic expectation. The missing identification numbers may have resulted in the individual being classified (according to the algorithm) as having atopic dermatitis at a later age.

Methodological considerations

Pharmacoepidemiology is the study of drug use and outcomes and applies the principles of epidemiologic research in the same manner as any other noninterventional study [280]. Many pharmacoepidemiologic studies are conducted using longitudinal public health databases. They take advantage of large study populations with an extended follow-up period but forgo the controlled and detailed data collection characteristic of primary data collection [280]. In contrast to clinical trials, pharmacoepidemiology takes the reality of clinical practice as a starting point to describe and explain drug use [365]. Pharmacoepidemiology is concerned with the interactions between human populations and drugs and examines the risks, benefits, and use of drugs under real-world conditions [365].

We have taken a pharmacoepidemiologic approach to study atopic dermatitis for several reasons. National registry-based research offers the potential for large sample sizes studies covering representative populations (and thus generalizability and robustness) and long-term close follow-up. Using real-world data provides the opportunity to conduct large-scale epidemiologic studies in a real-world clinical setting [106]. Additionally, they do not rely on patient consent to participate or have recall bias and include a comprehensive database of prescriptions dispensed with considerable detail. In addition, the large number of individuals who remained in the research during the follow-up period made it possible to conduct subgroup analysis and stratification without compromising the overall power of the study. Finally, standardized clinical trials in large-scale research involving patients with and without atopic dermatitis are not feasible for various reasons, including ethical, financial, and practical considerations. The timing of clinical trials is crucial in the process of evaluating whether or not a person has symptoms (skin lesions) of atopic dermatitis. Many individuals with atopic dermatitis go through periods without visible skin lesions or troublesome symptoms. Therefore, a prevalence done at a specific time underestimates the prevalence of the disease, and observation over a more extended period should be preferred. Because of the heterogeneity of the disease (determined by remission and relapse of clinical symptoms) occurring in the same individual over time, more extended periods of observation should be reflected in the prevalence identified.

It is difficult to find appropriate measures that may be used to determine the prevalence and incidence of atopic dermatitis in a population. The majority of epidemiologic studies that

have been conducted to investigate the incidence of atopic dermatitis have used health surveillance questionnaires. In extensive studies, clinical examination of children with and without atopic dermatitis is neither financially nor practically feasible. In recent years, databases of health data have become increasingly available for scientific research. Registry-based research in children is a valuable research tool with high data quality for conducting longitudinal studies and investigating pharmacoepidemiology in a real-world, pragmatic study setting. Individuals generally benefit from registry-based research because it increases knowledge about the disease and associated risk factors. However, the validity of the proxy used in this work should be further investigated.

Specific methodological issues associated with measuring atopic dermatitis and using dispensed prescription as a proxy for atopic dermatitis have been discussed in the chapter: *Dispensed prescriptions used as a proxy measure and the validity of the algorithm.*

Random error

Random errors ("chance variation") are assumed to display no consistent direction or structure beyond that described by probability distributions [280]. Increasing the sample size of the study can improve the precision of the estimate (reducing variance) [280]. Thus, the larger the sample size of the study, the higher the precision. As indicated by the width of the confidence interval, a high degree of accuracy denotes a low probability that the observed results are attributable to chance. For studies with large databases such as NorPD (relatively large study population), precision is high. Confidence intervals are narrow for most analyses in *Paper I - III,* suggesting good precision. However, results should be interpreted cautiously for some subgroups with small sample sizes in *Papers II and III.*

Systematic error

Unlike random errors, systematic errors have a consistent direction and structure and are not dependent on study size or chance [280]. Systematic errors are a perennial issue in the field of

research and can present a more significant challenge than random errors when it comes to epidemiology investigations. Systematic errors can arise at all phases of the research process, reducing the estimate's validity. Validity can be divided into internal validity (source populations) and external validity (individuals outside the population). Nevertheless, there is a possibility of making systematic errors, which are challenging to evaluate and take into account when interpreting the results and the magnitude of their impact. Systematic errors can contribute to both an underestimating and an overestimating of associations. We attempted to limit the introduction of various biases during the research process in *Paper I- III.*

Selection bias

When the estimate of occurrence or etiologic effect acquired from a study population diverges systematically from the estimate that would have been received if the information were available from the source population, it is an example of selection bias [280]. Suppose specific individuals are chosen for the study or are eliminated from the study population before the data are analyzed. In that case, the population studied is a nonrepresentative sample of the source population. Although the direction of the bias can be revealed, it is difficult to define the extent of the selection bias and how it would influence the generalizability of the results.

Individuals studied *(Paper I)* were under six and eleven years of age *(Paper II)*, with subgroup analysis for children up to six years of age *(Paper I-II)*. *In Paper III,* individuals were under 23 years of age. The effect of selective survival of healthier individuals in the analysis *(Papers I- III)* was considered negligible. The relatively small number of people who could not be followed up is mainly due to the emigration in the *Papers I- III.*

The data in the three papers are based on dispensed rather than prescribed medications. This excludes primary nonadherence, which is a problem when using prescription data. The age group studied was under six years old in *Paper I,* under eleven years old in *Paper II*, and under 23 years old in *Paper III.* The effect of selective survival of healthier individuals concerning disease-specific medications or diagnosis of atopic dermatitis was considered insignificant.

Although dispensed medication for use in the hospitals is not included in the individual-level database, all Norwegian residents who received medications dispensed by Norwegian pharmacies are included, reducing the risk of selection bias (without self-selection). Only a tiny proportion of individuals in this age group are permanently hospitalized, so NorPD should capture most drug users in this age group. In 2009, 94% of the drugs measured in defined daily doses (DDDs) in Norway were supplied to private individuals [364]. Supplies to hospitals and nursing homes accounted for 5.4% of the total number of DDDs and approximately 0.5% of the total number of DDDs were issued for use in the prescriber's practice [364]. An American study found that hospitalization rates for atopic dermatitis decreased significantly from 1997 to 2017 in children with atopic dermatitis (from 9.3% to 5.2%) and in children without atopic dermatitis (from 8.3% to 5.2%) [366]. It is not currently known what the hospital rates are for Norwegian children with atopic dermatitis. However, most likely, they are low and do not significantly impact the results. The estimated loss of data on medications used in hospitals for atopic dermatitis in patients younger than 23 years is estimated to be low.

Longitudinal studies are prone to selection bias due to loss-to-follow-up, leading to biased estimates of occurrence and association between exposure and outcome. Most likely, relatively few individuals could not be followed up. The primary cause of loss to follow-up was most likely emigration or death. Mortality in these age groups is estimated to be low. In the analyzes performed, a sensitivity analysis was performed by age and sex.

Net immigration to Norway was consistently high during the study period [263]. Prescribed treatment for atopic dermatitis decreases with age. Patients with atopic dermatitis treated with isotretinoin may have artificially low prevalence estimates because immigrants with unknown medical records and, thus, previous records of a possible diagnosis of atopic dermatitis or dispensed disease-specific medications will not be included in the study *(paper III)*. This could also lead to an underestimation of the number of patients with atopic dermatitis and severe acne in *Paper III.*

Other medications, such as moderate, potent, and very potent topical steroids, as well as tacrolimus and pimecrolimus, are fully covered. In addition, prescription antibiotics for topical use, antihistamines, antiseptics, and disinfectants including hydrogen peroxide,

calcineurin inhibitors including ciclosporin, dibrompropamidine, dupilumab, folic acid analogues including methotrexate, interferons including interferon gamma, other immunosuppressants including azathioprine, selective immunosuppressants including mycophenolic, systemic antihistamines, treatment for antibiotics for topical use, appear to be complete. However, potassium permanganate is an over-the-counter product, and data coverage is incomplete, leading to a possible underestimation of skin infections in patients with atopic dermatitis in *Paper II.*

The validity of the algorithm and how over-the-counter purchase of weak topical corticosteroids may have influenced the results in *Paper I - III* were discussed in the Chapter; *Dispensed prescriptions used as a proxy measure and the validity of the algorithm.*

Information bias

Errors accurateness of the data/knowledge obtained for variables can lead to information bias (or misclassification if discrete variables are used) [280]. Nondifferential misclassification occurs when there is no difference between the groups in the study in terms of the probability of misclassification. Differential misclassification occurs when the likelihood of misclassification differs between groups in a study [367]. The effects of nondifferential information bias are random between variables and dilute the true association (bias toward the null). Differential information bias, however, can either underestimate or exaggerate the association. Recall bias is avoided when the data are obtained from prescription databases such as NorPD [278].

Misclassification of diagnoses made by the physician cannot be ruled out. The individuals who are misdiagnosed cause a false association to be observed. Whether the misclassifications are the same in all age groups and both sexes cannot be determined. The use of ICD-10 and ICPC-2 diagnoses as a proxy for atopic dermatitis is discussed further in the chapter: *Dispensed prescriptions used as a proxy measure and the validity of the algorithm.*

As the disease severity increases, the risk of detection bias decreases. In most cases, dermatologists prescribe isotretinoin, while general practitioners prescribe the treatment of atopic dermatitis in Norway. However, detection bias [280] may contribute to the increased occurrence of severe acne observed in patients with atopic dermatitis treated with isotretinoin in *Paper III*. Patients with atopic dermatitis seek medical attention more frequently than healthy individuals. As a result, additional health problems become known to the physician. However, this bias may also work in the other direction; mild, undiagnosed atopic dermatitis may be more easily detected in individuals who see a physician for different reasons.

All articles *(Papers I - III)* in this thesis are based on the use of dispensed medicines registered in the NorPD, which rules out primary non-compliance. Throughout *Papers, I - II,* the terms "redeeming," "receiving," or "dispensed" is used interchangeably with the term "drug use" and essentially mean that the prescription has been dispensed at the pharmacy. When attempting to understand the meaning of the term "drug use," it is essential to consider the possibility that drugs obtained are not utilized. The timing of the used drug is most likely also over a more extended period of time and not on the dispensing date. Topical preparations in tubes have a recommended expiration date of three months after opening, and liquids and lotions have an expiration date of six months after opening (unless otherwise stated by the manufacturer). However, the correlation between prescriptions dispensed and actual drug usage is unknown, and any estimate made in this regard ought to be taken as the maximum possible value. On the other hand, it seems less likely that patients would not take their medication if provided with the same or equivalent medicines more than once. Criterion 2 of the algorithm states that at least two prescriptions for topical corticosteroids (at least 14 days apart) must be considered. In addition to this, atopic dermatitis is a long-term condition that frequently runs in families. Although it is not recommended, it does happen that prescribed medications are passed down in the family (familial sharing). This is another vital aspect to consider when analyzing the occurrence of atopic dermatitis based on the prescriptions dispensed. In addition, the timing of when patients fill their prescriptions may impact whether or not they are registered that year. Suppose they fill their prescription just before their birthday. In that case, they will be registered as having atopic dermatitis in the age group in which they fill the prescription, even if they mostly use the medication the following year (age). This could affect the estimates of the debut and frequency of atopic dermatitis in the three studies *(Paper I - III).*

Confounding

K. Rothman writes "*Confounders are factors that explain or produce all or part of the difference between the measure of association and the measure of effect that would be obtained with a counterfactual ideal*" [280].

In the realm of health sciences and epidemiological research, the concept of confounding variables was initially developed to address variables that have the potential to significantly impact study outcomes [368]. Confounding can bias the association away from and toward the null and can be accounted for or corrected for in the analysis. The epidemiological literature on Directed Acyclic Graphs (DAGs) has emerged. In a DAG, causal relationships are represented by arrows pointing, hence, linking cause and effect [369].

In all *Papers (Papers I - III)* included in this thesis, we performed stratification by sex, subgroups, and age. Stratification by year was conducted in *Papers I and II.*

The influence of unmeasured and unidentified confounding factors cannot be excluded (residual confounding).

Generalizability

Generalizability and transferability refer to whether a study's estimate of occurrence or etiologic effect applies to the target population (external validity) [370]. If a study has poor internal validity, its results are not generalizable or transferable to the target population [370].

Nationwide, register-based research is readily available. The possibility of 100% long-term follow-up is unique (as in some other Nordic countries) because data collection has been conducted in Norway for almost a decade. This thesis (*Papers I – III)* have a population-based study design with a large sample size, high precision, and decreased risk of selection bias. The associations are expected to generalize to other high-income countries in temperate climates.

6 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Atopic dermatitis currently has no known cure. To manage the disease, preventing and alleviating its symptoms is the only approach. Caregivers of children affected by this condition often seek assistance from general practitioners and medical staff at health centers. Diagnosis of atopic dermatitis is primarily based on clinical examination, and primary care physicians are responsible for providing treatment to the majority of affected patients. It is important to note that only a minority of children are referred to the second line (the specialized health service) or National Eczema Schools.

Our research suggests that atopic dermatitis represents a substantial and potentially escalating burden during early childhood, as evidenced by the many prescriptions dispensed. However, whether individuals afflicted with this chronic condition and their caregivers are receiving adequate and appropriate care, support, and educational resources remains uncertain. Atopic dermatitis is a recurrent skin disease often notoriously difficult to manage and necessitates long-term treatment. The factors contributing to the different phenotypes, the generally low adherence rate to topical corticosteroids, comorbidities, and the chronic relapsing nature of the disease result in complicated disease courses and outcomes. Given the chronicity of atopic dermatitis, it is imperative to provide patients and their caregivers with the necessary resources and support to manage the disease and effectively enhance their quality of life. Thus, further research is warranted. More resources should be allocated to research, particularly on what treatments are offered, the extent to which and how patients and caregivers are educated about the disease, and what treatment options are available.

This thesis's results show a high risk of being treated for atopic dermatitis before the age of six, suggesting that atopic dermatitis in children is an increasing public health problem in Norway. The studies also highlight the need for more research to understand how to allocate more resources to optimize the treatment of pediatric patients with atopic dermatitis. There is still limited scientific evidence to explain patients' behavior and clinical features [371]. In addition, the disease course of atopic dermatitis has not been fully elucidated [12, 130, 131].

Despite the extensive studies on atopic dermatitis, little is known about the factors associated with disease persistence and severity [3, 119, 136, 253].

To provide a tailored prognosis and arrange appropriate medical care, it is essential to have knowledge of the disease's predictive factors and comorbidities. Moreover, in determining the appropriate potency of medications for young children, especially those under two years of age, it is important to consider the age of the child, the severity of the condition, and the site of application [305]. More specific guidelines tailored to the child's age would be better to ensure safe and effective treatment. When selecting a treatment plan for atopic dermatitis, it is essential to consider each patient's needs and circumstances. Following these steps can ensure the best possible treatment for our youngest patients.

Because of the widespread prevalence and chronicity of atopic dermatitis (atopic dermatitis) and acne, dermatologists routinely prescribe isotretinoin to patients with atopic dermatitis (or a history thereof). To our knowledge, there are no nationwide studies on the prevalence of severe acne and few data on the tolerability of isotretinoin treatments in patients with atopic dermatitis. Through our research, we have uncovered an unexpected correlation between the occurrence of acne and atopic dermatitis among young adults. This contradicts previous understandings of these skin conditions and emphasizes the complexity of such disorders. Further research is warranted to better comprehend this coexistence and improve our knowledge of these dermatological issues. It is imperative to take into account the compromised skin barrier in individuals with atopic dermatitis when managing coexisting acne. This poses a challenge in achieving optimal treatment outcomes, thus necessitating thorough investigation on how best to address this condition in affected patients. By doing so, healthcare providers can advance the quality of care and improve the prognosis for those experiencing the dual burden of atopic dermatitis and acne. We need more information on the frequency and severity of acne in this specific patient population. Further studies are required to determine whether the coexistence of atopic dermatitis and acne impacts quality of life more than either condition alone [209].

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Papers I - III

I

JAMA Network Open

Original Investigation | Dermatology

Incidence Trends of Atopic Dermatitis in Infancy and Early Childhood in a Nationwide Prescription Registry Study in Norway

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Abstract

IMPORTANCE With increasing prevalence of atopic dermatitis (AD) and its manifestation in most countries, together with the supporting evidence of the progression to other atopic phenotypes, AD has developed into a worldwide public health concern. The presence of the disease of has increased since the 1950s, but some recent studies suggest a stationary or decreasing trend.

OBJECTIVE To analyze a nationwide health register based on prescription data to determine the incidence rate (IR) of AD in an entire pediatric population.

DESIGN, SETTING, AND PARTICIPANTS All children resident in Norway younger than 6 years from January 1, 2009, through December 31, 2015, were included in this cohort study. Medical diagnoses and disease-specific medications were used as a proxy for identifying children with AD in this population-based prescription registry study. The prescription study was terminated in 2016. The total number of 295 286 disease-specific prescriptions was analyzed from August 2016 through December 2017. The hypothesis was formulated before, during, and after the data collection.

MAIN OUTCOMES AND MEASURES All children with a medical diagnosis of AD or eczema based on at least 2 prescriptions of topical corticosteroids or at least 1 prescription of topical calcineurin inhibitors. Incidence rates per person-year (PY) and IR ratios were calculated.

RESULTS A total of 295 286 disease-specific prescriptions were dispensed to 122 470 children, of whom 63 460 had AD and 56 009 (88.3%) had reimbursed prescriptions and associated AD diagnoses. The annual Norwegian study population (aged <6 years) increased from 357 451 children in 2009 to 373 954 in 2015. The overall IR increased from 0.028 per PY (95% CI, 0.028-0.029 per PY) in 2009 to 0.034 per PY (95% CI, 0.033-0.035 per PY) in 2014. For children younger than 1 year, the IR increased from 0.052 per PY (95% CI, 0.050-0.053 PY) in 2009 to 0.073 per PY (95% CI, 0.071-0.075 per PY) in 2014. In this age group, the IR was 53% higher in boys compared with girls (IR ratio, 1.53; 95% CI, 1.49-1.57; $P < .001$). The incidence proportion before the age of 6 years was 17.4% (95% CI, 17.2%-17.7%). The primary seasons for the onset of AD were winter and spring.

CONCLUSIONS AND RELEVANCE This nationwide study suggests an increase in the IR of pediatric AD, especially among children younger than 1 year. This study's findings suggest that increase occurred with a higher IR during winter and spring seasons. Atopic dermatitis had an earlier onset in boys than in girls. During the study period, more than 1 in 6 children younger than 6 years had, at some point, been affected by AD.

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Key Points

Question Is the incidence rate of pediatric atopic dermatitis still increasing?

Findings In this cohort study, all children resident in Norway younger than 6 years from January 1, 2009, through December 31, 2015, were included. The overall incidence rate of atopic dermatitis increased from 0.028 per person-year in 2009 to 0.034 per person-year in 2014, and for children younger than 1 year, the incidence rate increased from 0.052 per person-year in 2009 to 0.073 per person-year in 2014.

Meaning This nationwide study suggests an increase in the incidence rate of pediatric atopic dermatitis, especially among children younger than 1 year.

+ Invited Commentary

+ Supplemental content

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Introduction

Atopic dermatitis (AD) is a common chronic, pruritic inflammatory skin condition affecting children and adults around the world. The disease episodically relapses and typically has an early onset, where approximately 80% develop the disease before 5 years of age.[1] An increase in the occurrence of AD has been found in the Nordic countries since the 1950s.[2-7] Although most of these studies have shown a growing trend, recent studies from Sweden and Denmark[3,8,9] suggest that the frequency of small children with AD has stabilized or even decreased.

The pathogenesis of this chronic disease is heterogeneous, complex, and multifactorial.[10-13] Inherited or acquired mutations in epidermal barrier proteins (such as filaggrin) are considered to be major drivers of change in the disease burden. Growing evidence suggests that environmental exposures play a key role in the pathogenesis of AD.[13-15] The substantial variations in reported occurrences of AD between and within countries and between the seasons in temperate climate areas suggest that genetics alone cannot explain these variations.[8,16-19] At present, a full understanding of how the seasons affect the occurrence of the disease is lacking.

Many scoring systems and diagnostic tools for AD diagnosis have been translated, validated, and used in numerous countries. In the absence of a uniform valid criterion standard test, an elevated risk of misclassification of the disease exists. Although several validated AD criteria are known for children and adults, the nomenclature associated with this (perhaps dichotomous[20]) disease is still under debate. The variety of existing clinical scoring systems, cross-sectional studies, and questionnaires (where the self-reporting of data can lead to recall bias) complicates the interpretation of the outcome, also preventing their comparison.[21] Recently, national population-wide health registers containing prescription data have become available for research purposes, thereby providing a powerful epidemiologic research tool for identifying patients through dispensed prescriptions of disease-specific medication.[22-26] The aim of this nationwide, retrospective register study was to examine the trends in the incidence rate (IR) of pediatric AD, using an algorithm for prescription data to determine the onset and seasonality in Norwegian children younger than 6 years.

Methods

Ethical Approval

This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. The research study was approved in November 2015 by the Regional Committees for Medical and Health Research Ethics and the Norwegian Social Science Data Services, and both waived the need for informed consent because patient data were deidentified.

Registers and Coding Classifications

The Norwegian Prescription Database (NorPD) monitors all prescribed medications that are dispensed in Norway, covering 5.2 million inhabitants (as of December 2015).[27] Norwegian pharmacies are obliged to forward dispensed prescription data electronically to the NorPD. All dispensed prescriptions of topical corticosteroids (Anatomical Therapeutic Chemical Classification [ATC] code D07A) and the calcineurin inhibitors tacrolimus (ATC code D11AH01) and pimecrolimus (ATC code D11AH02) for external use were extracted from the NorPD database. The prescriptions were assigned with a pseudonym identification number, age, sex, month and year of birth and death, dispensing date, generic medication name, and ATC codes.[28,29] Only the reimbursed prescriptions had associated codes from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), and *International Classification of Primary Care, Version 2* (*ICPC-2*). The reimbursed prescriptions are primarily prescribed for chronic illnesses and require a minimum of 3 months' use annually.[30] The population statistics were obtained from Statistics Norway.[27]

Study Population

All children resident in Norway aged 0 to 6 years from January 1, 2009, through December 31, 2015, were included. The annual study population (aged <6 years) increased from 357 451 children in 2009 to 373 954 in 2015. Children who were dispensed AD-specific medication (topical corticosteroids or calcineurin inhibitors or both for external use) were investigated to determine whether they had AD. Children who were dispensed AD-specific medication before December 31, 2008, were excluded from this study.

Algorithm for Identifying Children With AD

Children were considered to have AD if they met at least 1 requirement for criterion 1 or 2. Criterion 1, based on a medical diagnosis, included children with recorded reimbursement prescriptions containing associated disease-specific diagnoses of AD or eczema recorded as *ICD-10* code L20 or *ICPC-2* code S87. Criterion 2, based on dispensed disease-specific medication, included children with nonreimbursement prescriptions (not containing an AD diagnosis as in criterion 1). The child was considered to have AD if he or she, within 1 year, had at least 2 prescriptions of topical corticosteroids or at least 1 prescription of topical calcineurin inhibitors.

Children classified by criterion 2 with co-occurring *ICD-10* or *ICPC-2* codes for skin diagnoses (which might lead to identical treatments) or co-occurring skin disease–specific medications (primarily prescribed for other diseases) were not considered to have AD. eMethods in the Supplement provides further explanations of the algorithm used. According to the requirement of more than 2 prescriptions of topical corticosteroids within 1 year (criterion 2), the IR based on dispensed disease-specific medication for 2015 could not be calculated.

Statistical Analysis

The data were analyzed from August 2016 through December 2017 using Stata/MP software (version 14.2; StataCorp LLP). We used the Poisson regression procedure to calculate the IR per person-year (PY) and incidence rate ratios (IRRs) with 95% CIs. Differences between the IRs were tested by χ^2 tests. $P < .05$ (2-sided test) was deemed statistically significant. We calculated the IRs according to sex, age, calendar year, and their interactions. To determine the trends over time, 2009 was set as the reference year. Incidence proportion (cumulative incidence) of AD onset was estimated as the proportion of children in the population who, based on the algorithm, ever had AD using the Kaplan-Meier method.[31]

In a separate analysis, we used the Poisson regression procedure to investigate the seasonal variations in the IRs for AD. The seasons were defined as spring (March-May), summer (June-August), autumn (September-November), and winter (December-February).

Results

Prescription and Patient Selection

A total of 295 286 disease-specific prescriptions were dispensed to 122 470 children. Of these, 63 460 children had AD according to the algorithm. Furthermore, 56 009 of these children (88.3%) had been provided by physician with reimbursed prescriptions and associated AD diagnoses (criterion 1).

Trends in IR of AD and Incidence Proportion

The IR for the children with AD showed that, excluding 2010, a steady increase occurred throughout the study period. The IR increased from 0.028 per PY (95% CI, 0.028-0.029 per PY) in 2009 to 0.034 per PY (95% CI, 0.033-0.035 per PY) in 2014, which represents an increase of 16.8% (IRR, 1.17; 95% CI, 1.14–1.20; $P < .001$) (**Figure 1** and eTable 1 in the Supplement).

The increasing trend displayed in Figure 1 was mainly attributable to children younger than 1 year (**Figure 2** and eTable 2 in the Supplement). The IR in this specific age group increased from

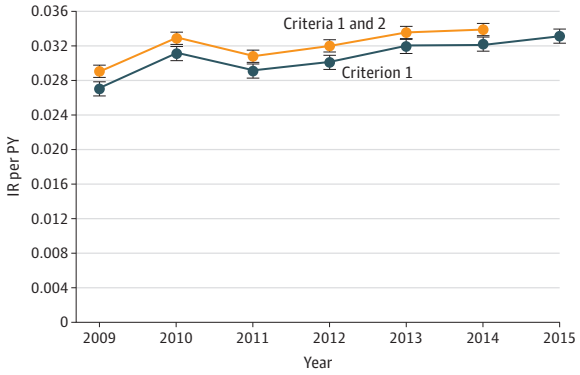
0.052 per PY (95% CI, 0.050-0.053 per PY) in 2009 to 0.073 per PY (95% CI, 0.071-0.075 per PY) in 2014, which corresponds to an increase of 42.0% (IRR, 1.42; 95% CI, 1.32–1.53; *P* < .001).

During the first year of life, the IRs of boys increased from 0.063 per PY (95% CI, 0.061-0.066 per PY) in 2009 to 0.088 per PY (95% CI, 0.085-0.092 per PY) in 2014, representing an increase of 41% (IRR, 1.41; 95% CI, 1.33-1.49; *P* < .001). In comparison, the IRs in girls in the same age group ranged from 0.040 per PY (95% CI, 0.038-0.043 per PY) in 2009 to 0.057 per PY (95% CI, 0.055-0.060 per PY) in 2014, representing an increase of 42% (IRR, 1.42; 95% CI, 1.32-1.53; *P* < .001). The IRs in the remaining age groups (>1 year) were considered to be stable (Figure 2).

We found an interaction between age and sex, with boys having a higher IR compared with girls, especially those younger than 1 year (**Figure 3**). During the first year of life, the IR for boys was 0.076 per PY (95% CI, 0.075-0.077 per PY) compared with 0.050 per PY for girls (95% CI, 0.049-0.051 per PY). In this age group, boys thus had a 53% (IRR, 1.53; 95% CI, 1.49-1.57; *P* < .001) higher IR than girls (**Table**). During the second year of life, the overall IRs for boys and girls were 0.054 per PY (95% CI, 0.053-0.056 per PY) and 0.047 per PY (95% CI, 0.046-0.048 per PY), respectively. In this age group, boys had a 15% (IRR, 1.15; 95% CI, 1.12-1.19; *P* < .001) higher IR compared with girls. After 2 years of age, the IRs of AD were considered as equal for both sexes (Figure 3).

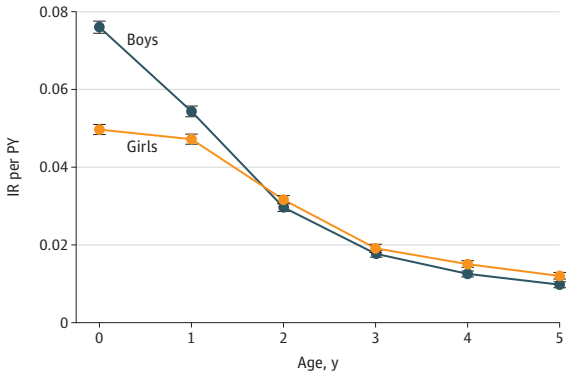
The IRR of boys compared with girls varied between years, ranging from a maximum 19% (IRR, 1.19; 95% CI, 1.14-1.24; *P* < .001) higher IR in boys in 2009 to the minimum 13% (IRR, 1.13; 95% CI, 1.11-1.21; *P* < .001) in 2012 (**Figure 4**). The IR of AD for both sexes was highest during the first year of life, ranging from 0.063 per PY (95% CI, 0.062-0.064 per PY) at younger than 1 year to 0.011 per PY (95% CI, 0.010-0.011 per PY) at younger than 5 years. Overall, during the 6 years of the study period,

Figure 1. Incidence Rate (IR) per Person-Year (PY) of Atopic Dermatitis During the First 6 Years of Life



Data are from the Norwegian Prescription Database from January 1, 2009, through December 31, 2015. Error bars indicate 95% CI. The upper curve displays the IR per PY determined by reimbursed (criterion 1) and nonreimbursed (criterion 2) medications as proxies for atopic dermatitis; the lower curve (year 2009-2015) displays the IR for reimbursed medication only (criterion 1).

Figure 2. Interaction of the Incidence Rate (IR) per Person-Year (PY) of Atopic Dermatitis Between Age and Sex



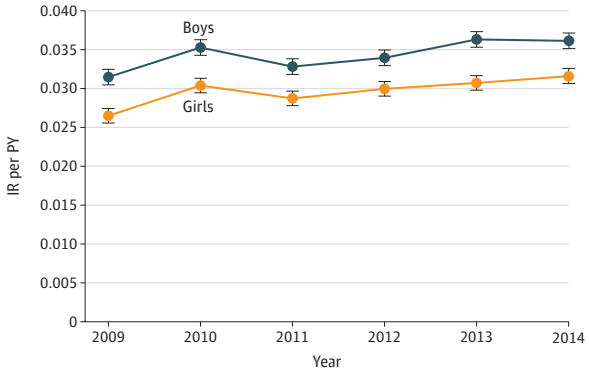
Data are from the Norwegian Prescription Database from January 1, 2009, through December 31, 2015. Error bars indicate 95% CI.

the incidence proportion of AD among those younger than 6 years was 17.4% (95% CI, 17.2%-17.7%) (Table).

Seasonality

The seasonal debut (seasonal IR) of AD peaked during winter and spring. The seasonal IRs for Norwegian children with AD were 0.036 per PY (95% CI, 0.036-0.037 per PY [n = 17 778]) in the winter and 0.038 per PY (95% CI, 0.038-0.039 per PY [n = 18 835]) in the spring. The lowest seasonal IR occurred in the summer at 0.026 per PY (95% CI, 0.025-0.026 per PY [n = 12 475]) and the second lowest in the autumn at 0.030 per PY (95% CI, 0.029-0.030 per PY [n = 14 372]). Thus,

Figure 3. Incidence Rate (IR) per Person-Year (PY) in Children with Atopic Dermatitis According to the Indicated Age Group



Includes boys and girls younger than 6 years. Data are from the Norwegian Prescription Database from January 1, 2009, through December 31, 2014. Error bars indicate 95% CI.

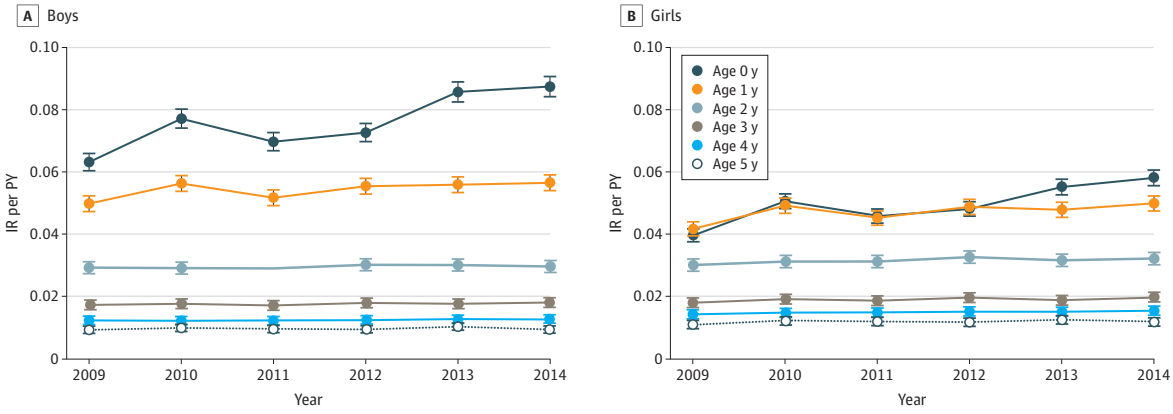
Table. Incidence Proportion During the Years 2009-2014[a]

Age, y	No. of AD Events	Incidence Proportion (95% CI), %
0	22 285	6.30 (6.22-6.39)
1	39 548	11.06 (10.91-11.21)
2	49 695	13.79 (13.59-13.98)
3	55 675	15.37 (15.14-15.61)
4	60 064	16.54 (16.27-16.80)
5	63 460	17.44 (17.15-17.74)

Abbreviations: AD, atopic dermatitis.

[a]Data are given as the incidence proportion of children (percentage) with AD during the years 2009 through 2014.

Figure 4. The Annual Incidence Rate (IR) per Person-Year (PY) of Atopic Dermatitis for Boys and Girls



Includes children younger than 6 years. Data are from the Norwegian Prescription Database from January 1, 2009, through December 31, 2014. Error bars indicate 95% CI.

the seasonal IR in the spring was 49.6% higher (IRR, 1.50; 95% CI, 1.46-1.53; $P < .001$) than in the summer (reference category). The IRRs for autumn and winter were 1.16 (95% CI, 1.13-1.19) and 1.41 (95% CI, 1.38-1.45), respectively.

Discussion

This nationwide study, based on disease-specific dispensed prescriptions, displays an increase in the IR of AD, especially among children younger than 1 year. More than 1 in 6 children younger than 6 years had, at some point during the study period, been affected by AD. To convey the true magnitude of disease risk and disease onset in the study population, we presented population-based incidence estimates regarding AD. However, to date only a few nationwide studies report IRs for AD in children. What, to our knowledge, is the only globally and uniform validated research study of AD, the International Study of Asthma and Allergies in Childhood (ISAAC), showed that more than 20% of children are affected by AD in some countries.[32] The latest available data (phase 3) revealed that AD continues to increase worldwide, especially in young children (ages 6-7 years).[32]

Although the ISAAC study found an increasing trend of small children with AD, a 2015 register study of the IRs of AD in Denmark and Sweden by Henriksen et al[8] concluded that the number of children with AD had stabilized during the same period. In contrast to our study, the report of Henriksen et al[8] only applied *ICD-10* diagnoses used in hospital settings to examine the trends in the IR of AD. Most patients with AD, however, only occasionally require hospital or specialist therapy. Consequently, the diagnoses in primary care (*ICPC-2*) should correspond better to the general population as a less restricted group, compared with those in hospitals.

Three cross-sectional questionnaire studies of AD among Norwegian schoolchildren found self-reported prevalence rates of 13.4%, 21.1%, and 20.8% in 1985, 1995, and 2000, respectively.[4,5] The analysis included children aged 9 to 11 years with questionnaires that sought to determine whether the child had ever displayed symptoms of AD. Despite the obvious methodologic differences, these findings are compatible with our data showing that 17.4% of the children were affected by AD before reaching the age of 6 years.

Our results showed that AD had an earlier onset in boys than in girls. After the age of 2 years, the sex differences were leveled out. The results from a Danish birth cohort study describe similar findings in infants to the age of 18 months.[33] Sex differences among children diagnosed with asthma is a recognized phenomenon, but large-scale longitudinal studies of age-related sex differences in young children with AD are limited.[33-36] Skin hydration, surface pH, and sebum content have repeatedly been observed in infants according to sex and age without consistent findings.[37-39] However, the temperament of infants may differ between sexes.[40,41] An experimental study of a group of US infants[42] showed that boys appear to have a more limited capacity for self-regulation compared with girls at the same age. Theoretically, if boys with AD express more discomfort compared with girls, boys would be more likely to visit a physician at a younger age than girls.

Our study showed an increasing IR during a short time span, which may be a consequence of a change in exposure to environmental factors. Two previous observational studies from Finland and Germany of children with AD and allergies and living in geographically adjacent areas (who were genetically related)[43,44] have shown that the environment rather than a genetic predisposition could have aggravated the condition. An alteration in genetically predisposed individuals may not be ruled out, but in the German study[43] and the present study, these effects are conceivably less relevant because the increase in the IR occurred during a short period. Moreover, the Norwegian, Danish, and Swedish people are genetically related, which means that the environment, together with disparities in design and methods, could have caused the divergent findings in the present study compared with the study of Henriksen et al.[8]

In the present study, seasonal variations in the IR of AD showed a distinct peak during winter and spring seasons, a result of which has previously been shown by other researchers.[8,13,45,46] Former studies have demonstrated the association between the onset of pollination and the

manifestation of AD and pruritus.[15,17-19] Although airborne pollen may contribute to the identified springtime peak, as yet no clear explanations exist for the seasonal peak in the IR for AD during the winter season. According to a recent experimental study, infants' stratum corneum water content indicated a significant seasonal difference (higher in early summer than in autumn).[47] One may speculate whether the water content is affected by the ambient temperature and has relevance for the skin barrier. Our results suggest that environmental conditions associated with season may play a role in the onset and perhaps worsening of the disease.

Our results showed a higher IR of AD in 2010. According to the climate statistics, the winter of 2010 in Norway and Sweden was extraordinarily cold.[48] The Norwegian sales of topical corticosteroids and glucocorticoid inhalers for children, the IR for AD in the present study (Figure 1), and the IR of asthma in Sweden peaked in the same year.[8,49] The ISAAC study[45] found that lower latitudes and eastern longitudes were slightly but significantly associated with higher prevalence of current symptoms of AD, globally and in all age groups. Our hypothetical speculation, however, is merely based on an ecological comparison of geoclimatic factors, and more studies are required to understand the seasonal variations in this complex and heterogeneous skin disease.

Strengths and Limitations

The main strength of this study is the large volume of data, which allowed us to examine the IRs of AD for the entire Norwegian child population younger than 6 years, thereby obtaining reliable results with high significance. The Norwegian child welfare remained practically unchanged during this short study period. However, whether improved awareness of AD, increased urbanization or access to health care facilities, changes in consultation practice, increased environmental exposures, or genetic alterations contributed to the increasing trend found in the NorPD database is a question with important public health implications. Most likely a combination of many relevant causal processes together with an actual increase of children with AD are responsible.

The identification number on the dispensed prescription was missing in 4.5% of all the received prescriptions from the NorPD. These prescriptions were excluded from the present study.[29] However, AD is defined as a chronic illness. Hence, a child with AD likely would have received prior or subsequent (or both) medical treatment. Thus, we suspect that the excluded prescriptions belong to children already included in this study. Our results should accordingly be robust regarding the missing prescriptions.

Minor episodes of AD may have gone undetected in our study. In Scandinavian countries, the mildest topical corticosteroids can be obtained over the counter. However, Norwegian children with chronic illnesses (including AD) have the right to receive reimbursed prescriptions, which provides the child with necessary medical treatments and medications free of charge. In comparison, purchase of over the counter medications vs reimbursed medication stands out as a more expensive alternative.[30,50] Moreover, the diagnoses assessed based on reimbursement prescriptions (criterion 1) are more likely to reflect children with higher disease burden, which may have led to fewer diagnostic errors. The reimbursed prescriptions additionally provided this study with a high probability to have covered children with AD from all socioeconomic strata.

Topical corticosteroids are frequently prescribed for a relatively broad group of skin disorders, which may lead to uncertainty about the validity of the medication proxies used to identify children with AD.[22-24] The algorithm used in the present study was primarily based on physician-given diagnoses (criterion 1 [88.3%]), and the use of medication proxy (criterion 2) was minimized to only 11.7% of the participants considered. Mulder et al[23] proposed that 2 or more annual prescriptions of topical corticosteroids yield a sensitivity value of only 40% and a positive predictive value of 60%.[24] Compared with the proposed values, our algorithm covered a higher fraction of the children with AD, providing us with a higher sensitivity value. The set of non-AD criteria (criterion 3) additionally increased the positive predictive value.

Conclusions

The present nationwide study outlines a recent longitudinal increase in the IR of pediatric AD, mainly among children younger than 1 year. This increase has occurred during a short period and is possibly related to environmental and lifestyle factors in genetically predisposed individuals. Atopic dermatitis is more common among boys than girls at an early age, and with a higher IR during the winter and spring seasons.

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SUPPLEMENT.

eMethods. Algorithm for Defining Children With Atopic Dermatitis (AD)

eTable 1. Incidence Rates (IR) and Incidence Rate Ratio (IRR) per Person-Year for Atopic Dermatitis (AD)

eTable 2. The Number of Events and IRs per Person-Year for Boys and Girls With AD by Age

Supplementary Online Content

Mohn CH, Blix HS, Halvorsen JA, Nafstad P, Valberg M, Lagerløv P. Incidence trends of atopic dermatitis in infancy and early childhood in a nationwide prescription registry study in Norway. *JAMA Netw Open*. 2018:1(7):e184145. doi:10.1001/jamanetworkopen.2018.4145

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Algorithm for Defining Children With Atopic Dermatitis (AD)

Children were considered to have AD if they met at least one requirement for either Criteria 1 or 2.

Criterion 1 - based on ICD-10 or ICPC-2 diagnoses:

- ≥ 1 hospital or specialist (dermatologist) contact for: L20 "atopic dermatitis"
- ≥ 1 GP contact for: S87 "dermatitis/atopic dermatitis"

Criterion 2 - based on disease-specific medication (ATC-codes):

- ≥ 1 dispensed prescription for: D11AH "agents for dermatitis: tacrolimus or pimecrolimus" [1]
- ≥ 2 dispensed prescriptions for: D07 "corticosteroids for topical use" within 12 months **without any of the following non-AD Criteria.**

NON-AD CRITERIA

Children with co-occurring medical skin diagnoses (that might lead to identical treatment) or with co-occurring disease-specific medication (primarily prescribed for other diseases) were not considered to have AD by the following non-AD Criteria.

Co-occurring skin diagnoses (based on ICD-10 or ICPC-2):

≥ 1 diagnosis of either:

- **ICD-10**: L21 "seborrhoeic dermatitis," L22 "diaper dermatitis" L23 "allergic contact dermatitis," L24 "irritant contact dermatitis," L25 "unspecified contact dermatitis," L26 "exfoliative dermatitis," L27 "dermatitis due to substances taken internally," L28 "lichen simplex chronicus and prurigo," L30 "other dermatitis," L40–L45 "papulosquamous disorders," L53 "other erythematosus conditions," L55 "sunburn," L56 "other acute skin changes due to ultraviolet radiation," L80 "vitiligo," L90 "atrophic disorders of the skin," L93 "lupus erythematosus" OR
- **ICPC-2**: S86 "seborrhoeic dermatitis," S88 "dermatitis contact/allergic," S89 "diaper dermatitis" L88 "allergic contact dermatitis," S80 "solar keratosis/sunburn," S82 "exfoliative dermatitis," S06 "rash localized," S07 "rash generalized," S08 "skin color change," S91" psoriasis," S99 "skin diseases" OR

Co-occurring disease-specific medication (based on ATC):

≥ 1 dispensed prescription for either:

- D05 "antipsoriasics" or D02AF "salicylates for dermatological use" or D07AD "corticosteroids (group IV) including clobetasol" [*2]

[*1] *Calcineurin inhibitor crème/ointment 0.03% is indicated for adults, adolescents, and children from 2 years of age and are only prescribed for moderate-to-severe AD.* [1E]

[*2] *For prescriptions of corticosteroid group IV (without ever having a diagnosis of AD). AD is not treated singly with group IV.*

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eTable 1. Incidence Rates (IR) and Incidence Rate Ratio (IRR) per Person-Year for Atopic Dermatitis (AD)

Annual IR and IRR per person-year of children with AD (with 95% CIs)				
Year	IR	95% CI	IRR	95% CI
2009	0.029	0.028 - 0.030	1.00	Reference
2010	0.033	0.032 - 0.033	1.13	1.10 - 1.16
2011	0.031	0.030 - 0.031	1.06	1.03 - 1.09
2012	0.032	0.031 - 0.033	1.10	1.07 - 1.13
2013	0.034	0.033 - 0.034	1.16	1.13 - 1.19
2014	0.034	0.033 - 0.035	1.17	1.14 - 1.20

Data show he relatively steady increase (excluding 2010) during the study period (Figure 1) presented with 95% CIs.

eTable 2. The Number of Events and IRs per Person-Year for Boys and Girls With AD by Age

IR per person-year of children with AD, by age and gender

Age	Boys	IR for Boys	Girls	IR for Girls	Total
0	13693	0.076	8592	0.050	22285
1	9352	0.054	7911	0.047	17263
2	4975	0.030	5172	0.032	10147
3	2912	0.018	3068	0.019	5980
4	2025	0.013	2364	0.015	4389
5	1546	0.010	1850	0.012	3396
Total	34503		28957		63460

Data are shown in Figure 2.

II

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ORIGINAL RESEARCH

Treatment Patterns of Atopic Dermatitis Medication in 0–10-Year-Olds: A Nationwide Prescription-Based Study

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ABSTRACT

Introduction: The literature on treatment patterns for paediatric atopic dermatitis (AD) is scarce and is rarely based on real-world data. Using national registers, we sought to establish up-to-date, population-based prevalence estimates, predictors of risk and disease burden and a comprehensive overview of treatment patterns and course for paediatric patients with AD.
Methods: Dispensed prescriptions for the entire Norwegian child population aged 0–10 years from 2014 to 2020 were analysed.
Results: There were 176,458 paediatric patients with AD. Of these, 99.2% received topical corticosteroids, 5.1% received topical calcineurin inhibitors, 37.1% received potent topical corticosteroids and 2.1% received systemic corticosteroids. Of the 59,335 live births in Norway (2014), 14,385 [24.8%; 95% confidence interval (CI) 24.5–25.1] paediatric patients were treated

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for AD before the age of 6 years, and of these, only 934 (6.5%; 95% CI 6.1–6.9) received medication annually for 5 years or more. Compared with girls, 17.9% (95% CI 6.5–27.9) more boys were treated for at least 5 years, receiving 6.4% (95% CI 1.2–11.3) more potent topical corticosteroids and 12.4% (95% CI 6.5–18.0) more were treated for skin infections. Compared with patients with late-onset treatment, 18.9% (95% CI 7.5–29.0) more paediatric patients with early-onset treatment were still receiving treatment at 5 years of age, 15.7% (95% CI 7.1–23.4) more paediatric patients received potent topical corticosteroids and 44.4% (95% CI 36.5–51.2) more paediatric patients were treated for skin infections.

Conclusion: Most paediatric patients were treated for a mild disease for a limited period. Although the prevalence of AD is higher at a younger age, these paediatric patients were the least likely to receive potent topical corticosteroids. Male sex and early-onset AD are associated with and are potential predictors of long-term treatment and treatment of potent topical corticosteroids, antihistamines and skin infections, which may have clinical utility for personalised prognosis, healthcare planning and future AD prevention trials.

Keywords: Child; Atopic dermatitis; Dermatologic agents; Eczema; Emollients; Pharmacoepidemiology; Prescriptions; Topical calcineurin inhibitor; Topical corticosteroids

Key Summary Points

Why carry out this study?

The literature on treatment patterns and disease severity, particularly in paediatric patients under 2 years of age, is sparse and is rarely based on real-world data. Further details on predictors of risk are needed to better facilitate interventions that may halt this epidemic rise of atopic dermatitis in our paediatric populations.

Covering an entire nation of children up to 10 years of age, we sought to establish up-to-date, population-based prevalence estimates and predictors of risk and disease burden and a comprehensive overview of treatment patterns and course for paediatric patients with atopic dermatitis.

What was learned from the study?

We found that male sex and early-onset atopic dermatitis are associated with and are potential predictors of long-term treatment and treatment of potent topical corticosteroids, antihistamines and skin infections.

The highest burden of AD was evident during the first years of life, with a peak prevalence at 1 year of age. We encourage further research to investigate the presumed unmet therapeutic needs of this vulnerable patient group and the applicability of current guidelines, particularly in paediatric patients under 2 years of age.

INTRODUCTION

Atopic dermatitis (AD) causes the most significant burden of disability in the global context of skin diseases and substantial morbidity, including pruritus and reduced personal and family quality of life [1].

Although AD has lagged behind psoriasis in treatment development, a broader therapeutic landscape for AD has emerged in recent years. In the nineteenth century, conventional treatment mainly compromised ointments [2]. Systemic and topical corticosteroids (TCSs) were introduced in the 1950s [3]. Immunosuppressive agents, such as cyclosporine and azathioprine, became available treatment options in the mid-1990s [4]. More recently, second-line systemic options for AD (e.g. JAK inhibitors) have gained a place in therapy but are rarely used and are not approved for young paediatric patients.

The heterogeneity of the clinical picture and disease course of patients with AD indicates a complex reality and uncertain disease trajectories. The literature on treatment patterns and disease severity, particularly in patients under 2 years of age, is sparse [5, 6]. A review by Siegfried et al. [6] revealed limited data on long-term and combination treatment, treatment of severe AD, and systemic corticosteroids in children [6]. In addition, methodological divergence, assessments of AD signs, variations in participants, clinical settings and countries studied were evident.

National health registers from the Nordic countries provide valid, real-world epidemiological data, identifying patients at the individual level on the basis of dispensed prescriptions for disease-specific medications [7–9]. Unique person identifiers and a nationwide sample size provide advanced access to comparative longitudinal data that enable large-scale nationwide cohort studies. We conducted a study covering all paediatric patients who were dispensed prescriptions for AD specific medication up to the age of 10 years from 2014 to 2020 using a novel dataset. The primary objective was to obtain a comprehensive up-to-date overview of prescription-based treatments in paediatric AD. Our secondary objective was to identify treatment patterns and how these relate to long-term and potent topical AD treatment.

METHODS

Ethics Approval and Consent

The observational study was conducted between January 2020 and October 2021. The study was approved by the Regional Committees for Medical and Health Research Ethics Southeast Norway (Ref, REK: 2015/1927) in November 2015 and September 2019, and by the Norwegian Social Science Data Services (NSD) in December 2015. This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the ICMJE requirements on privacy and informed consent. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Study Population

The study covers an annual child population from birth to age 10, consisting of 683,468 patients in 2014 and decreasing to 672,188 in 2020. A total of 59,335 children born in 2014 were followed for 6 years. All children residing in Norway aged 0 to 10 years who had received AD-specific medication [TCSs or topical calcineurin inhibitors (TCIs) or both for external use] were followed up from 1 January 2014 to 31 December 2020.

Registers and Coding Classifications

The nationwide Norwegian Prescription Database (NorPD) holds a unique encrypted personal identifier for all prescriptions dispensed by pharmacies to the Norwegian population, enabling us to track dispensing at the individual level over time.

All dispensed prescriptions for TCSs [Anatomical Therapeutic Chemical Classification (ATC) code D07A], tacrolimus (D11AH01), or pimecrolimus (D11AH02) for external use were extracted from the NorPD according to the ATC/DDD index 2021. In addition, all other prescriptions issued to these patients were extracted. Other medications analysed were combined corticosteroid/antibiotic preparations (D07C), antibiotics for topical use (D06A), antiseptics and disinfectants including hydrogen peroxide (D08AX01), potassium permanganate (D08AX06), dibrompropamidine (D08AC01), systemic antihistamines (R06A), selective immunosuppressants including mycophenolic (L04AA06), calcineurin inhibitors including ciclosporin (L04AD01), other immunosuppressants including azathioprine (L04AX01) and dupilumab (D11AH05), folic acid analogues including methotrexate (L01BA01) and interferons including interferon gamma (L03AB03).

A unique pseudonym replaced the patient number ID. Patient characteristics included age, month and year of birth, date of death, sex, dispense date, generic drug name and ATC codes. Reimbursable prescriptions included codes from the International Statistical Classification of Diseases, Tenth Revision (ICD-10) and the International Classification of Primary Care, version two (ICPC-2) [10].

In Norway, reimbursable prescriptions are issued for chronic diseases. Population statistics were obtained from Statistics Norway.

Algorithm for Identifying Paediatric Patients with Atopic Dermatitis Treatment

Patients were considered to have AD if they met at least one requirement for either criterion, 1 or 2.

1. Criterion 1, on the basis of medical diagnoses: patients with recorded reimbursement prescriptions including associated disease-specific diagnoses of "atopic dermatitis/eczema", recorded as ICD-10 (L20) or ICPC-2 (S87).
2. Criterion 2, on the basis of disease-specific medication dispensed: patients with non-reimbursable prescriptions (no AD diagnosis as in criterion **1)** were considered to have AD if the child, within 1 year, the child had either:

- ≥ two prescriptions of TCS (minimum 14 days apart)
- ≥ one prescription of TCI

3. *Non-AD criteria*: Patients classified under criterion 2, with co-occurring ICD-10/ICPC-2 skin diagnoses (which could lead to identical treatments) or co-occurring skin disease-specific medications (primarily prescribed for other conditions), were not considered to have AD.

The online Supplementary Material provides further explanations of the algorithm employed.

Categorising Paediatric Patients based on the Potency of TCSs

Patients were categorised into three levels on the basis of the highest potency of TCS treatment received (with or without TCIs, systemic treatment including corticosteroids, immunosuppressants, calcineurin inhibitors, folic acid analogues and interferons). Level 1 was defined as patients treated exclusively with weak TCSs (group I). Level 2 was defined as moderate TCSs (group II). Level 3 was defined as potent or very potent TCSs (group III/IV). A more potent TCS class overruled a less potent one.

Statistical Analysis

We used Poisson regression based on the algorithm to calculate the 1-year prevalence of dispensed drugs with a 95% confidence interval (CI). Data were stratified by age and sex, early and late treatment initiation, and years of treatment. The dataset was adjusted for sex differences within the population. Descriptive statistics were reported as mean, standard deviation (SD) or median for continuous variables, and as frequency (per cent) for categorical variables. A chi-square test tested the differences between rates. $P < 0.05$ (2-sided test) was considered statistically significant.

The annual prevalence (based on age) was measured as the number of individuals receiving at least one prescription of AD medication per age. Continuous assessments of the same individuals over time can occur. The dominator from Statistics Norway was presented by sex and age on the basis of the midyear Norwegian population each year.

The 2014 birth cohort was stratified by index age (baseline age), defined as the age of exposure (dispensed prescription of AD medication). Patients with an index age of 0–6 months were set as the reference group to stratify and assess the treatment pattern and predictor of severity and long-term AD treatment. The 2014 birth cohort was divided into four cohorts (6-month periods) according to index age. Patients with an early index age (0–6 months) were compared with patients with a late index age

(18–24 months). Age- and sex-specific analyses and analyses of the strength of TCSs dispensed were performed.

The total number of years of AD treatment were analysed to assess the duration of treatment. We also analysed the number of patients receiving regular AD treatment (persistence) with a maximum interval of 1 year between redemptions for at least 2 years, from index age to 6 years of age.

Days of follow-up were defined as the period between indexation (index age) and the first date of emigration, death or cut-off date of the NorPD data (31 December 2020), whichever occurred first. Data were analysed using Stata/MP software (version 17.0; StataCorp LLP).

RESULTS

Prescription and Patient Selection

From 2014 to 2020, 176,458 patients were treated for AD according to the algorithm. Overall, 90.7% (160,022) of the included patients had a physician-issued reimbursable prescription and associated AD diagnoses (criterion 1). There were 589,687 topical AD medication prescriptions (317,593 dispensed to 92,436 boys and 262,094 to 84,022 girls). The median observation period per child was 38.2 months (interquartile range 16.0; 60.0).

Treatment Patterns in Paediatric Patients Aged 0–10 years, (Table 1)

The period prevalence for all ages combined was 6.7% (95% CI 6.7–6.8). The statistics displayed a significant preponderance of boys receiving AD treatment. There were no significant differences between the sexes after the age of 4. The average prescriptions dispensed per year per child, and the mean number of grams of prescribed topical treatment indicated a steady decline with increasing age.

Almost all patients were dispensed TCSs. Only 1435 patients (0.8%; 95% CI 0.8–0.9) were prescribed TCIs as single therapy (excluding other topical therapies). Only a minority were prescribed very potent (group IV) TCSs. The number of patients receiving potent TCSs (group III) and TCIs increased with age.

Patients were categorised into three levels on the basis of the highest potency of TCSs received. Overall, 107,795 (61.1%; 95% CI 60.9–61.3) received only weak or moderately potent TCSs. In addition, 21,610 (12.2%; 95% CI 12.1–12.4) patients received potent or very potent TCSs without previously having received weak or moderately potent TCSs.

Overall, dispensed systemic immunosuppressant was marginal: azathioprine ($n = 131$), cyclosporine ($n = 186$), interferon gamma ($n = 0$), methotrexate ($n = 1$), mycophenolate mofetil ($n = 70$), baricitinib ($n = 0$) and dupilumab ($n = 2$).

Characteristics of the 2014 Birth Cohort, (Table 2)

Of the 59,335 live births in Norway (2014), 14,385 (24.8%; 95% CI 24.5–25.1) patients were treated for AD before the age of 6 years. Of these, 934 patients (6.5%; 95% CI 6.1–6.9) received AD medication annually for 5 years (or more).

The analysis revealed (387/6,658 girls compared with 547/7727 boys) 17.9% (95% CI 6.5–27.9) more boys than girls received at least 5 years of dispensed AD treatment (or more). However, there was no statistically significant difference between the sexes in terms of persistence (regular redemption of AD treatment). Accordingly, (2428/6658 girls compared with 3010/7727 boys) 6.4% (95% CI 1.2–11.3) more boys received potent/very potent TCSs than girls. In addition, (2428/6658 girls compared with 3010/7727 boys) 12.4% (95% CI 6.5–18.0) more boys were treated for skin infections (at least one of the following: weak TCSs in combination with antibiotics or topical antibiotics, antiseptics or disinfectants). We found that (1956/6658 girls compared with 2412 /7727 boys) 5.9% (95% CI 0.1–11.3) more boys than girls received antihistamines before the age of 6 and (122 /6658 girls compared with 195/7727 boys) 27.4% (95% CI 9.0–42.1) more boys received systemic corticosteroids.

Table 1 Demographics, treatment category and clinical characteristics of the 176,458 patients with AD, by ages 0–10, years 2014–2020

Patient characteristics by age (per cent of total)[a]	**Age 0, *n* = 45,281 (25.7%)**	**Age 1, *n* = 50,055 (28.4%)**	**Age 2, *n* = 39,627 (22.5%)**	**Age 3, *n* = 31,319 (17.7%)**	**Age 4, *n* = 27,296 (15.5%)**	**Age 5, *n* = 24,723 (14.0%)**
Demographics						
Norwegian population (2014–2020)	404,632	415,257	424,007	431,976	438,031	442,587
Prevalence, per cent (95% CI)	11.1(11.1–11.3)	12.1(11.9–12.2)	9.3 (9.3–9.4)	7.3 (7.2–7.3)	6.2 (6.2–6.3)	5.6 (5.5–5.7)
Age, years, mean ± SD; median	0.6 ± 0.2; 0.5	1.5 ± 0.3; 1.4	2.4 ± 0.3; 2.4	3.4 ± 0.3; 3.4	4.5 ± 0.3; 4.4	5.5 ± 0.3; 5.4
Sex, male	26,490 (58.5)	27,624 (55.2)	21,368 (53.9)	16,550 (52.8)	14,122 (51.7)	12,472 (50.5)
Total received prescriptions of TCS and TCI. Mean ± SD; median	2.1 ± 1.7; 1.0	1.9 ± 1.6; 1.0	1.9 ± 1.6; 1.0	1.8 ± 1.6; 1.0	1.8 ± 1.6; 1.0	1.8 ± 1.6; 1.0
Total gram of TCSs and TCIs. Mean ± SD; median	127.0 ± 134.7; 100.0	123.1 ± 134.8; 100.0	122.9 ± 134.9; 100.0	123.4 ± 140.2; 100.0	122.5 ± 146.2; 100.0	122.2 ± 148.1; 100.0
Number of dispensed prescriptions of TCSs or TCIs per age						
≥ 2	22,427 (49.5)	22,738 (45.4)	16,888 (42.6)	12,850 (41.0)	10,675 (39.1)	9425 (38.1)
≥ 3	10,240 (22.6)	9523 (19.0)	7179 (18.1)	5223 (16.7)	4406 (16.1)	3714 (15.0)
Annual combination therapy with ≥ 2 distinct treatments of TCSs or TCIs[c]	15,587 (34.4)	14,426 (28.8)	10,725 (27.1)	7942 (25.4)	6606 (24.2)	5783 (23.4)
TCSs						
Any potency	45,182 (99.8)	49,767 (99.4)	39,165 (98.8)	30,917 (98.7)	26,888 (98.5)	24,345 (98.5)
Weak (group I)	29,009 (64.1)	24,907 (49.8)	16,499 (41.6)	11,866 (37.9)	9498 (34.8)	8106 (32.8)

Table 1 continued

Patient characteristics by age (per cent of total)[a]	Age 0, *n* = 45,281 (25.7%)	Age 1, *n* = 50,055 (28.4%)	Age 2, *n* = 39,627 (22.5%)	Age 3, *n* = 31,319 (17.7%)	Age 4, *n* = 27,296 (15.5%)	Age 5, *n* = 24,723 (14.0%)
Moderately potent (group II)	25,163 (55.6)	28,699 (57.3)	22,729 (57.4)	17,270 (55.1)	14,539 (53.3)	12,696 (51.4)
Potent (group III)	8498 (18.8)	11,529 (23.0)	10,884 (27.5)	9639 (30.8)	9137 (33.5)	8833 (35.7)
Very potent (group IV)	171 (0.4)	340 (0.7)	479 (1.2)	532 (1.7)	636 (2.3)	680 (2.8)
TCIs	748 (1.7)	1156 (2.3)	1528 (3.9)	1292 (4.1)	1237 (4.5)	1140 (4.6)
Highest TCSs potency received[d]						
1. Weak (group I)	15,421 (34.0)	13,851 (27.7)	9320 (23.3)	6963 (22.2)	5734 (21.0)	4932 (20.0)
2. Moderately potent (group II)	21,230 (46.9)	24,427 (48.8)	19,062 (48.1)	14,310 (45.7)	11,936 (43.7)	10,417 (42.1)
3. Potent/Very potent (group III/IV)	8630 (19.1)	11,777 (23.5)	11,245 (28.4)	10,046 (32.1)	9626 (35.3)	9374 (37.9)
Weak TCSs in combinations with antibiotics, topical antibiotics, topical antiseptics and disinfectants[e]	5527 (12.2)	4979 (10.0)	3869 (9.8)	2902 (9.3)	2597 (9.5)	2398 (9.7)
Systemic treatments						
Antihistamines[f]	4240 (9.4)	9593 (19.2)	9186 (23.2)	8044 (25.7)	7623 (27.9)	5225 (27.9)
Corticosteroids[g]	283 (0.6)	754 (1.5)	522 (1.3)	409 (1.3)	338 (1.2)	317 (1.3)
Antineoplastic and immunomodulating agents[h]	8 (0.0)	16 (0.0)	23 (0.1)	10 (0.0)	20 (0.1)	25 (0.1)

Table 1 continued

Patient characteristics by age (per cent of total)[a]	Age 6, *n* = 22,572 (12.8%)	Age 7, *n* = 21,153 (12.0%)	Age 8, *n* = 21,153 (11.7%)	Age 9, *n* = 20,137 (11.4%)	Age 10, *n* = 19,775 (11.2%)	Total, *n* = 176,458 (100.0%)
Demographics						
Norwegian population (2014–2020)	445,160	447,933	447,508	446,809	444,104	–
Prevalence, per cent (95% CI)	5.1 (5.0–5.1)	4.7 (4.7–4.8)	4.6 (4.5–4.7)	4.5 (4.4–4.6)	4.5 (4.4–4.5)	–
Age, years, mean ± SD; median	6.5 ± 0.3; 6.4	7.5 ± 0.3; 7.4	8.5 ± 0.3; 8.4	9.5 ± 0.3; 9.3	10.5 ± 0.3; 10.4	–
Sex, male	11,117 (49,2)	19,282 (48.6)	10,193 (49.5)	9969 (49.5)	9856 (49.8)	92,436 (52.7)
Total received prescriptions of TCS and TCI. Mean ± SD; median	1.7 ± 1.6; 1.0	1.7 ± 1.5; 1.0	1.7 ± 1.5; 1.0	1.7 ± 1.5; 1.0	1.7 ± 1.5; 1.0	–
Total gram of TCSs and TCIs. Mean ± SD; median	119.7.1 ± 151.0; 100.0	119.4 ± 145.5; 100.0	120.0 ± 146.1; 100.0	120.4 ± 142.9; 100.0	121.6 ± 146.1; 100.0	–
Number of dispensed prescriptions of TCSs or TCIs per age						
≥ 2	8349 (37.0)	7810 (36.9)	7519 (36.5)	7475 (37.1)	7294 (36.9)	23,476 (38.8)
≥ 3	3223 (14.3)	3007 (14.2)	2935 (14.2)	2871 (14.3)	2867 (14.5)	8696 (14,4)
Annual combination therapy with ≥ 2 distinct treatments of TCSs or TCIs[c]	5061 (22.4)	4791 (22.6)	4576 (22.2)	4518 (22.4)	4427 (22.4)	45,749 (25.9)
TCSs						
Any potency	22,185 (98.3)	20,758 (98.1)	20,187 (98.0)	19,694 (97.8)	19,284 (97.5)	175,023 (99.2)
Weak (group I)	6893 (30.5)	6062 (28.7)	5708 (27.7)	5447 (27.1)	5041 (25.5)	91,051 (51.6)
Moderately potent (group II)	11,296 (50.0)	10,269 (48.6)	9688 (47.0)	9077 (45.1)	8624 (43.6)	108,373 (61.4)
Potent (group III)	8508 (37.7)	8548 (40.4)	8708 (42.3)	8926 (44.3)	9146 (46.3)	65,520 (37.1)
Very potent (group IV)	779 (3.5)	797 (3.8)	799 (3.9)	863 (4.3)	953 (4.8)	5754 (3.3)

Table 1 continued

Patient characteristics by age (per cent of total)[a]	Age 0, *n* = 45,281 (25.7%)	Age 1, *n* = 50,055 (28.4%)	Age 2, *n* = 39,627 (22.5%)	Age 3, *n* = 31,319 (17.7%)	Age 4, *n* = 27,296 (15.5%)	Age 5, *n* = 24,723 (14.0%)
TCIs	1006 (4.5)	1057 (5.0)	1072 (5.2)	1119 (5.6)	1173 (5.9)	9044 (5.1)
Highest TCSs potency received[d]						
1. Weak (group I)	4308 (19.1)	3800 (18.0)	3643 (17.7)	3481 (17.3)	3292 (16.7)	31,750 (18.0)
2. Moderately potent (group II)	9162 (40.6)	8234 (38.9)	7689 (37.3)	7123 (35.4)	6681 (33.8)	76,045 (43.1)
3. Potent/Very potent (group III/IV)	9102 (40.3)	9119 (43.1)	9275 (45.0)	9533 (47.3)	9802 (49.6)	68,663 (38.9)
Weak TCSs in combinations with antibiotics, topical antibiotics, topical antiseptics and disinfectants[e]	2031 (9.0)	1931 (9.1)	1760 (8.5)	1727 (8.6)	1604 (8.1)	35,106 (19.9)
Systemic treatments						
Antihistamines[f]	7289 (29.3)	6494 (30.7)	6619 (32.2)	6715 (33.4)	6751 (34.1)	51,844 (29.4)
Corticosteroids[g]	279 (1.2)	281 (1.3)	299 (1.5)	354 (1.8)	327 (1.7)	3614 (2.1)
Antineoplastic and immunomodulating agents[h]	25 (0.1)	34 (0.2)	39 (0.2)	44 (0.2)	52 (0.3)	203 (0.1)

All values are expressed in *N* (percent) unless otherwise specified. Percentages are calculated according to total number of patients (*N*) in the corresponding age group

[a]Continuous assessments of the same individuals over time can occur. Age is defined as the time medication was dispensed

[b]Annually dispensed topical treatment from two groups of TCSs or TCS(s) combined with TCI(s)

[c]Patients were categorised into three levels on the basis of the highest potency of TCS treatment received during the observation period [with or without receiving TCI(s), systemic corticosteroids, azathioprine, cyclosporine A, methotrexate, mycophenolate mofetil, interferon gamma or intravenous immunoglobulin]. Level 1 was defined as the exclusive use of weak TCS (group I). Level 2 was defined as moderate TCS (group II). Level 3 was defined as potent or very potent TCS (group III/IV). A more potent TCS class overruled a less potent one

[d]"Corticosteroids, combinations of antibiotics (D07C)", 'Antibiotics for topical use (D06A)" and "Antiseptics and disinfectants including hydrogen peroxide (D08XC01), potassium permanganate (D08AX06) and dibrompropamidine (D08AC01)' prescribed at the same age the patient received TCSs or TCIs or both

[e]"Systemic antihistamines (R06A) – Comprises plain and combined antihistamine preparations for systemic use" prescribed at the same age the patient received TCS(s) or TCI(s) or both

[f]"Systemic corticosteroids (H02A) – Only plain preparations are classified in this group' – prescribed at the same age the patient received TCS(s) or TCI(s) or both

[g]"Selective immunosuppressants including mycophenolic acid (L04AA06)", 'Calcineurin inhibitors including ciclosporin (L04AD01)", 'Other immunosuppressants including azathioprine (L04AX01) and dupilumab (D11AH05)', "Folic acid analogues including methotrexate (L01BA01)" and 'Interferons including interferon gamma (L03AB03)" – prescribed at the same age the patient received TCS(s) or TCI(s) or both

Table 2 Demographics, treatment category and clinical characteristics of patients with AD born in 2014, followed until the age of 6 (on the basis of the 59,335 0-year-olds born in 2014)

Patient characteristics	Total, *n* = 14,385 (100.0%)	Female, *n* = 6658 (46.3%)	Male, *n* = 7727 (53.7%)	Index age 0–6 months, *n* = 2505 (17.4%)	Index age 6–12 months, *n* = 2953 (20.5%)	Index age 12–18 months, *n* = 2055 (14.3%)	Index age 18–24 months, *n* = 1799 (12.5%)
Demographics							
Age, years, mean ± SD; median[a]	2.6 ± 1.7; 2.3	2.8 ± 1.7; 2.5	2.5 ± 1.6; 2.2	1.9 ± 1.7; 1.4	2.2 ± 1.6; 1.7	2.5 ± 1.4; 1.5	2.8 ± 1.3; 2.3
Sex, male	7,727 (53.7)	(–)	(–)	1575 (62.9)	1701 (57.6)	1103 (53.7)	920 (51.1)
Total years receiving TCSs or TCIs							
1 year	6357 (44.2)	2968 (44.6)	3389 (43.9)	717 (28.6)	868 (29.4)	892 (43.4)	727 (40.4)
2 years	4047 (28.1)	1929 (29.0)	2118 (27.4)	620 (24.8)	892 (30.2)	610 (29.7)	553 (30.7)
3 years	2004 (13.9)	925 (13.9)	1079 (14.0)	451 (18.0)	540 (18.3)	283 (13.8)	303 (16.8)
4 years	1043 (7.3)	449 (6.7)	594 (7.7)	314 (12.5)	311 (10.5)	169 (8.2)	128 (7.1)
5 years	592 (4.1)	247 (3.7)	345 (4.5)	(–)	(–)	(–)	(–)
6 years	342 (2.4)	140 (2.1)	202 (2.6)	(–)	(–)	(–)	(–)
Persistence: regularly received prescriptions of TCS or TCI[b]	1857 (12.9)	825 (12.4)	1032 (13.4)	473 (18.9)	319 (10.8)	263 (12.8)	205 (11.4)
Received TCSs at age 5	3786 (26.3)	1907 (28.6)	1879 (24.3)	596 (23.8)	618 (20.9)	425 (20.7)	347 (19.3)
Received group III/IV TCSs at age 5	5438 (37.8)	2428 (36.5)	3010 (40.0)	1088 (43.4)	1098 (37.2)	790 (38.4)	659 (36.6)
Total received prescriptions of TCS and TCI per age. Mean ± SD; median	1.8 ± 1.4; 1.0	1.7 ± 1.3; 1.0	1.9 ± 1.5; 1.0	2.8 ± 2.2; 2.0	1.6 ± 1.0; 1.0	1.9 ± 1.4; 2.0	1.4 ± 0.8; 1.0
Total gram of TCSs and TCIs per age. Mean ± SD; median	106.9 ± 110.8; 90.0	99.1 ± 100.0; 80.0	113.6 ± 118.9; 100.0	169.0 ± 175.4; 100.0	88.6 ± 82.6; 60.0	111.0 ± 112.6; 100.0	82.0 ± 65.0; 60.0

Table 2 continued

Patient characteristics	Total, *n* = 14,385 (100.0%)	Female, *n* = 6658 (46.3%)	Male, *n* = 7727 (53.7%)	Index age 0–6 months, *n* = 2505 (17.4%)	Index age 6–12 months, *n* = 2953 (20.5%)	Index age 12–18 months, *n* = 2055 (14.3%)	Index age 18–24 months, *n* = 1799 (12.5%)
Total received prescriptions of TCS or TCI per age							
≥ 2 treatments	5820 (40.5)	2564 (38.5)	3256 (42.1)	1540 (61.5)	1154 (39.1)	892 (43.4)	555 (30.9)
≥ 3 treatments	2359 (16.4)	977 (14.7)	1382 (17.8)	877 (35.0)	452 (15.3)	361 (17.6)	171 (9.5)
Highest potency of TCSs received[d]							
1. Weak (group I)	2458 (17.1)	1167 (17.5)	1291 (16.7)	360 (14.4)	490 (16.6)	379 (18.4)	310 (17.2)
2. Moderately potent (group II)	6489 (45.1)	3063 (46.0)	3426 (44.3)	1057 (42.2)	1365 (46.2)	886 (43.1)	830 (46.1)
3. Potent/very potent (group III/IV)	5438 (37.8)	2428 (36.5)	3010 (39.0)	1088 (43.4)	1098 (37.2)	790 (38.4)	659 (36.6)
TCIs	698 (4.9)	310 (4.7)	388 (5.0)	174 (7.0)	140 (4.7)	93 (4.5)	79 (4.4)
Weak TCSs in combination with antibiotics, topical antibiotics, topical antiseptics and disinfectants[)]	2791 (19.4)	1204 (18.1)	1587 (21.8)	776 (31.0)	667 (22.6)	379 (18.4)	310 (17.2)
Systemic treatments							
Antihistamines[f]	4368 (30.4)	1956 (29.4)	2412 (33.1)	984 (39.3)	902 (30.6)	620 (30.2)	559 (31.1)
Corticosteroids[g]	317 (2.2)	122 (1.8)	195 (2.5)	68 (2.7)	69 (2.3)	56 (2.7)	35 (2.0)

Table 2 continued

Patient characteristics	Total, *n* = 14,385 (100.0%)	Female, *n* = 6658 (46.3%)	Male, *n* = 7727 (53.7%)	Index age 0–6 months, *n* = 2505 (17.4%)	Index age 6–12 months, *n* = 2953 (20.5%)	Index age 12–18 months, *n* = 2055 (14.3%)	Index age 18–24 months, *n* = 1799 (12.5%)
Antineoplastic and immunomodulating agents[h]	12 (0.1)	8 (0.1)	4 (0.1)	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)

Unless otherwise specified, all values are expressed in *N* (percentages)

Percentages are calculated according to total patients *(N)* in the corresponding age group

The index age for patients with 5 and 6 years of treatment could not be determined owing to the short follow-up period

[a]Age at the time medication was dispensed

[b]The number of patients receiving regular AD treatment (persistence) from the index age until the age of 6, for at least 2 years with a maximum 1-year gap between redemptions

[c]Annually dispensed topical treatment from two groups of TCSs or TCS(s) in combination with TCI(s)

[d]Patients were categorised into three levels on the basis of the highest potency of TCS treatment received during the observation period [with or without receiving TCI(s), systemic corticosteroids, azathioprine, cyclosporine A, methotrexate, mycophenolate mofetil, interferon gamma or intravenous immunoglobulin]. Level 1 was defined as the exclusive use of weak TCS (group I). Level 2 was defined as moderate TCS (group II). Level 3 was defined as potent or very potent TCS (group III/IV). A more potent TCS class overruled a less potent one

[e]"Corticosteroids, combinations of antibiotics (D07C)", "Antibiotics for topical use (D06A)" and 'Antiseptics and disinfectants including hydrogen peroxide (D08AX01), potassium permanganate (D08AX06), dibrompropamidine (D08AC01)" prescribed at the same age the patient received TCSs or TCIs or both

[f]"Systemic antihistamines (R06A) – Comprise plain and combined antihistamine preparations for systemic use" prescribed at the same age the patient received TCS(s) or TCI(s) or both

[g]"Systemic corticosteroids (H02A) – Only plain preparations are classified in this group' – prescribed at the same age the patient received TCS(s) or TCI(s) or both

[h]"Selective immunosuppressants including mycophenolic acid (L04AA06)", "Calcineurin inhibitors including ciclosporin (L04AD01)", 'Other immunosuppressants including azathioprine (L04AX01) and dupilumab (D11AH05)', "Folic acid analogues including methotrexate (L01BA01)" and 'Interferons including interferon gamma (L03AB03)" – prescribed at the same age the patient received TCS(s) or TCI(s) or both

Overall, (596/2505 early index age compared with 347/1799 late index age) 18.9% (95% CI 7.5–29.0) more patients with an early index age (0–6 months) were still receiving AD treatment at 5 years of age compared with patients with a late index age (18–24 months). In terms of persistence, (473/2505 early index age compared with 205/1799 late index age) 39.7% (95% CI 28.9–48.8) more patients with an early index age received regular medication compared with patients with a late index age.

Compared with patients with a late index age, (1088/2505 early index age compared with 659 /1799 late index age) 15.7% (95% CI 7.1–23.4) more patients with early index age received potent or very potent TCSs. When comparing patients with an early and late index age, (877/2505 early index age compared with 171/1799 late index age) 72.8% (95% CI 68.0–77.0) more patients with an early index age patients received three (or more) types of topical treatment (TCSs or TCSs combined with TCIs) per year.

Moreover, (776/2505 early index age compared with 310/1799 late index age) 44.4% (95% CI 36.5–51.2) more patients with an early compared with a late index age were treated for skin infections before age 6. Patients with an early index age received (174/2505 early index age compared with 79 /1799 late index age) 37.1% (95% CI 18.0–51.8) more TCIs than patients with a late index age.

When we analysed antihistamines received before the age of 6, we found (964/2505 early index age compared with 559/1799 late index age) 20.9% (95% CI 12.2–28.7) more patients with an early index age than a late index age. We also found an increased rate of prescribed systemic corticosteroids in patients with an early index age. However, the results were not statistically significant.

DISCUSSION

Globally, to our knowledge, this is the only nationwide study to quantify paediatric AD disease-specific prescriptions and provide a real-world overview of prevalence, treatment patterns, course and predictors, including subgroup characteristics.

The prevalence of Norwegian children receiving AD treatment has decreased with age, ranging from 11% at age 1 to under 5% at age 10 (Table 1). The decline was expected on the basis of the commonly observed disease course of early AD onset, followed by improvement in adolescence. In a 2020 US claims data analysis of AD paediatric patients, Paller et al. [5] observed that most patients receiving AD treatment were 0–1 years old. This study confirms their findings regarding the high prevalence of early-onset treatment.

In the 2014 birth cohort, most patients received short-term treatment of TCSs/TCIs. Around 7% of the patients received AD medication annually for 5 years (or longer) and merely one in four patients were still receiving AD treatment at age 5. In a review of 45 studies involving 110,651 children, the authors found that 80% of childhood AD did not persist by age 8 [11], which underlines our findings.

A substantial proportion of young patients with flexural and facial skin involvement may explain why approximately 80% of them, in the first year of life, received weak or moderately potent TCSs as the highest potency, dropping to 50% by age 10. This finding, together with the general short-term need for AD treatment, is consistent with current knowledge that AD is a mild disease in the majority of cases [5, 12–14].

The number of TCI prescriptions increased with age, accompanied by more potent TCSs, confirming the findings in the US study. A minority of patients received very potent TCSs or systemic therapy. Four out of ten patients received (at least once before the age of 10) potent or very potent TCSs, indicating moderate to severe disease. Since AD is not treated with systemic therapy alone, the prevalence of severe AD before the age of 6 is estimated to be 9.2% in the 2014 birth cohort (according to the proxy). A recent study by Silverberg et al. estimated the proportion of severe AD in 18 countries to be 3.1%-11.0% (except Israel; 24.9%) in children under 6 years of age [15]. These paediatric patients with severe and complex disease are potential candidates for future systemic medication.

Although AD is a chronic disease, the age of onset and disease expression varies across individuals and within seasons. In addition, AD often runs within families. Although it is not recommended, familial sharing of prescribed medication does occur. Moreover, patients may fill their prescriptions just before their birthday, which means they might have received sufficient medication for the following year. If we account for the age of onset (of AD treatment) and frequency of redemption (at least every second year), the proportion of patients receiving regular AD treatment was roughly 13%, which could reinforce the assumption of generally poor adherence in patients with AD [16].

In the 2014 birth cohort, nearly one in five patients received early-onset AD treatment (index age: 0–6 months). We suggest that early-onset AD treatment is associated with significantly severe AD patterns. Overall, patients with early-onset AD treatment were treated with more TCSs and TCIs (higher number of prescriptions and number of grams), they received prescriptions more regularly with more potent (or very potent) TCSs and more were treated for skin infections. In addition, significantly more patients with early-onset AD treatment were still receiving AD treatment at age 5 compared with patients with late-onset AD treatment (index age: 18–24 months). A Danish study of AD disease severity in paediatric patients found that early-onset AD (< 1 year of age) was associated with more severe disease [17]. Previous research suggests that patients with early-onset AD have a significantly higher frequency of filaggrin loss-of-function mutations, increased AD duration and hospitalisation, inadequate disease control and increased persistence [18, 19]. All these studies are consistent with our findings.

The highest burden of AD was evident during the first years of life, with a peak prevalence at 1 year of age. A Danish study [20] concluded that children with AD had the highest disease burden in the second year of life. In the present study, the mean annual number of grams of AD medication per child hardly decreased with age. However, more medication was prescribed to the youngest patients relative to body size. Moreover, the highest annual number of prescriptions and the highest number of combination treatments and skin infection treatments were associated with early onset AD treatment, confirming our findings that AD is a more common and severe condition in the first years of life [20]. Although the prevalence and burden of AD is substantially higher at a younger age, these patients were the least likely to receive potent TCSs [5]. Overall, treatment with more potent TCSs could lead to more rapid skin improvement and disease control, ultimately resulting in fewer TCSs being used overall and fewer physician visits and prescriptions (implying it is also more cost effective) [21–26]. Conclusively, guidelines for the potency of medications adapted to the severity of the disease and the anatomical site of the application according to age, especially in patients under 2 years of age, need to be more specific [27]. It could enhance the potential to treat young paediatric patients more effectively and safely.

The preponderance of boys receiving early-age AD treatment reflects previous research [28–30]. A recent Norwegian study showed that the male sex was predictive of high transepidermal water loss at 3 months of age [31]. According to another recent review, the point prevalence of AD in girls was 24% compared with 35% in boys before age 1. In school-aged children, the prevalence was around 11% in girls and 8% in boys [32]. In addition, the Danish study concluded that disease severity was associated with the male sex, which is consistent with our findings that increased prescription of potent/very potent TCSs are associated with a prolonged disease course and increased risk for skin infections.

There are notable discrepancies in the literature regarding paediatric patients treated with TCIs. In a review by Siegfried et al., TCI treatment ranged from 0% to 52% [6]. Accordingly, we found that only 5% of the patients received TCIs, consistent with Paller et al. The 2005/2006 warnings about the long-term effects (i.e. lymphoma) may have led to less frequent prescribing of TCIs [33]. In addition, the preparations are expensive and not approved as a reimbursement prescription (although individual reimbursement can be granted).

While mainly prescribed for allergies, antihistamines were commonly prescribed for AD. The proportion of dispensed antihistamines was significantly higher in patients with early-onset AD treatment than late-onset treatment. Notably, early-onset AD is associated with a higher risk of seasonal allergies and asthma than late-onset AD [34]. However, another observational cohort study suggests that early-onset and early-resolving AD are not associated with the development of allergic disease at 3 years of age [35]. The published literature on early-onset and early-resolving AD is scarce, and the heterogeneity of AD needs further investigation.

Although systemic corticosteroids can lead to rapid clearing of AD, their use is limited owing to the side effects and the risk of severe rebound flare when discontinued [36]. The total number of systemic corticosteroids administered in the study population was low, close to 2% (a maximum estimate considering the number of prescriptions without ICD/ICPC coding). Furthermore, the high number of dispensed systemic corticosteroids is probably determined by the burden of comorbid asthma and hay fever. A more reasonable estimate would be around 1%, which contrasts with the high consumption (24%) in US paediatric patients recorded by Paller et al. As the course and severity of paediatric AD are likely to be similar in the USA and Norway, this result suggests that non-medical factors (e.g. extent of private health care and treatment traditions) play an essential role in clinical decisions.

In the US database study, prescribed systemic treatment, including immunosuppressants, calcineurin inhibitors, folic acid analogues and interferons ranged from 0.0% in patients aged 1 year to 0.3% in patients aged 10 years [5]. Such marginal prescribing might be rooted in the lack of robust long-term data on the effects of these drugs on paediatric patients [37].

Strengths and Limitations

The large sample size of the longitudinal individual-based novel dataset for the entire population of Norwegian children under the age of 11 ensures robustness with high significance and generalisability. Another strength is that children from all social strata are included in the study, as the social welfare system in Norway is free of charge for paediatric patients. Moreover, Norway has a high number of practising physicians who provide accessible healthcare throughout the country. Another major strength is the NorPD's complete coverage of all prescriptions dispensed by pharmacies to the Norwegian population, including all outpatients.

Topical hydrocortisone 1% is available over the counter and could affect sensitivity. However, the Norwegian welfare system provides reimbursement prescriptions (free of charge) for paediatric patients with chronic diseases such as AD. Consequently, an over-the-counter purchase is a more expensive option, and the analysed sample is expected to be representative [38]. Finally, although this study is performed retrospectively, the actual data are collected in a prospective fashion independent of the study itself, thus eliminating some of the inherent biases commonly identified for traditional retrospective studies (e.g. recall bias, information bias, interview bias, data collection biases and primary non-compliance [39].

Several potential limitations should be discussed. Firstly, the prevalence of AD treatment is closely linked with outcome definitions and should be interpreted cautiously. Secondly, the correspondence between prescriptions dispensed and actual medication use is unknown and should be considered a maximum estimate. Conversely, the time between the first and last prescription received should be interpreted as a minimum estimate, as the time course of administration is unknown. Thirdly, TCSs are prescribed for a broad group of skin conditions, perhaps distorting the true picture of AD drug treatment in the study population [7, 8]. Although often used as the gold standard in studies, physician-recorded diagnoses may lead to incorrect coding and interfere with the prescribing proportions' denominators. This study's algorithm was predominantly based on physician-recorded diagnoses (criterion one). The criterion two (algorithm) was minimised to only 9.3% of the patients included. A validation study [7] found that two or more annual

prescriptions of TCS yielded a sensitivity value of 40% and a positive predictive value of 60%. However, the non-AD criteria (criterion 3) increased the positive predictive value. Fourthly, 1.0% of prescriptions lacked identification numbers and were excluded. However, AD is defined as a chronic disease, and a paediatric AD patient would presumably have received prior or subsequent medical treatment. It is therefore conceivable that the majority of the excluded prescriptions belong to the included patients.

Finally, this study does not address carbamide (urea) creams. Dupilumab was licensed in 2020 for patients over 12 years of age, and crisaborole was not licenced AD treatment during the study period. Moreover, this study does not include phototherapy and climate therapy under the auspices of the public health service.

CONCLUSIONS

In this nationwide real-world registry study, all topical and systemic medications dispensed were documented up to the age of 10 years.

We found that AD was a mild and short-term condition in most paediatric patients. Only a minority of the patients received potent TCSs. Male sex and early-onset AD are associated with, and are potential predictors of, long-term treatment and treatment of potent topical corticosteroids, antihistamines and skin infections. Systemic treatments such as corticosteroids, immunosuppressants, calcineurin inhibitors, folic acid analogues and interferons were marginally prescribed.

There is a need for real-world global knowledge transfer, learning from longitudinal existing treatment patterns in paediatric patients and how differences in treatment patterns are associated with the subsequent prevalence and course of AD in older patients. Although the recommended clinical guidelines were followed, we encourage further research to investigate the presumed unmet therapeutic needs of this vulnerable patient group and the applicability of current guidelines, particularly in paediatric patients under 2 years of age.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors have read and approved the manuscript. The principal investigator, Cathrine Helene Mohn, had

full access to the data and takes responsibility for data integrity and accuracy of the data analysis. Study concept, methodology and design: All authors. Acquisition, analysis and interpterion of data: All authors. The first draft of the manuscript was written by Cathrine Helene Mohn and Jon Anders Halvorsen. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Cathrine Helene Mohn. Administrative, technical or material support: All authors Study supervision: Jon Anders Halvorsen

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Compliance with Ethics Guidelines. The observational study was conducted between January 2020 and October 2021. The study was approved by the Regional Committees for Medical and Health Research Ethics Southeast Norway (Ref, REK: 2015/1927) in November 2015 and September 2019 and by the Norwegian Social Science Data Services (NSD) in December 2015. This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the ICMJE requirements on privacy and informed consent. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Title

Treatment Patterns of Atopic Dermatitis Medication in 0-10 Year-Olds: A Nationwide Prescription-Based Study

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Algorithm for defining children with atopic dermatitis (AD)

Children were considered to have AD if they met at least one requirement for either Criteria 1 or 2:

- Criterion 1 - based on disease-specific diagnoses:
  - ≥ 1 L20 (ICD-10) "Atopic dermatitis"
  - ≥ 1 S87 (ICPC-2) "Dermatitis/atopic dermatitis"
- Criterion 2 - based on disease-specific medication (ATC-codes):
  - ≥ 1 dispensed prescription for D11AH "agents for dermatitis: tacrolimus or pimecrolimus"[a]
  - ≥ 2 dispensed prescriptions for D07 "corticosteroids for topical use" within 12 months without any of the following *exclusion criteria*:

Exclusion criteria: Dispensed prescriptions with diagnoses (based on ICD-10 or ICPC-2) of either:
- ICD-10: L26 "exfoliative dermatitis," L27 "dermatitis due to substances taken internally," L28 "lichen simplex chronicus and prurigo," L40–L45 "papulosquamous disorders," L53 "other erythematosus conditions," L55 "sunburn," L56 "other acute skin changes due to ultraviolet radiation," L80 "vitiligo," L90 "atrophic disorders of the skin," L93 "lupus erythematosus" OR
- ICPC-2: S80 "solar keratosis/sunburn," S82 "exfoliative dermatitis," S08 "skin color change," S91" psoriasis,"

Non-AD criteria

Children with co-occurring medical skin diagnoses (that might lead to identical treatment) or with co-occurring disease-specific medication (primarily prescribed for other diseases) were not considered to have AD by the following non-AD criteria:
- Co-occurring skin diagnoses (based on ICD-10 or ICPC-2):
  ≥ 1 diagnosis of either:
  - ICD-10: L40–L45 "papulosquamous disorders," L80 "vitiligo," L90 "atrophic disorders of the skin," L93 "lupus erythematosus" OR
  - ICPC-2: S91 "psoriasis" OR
- Co-occurring disease-specific medication (based on ATC):
  ≥ 1 dispensed prescription for either:
  - D05 "antipsoriatics" OR
  - D02AF "salicylates for dermatological use" OR
  - D07AD "corticosteroids (group IV) including clobetasol" [b]

a. Calcineurin inhibitor ointment 0.03% is indicated for adults, adolescents, and children from the age of 2 years and is prescribed for moderate-to-severe AD [1].

b. Prescriptions of corticosteroid group IV (without having a diagnosis of AD) because AD is not treated singly with group IV.

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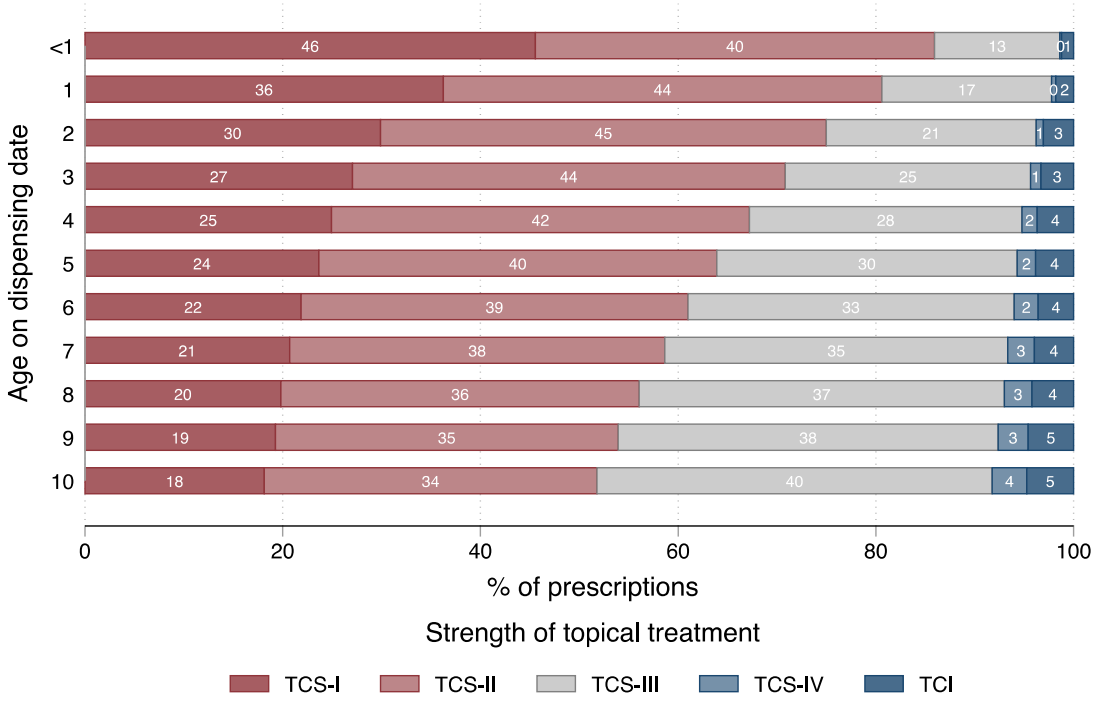
Fig S1. The relative share (per cent) of all dispensed AD treatment to paediatric patients 0-10 per age, using topical corticosteroids and topical calcineurin inhibitors from 2014-2020.



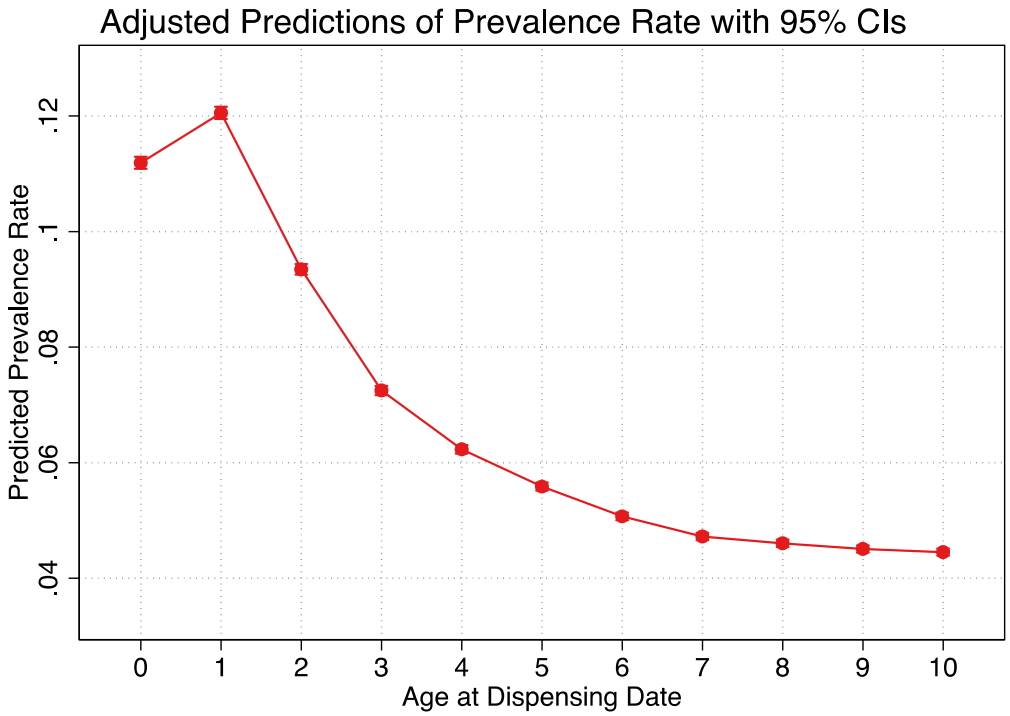
Data are from the Norwegian Prescription Database from January 1, 2014, through December 31, 2020. The bars represent the percentage of topical corticosteroids (presented in groups I-IV according to the potency) and topical calcineurin inhibitors (TCI) dispensed to paediatric patients aged 0-10.

Table S3. Treatment patterns of dispensed topical corticosteroids (x). The number and per cent of paediatric patients with atopic dermatitis with unique treatment patterns among paediatric patients in Norway, 2014-2020.

Weak [a)]	Moderate	Potent	Very potent	Freq	Per cent
-	x	-	-	44287	25,1
x	x	-	-	31758	18,0
x	-	-	-	30315	17,2
-	-	x	-	21610	12,2
x	x	x	-	15263	8,6
-	x	x	-	14537	8,2
x	-	x	-	11499	6,5
-	-	-	-	1435	0,8 [b)]
-	-	-	x	1294	0,7
-	-	x	x	875	0,5
-	x	-	x	747	0,4
x	x	x	x	715	0,4
x	-	-	x	658	0,4
-	x	x	x	622	0,4
x	x	-	x	444	0,3
x	-	x	x	399	0,2

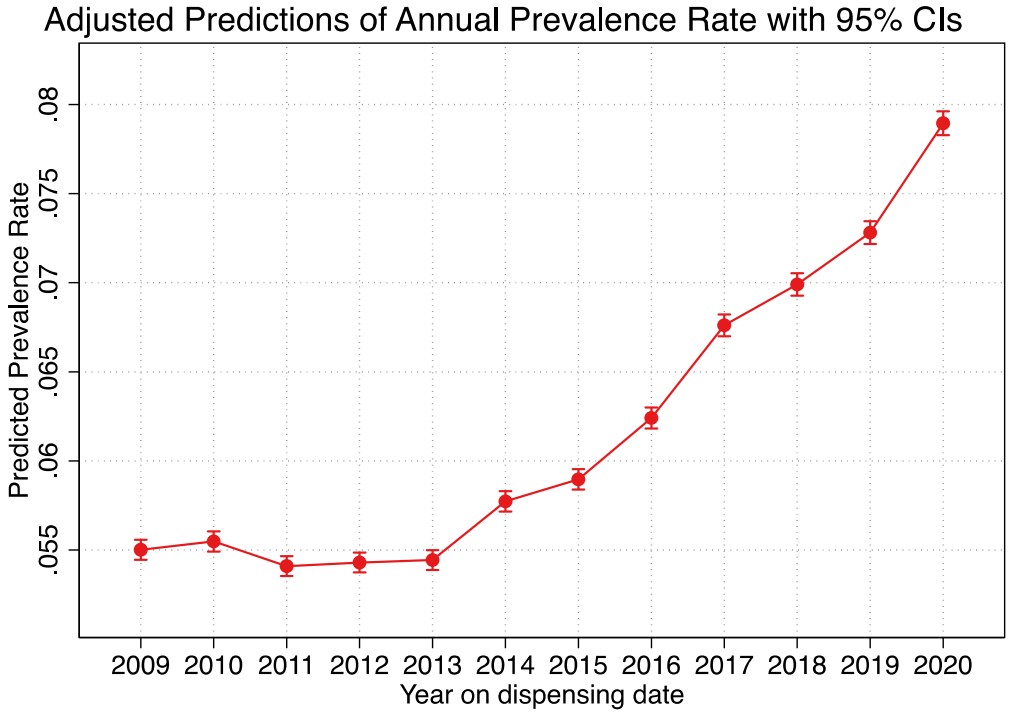
a) Weak topical corticosteroids are also available as an over-the-counter drug and may be underreported.
b) Children treated with topical calcineurin inhibitor as the only treatment.

Fig. S2. The prevalence rate in paediatric patients with atopic dermatitis according to the indicated age group at dispensing date year 2014 - 2020



Data are from the Norwegian Prescription Database from January 1, 2104, through December 31, 2020. Error bars indicate 95% CI. The curve displays the prevalence determined by reimbursed (criterion 1) and non-reimbursed (criterion 2) medications as proxies for atopic dermatitis.

Fig. S3. The annual prevalence rate in paediatric patients with atopic dermatitis year 2009 - 2020, age 0-10.



Data are from the Norwegian Prescription Database from January 1, 2009, through December 31, 2020. Error bars indicate 95% CI. The curve displays the prevalence determined by reimbursed (criterion 1) and non-reimbursed (criterion 2) medications as proxies for atopic dermatitis.

III

ORIGINAL REPORT

Prevalence of Isotretinoin Therapy in Adolescents and Young Adults With and Without Atopic Dermatitis: A Nationwide Prescription-based Population Study

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Although isotretinoin has anti-inflammatory and immunomodulatory properties, it can exacerbate atopic dermatitis. National estimates of the extent to which patients with atopic dermatitis are affected by severe acne and isotretinoin tolerability are lacking. The aim of this study is to investigate isotretinoin therapy in patients with atopic dermatitis and to compare the nationwide prevalence with individuals without atopic dermatitis. All Norwegian residents were followed for 17 years until age 20–22 years in 2020. Approximately 28% of patients with atopic dermatitis had been treated for acne, and 8% had received isotretinoin before age 23 years. In those over 17 years old, significantly more patients with atopic dermatitis were treated with isotretinoin than those without. At age 22 years, 2.21% (95% confidence interval 1.92–2.49) of patients with atopic dermatitis were treated with isotretinoin, compared with 1.55% (95% confidence interval 1.44–1.65) of those without, representing 42.8% (1.43; 95% confidence interval 1.24–1.65) higher use in patients with atopic dermatitis. Patients who received long-term treatment (probable severe atopic dermatitis) tolerated isotretinoin similarly to patients who received short-term treatment (probable mild atopic dermatitis). There was significantly higher use of topical corticosteroids during isotretinoin therapy in patients with atopic dermatitis. Conclusively, severe acne (isotretinoin therapy) was associated with atopic dermatitis at the population level in young adults.

Key words: acne; dermatitis; atopic; dermatological agents; eczema; isotretinoin; pharmacoepidemiology; topical acne treatment; topical calcineurin inhibitor; topical corticosteroids.

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SIGNIFICANCE

There are no nationwide studies on the estimated prevalence and tolerability of isotretinoin treatment in patients with atopic dermatitis (AD). Although isotretinoin has anti-inflammatory effects, isotretinoin therapy causes dryness in patients with AD who have an already impaired skin barrier. The results suggest that patients with AD, who had long-term (probable severe) disease courses, tolerated isotretinoin similarly to patients with AD with brief disease (probable mild) courses. At age 18–22 years, the frequency of severe acne was significantly higher in the population with AD than in those without. Contrary to previous assumptions, the results suggest that severe acne is a comorbidity in young adults with AD.

Atopic dermatitis (AD) affects up to 20% of children and 10% of adults in high-income countries (1). Another prevalent inflammatory (sometimes chronic) skin disease is acne vulgaris. Both conditions exhibit ceramide deficiency, which contributes to skin barrier dysfunction related to follicular hyperkeratinization and promotes comedone formation (2–8). Lipids, the key components of the skin barrier, are reduced in patients with AD (4, 9–11). Isotretinoin has extensive anti-inflammatory and immunomodulatory properties (12). However, isotretinoin drastically reduces sebum secretion in the stratum corneum, which can lead to excessive dryness and exacerbate AD (13). The diminished skin barrier function, inflammatory component and increased risk of infections in patients with AD raise the questions as to what extent patients are affected by acne and how tolerable is isotretinoin treatment.

The occurrence of acne has been associated with oral JAK inhibitors (a systemic immunosuppressant used to treat severe AD), particularly in the population with AD, compared with other indications (14). The association between AD and acne has been poorly studied at the population level. In a small Danish study with data from 1998, no association was found (15). In another Danish study of 6,600 patients with AD, the risk of acne was increased in patients over 30 years of age (16).

The authors are unaware of any up-to-date studies on the nationwide prevalence estimates for severe acne and the tolerability of acne treatment in patients with AD. Therefore, the objectives of this study were to: (*i*) compare the 12-month prevalence for severe acne (dispensed isotretinoin) in the population with or without AD; (*ii*) evaluate treatment days and discontinuation rates of

isotretinoin treatment by severity (years of treatment) of AD; and (*iii*) examine whether topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) treatment increases during isotretinoin therapy in patients with AD.

METHODS

Study population

The study covered individuals born between 1998 and 2000 and residing in Norway. All children aged 4–6 years in 2004, when the Norwegian Prescription Database (NorPD) was established, were followed for 17 years to age 20–22 years in 2020.

In 2004, the Norwegian population included 60,316 4-year-olds, 59,667 5-year-olds, and 61,324 6-year-olds. In 2020, the population of 20-, 21-, and 22-year-olds was 66,813, 66,164, and 67,817, respectively.

Registers and coding classifications

The NorPD contains data on all prescription drugs dispensed by pharmacies, together with unique, encrypted personal identifiers that can be used to track medication dispensing at the individual level over time (17). All prescriptions dispensed for TCSs (Anatomical Therapeutic Chemical Classification (ATC) code D07) (18), tacrolimus (D11AH01), or pimecrolimus (D11AH02) were extracted from NorPD (using the 2021 ATC/DDD index). All other prescriptions dispensed for these patients were also extracted.

Patient characteristics catalogued included age, month and year of birth, sex, dispensing date, date of death, generic drug name and ATC codes. Reimbursable prescriptions were assigned codes from the International Statistical Classification of Diseases, Tenth Revision (ICD-10), and the International Classification of Primary Care, Version Two (ICPC-2) (17). Population statistics were obtained from Statistics Norway (19).

Algorithm for identifying patients with atopic dermatitis

Patients were considered to have AD if they met at least 1 requirement for either Criterion 1 or Criterion 2.

- *Criterion 1 (based on medical diagnoses):* patients with recorded reimbursement prescriptions, including associated disease-specific diagnoses of "atopic dermatitis/eczema", recorded as ICD-10 (L20) or ICPC-2 (S87).
- *Criterion 2 (based on disease-specific dispensed medication):* patients with non-reimbursable prescriptions were considered to have AD if, within 1 year, the patients had either:
  - ≥2 prescriptions for TCSs
  - ≥2 prescription for TCI

Appendix S1 provides further explanation of the algorithm employed.

Because AD is considered a chronic disease, patients identified by the algorithm were defined as "having AD". Patients with AD treated topically for more than 9 years were defined as "having a long-term disease course". Patients with AD treated topically for less than 5 years were defined as "having a short-term disease course".

Identifying individuals with acne

Topical retinoids (D10AD), anti-infectives (D10AF), and azelaic acid (D10AX) were defined as topical acne preparations.

Doxycycline (J01AA02), lymecycline (J01AA04), oxytetracycline (J01AA06), and tetracycline (J01AA07) were defined as tetracyclines. A cut-off value of 50 tablets of tetracyclines was chosen to exclude prescriptions for respiratory tract infections and sexually transmitted diseases. Isotretinoin (D10BA01), cyproterone and oestrogen (G03HB01) and tetracyclines were defined as systemic acne preparations.

The defined daily dose (DDD) was used as the assumed mean maintenance dose per day (set at 30 mg per day by the World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology) (17).

In Norway, isotretinoin is indicated for treating severe acne vulgaris (20). Therefore, this study defined individuals treated with isotretinoin as having severe acne. Individuals treated with topical retinoids, anti-infectives, azelaic acid, tetracycline, cyproterone and oestrogen, or isotretinoin were defined as having acne.

Persistence, attempts, and discontinuation of isotretinoin

Drug persistence was defined as the duration between the date of the first prescription and the presumed discontinuation date (days, according to DDDs, were added to the date of the last prescription). The discontinuation rate was referred to as a measure of isotretinoin tolerability. The number of days of drug supply was calculated by multiplying the number of dispensed packages by the number of DDDs per pack.

The recommended treatment interval between 2 isotretinoin treatments is at least 8 weeks, to which we added 1 month (since a patient might have accumulated a stockpile of medication). The date of the subsequent prescription was then considered the start of a new attempt if 3 months had elapsed since the presumed discontinuation date. A 16–24-week treatment duration is usually sufficient to achieve remission (21). A cut-off of 16 weeks was set to determine whether an individual had discontinued treatment. Individuals whose presumed end of treatment was in the last 3 months of the available data set were excluded from the persistence analysis (**Table I**).

Statistical analyses

The Poisson regression procedure was used to calculate 12-month prevalence (P) and prevalence ratio (PR) with 95% confidence

Table I. Prescribing information for isotretinoin, the number of attempts and drug persistence of the study population with atopic dermatitis the number of years treated with topical corticosteroids (TCSs)/topical calcineurin inhibitors (TCIs)

Number of years treated with TCSs/TCIs	Group I (1–4 years)	Group II (5–8 years)	Group III (9–19 years)	Total (all age groups)
Number of attempts, *n* (%)				
1 attempt	1,889 (100.0)	344 (100.0)	100 (100.0)	2,333 (100.0)
2 attempts	346 (18.3)	70 (20.3)	22 (22.0)	438 (18.7)
>2 attempts	85 (4.5)	15 (4.4)	4 (4.0)	104 (4.5)
Discontinued treatments (all attempts incl.), *n* (%)	403 (17.1)	78 (18.0)	27 (21.3)	508 (17.4)
Age, median (IQR)	18.1 (16.6–19.7)	18.2 (16.9–19.7)	18.2 (16.3–19.4)	18.3 (16.8–19.8)
Female/male (%)	51.0/49.0	54.7/45.4	56.5/43.5	51.6/48.4
Days of drug supply (based on DDDs), median (IQR)	240.0 (140.0–300.0)	240.0 (120.0–300.0)	220.0 (140.0–300.0)	240.0 (140.0–300.0)
Drug persistence (days of treatment), median (IQR)	196.0 (142.7–244.0)	198.7 (140.0–248.0)	204.7 (137.0–257.0)	196.0 (141.0–246.0)

Of the 2,479 patients with AD who were treated with isotretinoin, 146 patients (who had started treatment in the last 112 days of the study) were excluded.
AD: atopic dermatitis; TCS: topical corticosteroids; TCI: topical calcineurin inhibitors; IQR: interquartile range; DDDs: defined daily doses.

intervals (95% CIs). Estimates were tested with χ^2 tests. p-value <0.05 (2-sided test) was considered statistically significant. Ps by age, sex, years of treatment (groups) and interactions were calculated.

Patients with AD were divided into 3 groups based on the number of years with TCS or TCI therapy. Patients with 1–4 years of treatment (group I) were set as the reference group to stratify and assess predictors and risk.

Descriptive statistics for continuous variables were reported as mean (SD), median (interquartile range; IQR), and frequency (percentage) for categorical variables. Population statistics from Statistics Norway (SSB) were presented by year of birth, sex, and age (based on the annual mid-year population in Norway). Data were analysed using Stata/MP software (version 17.0; StataCorp LLP; College Station, Texas, USA).

RESULTS

Patients with atopic dermatitis

The total number of patients with AD comprised 10,689 from the 1998 birth cohort, 10,697 from the 1999 birth cohort, and 11,025 from the 2000 birth cohort.

The follow-up period for all patients was 17 years. Most patients with AD received brief medical treatment. Thus, 22,968 patients (77.1%) were treated for 1–4 years (group I), 5,392 (17.7%) for 5–8 years (group II), and 2,010 (6.2%) for 9–17 years (group III). The proportion of females in the AD population was 54.4% ($n = 17,593$).

Prevalence of isotretinoin treatment

In over 17-year-olds, significantly more patients with AD than those without were treated with isotretinoin (increasing with age). This increased from 16.2% more (PR 1.16; 95% CI 1.07–1.26) at age 18 years to 42.8% (PR 1.43; 95% CI 1.24–1.65) at 22 years. Between the ages of 18 and 22 years, the prevalence of isotretinoin-treated individuals without AD decreased by 54.1% (PR 0.54; 95% CI 0.48–0.60), whereas it remained stable in patients with AD (**Fig. 1** and Table SI).

Between the ages of 17 and 22 years, a significantly larger proportion of males with AD were treated with isotretinoin than were males without AD, ranging from 13.5% (PR 1.13; 95% CI, 1.00–1.28) more at age 17 years to 14.0% (PR 1.40; 95% CI 1.07–1.82) more at age 22 years. Between the ages of 20 and 22 years, more females with AD were treated with isotretinoin than were females without AD, ranging from 15.3% (PR 1.15; 95% CI 1.04–1.28) more at age 20 years to 33.5% more (PR 1.33; 95% CI, 1.12–1.59) at 22 years.

Acne treatment by group and discontinuation of isotretinoin

Of the 32,371 patients with AD, 28.2% ($n = 9,114$) were treated for acne, with 7.6% ($n = 2,479$) treated for severe acne (receiving isotretinoin), before the age of 22 years.

In group II, 14.3% (PR 0.86; 95% CI 0.77–0.96) fewer patients received isotretinoin than those in group I. Correspondingly, group III received 31.6% (PR 0.68; 95% CI 0.56–0.83) less isotretinoin treatment than group I. Group III received 30.3% (PR 0.70; 95% CI 0.51–0.95) less hormone therapy than group I (**Table II**). Discontinuation of isotretinoin ranged from 17.1% in group I to 22.3% in group III (statistically non-significant) (Table I).

Topical corticosteroids dispensed during isotretinoin therapy

Only 1,340 (54.1%) of the 2,479 patients with AD treated with isotretinoin received TCSs/TCIs during isotre-

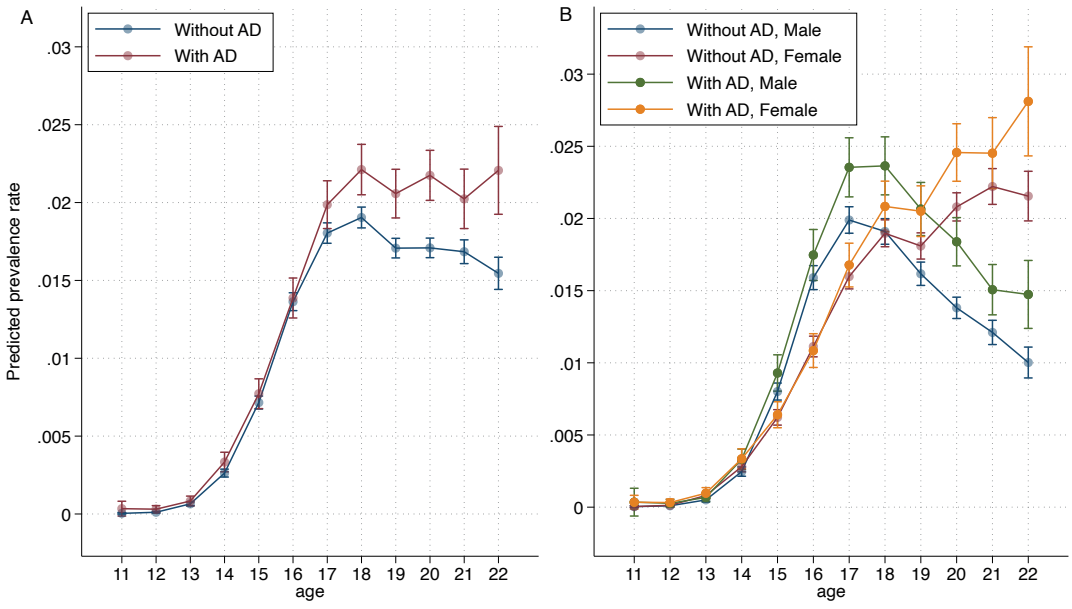

Fig. 1. Estimated 1-year prevalence in patients with atopic dermatitis (AD) and individuals without AD born in 1998, 1999, and 2000 receiving isotretinoin by (A) age and by (B) age and sex. Error bars indicate 95% confidence interval.

Table II. Number of patients with atopic dermatitis (AD) treated for acne by groups (the number of years treated with topical corticosteroids (TCSs)/topical calcineurin inhibitors (TCIs) and sex

Number of years treated with TCSs/ TCIs	Group I (1–4 years)	Group II (5–8 years)	Group III (9–17 years)	Total	Females	Males
Patients with AD, *n* (%)	24,969 (77.1)	5,392 (17.7)	2,010(6.2)	32,371 (100)	17,593 (54.3)	14,778 (45.7)
Topical acne treatment, *n* (%)						
Azelaic acid	1,311 (5.3)	350 (6.5)	91 (4.5)	1,752 (5.4)	1,231 (7.0)	521 (3.0)
Topical retinoids	5,551 (22.2)	1,190 (22.1)	424 (21.1)	7,165 (22.1)	4,434 (25.2)	2,731 (15.5)
Topical anti-infectives	1,752 (7.0)	399 (7.4)	137 (6.8)	2,288 (7.1)	1,453 (8.3)	835 (4.7)
Systemic acne treatment, *n* (%)						
Tetracyclines	431 (1.7)	91 (1.7)	37 (1.8)	559 (1.7)	294 (1.7)	265 (1.5)
Cyproterone and oestrogen	749 (3.0)	176 (3.3)	42 (2.1)	967 (3.0)	966 (5.5)	1 (0.0)
Isotretinoin	1,999 (8.0)	370 (6.9)	110 (5.5)	2,479 (7.7)	1,305 (7.4)	1,174 (6.7)
Patients treated for acne, *n* (%)	7,025 (28.5)	1,553 (29.0)	536 (27.4)	9,114 (28.2)	5,674 (32.3)	3,440 (19.6)

All combination preparations with retinoids for topical use were categorized as topical retinoids.

tinoin treatment. In groups I, II, and III, respectively, 48.2% (*n* = 964/1,999), 74.1% (*n* = 274/370), and 92.7% (*n* = 102/110) of patients received TCSs or TCIs during isotretinoin treatment. In groups II and III, 53.6% (PR 1.54; 95% CI 1.34–1.76) and 92.3% (PR 1.19; 95% CI 1.57–2.36) more patients received TCSs during isotretinoin treatment than in group I (**Fig. 2** and Table SII).

More prescriptions (TCSs or TCIs) were dispensed in the first month of isotretinoin treatment, ranging from 155.6% (PR 2.56; 95% CI, 1.96–3.34) more in the first month to 41.7% (PR 1.42; 95% CI 1.06–1.90) more in the seventh month. This was calculated using the median number of prescriptions 18 months prior to isotretinoin treatment as the reference group (75.5; IQR; 69.2–81.8).

During the first 6 months of isotretinoin treatment, dispensed prescriptions of moderate potent and potent TCSs were significantly increased. Table SII provides further details.

There was no significant increase in TCIs, weak TCSs, or very potent TCSs.

DISCUSSION

These results suggest that severe acne is a comorbidity in young adults with AD. In patients under 18 years of age, no significant differences were observed in the 1-year prevalence of isotretinoin therapy between the populations with or without AD. This was consistent with the Danish studies (15, 22). The prevalence of isotretinoin-treated individuals in the population without AD decreased between the ages of 18 and 22 years. In contrast, it remained stable in patients with AD. At age 22 years, isotretinoin therapy was 42% higher in patients with AD than in individuals without AD. Although it can be speculated that patients with AD are more likely to use topical comedogenic treatments to treat xerosis, which may contribute to acne, this is unlikely to be the sole explanation. The pathogenesis of AD involves a complex interplay of various factors (skin barrier defects, immune dysregulation, and skin microbiome) that may predispose patients with AD to cutaneous inflammatory alterations and infections such as acne (23, 24).

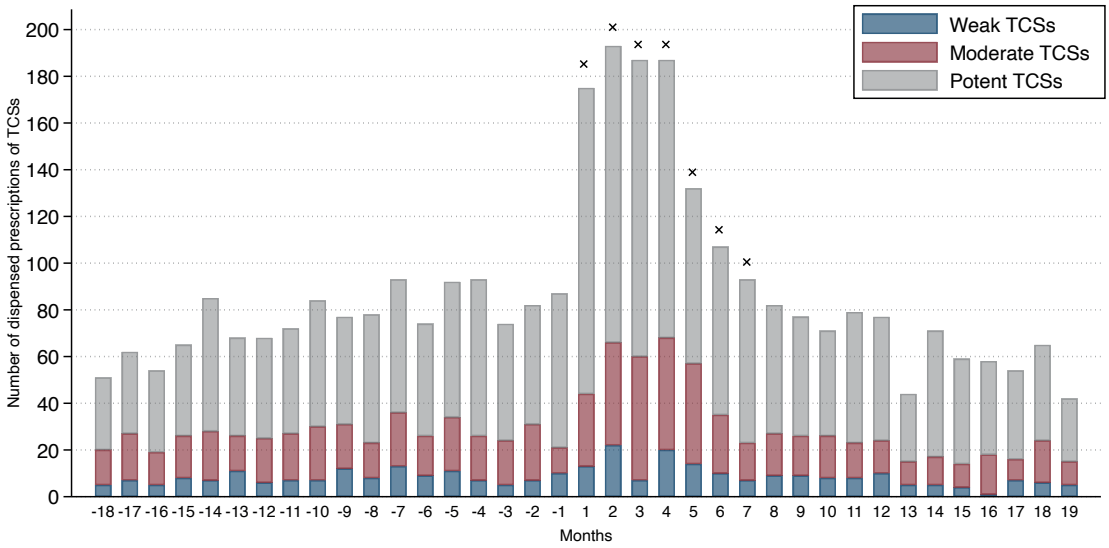

Fig. 2. Dispensed prescriptions to the 1,340 (of 2,479) patients with atopic dermatitis (AD) who received (weak, moderate, and potent) topical corticosteroids (TCSs) 18 months before and after initiation of isotretinoin treatment. Month 1 denotes the month in which the first isotretinoin was dispensed. × denotes months with a significantly higher number of total (all potencies) prescriptions dispensed compared with the median number of prescriptions 18 months before isotretinoin treatment. If patients had more than 1 treatment attempt with isotretinoin, only the first attempt was included in the graph. Table SII provides further details on monthly TCSs dispensed.

In the Danish study, the 12-month prevalence of acne was 3.7% in the general population and 3.9% among patients with AD (16). The risk of severe acne in patients with AD increased with age, which is consistent with the current findings. However, in contrast to the current study, the risk of being treated for severe acne was lower in patients with AD who were younger than 30 years.

Patients with 9 or more years of AD therapy had a 30% lower risk of being treated with isotretinoin or hormone therapy than patients treated for only a few years. Patients with long-term disease course (and severe AD) are likely to have easier access to a dermatologist, which is the specialty that prescribes most isotretinoin in Norway. Consequently, the significantly lower use of isotretinoin in patients with long-term disease course is a robust finding. The explanation could be that some dermatologists are hesitant to prescribe isotretinoin to patients with severe and long-term disease course due to its side-effects (xerosis) or the higher prevalence of psychological problems in patients with AD (25).

Discontinuation of isotretinoin may be caused by various factors, including time-consuming/prolonged follow-up and side-effects, such as xerosis, retinoid dermatitis, pruritus, which are more common in patients with AD (26). No significant differences in the number of patients with AD who discontinued isotretinoin treatment by group were observed, suggesting that patients with nearly a decade or more of AD therapy, tolerated isotretinoin as well as patients with a shorter history. A study from 2020 found that 17% of the subjects with acne discontinued isotretinoin treatment due to side-effects (27), which is consistent with the results of the current study and, furthermore, signifies that patients with AD as well as individuals without AD tolerate isotretinoin.

Retinoid-induced skin irritation may be alleviated by moisturizer (28). Patients with severe AD may be accustomed to applying moisturizers regularly, which could prevent AD flare-ups and irritation, and thereby increase tolerance of isotretinoin. Moreover, alitretinoin (systemic retinoid), indicated for the treatment of chronic hand eczema (CHE), binds to the intracellular retinoic acid receptors A (RAR) and X (RXR) (29). In contrast, isotretinoin binds selectively to RAR (29). Although binding to both receptors is thought to be required for the control of CHE, isotretinoin has been shown to have extensive anti-inflammatory and immunomodulatory properties that may affect treatment tolerability in patients with AD (12).

According to a Belgian study (using similar methods to the current study) (30), the median duration of isotretinoin treatment in the study population was 19.9 weeks, which is shorter than the results of the current study (28 weeks). Treatment guidelines are the same in Belgium and Norway, and the study period partially overlapped (2012–2015). Some of the patients with AD in the current study may have received "lower-dose" isotretinoin treatment for an extended period to reduce side-effects (31). Therefore, the final period (from the last dispensing to treatment discontinuation) may be longer than estimated.

A significant increase in the prescription of moderately potent and potent TCSs dispensed during the first seven months of isotretinoin therapy was observed. Only approximately half of patients with short-term disease course received TCSs or TCIs during isotretinoin treatment, compared with more than 9 in every 10 patients with long-term disease course. If the increase in TCSs was a preventive treatment strategy to avoid exacerbation, a similar increase would have been expected with all topical AD preparations. However, some patients may have collected TCS at the pharmacy, while simultaneously collecting their prescription for isotretinoin. Notwithstanding, there is no indication that patients would accumulate TCSs during their isotretinoin treatment when they do not need it, especially since those over 16 years of age must pay for some of the medication themselves. Therefore, it is reasonable to assume that the need for moderate potent and potent TCSs was high for at least 28 weeks, which is consistent with the mean duration of isotretinoin treatment in the current study (28 weeks).

Cyclosporine and JAK inhibitors have acne as a side-effect. None of the patients with AD were prescribed JAK inhibitors during the study period. Adjustments for cyclosporine yielded the same results. Other prescription drugs with acne side-effects were not adjusted for because they are assumed to be evenly distributed in the populations with and without AD.

Strengths and limitations

The Nordic countries have national health registries with validated, real-world epidemiological data (32). The large size of the novel longitudinal individual-based dataset and the complete coverage of all prescriptions dispensed by pharmacies to the entire Norwegian population ensures robustness with high significance and generalizability.

Overall, the prevalence of patients with severe acne is probably underestimated because the occurrence of untreated severe acne is unknown. Patients treated with isotretinoin are monitored regularly during the long follow-up period, which also reduces the risk of overestimating actual drug use.

Although an indication for isotretinoin treatment is severe acne (20), some individuals with moderate (and mild) disease may have been treated. However, in patients with AD, physicians are more likely to undertreat than overtreat acne for fear of aggravating the disease. In addition, Norway constantly had a positive net migration during the study period (19). Immigrants with unknown medical records may lead to artificially low prevalence estimates for isotretinoin-treated patients

with AD. Overall, the prevalence of isotretinoin therapy in patients with AD is most likely underestimated and correspondingly robust.

The cost for an amount equivalent to 3 months of isotretinoin use is NOK 520.00 (October 2022). Moreover, social factors and the availability of a dermatologist may play a role in the accessibility of treatment.

Although more expensive, and sold in smaller packages than prescription medications, mild TCSs are available over the counter (OTC). However, the Norwegian social welfare system provides reimbursement for prescription drugs (free of charge until age 16 years/deductible fee after age 16 years) for chronic diseases such as AD. Consequently, an OTC purchase is expensive, and the analysed sample of patients with AD is probably representative (33).

TCSs are prescribed for a broad group of skin conditions, which may distort the accurate representation of AD drug treatment in the study population (34, 35). In addition, diagnoses recorded by physicians may be incorrect, leading to misclassification. A total of 28,612 (88.4%) of the 32,372 patients were diagnosed with AD (Criterion 1). According to a study, 2 or more annual TCS prescriptions yielded a sensitivity value of 40% and a positive predictive value (PPV) of 60% (34). Criterion 3 further increased the PPV.

Nearly 1.0% of prescriptions for TCSs or TCIs were excluded because of missing identification. AD, however, is defined as a chronic disease. Patients with AD would likely have received prior or subsequent medical treatment during the 17 years of follow-up. It is possible that most of the excluded prescriptions were among the included patients.

Conclusion

Treatment with isotretinoin was associated with AD at the population level after the age of 17 years. The number of TCSs/TCIs dispensed increased significantly during isotretinoin therapy, especially in patients with AD with a long-term disease course. There were no significant differences in discontinuation rates, the number of treatment attempts, suggesting that patients with a long-term disease course (probable severe AD) tolerated isotretinoin similarly to patients with a short-term disease course (probable mild AD).

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The datasets generated and/or analysed during this study are available from the corresponding author upon reasonable request. The observational study was analysed between January 2020 and October 2021.

The study was approved by the Regional Committees for Medical and Health Research Ethics Southeast Norway (Ref, Norway (Ref, REK: 1927) in 2015, 2019, and 2021 and by the Norwegian Social Science Data Services (NSD) in December 2015. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, the Consolidated Standards of Reporting Trials (CONSORT) statement and the ICMJE requirements on privacy and informed consent. The study was performed in accordance with the Declaration of Helsinki 1964, and its later amendments.

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Conflicts of interest: JAH has financial/personal connections to AbbVie and Celgene. CHM received a research grant from Sanofi Genzyme in 2021. The remaining authors have no conflicts/competing interest to declare.

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APPENDIX S1

ALGORITHM FOR DEFINING PATIENTS WITH ATOPIC DERMATITIS (AD)

Patients were considered to have AD if they met at least one requirement for either criteria 1 or 2:

- *Criterion 1–based on disease-specific diagnoses:*
  - ≥ 1 (ICD-10) L20 "Atopic dermatitis"
  - ≥ 1 (ICPC-2) S87 "Dermatitis/atopic dermatitis"
- *Criterion 2–based on disease-specific medication (ATC-codes):*
  - ≥ 1 dispensed prescription for D11AH "Agents for dermatitis, excluding corticosteroids" (tacrolimus or pimecrolimus) without any of the following prescription exclusion criteria [a)]
  - ≥ 2 dispensed prescriptions for D07 "Corticosteroids, dermatological preparations" for topical use (min. 14 days apart) within 12 months without any of the following prescription exclusion criteria.

Prescription exclusion criteria:

Patients WITHOUT a diagnosis of (ICD-10) L20 "Atopic dermatitis" or (ICPC-2) S87 "Dermatitis/atopic dermatitis": Dispensed prescriptions with diagnoses:

- ICD-10: L21 "Seborrhoeic dermatitis", L22 "Diaper dermatitis", L23 "Allergic contact dermatitis", L24 "Irritant contact dermatitis", L25 "Unspecified contact dermatitis", L26 "Exfoliative dermatitis", L27 "Dermatitis due to substances taken internally", L28 "Lichen simplex chronicus and prurigo", L40–L45 "Papulosquamous disorders", L53 "Other erythematosus conditions", L55 "Sunburn", L56 "Other acute skin changes due to ultraviolet radiation", L80 "Vitiligo", L90 "Atrophic disorders of the skin", L93 "Lupus erythematosus".
- ICPC-2: S86 "Dermatitis seborrhoeic", S88 "Dermatitis contact/allergic", S89 "Diaper rash", S80 "Solar keratosis/sunburn", S82 "Exfoliative dermatitis", S08 "Skin color change", S91 "Psoriasis", S99 "Skin disease, other".

Non-AD criteria (exclusion criteria)

Patients with co-occurring medical skin diagnoses (that might lead to identical treatment) or with co-occurring disease-specific medication (primarily prescribed for other diseases) were NOT considered to have AD and were excluded by the following non-AD Criteria:

- *Co-occurring skin diagnoses (based on ICD-10 or ICPC-2):*

≥ 1 diagnosis of either:

- ICD-10: L40–L45 “Papulosquamous disorders”, L80 “Vitiligo”, L90 “Atrophic disorders of the skin”, L93 “Lupus erythematosus”
- ICPC-2: S91 “Psoriasis”

- *Co-occurring disease-specific medication (based on ATC):*

≥ 1 dispensed prescription for either:

- D05 “Antipsoriatics”, D02AF “Salicylates acid preparations”, D07AD “Corticosteroids, very potent (group IV)” including clobetasol [b)]

Note:

a) Calcineurin inhibitor ointment (0.03%) is indicated for adults, adolescents, and patients from the age of 2 years and is prescribed for moderate-to-severe AD (S1)

b) Prescriptions of corticosteroid group IV (without being diagnosed with AD) because AD is not treated singly with group IV.

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Table SI. Estimated one-year prevalence in patients with AD and individuals without AD, born in 1998, 1999, and 2000, treated with isotretinoin by age with 95% (CIs).

	Patients with AD		*Individuals without AD*	
Age, y	Number of Events	Proportion, 95%CIs	Number of Events	Proportion, 95%CIs
10	-	-	-	-
11	2	0.03(-0.01–0.08)	3	0.00 (0.00–0.01)
12	7	0.03 (0.01–0.05)	17	0.01 (0.01–0.02)
13	27	0.08 (0.05–0.11)	101	0.07 (0.05–0.08)
14	108	0.33 (0.27–0.40)	411	0.26 (0.24–0.29)
15	250	0.77 (0.68–0.87)	1,128	0.72 (0.67–0.76)
16	449	1.39 (1.26–1.52)	2,167	1.36 (1.31–1.42)
17	643	1.99 (1.83–2.14)	2,910	1.80 (1.74–1.87)
18	716	2.21 (2.05–2.37)	3,117	1.90 (1.84–1.97)
19	666	2.06 (1.90–2.21)	2,826	1.71 (1.64–1.77)
20	704	2.17 (2.01–2.34)	2,842	1.71 (1.65–1.77)
21	432	2.02 (1.83–2.21)	1,875	1.68 (1.61–1.76)
22	235	2.21 (1.92–2.49)	858	1.55 (1.44–1.65)

AD: Atopic Dermatitis; y: year; CIs: Confidence Intervals

Table SII. Estimated proportion of prescriptions dispensed for weak, moderate, and potent TCS per month with 95% CIs during isotretinoin treatment in patients with AD.

TCS Potency	*Month*	*Proportion*	*95% Cis*
Weak TCSs:	1	1.61	(0.67–3.89)
	2	2.73	(1.22–6.12)
	3	0.87	(0.32–2.39)
	4	2.48	(1.10–5.63)
	5	1.74	(0.73–4.13)
	6	1.24	(0.49–3.14)
	7	0.87	(0.32–2.39)
Moderate	1	1.67	(0.94–2.96)
potent TCSs:	2	2.36	(1.38–4.06)
	3	2.85	(1.68–4.83)
	4	2.58	(1.51–4.40)
	5	2.31	(1.34–3.98)
	6	1.34	(0.74–2.45)
	7	0.86	(0.44–1.68)
Potent TCSs:	0	2.68	(1.93–3.73)
	2	2.60	(1.87–3.62)
	3	2.60	(1.87–3.62)
	4	2.44	(1.75–3.40)
	5	1.54	(1.07–2.20)
	6	1.47	(1.03–2.12)
	7	1.43	(0.99–2.07)

AD: Atopic Dermatitis; CIs: Confidence Intervals; TCSs: Topical Corticosteroids

Errata

Errata

Ph.d.-kandidat:	Cathrine Helene Mohn
Fakultet:	Det MEDISINSKE fakultet,
Tittel:	Occurrence and treatment patterns in children with atopic dermatitis and subsequent comorbidity in the form of severe acne - a nationwide prescription registry study
Errata:	Feil er korrigert ved å understreke både ordet som var feil og ordet som er korrigert.
Hovedveileder:	Jon Anders Halvorsen
Jeg mottok informasjon om at avhandlingen min er godkjent for disputas:	*14.02.2024*
Planlagt dato for disputas er:	*20.06.2024*

Errataliste:

Side	Linje	Endret fra	Endret til
20	30-33	The pathophysiology of atopic dermatitis is thought to be influenced by changes in proteases and protease inhibitors, as well as by changes in the composition of epidermal lipids consisting of cholesterol, free fatty acids and ceramides [47-49].	The pathophysiology of atopic dermatitis is thought to be influenced by changes in proteases and protease inhibitors, as well as by changes in the composition of epidermal lipids consisting of cholesterol, free fatty acids and ceramides [49,50].
39	11-12	Topical corticosteroids come in a variety of potencies. The potency of topical corticosteroids is classified from mild (Class I) to super-potent (Class IV), according to Nieder et al. [229, 230]	På grunn av en inkurie ble disse setningene stående selv om de burde vært fjernet. Den endelige versjonen av setningene står under.
43	5-7	Reducing the incidence of atopic dermatitis will alleviate the disease and decrease the risk of related comorbidities **[**68**].**	Reducing the incidence of atopic dermatitis will alleviate the disease and decrease the risk of related comorbidities [252].
56	14-15	Although the analysis is retrospective, the NorPD data were collected prospectively [228].	Although the analysis is retrospective, the NorPD data were collected prospectively [280].
60	10-13	**Figure 11** Flowchart illustrating the selection of prescriptions and patients in *Paper II.*	**Figure 11** Flowchart illustrating the selection of prescriptions and patients in *Paper III.*
88	20-22	These findings align with what was discovered in *Paper III*, and they may also suggest that individuals with atopic	These findings align with what was discovered in *Paper III*, and they may also suggest that individuals with atopic

		dermatitis tolerate isotretinoin and patients who do not have atopic dermatitis.	dermatitis tolerate isotretinoin as patients who do not have atopic dermatitis.

Dato og signatur:	
Ph.d.-kandidat	Cathrine Helene Mohn
Dato	*07.04.2024*
Signatur	*Ph.d.-kandidatens innsending per e-post til fakultetet erstatter håndskreven signatur.*